Bioética

Enero-Junio 2015

Delirium in awake patients with mechanical ventilation in intensive care unit

DELIRIUM EN PACIENTES DESPIERTOS CON VENTILACIÓN MECÁNICA EN LA UNIDAD DE CUIDADO INTENSIVO

DELIRIUM EN DOENTES ACORDADOS COM VENTILAÇÃO MECÂNICA EM UNIDADE DE TERAPIA INTENSIVA

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▸ Fecha de recepción: junio 24 de 2014 ▸ Fecha de evaluación: agosto 15 de 2014 ▸ Fecha de aceptación: octubre 14 de 2014

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rev.latinoam.bioet. / ISSN 1657-4702 / Volumen 15 / Número 1 / Edición 28 / Páginas 120-129 / 2015

RESUMEN

Objetivos: identificar la incidencia de delirium en pacientes despiertos que reciben profilaxis primaria durante la ventilación mecánica en la unidad de cuidados intensivos en la Clínica Palermo, Bogotá-Colombia. Metodología: estudio descriptivo transversal. Se exploró la relación del delirium con la enfermedad médica, la profilaxis primaria, la historia personal y asociación con delirium. El tamaño de la muestra (n = 102) se calculó teniendo en cuenta la frecuencia de pacientes despiertos en ventilación mecánica con una estancia media hospitalaria de 7 días. Análisis estadísticos univariado, bivariado y multivariado. Resultados: el delirium se presentó en 8 de cada 102 pacientes (22 %) se observaron diferencias significativas entre los que deliraron y los que no deliran por edad y Marshall. Relaciones significativas entre el delirium y el Apache II, Tiss 28, y Marshall no se han demostrado a través de la regresión logística. Conclusiones: la edad (más de 60 años) es un factor predisponente para la presencia de delirium, así como los antecedentes de tabaquismo. La administración de medicamentos para la profilaxis primaria no mostró ninguna asociación con la ausencia de delirium en pacientes despiertos en ventilación mecánica en la UCI.

Palabras clave

Delirium, cuidado intensivo, enfermería, respiración artificial.

SUMMARY

Objectives: Identify the incidence of delirium in awake patients who receive primary prophylaxis during mechanical ventilation in the intensive care unit in the Palermo Clinic, Bogota- Colombia. Methodology: Prospective cohort study. This study explored the relationship of delirium with primary prophylaxis, medical illness and personal history The sample size (n = 102) was calculated by taking into account the traced frequency of awake patients on mechanical ventilation with an average hospital stay of 7 days univariate, bivariate, and multivariate statistical analyses. Results: Delirium was presented in 8 out of 102 patients (22 %) significant differences were noted between those who raved and those who did not rave for age and Marshall. Significant relationships among delirium Apache, Tiss 28, and Marshall were not proven via logistic regression. Conclusions: Advance age (over 60 years old) is a predisposing factor for the presence of delirium as well as smoking history. The medication administration in the primary prophylaxis did not show any association with the absence of delirium in awake patients on mechanical ventilation in the ICU.

Keywords

Delirium; Intensive care; Nursing; Artificial respiration.

RESUMO

Objetivos: Identificar a incidência de delirium em pacientes acordados que recebem profilaxia primária durante a ventilação mecânica na unidade de terapia intensiva na Clínica Palermo, Bogotá-Colômbia. Metodologia: Estudo descritivo transversal. Explorou-se a relação do delirium com a doença médica, a profilaxia primária, a história pessoal e associação com delirium. O tamanho da amostra (n = 102) foi calculado tendo em conta a frequência de pacientes acordados em ventilação mecânica com um tempo médio de internação de 7 dias. Análises estatísticas univariadas, bivariadas e multivariadas. Resultados: O delirium se apresentou em 8 de cada 102 pacientes (22%) Se observaram diferenças significativas entre aqueles que deliraram e os que não deliraram pela idade e Marshall. Relações significativas entre delirium e o Apache II, Tiss 28 e Marshall não foram demonstrados por meio de regressão logística. Conclusões: a idade (mais de 60 anos) é um fator predisponente para a presença de delirium e assim como os antecedentes de tabagismo. A administração de medicamentos para profilaxia primária não mostrou associação nenhuma com a ausência de delirium em pacientes acordados em ventilação mecânica na UTI.

Palavras-Chave

Delirium, cuidados intensivos, enfermaria, respiração artificial.

INTRODUCTION

Delirium is defined as an acute variation of the state of mind with a fluctuating course, characterized by lack of attention and disorganized thought (Bourne, 2008). In patients admitted to the intensive care unit (ICU), delirium is an independent predictor of mortality in patients under mechanical ventilation HR 3.23. 95 % CI 1.4-7.7. p. 0.008 (Wesley et al., 2004) (McCusker, Cole, Abrahamowicz, Primeau, & Belzile, 2002). Delirium has a great importance in the patient care in an intesive care unit. However, permanent, preventive and predictable attention is not always guaranteed. Patients with delirium presented higher mortality in the intensive care unit compared to a rate of non-delirium patients (63,6 % *vs.* 32,5 %, respectively), with RR of 2.57 (95 % CI 1.56-8.15) (Shu-Min et al., 2004).

The motor subtypes of delirium are classified as: Hyperactive delirium characterized by increased psychomotor function with agitated behavior, or in some cases with aggressiveness, combative and overly alert (Meagher & Hanlon, 2000). Hypoactive delirium presents reduced psychomotor behavior or subjects may appear tranquil and slow, with reduced surveillance, apathetic and often misdiagnosed as depressive or with dementia (Irwin & Rippe, 2002). Mixed delirium ranges between hyperactivity and a manifestation of hypoactivity throughout the day or during course of several days. Both manifestations have been proven common in ICUs.

Two categories of risk factors exist for the presence of delirium (Inouye, Viscol, Horwitz, Hurst & Tinetti, 1993): the first, predisposing factors are those factors with which patients are admitted to the hospital and indicate vulnerability. Among these, there are age over 70 years, antecedents of depression, dementia, epilepsy, prior cerebrovascular disease, treatment with psychoactive substances, alcoholism, and hypo or hypernatremia. Among the medical history antecedents setting the relationship, there are hypertension, alcoholism, history of cigarette smoking, and abnormal levels of bilirubin (Alexander, 2009) (Dubois, Bergeron, Dumont, Dial & Skrobik, 2001). Precipitating factors, that is, those occurring during the stay in the intensive care unit, are secondary to the patient's disease, including the severity of the disease, metabolic disturbances (sodium, calcium, and blood urea nitrogen [BUN] levels), along with infection (Capuzzo et al., 2004), hypoxemia, anemia (Granberg, Malmros, Bergbom & Lundberg, 2002), acidosis, hypotension, and environmental factors in the intensive care unit. Use of epidural anesthesia and morphine are significantly associated to the presence of delirium. Delirium is also manifested with self-extubation, elimination of catheters, prolonged hospital stay, and ventilator dependence in sedated patients (Dubois, Bergeron, Dumont, Dial & Skrobik, 2001)

The importance of cognitive monitoring, besides the physiological constant, is the priority in ICU. Integrity and cognitive recovery of ICU patients is probably as important as the physical recovery if not the most important for patients and families. It is possible to live and adapt to some type of physical disability only with a sane mind or at least at the pre-morbid level of mental function. Every effort must be undertaken to help patients and their families to overcome the negative psychological effects of ICU, particularly within the three principal environments of patients' recollection: procedures, comfort, and the healthcare team (Roberts & Wendy, 2004).

The diagnosis of delirium in awake patients under mechanical ventilation is useful to identify modifiable factors to obtain higher survival rate opportunity (Thomason et al., 2005). Adequate and timely assessment of delirium in patients facilitates empowerment of the nurse in individualized care, which reduces the consequences related to mortality, increased hospitalization days and complications (Bourne, 2008).

From its practice, nursing highlights the importance of psychological recovery in patients in ICU and it is as important as physical recovery. This study puts to the test our hypothesis that the awake patients on mechanical ventilation with primary prophylaxis was associated with a lower presence of delirium during ICU stay that is on average of 7 days.

MATERIALS AND METHODS

The study's sample calculation was 102 patients through non-probabilistic sampling, using the finite population calculation. The following parameters were considered: expected frequency of the parameter is 0.17 as prevalence of delirium reported in ventilated patients in Colombia (Ramos, Perez, Takao & Almanza, 2007), with a 0,05 expected error in a population of 192 awake patients with mechanical ventilation who fulfilled the inclusion criteria during one year, in selected ICUs, with the calculation of N=102 for the sample.

Inclusion criteria: a) informed consent signed by a family member of the patient, b) male or female over 18 years of age, c) hospitalized in the intensive care unit, d) awake patient with mechanical ventilation since the moment of admission until the day of extubation. Exclusion criteria included: a) patients with mechanical ventilation under the effects of deep sedation or coma, b) patients in clinical condition of schizophrenia, encephalopathy, cerebrovascular disease, and clinical history of some type of dementia (Colombo, Corona & Praga, 2012), c) patients in neurosurgery postoperative, severe cranioencephalic (this term does not appear in medical dictionary) trauma, or increased intracranial pressure, Glasgow < 13, and d) pregnant patients.

Another characteristic of the participants in this investigation was the physician-pharmacological management of patients with mechanical ventilation who mostly received antipsychotics such as clozapine, haloperidol and morphine in intermittent dosage. None of the members from the sample received intravenous sedatives or muscle relaxants, which permitted maintaining consciousness; thus, facilitating the implementation of the CAM-ICU to diagnose delirium and the relevance of this study.

The Confusion Assessment Method for ICU (CAM-ICU) was the instrument selected for the study among the tools available for delirium assessment of delirium (Wesley et al., 2001) in the ICU. The CAM-ICU is an instrument validated and recommended by international guides and it permitted detection of delirium with RASS (Richmon Agitation-Sedation Scale) (Wesley & Truman, 2003). Within the psychometric quality of the CAM-ICU criterion validity reports are presented confirmed by the sensitivity and specificity of the test in its cultural adaptation and Spanish version. The translation and cultural adaptation process was carried out according to international recommendations currently in effect; 65 evaluations were conducted in 29 patients. The instrument's internal agreement was adequate, reaching Cronbach's alpha of 0,84 (unilateral 95 % CI: 0,77). Sensitivity of the Spanish version CAM-ICU for observer A (physician) was 80%, with 96% specificity. While for observer B (nurse) sensitivity was 83 %, with 96 % specificity. (Tobar, Romero & Galleguillos, 2010) (Toro, Escobar & Franco, 2010).

The diagnosis of delirium was carried out via the CAM-ICU test, which evaluates the motor response of awake patients with invasive mechanical ventilation, founded on four key criteria of delirium: (a) acutely changed mood, (b) lack of attention, (c) disorganized thought, and (d) altered levels of consciousness. Clinically, delirium is considered present if criteria (a - b and c, d) are manifested (Tobar, Romero & Galleguillos, 2010); the CAM-ICU shows good specificity and validity when applied by nurses and physicians in ICU (McNicoll, Pisani, Wesley, Gifford & Inouye, 2005).

DATA COLLECTION PROCEDURE

Monitoring of delirium was conducted in two phases: 1). A first follow-up (noun), which was comprised from the moment the patient was admitted to ICU fulfilling the study's inclusion criteria capturing antecedents of the record in the clinical history of predisposing factors of hypertension, smoking history and alcohol, motive of admission to ICU; laboratory results (electrolyte-BUN), the variables that were measured during ICU hospitalization included the severity of the disease given by the APACHE (Multiple Organ Dysfunction Score) (Knaus, Draper, Wagner & Zimmerman, 1985) and TISS 28 scales (Simplified Therapeutic Intervention Scoring System) (Miranda, Rijk & Schaufell, 1996), MARSHALL (Multiple Organ Dysfunction Score) (Marshall & Cook, 1995) followed by a second monitoring phase, which diagnoses delirium via CAM – ICU. The presence or absence of delirium was monitored through daily registries during different schedules, three times a day (morning, afternoon, and evening shifts) by the nursing personnel working in ICU and the principal investigator trained to evaluate delirium in patients and their level of consciousness during hospitalization. A format created for said purpose was used during a maximum of seven days of hospitalization. The seven days are an average hospital stay for awake patients with mechanical ventilation in the ICU. The primary prophylaxis for delirium with antipsychotics was also recorded daily for each of the patients and the use of drugs such as clozapine, haloperidol and morphine regardless of the dose. Data was gathered from September 2011 to March 2012 in a private catholic institution offering high-complexity services. The unit has 12 individual beds, each with individualized nursing care. This study was approved by the ethics committee at the Faculty of Nursing in Universidad Nacional de Colombia and at the Palermo Clinic. This study was defined with minimal risk, reflects the

principles that reflect the concern of the researcher to do right, good and just and thus lay the ethical principles of non-maleficence, beneficence and justice during the course of the study, are the guidelines on professional ethics, which behave like moral norms, using the informed consent which was signed by the patient family (Ministerio de Salud, República de Colombia, 1993).

DATA ANALYSIS

Analysis of the clinical records of delirium diagnosis was performed for each of the patients studied; thus, managing to identify the behavior of each of the variables. This was accomplished through daily registries during different schedules (morning, afternoon, and evening shifts) for seven days. Data analysis was conducted with the SPSS statistical package version 19, calculating the incidence of delirium for this population. Descriptive analysis was used to determine the presence of delirium in the population; quantitative variables (age, Apache II, TISS 28. Marshall,) were expressed as mean and typical deviation. Qualitative variables were expressed as absolute and relative (%) frequencies (N°).

RESULTS

During the study period, 130 patients were admitted to the intensive care unit of which only 102 complied with the inclusion criteria. Sample distribution by gender was 55 % female and 45 % male, mean age was 58 years.

Table 1 presents the description of the motives for admission to ICU of patients prioritizing surgical post-operative admission with 40% (41 cases), followed by respiratory deficiency 26 % (27 cases), sepsis 5 % (5 cases) and pneumonia with 4 % (4 cases). To detect delirium as inclusion criterion, the sample had a level of consciousness evaluated institutionally via a Glasgow scale of 15/15 in 91 % of the patients (93 cases) and a Glasgow scale of 14/15 in 9 % of the patients (9 cases). A fact that permitted the patients to have an adequate motor response (shaking hands with the researcher according to instructions) at the moment of assessing delirium with the CAM-ICU instrument.

The incidence of delirium occurred in 22 patients, that is, in 22 % of the sample of 102 patients, hypoactive delirium 10 %, hyperactive 12 % delirium. Among the personal antecedents of the sample monitored for the presence of delirium while under mechanical ventilation, personal antecedents were found of hypertension with 3408201%, followed by alcoholism at 908201%, and smoking at 708201%. After ascertaining the validation

Table 1. Motive for admission to adult intensive care unit of awake patients with mechanical ventilation.

Cause	Frequency	Percentage
Surgical	41	40
Respiratory deficiency	27	26
Cardiovascular CX	10	10
Other causes	8	8
Cardiac-Failure, AMI Cardiac Plugging	6	6
Sepsis	5	5
Pneumonia	4	4
Without information	1	1
Total	102	100

Fuente: Henao Castaño & Amaya-Rey (2012)

Table 2. Student's t test assessment for averages of the scales in patients monitored for the presence of delirium in ICU, n = 102.

VARIABLE	MEAN		T(GL)	P_VALUE
	Delirium	No delirium		
Apache II	19	17	-1903(100)	0,060
TISS 28	38	37	0,501 (100)	0,618
Marshall	5	4	-2298 (27.307)	0,029 *

Fuente: Henao Castaño & Amaya-Rey (2012)

Table 3. Significance of means of patients monitored for the presence of delirium in ICU.

		PRESENCE OF DELIRIUM		
		YES	NO	P_value
Age. Age (SD)		72.56 (5.943)	56.79 (20.162)	*0.001
Gender	Male	11 (50%)	35 (35%)	
	Female	11 (50%)	45 (45%)	
Cause Admission I.C.U.	Surgical	7 (31.8%)	34 (43%)	
	Acute Respiratory Deficiency	10 (45.5%)	17(21.5%)	0.079
	Sepsis, Pneumonia	5 (22%)	29(36.25%)	

Fuente: Henao Castaño & Amaya-Rey (2012)

of assumptions of normality according to Konmogorov Smirnof, Table 2 presents Student's t test to evaluate the presence of possible significant differences in the average values among patients with and without delirium events in each of the scales. For the APACHE II (p = 0,060) and TISS 28 (p = 0,618) averages, no significant difference was noted among the averages of patients who presented or did not present delirium. The Marshall scale (p = 0,029) presents a significant difference among averages of patients who presented delirium and those who did not.

Table 3 presents the mean difference significance by age, gender and motive for admission to ICU in patients who had and those who did not have delirium, finding that only age was significant. Likewise, the mean differences were calculated among patients who raved and did not rave by antecedents of hypertension, alcoholism, smoking, administration of morphine and other medications, only finding significance among patients who raved and who did not rave in the smoking factor.

Based on Table 3 and 4: It can be noted that significant values do not exist to infer a possible degree of statistical association among the independent variables, which is why it is concluded that no collinear problems exist among the variables associated to the presence or not of delirium events. Table 4 presents the multiple logistic regression models, which includes the three variables that showed statistical significance.

Upon adjusting a multiple logistic regression model to evaluate the joint effect observed from the MARSHAL score, age and the presence of smoking antecedent on

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Table 4. Personal history (predisposing factors) in the patients monitored for the presence of delirium in the ICU. n=102

		DELIRIUM		
		YES	NO	p-valor
Hypertension	YES	8 (36,4 %)	27 (33,8 %)	0,819
	NO	14 (63,6 %)	53 (66,3 %)	
Smoking	YES	4 (18,2 %)	3 (3,8 %)	*0,018
	NO	18 (81,8 %)	77 (96,3 %)	
Alcohol	YES	4 (18,2 %)	5 (6,3 %)	0,081
	NO	18 (81,8 %)	75 (93,8 %)	
Morphine		12(60,0 %)	36 (78,3 %)	0,126
Clozapine		8 (40,0 %)	10 (21,7 %)	

Fuente: Henao Castaño & Amaya-Rey (2012)

Table 5. Adjusted Logistic Regression Model for factors associated to the presence of delirium in ICU

VARIABLE	MODALITIES	PARAMETER	E.E.	P_VALUE	OR	95% CI (OR)
Intercept		-6029	1633	<0,001	N.A.	
Age	Age	**0,061**	**0,022**	**0,007**	**1062**	1.018-1.110
Marshal score	MARSHAL	0,096	0,083	0,249	1101	0.935-1.295
Antecedents of Smoking	Yes	1493	0,938	0,112	4451	0.708-27.980

Fuente: Henao Castaño & Amaya-Rey (2012)

the likelihood of delirium occurrence; it was found —as shown in Table 5— that only age presented a positive effect on the probability of delirium occurrence; specifically, the older the patient, the higher the probability of delirium occurrence (see positive parameter in the table).

Likewise, it is worth noting that smoking and the MARSHAL score were not significantly associated from a multivariate perspective. A probable explanation for this phenomenon is the low number of patients who stated they were smokers (7 of 102), which led to the OR estimated (4451) with 95 % CI (0,708-27.980) not being significant in spite of its high value. Similarly, the slight magnitude of the bivariate association found between the Marshal score and the presence or not of delirium (p = 0,02) could be the cause of no association found from a multivariate perspective.

Due to the aforementioned, new studies are suggested that permit increasing the simple size to evaluate the joint effect of the variables studied herein.

CONCLUSIONS

The 22% incidence in the current study of this finding is lower compared with the international data from 60 to 80 % of the presence of delirium (Girard, Pandharipande & Wesley, 2008). The study in Colombia's Central Military Hospital reported delirium incidence at 29 % in critically ill patients with mechanical ventilation who were sedated during mechanical ventilation and with pharmacological treatment with opioids and benzodiazepines (Ramos, Perez, Takao & Almanza, 2007). Also, at the Reina Sofía Clinic in Bogotá, Colombia, found 21 % incidence of patients

with delirium, but the difference is that all the patients from these two studies were sedated patients (benzodiazepines and opioids) with mechanical ventilation (Florez & Velasquez, 2009) . It is remarkable that for Colombia the incidence of delirium behaved with a similar intensity in the three studies, while —in contrast— in the United States the incidence of delirium in sedated patients, critically ill patients and in ICUs ranges between 60 and 80 % (Serpa, Nassar & Cardoso, 2012). In two studies, reports that patients studied with this incidence of delirium were sedated with Midazolam, opioids, and propofol (Bourne, 2008), and in another study the patients were sedated with benzodiazepines and meperidine (Girard, Pandharipande & Wesley, 2008). The marked difference among the studies carried out in Colombia with authors mentioned may lead us to think that while in Colombia there may be underreporting due to diagnostic deficiencies, in the United States the formation of an interdisciplinary group to diagnose delirium facilitates early detection and typification of delirium impacting on the incidence reported in that country. Additionally, the state of minimum sedation as a physician management protocol of patients under mechanical ventilation maintains patients awake in contrast with prolonged deep sedation management.

All the awake patients under mechanical ventilation are susceptible to being evaluated for early detection of delirium. The intensive care unit in which this study was conducted, presented advantages to evaluate the presence of delirium in patients under mechanical ventilation, given that they were already awake, permitting application of the test without difficulties in comprehension and rapid administration. In contrast with the studies analyzed, as antecedent and for the present discussion, it is known that the diagnostic tests of delirium occur during the sedation weaning process and detection of delirium is hindered, given that states of deep sedation, stupor, or coma do not permit performing the CAM-ICU test in elderly adults (McNicoll, Pisani, Wesley, Gifford & Inouye, 2005). This diagnostic medium of delirium diagnosis is delayed and only until the moment of ventilatory support weaning and the patient's recovery of consciousness can present motor response to enable application of the CAM-ICU test to diagnose delirium.

The moments to assess delirium in this study were three times per day and upon presenting some type of change in the patient's behavior (hypo or hyperactivity). This decision to monitor delirium was consistent with that recommended by (Zaal & Slooter, 2012). In the literature, most research conducted in ICUs has measured delirium at a given moment during a 24-hour period in the morning, evening and at night and when changes in patient's behavior were suspected for the presence of delirium. Two publications evaluated delirium more than once per day (Pun et al., 2005) (Peterson et al., 2006). However, for this study, several measurements were made, one per shift, because delirium is of acute and fluctuating nature, and the measurements besides being easy and rapid (from one to three minutes) are highly sensitive for detection, given that delirium tends to be underestimated by healthcare teams (Balas et al., 2012).

In this study, data related to sample size (n = 102), incidence of delirium (22 %), and the manner of assessment to detect delirium through the CAM-ICU test, as well as the range of time between day one and day five

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to detect the presence of delirium is similar to the study in Taiwan (Lin, Liu & Whang, 2004). Both studies report that the sample was with patients in critical state and with mechanical ventilation. The difference between the studies lies in that in the present study all the patients were awake and medicated with clozapine and/or haloperidol and morphine according to pain. In contrast, the patients from the study in a hospital in Taiwan were medicated with high dosages of morphine (50 mg/day) or midazolam (0,09 mg/kg/h). Although the article does not state the number of days the medication was maintained, most likely the patients sedated with these doses cannot be evaluated with the CAM-ICU test. Hence, it is not precisely known what moment is considered day one of the evaluation and the continuity of assessments to detect delirium, to interpret the findings related to the 22 % incidence and the report of delirium between the first day and the fifth day; given the circumstance that the measurement makes us think that it is possibly ventilatory support post-weaning.

Broader research is required with greater coverage of factors to verify predisposing and precipitating factors inside and outside the ICUs with and without sedation during mechanical ventilation and without mechanical ventilation with adults.

Review the literature circumscribed to awake patients under mechanical ventilation or consider the possibility of multi-centered research at the national and international levels to contrast with different places under the same therapeutic management.

LIMITATIONS

The inclusion criteria considered for this study, among which patients had to be without sedation effects or with minimum effects during mechanical ventilation, makes the sample size require greater time to gather data and increase sample size.

The exclusion criteria used for this study may keep some patients from being diagnosed as hypoactive delirium, causing the sample to be underestimated or restricted to Glasgow scores above 13.

Use of prognosis tools like the TISS 28 and Marshall do not easily permit contrasting because literature and the ICU scenarios do not always use them.

Medical clinical management of adult patients predominates in mechanical ventilation with sedation, thereby, not many broad samples are available with critically ill awake patients or patients with minimum sedation under mechanical ventilation.

ACKNOWLEDGMENTS

We thank Alonso Gomez, MD and the Palermo Clinic of Bogota-Colombia for their insights and helpful contributions that guided us in our approach to this manuscript.

We thank the Universidad Nacional de Colombia, Doctoral Program in Nursing for the academic discussions and we are deeply appreciative of the patients and nursing staff who made this study possible.

No conflict of interest Arises. Study self-funded

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Nawijn et al. World Journal of Emergency Surgery (2020) 15:4
https://doi.org/10.1186/s13017-019-0286-6

World Journal of Emergency Surgery

REVIEW Open Access

Time is of the essence when treating necrotizing soft tissue infections: a systematic review and meta-analysis

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Abstract

Background: Although the phrase "time is fascia" is well acknowledged in the case of necrotizing soft tissue infections (NSTIs), solid evidence is lacking. The aim of this study is to review the current literature concerning the timing of surgery in relation to mortality and amputation in patients with NSTIs.

Methods: A systematic search in PubMed/MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Controlled Register of Trials (CENTRAL) was performed. The primary outcomes were mortality and amputation. These outcomes were related to the following time-related variables: (1) time from onset symptoms to presentation; (2) time from onset symptoms to surgery; (3) time from presentation to surgery; (4) duration of the initial surgical procedure. For the meta-analysis, the effects were estimated using random-effects meta-analysis models.

Result: A total of 109 studies, with combined 6051 NSTI patients, were included. Of these 6051 NSTI patients, 1277 patients died (21.1%). A total of 33 studies, with combined 2123 NSTI patients, were included for quantitative analysis. Mortality was significantly lower for patients with surgery within 6 h after presentation compared to when treatment was delayed more than 6 h (OR 0.43; 95% CI 0.26–0.70; 10 studies included). Surgical treatment within 6 h resulted in a 19% mortality rate compared to 32% when surgical treatment was delayed over 6 h. Also, surgery within 12 h reduced the mortality compared to surgery after 12 h from presentation (OR 0.41; 95% CI 0.27–0.61; 16 studies included). Patient delay (time from onset of symptoms to presentation or surgery) did not significantly affect the mortality in this study. None of the time-related variables assessed significantly reduced the amputation rate. Three studies reported on the duration of the first surgery. They reported a mean operating time of 78, 81, and 102 min with associated mortality rates of 4, 11.4, and 60%, respectively.

Conclusion: Average mortality rates reported remained constant (around 20%) over the past 20 years. Early surgical debridement lowers the mortality rate for NSTI with almost 50%. Thus, a sense of urgency is essential in the treatment of NSTI.

Keywords: Necrotizing soft tissue infection, Necrotizing fasciitis, Surgery, Debridement, Mortality, Amputation, Systematic review, Meta-analysis

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Background

Necrotizing soft tissue infections (NSTIs) are notorious for their acute, aggressive, and rapidly progressive character. Of all NSTIs, necrotizing fasciitis is the most well known and most common NSTI; other NSTIs are myonecrosis and necrotizing cellulitis [1]. Mortality and amputation rates for NSTI are considered high, with described mortality rates varying between 6 and 33% [2–5]. Factors such as advanced age, female sex, multiple comorbidities, and sepsis upon presentation have previously been linked to increased mortality rates [2, 5, 6]. The bacteria causing NSTI can spread rapidly along the fascial planes; therefore, the saying "time is fascia" seems suitable. This resulted in the established belief that source control with early surgical resection of necrotic and infected tissue reduces progression of the infection and improves outcomes [1, 7]. However, the achievability of early treatment is sometimes hindered by a prolonged interval between the onset of symptoms and the patient seeking medical care (patient delay), or between hospital presentation and the eventual diagnosis (doctor delay) [8]. Furthermore, logistical challenges within hospitals might cause unwanted delays in treatment (system delay). In these cases, it is interesting to know if the prognosis can be predicted by the time frame in which the initial surgery is performed. If such a "golden" time frame exists, it could also indicate that when the delay was already too great, a higher mortality or amputation rate can be expected after initial surgery. There is still no consensus on a potential cut off point for such a time frame [9]. Multiple cohort studies have previously assessed the relation between surgical timing and mortality and amputation; however, a large number of studies are under-powered and were unable to reject the null hypothesis [10–14]. Therefore, the aim of this review was to analyze the current literature concerning the timing of surgery in relation to mortality and amputation in patients with necrotizing soft tissue infections.

Review methods

A study protocol was developed a priori and submitted to PROSPERO for registration. This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search and study selection

Published cohort studies and randomized controlled trials (RCT) reporting on mortality or amputation rates for NSTIs were included. These studies had to evaluate one of the following time-related variables: (1) time from onset symptoms to presentation; (2) time from onset symptoms to surgery; (3) time from presentation to surgery; and/or (4) duration of the initial surgical procedure. Studies written in English or Dutch were included. Conference abstracts, studies including pediatric patients, study protocols, reviews, animal studies, case reports, and studies reporting the results for the time variables for less than five patients were excluded.

Two reviewers (FN and DS) independently conducted a systematic search in PubMed/MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Controlled Register of Trials (CENTRAL) for articles published from inception of the databases up to October 29, 2019. The search syntax is available in Additional file 1. No filters were applied during the search. Titles and abstract were screened for potential eligible studies, after which duplicates were removed. The full texts of the potential eligible studies were screened by one reviewer (FN) for the reporting of one or more of the time-related variables. If the full-text article was not available online, attempts were made to request the article from the library or the authors. After screening the available full texts, the remaining articles were read in full to determine eligibility. In the case of uncertainty, the eligibility of a study was discussed between both reviewers. Disagreement of eligibility between reviewers was solved by discussion with a third independent reviewer (FH).

Data extraction

The following data were extracted if available: first author, year of publication, country in which the study was conducted, study design, inclusion period, number of participating medical institutions, number of patients included, mean age of included patients, the anatomical regions affected by NSTI, inclusion and exclusion criteria, diagnostic criteria used for diagnosing NSTI (e.g., operative findings, histopathologic results, microbiology results, clinical signs during physical examination), time onset symptoms to presentation or surgery, time from presentation to surgery, duration of first surgery, mortality rate, and amputation rate. Data was extracted including the available odds ratio (OR), confidence intervals (CIs), and p values.

Outcomes

The primary outcomes were mortality and amputation in NSTI patients. The previous mentioned time-related variables were assessed in relation to these outcomes. Due to heterogeneity in the reporting of the time variables, we assumed that time of presentation would be equal to time of hospital admittance or diagnosis, since NSTI patients often present septic and require immediate treatment hence the immediate hospital admission. We assumed that mortality rates reported in studies were in-hospital mortality rates, unless reported otherwise.

Quality assessment

The methodological quality of the studies included in the meta-analysis was independently assessed by two reviewers

(FN and DS). Since no suitable tool was available for this non-intervention-non-diagnostic study, a modified quality assessment tool based on the most applicable criteria from the Quality in Prognosis Studies (QUIPS) tool and Methodological Index for Non-Randomized Studies (MINORS) was used (Additional file 2) [15, 16]. Disagreement between reviewers during the quality assessment was resolved by discussion with a third independent reviewer (FH).

Statistical analysis

Data management and statistical analysis were performed using Review Manager software (RevMan, version 5.3; Cochrane, Copenhagen, Denmark). Studies with data available for one or more of the time-related variables as categorical or dichotomous data in relation to either mortality or amputation were identified and included in the meta-analysis. If there was insufficient quantitative data to perform a meta-analysis for one or more of the time-related variables in relation to the outcomes, the time variable was assessed qualitatively. If required, data were manually categorized or calculated based on the available text or tables and was converted in the same units.

The stratification of time categories was data-driven. If the same time category (e.g., 6, 12, and 24 h) was compared in relation to mortality or amputation by ≥ 2 studies, this time categories were evaluated in a meta-analysis. Therefore, the available data per time category determined the stratification of the analyses for mortality and amputation. For the meta-analysis with amputation as outcome, the sample size was corrected to only include the patients with NSTI of the extremity or NSTI affecting multiple body areas. This was done to prevent underestimating the amputation rate if also NSTIs involving the trunk or perineum were included in the calculation of the amputation rate. The effect estimate for all analyses was an OR with a 95% CI calculated using the Mantel–Haenszel method. A p value < 0.05 in the overall effect Z test was considered statistically significant. Heterogeneity was evaluated using the following statistical measures: τ^2, I^2, and χ^2. All analyses were performed using the random-effects model. Potential publication bias was assessed by eyeballing the funnel plots.

Subgroup analyses

A priori, the following subgroup analyses were planned for each time-related variable if ≥ 2 studies were found for the subgroup analyses: (1) high-quality studies (a quality assessment score of 6 or higher out of a possible score of 8); (2) studies published in the last decade; (3) studies assessing NSTI of the entire body without excluding specific body regions; (4) studies that assessed all microbial NSTI entities without excluding specific microorganism.

Review results

Search

After full text screening, 109 eligible studies were identified. The studies from Tsai et al. from 2004 [17] and 2009 [18] were excluded based on overlap in patient populations with a later published study from their group in 2010 [19]. The studies by Ahn et al., Holena et al., and Sugihara et al. were excluded, since they included patients from nationwide financial code-based databases without evident review of the included patient medical charts on content for eligibility [13, 20, 21]. All 109 articles combined; 6051 patients were included. Of these 6051 NSTI patients, 1277 patients died (21.1%) and 529 of the 2781 patients with NSTI of the extremity underwent an amputation (19.0%). Comparing mortality rates before and after 2000, there was a significant reduction in mortality from 28.3 to 20.6% ($p = 0.004$). However, average mortality rates reported remained constant (around 20%) over the past 20 years (Fig. 1). The baseline characteristics are summarized in Table 1. The elaborate baseline characteristics, study inclusion and exclusion criteria, the time-related variables assessed, and outcomes can be found in Additional file 3. A total of 33 studies were included for quantitative analysis. The selection process and reasons for exclusion can be found in Fig. 2.

Baseline characteristics of studies in quantitative analysis

The 33 studies available for quantitative and thorough analysis included a combined number of 2123 NSTI patients with a mean age of 54 years. Of the 2123 patients, 417 patients (19.6%) died due to the NSTI. The number of patients included per study ranged between 9 and 472 patients. The majority of the studies included NSTI patients without having exclusion criteria for specific body regions affected ($n = 23$, 70%) (Table 1).

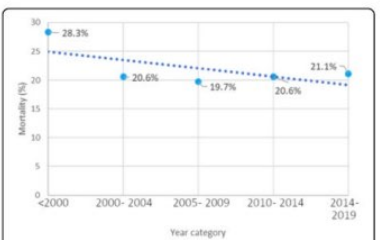

Fig. 1 Historical cumulative mortality rates for necrotizing soft tissue infections based on included studies

Table 1 Baseline study characteristics of necrotizing soft tissue infection studies assessing surgical timing

	Eligible studies ($n = 109$)	Studies in meta-analyses ($n = 33$)
Publication year, *n* (%)		
1989 and older	8 (7)	3 (9)
1990–1999	7 (6)	4 (12)
2000–2009	29 (27)	7 (21)
2010–2019	65 (60)	19 (58)
Continent where study was performed[a], *n* (%)		
Africa	8 (7)	0 (0)
Asia	42 (39)	14 (43)
Europe	23 (21)	7 (21)
North America	32 (30)	12 (36)
Oceania	3 (3)	0 (0)
South America	0 (0)	0 (0)
Type of study[b], *n* (%)		
Retrospective cohort study	89 (90)	27 (93)
Prospective cohort study	9 (9)	2 (7)
Randomized controlled trial	1 (1)	0 (0)
Study period in years, median (IQR; range)	7 (5–11; 2–24)	6 (5–11; 2–16)
Number of participating medical institutions[a], median (IQR; range)	1 (1–1; 1–6)	1 (1–1; 1–2)
Number of included patients per study, median (IQR; range)	35 (20–67; 5–472)	33 (20–84; 9–472)
Body regions affected by NSTI assed per study, *n* (%)		
Head and/or neck	9 (8)	1 (3)
Extremities	8 (8)	3 (9)
Trunk	2 (2)	1 (3)
Fournier	32 (29)	4 (12)
Full body	58 (53)	24 (73)

IQR interquartile range, *NSTI* necrotizing soft tissue infection
[a]1 missing case
[b]10 missing cases

Time from presentation at hospital to surgery

Surgery within 6 h

Ten (30%) of the 33 included studies reported the number of patients operated on within and after 6 h after presentation. The mortality was significantly lower for surgery within 6 h after presentation compared to surgical treatment delayed more than 6 h, with an OR of 0.43 (95% CI 0.26–0.70, $p < 0.01$) (Fig. 3a). Surgical treatment within 6 h resulted in a 19% mortality rate and surgical treatment after 6 h in a mortality rate of 32%. Surgery within 6 h did not result in a significant reduction in the amputation rate, with an OR of 0.68 (95% CI 0.34–1.39, $p = 0.30$) (Table 2 and Additional file 4).

Surgery within 12 h

Sixteen (48%) of the 33 included studies reported the number of patients operated on within and after 12 h after presentation. The mortality was significantly lower for surgery within 12 h after presentation compared to surgical treatment delayed more than 12 h, with an OR of 0.41 (95% CI 0.27–0.61, $p < 0.01$) (Fig. 3b). Surgical treatment within 12 h resulted in a 19% mortality rate and surgical treatment after 12 h in a mortality rate of 34%. Surgery within 12 h did not result in a significant lower amputation rate, with an OR of 0.71 (95% CI 0.28–1.82, $p = 0.48$) (Table 2 and Additional file 4).

Surgery within 24 h

Eighteen (55%) of the 33 included studies reported the number of patients operated on within and after 24 h after presentation. Analysis showed no significant reduction in the mortality or amputation rate between surgical treatment within or after 24 h, with an OR of 0.79 (95% CI 0.52–1.20, $p = 0.26$) for mortality and an OR of 0.63 (95% CI 0.20–2.05, $p = 0.45$) for amputation (Table 2 and Additional file 4).

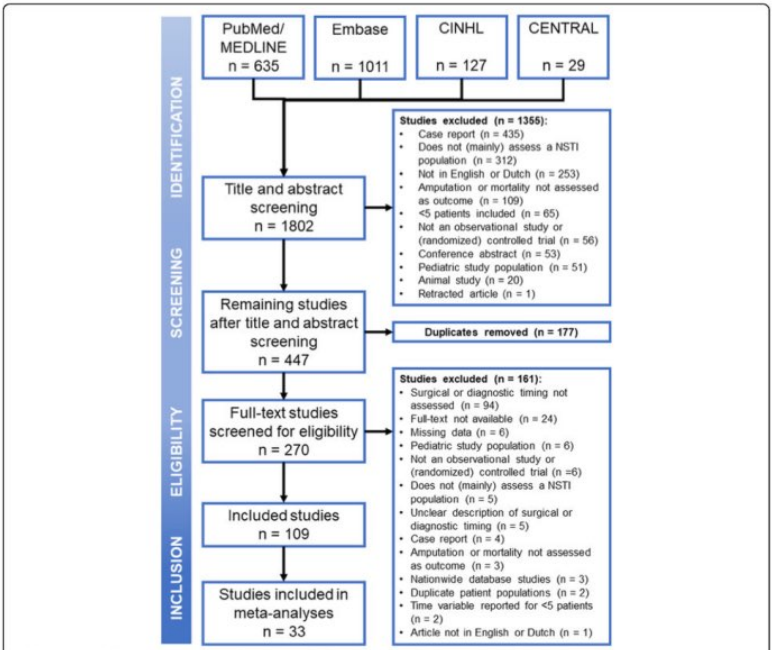

Fig. 2 Flowchart of study inclusion process for meta-analysis of surgical timing of necrotizing soft tissue infections

Time from onset symptoms to presentation at hospital

Forty-three studies included in the qualitative analysis reported on time from onset symptoms to presentation. The average time weighted by study sample sizes was 4.5 days (range 1.0–13.3 days). Since continuous independent variables cannot be used in meta-analyses, only studies with similar dichotomous variables were included in this meta-analysis. Eight (24%) of the 33 studies included for meta-analysis reported the number of patients presenting to the hospital within and after 3 days after the onset of the symptoms. Presentation to the hospital within 3 days after the onset of symptoms did not result in significant lower mortality than patients presenting after 3 days, with an OR of 0.49 (95% CI 0.16–1.44) (Table 2 and Additional file 4).

Time from onset symptoms to surgery

Thirteen studies included in the qualitative analysis reported on time from onset symptoms to surgery. The average time weighted by study sample sizes was 4.6 days (range 2.1–7.5 days). Only studies with similar dichotomous variables were included in this meta-analysis. Three (9%) of the 33 included studies reported the number of patients operated on within and after 3 days after onset of symptoms. Surgery within 3 days after onset of symptoms did not result in significant lower mortality than patients operated after 3 days, with an OR of 0.40 (95% CI 0.15–1.08) (Table 2 and Additional file 4).

Duration of first surgery

Only three studies reported on the duration of the first surgery. Corman et al. found a mortality rate of 4% (1

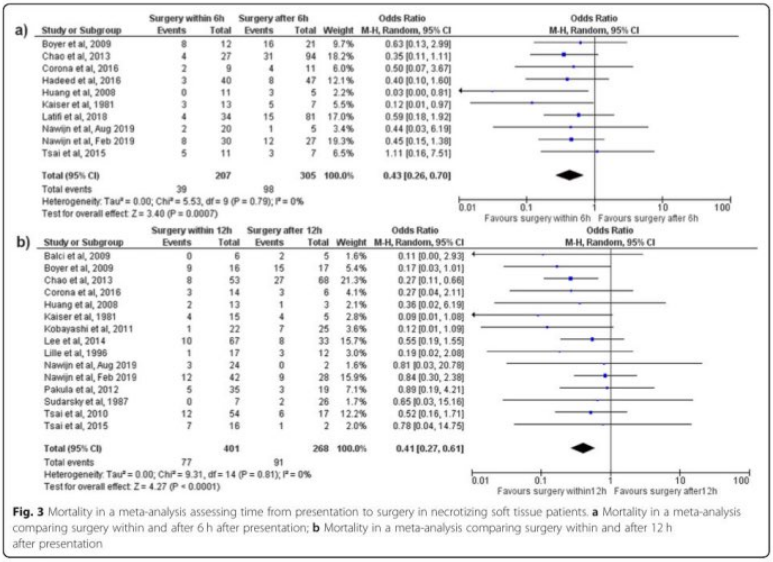

Fig. 3 Mortality in a meta-analysis assessing time from presentation to surgery in necrotizing soft tissue patients. **a** Mortality in a meta-analysis comparing surgery within and after 6 h after presentation; **b** Mortality in a meta-analysis comparing surgery within and after 12 h after presentation

out of 26 patients) with an associated mean duration of the initial surgery of 78 min; Elskaket et al. reported a mortality rate of 11.4% (5 out of 44 patients) associated with a mean duration of the initial surgery of 81 min, while Hong et al. reported a mortality rate of 60% (9 out of 15 patients) associated with a mean duration of the initial surgery of 102 min.

Quality assessment

The elaborate results of the quality assessment for each study can be found in Additional file 5. The mean quality score was 5 ± 2. Ten (30%) studies scored 6 or higher, indicating high quality.

Subgroup analyses

The subgroup analyses either using only studies published in the last decade, studies assessing NSTI of the entire body without excluding specific body regions, or studies that assessed all microbial NSTI entities without only including a specific microorganism did not result in new results. No outcomes changed direction or significance (Table 2 and Additional file 4).

Assessment of publication bias

The funnel plot for the analysis of time from presentation to surgery within and after 6 and 12 h in relation to mortality are presented in Fig. 4. Upon eyeballing the funnel plots, both showed relative symmetry indicating a low risk of publication bias in these meta-analyses.

Discussion

This study clearly shows that the average mortality rate for NSTI did not improve over the past 20 years. Timely initial surgery after presentation to the hospital for NSTI cuts mortality almost in half. This stresses the need for early surgical treatment of all NSTIs.

There is only one similar meta-analysis published that assesses the time to surgery for NSTIs. Gelbard et al. pooled the results from six studies and found an OR of 0.43 (95% CI 0.24–0.78) in favor of surgery within 12 h (13% mortality) compared to surgery after 12 h from presentation (26% mortality) [8]. Our study shows a similar reduction in mortality if the initial surgery is performed within 12 h after presentation (19 vs. 34%), but even more, also found such an association for surgery within 6 h (19 vs. 32%). Based on our results, initial

Table 2 Results of meta-analyses assessing influence of surgical timing on outcomes in necrotizing soft tissue infections

Mortality analyses

			Subgroup analyses			
Outcome	Events/total patients (*n*)	Result (OR, 95% CI)	High-quality studies[a] (OR, 95% CI)	Studies published ≥ 2009[b] (OR, 95% CI)	Studies without limitation on affected body region by NSTI[c] (OR, 95% CI)	Studies without limitation based on specific microbial types of NSTI[d] (OR, 95% CI)
Surgery within 6 h after presentation	137/512	**0.43 (0.26–0.70)**	**0.46 (0.27–0.80)**	**0.49 (0.30–0.82)**	**0.44 (0.25–0.75)**	**0.45 (0.25–0.79)**
Surgery within 12 h after presentation	168/669	**0.41 (0.27–0.61)**	**0.40 (0.23–0.69)**	**0.43 (0.28–0.67)**	**0.45 (0.29–0.70)**	**0.41 (0.22–0.74)**
Surgery within 24 h after presentation	271/1372	0.79 (0.52–1.20)	0.63 (0.29–1.34)	0.84 (0.52–1.37)	0.85 (0.53–1.38)	1.11 (0.77–1.60)
Surgery within 3 days after onset symptoms	33/172	0.40 (0.15–1.08)	0.41 (0.13–1.29)	0.35 (0.12–1.02)	0.46 (0.16–2.42)	0.13 (0.01–2.42)
Hospital admission within 3 days after onset symptoms	98/326	0.49 (0.16–1.44)	0.66 (0.15–2.83)	0.61 (0.17–2.24)	0.41 (0.08–2.13)	1.01 (0.37–2.74)

Amputation analyses

			Subgroup analyses			
Outcome	Events/total patients (*n*)	Result (OR, 95% CI)	High-quality studies[a] (OR, 95% CI)	Studies published ≥ 2009[b] (OR, 95% CI)	Studies without limitation on affected body region by NSTI[c] (OR, 95% CI)	Studies without limitation based on specific microbial types of NSTI[d] (OR, 95% CI)
Surgery within 6 h after presentation	45/197	0.68 (0.34–1.39)	0.57 (0.23–1.42)	0.65 (0.31–1.38)	0.64 (0.30–1.38)	0.61 (0.28–1.32)
Surgery within 12 h after presentation	26/138	0.71 (0.28–1.82)	0.54 (0.11–2.54)	0.71 (0.25–1.98)	0.71 (0.24–2.11)	0.55 (0.19–1.54)
Surgery within 24 h after presentation	21/102	0.63 (0.20–2.05)	0.25 (0.04–1.60)	0.70 (0.19–2.58)	0.41 (0.08–2.26)	0.53 (0.14–2.06)

Results in bold are statistically significant results
CI confidence interval, *NSTI* necrotizing soft tissue infection, *OR* odds ratio
[a]Excluding Bair, Balci, Catena, Corona, Ferretti, George, Huang 2008, Kaiser, Kalaivani, Knutson, Lille, Liu, Mittapalli, Ogilvie, Pakula, Palmer, Park, Stephenson, Sudarsky, Tsai 2010, Tsai 2015, Wang, Yu
[b]Excluding Catena, Huang 2008, Kaiser, Knutson, Lille, Ogilvie, Palmer, Stephenson, Sudarsky, Wang, Yu
[c]Excluding Balci, Boyer, Corona, Ferretti, Huang 2008, Liu, Palmer, Stephenson, Sugihara, Wang
[d]Excluding Chao, Huang 2008, Knutson, Lee, Tsai 2010, Tsai 2015

surgery within 12 h should be regarded as the minimal "golden" time frame for operating patients with NSTIs, while surgery within 6 h might be strongly preferred. However, based on these analyses, it is difficult to give a prognosis for the patients operated on between 6 and 12 h. Based on the analyses comparing surgery within and after 12 h, these patients were less likely to die (OR 0.41 for surgery within 12 h; 95% CI 0.27–0.61), while in the analysis comparing surgery within and after 6 h, this group of patients had worse outcomes (OR 0.43 for surgery within 6 h; 95% CI 0.26–0.70). Although surgery within 12 h is essential, surgery within 6 h might be beneficial. However, to determine a more exact cutoff point for the "golden" time frame, more research is necessary.

Patient delay (time from onset of symptoms to surgery) did not seem to affect mortality, although availability and robustness of the data for this part of the question was limited. Nevertheless, based on the presented mortality data in this review, the time from presentation to surgery (which encompasses both doctor delay and part of the system delay) has significant effect on outcome. On the other hand, this study did not find an association between timing of surgery and the amputation rate, indicating that

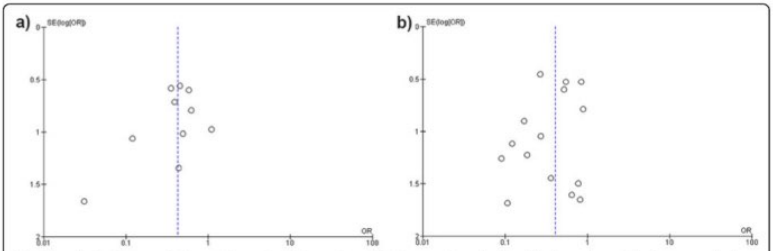

Fig. 4 Funnel plot of meta-analysis assessing surgical timing and mortality in necrotizing soft tissue infections. **a** Funnel plot for meta-analysis comparing mortality in necrotizing soft tissue infection patients operated within or after 6 h after presentation; **b** Funnel plot for meta-analysis comparing mortality in necrotizing soft tissue infection patients operated within or after 12 h after presentation

other factors, such as comorbidities, the local situation of the tissue (e.g., the presence of bullae), or the severity of disease (e.g., severe sepsis), are more predictive for amputation [22, 23]. However, those factors were outside the scope of this review.

The goal of the initial surgical procedure for NSTIs is to gain control and prevent further (trans-fascial and hematogenous) spreading of the infection by complete debridement of all the infected and necrotic tissue [1, 9]. Sarani et al. suggested that each hour delay of surgical treatment can lead to a local spread of the infection as fast as an inch per hour and results in higher chances of systematic spread [24]. Early surgical treatment does not only reduce the mortality rate, but several studies also found that it can reduce the risk of septic shock, number of surgical debridement, and the length of hospital stay [14, 25]. The exact pathophysiology behind the rapid spread of bacteria across the fascia is still poorly understood. However, it is thought that especially during NSTIs the microbial virulence caused by the toxins produced by the involved bacteria outweighs the host defense system providing the opportunity for rapid spreading of the infection [24, 26]. Early resection of necrotic and infected tissue results in a lower microbial load. As a result, the immune system combined with broad spectrum antibiotics has better odds at controlling the infection [1, 27]. Thus, time is of the essence.

However, clinical implementation of the desired urgent debridement is often hindered by multiple factors. First, patient delay is a problem not easily influenced by medical personnel. The time a patient waits before seeking medical care is dependent on a wide variety of clinical, economic, and social factors. The physical and financial access to emergency care, the nature of the acute illness, the underlying chronic comorbidities, and understanding of the severity of symptoms all influence the likelihood of a patient seeking emergency care [28].

Next, doctor delay is a well-known problem for this disease. Before NSTI can be treated, the accurate diagnosis must be made. Awareness of NSTI is frequently described as low, due to its low incidence, compared to non-necrotizing soft tissue infections with a higher a priori chance such as cellulitis and erysipelas [3, 29]. Furthermore, symptoms of NSTI mimic those of cellulitis and erysipelas and no pathognomic symptoms for NSTI are known [23, 30, 31]. Wong et al. developed the laboratory risk indicator for necrotizing fasciitis (LRINEC) score to help physicians with identifying NSTIs [32]. However, a meta-analysis performed by Fernando et al. showed that this is a suboptimal score for identifying patients with NSTI due to its low sensitivity [30]. The substantial problem of misdiagnosing is illustrated in a systematic review by Goh et al. They reported that 71.4% of the NSTIs were initially misdiagnosed and that the mortality rate increased with the percentage of initially missed diagnoses [23]. Interoperative diagnostic accuracy can be increased by using the method of triple diagnostics. In the case of ambivalent signs of NSTI upon intra-operative macroscopic evaluation, samples should be taken for intra-operative assessment of fresh frozen sections and Gram stains. Based on those results, the NSTI diagnosis can be confirmed or waived [7, 33]. A solution for improving pre-operative diagnostics is a strongly recommended focus for future studies.

Finally, the medical system should be organized with enough surgical capacity to prevent system delay. After the accurate diagnosis is made, the logistics needs to be in place to facilitate urgent surgical debridement. The initial debridement for NSTI holds the highest surgical priority. McIsaac et al. reported that 27% of the urgent or emergency surgeries at their hospital with the highest priority were delayed beyond the waiting time appointed to surgeries with the highest priority. The main reasons for the delays were unavailability of surgeons, followed

by unavailability of resources such as operating rooms [34]. Improving the availability of the appropriate surgeons and resources at the presenting hospital is crucial, since transfer, even to a center specialized in NSTIs, increases the delay and therefore the risk at mortality [21]. To improve immediate availability of the appropriate resources, the system using 24/7 in-house attending surgeon and the 24/7 readiness of an operating room could significantly decrease the time to surgery and mortality [35, 36].

Not only the time to surgery influences the outcomes, but shorter operative times of emergency surgeries are also associated with less postoperative complications [37]. Matsuyama et al. reported that the mortality and morbidity are significantly lower if emergency surgeries in adults were completed within 120 min, and Kaushal-Deep et al. reports better outcomes if operative times are less than 100 min for pediatric emergency surgeries [37, 38]. In severely physiologically compromised trauma patients, the damage control strategy is indicated if the operative time would be longer than 90 min [39]. Unfortunately, our study is unable to comment on the ideal duration of the initial debridement for NSTI and remains therefore unknown. However, since most NSTI patients are severely physiologically compromised, short and efficient debridements might be recommended, as a major difference in mortality rate was noted between the published results of patients with an operating time shorter and longer than 90 min. The risk at more postoperative complications associated with longer operative times should be considered when skin-sparing debridement for NSTIs is contemplated [37, 40]. Therefore, the clinical condition of the patient should determine the course of actions and surgical strategy.

The limitations of this study need to be kept in mind during the interpretation of the results. For example, we were unable to vary between time from diagnosis to surgery and time from presentation to surgery. The time from presentation to diagnosis is often underreported and could not be assessed. Furthermore, even though we used a broad search, there is still a possibility of missing studies. Finally, for the interpretation of the cumulative mortality rates, it should be kept in mind that the included studies used different and sometimes very specific inclusion and exclusion criteria, limiting the generalizability of mortality rates to the entire NSTI population. For example, eight studies excluded patients that did not undergo surgery, which indicates that those patients were unsuitable for surgery (i.e., based on severity of illness or patients' wishes) [10, 41–47]. Excluding these patients from the mortality rate could result in a seemingly better mortality rate than the reality, since these patients are likely to have died of NSTI. The strength of this meta-analysis is the relatively low heterogeneity in the meta-analysis, and the risk at publication bias is estimated to be limited. Furthermore, this meta-analysis contributes to solving the problem of underpowered studies, which is especially relevant in the field of NSTI research. The incidence of NSTI has been estimated to be 3.64 per 100,000 person years; this suggests that most single-center NSTI study would automatically be underpowered due to the limited incidence of NSTI to that hospital [3]. Therefore, meta-analyses remain an efficient way of increasing the body of evidence if only studies with limited sample sizes are available.

Conclusion

Average mortality rates reported remained constant (around 20%) over the past 20 years. Surgical debridement as soon as possible lowers the mortality rate for NSTI with almost 50%. However, early surgical treatment did not reduce the amputation rate. Nevertheless, this systematic review and meta-analysis show that early surgical treatment of NSTIs within 12 h is essential for reducing the mortality rate, while surgical treatment within 6 h might even further improve outcomes.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13017-019-0286-6.

Additional file 1: Search syntax for systematic review assessing surgical timing in relation to mortality and amputation due to necrotizing soft tissue infections.

Additional file 2: Quality assessment tool for systematic review assessing surgical timing in relation to mortality and amputation due to necrotizing soft tissue infections.

Additional file 3: Extracted data from eligible studies assessing surgical timing related to mortality and amputation due to necrotizing soft tissue infection.

Additional file 4: Forest plots for all (subgroup) analyses assessing surgical timing in relation to mortality and amputation due to necrotizing soft tissue infections.

Additional file 5: Results from quality assessment of articles included in meta-analyses assessing surgical timing in relation to mortality and amputation due to necrotizing soft tissue infections.

Abbreviations

CENTRAL: Cochrane Controlled Register of Trails; CI: Confidence interval; CINAHL: Cumulative Index to Nursing and Allied Health Literature; IQR: Interquartile range; MD: Mean difference; MINORS: Methodological Index for Non-Randomized Studies; NSTI: Necrotizing soft tissue infection; OR: Odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; QUIPS: Quality in Prognosis Studies; RCT: Randomized controlled trials; SD: Standard deviation

Acknowledgements

Not applicable

Authors' contributions

FH and FN conceived the study. FN and DS created the search syntax and performed the search, in-depth screening, and quality assessment. FN extracted the result, performed the analyses, and drafted the manuscript. FH supervised the study and was the third independent party in case of

disagreement about the inclusion criteria and the quality assessment. DS, FH, RH, and LL critically revised the article. All authors contributed substantially to the study and approved the final manuscript.

Funding
Not applicable

Availability of data and materials
The data supporting the conclusions of this article are included within the article and its additional files.

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Received: 11 November 2019 Accepted: 24 December 2019
Published online: 08 January 2020

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Publisher's Note

Infectious Diseases in Obstetrics and Gynecology 1:16–22 (1993)

Necrotizing Fasciitis: A Review of Management Guidelines in a Large Obstetrics and Gynecology Teaching Hospital

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ABSTRACT

Necrotizing fasciitis is a severe, life-threatening soft tissue infection that results in rapid and progressive destruction of the superficial fascia and subcutaneous tissue. Because of its varied clinical presentation and bacteriological make-up, it has been labelled with many other names such as acute streptococcal gangrene, gangrenous erysipelas, necrotizing erysipelas, hospital gangrene, and acute dermal gangrene. Although described by Hippocrates and Galen, it has received increasing attention in obstetrical and gynecological literature only within the last 20 years. This review includes two recent cases successfully managed at Parkland Memorial Hospital, Dallas, Texas. The first patient was a 50 year old, morbidly obese, diabetic woman who presented with a small, painful lesion on the vulva. After failing triple antibiotic therapy with ampicillin, clindamycin, and gentamicin, the diagnosis of necrotizing fasciitis of the vulva was made, and she was taken to the operating room for extensive excision. She was discharged home on hospital day 29. The second patient was a 65 year old, obese, diabetic woman with risk factors for atherosclerosis who had a wound separation after an abdominal hysterectomy. Two days later a loss of resistance to probing was noted in the subcutaneous tissue. Necrotizing fasciitis was suspected, and she was taken to the operating room for resection. The patient was discharged home on hospital day 27. The mortality rate after diagnosis of necrotizing fasciitis has been reported to be 30% to 60%. We review the literature and outline the guidelines used in a large Ob/Gyn teaching hospital to minimize the adverse outcome. Lectures on soft-tissue infections are included on a regular basis. The high-risk factors of age over 50, diabetes, and atherosclerosis are emphasized. The need for early diagnosis and surgical treatment within 48 hours is stressed, and any suspicious lesions or wound complications are reported to experienced senior house officers and staff. We use two recent cases to highlight the diagnostic clues and management strategies for this often fatal polymicrobial infection. © 1993 Wiley-Liss, Inc.

KEY WORDS

Soft tissue infections, gynecologic infections, obstetrical infections

CASE REPORTS

Case 1

A 50 year old white woman (G_2P_2) originally presented to the Parkland Memorial Hospital Ob/Gyn Emergency Room complaining of a painful "boil on my vagina." She had a 1 cm follicular abscess on the left vulva at the intertriginous fold that would rub against her thigh as she walked. She denied fever, chills, or other systemic symptoms. Her past medical history was significant for a total abdominal hysterectomy with bilateral salpingo-oophorectomy and appendectomy in 1963, a ventral hernia repair in 1970, and a 20-year history of adult onset diabetes mellitus controlled with glyburide 7.5 mg daily. Her serum glucose was 128 mg/dl. She had a 22 pack/year history of smoking and denied the use of alcohol. Physical examination revealed a morbidly obese (327 pounds) woman who was generally healthy, other than her present-

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Clinical Study

Received July 10, 1992
Accepted December 15, 1992

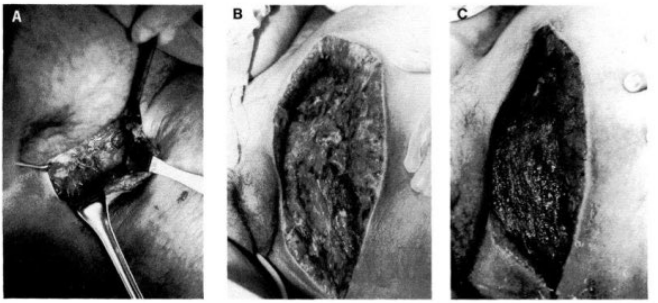

Fig. 1. Photographs of the vulvar area from case 1. **A:** Large area of involvement developed in 24 hours and was extensively débrided. **B:** Continued tissue necrosis and loss of resistance to probing was noted at 36 hours and required repeat excision. **C:** Granulation tissue and healing of wound bed 14 days after original surgery.

ing complaint. The abscess was needle aspirated, and the patient was sent home on oral dicloxacillin 500 mg q6h.

The following day, she returned to the emergency room complaining of increased pain and redness in the left groin area and subjective fever. Exam was significant for a temperature of 38°C, blood pressure 138/78, heart rate 88, respiratory rate 20. The left vulva was slightly edematous and erythematous. The left groin had an 8 × 10 cm erythematous area that extended down the inner thigh and was warm and tender to the touch. She had no clubbing or cyanosis of her extremities, nor did she have any pelvic masses or tenderness. She was alert and oriented and had a normal neurological exam.

She was admitted to the hospital and placed on intravenous ampicillin (2 mg IV q4h), gentamicin (1 mg/kg IV q8h), and clindamycin (900 mg IV q8h). Laboratory evaluation revealed an elevated white blood cell count of 17,400/mm^3 and a glucose of 168 mg/dl. The next day the area of inflammation had extended to 20 cm down the left inner thigh, and foul-smelling purulent material exuded from the aspirated lesion. The patient was taken to the operating room where exploration of the groin area revealed multiple loculated abscess cavities extending from the left groin superior to the inguinal ligament and inferior to the femoral triangle and containing foul-smelling yellow-greenish pus. This material was sent for gram stain and aerobic and anaerobic cultures. Blood was sent for *Clostridium* toxin and aerobic and anaerobic cultures. The involved area was dissected underneath the subcutaneous tissue to the inferior margin of the left vulva (Fig. 1A). The necrotic tissue was excised to the point of bleeding with no loss of resistance to probing, and the area was irrigated with 6 liters of saline and packed.

Post-operatively, she was managed with subcutaneous insulin to maintain tight glucose control. Deep vein thrombosis (DVT) prophylaxis with a pneumatic compression hose on both legs and subcutaneous heparin 5,000 units twice daily was initiated in the operating room and continued postoperatively. Wound debridement and cleaning with one-quarter strength Dakin's solution (163 ml sodium hypochlorite 5.25% plus 0.325$_g$ sodium bicarbonate in 3,637 ml water) were performed twice daily, and sterile gauze was used for packing the wound. After 36 hours, further necrosis of the wound edges was apparent. She was again taken to surgery, where blunt probing revealed loss of tissue resistance superiorlaterally close to the margin of the inguinal ligaments as well as medially past the inferior margin of the vulva and inner thigh (Fig. 1B). The skin, superficial fascia, and subcutaneous tissue of the areas were excised to the point of bleeding and no loss of resistance to probing.

Hemostasis was attained, and the wound was packed with sterile gauze.

Ampicillin, clindamycin, and gentamicin were continued, as were sliding scale insulin, DVT prophylaxis, and twice daily wound débridement and dressing changes. Aztreonam (2 g IV q6h) was substituted to reduce the risk of renal toxicity, which was significant in this patient. When no further signs of infection were present in the wound bed, one-quarter strength Dakin's solution was deleted, and sterile saline was substituted for wound care. The wound was cleaned with Biolex spray (a dilute aloe vera solution) and gel to promote granulation. Antibiotics were stopped after 10 additional days, after she had been afebrile for 48 hours. By this time, the wound was granulating well (Fig. 1C).

Aerobic cultures demonstrated both gram-negative (*E. coli, Klebsiella pneumoniae*) and gram-positive rods (*Corynebacterium* sp). Anaerobic cultures showed gram-negative rods (*Bacteroides* sp). Blood cultures and *Clostridium* toxin assay were negative. Pathological examination revealed necrotic skin with abscess and underlying fat necrosis. The patient was discharged home on hospital day 25 on twice daily dressing changes, and was followed with weekly visits for 6 weeks. She was doing well at her 6-month follow-up.

Case 2

A 65 year old black woman ($G_7P_5A_2$) was admitted to Parkland Memorial Hospital for a hysterectomy after fractional dilatation and curettage revealed dysfunctional endometrium with cellular atypia. Because of her significant medical problems including hypertension, coronary artery disease, non-insulin dependent diabetes mellitus, degenerative joint disease, and a history of a mild stroke, she was evaluated by the medicine department consult staff and cleared for surgery. She had a 30 pack/year history of smoking and denied alcohol use. Physical examination revealed an obese (235 pounds) woman, blood pressure 150/90, heart rate 90, respiratory rate 20, temperature 37°C. She underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy without complication. Pathology revealed multiple leiomyomata and no gross endometrial tumor.

On post-operative day 1 (POD 1), she had a maximum temperature of 38.5°C. Her incision was draining a small amount of serosanguineous fluid but did not look infected. On POD 2 she had a maximum temperature of 38.5°C, which was attributed to pulmonary atelectasis. She quickly defervesced and remained afebrile. On POD 4, a slight serosanguineous discharge was noted with wound separation apparent on probing. Her staples were removed to allow drainage, and the wound was packed with saline-moistened sterile gauze covered with dry sterile dressing and changed twice daily.

She remained afebrile until POD 6, when her temperature spiked to 38.4°C. At this time, her bandages contained greenish purulence, and the wound edges were necrotic and foul-smelling. When the wound was probed, loss of resistance of the subcutaneous tissue superficial to the rectal fascia extended 6 cm bilaterally. Only minimal skin erythema was present, but the wound margins were anesthetic. Importantly, the patient maintained normal bowel function, and her fluid balance and electrolytes were well controlled. Necrotizing fasciitis was suspected, and the patient was placed on IV ampicillin (2 g IV q4h), gentamicin (1 mg/kg IV q8h), and clindamycin (900 mg IV q8h) and taken to the operating room that same day. The areas of necrosis were excised to the point at which no loss of resistance was encountered and brisk capillary bleeding was evident. Tissue was sent for aerobic and anaerobic cultures. The wound was irrigated with 3 liters of saline and packed with sterile gauze.

Post-operatively, she was maintained with careful fluid management, and her triple antibiotics were continued. The wound was debrided and cleaned with one-quarter strength Dakin's solutin twice daily. The patient defervesced after 6 days, and granulation tissue became apparent. Hydrotherapy in a whirlpool bath was begun at this time. The wound occasionally required sharp débridement of necrotic debris, but otherwise it continued to granulate well. The wound culture revealed *Proteus mirabilis*. Pathology showed marked acute and chronic inflammation, necrosis, ulceration, and organizing fat necrosis. The patient was discharged 27 days after her admission on twice daily dressing changes and weekly follow-up in clinic for 6 weeks. She was doing well 4 months post-operatively.

DISCUSSION

One of the earliest descriptions of hospital gangrene was written in 1871 by Joseph Jones, a Con-

TABLE 1. Risk factors for necrotizing fasciitis

Age over 50[a]
Arteriosclerosis[a]
Diabetes[a]
Obesity
Smoking
Previous radiation
Operative trauma

[a]Major risk factors.

federate Army surgeon: "a purple or blue spot is first perceived that is sometimes raised, and contains serum below. The skin in the affected spot may melt away in 24 hours, whilst a deep blue and purple, almost black, areola surrounding the dead mass, spreads rapidly in an ever increasing circle. This is witnessed most generally in the worst and fatal cases."[4] The first large series was published by Meleney in 1924.[5] He studied 20 cases in China from which he cultured hemolytic streptococci and hence called the disease hemolytic streptococcal gangrene. The term *necrotizing fasciitis* was coined in 1952 by Wilson.[6] The first vulvar cases were described in 1972 by Roberts.[7]

The exact incidence of necrotizing fasciitis is not known, but fortunately it is uncommon. It has been described in all ages and in almost every site of the body. It is most commonly found in the lower extremities, followed by the upper extremities, abdomen, perineum, groin, back, and buttocks.[2,8] The initiating event is usually a minor penetrating injury and involves a surgical site less than half the time. In Rea's series of 44 patients with necrotizing fasciitis, 80% of the cases originated outside the hospital with minor injuries such as abrasions, cuts, bruises, boils, and insect bites, and only 20% were post-surgical infections.[2] In eight of the cases, no specific initiating factor could be found.

Those at highest risk of necrotizing fasciitis are those whose repair mechanisms are compromised due to peripheral vascular damage. The most common risk factors are summarizd in Table 1. The most frequent predisposing risk factors are advanced age followed closely by arteriosclerosis and diabetes. Rea first noticed the association of these factors with necrotizing fasciitis in 1970.[2] Of 44 cases studied, 45.5% were over age 50, 22.2% had arteriosclerosis, and 18.2% had diabetes.[2] In Roberts and Hester's and Roberts's collective cases of 22 patients with necrotizing fasciitis of the vulva, 68.1% were over age 50, and all but one, or 95.5%, were diabetic.[7,9] He did not comment on patients with arteriosclerosis. Other factors thought to predispose to necrotizing fasciitis are hypertension, vascular disease, obesity, renal failure, immunosuppression, a history of radiation therapy, and operative trauma.[10,11]

Necrotizing fasciitis is often misdiagnosed as cellulitis or a simple abscess because of the misleading symptoms and signs of its victims. Early skin changes include erythema, tenderness, and edema extending beyond the area of erythema.[1] These are usually accompanied by fever, malaise, and other systemic toxic signs. Early on, the skin may be intact.[11] Late signs include a purple or bluish discoloration, vesicles filled with red-black fluid, crepitance, cutaneous anesthesia, and necrosis. Once these late signs appear, however, the area of underlying destruction is usually large, and severe systemic toxicity develops.

The pathognomonic sign present in 100% of the cases is subcutaneous and superficial fascial necrosis.[2] Classically, this extends along fascial planes beyond the area of skin involvement. When blunt dissection with a probe or even a finger is carried out, the superficial tissue is sheared away without resistance. Wilson admonished that when undermining of this nature is demonstrated, the patient should receive immediate surgical therapy.[6]

The bacterial etiology of necrotizing fasciitis is polymicrobial (Table 2). In Meleney's series of 20 in 1924, the predominant organism was the hemolytic streptococcus, which was present in all cases.[5] Staphylococci was found in only 10%. Wilson, in contrast, reported in 1952 that 88% of his cases were infected with staphylococci.[6] Rea showed that streptococci and staphylococci were present in equal proportions, representing 43% each among his cases.[2] The majority of his cases grew out more than one organism, however. In a recent series by Stephenson the organisms most currently found were anaerobic *Peptostreptococcus* and *Bacteroides*.[12] These differences are most likely attributed to the improved techniques for culturing anaerobic organisms in recent years. Other bacteria reported to be involved include *E. coli*, *K. pneumoniae*, *Enterobacter*, *Peptococcus*, and *Pseudomonas*.[11] *Vibrio* sp. can be seen in wounds exposed to sea water.[13] *Clostridium* sp. are found less commonly in necrotizing fasciitis, even in those cases with subcutane-

TABLE 2. Polymicrobial etiology of necrotizing fasciitis

Aerobes	Anaerobes
Gram-positive	
Cocci	
Group A, B, D streptococci[a]	*Peptostreptococcus* sp.[a]
Other α- and γ-streptococci	*Peptococcus* sp.[a]
Staphylococcus aureus[a]	
Staphylococcus epidermidis	
Rods	
Lactobacilli	*Clostridium* sp.
Diphtheroids	*Propionibacterium* sp.
	Eubacterium sp.
Gram-negative	
Cocci	
Neisseria gonorrhoeae	*Veillonella* sp.
Rods	
E. coli[a]	*Bacteroides fragilis* group[a]
Klebsiella pneumoniae[a]	Other *Bacteroides* sp.
Enterobacter sp.[a]	*Fusobacterium* sp.
P. mirabilis	
Pseudomonas aeruginosa[a]	

[a]Most common isolates.

TABLE 3. Diagnostic clues for necrotizing fasciitis

Cellulitis that fails to respond to antibiotic therapy
Edema beyond the area of erythema
Development of ecchymosis or vesicles over an area of cellulitis
Presence of gas in the tissue as demonstrated by palpation (crepitus)

ous emphysema. Subcutaneous emphysema is thought to occur by aerobic and anaerobic bacteria synergistically forming hydrogen and nitrogen gas.[1] Gas formation is mostly associated with *E. coli*, microaerophilic *Streptococcus*, and *Bacteroides* sp.[13]

Diagnosis of necrotizing fasciitis can be difficult and is often made after the disease is widespread. A high clinical suspicion must be maintained to enable early and accurate diagnosis. Important diagnostic clues that lead to high suspicion for necrotizing fasciitis are listed in Table 3. Fisher emphasized the importance of radiological studies to demonstrate soft-tissue gas.[14] He showed that while crepitus was found in 29% of patients with necrotizing fasciitis, soft-tissue gas was found by x-ray in 100%. Fisher also gave six clinical criteria to satisfy the diagnosis of necrotizing fasciitis: 1) extensive necrosis of supeficial fascia with widespread undermining of surrounding tissue; 2) moderate to severe systemic toxic reaction with altered mental status; 3) absence of muscle involvement (vs. the prominent myonecrosis seen in certain clostridial infections and synergistic necrotizing cellulitis); 4) failure to demonstrate clostridia in wound and blood cultures; 5) absence of major vascular occlusion; and 6) pathological examination of débrided tissue showing intense leukocyte infiltration, focal necrosis of fascia and surrounding tissue, and thrombosis of the microvasculature.[14] Although clostridial species are typically not present in necrotizing fasciitis, it is important to rule out the presence of this pathogen in the wound, as this may mean the deep fascia and muscle are involved (clostridial myonecrosis). At surgery, a frozen section can aid in this diagnosis. Classically, necrotizing fasciitis shows necrosis of the superficial fascia and subcutaneous tissue with an intense polymorphonuclear infiltration and presence of multiple microorganisms on gram stain.[11,13] A clostridial infection will be remarkable for the absence of an inflammatory infiltrate and the presence of many gram-positive rods.[13] If the latter is the case, close inspection of the deep fascia and underlying muscle is warranted. Stephenson et al.[12] reported the presence of *Clostridium tetani* in one patient with necrotizing fasciitis of the vulva but indicated that no myonecrosis was present, as has been reported in cases with *Clostridium perfringens*.

Once suspicion is high for necrotizing fasciitis, the patient should be taken to the operating room for exploration and surgical débridement. Brewer and Meleney are credited with the first two successful surgical treatments of necrotizing fasciitis, then called progressive gangrenous infection of the skin and subcutaneous tissues, which occurred in and around abdominal incisions for operative care of acute perforative appendicitis.[15] In one case, an incision was made circumferentially around the infected area, down to the deep fascia, and the wound was packed. The enclosed area sloughed, but there was no progression of disease, so the wound ultimately granulated closed. The other case was successfully treated with excision of involved tissue to viable margins.

If inspection shows the characteristic skin ecchymosis, it is likely that the area of undermining is great. It is important, however, to incise and débride the entire extent of disease, until there is no further loss of resistance to blunt probing and until the tissue bleeds easily when cut. As Wilson stated, "to postpone surgery and use massive doses of antibiotics is ineffective and, in addition, the incision

which must eventually be made must then be more extensive in a sicker patient."[6] In such a patient, the post-operative care should be in an intensive care unit in isolation, much like that of a burn victim. Insensible fluid losses will be great, and the prospect of hypovolemia with hemoconcentration is high.[13] Aggressive fluid and electrolyte management is important, along with periodic blood transfusions to correct anemia due to red cell destruction. Broad spectrum antibiotics (i.e., ampicillin, gentamicin, clindamycin) should be used until the identity and sensitivities of pathogens are known. We have found twice daily dressing changes and wound débridement to be sufficient for wound care. The wound is cleaned in this manner with 3% hydrogen peroxide or one-quarter strength Dakin's solution, and packed with sterile gauze. When the old dressings no longer have a foul odor, saline can be substituted for one-quarter strength Dakin's solution for wound cleaning. We also use Biolex gel (an aloe vera-containing gel) to promote wound healing.

Hyperbaric oxygen treatments have been cited as reducing edema, halting progression of tissue necrosis, and decreasing mortality, especially among wounds infected with clostridia.[13,16] Split-thickness skin grafting is an option for re-epithelializing large areas after adequate granulation. Fortunately, in our cases the extent of the disease was not so severe as to require disfiguring surgery, and the wounds were able to granulate in completely.

Mortality rates for necrotizing fasciitis are generally quoted as 30–60%,[8] and antibiotics have not significantly changed this.[2] Death is usually immediately attributed to overwhelming sepsis, complications of diabetes (ketoacidosis), vascular insufficiency, and hemodynamic collapse.[3,8] Not only do old age and diabetes seem to be the most important predisposing factors for necrotizing fasciitis, but they are also the two leading factors for a grave prognosis.[3] Rea showed the mortality rate in patients over 50 years of age to be 67%, while that in diabetics to be 63%.[2] Roberts and Hester and Roberts had a mortality rate from his cases of 47% and 38%, respectively.[7,9] Stephenson reported a 62% mortality in patients over age 50 and a 55% mortality rate in diabetic patients.[12] Significantly, all of the fatalities had one or both of these significant high-risk factors. The most important factors for survival are rapid diagnosis, and rapid and adequate surgical treatment. Rea once again stresses this fact by showing that the average time from onset of disease to diagnosis and treatment of those who lived was 4 days, while that of those who died was 7 days.[2] Stephenson found that 48 hours was a more significant time frame, after which the mortality rate was 75%.[12] The mortality rate in Wilson's collection was only 8.7%; this low number may be attributed in part to the expertise of the house officers in the teaching program at Parkland Memorial Hospital, who had been trained to recognize the clinical manifestations of the disease.[6]

SUMMARY

We have presented two cases of necrotizing fasciitis recently managed at a large Ob/Gyn residency training program. We have reviewed the patients' histories, risk factors, signs and symptoms, bacteriology, pathology, therapy, and mortality factors associated with this life-threatening disease process. Our patients were both in a high mortality risk category for necrotizing fasciitis in that both were over 50 years old, had diabetes, and were obese. One patient had documented arteriosclerosis, and the other had risk factors for it (obesity, smoking, and diabetes). Despite these high risk factors, both of these patients did well. We agree with Wilson that high suspicion and prompt action on the part of the house officers involved in the care of these women were the keys to their successful outcome.[6] Some of the general guidelines for the management of necrotizing fasciitis at Parkland Memorial Hospital are listed in Table 4. In the first case, the main clinical clue was the failure of the presumed cellulitis to respond to antibiotics. In the second, it was the loss of tissue resistance to blunt probing. Both were taken to surgery within 3 days of the presenting problem.

The first case showed the typical polymicrobial nature of necrotizing fasciitis, whereas in the second only one organism (*P. mirabilis*) was cultured. This may be due to the perioperative broad spectrum antibiotic prophylaxis given to this patient at the time of her hysterectomy.

Necrotizing fasciitis can occur in any surgical or nonsurgical insult. In the recent Ob/Gyn literature alone, there are cases reported from episiotomy, mini-laparotomy, diagnostic laparoscopy, and suprapubic catheter placement.[16–19] There are also reports of patients without an obvious original nidus of infection, or patients on standard treatment

TABLE 4. Guidelines for managing necrotizing fasciitis at PMH

1. Patients with suspicious lesions in the vulvar, groin, or thigh region with high-risk factors for necrotizing fasciitis are admitted for observation
2. Patients with presumed cellulitis who fail to respond to IV antibiotics are taken to surgery for wound exploration
3. Post-operative patients who have high-risk factors for necrotizing fasciitis and have wound separation with loss of tissue resistance are started on IV antibiotics and taken to the operating room for exploration
4. Junior house officers notify senior house officers and faculty experienced in the care of necrotizing fasciitis about any suspicious lesions or wound complications
5. Lectures on soft-tissue infections are included on a regular basis for residents and medical students
6. Wound care is managed by the same upper level resident on any service, and additional débridement and/or return to the operating room is performed as needed
7. Survival depends on early recognition and immediate surgical débridement to healthy tissue margins
   - Remove all indurated, edematous, crepitant tissue
   - Incise tissue to margins that bleed easily
   - Change wound dressings frequently
   - Initiate broad spectrum antibiotics

regimens such as radiotherapy, chemotherapy, and anti-inflammatory drugs.[20–22]

It is often said that anyone who uses a certain kind of intervention or therapy should be prepared to deal with the consequences of that intervention or therapy. Among the surgical specialties, obstetricians and gynecologists frequently deal with heavily contaminated body areas; therefore, knowledge of surgical complications is imperative, especially one as life-threatening as necrotizing fasciitis.

ACKNOWLEDGMENTS

The authors acknowledge the many hours of medical care provided to these patients by the following physicians: Deborah Lenart, M.D., Stacy Travis, M.D., and Michael Bevers, M.D. We appreciate the skillful manuscript preparation by Ms. Maria McFarland.

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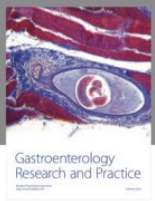

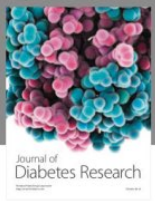

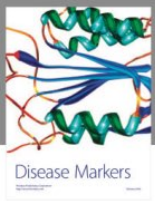

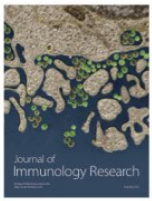

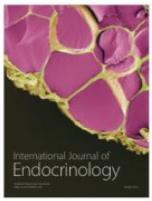

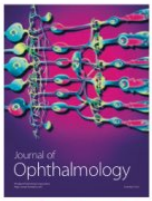

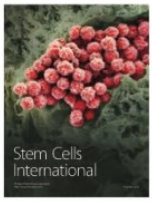

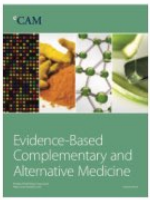

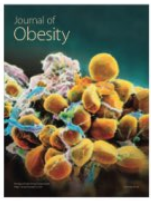

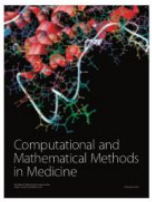

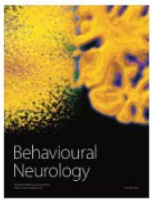

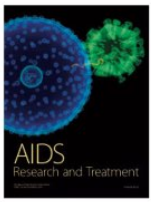

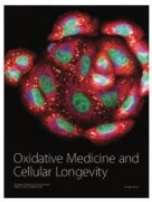

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NICE National Institute for Health and Care Excellence

NICE guideline

Endometriosis: diagnosis and management

NICE guideline
Published: 6 September 2017
www.nice.org.uk/guidance/ng73

Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guideline is the basis of QS172.

Overview

This guideline covers diagnosing and managing endometriosis. It aims to raise awareness of the symptoms of endometriosis, and to provide clear advice on what action to take when women with signs and symptoms first present in healthcare settings. It also provides advice on the range of treatments available.

This guideline updates and replaces the recommendations on endometriosis in NICE's fertility problems guideline, which includes recommendations on fertility tests and treatments such as assisted reproduction.

Who is it for?

- Healthcare professionals
- Commissioners and providers
- Women with suspected or confirmed endometriosis, their families and carers

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

NICE has also produced a patient decision aid on hormonal treatment for endometriosis.

1.1 Organisation of care

1.1.1 Set up a managed clinical network for women with suspected or confirmed endometriosis, consisting of community services (including GPs, practice nurses, school nurses and sexual health services), gynaecology services and specialist endometriosis services (endometriosis centres).

1.1.2 Community, gynaecology and specialist endometriosis services (endometriosis centres) should:

- provide coordinated care for women with suspected or confirmed endometriosis
- have processes in place for prompt diagnosis and treatment of endometriosis, because delays can affect quality of life and result in disease progression.

Gynaecology services for women with suspected or confirmed endometriosis

1.1.3 Gynaecology services for women with suspected or confirmed endometriosis should have access to:

- a gynaecologist with expertise in diagnosing and managing endometriosis, including training and skills in laparoscopic surgery
- a gynaecology specialist nurse with expertise in endometriosis
- a multidisciplinary pain management service

- a healthcare professional with an interest in gynaecological imaging
- fertility services.

Specialist endometriosis services (endometriosis centres)

1.1.4 Specialist endometriosis services (endometriosis centres) should have access to:

- gynaecologists with expertise in diagnosing and managing endometriosis, including advanced laparoscopic surgical skills
- a colorectal surgeon with an interest in endometriosis
- a urologist with an interest in endometriosis
- an endometriosis specialist nurse
- a multidisciplinary pain management service with expertise in pelvic pain
- a healthcare professional with specialist expertise in gynaecological imaging of endometriosis
- advanced diagnostic facilities (for example, radiology and histopathology)
- fertility services.

1.2 Endometriosis information and support

1.2.1 Be aware that endometriosis can be a long-term condition, and can have a significant physical, sexual, psychological and social impact. Women may have complex needs and require long-term support.

1.2.2 Assess the individual information and support needs of women with suspected or confirmed endometriosis, taking into account their circumstances, symptoms, priorities, desire for fertility, aspects of daily living, work and study, cultural background, and their physical, psychosexual and emotional needs.

1.2.3 Provide information and support for women with suspected or confirmed endometriosis, which should include:

- what endometriosis is

- endometriosis symptoms and signs
- how endometriosis is diagnosed
- treatment options
- local support groups, online forums and national charities, and how to access them.

1.2.4 If women agree, involve their partner (and/or other family members or people important to them) and include them in discussions. For more guidance on providing information to people and involving family members and carers, see the NICE guideline on patient experience in adult NHS services.

1.3 Endometriosis symptoms and signs

1.3.1 Suspect endometriosis in women (including young women aged 17 and under) presenting with 1 or more of the following symptoms or signs:

- chronic pelvic pain
- period-related pain (dysmenorrhoea) affecting daily activities and quality of life
- deep pain during or after sexual intercourse
- period-related or cyclical gastrointestinal symptoms, in particular, painful bowel movements
- period-related or cyclical urinary symptoms, in particular, blood in the urine or pain passing urine
- infertility in association with 1 or more of the above.

1.3.2 Inform women with suspected or confirmed endometriosis that keeping a pain and symptom diary can aid discussions.

1.3.3 Offer an abdominal and pelvic examination to women with suspected endometriosis to identify abdominal masses and pelvic signs, such as reduced organ mobility and enlargement, tender nodularity in the posterior vaginal fornix, and visible vaginal endometriotic lesions.

1.3.4 If a pelvic examination is not appropriate, offer an abdominal examination to exclude abdominal masses.

1.4 Referral for women with suspected or confirmed endometriosis

1.4.1 Consider referring women to a gynaecology service for an ultrasound or gynaecology opinion if:

- they have severe, persistent or recurrent symptoms of endometriosis
- they have pelvic signs of endometriosis or
- initial management is not effective, not tolerated or is contraindicated.

1.4.2 Refer women to a specialist endometriosis service (endometriosis centre) if they have suspected or confirmed deep endometriosis involving the bowel, bladder or ureter.

1.4.3 Consider referring young women (aged 17 and under) with suspected or confirmed endometriosis to a paediatric and adolescent gynaecology service, gynaecology service or specialist endometriosis service (endometriosis centre), depending on local service provision.

1.5 Diagnosing endometriosis

1.5.1 Do not exclude the possibility of endometriosis if the abdominal or pelvic examination, ultrasound or MRI are normal. If clinical suspicion remains or symptoms persist, consider referral for further assessment and investigation.

Ultrasound

1.5.2 Consider transvaginal ultrasound:

- to investigate suspected endometriosis even if the pelvic and/or abdominal examination is normal
- to identify endometriomas and deep endometriosis involving the bowel, bladder or ureter.

1.5.3 If a transvaginal scan is not appropriate, consider a transabdominal ultrasound scan of the pelvis.

Serum CA125

1.5.4 Do not use serum CA125 to diagnose endometriosis.

1.5.5 If a coincidentally reported serum CA125 level is available, be aware that:

- a raised serum CA125 (that is, 35 IU/ml or more) may be consistent with having endometriosis
- endometriosis may be present despite a normal serum CA125 (less than 35 IU/ml).

MRI

1.5.6 Do not use pelvic MRI as the primary investigation to diagnose endometriosis in women with symptoms or signs suggestive of endometriosis.

1.5.7 Consider pelvic MRI to assess the extent of deep endometriosis involving the bowel, bladder or ureter.

1.5.8 Ensure that pelvic MRI scans are interpreted by a healthcare professional with specialist expertise in gynaecological imaging.

Diagnostic laparoscopy

Also refer to section 1.10 on surgical management, and section 1.11 on surgical management if fertility is a priority.

1.5.9 Consider laparoscopy to diagnose endometriosis in women with suspected endometriosis, even if the ultrasound was normal.

1.5.10 For women with suspected deep endometriosis involving the bowel, bladder or ureter, consider a pelvic ultrasound or MRI before an operative laparoscopy.

1.5.11 During a diagnostic laparoscopy, a gynaecologist with training and skills in laparoscopic surgery for endometriosis should perform a systematic inspection of the pelvis.

1.5.12 During a diagnostic laparoscopy, consider taking a biopsy of suspected endometriosis:

- to confirm the diagnosis of endometriosis (be aware that a negative histological result does not exclude endometriosis)
- to exclude malignancy if an endometrioma is treated but not excised.

1.5.13 If a full, systematic laparoscopy is performed and is normal, explain to the woman that she does not have endometriosis, and offer alternative management.

1.6 Staging systems

1.6.1 Offer endometriosis treatment according to the woman's symptoms, preferences and priorities, rather than the stage of the endometriosis.

1.6.2 When endometriosis is diagnosed, the gynaecologist should document a detailed description of the appearance and site of endometriosis.

1.7 Monitoring for women with confirmed endometriosis

1.7.1 Consider outpatient follow-up (with or without examination and pelvic imaging) for women with confirmed endometriosis, particularly women who choose not to have surgery, if they have:

- deep endometriosis involving the bowel, bladder or ureter **or**
- 1 or more endometrioma that is larger than 3 cm.

1.8 Pharmacological pain management

Analgesics

1.8.1 For women with endometriosis-related pain, discuss the benefits and risks of analgesics, taking into account any comorbidities and the woman's preferences.

1.8.2 Consider a short trial (for example, 3 months) of paracetamol or a non-steroidal anti-inflammatory drug (NSAID) alone or in combination for first-line management of endometriosis-related pain.

1.8.3 If a trial of paracetamol or an NSAID (alone or in combination) does not provide adequate pain relief, consider other forms of pain management and referral for further assessment.

Neuromodulators and neuropathic pain treatments

1.8.4 For recommendations on using neuromodulators to treat neuropathic pain, see the NICE guideline on neuropathic pain.

Hormonal treatments

NICE has produced a patient decision aid on hormonal treatment for endometriosis.

1.8.5 Explain to women with suspected or confirmed endometriosis that hormonal treatment for endometriosis can reduce pain and has no permanent negative effect on subsequent fertility.

1.8.6 Offer hormonal treatment (for example, the combined oral contraceptive pill or a progestogen)[i] to women with suspected, confirmed or recurrent endometriosis.

1.8.7 If initial hormonal treatment for endometriosis is not effective, not tolerated or is contraindicated, refer the woman to a gynaecology service, specialist endometriosis service (endometriosis centre) or paediatric and adolescent gynaecology service for investigation and treatment options.

1.9 Non-pharmacological management

1.9.1 Advise women that the available evidence does not support the use of traditional Chinese medicine or other Chinese herbal medicines or supplements for treating endometriosis.

1.10 Surgical management

1.10.1 Ask women with suspected or confirmed endometriosis about their symptoms, preferences and priorities with respect to pain and fertility, to guide surgical decision-making.

1.10.2 Discuss surgical management options with women with suspected or confirmed

endometriosis. Discussions may include:

- what a laparoscopy involves
- that laparoscopy may include surgical treatment (with prior patient consent)
- how laparoscopic surgery could affect endometriosis symptoms
- the possible benefits and risks of laparoscopic surgery
- the possible need for further surgery (for example, for recurrent endometriosis or if complications arise)
- the possible need for further planned surgery for deep endometriosis involving the bowel, bladder or ureter.

1.10.3 Perform surgery for endometriosis laparoscopically unless there are contraindications.

1.10.4 During a laparoscopy to diagnose endometriosis, consider laparoscopic treatment of the following, if present:

- peritoneal endometriosis not involving the bowel, bladder or ureter
- uncomplicated ovarian endometriomas.

1.10.5 As an adjunct to surgery for deep endometriosis involving the bowel, bladder or ureter, consider 3 months of gonadotrophin-releasing hormone agonists[-] before surgery.

1.10.6 Consider excision rather than ablation to treat endometriomas, taking into account the woman's desire for fertility and her ovarian reserve. Also see ovarian reserve testing in the NICE guideline on fertility problems.

Combination treatments

1.10.7 After laparoscopic excision or ablation of endometriosis, consider hormonal treatment (with, for example, the combined oral contraceptive pill)[-], to prolong the benefits of surgery and manage symptoms.

Hysterectomy in combination with surgical management

1.10.8 If hysterectomy is indicated (for example, if the woman has adenomyosis or heavy menstrual bleeding that has not responded to other treatments), excise all visible endometriotic lesions at the time of the hysterectomy.

1.10.9 Perform hysterectomy (with or without oophorectomy) laparoscopically when combined with surgical treatment of endometriosis, unless there are contraindications.

1.10.10 For women thinking about having a hysterectomy, discuss:

- what a hysterectomy involves and when it may be needed
- the possible benefits and risks of hysterectomy
- the possible benefits and risks of having oophorectomy at the same time
- how a hysterectomy (with or without oophorectomy) could affect endometriosis symptoms
- that hysterectomy should be combined with excision of all visible endometriotic lesions
- endometriosis recurrence and the possible need for further surgery
- the possible benefits and risks of hormone replacement therapy after hysterectomy with oophorectomy (also see the NICE guideline on menopause).

1.11 Surgical management if fertility is a priority

The recommendations in this section should be interpreted within the context of NICE's guideline on fertility problems. The management of endometriosis-related subfertility should have multidisciplinary team involvement with input from a fertility specialist. This should include the recommended diagnostic fertility tests or preoperative tests, as well as other recommended fertility treatments such as assisted reproduction that are included in the NICE guideline on fertility problems.

1.11.1 Offer excision or ablation of endometriosis plus adhesiolysis for endometriosis not involving the bowel, bladder or ureter, because this improves the chance of spontaneous pregnancy.

1.11.2 Offer laparoscopic ovarian cystectomy with excision of the cyst wall to women with endometriomas, because this improves the chance of spontaneous pregnancy and reduces recurrence. Take into account the woman's ovarian reserve. (Also see ovarian reserve testing in the NICE guideline on fertility problems.)

1.11.3 Discuss the benefits and risks of laparoscopic surgery as a treatment option for women who have deep endometriosis involving the bowel, bladder or ureter and who are trying to conceive (working with a fertility specialist). Topics to discuss may include:

- whether laparoscopic surgery may alter the chance of future pregnancy
- the possible impact on ovarian reserve (also see ovarian reserve testing in the NICE guideline on fertility problems)
- the possible impact on fertility if complications arise
- alternatives to surgery
- other fertility factors.

1.11.4 Do not offer hormonal treatment to women with endometriosis who are trying to conceive, because it does not improve spontaneous pregnancy rates.

Terms used in this guideline

Chronic pelvic pain

Defined as pelvic pain lasting for 6 months or longer.

Paediatric and adolescent gynaecology service

Paediatric and adolescent gynaecology services are hospital-based, multidisciplinary specialist services for girls and young women (usually aged under 18).

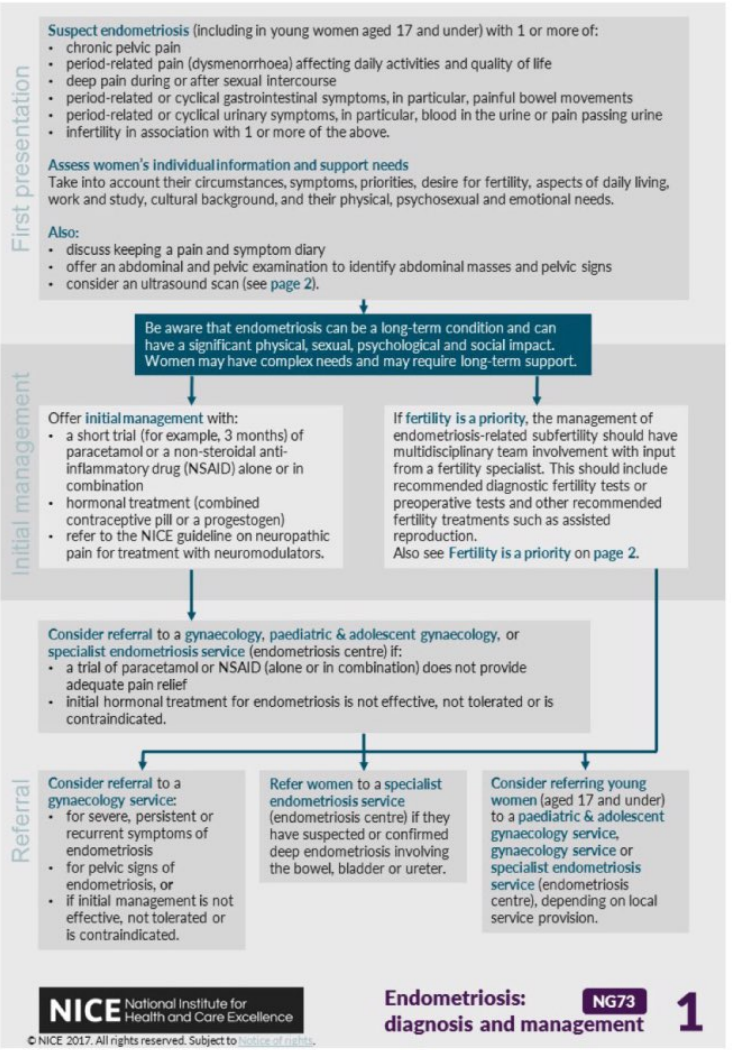
Ovarian cystectomy

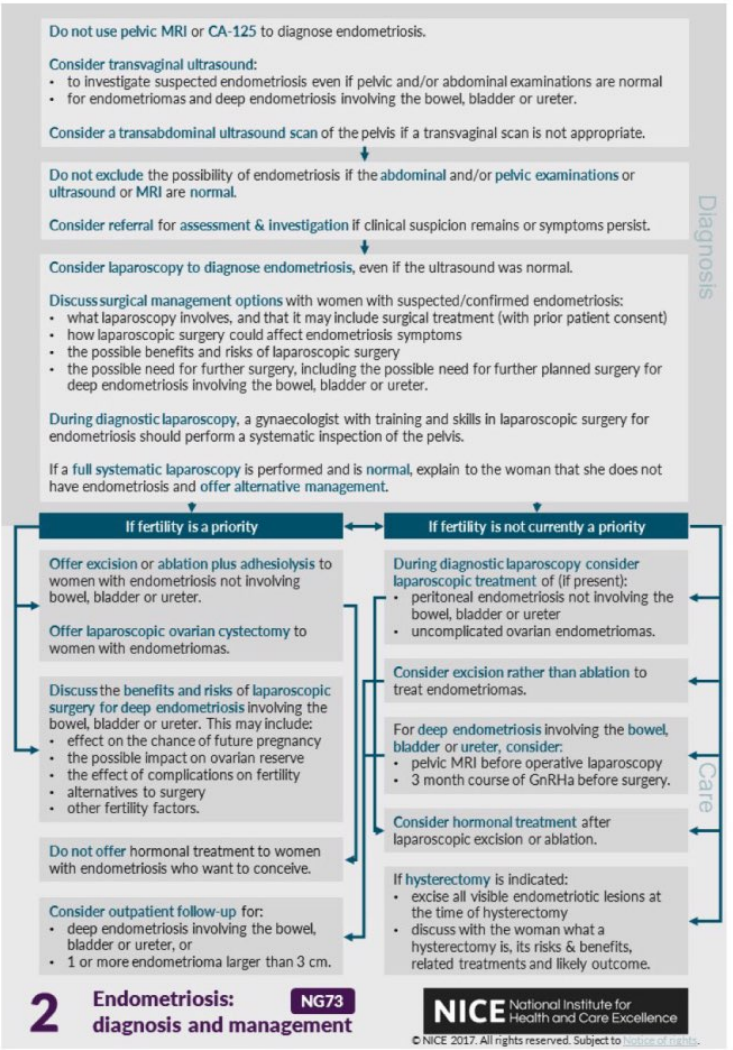
Ovarian cystectomy is a surgical excision of an ovarian endometriotic cyst. An ovarian endometrioma is a cystic mass arising from ectopic endometrial tissue within the ovary.

Managed clinical networks

Linked groups of healthcare professionals from primary, secondary and tertiary care providing a coordinated patient pathway. Responsibility for setting up these networks will depend on existing service provision and location.

Endometriosis algorithm





[i] At the time of publication (September 2017), not all combined oral contraceptive pills or progestogens have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[j] At the time of publication (September 2017), not all gonadotrophin-releasing hormone agonists have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[j] At the time of publication (September 2017), not all hormonal treatments (including not all combined oral contraceptive pills) have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Context

Endometriosis is one of the most common gynaecological diseases needing treatment. It is defined as the growth of endometrial-like tissue (the womb lining) outside the uterus (womb). Endometriosis is mainly a disease of the reproductive years and, although its exact cause is unknown, it is hormone mediated and is associated with menstruation.

Endometriosis is typically associated with symptoms such as pelvic pain, painful periods and subfertility. Endometriosis is also associated with a lower quality of life. Women with endometriosis report pain, which can be frequent, chronic and/or severe, as well as tiredness, more sick days, and a significant physical, sexual, psychological and social impact. Endometriosis is an important cause of subfertility and this can also have a significant effect on quality of life.

Women may also have endometriosis without symptoms, so it is difficult to know how common the disease is in the population. It is also unclear whether endometriosis is always progressive or can remain stable or improve with time.

Delayed diagnosis is a significant problem for women with endometriosis. Patient self-help groups emphasise that healthcare professionals often do not recognise the importance of symptoms or consider endometriosis as a possibility. In addition, women can delay seeking help because of a perception that pelvic pain is normal. Delays of 4 to 10 years can occur between first reporting symptoms and confirming the diagnosis. Many women report that the delay in diagnosis leads to increased personal suffering, prolonged ill health and a disease state that is more difficult to treat.

Diagnosis can only be made definitively by laparoscopic visualisation of the pelvis, but other, less invasive methods may be useful in assisting diagnosis, including ultrasound. Management options for endometriosis include pharmacological, non-pharmacological and surgical treatments. Endometriosis is an oestrogen-dependent condition. Most drug treatments for endometriosis work by suppressing ovarian function, and are contraceptive. Surgical treatment aims to remove or destroy endometriotic lesions. The choice of treatment depends on the woman's preferences and priorities in terms of pain management and/or fertility.

Endometriosis can be a chronic condition affecting women throughout their reproductive lives (and sometimes beyond). Women's priorities and preferences may change over time, and management strategies should change to reflect this.

Women with endometriosis typically present to community services (including GPs, practice

nurses, school nurses and sexual health services) with pain, and may then be referred to gynaecology services for diagnosis and management. Some women may present to fertility services. Complex surgical treatment is carried out in specialist endometriosis services (endometriosis centres), which incorporate a multidisciplinary team.

This guideline makes recommendations for the diagnosis and management of endometriosis in community services, gynaecology services and specialist endometriosis services (endometriosis centres).

The guideline also covers the care of women with confirmed or suspected endometriosis, including recurrent endometriosis. It includes women who do not have symptoms but have endometriosis discovered incidentally. Special consideration was given to young women (aged 17 and under). The guideline does not cover the investigation of fertility problems related to endometriosis, care of women with endometriosis occurring outside the pelvis, nor postmenopausal women.

Finding more information and committee details

You can see everything NICE says on this topic in the NICE Pathway on endometriosis.

To find NICE guidance on related topics, including guidance in development, see our web pages on gynaecological conditions and fertility.

For full details of the evidence and the guideline committee's discussions, see the full guideline. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting NICE guidelines into practice, see resources to help you put guidance into practice.

Recommendations for research

The guideline committee has made the following recommendations for research.

1 Pain management programmes

Are pain management programmes a clinically and cost-effective intervention for women with endometriosis?

Why this is important

Pain is one of the most debilitating symptoms of endometriosis. Endometriosis-related pain can be acute or chronic, and can adversely affect the woman's quality of life, ability to work, and can affect partners and their families.

Pain management programmes have been found to be effective in managing chronic pelvic pain, and can improve quality of life. However, it is unclear how much of this small evidence base can be generalised to women with endometriosis for which evidence is lacking. Furthermore, pain management programmes have not been compared with other treatments available for endometriosis. Pain management programmes promote self-management and are often provided in the community.

If found to be effective for endometriosis, pain management programmes would provide an additional or alternative treatment option for women experiencing endometriosis-related pain. Groups of particular interest are women for whom hormonal and surgical options have been exhausted, women who would prefer an alternative to a pharmacological or surgical approach, and women who may be prioritising trying to conceive.

2 Laparoscopic treatment of peritoneal endometriosis (excision or ablation)

Is laparoscopic treatment (excision or ablation) of peritoneal disease in isolation effective for managing endometriosis-related pain?

Why this is important

Isolated peritoneal endometriosis can be an incidental finding in women who may or may not

experience pain or other symptoms.

Research is needed to determine whether laparoscopic treatment of isolated peritoneal endometriosis in women with endometriosis-related pain results in a clinical and cost-effective improvement in symptoms.

The current literature does not provide a clear answer because the stage of endometriosis is often not sufficiently clearly defined in research studies, and the treatment modalities used are multiple and varied. The resultant amalgamation of various stages of endometriosis and variable treatment modalities leads to loss of certainty of outcome in this specific group of women.

Establishing whether treating isolated peritoneal endometriosis is cost effective is important, because this forms a large part of the workload in general gynaecology, and uses considerable resources.

3 Lifestyle interventions (diet and exercise)

Are specialist lifestyle interventions (diet and exercise) effective, compared with no specialist lifestyle interventions, for women with endometriosis?

Why this is important

Endometriosis is a long-term condition that can cause acute and chronic pain, and fatigue. It has a significant and sometimes severe impact on the woman's quality of life and activities of daily living, including relationships and sexuality, ability to work, fertility, fitness and mental health.

Supporting self-management is critical to improving quality of life for women living with endometriosis. In order to successfully self-manage the condition, women need evidence-based, easily accessible information about the condition and ways of managing it that support surgical and medical treatment. However, no high-quality research was identified on the effectiveness of lifestyle interventions such as diet or exercise and other non-medical treatments in reducing pain, fatigue and other symptoms.

Studies should aim to provide evidence-based options to support self-management of endometriosis. This would improve the quality of life of women with endometriosis, enabling them to manage pain and fatigue, and reducing the negative impact on their career, relationships, sex lives, fertility, and physical and emotional wellbeing.

4 Information and support

What information and support interventions are effective to help women with endometriosis deal with their symptoms and improve their quality of lives?

Why this is important

This guideline has identified that women with endometriosis and their partners feel that information and support is not always provided in the way that best meet their needs. However, the direct effectiveness of different types or formats of information and support interventions on measurable outcomes such as health-related quality of life and level of function (for example, activities of daily living) have not been tested. Good practice in this area in non-specialist and specialist settings can improve satisfaction with the care provided. It may also improve quality of life and positively affect relationships between healthcare professionals and the woman with endometriosis, as well as the woman's personal family relationships.

Update information

Minor changes since publication

December 2019: We added links to our patient decision aid on hormonal treatment for endometriosis.

ISBN: 978-1-4731-2661-9

Accreditation

REVIEW

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ABIM CME MOC ACCREDITED

Sepsis and septic shock: Guideline-based management

ABSTRACT

Sepsis is a life-threatening organ dysfunction that results from the body's response to infection. It requires prompt recognition, appropriate antibiotics, careful hemodynamic support, and control of the source of infection. With the trend in management moving away from protocolized care in favor of appropriate usual care, an understanding of sepsis physiology and best practice guidelines is critical.

KEY POINTS

Tools such as the Systemic Inflammatory Response Syndrome criteria and the quick version of the Sequential Organ Failure Assessment can help with early diagnosis and triage.

The initial antibiotic should be broad-spectrum, based on local sensitivity patterns, with daily assessment of appropriate antibiotic de-escalation and cessation.

Resuscitation with initial fluid boluses should be followed by weighing benefits and risks of additional fluid administration based on dynamically assessed volume status, and then aggressive fluid removal during recovery.

During resuscitation, a goal mean arterial pressure of 65 mm Hg is preferred, using norepinephrine (with vasopressin if needed) to achieve it.

Glucocorticoids are not recommended if fluid resuscitation and vasopressors are sufficient to restore hemodynamic stability.

doi:10.3949/ccjm.87a.18143

SEPSIS AND PARTICULARLY SEPTIC SHOCK should be recognized as medical emergencies in which time matters, as in stroke and acute myocardial infarction. Early recognition and rapid institution of resuscitative measures are critical. But recognizing sepsis can be a challenge, and best management practices continue to evolve.

This article reviews guidance on the diagnosis and management of sepsis and septic shock, with attention to maximizing adherence to best practice statements, and controversies in definitions, diagnostic criteria, and management.

COMMON AND LIFE-THREATENING

Sepsis affects 750,000 patients each year in the United States and is the leading cause of death in critically ill patients, killing more than 210,000 people every year.[1] About 15% of patients with sepsis go into septic shock, which accounts for about 10% of admissions to intensive care units (ICUs) and has a death rate of more than 50%.

The incidence of sepsis doubled in the United States between 2000 and 2008,[2] possibly owing to more chronic diseases in our aging population, along with the rise of antibiotic resistance and the increased use of invasive procedures, immunosuppressive drugs, and chemotherapy.

The cost associated with sepsis-related care in the United States is more than $20.3 billion annually.[3]

DEFINITIONS HAVE EVOLVED

In 1991, *sepsis* was first defined as a systemic inflammatory response syndrome (SIRS) due

to a suspected or confirmed infection with 2 or more of the following criteria[4]:

- Temperature below 36°C or above 38°C
- Heart rate greater than 90/minute
- Respiratory rate above 20/minute, or arterial partial pressure of carbon dioxide less than 32 mm Hg
- White blood cell count less than 4×10^9/L or greater than 12×10^9/L, or more than 10% bands.

Severe sepsis was defined as the progression of sepsis to organ dysfunction, tissue hypoperfusion, or hypotension.

Septic shock was described as hypotension and organ dysfunction that persisted despite volume resuscitation, necessitating vasoactive medication, and with 2 or more of the SIRS criteria listed above.

In 2001, definitions were updated with clinical and laboratory variables.[5]

In 2004, the Surviving Sepsis Campaign guidelines adopted those definitions, which led to the development of a protocol-driven model for sepsis care used worldwide.[6] The US Centers for Medicare and Medicaid Services (CMS) followed suit, defining sepsis as the presence of at least 2 SIRS criteria plus infection; severe sepsis as sepsis with organ dysfunction (including serum lactate > 2 mmol/L); and septic shock as fluid-resistant hypotension requiring vasopressors, or a lactate level of at least 4 mmol/L.[7]

Appropriate antimicrobials should be started within an hour of recognizing sepsis

In 2016, the Sepsis-3 committee[8] issued the following new definitions:

- *Sepsis*—A life-threatening condition caused by a dysregulated host response to infection, resulting in organ dysfunction
- *Septic shock*—Circulatory, cellular, and metabolic abnormalities in septic patients, presenting as fluid-refractory hypotension requiring vasopressor therapy with associated tissue hypoperfusion (lactate > 2 mmol/L).

The classification of severe sepsis was eliminated.

Multiple definitions create confusion

Both the CMS and international consensus definitions are currently used in clinical practice, with distinct terminology and different identification criteria, including blood pressure and lactate cutoff points. The CMS definition continues to recommend SIRS for sepsis identification, while Sepsis-3 uses sequential organ failure assessment (SOFA) or the quick version (qSOFA) to define sepsis (described below). This has led to confusion among clinicians and has been a contentious factor in the development of care protocols.

TOOLS FOR IDENTIFYING HIGH RISK: SOFA AND qSOFA

SOFA is cumbersome

SOFA is an objective scoring system to determine major organ dysfunction, based on oxygen levels (partial pressure of oxygen and fraction of inspired oxygen), platelet count, Glasgow Coma Scale score, bilirubin level, creatinine level (or urine output), and mean arterial pressure (or whether vasoactive agents are required). It is routinely used in clinical and research practice to track individual and aggregate organ failure in critically ill patients.[9] But the information needed is burdensome to collect and not usually available at the bedside to help with clinical decision-making.

qSOFA is simpler…

Singer et al[8] compared SOFA and SIRS and identified 3 independent predictors of organ dysfunction associated with poor outcomes in sepsis to create the simplified qSOFA:

- Respiratory rate at least 22 breaths/minute
- Systolic blood pressure 100 mm Hg or lower
- Altered mental status (Glasgow Coma Scale score < 15).

A qSOFA score of 2 or more with a suspected or confirmed infection was proposed as a trigger for aggressive treatment, including frequent monitoring and ICU admission. qSOFA has the advantage of its elements being easy to obtain in clinical practice.

…but has limitations

Although qSOFA identifies severe organ dysfunction and predicts risk of death in sepsis, it needs careful interpretation for defining sepsis. One problem is that it relies on the clinician's ability to identify infection as the cause of organ dysfunction, which may not be apparent early on, making it less sensitive than SIRS for diagnosing early sepsis.[10] Also, preexisting chronic diseases may influence

accurate qSOFA and SOFA measurement.[11] In addition, qSOFA has only been validated outside the ICU, with limited utility in patients already admitted to an ICU.[12]

Studies have suggested that the SIRS criteria be used to detect sepsis, while qSOFA should be used only as a triaging tool.[11,13]

ANTIMICROBIAL THERAPY

Prompt, broad-spectrum antibiotics

Delay in giving appropriate antibiotics is associated with a significant increase in mortality rate.[14–16] Appropriate antimicrobials should be initiated within the first hour of recognizing sepsis, after obtaining relevant samples for culture—provided that doing so does not significantly delay antibiotic administration.[17]

The initial antimicrobial drugs should be broad-spectrum, covering all likely pathogens. Multidrug regimens are favored to ensure sufficient coverage, especially in septic shock. The empiric choice of antimicrobials should consider the site of infection, previous antibiotic use, local pathogen susceptibility patterns, immunosuppression, and risk factors for resistant organisms. Double coverage for gram-negative organisms and for methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered for patients with a high likelihood of infection with such pathogens.[18] Double gram-negative coverage may be appropriate when a high degree of suspicion exists for infection with multi-drug-resistant organisms such as *Pseudomonas* or *Acinetobacter*. If a nosocomial source of infection is suspected to be the cause of sepsis, anti-MRSA agents are recommended.

Appropriate dosing is also important, as efficacy depends on peak blood level of the drug and on how long the blood level remains above the minimum inhibitory concentration for the pathogen. An initial higher loading dose may be the best strategy to achieve the therapeutic blood level, with further dosing based on consultation with an infectious disease physician or pharmacist, as well as therapeutic drug monitoring if needed.[17]

Consider antifungals

The last few decades have seen a 200% rise in the incidence of sepsis due to fungal organisms.[19] Antifungals should be considered for patients at risk, such as those who have had total parenteral nutrition, recent broad-spectrum antibiotic exposure, perforated abdominal viscus, or immunocompromised status, or when clinical suspicion of fungal infection is high.

Risk factors for fungal infection in septic shock should trigger the addition of echinocandins or liposomal amphotericin B. Azoles are considered appropriate for hemodynamically stable patients.[20]

De-escalation and early cessation

Antibiotics are not harmless: prolonged use of broad-spectrum antibiotics is associated with antimicrobial resistance, *Clostridium difficile* infection, and even death.[21]

A robust de-escalation strategy is needed to balance an initial broad-spectrum approach. A pragmatic strategy may involve starting with broad-spectrum antimicrobials, particularly in the setting of hypotension, and then rapidly de-escalating to an antimicrobial with the narrowest spectrum based on local sensitivity patterns. If the clinical course suggests the illness is not actually due to infection, the antibiotics should be stopped immediately. A rapid nasal polymerase chain reaction test for MRSA to guide de-escalation has been shown to be safe and to significantly reduce empiric use of vancomycin and linezolid.[22,23]

A robust antimicrobial de-escalation strategy needs to balance an initial broad-spectrum approach

Antibiotic de-escalation should be discussed daily and should be an essential component of daily rounds.[17] A 7- to 10-day course or even shorter may be appropriate for most infections,[24,25] although a longer course may be needed if source control cannot be achieved, in immunocompromised hosts, and in *S aureus* bacteremia, endocarditis, or fungal infections.

FLUID RESUSCITATION

Sepsis is associated with vasodilation, capillary leak, and decreased effective circulating blood volume, reducing venous return. These hemodynamic effects lead to impaired tissue perfusion and organ dysfunction. The goals of resuscitation in sepsis and septic shock are to restore intravascular volume, increase oxygen delivery to tissues, and reverse organ dysfunction.

A crystalloid bolus of 30 mL/kg is recommended within 3 hours of detecting severe sepsis or septic shock.[17] However, only limited

data support the benefits of this recommendation, and evidence of harm from sustained positive fluid balance is growing.

Some have cautioned against giving too much fluid, especially in patients who have limited cardiorespiratory reserve.[26] Overzealous fluid administration can result in pulmonary edema, hypoxemic respiratory failure, organ edema, intra-abdominal hypertension, prolonged ICU stay and time on mechanical ventilation, and even increased risk of death.[26,27]

With this in mind, fluid resuscitation should be managed as follows during consecutive phases[28]:

- **Rescue:** During the initial minutes to hours, fluid boluses (a 1- to 2-L fluid bolus of crystalloid solution) are required to reverse hypoperfusion and shock
- **Optimization:** During the second phase, the benefits of giving additional fluid to improve cardiac output and tissue perfusion should be weighed against potential harms[27]
- **Stabilization:** During the third phase, usually 24 to 48 hours after the onset of septic shock, an attempt should be made to achieve a net-neutral or a slightly negative fluid balance
- **De-escalation:** The fourth phase, marked by shock resolution and organ recovery, should trigger aggressive fluid removal strategies.[27]

Antibiotic de-escalation should be discussed daily

Assess volume with dynamic measures

Clinicians should move away from using static measures to assess volume status. Central venous pressure, the static measure most often used to guide resuscitation, has been found to be accurate in only half of cases, compared with thermodilution using pulmonary artery catheters to assess change in cardiac output with volume administration.[29] A 2017 meta-analysis[30] showed that the use of dynamic assessment in goal-directed therapy is associated with lower mortality risk, shorter ICU stay, and shorter duration of mechanical ventilation.

Dynamic measures are used to estimate the effects of additional volume on cardiac output. Two methods are used: either giving a fluid bolus or passively raising the legs. The latter method returns 200 to 300 mL of blood from the lower extremities to the central circulation and is performed by starting the patient in a semirecumbent position, then lowering the trunk while passively raising the legs.

With either method, the change in cardiac output is measured either directly (eg, with thermodilution, echocardiography, or pulse contour analysis) or using surrogates (eg, pulse pressure variation).

Alternatively, changes in cardiac output can be evaluated by heart-lung interactions in a patient on a mechanical ventilator. Changes in intrathoracic pressure are assessed during the inspiratory and expiratory cycle to detect changes in cardiac output using pulse pressure variation, stroke volume variation, and variation in inferior vena cava size.

The dynamic measures mentioned above are more accurate than static measurements in predicting preload responsiveness, so they are recommended to guide fluid management.[31,32] But they do have limitations.[33] Although giving a fluid bolus remains the gold standard for critically ill patients, indiscriminate fluid administration carries the risk of fluid overload. Heart-lung interactions are imprecise for patients with arrhythmias, those who are spontaneously breathing with active effort on the ventilator, and those with an open chest or abdomen. Thus, their use is limited in most critically ill patients.[34]

Unlike other dynamic tests, the passive leg-raise test is accurate in spontaneously breathing patients, for patients with cardiac arrhythmias, and for those on low tidal volume ventilation.[35] Due to its excellent sensitivity and specificity, the passive leg-raise test is recommended to determine fluid responsiveness.[17,32]

Lactate level as a resuscitation guide

Lactate-guided resuscitation can significantly lessen the high mortality rate associated with elevated lactate levels (> 4 mmol/L).[36,37] A rise in lactate during sepsis can be due to tissue hypoxia, accelerated glycolysis from a hyperadrenergic state, medications (epinephrine, beta-2 agonists), or liver failure. Measuring the lactate level is an objective way to assess response to resuscitation, better than other clinical markers, and it continues to be an integral part of sepsis definitions and the Sur-

viving Sepsis Campaign care bundle.[7,8,17] Even though lactate is not a direct surrogate of tissue hypoperfusion, it is a mainstay for assessing end-organ hypoperfusion.

Central venous oxygen saturation-guided resuscitation (requiring central vascular access) does not offer any advantage over lactate-guided resuscitation.[38] Microvascular assessment devices are promising tools to guide resuscitation, but their use is still limited to clinical research.

Although optimal resuscitation end points are not known, key variables to guide resuscitation include a composite of physical examination findings plus peripheral perfusion, lactate clearance, and dynamic preload responsiveness.[17,39]

Balanced crystalloids are preferred over isotonic solutions

Crystalloid solutions (isotonic saline or balanced crystalloids) are recommended for volume resuscitation in sepsis and septic shock. The best one to use is still debated, but over the last decade, balanced solutions have come to be favored for critically ill patients. Growing evidence indicates that balanced crystalloids (lactated Ringer solution, Plasma-Lyte) are associated with a lower incidence of renal injury, less need for renal replacement therapy, and lower mortality in critically ill patients. Moreover, isotonic saline is associated with hyperchloremia and metabolic acidosis, and it can reduce renal cortical blood flow.[40–42]

No proven benefit from colloids

The rationale for using colloids is to increase intravascular oncotic pressure, reducing capillary leak and consequently reducing the amount of fluid required for resuscitation. But in vivo studies have failed to demonstrate this benefit.

One can consider using albumin in sepsis if a significant amount of resuscitative fluid is required to restore intravascular volume.[17] But comparisons of crystalloids and albumin, either for resuscitation or as a means to increase serum albumin in critically ill patients, have found no benefit in terms of morbidity or mortality.[43–45] When considering albumin to treat sepsis or septic shock, clinicians should remember its lack of benefit and its substantial cost—20 to 100 times as much as crystalloids, with an additional cost greater than $30,000 per case with use of albumin.[46]

Hydroxyethyl starch, another colloid, was associated with a higher mortality rate and a higher incidence of renal failure in septic patients and should not be used for resuscitation (**Table 1**).[47]

TABLE 1

Randomized controlled trials of volume replacement in sepsis and septic shock

Author and year	Number of patients	Major findings
Finfer et al,[43] 2004	6,997	No reduction in mortality with albumin compared with saline
Perner et al,[47] 2012	804	Higher risk of death and renal replacement therapy with hydroxyethyl starch compared with Ringer solution
Annane et al,[45] 2013	2,587	No reduction in mortality, need for renal replacement therapy, duration of resuscitation, or length of stay with colloids compared with crystalloids
Caironi et al,[44] 2014	1,818	No reduction in mortality, need for renal replacement therapy, or length of stay with albumin replacement
Young et al,[41] 2015	2,278	No difference in incidence of acute kidney injury, need for renal replacement therapy, or length of stay with balanced solution compared with saline
Semler et al,[40] 2018	15,802	Lower rates of mortality and need for renal replacement therapy with balanced solutions compared with saline

EARLY SOURCE CONTROL

Source control is imperative in managing sepsis and septic shock. Inadequate source control may lead to worsening organ function and hemodynamic instability despite appropriate resuscitative measures.[17] A thorough examination and appropriate imaging studies should be performed to determine the optimal way to control the source and assess the risks associ-

ated with each intervention. If appropriate, source control should be achieved within 6 to 12 hours of diagnosis, once initial resuscitation is completed.[48] The source control can range from removal of infected intravascular devices to a chest tube for empyema to percutaneous or surgical intervention in cases of cholecystitis and pyelonephritis.

RESTORING BLOOD PRESSURE

Persistent hypotension and tissue hypoperfusion after adequate fluid resuscitation are caused by loss of normal sympathetic vascular tone, leading to vasodilation, neurohormonal imbalances, myocardial depression, microcirculatory dysregulation, and mitochondrial dysfunction. Vasopressors and inotropes restore oxygen delivery to tissues by increasing arterial pressure and cardiac output respectively.

Mean arterial pressure is the preferred blood pressure to target during resuscitation. The recommended initial goal is 65 mm Hg. A higher goal of 80 to 85 mm Hg may help patients with chronic hypertension,[49] while a lower target may be better tolerated in patients with reduced systolic function, older patients, and patients with end-stage liver disease.

The passive leg-raise test has excellent sensitivity and specificity for determining fluid responsiveness

These recommendations are based on our understanding of autoregulation of blood flow in the vascular beds of central organs (brain, heart, kidneys). After blood pressure falls below a critical threshold, tissue perfusion decreases linearly. That critical threshold can vary between organ systems and individuals, and the target can later be personalized based on global and regional perfusion as assessed with urine output, mental status, or lactate clearance.[50]

Decisions to titrate vasopressors to achieve mean arterial pressure goals should be balanced against potential adverse effects, including arrhythmias, cardiovascular events, and ischemia.

Norepinephrine is the first-line vasopressor

Few large, multicenter randomized controlled studies have been done to determine the most effective initial and adjunctive vasoactive agents for septic shock. Norepinephrine has shown survival benefit with lower risk of arrhythmia than dopamine.[51–53] On the other hand, 2 systematic reviews found no difference in clinical outcomes and mortality with norepinephrine vs epinephrine, vasopressin, terlipressin, or phenylephrine.[53,54]

Without convincing evidence to support other agents as first-line therapy for septic shock, norepinephrine remains the preferred vasopressor for achieving the target mean arterial pressure and is strongly recommended by the Surviving Sepsis Campaign guidelines, albeit supported by only moderate-quality data.[17,55]

Adding a second vasopressor or inotrope

Another sympathomimetic drug such as vasopressin or epinephrine can be used to either achieve target mean arterial pressures or decrease the norepinephrine requirement. A second vasopressor is routinely added when norepinephrine doses exceed 40 or 50 µg/min.

Vasopressin. Septic shock involves relative vasopressin deficiency. Adding vasopressin as a replacement hormone has been shown to have a sparing effect on norepinephrine, resulting in a lower dose needed. A randomized controlled trial comparing vasopressin plus norepinephrine vs vasopressin monotherapy failed to show any survival benefit or reduction in kidney failure.[56,57] Evidence supporting the use of vasopressin over norepinephrine as a first-line agent remains limited, but vasopressin remains the preferred adjunct with norepinephrine.[56,57]

Epinephrine is recommended by the Surviving Sepsis Campaign guidelines as a second-line vasopressor. It has potent alpha- and beta-adrenergic activity, which increases mean arterial pressure by increasing cardiac output and vasomotor tone. Use of epinephrine is limited by significant risk of tachycardia, arrhythmia, and transient lactic acidosis.[58]

Dopamine use is discouraged in sepsis owing to its propensity to induce tachyarrhythmia and significantly worsen outcomes in this setting.[51,52]

Phenylephrine is a pure alpha-adrenergic agonist that is routinely used in septic shock, albeit with limited data on its efficacy and safety. Vail et al[59] found increased mortality associated with phenylephrine use in septic shock in a multicenter cohort study conducted during a norepinephrine shortage. Phenyl-

ephrine use should be limited to septic shock complicated by significant tachyarrhythmia or as an adjunct for refractory vasodilatory shock until there is more evidence of its benefits.[17]

Angiotensin II was recently approved as a vasopressor for use in septic shock. It activates angiotensin type 1a and 1b receptors to increase intracellular calcium in smooth muscle, promoting vasoconstriction. Clinical data related to its use are limited to a recent trial that showed that the addition of angiotensin II improved blood pressure in patients with refractory vasodilatory shock receiving high-dose vasopressors.[60] The data are still sparse on its safety, and its precise role in refractory shock treatment algorithms has yet to be defined.

Inotropic agents may be required for patients with inadequate cardiac output after fluid resuscitation due to sepsis-induced cardiomyopathy or combined shock. Data are limited suggesting an optimal inotropic agent in septic shock, but epinephrine and dobutamine are most commonly used.[61,62] A comparison of norepinephrine plus dobutamine vs epinephrine in septic shock found no difference in mortality, side effects, or shock duration.[62] Milrinone and levosimendan (not approved in the United States) have been studied, with limited data to support their use over dobutamine.[63,64] The response to use of inotropes should be monitored by measuring changes in cardiac output, central venous oxygen saturation, or other indices of tissue perfusion (**Table 2**).

TABLE 2

Randomized controlled trials of vasopressors and inotropes in septic shock

Author and year	Number of patients	Major findings
Annane et al,[62] 2007	330	No difference in mortality with epinephrine vs norepinephrine ± dobutamine; higher lactate elevation and lower pH in epinephrine group
Russell et al,[57] 2008	780	No reduction in mortality with addition of vasopressin to norepinephrine Survival benefit in patients with septic shock requiring norepinephrine < 15 µg/min Vasopressin had norepinephrine-sparing effect.
De Backer et al,[51] 2010	1,679	Higher rates of mortality and arrhythmia with dopamine than with norepinephrine
Gordon et al,[56] 2016	409	No improvement in kidney failure-free days, use of renal replacement therapy, or mortality with vasopressin
Khanna et al,[60] 2017	344	Angiotensin II increased blood pressure in refractory vasodilatory shock

ROLE OF CORTICOSTEROIDS IS QUESTIONED

Corticosteroids downregulate the maladaptive inflammatory response seen in sepsis and help address relative adrenal insufficiency caused by adrenal suppression or glucocorticoid tissue resistance.[65] In septic shock, they have a vasopressor-sparing role and reduce the duration of shock, ventilator use, and ICU stay.

However, the evidence is not conclusive that giving corticosteroids for sepsis improves clinical outcomes or survival,[66–71] and so they are not recommended in sepsis or severe sepsis if fluid resuscitation and vasopressors are sufficient to restore hemodynamic stability. Rather, they can be added as adjunctive therapy for patients requiring higher doses of vasopressors.[17,65]

Adverse events in studies of corticosteroids were limited to hyperglycemia, hypernatremia, and hypertension, with no increase in superinfections.[71] The limited adverse events, along with a uniform demonstration of shorter shock duration, ventilator duration, and ICU stay, suggest steroids may have a role in managing refractory septic shock.[66–69]

If corticosteroids are used in septic shock, current guidelines recommend hydrocortisone 200 mg per day intravenously as a continuous drip or 50 mg bolus in 4 divided doses for at least 3 days, based on a systematic review showing a longer course of low-dose steroids is associated with a lower mortality rate.[72] There is no clear consensus on whether steroids should be tapered or if abrupt cessation is appropriate, as larger randomized clinical tri-

TABLE 3

Randomized controlled trials of corticosteroids in septic shock

Author and year	Number of patients	Major findings
Annane et al,[68] 2002	300	Lower mortality rate and shorter duration of shock in corticotropin nonresponders with hydrocortisone + fludrocortisone, but not in all patients
Sprung et al,[69] 2008	499	No difference in mortality rate, but shorter duration of shock and no increased risk of superinfection with hydrocortisone
Keh et al,[70] 2016	380	No benefit of hydrocortisone in preventing septic shock or decreasing mortality in severe sepsis
Annane et al,[66] 2018	1,241	Lower mortality rate and shorter duration of shock and mechanical ventilation with addition of hydrocortisone + fludrocortisone.
Venkatesh et al,[67] 2018	3,800	No reduction in mortality with addition of hydrocortisone, but reduced duration of shock, mechanical ventilation and length of stay in intensive care unit

als did not use a tapering strategy and found no difference in shock recurrence.[66,67] In most cases, steroids are stopped after cessation of vasopressors.[65]

Future research should focus on appropriate timing of glucocorticoid initiation after onset of shock and comparing a fixed duration regimen to a clinically guided one.

Etomidate as an induction agent for intubation has been associated with suppression of cortisol synthesis and a reduced response to exogenous steroids. Whether it affects outcomes is unclear. Nonetheless, clinicians should practice extreme caution with etomidate use in septic shock (**Table 3**).[73]

BIOMARKERS

Biomarkers facilitate early diagnosis, identify patients at high risk, and monitor disease progression to guide resuscitation goals and tailor management.

C-reactive protein and erythrocyte sedimentation rate have been used in the past, but with limited success.[74]

Procalcitonin has emerged as a method to help detect bacterial infections early and to guide de-escalation or discontinuation of antibiotics.[75,76] Procalcitonin-guided de-escalation of antibiotics reduces duration of antibiotic exposure, with a trend toward decreased mortality.[77,78]

Galactomannan and beta-D-glucan can be used to detect infections with fungi, specially *Aspergillus*. Beta-D-glucan is more sensitive for invasive *Aspergillus*, while galactomannan is more specific.[79]

Cytokines such as interleukins (eg, IL-6, IL-8, IL-10), tumor necrosis factor alpha, acute-phase proteins, and receptor molecules are currently being studied to determine their utility in sepsis care.

The limited sensitivity and specificity of single biomarkers may be overcome by using a combination of biomarkers, which is a current focus of research.[80] For now, the decision to initiate, escalate, and de-escalate therapy should be based on clinical assessment, with procalcitonin or other biomarkers used as an adjunct to other clinical factors.[17]

USUAL CARE VS PROTOCOLIZED INITIAL RESUSCITATION

In 2001, Rivers et al[61] compared usual care for severe sepsis or septic shock with a protocolized targeting of physiologic end points as goals of resuscitation for the 6 hours before admission to the ICU in a single center. They found a significantly lower mortality rate in the goal-directed therapy group. This finding heavily influenced the bundle-based, goal-directed management strategy recommended by the Surviving Sepsis Campaign in 2004.[81]

However, the protocolized approach has been challenged since then, with 3 large multicenter trials finding that usual care was not inferior to protocolized care in sepsis, with no difference in mortality or length of stay.[82–84] Further, usual care was associated with significantly reduced need for central vascular access, blood transfusions, and dobutamine. A meta-analysis involving nearly 4,000 patients at 138 hospitals in 7 countries found that usu-

al care emphasizing detecting sepsis early and rapidly implementing appropriate antimicrobial therapy and adequate fluid resuscitation was not only equivalent to protocolized care in outcomes but was more cost-effective.[85] (Table 4).

Is SEP-1 appropriate?

In January 2013, the State of New York mandated that all state hospitals initiate processes for early detection and treatment of sepsis. In October 2015, the National Quality Forum and CMS implemented these processes nationwide.[7] The resultant CMS SEP-1 quality measure standardizes early management of severe sepsis and septic shock, with the goal of improving outcomes. Its elements are based on the Surviving Sepsis Campaign guidelines and consist of a series of steps that need to be completed within 3 and 6 hours after sepsis is recognized.

Steps to be performed within 3 hours include measuring the serum lactate level, drawing blood cultures, and starting appropriate antibiotics, intravenous fluid resuscitation, and vasopressor support if needed. A lactate level is repeated within 6 hours, and static and dynamic assessment of perfusion must be done to determine the need for additional fluid or vasopressors to improve end-organ perfusion.

SEP-1 overall hospital performance is publicly available on the CMS website (medicare.gov/hospitalcompare/search.html?) and has the potential to be used for financial incentives centered on SEP-1 measure compliance performance.[86]

Although SEP-1 has been adopted as a quality measure, some question its clinical relevance, as many of the core recommendations are not supported by strong evidence.[86,87] Three major trials found that the mortality rate was no lower with bundled sepsis care than with usual care.[82–84] Seymour et al[28] collected New York State Department of Health data for 49,331 patients with sepsis and septic shock and found that more rapid completion of the 3-hour bundle—particularly of antibiotic administration but not of fluids—was associated with decreased hospital mortality. A multicenter retrospective cohort study[88] found that failure to meet SEP-1 criteria for any step other than giving antibiotics did not translate to poor outcomes.

TABLE 4

Randomized controlled trials evaluating early goal-directed care in septic shock

Author and year	Number of patients	Major findings
Rivers et al,[61] 2001	268	Significantly lower mortality rate with protocolized care
Peake et al,[82] 2014	1,600	No reduction in mortality, need for advanced respiratory or renal support, or intensive care unit length of stay with protocolized care
Rowan et al,[85] 2014	1,351	No reduction in mortality, need for advanced respiratory or renal support, or intensive care unit length of stay with protocolized care
Mouncey et al,[83] 2015	1,260	No reduction in mortality, need for advanced respiratory, cardiovascular or renal support, or intensive care unit length of stay with protocolized care

A major concern about mandating SEP-1 is that fluids and broad-spectrum antibiotics will be overprescribed as healthcare systems try to meet CMS-mandated quality measures. Indiscriminate use of these therapies has the potential to cause harm and puts an undue strain on healthcare resources.[89]

The lactate level remains an objective guide to assess response to resuscitation

A call to refine guidance

Sepsis is a multifaceted disease, and its management is complex. Simplified guidelines and quality measures based on sound evidence are needed. Electronic medical record systems show promise for assisting with early and accurate detection of sepsis and have the potential to play an important role.[90,91] Checklists that allow bedside caregivers to exercise their clinical acumen are another approach. The success of optimal care initiatives requires sustained, collaborative quality improvement across different specialties in medicine, nursing, and hospital administration.[92] ■

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The Brazilian Journal of
INFECTIOUS DISEASES

www.elsevier.com/locate/bjid

Original article

Necrotizing fasciitis: eight-year experience and literature review

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ARTICLE INFO

Article history:
Received 1 July 2013
Accepted 20 August 2013
Available online 22 November 2013

Keywords:
Necrotizing fasciitis
Comorbidity
Debridement
Antibiotics

ABSTRACT

Objectives: To describe clinical, laboratory, microbiological features, and outcomes of necrotizing fasciitis.
Methods: From January 1, 2004 to December 31, 2011, 115 patients (79 males, 36 females) diagnosed with necrotizing fasciitis were admitted to Mackay Memorial Hospital in Taitung. Demographic data, clinical features, location of infection, type of comorbidities, microbiology and laboratory results, and outcomes of patients were retrospectively analyzed.
Results: Among 115 cases, 91 survived (79.1%) and 24 died (20.9%). There were 67 males (73.6%) and 24 females (26.4%) with a median age of 54 years (inter-quartile ranges, 44.0–68.0 years) in the survival group; and 12 males (50%) and 12 females (50%) with a median age of 61 years (inter-quartile ranges, 55.5–71.5 years) in the non-surviving group. The most common symptoms were local swelling/erythema, fever, pain/tenderness in 92 (80%), 87 (76%) and 84 (73%) patients, respectively. The most common comorbidies were liver cirrhosis in 54 patients (47%) and diabetes mellitus in 45 patients (39%). A single organism was identified in 70 patients (61%), multiple pathogens were isolated in 20 patients (17%), and no microorganism was identified in 30 patients (26%). The significant risk factors were gender, hospital length of stay, and albumin level.
Discussion: Necrotizing fasciitis, although not common, can cause notable rates of morbidity and mortality. It is important to have a high index of suspicion and increase awareness in view of the paucity of specific cutaneous findings early in the course of the disease. Prompt diagnosis and early operative debridement with adequate antibiotics are vital.

Introduction

Necrotizing fasciitis is a rapidly progressive infectious disease that primarily involves the fascia and subcutaneous tissue. It is an uncommon but life threatening infection. It can affect all parts of body and the lower extremities are the most common sites of infection.[1–3] The predisposing conditions are diabetes mellitus, liver cirrhosis, alcoholism, hypertension, chronic renal insufficiency, and malignancy. Prompt diagnosis and early treatment with adequate antibiotic with or without surgical intervention are vital because of high mortality. We

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http://dx.doi.org/10.1016/j.bjid.2013.08.003

herein describe clinical, laboratory, microbiological features, and outcomes of 115 patients diagnosed with necrotizing fasciitis during a consecutive eight-year period and review the relevant literature.

Patients and methods

We retrospectively reviewed all necrotizing fasciitis cases at Mackay Memorial Hospital, Taitung from January 1, 2004 to December 31, 2011. Demographic data, clinical features, site of infection, type of comorbidities, microbiological and laboratory findings and outcomes were analyzed. The severity of liver cirrhosis was classified according to the Child–Pugh score. Diagnosis was made by operation and based on lack of resistance to blunt dissection of the normally adherent fascia, presence of necrotic fascia, and purulent discharge with a foul fish-water odor. Histopathological findings of surgical specimens typically show neutrophils and bacterial clumps infiltration between collagen bundles with focal necrosis were used to confirm the diagnosis when available. Blood and pus cultures were obtained at the time of first operative debridement. The number of operative debridement, the need for amputation, the duration of hospitalization, and in-hospital mortality rate were also documented.

The continuous variables, presented as medians and inter-quartile ranges (IQR, the range between the 25th and 75th percentile) due to the small sample size, were compared between surviving and non-surviving groups by the Mann–Whitney *U* test. Likewise the categorical variables were expressed by count and percentage and compared using the Yate's continuity correction or Fisher's exact test. To investigate the independent factors associated with death, simple and multiple logistic regression models were performed. All significant factors on univariate analyses were considered for the initial multivariate models. The final multiple logistic regression model was determined using the backward selection technique, wherein variables that did not improve model fit at $p < 0.1$ were discarded; however, the potential confounders such as age and gender were always forced in all multivariate models for adjustment. Moreover, multicollinearity was also evaluated by variance inflationary factor (VIF). Variables with VIF > 5 were then considered to have multicollinearity with other covariates and would be excluded from the multivariate analyses. The statistical analyses were performed with SAS software version 9.2 (SAS Institute Inc., Cary, NC). A two-sided p-value < 0.05 was considered as statistically significant.

Results

Clinical findings

Out of 115 cases of necrotizing fasciitis enrolled 91 survived (79.1%) and 24 died (20.9%). There were 67 males (73.6%) and 24 females (26.4%) with a median age of 54 years (IQR, 44.0–68.0 years) in the surviving group; and 12 males (50%) and 12 females (50%) with a median age of 61years (IQR, 55.5–71.5 years) in the non-surviving group, respectively. Table 1 summarizes the clinical features of patients. The most common comorbidity was liver cirrhosis in 54 patients (47%) and diabetes mellitus in 45 patients (39%). Among the 54 patients with liver cirrhosis, 33 patients were chronic alcohol abusers, nine had chronic hepatitis B and 16 had chronic hepatitis C. Eight patients had no comorbidity. Local swelling/erythema, fever, pain/tenderness were the most common clinical features at presentation in 92 (80%), 87 (76%) and 84 (73%), respectively.

Table 1 – Clinical features of the 115 necrotizing fasciitis patients.

Clinical features	No. of patients (% of total)
Local swelling/erythema	92 (80%)
Fever	87 (76%)
Pain/tenderness	84 (73%)
Tachycardia	43 (37%)
Shortness of breath	32 (28%)
Shock	30 (26%)
Bullous lesion	25 (22%)
Consciousness change	7 (6%)
Crepitus	7 (6%)

Site of infection

The infection involved the head and neck in four cases (3%), the upper limb in 15 cases (13%), the trunk in 15 cases (13%), the lower limb in 70 cases (61%), bilateral lower limb in four cases (3%) and the perineum and scrotum in 11 cases (10%), as shown in Table 2.

Laboratory findings

An initial blood count revealed leukocytosis (total white count $>12 \times 10^3/\mu L$) in 60 of the 115 patients (52%), leucopenia (total white count $<4 \times 10^3/\mu L$) in nine of 115 patients (8%) and thrombocytopenia (platelet count $>150 \times 10^3/\mu L$) in 46 of the 115 patients (40%). Hemoglobin <10 mg/dL is observed in 42 of the 115 patients (37%). Prothrombin and activated partial thromboplastin time (>12 s and >36 s, respectively) were prolonged in 64 (56%) and 44 (38%) of the 115 patients respectively. Acute renal failure was diagnosed in 26 (23%) of the 115 patients but serum sodium and potassium remained normal in most cases. In 74 cases (64%), serum albumin level was below 3 g/dL, of whom 18 (16%) were Child–Pugh class C.

Table 2 – Anatomical sites involved with necrotizing fasciitis.

Anatomical location	Number of cases (%)
Head and neck	4 (3%)
Upper limb	15 (13%)
Right	8 (7%)
Left	7 (6%)
Lower limb	70 (61%)
Right	28 (24%)
Left	38 (33%)
Bilateral	4 (3%)
Perineum and scrotum	11 (10%)
Trunk	15 (13%)

Table 3 – Microorgansims isolated in patients with necrotizing fasciitis.

Microorganisms	Total ($n = 115$)	Survival ($n = 91$)	Nonsurvival ($n = 24$)	Mortality rate of pathogen (%)
Gram positive	60 (52.2%)	49 (53.8%)	11 (45.8%)	18.3%
MRSA	13 (11.3%)	10 (11%)	3 (12.5%)	23%
MSSA	12 (10.4%)	11 (12.1%)	1 (4.2%)	8.3%
CoNS	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Group A *Streptococcus*	14 (12.1%)	9 (9.9%)	5 (20.8%)	35.7%
Group B *Streptococcus*	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Group D *Streptococcus*	2 (1.7%)	1 (1.1%)	1 (4.2%)	50%
Non-group ABD *Streptococcus*	6 (5.2%)	6 (6.6%)	0 (0%)	0%
α-Hemolysis *Streptococcus*	4 (3.5%)	3 (3.3%)	1 (4.2%)	25%
Enterococcus	7 (6.1%)	7 (7.7%)	0 (0%)	0%
Gram negative	57 (49.6%)	42 (46.2%)	12 (50%)	21.1%
Escherichia coli	11 (9.6%)	10 (11%)	1 (4.2%)	9.1%
Klebsiella pneumonia	7 (6.1%)	5 (5.5%)	2 (8.3%)	28.6%
Enterobacter species	4 (3.5%)	4 (4.4%)	0 (0%)	0%
Serratia marcescens	3 (2.6%)	3 (3.3%)	0 (0%)	0%
Citrobacter freundii	3 (2.6%)	2 (2.2%)	1 (4.2%)	33.3%
Proteus mirabilis	7 (6.1%)	7 (7.7%)	0 (0%)	0%
Aeromonas hydrophila	7 (6.1%)	2 (2.2%)	5 (20.8%)	71.4%
Vibrio vulnificus	2 (1.7%)	0 (0%)	2 (8.3%)	100%
Morganella	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Pseudomonas aeroginosa	5 (4.3%)	4 (4.4%)	1 (4.2%)	20%
Salmonella group B	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Shewanella putrefaciens	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Acinetobacter species	2 (1.7%)	2 (2.2%)	0 (0%)	0%
Anaerobes	3 (2.6%)	2 (2.2%)	1 (4.2%)	33.3%
Provetella dentiola	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Bacteroides fragilis	2 (1.7%)	1 (1.1%)	1 (4.2%)	50%

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; CoNS, coagulase negative *Staphylococcus*.

Microbiological findings

Isolated microorganisms are summarized in Table 3. A single organism was identified in 70 patients (61%) and multiple pathogens were isolated in 20 patients (17%) and no organism was identified in 30 patients (26%). The most common Gram positive bacteria were group A *Streptococcus*, followed by methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA). *Escherichia coli* was isolated in 11 patients and it was the most common Gram negative bacteria. *Aeromonas hydrophila* was isolated in seven patients and five patients (71%) died. *Vibrio vulnificus* was identified in two patients and both have expired. Blood culture was positive in 33 patients (29%): seven among group A *Streptococcus* and in five cases of *Aeromonas hydrophila*.

Treatment

Surgical debridement and amputation were performed in 102 patients and 8 patients, respectively. Five patients were not operated on. Two patients were too critical to be operated at the time of visit to the emergency department and the family refused operation in three patients due to old age and multiple comorbidities. All patients of *Aeromonas hydrophila* and *Vibrio vulnificus* infection received surgical intervention immediately but five of seven *Aeromonas hydrophila* patients and all *Vibrio vulnificus* patients died. One, two and three and above three surgical debridement were performed in 31, 33, 35 patients respectively. The mean hospitalization time was 24.5 days (SD 16.29 days).

Clinical outcome and factors predictive of death

Of the 115 patients, 24 (20.9%) died and 91 (79.1%) survived. Baseline comparisons between surviving and non-surviving patients with necrotizing fasciitis are shown in Table 4. There were significant differences in age, gender, hospital days, peptic ulcer disease, hemoglobin, platelet, prothrombin time, activated partial thromboplastin time, and all biochemistry tests. The non-surviving group was older, had higher prothrombin time, activated partial thromboplastin time, and glucose, creatinine, aspartate aminotransferase and alanine aminotransferase serum levels (all $p \leq 0.046$); additionally, this group had shorter length of hospital stay, and lower hemoglobin, platelet and albumin levels (all $p < 0.001$). The percentage of peptic ulcer disease was higher in the non-surviving group (58.3%) than in the survival group (30.8%, $p = 0.024$).

Risk factors associated with death are listed in Table 5. In univariate analysis, gender, hospital days, diabetic mellitus, peptic ulcer disease, hemoglobin, platelet, prothrombin time, activated partial thromboplastin time, glucose, creatinine, aspartate aminotransferase, alanine aminotransferase and albumin were significant predictors of death (all $p \leq 0.034$). In multivariate analysis, after adjusting for age and gender, which were forced in the model for controlling for potential confounding effect, the significant risk factors were gender,

Table 4 – Summary of baseline characteristics by outcome.

	Survival ($n = 91$)	Death ($n = 24$)	p-Value
Demographics			
Age (years)[a]	54.0 (44.0, 68.0)	61.0 (55.5, 71.5)	0.046*
Gender[b]			0.049*
Female	24 (26.4)	12 (50.0)	
Male	67 (73.6)	12 (50.0)	
Hospital days (days)	23.0 (15.0, 35.0)	11.5 (4.0, 25.5)	0.001*
Comorbidities[b]			
Diabetes mellitus	31 (34.1)	14 (58.3)	0.053
Hypertension	25 (27.5)	8 (33.3)	0.756
Liver cirrhosis	42 (46.2)	12 (50.0)	0.916
Cardiovascular disease	20 (22.0)	9 (37.5)	0.196
Chronic renal disease	26 (28.6)	12 (50.0)	0.082
Malignancy	6 (6.6)	2 (8.3)	0.672
Peptic ulce disease	28 (30.8)	14 (58.3)	0.024*
Gout	16 (17.6)	2 (8.3)	0.356
Hematology[a]			
HB (g/dL)	11.9 (9.5, 13.1)	9.9 (8.6, 10.8)	0.001*
WBC ($10^3/\mu L$)	13.9 (9.8, 22.2)	14.2 (9.7, 21.3)	0.682
PLT ($10^3/\mu L$)	243.0 (146.0, 332.0)	78.0 (48.0, 110.0)	<0.001*
PT (s)	12.0 (11.0, 12.9)	14.5 (12.9, 16.6)	<0.001*
APTT (s)	33.1 (29.8, 36.0)	49.4 (39.4, 59.4)	<0.001*
Biochemistry[a]			
GLU (mg/dL)	120.0 (100.0, 174.0)	280.0 (198.5, 382.0)	<0.001*
Cr (mg/dL)	1.3 (0.9, 2.4)	3.6 (2.5, 4.4)	<0.001*
AST (IU/L)	35.0 (19.0, 53.0)	130.5 (38.0, 161.5)	<0.001*
ALT (IU/L)	24.0 (14.0, 36.0)	98.5 (20.0, 125.5)	<0.001*
Albumin (g/dL)	2.8 (2.3, 3.1)	1.7 (1.2, 2.0)	<0.001*

HB, hemoglobin; WBC, white cell count; PLT, platelet; PT, prothrombin time; APTT, activated partial thromboplastin time; GLU, glucose; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a] The continuous data were presented as median (IQR), and compared between different groups by Mann–Whitney U test.

[b] The categorical variables were expressed by counts and percentages, and compared between different groups by the Yate's continuity correction or the Fisher's exact test, as appropriate.

* Indicated a significant difference between survival and death.

hospital days and albumin (both $p \leq 0.032$). Controlling for age, hospital days and albumin, males had a lower risk of dying than females (OR = 0.18, 95% CI: 0.04–0.86, $p = 0.032$); controlling for age, gender and albumin, for every one day increase in hospital stay, death OR decreased by 0.91 (95% CI: 0.85–0.97, $p = 0.004$); controlling for age, gender and hospital stay, for every one g/dL increase in albumin, death OR decreased by 0.05 (95% CI: 0.01–0.18, $p < 0.001$).

The comparisons between survival and death in necrotizing fasciitis patients with liver cirrhosis were shown in Table 6. There were significant differences in initial Child–Pugh class between survival and death ($p < 0.001$). The percentage of class C was higher in the non-surviving group (83.3%) than in the survival group (19.0%, $p < 0.001$).

Discussion

The term necrotizing fasciitis was introduced by Wilson in 1952 when he observed a rapid progressive inflammation and necrosis of subcutaneous tissue, superficial fascia, and superficial part of the deep fascia with variable presence of cutaneous gangrene. It has been divided into distinct groups on the basis of microbiological cultures. Type 1 infections are polymicrobial infections that are usually caused by non-group A streptococcus, other aerobic and anaerobic microorganisms. Type 2 infections are usually caused by *Streptococcus pyogenes* alone or with *Staphylococci*.[4–7]

Patients usually present with the triad of pain, swelling, and fever. Tenderness, erythema, and fever are common signs of early necrotizing fasciitis. In our study, local swelling/erythema, fever, pain/tenderness were noted in 92 patients (80%), 87 patients (76%), 84 patients (73%), respectively. It is important to recognize the early stage, which can present with minimal cutaneous manifestations, making prompt diagnosis difficult. Pain out of proportion at the physical examination is the most consistent feature noted at the time of presentation. An apparent cellulitis that does not respond to appropriate antibiotic therapy should raise suspicion of necrotizing fasciitis especially in patients who have an underlying disease. The presence of bullae filled with serous fluid is an important diagnostic clue and should raise the suspicion of this condition. As the infection progresses, the skin characteristically becomes more erythematous, painful and swollen with indistinct borders. The skin develops a violaceous hue, may become necrotic with bullae formation and eventually appears hemorrhagic and gangrenous lesion. But

Table 5 – Univariate and multivariate logistic regression models for the event of death.

	Univariate			Multivariate		
	OR	(95% CI)	p-Value	Adjusted OR	(95% CI)	p-Value
Age (years)	1.03	(1.00, 1.07)	0.060	1.04	(0.99, 1.09)	0.164
Gender (male)	0.36	(0.14, 0.90)	0.030*	0.18	(0.04, 0.86)	0.032*
Hospital days (day)	0.94	(0.89, 0.98)	0.003*	0.91	(0.85, 0.97)	0.004*
Diabetes mellitus	2.71	(1.08, 6.80)	0.034*			
Hypertension	1.32	(0.50, 3.47)	0.573			
Liver cirrhosis	1.17	(0.47, 2.87)	0.737			
CV dis	2.13	(0.81, 5.58)	0.124			
Chronic renal dis	2.50	(1.00, 6.28)	0.051			
Malignancy	1.29	(0.24, 6.83)	0.766			
Peptic ulcer disease	3.15	(1.25, 7.95)	0.015*			
Gout	0.43	(0.09, 2.00)	0.279			
HB (g/dL)	0.69	(0.54, 0.86)	0.001*			
WBC ($10^3/\mu L$)	0.98	(0.93, 1.04)	0.594			
PLT ($10^3/\mu L$)	0.98	(0.98, 0.99)	<0.001*			
PT (s)	1.31	(1.11, 1.55)	0.002*			
APTT (s)	1.23	(1.13, 1.34)	<0.001*			
GLU (mg/dL)	1.01	(1.00, 1.01)	<0.001*			
Cr (mg/dL)	3.24	(2.00, 5.26)	<0.001*			
AST (IU/L)	1.03	(1.02, 1.04)	<0.001*			
ALT (IU/L)	1.04	(1.02, 1.06)	<0.001*			
Albumin (g/dL)	0.06	(0.02, 0.19)	<0.001*	0.05	(0.01, 0.18)	<0.001*

HB, hemoglobin; WBC, white cell count; PLT, platelet; PT, prothrombin time; APTT, activated partial thromboplastin time; GLU, glucose; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TB, total bilirubin; DB, direct bilirubin.

* Indicates a significant association with the event of death.

large hemorrhagic bullae, skin necrosis, fluctuance, crepitus and sensory and motor deficits are late signs of necrotizing fasciitis. It is crucial to be alert to these characteristics because the earlier diagnosis of necrotizing fasciitis is made the better outcome and fewer complications will ensue. In our study, 25 patients (22%) had bullae and seven patients (6%) were noted with crepitus.[8,9]

Necrotizing fasciitis develops not only in the extremities but also in head and neck, trunk, perineum and scrotum. Infections of the head and neck region are associated with high mortality. Mao et al.[10] previously reported the poorer survival of patients with thoracic extension (60%) when compared to those without thoracic extension (100%). In our study all patients with head and neck infections have not extended to thorax and no one has died. It might have been due to the alertness of poor outcomes associated with infections of the cranio-cervical region and a more aggressive treatment was implemented in these patients.

Table 6 – Summary of characteristics by outcome (survival or death) in necrotizing fasciitis patients with liver cirrhosis.

	Survival (n = 42)	Death (n = 12)	p-Value
Demographics			
Alcoholism	25 (59.5)	8 (66.7)	0.747
Disease			
Initial Child–Pugh class			<0.001*
A and B	34 (81.0)	2 (16.7)	
C	8 (19.0)	10 (83.3)	
Hepatitis B	7 (16.7)	2 (16.7)	1.000
Hepatitis C	13 (31.0)	3 (25.0)	1.000

The categorical variables were expressed by counts and percentages, and compared between different groups by the Fisher's exact test, as appropriate.

* Indicated a significant difference between survival and death.

Alcohol consumption compromises the integrity of natural barriers to infection in the mouth and decrease saliva flow, resulting in an increased concentration of bacteria which predisposed to cervical necrotizing fasciitis. Although the involvement of extemities is often secondary to trauma, illicit drug use or insect bite, necrotizing fasciitis often develops without any obvious portal of entry in liver cirrhotic patients. Moreover, liver cirrhotic patients usually have chronic edema of the lower limbs, which may predispose them to minor trauma, resulting in an entry port of bacteria. On the other hand, bacteremia may first occur via the intestinal–portal route, because liver cirrhosis weakens the barrier to the passage of bacteria from the intestine to the systemic circulation. Bacteria in the bloodstream may subsequently seed in the edematous soft tissue of lower limbs and then cause infection.[11,12] In our study, necrotizing fasciitis in extremities, trunk and perineum occurred in 85 patients (74%), 15 patients (13%), and 11 patients (10%) respectively. It is consistent with other studies.

Some laboratory findings are common in necrotizing fasciitis, but are by no means diagnostic. Anemia, hypoalbuminemia, altered coagulation profile and elevated white cell count were common. In 74 cases (64%), serum albumin level was below 3 g/dL, which is probably due to associated malnutrition, compromised liver function due to alcoholism, hepatitis B, C, and the effect of bacterial toxins. Hemoglobin < 10 mg/dL was noted in 42 of the 115 patients (37%) because the red mass was frequently diminished by

thrombosis, echymoses, sequestration by the reticuloendothelial system and hemolysis. Production of red cells by the bone marrow was often depressed by infection and toxemia in these patients. The association of thrombocytopenia, altered coagulative profile and elevated creatinine level with higher mortality found in our study is similar to previously reported articles. It may be due to disseminated intravascular coagulation and toxic shock syndrome. In multivariate analysis, negative prognostic factors for survival were gender, decrease albumin level and decreased length of hospitalization time. It might be due to critical initial presentation with fulminant clinical evolution. Survivors were healthy enough to tolerate further debridement and this increased the length of hospitalization time as found in our series.[13–15]

Although it is rare, its mortality rate remains high. The etiology is still not fully understood and cannot be identified in many cases. However, it may result from prior history of trauma and certain conditions such as immunosuppression, diabetes mellitus, malignancy, drug abuse and chronic renal disease. Diabetes mellitus is the most common predisposing factor for necrotizing fasciitis and longer hospitalization and higher mortality have been reported. In our study, a higher mortality rate of 58.3% was noted in diabetic patients compared to non-diabetic patients. Hypertensive disease may result in impaired immunity by causing microvascular injury leading to impaired tissue oxygenation and antimicrobial delivery. A mortality rate of 33.3% was found in our hypertensive patients. The percentage of peptic ulcer disease was higher among non-surviving group (58.3%) than in survival group (30.8%).

Group A *Streptococcus* and *S. aureus* were the predominant pathogens causing necrotizing fasciitis in the USA and Europe. However, monomicrobial Gram negative aerobic pathogens such as *E. coli*, *A. hydrophila*, *V. vulnificus* were the most frequently isolated microorganisms in Asia. In our series, monomicrobial infections were found in 70 (61%) of 115 patients and polymicrobial infections were found in 20 (17%) of 115 patients. In our study, *Vibrio* spp. and *Aeromonas* spp. were not uncommonly detected as the causative organisms, in contrast to other studies. Two patients had Vibrio infection and seven patients had *Aeromonas* infection. One possible reason for this finding is that *Vibrio* spp. and *Aeromonas* spp. are natural inhabitants of seawater, and they are the two common causative pathogens of disseminated bacteremia in patients with liver cirrhosis, and chronic hepatitis. In our study, seven patients had *Aeromonas* infection and four of them had liver cirrhosis, chronic hepatitis. Two patients had *Vibrio* infection all had liver cirrhosis and chronic hepatitis. While clinical isolates of *A. hydrophila* are susceptible to a wide range of antimicrobial agents, they are universally resistant to penicillin, ampicillin, carbenicillin, erythromycin, streptomycin, cefazolin, and clindamycin, and are susceptible to chloramphenicol, ciprofloxacin, co-trimoxazole, aminoglycosides, and third generation cephalosporins. Antibiotic resistance in *Aeromonas* species poses a potential problem in antibiotic therapy. Intravenous administration of gentamycin or a fluoroquinolone such as ciprofloxacin is recommended for treatment of serious *Aeromonas* infections, with broad-spectrum penicillins and cefazolin being avoided as first choice agents, particularly for invasive infections. Since in many cases streptococcal or staphylococcal soft tissue infections will be suspected, empirical therapy directed against these organisms most often included penicillin-based antibiotics such as cloxacillin or cefazolin, to which *A. hydrophila* is intrinsically resistant. The possibility of *A. hydrophila* infection should be considered when confronted clinically by Gram negative bacilli in purulent exudates and soft tissue swabs. Only then can truly effective antibiotic treatment be provided. Tetracycline and third-generation cephalosporins have been the suggested treatment for *Vibrio* spp. Once *Vibrio* infection is suspected, appropriate effective early initiation of antibiotic treatment is important because it significantly improves mortality in *Vibrio* infection.[16–21]

Plain X-rays of involved area may show evidence of soft tissue air. In equivocal cases, Computerized Tomography and Magnetic Resonance Imaging are helpful in defining the presence and extent of infection. Although it cannot be overemphasized, these have been used primarily for patients in whom the diagnosis is doubtful. However, the extent of debridement is determined by physical findings at the time of surgery and not by Computerized Tomography findings.

Fournier's gangrene, a necrotizing fasciitis of the perineal, genital and perianal region was first described by Baurienne in 1764. Fournier's gangrene has a high death rate ranging from 15 to 50%, and is an acute urological emergency.[22,23] In our series, 11 patients were diagnosed Fournier's gangrene and only three patients survived (27%).

It has been reported to have a mortality rate of 34% (range 6–76%) in necrotizing fasciitis patients and a review involving affection of upper extremities found a mortality rate of 35.7%. Our mortality rate was 20.9%. Death usually occurred as a result of bacterial infection with septic shock, disseminated intravascular coagulation, and/or multiple organ failure. So, early recognition of necrotizing fasciitis followed by appropriate antibiotic therapy with or without surgical intervention is necessary to reduce mortality.[24,25]

Conclusion

Despite being a relatively uncommon infection, the present retrospective study highlights that necrotizing fasciitis can be the cause of notable morbidity and mortality among immunocompromised persons. *Aeromonas hydrophila* and *Vibrio vulnificus* infection may be frequently overlooked as the cause of skin and soft tissue infection. The rapid onset of cellulitis in the setting of soft tissue trauma should alert the clinician to the possibility of these two organisms intrinsically resistant to common antibiotics used for cellulitis. Therefore, it is important to have a high index of suspicion and increase awareness at initial presentation. Delayed diagnosis and treatment with adequate antibiotics were crucial for patient survival. Outcomes depend on the promptness of diagnosis, surgical treatment and management of post operative complications.

Conflicts of interest

The authors declare no conflicts of interest.

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medad y a la existencia de formas asintomáticas de endometriosis. Esta actu
tiene por objeto esclarecer la relación entre las características de las lesiones
metriosis y la semiología de las APC, y proponer aplicaciones prácticas. En las
que presentan una endometriosis diagnosticada, esta enfermedad de hecho
responsable de APC en un poco más del 50% de los casos. La interpretació
APC en la endometriosis es difícil, porque existe una variabilidad importante
a los mecanismos fisiopatológicos causales, por una parte, y a la percepción d
tomas dolorosos, por otra parte. Sin embargo, se observa cierto grado de pa
anatomoclínico en las formas más graves de la enfermedad. Existe una asocia
documentada entre la dismenorrea grave y la endometriosis. Este síntoma e
a todas las formas y localizaciones de endometriosis y probablemente se exp
microhemorragias menstruales recidivantes, en el seno de las lesiones endome
En cuanto a los demás síntomas dolorosos, existen argumentos histológicos y
lógicos en favor de la responsabilidad de la endometriosis subperitoneal profun
génesis. Estos dolores tienen relación con la compresión o la infiltración de lo
del espacio pelvi-subperitoneal por las lesiones de endometriosis subperitoneal p
Por ello, los síntomas dolorosos causados por la endometriosis subperitoneal
presentan características particulares. Son específicos de la afectación de una
ción anatómica precisa (dispareunia profunda, dolor a la defecación) o de u
preciso (signos funcionales urinarios o digestivos). Estos síntomas pueden calif
«dolores localizadores». Además, cabe señalar la existencia de mecanismos de
doloroso relacionados con los diferentes niveles del sistema nervioso implicad
transmisión de los mensajes dolorosos. Estos mecanismos intricados y favore
las propias lesiones, pero susceptibles de persistir después del tratamiento de
medad, pueden plantear problemas diagnósticos y terapéuticos. El análisis ser
preciso de las características de las APC es útil para el diagnóstico y el tratamie
endometriosis en el marco de las APC. La utilización de autocuestionarios estand
puede proporcionar una ayuda en este análisis.

Palabras clave: Endometriosis; Algias pélvicas crónicas; Dismenorrea; Dispareunia; Anamnesis; Cuestionarios; Modelos diagnósticos

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http://dx.doi.org/10.1016/S1283-0851(15)74795-3

una ligadura tubárica) [2–10]. Por otra parte, las APC son extremadamente frecuentes en la población general [11,12]. Por ejemplo, en las mujeres que presentan APC y que han sido diagnosticadas de endometriosis, ésta no siempre es la causa de los síntomas dolorosos (Fig. 1) [13].

Dado que no existe, en el momento actual, ningún criterio de certeza para determinar si el dolor de una paciente se debe o no a la endometriosis, algunos recomiendan la ablación meticulosa de todas las lesiones (de endometriosis u otras enfermedades) observadas durante una laparoscopia practicada por dolor [13,14]. Sin embargo, el tratamiento quirúrgico completo de la endometriosis puede ser mutilante y producir complicaciones, en particular en caso de endometriosis subperitoneal profunda (EP) [15–19], e incluso podría dar lugar a dolor crónico relacionado con fibrosis cicatricial, adherencias o lesiones nerviosas [20]. Por ello, algunos equipos sólo proponen exéresis limitadas asociadas al empleo amplio del tratamiento médico [21,22].

El hecho de que los síntomas dolorosos generalmente atribuidos a la endometriosis aparezcan también en mujeres indemnes de la enfermedad constituye también uno de los retos del control clínico de esta enfermedad. Algunos estudios recientes sobre la neurofisiología del dolor pélvico han puesto en duda la relación entre los síntomas dolorosos y las propias lesiones [20]. Los autores de este artículo consideran pues esencial, antes de proponer un tratamiento, sea el que sea, intentar determinar si el tratamiento permitirá curar el dolor que padece la paciente y, por lo tanto, precisar lo mejor posible y de manera individual el mecanismo explicativo del dolor.

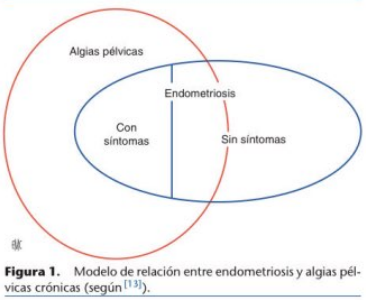

Figura 1. Modelo de relación entre endometriosis y algias pélvicas crónicas (según [13]).

cíclicos o no cíclicos. Esta definición [23,24] debe incluir la dismenorrea grave, la dispareunia profunda y los demás síntomas dolorosos localizados en los territorios neuroanatómicos referidos de la pelvis.

Al parecer de los autores de este artículo, estas definiciones precisas que oponen sin matices los síntomas dolorosos en cíclicos o no, espontáneos o provocados, parecen mal adaptadas a la caracterización de los síntomas de endometriosis, que suelen ser múltiples e intricados. A modo de ejemplo, los autores de este artículo han observado, durante la anamnesis de mujeres endometriósicas, la relación que existe entre el dolor espontáneo de tipo posterior, anal, y el dolor provocado por la defecación. Otra observación que han hecho es que las pacientes relacionan claramente el dolor pélvico espontáneo con la regla o la hemorragia y que no establecen prácticamente nunca una distinción clara entre el dolor pélvico crónico y la dismenorrea, que aparece como una extensión (Cuadro 1) [28].

Métodos de evaluación de los síntomas dolorosos

El estudio de las relaciones entre la endometriosis y las APC depende de la manera en que se evalúan los síntomas dolorosos. A modo de ejemplo, en un estudio de casos y controles realizado en población general [29], la relación entre la endometriosis y la dismenorrea aumenta con la gravedad de esta última evaluada según una escala compuesta (cf infra). En otro ejemplo extraído de los propios datos de los autores de este artículo, la existencia de una endometriosis diagnosticada quirúrgicamente podía deducirse por la existencia de marcadores de «gravedad» de la dismenorrea: puntuaciones elevadas en las escalas de autoevaluación de la intensidad dolorosa, consumo de analgésicos, repercusión sobre la actividad diaria y profesional, necesidad de acostarse, etc. Estos ejemplos señalan la importancia de la calidad clinimétrica de las herramientas utilizadas para medir los síntomas dolorosos al menos en los estudios destinados a establecer la relación entre los síntomas y las lesiones. La calidad metodológica de los estudios depende pues en gran medida de la utilización o no de una anamnesis estandarizada para la evaluación de las APC. Este tipo de anamnesis debe incluir, como mínimo, una escala de autoevaluación de la intensidad dolorosa: la escala verbal simple (EVS), la escala numérica simple (ENS) o una escala visual analógica (EVA) [30]. Otro enfoque válido para evaluar la gravedad de los síntomas dolorosos de manera más global es apreciar el impacto en términos de comportamiento (repercusión física, consumo de analgésicos, medidas de evitación, etc.). A

Dolor presente a lo largo de todo el ciclo, dolor presente todo el tiempo	9	5
El dolor se propaga a la espalda	9	2
Dolor antes, durante y después de la regla	9	–
Dolor como puñaladas	9	–
Dolor como pinchazos, que pica, como una picadura	9	–
Dolor en el bajo vientre de tipo quemadura	7	–
El dolor impide dormir o despierta por la noche	7	–
El dolor altera la vida cotidiana y el trabajo	7	1
El dolor se propaga a las piernas y las caderas	4	–
Asociación de dolores múltiples, varios síntomas dolorosos diferentes		3
Tema: dispareunia		
Dolor fuerte, vivo durante las relaciones sexuales	19	
Dolor que se siente en profundidad durante las relaciones sexuales	12	8
Dolor en ciertas posiciones durante las relaciones	12	4
Dolor que altera, impide o interrumpe las relaciones sexuales	10	2
Sensación de quemadura durante o después de las relaciones	10	
Tema: signos digestivos dolorosos		
Dolor en el momento de hacer de vientre, defecación dolorosa	21	6
Hinchazón del vientre, hinchazón abdominal	9	5
Diarrea en el momento de la regla	8	6
Espasmos, calambres, dolor intestinal antes de hacer de vientre	8	2
Estreñimiento en el momento de la regla	7	5
Náuseas, vómitos	7	1
Dolor en el ano	6	1
Alternancia de diarrea y estreñimiento		3
Emisión de sangre con las heces		2
Tema: signos funcionales urinarios dolorosos		
Ganas frecuentes de orinar, orina en pequeñas cantidades	9	3
Dolor al tener ganas de orinar, al aguantarse	9	1
Dolor que presiona en la vejiga	7	2
Dolor o ardor al orinar	6	4
Dificultades para empezar a orinar	4	6
Presencia de sangre en la orina		2
Tema: otros síntomas		
Fatiga intensa, agotamiento, ralentización	13	1
Cabeza que da vueltas, mareo	4	
Ciática en el momento de la regla		3
Dolor en el hombro derecho		3
Neumotórax		2
Depresión		2

	Moderado	(2) Dolor provocado extenso a la palpación
	Grave	(3) Tacto imposible debido al dolor
Induración palpable	Ausente	(0) Ausencia de induración
	Ligera	(1) Movilidad uterina normal, induración limitada al fondo de saco
	Moderada	(2) Empastamiento e induración del anexo y del fondo de saco, movilidad uterina reducida
	Grave	(3) Nódulo palpable anexial y del fondo de saco, útero a menudo fijo

este efecto, existen escalas multidimensionales (Cuadro 2) (cf infra).

Desde este punto de vista, cabe señalar que no existe, en este momento, ningún instrumento validado para evaluar los síntomas de endometriosis tal como los sienten las pacientes [28, 30, 31]. De hecho, las diferentes escalas de dolor y los cuestionarios de síntomas existentes se han desarrollado todos a partir de la descripción de los médicos [10, 32–36]. Así pues, los resultados del análisis cualitativo de los síntomas dolorosos que los autores de este artículo han realizado con mujeres afectadas de endometriosis aporta una luz nueva con respecto a la descripción de los médicos (Cuadro 1) [28].

Sesgos potenciales relacionados con los métodos de diagnóstico positivo de la endometriosis

El diagnóstico positivo de la endometriosis es quirúrgico, lo cual plantea el problema de la indicación de la cirugía. Ésta se decide generalmente en un marco preciso, tratamiento de una infertilidad, síntomas dolorosos, quiste de ovario, etc. La interpretación correcta de los estudios clínicos requiere tener en cuenta el riesgo de un sesgo llamado sesgo de verificación [37]. Se puede expresar este sesgo de la siguiente manera: como, evidentemente, los médicos se ven influidos por los resultados de la prueba diagnóstica estudiada (por ejemplo, el síntoma dismenorrea grave), las pacientes que tienen una prueba anormal son más susceptibles de ser sometidas a un examen de confirmación, como la laparoscopia. Así pues, en los estudios destinados a evaluar el rendimiento de la prueba, la prevalencia de los verdaderos negativos (prueba negativa y laparoscopia negativa) y la de los falsos negativos (prueba negativa y laparoscopia positiva) se subestiman artificialmente. Los valores calculados para la sensibilidad de la prueba, la especificidad y relaciones de probabilidad están sesgados, porque proceden de un pequeño grupo de pacientes preseleccionadas por el hecho de presentar pruebas anormales. El efecto de este tipo de sesgo es, en general, aumentar artificialmente la sensibilidad y disminuir la especificidad de la prueba [37]; más grave todavía, este sesgo puede conducir simplemente a eliminar cualquier asociación estadística entre el resultado de la prueba y su verificación. Por ejemplo, en un estudio minucioso realizado por el grupo de Stratton y Berkley, las características topográficas del dolor se identificaron de manera extremadamente precisa, mientras que todas las lesiones visibles se sometieron a una resección completa con verificación histológica. De manera decepcionante, no se observó ninguna asociación clara entre las características de las lesiones y la semiología dolorosa [38].

Este estudio ilustra también otro tipo de sesgo. En este sentido, los autores explicaban que las lesiones de endometriosis de las pacientes operadas en su estudio eran esencialmente superficiales, lo cual sugiere relaciones diferentes entre las lesiones y los síntomas en función del tipo de lesiones. Este sesgo, denominado sesgo de espectro, puede enunciarse por el hecho de que el rendimiento de una prueba diagnóstica (aquí, los síntomas dolorosos) puede variar según los subgrupos de pacientes en función de la gravedad y de la presentación clínica de la enfermedad [39].

Para limitar este riesgo de sesgos, algunos estudios han tomado como grupo de control a mujeres operadas de ligadura tubárica [7, 10, 36] o a mujeres que no han sido operadas [29, 34, 40]. Otro método es tomar grupos de mujeres muy homogéneos, basados en una sola indicación operatoria independiente del diagnóstico de endometriosis, definida de forma precisa por ejemplo a partir de una indicación de infertilidad [41], o bien tomar sólo mujeres operadas por un quiste de ovario [42].

El último problema afecta al diagnóstico visual de las lesiones de endometriosis. El diagnóstico laparoscópico es bastante poco fiable. En efecto, el 50% de las lesiones identificadas macroscópicamente como endometriosis no se confirma [43]. A la inversa, biopsias realizadas en peritoneo macroscópicamente sano podrían contener lesiones de endometriosis microscópicas en el 6% de las mujeres [7]. Existe pues un consenso actual para recomendar la documentación histológica de todas las lesiones endometriósicas visualizadas en la exploración quirúrgica [44–46]. Sin embargo, si bien esta estrategia soluciona el problema de los falsos positivos, no soluciona en absoluto el

la ausencia de sesgos [48,50,52-55].

Fisiopatología de los síntomas dolorosos de la endometriosis

Los dos estudios aleatorizados con doble anonimato que comparan el tratamiento quirúrgico con el placebo [56,57] demuestran de manera indiscutible que la enfermedad endometriósica es, en general, responsable de APC. Estos estudios demuestran, al contrario, que las lesiones de endometriosis diagnosticadas durante una laparoscopia practicada en un contexto de algias pélvicas no son automáticamente la causa de los síntomas dolorosos de los que se quejan las pacientes (Fig. 1). Las lesiones de endometriosis podrían ser efectivamente responsables de los síntomas dolorosos en más del 50% de los casos operados [58]. Es difícil estimar esta proporción en la realidad. Efectivamente, en la medida en que la cirugía ha podido ser incompleta en un número variable de casos, es posible que esta proporción sea más importante. En cambio, hay que recordar que las pacientes operadas en los estudios aleatorizados han sido cuidadosamente seleccionadas, lo cual sin duda aumenta esta proporción con respecto a la realidad. Así pues, en la población general, cuando se tienen en cuenta todos los tipos de endometriosis, incluidas las lesiones mínimas, los síntomas dolorosos graves no parecen mucho más frecuentes en las mujeres portadoras de endometriosis que en las mujeres indemnes de esta enfermedad [7,38]. Esta sorprendente diferencia entre los estudios de prevalencia y los ensayos controlados puede explicarse por el hecho de que las mujeres tratadas por «endometriosis dolorosa» presentan, en realidad, formas muy particulares de la enfermedad [59]. A la inversa, es posible que, en algunos estudios observacionales, las lesiones de endometriosis mínima detectadas no sean más que un fenómeno fisiológico transitorio [60,61]. Así pues, más que la presencia de una endometriosis por sí misma, lo que explicará las APC son las características de las lesiones y su extensión. El razonamiento del médico para atribuir la responsabilidad de las APC a la endometriosis debe pues utilizar a la vez la semiología de los síntomas dolorosos y las características de las lesiones de endometriosis.

Dismenorrea grave y endometriosis

En una revisión sistemática de estudios observacionales, los autores de este artículo han demostrado

– ≥ 12		53	1,9 (

OR: cociente de posibilidades acumulado; IC: intervalo de
[a] El OR representa el aumento del riesgo de sufrir disme
categoría más grave cuando la variable está presente.
[b] Índice de las adherencias anexiales calculado según la c
de la American Fertility Society, 1985.

claramente la existencia de una relación entre la
de dismenorrea grave y la existencia de una end
sis [58]. La naturaleza causal de la asociación entre
triosis y dismenorrea se sugiere por una relació
respuesta»: la demostración de una relación
lineal entre la gravedad de la dismenorrea y la
dad de diagnosticar endometriosis en la laparosc
el preoperatorio; la existencia de una relación
lineal entre la gravedad de la enfermedad y la fr
o la intensidad de la dismenorrea. La asociaci
la dismenorrea y la endometriosis no parece
de ningún tipo especial de endometriosis ni de
localización particular [58]. Este carácter general
dismenorrea debe ponerse en paralelo con el
universal de la lesión histológica (glándula end
y estroma). El mecanismo fisiopatológico ma
tor para explicar esta relación es el hecho d
dismenorrea «patológica» de las mujeres porta
endometriosis está provocada por microhem
menstruales recidivantes en el seno de las l
la inflamación que resulta de ello [1,62]. La
de estas microhemorragias menstruales es
al inicio de la evolución de la enfermedad en
tipos macroscópicos de endometriosis [62], lo cua
que la dismenorrea grave esté ligada a la pres
endometriosis, pero no a una forma particu
enfermedad, y también que la dismenorrea sea e
doloroso más precoz de la enfermedad [63].

Aun así, los autores de este artículo han podid
trar, en mujeres operadas por EP, la existencia
relación «dosis-efecto» entre la gravedad de l
norrea y el grado de infiltración del tabique rec
por las lesiones de EP, apreciada por la existenc
infiltración de la pared del recto, la vagina o
órganos (Cuadro 3) [64]. Este estudio también
manifiesto la hipótesis de las microhemorragias r
les recidivantes. De hecho, en este tipo de lesi
microhemorragias menstruales recidivantes tie
ción con microendometriomas que están presen
todo cuando la capa submucosa de la vagina o la
del recto están invadidas [62].

El papel de las adherencias en la génesis de
norrea es bastante incierto. Lo sugieren diversos
observacionales, que han establecido la relación
presencia de adherencias pélvicas, anexiales o

Modelo 6	SF digestivos	Intestino indemne	1	–
		Intestino afectado	4,4	1,7-11,4

DM; dismenorrea; DPNC: dolor pélvico crónico no cíclico; LUS: ligamentos uterosacros; SF: signos funcionales.
[a] Cada síntoma doloroso pélvico se incluyó como variable independiente (o predicha) en un modelo de regresión logística múltiple distinto.

de saco de Douglas y la dismenorrea (Cuadro 3) [64–67]. No obstante, en la medida en que muchas pacientes con enfermedad endometriósica tienen también adherencias, es difícil diferenciar entre lo que se puede atribuir a su propio papel y lo que correspondería a las lesiones asociadas.

«Dolor localizador» de la endometriosis profunda

En lo referente a las características de las lesiones de endometriosis, la EP es la única lesión macroscópica en la que se comprende bien la relación con las APC. La convicción de la naturaleza causal procede esencialmente de los resultados de los estudios de correlación histológica:

- en una población de pacientes con diferentes tipos de lesiones de endometriosis, las que presentan EP son las que padecen los síntomas dolorosos más graves [68];
- la relación entre la EP y el dolor puede explicarse por la compresión o la infiltración de los nervios de los espacios pelvi-subperitoneales por las siembras profundas [69]. En lo referente a los dolores, la EP es una entidad aparte; las lesiones profundas presentan características morfológicas e histológicas particulares [70, 71], que explican su capacidad para infiltrar los tejidos vecinos.

Los síntomas dolorosos de la EP presentan características particulares que los distinguen de los dolores de otros orígenes (dolor relacionado con otros tipos de endometriosis o relacionado con otras enfermedades) [58]. Estos dolores son verdaderamente específicos de la afectación de una localización anatómica precisa (dispareunia profunda, dolor a la defecación con recrudescencia menstrual) o de un órgano concreto (signos funcionales urinarios o digestivos) por las siembras profundas (Cuadro 3). La compresión o la infiltración de los nervios de la pelvis por las lesiones [69] explican el paralelismo entre la localización anatómica o el órgano afectado y la semiología dolorosa [65]. Estos síntomas pueden calificarse de «dolores localizadores». La mayoría de ellos son dolores de tipo provocado: la movilización de los órganos afectados por las lesiones de EP desencadenará o exacerbará el dolor.

El ejemplo típico de dolor localizador es la presencia de dolor a la defecación de recrudescencia menstrual (Cuadro 1). Este síntoma se ha atribuido específicamente a la infiltración del área posterior rectovaginal por la EP (Cuadro 4) [65, 72, 73]. Esta queja funcional bastante característica podría tener relación con las microhemorragias cíclicas y la inflamación relacionadas con la infiltración de la pared vaginal posterior, el tabique rectovaginal o la propia pared rectal por el nódulo [74]. Lo mismo sirve para explicar la relación entre las lesiones de EP posterior y la dispareunia profunda, que parece bien establecida [65, 66, 75, 76]. Por otra parte, los autores de este artículo han confirmado esta hipótesis demostrando, en un estudio prospectivo basado en un autocuestionario de síntomas, que la existencia de dispareunia profunda intensa o de dolor a la defecación con recrudescencia menstrual eran marcadores de EP del área posterior (Fig. 2) [35]. También han confirmado la validez de estos dos síntomas en mujeres portadoras de quistes endometriósicos para predecir la existencia de lesiones subperitoneales profundas asociadas [42].

Los signos funcionales urinarios presentes en la endometriosis (Cuadro 1) pueden interpretarse, en ciertos casos, como dolores localizadores [65]. Por otra parte, se ha demostrado que el uso de un cuestionario de signos funcionales urinarios inespecíficos permite identificar a las pacientes con endometriosis vesical entre las pacientes operadas por APC [77].

Diálogo cruzado de los órganos y semiología urinaria o digestiva

Según la experiencia de los autores de este artículo, se ha constatado con frecuencia que las pacientes endometriósicas presentaban signos funcionales urinarios, incluso en ausencia de localización vesical [28]. Estos síntomas son bastante similares a los observados en la cistitis intersticial [78]. Estos síntomas son la polaquiuria, la urgencia miccional y el dolor «vesical», dolor definido como un dolor supra o retropúbico que aparece durante el llenado vesical o persiste después de la micción (Cuadro 1) [28, 79].

De la misma manera, pueden existir síntomas digestivos (Cuadro 1) en ausencia de cualquier localización digestiva confirmada de la enfermedad [28]. La exploración sistemática de los síntomas en una serie consecutiva de 355 pacientes sometidas a una laparoscopia por sospecha de endometriosis ha demostrado que los síntomas funcionales digestivos como la diarrea, el estreñimiento, la presencia de hinchazón abdominal, náuseas o vómitos

EP posterior : no	57	81
EP posterior : sí	13	19

EP posterior : no	5	38
EP posterior : sí	8	62

eran casi tan frecuentes como los síntomas puramente ginecológicos en las mujeres con endometriosis y no reflejaban forzosamente una afectación digestiva [80]. Una de las explicaciones avanzadas para explicar esta observación es el hecho de que las lesiones de endometriosis, incluso cuando no afectan directamente al intestino, a menudo se sitúan en el compartimento posterior, cerca del rectosigmoide, de tal manera que la secreción local de prostaglandinas asociada a la inflamación de las lesiones explica los trastornos funcionales [81].

Sin embargo, es posible explicar los síntomas urinarios o digestivos relacionados con la endometriosis por la interconexión entre las siembras endometriósicas y el sistema nervioso periférico o central. Los estudios realizados en modelos animales sobre la cistitis intersticial crónica, el síndrome doloroso pélvico crónico y el intestino irritable han demostrado efectivamente que existe un diálogo cruzado, denominado sensibilización cruzada, entre los órganos pélvicos que producen respuestas dolorosas exacerbadas a distancia del lugar de inicio del dolor [82,83]. Este mecanismo de sensibilización cruzada también se ha constatado en el modelo de rata de la endometriosis [84]. El sustrato de este mecanismo está ligado, en especial, a la proliferación neuronal de las fibras nociceptivas eferentes pélvicas relacionadas con las siembras endometriósicas. Este tipo de respuesta dolorosa, a distancia del lugar de las lesiones, explicaría la similitud con la cistitis intersticial crónica o el trastorno funcional intestinal.

Hiperalgesia pélvica

Las propias algias pélvicas también pueden tener relación con desregulaciones de los mecanismos neurofisiológicos de control del dolor. Realmente, la transmisión de los mensajes dolorosos pone en juego el sistema nervioso de varias maneras y conduce a diferentes mecanismos, que modulan los mensajes nociceptivos locales directamente relacionados con las siembras endometriósicas. La sensibilización (*sensitization* en inglés) es una forma de plasticidad neuronal que conduce a una percepción exacerbada de los mensajes dolorosos y que pueden intervenir a varios niveles del sistema nervioso central; se habla de alodinia o de hiperalgesia [20]. Un estudio experimental controlado [85] ha mostrado que existe un mecanismo de sensibilización central responsable de una reacción de hiperalgesia pélvica generalizada en las mujeres afectadas de endometriosis. Este fenómeno también se ha observado en los estudios de cartografía dolorosa realizados en pacientes endometriósicas. La exis esta hiperalgesia pélvica generalizada en una endometriósica puede explicar la persistencia o l de las algias pélvicas después del tratamiento q de la endometriosis dolorosa [20].

Para terminar, hay que recordar que la ex dolorosa es una experiencia subjetiva. El sistema superior constituye una fuente importante de va de la experiencia dolorosa de las pacientes endo cas. Es un hecho demostrado que las pacientes p de lesiones de endometriosis idénticas en las características patológicas (localización, e profundidad, etc.) a veces pueden describir síntor rosos diferentes [28]. Se ha demostrado la import sistema nervioso central en el tratamiento de lo los dolorosos en numerosas enfermedades resp de dolores crónicos [86]. Debido a la gran plasti sistema nervioso central, es probable que los me del dolor asociado a la endometriosis, como en enfermedades dolorosas crónicas, incluyan me de sensibilización central que desempeñarán importante para modular la experiencia doloros

Evaluación clínica de una paciente que prese un síndrome doloroso pélv sugestivo de endometriosi

La anamnesis es un tiempo absolutamente c la evaluación de las pacientes endometriósicas. lizarla correctamente, primero no debe ser di después, en un segundo tiempo, debe comple un interrogatorio estandarizado.

En la práctica de los autores de este artículo, las pacientes al inicio de la consulta (y antes de gatorio específico) que expliquen libremente y d detallada los síntomas dolorosos, relacionado enfermedad (o percibidos como tales). Se trat entrevista libre, que no debe comportar ningún nario, sino una escucha «empática» que debe per paciente expresar claramente la vivencia de la ex dolorosa [28], así como sus expectativas respecto a A los autores de este artículo les parece importar der de esta manera para crear el clima indispens una alianza terapéutica [87].

instrumento muy ampliamente utilizado que se cita como uno de los instrumentos de referencia en más de 10 artículos [88]. En la práctica diaria de los autores de este artículo, este instrumento constituye el método de elección para la evaluación de la intensidad de los síntomas dolorosos [35], que utilizan sobre todo en forma de un autocuestionario.

La ENS [90] también se utiliza para la evaluación de la intensidad del dolor [64, 91], en especial durante la anamnesis por el médico, porque no requiere soporte, al contrario que la EVA, o bien en caso de dificultad de comprensión de la EVA. El paciente debe atribuir una cifra a la intensidad del dolor, de modo que 0 es la ausencia de dolor y 10 el dolor máximo imaginable.

Las EVS permiten también una evaluación de la intensidad dolorosa. Se basan en la elección de un adjetivo para definir la intensidad del dolor. A cada adjetivo le corresponde un índice. La medida se limita a cinco o seis niveles. Generalmente, se reservan a las personas que tienen una escasa capacidad de abstracción y, por lo tanto, tienen dificultades para utilizar los dos tipos de escalas anteriores.

Estas escalas permiten obtener una medida del dolor en el momento de la consulta, pero también de forma retrospectiva, de manera fiable [92, 93].

En la práctica, el paciente debe utilizar una sola de las tres escalas en función de su buena comprensión. Estas escalas pueden utilizarse en auto o en heteroevaluación. En autoevaluación, los autores de este artículo prefieren la EVA, que se utiliza bien en estas pacientes jóvenes. En heteroevaluación, la ENS es más simple, porque no requiere herramientas especiales. Por otra parte, los dos tipos de medidas correlacionan perfectamente [64].

El interés de estas escalas es su simplicidad de administración y de cálculo del índice. Son sensibles a los efectos de los diferentes tratamientos y a las otras medidas de gravedad del dolor; por lo tanto, tienen un valor descriptivo para un individuo dado y permiten un seguimiento [31]. Los índices no permiten, a priori, hacer comparaciones interindividuales, aunque estas escalas se han utilizado ampliamente en los estudios de correlación entre los síntomas y las lesiones [58].

Una importante limitación de estas escalas es la ausencia de control del carácter cíclico de los síntomas dolorosos. Para paliar esta dificultad, los autores de este artículo han modificado estas herramientas para medir una especie de valor medio, de forma que las cuestiones se formulan de la siguiente manera: «Basándose en los tres o cuatro últimos ciclos, indique con una cruz en la escala siguiente la intensidad media del dolor de la regla».

Para tener en cuenta el carácter cíclico de los síntomas dolorosos en tiempo real, en especial en los ensayos clínicos, podría ser interesante utilizar cuestionarios

Existen numerosos cuestionarios de tipo inventario que pretenden la exploración fina de los síntomas dolorosos de la endometriosis. Estos cuestionarios exploran principalmente cuatro grandes ámbitos (Cuadro 1): la dismenorrea grave y el dolor pélvico no menstrual o no cíclico [10, 33, 35, 67, 75, 76, 95–97], la dispareunia profunda [10, 35, 66], los síntomas rectales y digestivos [35, 65, 72, 73, 80, 97] y los signos funcionales urinarios [77, 97, 98]. Estos cuestionarios se utilizan principalmente con un objetivo de investigación, pero algunos equipos, como el de los autores de este artículo, utilizan este tipo de cuestionarios de rutina. Un ejemplo es el autocuestionario de dolor pélvico realizado en Cochin. La factibilidad de la utilización de este cuestionario de rutina ha sido objeto de una tesis que ha demostrado que esta herramienta era muy apreciada por las pacientes y que su cumplimentación no presentaba dificultades especiales [99]. Aparte de la investigación, los beneficios de la utilización de este cuestionario en la práctica corriente se ven, sin embargo, limitados por el número elevado de preguntas y la ausencia de uno o varios índices que resuman la información.

Por otra parte, es importante señalar el hecho de que ninguno de los cuestionarios de inventario de síntomas utilizados en el marco de la investigación sobre la endometriosis ha sido objeto de un desarrollo específico basado en la descripción cualitativa de la experiencia dolorosa de las pacientes [28].

Escalas compuestas

Al contrario de las anteriores, las escalas compuestas permiten, en principio, el cálculo de un índice que resume la información. Por esta razón, se utilizan corrientemente en los ensayos clínicos. Son escalas de varios ítems que evalúan a la vez los síntomas, su gravedad y el impacto funcional objetivo del dolor a partir del comportamiento específico de las mujeres. Utilizan, por ejemplo, la frecuencia del dolor, su repercusión sobre la «función», la existencia de medidas de exclusión o el consumo de analgésicos. Cada pregunta se asocia a un sistema de respuestas en dos, tres o cinco modalidades. Las modalidades de respuesta pueden en ocasiones adaptarse a los diferentes síntomas. Por ejemplo, para la dispareunia, se pregunta sobre la frecuencia y la repercusión refiriéndose a las relaciones sexuales, y, para la dismenorrea, refiriéndose a los ciclos y al período de las reglas.

La escala desarrollada por Andersch y Milsom, llamada «escala verbal multidimensional» [100] por sus autores, es una escala de comportamiento utilizada para clasificar la gravedad de la dismenorrea en cuatro clases de gravedad creciente:

síntomas dolorosos, la dismenorrea, la dispareunia y el dolor pélvico crónico, y dos signos de examen, el dolor provocado pélvico y la induración; cada uno de ellos se valora en una escala de 0 a 3 (o 4), en función de la gravedad del síntoma. Esta escala se utiliza ampliamente, pero tiene varios defectos clinimétricos importantes [31]. En primer lugar, el cálculo del índice se aumenta artificialmente debido a la valoración a 4 en las mujeres que presentan una amenorrea o en las que no son sexualmente activas. En segundo lugar, el método de cumplimentación de esta escala no está claramente definido; según los estudios, podía ser cumplimentada por la propia paciente, administrada por los médicos y el personal del estudio que recogía la información de la paciente o bien percibida como impresiones del médico de los síntomas de la paciente. Teniendo en cuenta la frecuencia de los síntomas dolorosos en la población general, también falta una norma que defina un nivel patológico o un nivel para definir la curación. El modo de cálculo de los índices también es extremadamente variable según los estudios [31,39]. En tercer lugar, como para las escalas de intensidad dolorosa, la variabilidad diaria no se tiene en cuenta de manera satisfactoria, porque su utilización tiene en cuenta de manera global un período de referencia de 4 semanas (Cuadro 2).

Escalas de calidad de vida de las pacientes

Para evaluar la calidad de vida de las pacientes, pueden utilizarse dos tipos de escalas: las escalas genéricas o las escalas específicas. Las escalas genéricas dan información sobre el estado de salud y la calidad de vida, sea cual sea la enfermedad que padece el paciente o incluso en ausencia de enfermedad. Suelen ser escalas de validez externa establecida, que permiten comparar grupos de individuos con enfermedades diferentes. El inconveniente de este tipo de evaluación es que no siempre es sensible al cambio; por consiguiente, las mejoras aportadas por el tratamiento pueden demostrarse poco. Las escalas genéricas de calidad de vida validadas en francés que más se utilizan en la endometriosis son la MOS-SF-36 [101] y la EuroQol [102].

En cambio, las escalas específicas tienen teóricamente la ventaja de ser más sensibles al cambio, pero también de estar más cercanas a la valoración clínica. En 2002, Jones et al [103] realizaron una revisión de la literatura sobre la medida de la calidad de vida de las pacientes que padecían enfermedades ginecológicas crónicas, como la endometriosis. En el conjunto de los artículos recogidos, sólo se encuentran dos escalas específicas de la endometriosis, publicadas por Colwell et al en 1998 [104] y por

de este artículo les parece que esta escala tiene l
des requeridas para un uso en la práctica clínica
En especial, presenta un carácter unidimensiona
mite el cálculo de un índice. Además, parece
una buena validez externa [116]. La cuestión de s
lidad al cambio sigue en suspenso, porque nu
evaluado. Actualmente, es objeto de una evalu
el grupo de los autores de este artículo.

La utilización de estas escalas de calidad de
mostrado su interés en investigación clínica
miden el bienestar de las pacientes y su capa
efectuar las tareas cotidianas, de manera relat
independiente de los síntomas dolorosos. Est
permiten la evaluación de las estrategias terap
su comparación, mediante la medida de la sensi
cambio [57,91,108,117]. Otro interés de estas escalas
facilitar la decisión médica compartida [87]; efecti
en algunos casos de cirugía importante, el equipo
ha demostrado que la valoración de la calidad d
el preoperatorio puede constituir un criterio pron
los resultados posoperatorios en términos de sat
de las pacientes [118].

En la práctica, los autores de este artículo
que lo mejor es utilizar escalas de calidad de
tas, la EQ-5D como escala generalista y el EHI
escala especializada. En uso clínico, estas escala
integrarse fácilmente en un cuestionario especí
endometriosis como hacen los autores de este
Sin embargo, hay que recordar que la utilidad
cuestionarios en la práctica clínica no se ha dem

Examen ginecológico de una paci sospechosa de endometriosis

Examen con espéculo

Puede demostrar lesiones mamelonadas azula
terísticas en la vagina. Hay que buscar estas lesio
zona retrocervical y en la parte superior de la pa
nal posterior [119]. Este tipo de lesiones se obse
5-17% de los casos de endometriosis según las
La existencia de signos de inspección permitiría
diagnóstico de certeza de endometriosis en el pr
rio.

Tactos pélvicos

Los elementos de la palpación tienen un v
dictivo positivo valorado de manera más dive
literatura en función de la prevalencia de la en
y de las diferentes formas de la enfermedad en
sión de los equipos que han publicado sobre el

el examen ginecológico, muy a menudo realizado por personal extremadamente experimentado en el manejo de la endometriosis, parece finalmente bastante eficaz en cuanto al valor predictivo positivo [121, 122]. Por supuesto, el valor del examen es variable según la localización y el tipo de endometriosis. Se ha demostrado que el valor diagnóstico del examen aumenta claramente en el período de reglas [123].

Modelos diagnósticos de la endometriosis basados en la clínica

Varios autores, entre ellos el equipo de los autores de este artículo, han propuesto modelos diagnósticos a fin de ayudar al médico en su actuación. Sin embargo, no hay que perder de vista que, a especificidad y sensibilidad iguales, el valor predictivo positivo de un signo varía considerablemente en función de la prevalencia de la enfermedad en el seno de la población estudiada. Así pues, en una población de pacientes no seleccionadas, el valor predictivo positivo de uno u otro signo es mucho más bajo que en una población seleccionada (consulta especializada, por ejemplo). Ahora bien, ninguno de los modelos se ha validado todavía en la población general.

Un primer modelo [123] asocia al examen clínico permenstrual una determinación de CA125 durante la fase folicular. Este modelo está basado en un estudio prospectivo con confirmación laparoscópica, indicada por dolor pélvico y/o infertilidad. La palpación de un nódulo doloroso pélvico en período menstrual asociado a una concentración de CA125 superior a 35 U/ml en fase folicular permite predecir una endometriosis grave (endometrioma, endometriosis profunda, adherencias pélvicas graves) con una especificidad del 97%, pero con una sensibilidad solamente del 42%; la existencia de uno u otro de estos dos elementos permite el diagnóstico con una especificidad del 83% y una sensibilidad del 87%. Actualmente, la determinación de CA125 no se recomienda para el diagnóstico de endometriosis [124]. En la práctica, hay que sacar de este modelo que, en caso de duda diagnóstica, el hecho de revisar clínicamente a la paciente en el momento de la regla a veces puede aportar un argumento suplementario.

Otro estudio [125] asocia una ecografía pélvica a la anamnesis y a la exploración física. El modelo de predicción desarrollado en este estudio se muestra de hecho extremadamente eficaz para el diagnóstico de los endometriomas, pero no para el diagnóstico de la endometriosis no ovárica.

Implicaciones y conclusiones

Contrariamente a una noción común, existe un paralelismo claro entre los síntomas dolorosos y las lesiones de endometriosis. Sin embargo, esta relación no siempre es fácil de demostrar, debido a la importancia de la variabilidad de la experiencia dolorosa referida por las pacientes [28]. Esta variabilidad de los síntomas se debe no sólo al hecho de que las lesiones provocan localmente dolores por diferentes mecanismos (por ejemplo, peritonitis químicas, inflamación ligada a microhemorragias, infiltración neural), sino también debido a las variaciones de la percepción y la descripción de los síntomas dolorosos referidos por las pacientes. Esto es susceptible de explicar las dificultades encontradas para construir cuestionarios de síntomas eficaces para caracterizar la experiencia dolorosa de las mujeres endometriósicas. La formulación inapropiada de las preguntas podría conducir a ambigüedades que podrían enmascarar el valor semiológico de la anamnesis y explicar así la falta de reconocimiento de la relación entre endometriosis y síntomas dolorosos.

La búsqueda sistemática de síntomas que caracterizan la dismenorrea grave, utilizando los marcadores de gravedad, podría utilizarse como prueba diagnóstica de la presencia de una enfermedad endometriósica, por ejemplo, en presencia de una paciente que consulta por una infertilidad o que presenta un quiste ovárico [33, 41]. Para reconocer mejor la enfermedad, el médico podría basarse en el concepto de dismenorrea grave en su acepción de síndrome doloroso perimenstrual atípico [28]. Otro punto característico es el impacto del síndrome doloroso sobre la actividad cotidiana y la calidad de vida. Desde este punto de vista, la escala de gravedad de Biberoglu y Behrman, que tiene en cuenta estos últimos criterios, parece interesante a los autores de este artículo [32–35].

Entre todos los tipos de endometriosis, las lesiones de EP son ciertamente las que tienen mejor establecida la relación con el dolor. Estos dolores llamados «localizadores» son específicos de la afectación por las lesiones profundas de una o varias localizaciones anatómicas precisas (dispareunia grave, dolor a la defecación) o de un órgano preciso (signos funcionales urinarios, signos digestivos). Para precisar la responsabilidad de la endometriosis en las APC presentadas por una paciente, recomendamos al médico un análisis individual de los síntomas dolorosos. La dispareunia grave y el dolor a la defecación con recrudescencia menstrual pueden utilizarse con una fiabilidad bastante buena para predecir en el preoperatorio, en un contexto de algias pélvicas o de quistes endometriósicos, la existencia de lesiones de EP que afecten al tabique

vica. La generalización del uso de esta herramienta pasa por la búsqueda de un consenso entre los diferentes equipos que se enfrentan al tratamiento de esta enfermedad, tanto en la forma como en el contenido de este cuestionario. La simplificación de esta herramienta será una ventaja importante para aumentar su difusión. Estos futuros cuestionarios de dolor deberían basarse en los descriptores utilizados por las pacientes más que en los utilizados por los médicos, de manera que se formulen preguntas fiables [28, 127].

Los modelos diagnósticos basados en la clínica, que asocian parámetros de interrogatorio estandarizados y examen ginecológico de la zona retrocervical por ginecólogos especializados en el tratamiento de la endometriosis, son útiles para diagnosticar las formas graves de la enfermedad. En el estado actual de su perímetro de utilización, estos modelos diagnósticos deben emplearse exclusivamente en poblaciones seleccionadas (APC o infertilidad), para mejorar el diagnóstico prequirúrgico de la endometriosis. Sin embargo, en el futuro, el empleo de modelos diagnósticos podría permitir seleccionar una población de pacientes en las que la prevalencia de la enfermedad fuera importante y que podrían entonces beneficiarse de exploraciones complementarias mediante pruebas de imagen o laparoscopia.

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Cualquier referencia a este artículo debe incluir la mención del artículo: Fauconnier A, Huchon C, Fritel X, Lafay-Pillet MC, Chapron C, Panel P. Aspectos clínicos de la endometriosis. EMC - Ginecología-Obstetricia 2015;51(4):1-14 [Artículo E – 149-A-10].

frontiers in SURGERY

REVIEW ARTICLE
published: 29 September 2014
doi: 10.3389/fsurg.2014.00036

Current concepts in the management of necrotizing fasciitis

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Necrotizing fasciitis (NF) is a severe, rare, potentially lethal soft tissue infection that develops in the scrotum and perineum, the abdominal wall, or the extremities. The infection progresses rapidly, and septic shock may ensue; hence, the mortality rate is high (median mortality 32.2%). Prognosis becomes poorer in the presence of co-morbidities, such as diabetes mellitus, immunosuppression, chronic alcohol disease, chronic renal failure, and liver cirrhosis. NF is classified into four types, depending on microbiological findings. Most cases are polymicrobial, classed as type I. The clinical status of the patient varies from erythema, swelling, and tenderness in the early stage to skin ischemia with blisters and bullae in the advanced stage of infection. In its fulminant form, the patient is critically ill with signs and symptoms of severe septic shock and multiple organ dysfunction. The clinical condition is the most important clue for diagnosis. However, in equivocal cases, the diagnosis and severity of the infection can be secured with laboratory-based scoring systems, such as the laboratory risk indicator for necrotizing fasciitis score or Fournier's gangrene severity index score, especially in regard to Fournier's gangrene. Computed tomography or ultrasonography can be helpful, but definitive diagnosis is attained by exploratory surgery at the infected sites. Management of the infection begins with broad-spectrum antibiotics, but early and aggressive drainage and meticulous debridement constitute the mainstay of treatment. Postoperative management of the surgical wound is also important for the patient's survival, along with proper nutrition. The vacuum-assisted closure system has proved to be helpful in wound management, with its combined benefits of continuous cleansing of the wound and the formation of granulation tissue.

Keywords: necrotizing fasciitis, Fournier's gangrene, gas gangrene, surgical debridement

INTRODUCTION

The term necrotizing fasciitis (NF) describes a group of relatively uncommon, but life-threatening infections of the skin, soft tissues, and muscles, which tend to progress rapidly through the fascia planes, causing gradual destruction of the fascia at a rate reaching 2–3 cm/h. Developing in the lower or upper extremities, the perineum and genital area (Fournier's gangrene) and in the abdominal wall, its swift clinical course is correlated with polymicrobial infection and synergy, which usually co-exists (1, 2). The majority of cases present anaerobic bacteria that proliferate in a hypoxic environment and produce gas, which accumulates in the soft tissue spaces, giving the characteristic image of gas gangrene on plain X-rays and computed tomography (CT) scans (3).

Early diagnosis of NF is mandatory. Any delay could prove fatal, given its association with more extensive surgery, higher rates of amputation, and higher mortality rates. Furthermore, if left untreated, the infection could lead to systemic inflammatory response syndrome (SIRS).

Necrotizing fasciitis was first recognized in 500 BC, when Hippocrates reported a clinical description of a complication of erysipelas disease, resembling the current description of NF (4). In France, Claude Colles, chief surgeon of the Hotel Dieu in Lyon, described a condition in 1783 that was very similar to modern descriptions of NF (5). The first description of "modern" NF was made by Joseph Jones, a military surgeon of the army of the Confederate States of America. In 1871, he reported 2,642 cases of gas gangrene treated in hospital during the American Civil War, with a mortality rate of approximately 46% (6). In 1883, Jean Alfred Fournier described a syndrome with necrosis of the perineum in five men; this type of NF was subsequently given his name and is known as *Fournier's gangrene* (7). In 1924, Meleney reported an association with beta-hemolytic streptococcus A in a study of a series of hospitalized cases in Beijing. Thereafter, these cases were described for several decades as *Meleney's gangrene* (8). In 1952, the term "*necrotizing fasciitis*" was proposed by Wilson, as a more accurate description of this disease (9). The late 1980s witnessed a renewed interest in this pathology. Stevens reported that, among 20 patients who presented with streptococcal shock, 11 were diagnosed as having NF. The disease was popularized by the media as "flesh-eating bacteria syndrome" (10).

EPIDEMIOLOGY

The annual incidence of NF is estimated at 500–1,000 cases annually, and its prevalence globally has been reported to be 0.40 cases

per 100,000 population (11). It is seen to have a predilection for men, with a male-to-female ratio of 3:1; this ratio is mainly correlated with the increased incidence of Fournier's gangrene in men. The disease affects all age groups, although middle-aged and elderly patients (over 50 years of age) are more likely to be infected (1). The median mortality ratio of NF is a controversial issue. In their review of the literature, Goh et al. concluded that the median mortality ratio was 21.5% (12). However, its range in the literature is extensive, varying from 8.7 to 76% (13). In regard to NF of the extremities, the mortality rate is slightly lower than that recorded for abdominal and perineal infections (14, 15). Patients with Fournier's gangrene that has not spread to the abdominal wall tend to have a better survival. As a general rule, without treatment, the mortality rate approaches 100%. Anaya et al. (16) have demonstrated that infection of the lower extremities is the most common site of NF (57, 8%), followed by the abdomen and the perineum. NF of the upper limbs is rare compared to that of the lower limbs (17).

ETIOLOGY

Trauma is the most common identifiable etiology. The majority of patients have a history of minor or major traumas, generally involving external injuries and surgical wounds. Appendicitis with perforation, infection following the repair of an incarcerated hernia, perforated diverticulitis, necrotic cholecystitis, gastroduodenal perforation, small bowel perforation, and obstructive colon cancer with perforation rank among the most frequent causes of complicated intra-abdominal infections that can lead to NF. Notably, the incidence of NF resulting from a surgical wound in the chest wall is greater than that recorded from analogous wounds in the lower abdominal wall. Such cases present a high risk of osteomyelitis, which substantially increases the mortality of these patients.

Fournier's gangrene is often the result of surgical wounds, skin abscess drainage, and pressure sores. It can also present as a complication of colorectal disease due to anorectal infection, ischiorectal abscesses, and colon perforations. Other causes include a possible urethral stricture and a trauma from an indwelling Foley catheter. In women, it has commonly been ascribed to Bartholin abscesses or vulval skin infections.

In Asia, consumption of raw or undercooked seafood or injury by fish fins can lead to NF (12). In this group of infections, bacteria such as *Vibrio* spp., *Aeromonas* spp., and *Shewanella* spp. are commonly involved and are usually known as "marine bacteria" (18).

CO-MORBIDITIES AND RISK FACTORS

The most frequent co-morbidity in patients with NF is diabetes mellitus. The prevalence of diabetes mellitus in patients with any type of NF ranges between 40 and 60% (12, 19). Other common co-morbidities include liver cirrhosis, chronic heart failure, obesity, alcohol abuse, immunodeficiency, systemic lupus erythematosus, Addison's disease, pre-existing hypertension, and peripheral vascular disease (20, 21). A septic condition and hypotension at the time of admission are significant predicting factors for mortality and outcome. Chronic renal failure is another indisputable predisposing factor for higher mortality in patients with NF. Elevated serum creatinine, along with elevated blood urea, is also strongly associated with higher mortality rates (22).

The use of non-steroidal anti-inflammatory drugs (NSAIDs) or steroid drugs can suppress fever, thereby hampering the diagnosis of NF (8). Furthermore, Martinschek et al. have demonstrated that an increase of serum creatine kinase and lactate parameters, as well as a decrease of serum antithrombin III, proved by a low INR, are significant parameters for an unfavorable outcome, particularly in regard to Fournier's gangrene (20). Other risk factors, such as systemic acidosis, low hematocrit, and albumin levels, are also strongly linked with a high mortality, while concomitant conditions increase the mortality rate further (23). Patients displaying accompanying diseases are usually characterized as critically ill and require prolonged intensive care. Diabetes, in particular, is a disease, which often combines many of the above co-morbidities, and is hence susceptible to the development of NF (24). However, the presence of diabetes mellitus has not been proven to affect mortality (25).

Advanced age constitutes another risk factor for higher incidence and mortality, although somewhat controversial. Large population-based studies have shown that advanced age is a strong, independent predictor of mortality (26). A study by Rea and Wyrick reported a mortality rate of 67% in patients over 50 years of age and 4% in patients under that age (27). Other studies have concurred that advanced age is a risk factor for higher mortality, but only when accompanied by other risk factors such as renal failure, or delayed surgical debridement (24). This combination is also associated with advanced disease and a more fulminant infection.

Whether or not patients with NF show a gender predilection with regard to mortality is also a topic of debate. Fournier's gangrene shows male predominance with a reported rate of 96% (28). Czymek et al. found that mortality was significantly higher among females (50% F vs. 7.7% M) (29). However, studies involving a larger study population have concluded that there is no statistical correlation between female gender and increased mortality (30).

The extension and variability of infection are assumed to increase mortality. NF can affect an entire extremity within 24 h (31), but it can also show slow progression over a period of several weeks. In some patients, the disease remains dormant and unexpectedly spreads rapidly without any readily apparent reason (24). The factors that lead to the fulminant form of NF, with a potentially lethal outcome within 24 h, remain unidentified (32). Some studies indicate that the spread of gangrene does not relate to a poorer prognosis. Notwithstanding, the extension of gangrene to the abdominal wall has been reported to be directly related to increased mortality (33).

PATHOPHYSIOLOGY

Infection begins in the hypodermis or the superficial fascia, as the more superficial layers (dermis and epidermis) are not affected at the beginning (34). The synergistic action of the virulence factors of bacteria and the specific factors of the host are implicated in the development of NF. The extension of the infection and necrosis is facilitated by the synergy between the different bacteria and toxins and the enzymes they produce (35). An anaerobic environment promotes growth of anaerobic bacteria. Necrosis of

the hypodermis and superficial fascia is directly related to bacterial enzymes that destroy the fascia and fat, and secondarily to vascular origin. Invasive bacteria cause thrombosis of the nutrient vessels, which are located in the hypodermis, leading to tissue ischemia aggravated by the presence of edema. Tissue ischemia promotes infectious dissemination leading to skin necrosis at a later stage. It also explains the intense pain phenomena that are usually observed, especially when the nerve branches are also affected. Such cases also display signs of regional hypoesthesia/anesthesia. The fascial and hypodermic necrotic spread is greater than the overlying skin changes. Lymphangitis and lymphadenopathy are rare due to thrombosis of the vessels. Gas formed by anaerobic bacteria may lead to crepitus.

MICROBIOLOGY

Recent studies have concluded that NF can be classified into four types, according to microbiological findings (35)(**Table 1**). The most common is type I, also known as the *polymicrobial type*. Accounting for 70–90% of cases, it typically affects patients with several co-morbidities, such as diabetes mellitus. Two or more pathogens are implicated in this infection (with an average of 4.4 species) and it is mostly found in the trunk and perineum.

Type II, otherwise known as monomicrobial, is defined as infection with beta-hemolytic Streptococcus A (*Streptococcus pyogenes*). *S. pyogenes* is commonly found in young and healthy patients with NF of the extremities. Its pathogenesis is explained by the several virulence factors produced by this organism (36). In some cases, the infection can be associated with *Staphylococcus aureus*. *S. aureus* secretes toxins, which cause leukocyte destruction and tissue necrosis. Found in the fulminant forms of NF, *S. aureus* is not easy to manage, especially when the responsible pathogen is the methicillin-resistant *S. aureus* (MRSA), which is the case in 10–30% of all patients. Typically, these infections occur after small incisions, and appear to be highly correlated with the use of NSAIDs (37). Specifically observed in patients without serious co-morbidities, the infection is most often found in the limbs. The risk of toxic shock syndrome is increased in such cases, and the outcome is unfavorable.

Type III includes monomicrobial infections involving the *Clostridium* species or Gram-negative bacteria. *Clostridium* species are anaerobic bacteria that can be produced by external injuries (deep wound or crush injury causing local devascularization) or surgical wounds (intestinal and obstetric). *Clostridium* infections are currently more frequent among drug addicts (38), and *C. perfringens* is the most common bacterium of the *C.* species. *Vibrios* spp. infections can also lead to type III NF. *Vibrio vulnificus* is a marine bacterium frequently isolated in Asia (21). *Aeromonas hydrophila* is found in freshwater or low salinity water and in the soil. The clinical symptoms of infections by these two bacteria are similar; hemorrhagic blisters, lesions, and purpuric necrosis are the dominant symptoms, along with the extremely rapid spread of disease.

Finally, type IV is the result of fungal infections, mainly *Candida* spp. and Zygomycetes. This type is found mainly in the immunocompromised host. Infections by these fungi often occur after trauma; the clinical image is aggressive and rapidly extensive, particularly in immunocompromised patients.

Microbiological diagnosis is obtained in almost 75% of all cases of NF (39), and is based on the good quality of the pre- and intra-operative samples and blood cultures. Blood cultures are positive in 25% of all cases, while cultures obtained from the site of injury during surgical debridement result as positive in 80% of cases (40).

DIAGNOSIS

CLINICAL SIGNS AND SYMPTOMS

Patients with NF usually present with the classic triad of symptoms: local pain, swelling, and erythema (12). Tachycardia (>100 beats/min) and fever are the most common vital sign abnormalities, followed by hypotension (SAP < 100 mmHg) and tachypnea (>20/min). These vital sign abnormalities, along with the skin erythema, are most useful in securing the diagnosis of NF from other soft tissue infections (41). The infected site displays tenderness, sclerosis, skin necrosis, and hemorrhagic bullae (42).

Depending on the development of the infection, the clinical image described above may not always be evident. Consequently, two groups of symptoms are considered, namely early and advanced symptoms (43). The most common early signs are erythema, local warmth, skin sclerosis, and edema. However, in the fulminant form of disease, the patient is critically ill with signs and symptoms of severe septic shock and multiple organ dysfunction syndrome, along with extensive necrosis of soft tissue. In this case, the clinical picture deteriorates rapidly within a few hours; pain is severe and usually manifests before the cutaneous signs. Remarkably, pain seems to be disproportionate to the clinical findings.

In contrast, the subacute form of the disease has a relatively slow clinical course, which may endure for days or weeks. The early clinical status of the subacute form is the result of an existing

Table 1 | Classification of responsible pathogens according to type of infection.

Microbiological type	Pathogens	Site of infection	Co-morbidities
Type I (polymicrobial)	Obligate and facultative anaerobes	Trunk and perineum	Diabetes mellitus
Type II (monomicrobial)	Beta-hemolytic streptococcus A	Limbs	
Type III	*Clostridium* species	Limbs, trunk, and perineum	Trauma
	Gram-negative bacteria		Seafood consumption (for *Aeromonas*)
	Vibrios spp.		
	Aeromonas hydrophila		
Type IV	*Candida* spp.	Limbs, trunk, perineum	Immunosuppression
	Zygomycetes		

condition leading to infection. The patient often presents with a skin infection, such as folliculitis or abscess, gangrene on the extremities, pressure sore(s), or a complicated surgical wound. Erythema or skin sclerosis is present at the site of infection. The patient usually feels pain at the site of the injury, and this is a very strong diagnostic hint. However, local nerves can also be infected, usually resulting in the partial loss of sensation (44).

As the infection develops, the pain becomes more intense. The clinical image is characterized by symptoms of general toxicity including fever, dehydration, confusion, dizziness, diarrhea, nausea, vomiting, weakness, and malaise (19). If the patient remains undiagnosed or untreated, the clinical status deteriorates rapidly. The cutaneous symptoms may progress to blisters and bullae, ultimately leading to circumscribed necrosis of the skin. Initially, the bullae contain serous fluid, but, as the infection progresses, they may become hemorrhagic. Gas formation can lead to crepitus in the overlying skin, indicating anaerobic infection, such as *C. perfringens*. This classical skin condition does not normally present until day five or later (45).

Symptoms of septic shock or MODS frequently appear in the late phase of its subacute form. As a result, the patient displays hypotension, elevated white blood cell count, metabolic acidosis, coagulopathy, changes in mental status, and weakness. In this late stage of the disease, the patient looks apathetic and indifferent. Additional symptoms pertaining to co-morbidities may also coexist.

The symptoms of disease are not characteristic; hence, it is often misdiagnosed as cellulitis or abscess. The most consistent feature of early NF is pain, which is not in proportion to the swelling or erythema (46). Moreover, as a consequence of the enzymatic and toxin action, tenderness to palpation extends beyond the area of apparent involvement, to spread along fascial plains. In addition, the margins of involvement are usually indistinct, and lymphangitis is rarely present, given that the infection is in the deep fascia rather than the skin (47).

Cases with upper limb infection do not always present a typical picture. In this instance, patients may appear systemically well (21). Another cause that complicates diagnosis is the absence of fever in most cases. Several drugs, such as NSAIDs, steroids, and antibiotics can lower body temperature and mask fever. For that reason, the absence of pyrexia does not necessarily exclude NF (12, 41).

Fournier's gangrene has a slightly different clinical course. It usually begins with pain and itching of the perineum and scrotal skin. In genitourologic types of Fournier's gangrene, the pathogens pass through the Buck's fascia of the penis and spread along the Darto's fascia of the scrotum and penis, Colle's fascia of the perineum, and Scarpa's fascia of the lower abdominal wall (19). Additional necrosis of the superficial fascia and fat produces a thin watery malodorous fluid and crepitus. Similarly, patients may present high fever, anxiety, altered mental status, leukocytosis, shock, and tachypnea, when shock is about to develop. Once clinical signs become obvious, the appearance resembles the late phase of NF, with visible bruising, bullae and cutaneous necrosis due to the extension of the necrotizing process.

BEDSIDE AND LABORATORY TESTS

Laboratory results in this disease are not usually specific. However, certain laboratory findings can help the clinician to differentiate NF from other skin diseases, such as necrotizing soft tissue infection. Specifically, leukocytosis is a common feature in patients with NF (48), and white blood cell count in excess of 20,000/L is highly suspect. Blood urea nitrogen >18 mg/dL and serum creatinine >1.2 mg/dL reflect ongoing renal failure, which is typically present in these patients. Serum creatine kinase is also elevated (CK) in patients with severe sepsis and MODS (48). Majeski et al. suggested that C-reactive protein >16 mg/dL or creatine kinase >600 IU/L generally precludes group A β-hemolytic streptococcal infection (49). However, this recommendation is rarely followed by clinicians.

Several laboratory-based scoring systems have been proposed for establishing early diagnosis of NF (50). The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) proposed by Wong et al. (51–53) is one such example (**Table 2**). In addition to enabling early recognition of the disease, this score can also facilitate the classification of patients into risk categories, and help in the allocation of diagnostic resources. Another scoring system is the Fournier's Gangrene Severity Index (FGSI) that has shown remarkable success in helping to determine whether or not the patient requires surgical debridement (54).

Bedside tests, imaging tests [CT or magnetic resonance imaging (MRI)], or frozen section biopsy can be carried out in patients with equivocal clinical findings and a moderate or high risk of NF based on the LRINEC score (>5). The finger test and frozen section biopsy are used as complementary diagnostic modalities in patients with an equivocal diagnosis. Surgical exploration is regarded as the mainstay for investigation and treatment. The *finger test* is a bedside procedure performed under local anesthesia by which, a 2-cm incision is made down to the deep fascia, at which level gentle probing of the index finger is applied. The presence

Table 2 | LRINEC scoring system for necrotizing fasciitis.

Variable	Score
CRP (mg/L)	
>150	4
WBC (g/L)	
<15	0
15–25	1
>25	2
Hemoglobin (g/dL)	
>13.5	0
11–13.5	1
<11	2
Sodium (mmol/L)	
<135	2
Creatinine (μmol/L)	
>141	2
Glucose (mmol/L)	
<10	1

of characteristic "dishwater pus," along with the lack of bleeding and lack of tissue resistance to blunt finger dissection are positive findings correlated with NF. Another useful bedside test is an incisional biopsy down to the fascial level with an immediate frozen section, culture, and Gram stain (55, 56).

The combination of surgical exploration and microbiological and histopathological analysis of 1 cm^3 of soft tissue is considered the gold standard for confirming diagnosis, when the latter is ambivalent.

IMAGING TESTS

Imaging investigation can help to establish the diagnosis of NF especially in equivocal cases. Although plain radiography has low sensitivity and specificity, it is capable of showing gas formation in the soft tissue (33), which is present in almost half of all patients, and it strongly indicates infection by the *Clostridium* species. CT and MRI are more sensitive and specific than plain radiography. A CT scan can show the extent of tissue infection, fascial swelling, inflammation, and gas formation. An MRI scan provides better accuracy than CT, though not widely used, due to cost. Ultrasonography is also a feasible option, providing useful information concerning the nature and extent of infection, especially when the diagnosis is unclear (57). In terms of diagnosis, the most significant finding is the hyperechoic foci with reverberation artifact and dirty shadowing at the site of infection (57), representing the subcutaneous gas. However, ultrasonography requires a highly skilled operator; this requirement hampers its use in the ICU, where patients with NF are usually treated.

TREATMENT

ANTIBIOTIC TREATMENT

Since ischemia and hypoxia compromise the adequate delivery of antibiotics to the infection site, conservative treatment with antibiotics alone has little value in the management of NF (58). However, they play a significant role in surgical management of the infection. Patients should be immediately treated with broad-spectrum antibiotics, when NF is suspected. The empirical usage of antibiotics is based on the microbiological classification of NF. Antibiotic treatment of a polymicrobial infection should be based on history, Gram stain, and culture. Initial treatment includes ampicillin or ampicillin–sulbactam combined with metronidazole or clindamycin (59). Anaerobic coverage is quite important for type 1 infection; metronidazole, clindamycin, or carbapenems (imipenem) are effective antimicrobials. Broad gram-negative coverage is necessary as an initial empirical therapy for patients who have recently been treated with antibiotics, or been hospitalized. In such cases, antibiotics such as ampicillin–sulbactam, piperacillin–tazobactam, ticarcillin–clavulanate acid, third or fourth generation cephalosporins, or carbapenems are used, and at a higher dosage.

Type 2 disease is treated with antibiotics against *S. pyogenes* and *S. aureus*, which usually coexist with the former. Hence, first or second generation of cephalosporins are used for the coverage of methicillin-sensitive *Staphylococcus aureus* (MSSA). MRSA tends to be covered by vancomycin, or daptomycin and linezolid in cases where *S. aureus* is resistant to vancomycin. Some studies suggest that clindamycin is superior to penicillin in managing streptococcal infections (60), but this has yet to be satisfactorily proven. Another study has proposed that clinicians should consider adding clindamycin to the beta-lactam antibiotic regimen when NF or myositis is present (61).

Type 3 NF should be managed with clindamycin and penicillin, which cover the *Clostridium* species. If Vibrio infection is suspected, the early use of tetracyclines (including doxycycline and minocycline) and third-generation cephalosporins is crucial for the survival of the patient, since these antibiotics have been shown to reduce the mortality rate drastically (59).

Finally, type 4 NF can be treated with amphotericin B or fluoroconazoles, but the results of this treatment are generally disappointing.

As in every empirical antibiotic therapy, the dosage should be tapered, based on the results of the initial blood, wound, and tissue cultures, but continued until the infection is under control and for at least 48 h after clinical and hemodynamic stabilization of the patient has been achieved. Antibiotics should be administered for up to 5 days after local signs and symptoms have resolved (62). The mean duration of antibiotic therapy for NF is 4–6 weeks.

Intravenous immunoglobulin (IVIG) has recently been described as a reasonable and desirable option for neutralizing streptococcal toxins (63). There is evidence that a high dose of IVIG may prove beneficial in severe streptococcal infections (64), but this has yet to be demonstrated with randomized studies.

SURGICAL MANAGEMENT

Emergency surgical debridement of the affected tissues is the primary management modality for NF. Surgical debridement, necrosectomy, and fasciotomy are the main aspects of surgical treatment. Surgical intervention is life-saving and must be performed as early as possible, since a delay in treatment beyond 12 h in fulminant forms of NF can prove fatal. Surgical debridement should be repeated during the next 24 h or later, depending on the clinical course of the necrotizing infection and vital functions. Many studies have pointed out that timing and the extent of the first debridement are the most important risk factors in terms of increased mortality rate. Mock et al. have shown that the relative risk of death was 7.5 times greater in cases of restricted primary debridement (65), whereas, other studies reported that the mortality rate was nine times greater when primary surgery was performed 24 h after the onset of symptoms (19).

Surgical management is indicated especially for patients displaying intense pain and skin color change, such as edema and/or ecchymoses, or signs of skin ischemia with blisters and bullae (**Figure 1**). Patients must be operated on urgently when they present with altered mental status, hypotension, an elevated band formed in the differential WBC count, and metabolic acidosis. These clinical and laboratory signs indicate that the patient has developed SIRS or MODS, and the NF score has risen to phase 3. The mortality rate in this phase is extremely high, reaching almost 70% (24).

Incisions are performed parallel to Langer's lines to achieve better surgical wound healing and less scarring. Surgery also minimizes the overall tissue loss as it inhibits infection spread to the fascial plane, reducing the need for amputation (66). After the release of pus and/or hemorrhagic fluid through incisions,

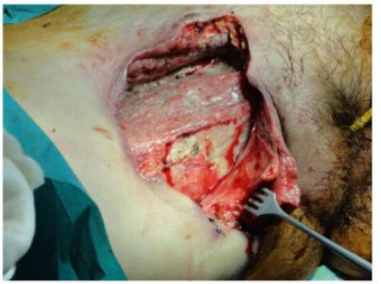

FIGURE 1 | The excision of the necrotic tissues should extend until healthy tissue is found, but should be limited to the edges of the infection.

ventricle incisions are made, keeping the wound open in order to allow drainage and to remove additional necrotic tissue.

Patients with NF should be closely monitored during the next 24 h; surgical wounds and tissue viability should be checked. Complicated surgical wounds command a "second-look operation" with radical surgical debridement. Patients with NF can require from 5 up to 40 additional operations, depending on the timing of the first surgical debridement, the adequacy of the primary debridement and necrosectomy, signs of hemodynamic instability, and concomitant illnesses, all of which are associated with a high mortality rate (67). Evidence of hemodynamic instability demands immediate resuscitation, transfer to an intensive care unit, nutritional support, and enteral feeding.

The extent of tissue extracted depends on the body region, which is infected. As a general rule, debridement will extend until healthy tissue is found, though some authors recommend that excision should be limited to the edges of infection (68). The general consensus is that careful trimming of the potentially salvageable soft tissue is also required (while non-infected skin remains unattached) (**Figure 1**) (69).

Nutritional support is required from the first day of the patient's admission to hospital (preferably the ICU), to replace lost proteins and fluid from large wounds and/or the resultant toxic shock. Metabolic demands are similar to those of other major trauma or burns, which means that the patient needs twice the basic caloric requirements.

Necrotizing fasciitis of the abdominal wall requires special consideration. Skin incision must be performed in the longitudinal direction along the muscle-fascial layers of the inner abdominal wall until healthy fascia is found. Parallel or ventricle incisions are not performed because the bridges of skin and skin islands will not usually survive. Postoperative management of abdominal wall wounds involves serial dressing changes over the following days, until the wound is free of recurrent or ongoing infection. The use of a vacuum-assisted wound closing device (VAC) can also be helpful. Aggressive surgical debridement should be repeated in cases of infection progression across the deep fascial planes of the abdominal wall. The extension of infection into the bowel, resulting in bowel ischemia, bowel obstruction, and peritonitis, is not an uncommon phenomenon. In such cases, an exploratory laparotomy is needed to estimate the extent of infection inside the abdominal wall. A radical surgical debridement at the site of infection and the retroperitoneal site is performed, followed by partial bowel excision, depending on the part of the bowel (usually right colon), which has been infected. A diverting colostomy is performed with multiple drainages of the infected intra-abdominal fluid collections. Surgical management of colonic perforation complicated with peritonitis is a topic with considerable debate in the literature. Hartmann's resection has been considered the procedure of choice in cases with diffuse peritonitis and remains a safe technique for colectomy in a perforated colon, especially in elderly patients with multiple co-morbidities. As concerns NF, Hartmann's resection is particularly preferred, since it allows time for reconstruction of the abdominal wall defects, and the diverting colostomy can be closed at a second stage. The primary defect on the abdominal wall is usually large and is repaired with advanced flaps using an abdominoplasty technique, biological mesh, or skin grafts (70).

Fournier's gangrene also requires special consideration. A pressure sore, perineal abscess, or paraplegia frequently predispose to the spread of infection into the scrotum, inguinal region, and lower abdominal wall (**Figure 2**). An orchiectomy, cystostomy, or diverting colostomy is often required dependent on whether the infection has extended to the scrotum, perineal area, or lower abdominal wall, respectively. Surgical management includes wide tissue incision, radical debridement, and drainage of the areas involved (71). The wound is washed with hydrogen peroxide, saline, and 1% povidone iodine solution. Finally, it is covered with occlusive and adsorptive dressing with antiseptic properties. Again the use of VAC can accelerate the recovery period, providing clean surgical wounds. Once the patient is clinically and hemodynamically stable, they can be submitted to reconstructive surgery.

Necrotizing fasciitis of the extremities needs special consideration. The extent of debridement is very important as additional fasciotomies are needed in cases with compromised tissue viability (67). The amount of tissue that needs to be excised is a controversial issue, because the skin in the extremities usually appears normal.

A study by Andreasen et al. showed that despite a normal external appearance soft tissue in patients with NF has extensive vascular microthromboses as well as vasculitis. The risk of full-thickness necrosis is high, and this can complicate a primary treated surgical wound (72). Consequently, it is recommended that clinicians also remove healthy soft tissue, bearing in mind that extremities showing NF may require amputation. The criteria for amputation have been recommended by Tang et al. (73), the most significant of which is extensive soft tissue necrosis with involvement of the underlying muscles and rapidly progressing infection with a large area of tissue necrosis. Other conditions that may justify amputation, are the presence of concurrent medical disease with high anesthetic risk (ASA score III and above), and the presence of shock

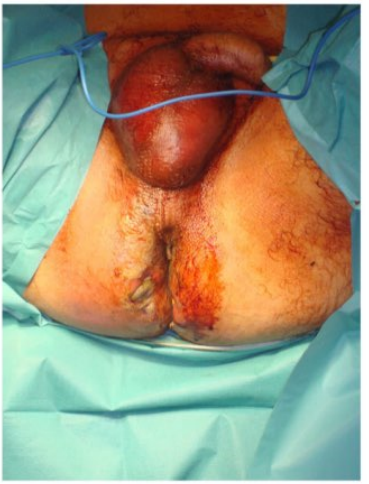

FIGURE 2 | A severe case of Fournier's gangrene with excessive erythema and edema in the perineal and gluteal regions as well as skin necrosis with bullae.

(toxic or cardiogenic) requiring treatment with more than one inotrope. Furthermore, concurrent vascular insufficiency further increases the need for amputation, especially when the patient is diabetic. Amputation is usually considered as a shorter procedure associated with less blood loss than a radical debridement. This explains why patients with hypotension and shock are best treated with amputation, as they cannot endure additional protracted operations. Studies have proved that, although amputation is not seen to reduce mortality, patients undergoing this procedure required fewer repeat operations, which is extremely important for patients presenting severe co-morbidities or a fulminant form of NF (74).

Recent reports of NF of the axilla require special consideration. A delay in surgical debridement can prove lethal, even more so than an infection in a common site (75). Tissue in the axillary region that is rich in blood vessels and lymphatics enables the infection to spread rapidly to distant sites. The clinician should keep in mind the need to avoid axillary contractures, after covering the exposed neurovascular network (75). Again, surgical reconstruction of the wound is essential for successful wound closure and should be planned after clinical stabilization (76, 77).

USE OF VACUUM-ASSISTED CLOSURE DEVICE

Lately, many surgeons worldwide have started using vacuum-assisted closure (VAC) therapy for fast and effective wound closure

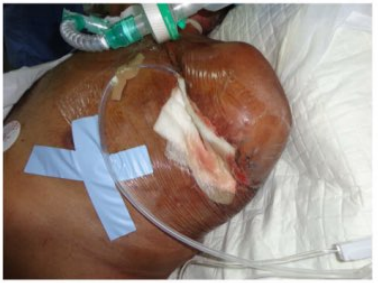

FIGURE 3 | After surgical debridement, the use of the VAC system helps wound healing by absorbing excess exudates; reducing localized edema, and finally drawing wound edges together.

(78). Several studies in the general surgery, orthopedic, and gynecological literature support the use of VAC devices. A VAC device consists of a sterile, open-cell foam sponge that is placed in the wound, the size of which is adjusted to the wound size. This is covered with a transparent adhesive drape to create an air-tight environment. The sponge is connected to a portable vacuum pump by means of non-collapsible tubing. Evacuation is applied to the sponge using the pump, which provides continuous negative pressure. The VAC device improves wound healing by providing microstrain (**Figure 3**). Several randomized studies have demonstrated improved wound healing and a significant reduction of wound surface area in full-thickness wounds treated with VAC devices as compared to conventional gauze therapy (79).

The VAC dressing must be changed every 24–72 h. VAC therapy has several benefits in wound management, with wound area reduction and formation of granulation tissue being the most prominent. Other benefits, such as effective wound cleaning and the ability to remove the exudate render VAC a promising adjuvant therapy for wound closure.

FUTURE THERAPIES

As a life-threatening condition, NF demands new management strategies. Unfortunately, there are no single new therapies that can manage NF; they all seem to play an assistive role. Undoubtedly, the use of VAC has many benefits in wound healing, and it will be adopted by more physicians in the future.

A study by Anaya et al. (13) highlighted the role of IVIG in the treatment of NSTI, especially if NSTI is associated with group A streptococcal infection. The authors concluded that the use of IVIG seemed rational in patients with group A streptococcal infection who developed streptococcal toxic shock syndrome and in those with a high mortality risk (advanced age, hypotension, and bacteremia). However, relevant studies investigating its use are contentious and difficult to compare because of the small number of patients and the different methodologies used.

An interesting study by Lu et al. (80) showed that kallistatin, originally found to be a tissue kallikrein-binding protein, can increase the survival of group A streptococcus infected mice. The researchers concluded that kallistatin significantly increased the survival rate of GAS-infected mice, and also reduced local skin damage and bacterial counts. Moreover, its use improved infiltrating cell viability in the local infection site, as well as bacterial clearance activity of immune cells (81). The efficiency of intracellular bacterial killing in neutrophils was directly enhanced by kallistatin administration. Several inflammatory cytokines, including tumor necrosis factor alpha, interleukin 1β, and interleukin 6, in local infection sites were reduced by kallistatin. Furthermore, kallistatin treatment was reported to reduce vessel leakage, bacteremia, and liver pathology after local infection. However, further studies are warranted before safe conclusions can be drawn concerning its use in gas-forming infections, such as NF (82).

CONCLUSION

Necrotizing fasciitis is a rare but life-threatening condition, with a high mortality rate (median mortality 32.2%) that approaches 100% without treatment. Numerous conditions are associated with this pathology, such as diabetes mellitus, immunosuppression, chronic alcohol disease, chronic renal failure, and liver cirrhosis, which can be conductive to the rapid spread of necrosis, and increase in the mortality rate. The diagnosis of NF is difficult and the differential diagnosis between NF and other necrotizing soft tissue infections more so. However, the clinician should do their utmost to secure the diagnosis of NF, as a delay in diagnosis can be fatal, and septic shock is inevitable if the disease remains untreated. The characteristic of NF is the clinical status change over time. The early clinical picture includes erythema, swelling, tenderness to palpation, and local warmth; once the infection develops, the infection site presents skin ischemia with blisters and bullae. The diagnosis of NF can be secured faster with the use of laboratory-based scoring systems, such as the LRINEC score or the FGSI score, especially in cases of Fournier's gangrene. However, the diagnosis is definitely established by performing explorative surgery at the infected site.

Management of the infection begins with antibiotic treatment. In the majority of cases with NF (70–90%) the reasonable pathogens are two or more, suggesting the use of broad-spectrum antibiotics. The value of antibiotic treatment in NF is relatively low, and early and aggressive drainage and debridement is required. In NF of the extremities, the clinician should consider amputating the infected limb, although this will not reduce the risk of mortality. Finally, postoperative management of the surgical wound is important, along with proper nutrition of the patient. The use of VAC therapy in wound management has greatly improved the results of postoperative management.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 08 April 2014; paper pending published: 31 May 2014; accepted: 24 August 2014; published online: 29 September 2014.
Citation: Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P and Machairas A (2014) Current concepts in the management of necrotizing fasciitis. Front. Surg. 1:36. doi: 10.3389/fsurg.2014.00036
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery.

Necrotizing Soft Tissue Infection: Diagnostic Accuracy of Physical Examination, Imaging, and LRINEC Score

A Systematic Review and Meta-Analysis

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Objective: We sought to summarize accuracy of physical examination, imaging, and Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score in diagnosis of necrotizing soft tissue infection (NSTI) in adults with a soft tissue infection clinically concerning for NSTI.

Summary of Background Data: NSTI is a life-threatening diagnosis. Delay to diagnosis and surgical management is associated with increased mortality.

Methods: We searched 6 databases from inception through November 2017. We included English-language studies reporting diagnostic accuracy of testing or LRINEC Score. Outcome was NSTI confirmed by surgery or histopathology. Two reviewers screened all citations and extracted data independently. Summary measures were obtained from the Hierarchical Summary Receiver Operating Characteristic model.

Results: From 2,290 citations, we included 23 studies (n = 5982). Of physical examination signs, pooled sensitivity and specificity for fever was 46.0% and 77.0% respectively, for hemorrhagic bullae 25.2% and 95.8%, and for hypotension 21.0% and 97.7%. Computed tomography (CT) had sensitivity of 88.5% and specificity of 93.3%, while plain radiography had sensitivity of 48.9% and specificity of 94.0%. Finally, LRINEC $\geq$ 6 had sensitivity of 68.2% and specificity of 84.8%, while LRINEC $\geq$ 8 had sensitivity of 40.8% and specificity of 94.9%.

Conclusions: Absence of any 1 physical examination feature (eg, fever or hypotension) is not sufficient to rule-out NSTI. CT is superior to plain radiography. LRINEC had poor sensitivity, and should not be used to rule-out NSTI. Given the poor sensitivity of these tests, a high clinical suspicion warrants early surgical consultation for definitive diagnosis and management.

Keywords: necrotizing soft tissue infection, necrotizing fasciitis, Laboratory Risk Indicator for Necrotizing Fasciitis, septic shock, critical care, computed tomography

(*Ann Surg* 2018;xx:xxx–xxx)

Necrotizing soft tissue infection (NSTI, commonly referred to a "necrotizing fasciitis") is a life-threatening skin and soft tissue diagnosis that is characterized by widespread tissue necrosis.[1,2] NSTI is often severe, rapidly progressive, and associated with sepsis and multisystem organ failure. Despite advances in care, mortality from NSTI remains high, estimated between 20% and 30%.[3,4] Rapid identification of NSTI and urgent surgical debridement of necrotic tissue are critical,[1,2] and delays to surgical intervention are associated with increased mortality.[5] NSTI is a rare disease, with an incidence of 0.3 to 5 per 100,000,[4,6] and therefore differentiation of NSTI from other more common clinical entities such as cellulitis can be difficult. Commonly described risk factors such as intravenous drug use, immunosuppression, and diabetes mellitus may also be seen in other severe skin infections.[7] To assist in making the diagnosis of NSTI, clinicians often rely upon physical examination, diagnostic imaging, and clinical decision instruments; however, little evidence validates the diagnostic utility of these assessments.

Some classic physical examination signs have been described to differentiate NSTI from other skin and soft tissue infections. These include erythema, soft-tissue edema, severe pain (often described as "pain out of proportion"), fever, and hemorrhagic bullae.[8] The presence of hypotension and shock are also thought to indicate those likely to have NSTI.[5] Various imaging modalities have also been utilized to help make the diagnosis. Plain radiography may demonstrate gas in the soft tissues.[1,2] Computed tomography (CT) performed with contrast may demonstrate fascial air or gas, soft tissue edema, or enhancement of the fascia.[9] Although thought to be more accurate, CT is time-consuming and can delay definitive surgical management.

Finally, laboratory values are often utilized to aid in the diagnosis of NSTI. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is a diagnostic clinical decision instrument validated for differentiating NSTI from other soft tissue infections.[10] LRINEC utilizes 6 laboratory serum parameters including white blood cell (WBC) count, hemoglobin, sodium, glucose, creatinine, and C-reactive protein. A score $\geq$ 6 (traditional threshold for diagnosis of NSTI) indicates a "moderate" risk of NSTI

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SMF, AT, and JJP conceived the study idea. SMF, AT, WC, and JJP coordinated the systematic review. SMF and AT designed the search strategy. SMF and AT screened abstracts and full texts. SMF and AT acquired the data and judged risk of bias in the studies. WC performed the data analysis. BR created the GRADE evidence profiles. SMF, AT, WC, BR, KK, AJES, KI, and JJP interpreted the data analysis and critically revised the manuscript. All authors have had the opportunity to review the final manuscript, and provided their permission to publish the manuscript. All authors agree to take responsibility for the work.

AJES holds patents related to multiorgan variability analysis, and has shares in Therapeutic Monitoring Systems Inc. None of the other authors report any conflict of interest.

Registration: PROSPERO CRD42017081976.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

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ISSN: 0003-4932/16/XXXX-0001

DOI: 10.1097/SLA.0000000000002774

(50–75% probability), whereas a score ≥8 indicates a "high" risk (greater than 75% probability).

We conducted a systematic review and meta-analysis with the primary objective of obtaining summary estimates of diagnostic performance (including sensitivity and specificity) across studies of physical examination, imaging, and LRINEC score for the diagnosis of NSTI in patients where the diagnosis was being considered.

METHODS

We structured this systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines,[11,12] the Cochrane Handbook for Diagnostic Test Accuracy,[13] and existing guidelines for reviews of diagnostic accuracy.[14] The study protocol was registered with the PROSPERO registry (CRD42017081976).

Search Strategy

We searched MEDLINE, PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Database of Systematic Reviews from their respective inception to November 13, 2017. An experienced health sciences librarian assisted in the development of the search strategy. The search was conducted using the terms "necrotizing fasciitis," "necrotizing skin and soft tissue infection," "necrotizing soft tissue infection," "gas gangrene," and "fournier's gangrene" (Search strategy is depicted in eFigure 1; http://links.lww.com/SLA/B411). We utilized Science Citation Index to retrieve reports citing the relevant articles identified from our search, and then entered them into PubMed. We then conducted further surveillance searches using the previously described 'Related Articles' feature[15] to identify further reports.

Study Selection

We included all English-language abstracts and full-text articles describing retrospective and prospective observational studies, as well as randomized controlled trials and quasi-randomized controlled trials. We included studies meeting the following criteria: (1) enrolled adult patients (≥16 years) with suspected NSTI; (2) conducted in the emergency department (ED), the hospital wards or intensive care unit (ICU); and (3) evaluated the test characteristics of: physical examination, imaging modalities, or LRINEC score for diagnosis of NSTI. Diagnosis of NSTI had to be defined by any of the following: Operative findings (presence of grayish necrotic fascia, demonstration of a lack of resistance to normally adherent muscular fascia to blunt dissection, lack of bleeding of the fascia during dissection, or the presence of foul smelling "dishwater" pus), histopathologic tissue examination, or death from suspected NSTI. We excluded case reports, case series, animal studies, pediatric studies and observational studies evaluating prognosis in cohorts of patients with confirmed NSTI only (ie, without controls). Each study was required to have a 2 × 2 table of true positive, false negative, true negative, and false positive counts, either extracted from the original article or calculated from other reported information such as declared sensitivity and specificity. In instances where these values could not be obtained from the reported data, we contacted authors. If the corresponding author did not respond after 3 attempts, the study was excluded.

We screened studies using Covidence software (Melbourne, Australia). Titles were imported into Covidence directly from the search databases, and duplicates were removed. In phase 1, 2 reviewers (SMF and AT) independently screened the titles and abstracts of all identified studies. Disagreements regarding citation inclusion were resolved by consensus, and no third-party adjudication was necessary. In phase 2, the same 2 reviewers independently assessed full texts of the selected articles from phase 1. Disagreements regarding citation inclusion were resolved by consensus.

Data Extraction

One investigator (SMF) collected the following variables from the included articles: author information, year of publication, study design, eligibility criteria, details regarding CT imaging technique, number of patients included, mean or median age, and number of deaths. We used a pre-designed data extraction sheet (eTable 1; http://links.lww.com/SLA/B411) to minimize the risk for transcriptional errors. Subsequently, 2 investigators (SMF and AT) independently collected the true positive, false positive, false negative, and true negative counts, total number of diagnosed NSTI cases, and stated sensitivity and specificity of diagnostic tests from all included trials.

Quality Assessment

Two reviewers (SMF and AT) independently assessed the risk of bias of the included studies, using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[16] Disagreements regarding risk of bias among citations were resolved through consensus. The QUADAS-2 assesses 4 potential areas for bias and applicability of the research question: (1) patient selection: risk of bias is considered high if there is non-consecutive enrollment, the use of case-control study design, or inappropriate exclusions; (2) index test: risk of bias is considered high if the index test results were interpreted without explicit blinding to the reference standard (ie, definitive diagnosis of NSTI); (3) reference standard (operative or histopathologic diagnosis of NSTI): risk of bias is considered high if the reference standard could misclassify the target condition; and (4) Flow and timing: risk of bias is considered high if not all patients had the diagnostic test applied using the same criteria, if the diagnostic test was calculated at an inappropriate time interval prior to definitive operative or histopathologic diagnosis, or if patients were excluded from analyses.

Evidence Synthesis

We presented individual study results graphically by plotting sensitivity and specificity estimates on one-dimensional forest plots (ordered by sensitivity) as well as on the Receiver Operating Characteristic (ROC) space, to visually assess for heterogeneity. To pool the results, we applied the Hierarchical Summary Receiver Operating Characteristic (HSROC) model[17] and obtained summary point estimates of the pairs of sensitivity and specificity, as well as Diagnostic Odds Ratios (OR) and likelihood ratios, with their 95% confidence intervals (CI). The HSROC model appropriately incorporates both within-study and between-study variability. Summary estimates of test accuracy were plotted in the ROC space together with the summary ROC curve. The analyses were conducted using MetaDAS (Version 1.3),[18] as recommended by the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[13] We conducted sensitivity analyses for parameters that had 3 or more studies remaining after excluding studies with high risk-of-bias. Univariate tests for heterogeneity in sensitivity and specificity are not recommended by the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy, as they do not account for heterogeneity explained by phenomena such as positive threshold effects.[13] Instead, it is preferable to demonstrate heterogeneity graphically through the scatterplot surrounding the summary ROC curve, and the confidence/prediction regions of the summary point in addition to the forest plots, as we have done in previous systematic reviews of diagnostic test accuracy.[19]

We assessed the overall confidence in pooled diagnostic effect estimates using the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) approach.[20] Assessments were based on the following criteria: risk-of-bias of the included

studies, precision, consistency, directness of the evidence, and risk of publication bias. The overall confidence in effect estimates were categorized into 1 of 4 levels, which included high, moderate, low, or very low. A GRADE evidence profile was created using the guideline development tool (gradepro.org).

RESULTS

Search Results

A total of 2290 citations were identified through the relevant searches (Fig. 1). Following removal of duplicates, 1661 studies were screened, and 30 studies underwent full-text review. Following this, we included 24 cohorts from 23 studies in the meta-analysis.[10,21–42] One study examining the LRINEC score[10] contained both an internal derivation cohort and an external validation cohort. Only the validation cohort was included in our analysis of LRINEC diagnostic accuracy. Only 3 physical examination findings had at least 3 relevant studies allowing for meta-analyses: fever, hemorrhagic bullae, and hypotension. Four studies evaluated the diagnostic accuracy of fever (defined as body temperature $\geq$38.0°C),[10,21,22,24] 5 studies evaluated the presence of hemorrhagic bullae,[21,24,32,38,39] and 6 studies evaluated the presence of hypotension (defined as a systolic blood pressure $\leq$90 mmHg).[10,21,24,25,38,39] Four studies investigated the diagnostic accuracy of plain radiography,[29,37–39] while 7 studies evaluated the presence of fascial gas on CT.[23,29,31,32,37,40,41] Six of the 7 studies investigating fascial gas also evaluated accuracy of the presence of any additional subtle findings on CT, namely fascial enhancement or fascial edema.[23,29,31,32,40,41] Finally, LRINEC was analyzed at 2 thresholds. 14 studies evaluated the diagnostic accuracy of a LRINEC score $\geq$6,[10,22–24,26–28,30,33–37,42] while 9 studies also evaluated a LRINEC score $\geq$8.[10,22,23,27,28,33,34,36,37] One study required contact with the corresponding author in order to obtain 2×2 table counts.[29]

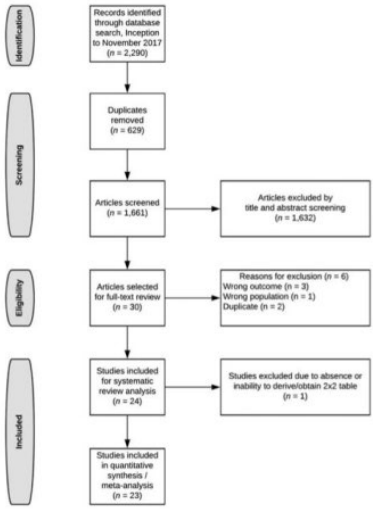

FIGURE 1. Flow chart summarizing evidence search and study selection.

TABLE 1. Characteristics of the 23 Included Studies

Description	Frequency (%)
Continent of Study	
North America	10 (43.5)
Asia	7 (30.4)
Europe	4 (17.4)
Australia/Oceania	2 (8.7)
Year of Publication	
2000–2004	4 (17.4)
2005–2009	1 (4.3)
2010–2014	7 (30.4)
2015–2017	11 (47.8)
Publication	
Full-Text Article	22 (95.7)
Published Conference Abstract	1 (4.3)
Study Design	
Retrospective Cohort	16 (69.6)
Prospective Cohort	2 (8.7)
Retrospective Case-Control	5 (21.7)
Definition of 'Suspicion of NSTI'	
All Skin and Soft Tissue Infections	6 (26.1)
Patients undergoing Imaging to rule-out NSTI	5 (21.7)
Patients taken to Operating Room to rule-out NSTI	2 (8.7)
Physician diagnosis of suspected NSTI	3 (13.0)
Case-Control design	5 (21.7)
Other	2 (8.7)

NSTI indicates necrotizing soft tissue infection.

Study Characteristics

Table 1 describes the 23 included studies, and eTable 2; http://links.lww.com/SLA/B411 provides more details on individual study characteristics. Of the studies included, 43.5% were conducted in North America, while 30.4% were conducted in Asia, and 17.4% were conducted in Europe. 16 studies (69.6%) were retrospective cohort studies, while 2 (8.7%) were prospective cohort studies, and 5 (21.7%) were retrospective case-control studies. There were no randomized controlled trials included. The included studies used variable definitions for 'suspected NSTI'. Six studies (26.1%) recruited all consecutive patients presenting with a skin and soft tissue infection.[30,35,37,39,40,42] A further 5 studies (21.7%) only included patients who underwent imaging for suspected NSTI.[23,27,31,32,41] Two studies (8.7%) included only patients taken to the operating room for suspected NSTI,[28,29] and 3 other studies (13.0%) included patients with a physician diagnosis of suspected NSTI.[26,34,36] Five studies (21.7%) utilized a case-control design,[10,21,22,33,38] including all consecutive cases of NSTI, and comparing them to a random selection of control cases with a non-necrotizing skin and soft tissue infection. Associative comparisons of patient demographic and risk factors between NSTI and non-NSTI control patients for each study are depicted in Table 2. Diabetes was found to be a significant NSTI risk factor in 4 of 8 studies, immunocompromised status in 4 of 6 studies and intravenous drug use in 2 of 3 studies. For physical exam findings, the classical "pain out of proportion" was a significant risk factor in 1 of 3 studies. Of the LRINEC score components, white blood cell count was most commonly found to be a significant predictor, noted in 6 of 8 studies.

TABLE 2. Comparisons of Demographic and Risk Factors in Included Studies

	Demographics		Comorbidities						Physical Exam Findings					Vital Signs		
	Age	Sex	Diabetes	Renal Failure	Liver Disease	Immune Compro-mised	Alcohol Abuse	IV Drug Use	Pain out of Proportion	Erythema	Edema	Necrosis	Crepitus	HR	T	SBP
Alayed (2015)		NS	NS	NS	NS	NS	NS	NS	✓	NS	NS	NS	✓	✓	✓	
Borschitz (2015)	NS	NS	✓	✓			✓									
Chao (2012)	NS	NS	NS	✓	✓	✓								✓	✓	
Cranendonck (2017)	NS	NS	NS	NS		✓										
Liao (2012)	NS	✓	✓	✓	✓	✓										
Martinez (2017)	NS	NS														
McGillicuddy (2011)	NS	NS	✓			✓	NS	✓		NS		✓	NS	NS		NS
Narasimhan (2017)	✓	NS	NS	NS	NS											
Neeki (2017)	✓		NS													
Wall (2000)a			NS						NS	NS	✓	✓	NS	NS	NS	✓
Wall (2000)b	NS	NS	NS		✓	NS		✓	NS	NS	✓	NS	NS	NS	NS	✓
Wang (2004)		NS	NS	NS	NS											
Wong (2004)		NS	✓												NS	✓

	LRINEC Components						
	White Blood Cell Count	Hemoglobin	Sodium	Creatinine	C-Reactive Protein	Glucose
Borschitz (2015)	NS	NS	NS	✓	✓	NS
Chao (2012)	✓	✓	✓	✓		✓
Cranendonck (2017)				NS	NS	
Kim (2013)	NS	NS	NS	✓	✓	NS
Liao (2012)	✓	NS	✓	✓	✓	✓
Martinez (2017)	✓	✓	NS	NS	NS	✓
McGillicuddy (2011)	✓	✓	NS	✓		✓
Neeki (2017)	✓	NS	✓	✓	✓	✓
Wall (2000)a	✓		NS			NS

✓ indicates significant difference; HR, heart rate; LRINEC, laboratory risk indicator for necrotizing fasciitis; NS, no significant difference between NSTI and control patients; SBP, systolic blood pressure; T, temperature.

TABLE 3. Summary Estimates of the Performance of Physical Examination Features, Imaging, and LRINEC Score in Diagnosing Necrotizing Soft Tissue Infection

	No. of Cohorts (No. of Patients)	Sensitivity (%)	Specificity (%)	Diagnostic Odds Ratio	Positive Likelihood Ratio	Negative Likelihood Ratio
Physical examination						
Fever	4 (647)	46.0 (38.9 to 53.2)	77.0 (59.7 to 88.1)	2.81 (1.34 to 5.88)	1.98 (1.12 to 3.51)	0.70 (0.59 to 0.84)
Hemorrhagic bullae	5 (951)	25.2 (12.8 to 43.7)	95.8 (87.3 to 98.7)	7.64 (3.81 to 15.32)	5.97 (2.89 to 12.32)	0.78 (0.66 to 0.93)
Hypotension	6 (1014)	21.0 (9.4 to 40.4)	97.7 (91.4 to 99.4)	11.38 (5.00 to 25.90)	9.20 (3.87 to 21.86)	0.81 (0.68 to 0.96)
Imaging						
Plain Radiography	4 (478)	48.9 (24.9 to 73.4)	94.0 (63.8 to 99.3)	15.03 (3.69 to 61.22)	8.17 (1.61 to 41.47)	0.54 (0.36 to 0.82)
Computed tomography (fascial gas only)	7 (787)	88.5 (55.5 to 97.9)	93.3 (80.8 to 97.9)	107.64 (12.32 to 940.18)	13.27 (4.24 to 41.50)	0.12 (0.03 to 0.62)
Computed tomography (fascial edema OR fascial enhancement OR fascial gas)	6 (700)	94.3 (81.2 to 98.5)	76.6 (21.3 to 97.5)	54.29 (5.51 to 534.73)	4.04 (0.62 to 26.47)	0.07 (0.02 to 0.24)
LRINEC Score						
≥6	14 (4339)	68.2 (51.4 to 81.3)	84.8 (75.8 to 90.9)	11.95 (5.32 to 26.83)	4.49 (2.74 to 7.35)	0.38 (0.24 to 0.60)
≥8	9 (1905)	40.8 (28.6 to 54.2)	94.9 (89.4 to 97.6)	12.71 (4.71 to 34.28)	7.94 (3.44 to 18.32)	0.62 (0.50 to 0.78)

LRINEC indicates laboratory risk indicator for necrotizing fasciitis.

Quality Assessment

Quality assessments using QUADAS-2 criteria are summarized in eFigure 2; http://links.lww.com/SLA/B411. 11 articles (47.9%) had unclear risk-of-bias in the utilization of the Index Test (either physical examination, imaging or LRINEC score), as it was not explicitly stated whether the Index Tests were interpreted without knowledge of the results of the reference standard (operative or histopathological diagnosis of NSTI),[22,24,26–30,34,35,38,39] 10 (43.5%) studies were noted for potential high risk-of-bias, and were therefore excluded in a sensitivity analysis. Five of these studies utilized a case-control design.[10,21,22,33,38] Another 5 were considered high risk-of-bias for applicability in patient selection, as 1 study only included patients admitted to the ICU,[25] 1 only included patients with confirmed *Vibrio vulnificus* infection,[24] and 3 only included patients with cervical NSTI.[35,37,42]

Results of Synthesis

Summary estimates of all diagnostic accuracy measures from the HSROC model are tabulated in Table 3. All summary estimates described are pooled values. GRADE evidence profiles are included in the supplemental data (eTables 3–9; http://links.lww.com/SLA/B411).

Physical Examination

The forest plots describing the reported sensitivity and specificity for fever, hemorrhagic bullae, and hypotension from the included studies are presented in Figure 2. Presence of fever had a sensitivity of 46.0% (95% CI 38.9%–53.2%) and a specificity of 77.0% (95% CI 59.7%–88.1%) for diagnosis of NSTI. Presence of hemorrhagic bullae was associated with a sensitivity of 25.2% (95% CI 12.8%–43.7%) and specificity of 95.8% (95% CI 87.3%–98.7%) for diagnosis of NSTI. Finally, hypotension had a sensitivity of

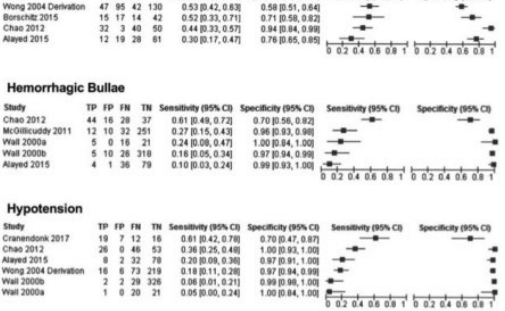

FIGURE 2. Forest plots of sensitivity and specificity for fever, hemorrhagic bullae, and hypotension for diagnosis of necrotizing soft tissue infection. CI indicates confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

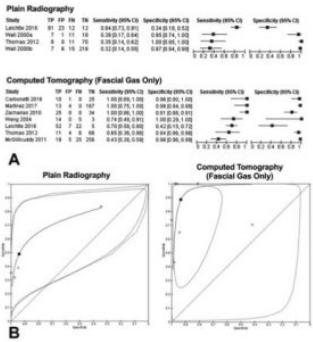

FIGURE 3. (A) Forest plots of sensitivity and specificity and (B) hierarchical summary receiver operating characteristic curves and bivariate summary points of (specificity, sensitivity), their 95% confidence regions (dotted lines), and 95% prediction regions (dashed lines) for diagnosis of necrotizing soft tissue infection. CI indicates confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

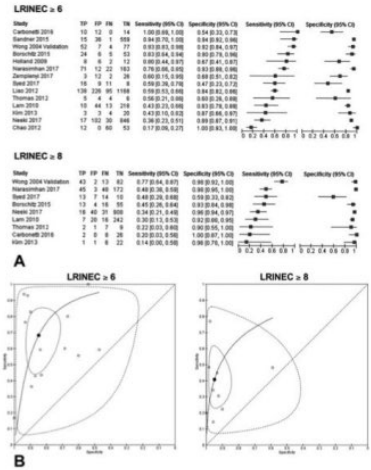

FIGURE 4. (A) Forest plots of sensitivity and specificity and (B) hierarchical summary receiver operating characteristic curves and bivariate summary points of (specificity, sensitivity), their 95% confidence regions (dotted lines), and 95% prediction regions (dashed lines) for LRINEC $\geq$ 6 and LRINEC $\geq$ 8 for diagnosis of necrotizing soft tissue infection. CI indicates confidence interval; FN, false negative; FP, false positive; LRINEC, laboratory risk indicator for necrotizing fasciitis; TN, true negative; TP, true positive.

21.0% (95% CI 9.4%–40.4%) and specificity of 97.7% (95% CI 91.4%–99.4%) for diagnosis of NSTI.

Imaging

The diagnostic accuracy of plain radiography and CT for diagnosis of NSTI were compared, and forest plots and HSROC curves describing reported sensitivity and specificity for each are presented in Figure 3. Visualization of soft tissue gas on plain radiography was associated with a sensitivity of 48.9% (95% CI 24.9%–73.4%) and specificity of 94.0% (95% CI 63.8%–99.3%) for diagnosis of NSTI. In comparison, visualization of fascial gas on CT was associated with a sensitivity of 88.5% (95% CI 55.5%–97.9%) and specificity of 93.3% (95% CI 80.8%–97.9%) for diagnosis of NSTI. Forest plot and HSROC curve for the composite findings of fascial enhancement, fascial edema, or fascial gas on CT are depicted in eFigure 4; http://links.lww.com/SLA/B411. The presence of any of these findings on CT was associated with a sensitivity of 94.3% (95% CI 81.2%–98.5%) and specificity of 76.6% (95% CI 21.3%–97.5%) for diagnosis of NSTI.

LRINEC

The LRINEC score was evaluated at 2 different thresholds, and forest plots and HSROC curves describing reported sensitivity and specificity for each are depicted in Figure 4. A LRINEC $\geq$6 was associated with a sensitivity of 68.2% (95% CI 51.4%–81.3%) and specificity of 84.8% (95% CI 75.8%–90.9%) for diagnosis of NSTI. In comparison, a LRINEC $\geq$8 had a sensitivity of 40.8% (95% CI 28.6%–54.2%) and specificity of 94.9% (95% CI 89.4%–97.6%).

Sensitivity Analyses: Excluding High Risk-of-Bias Studies

The results of the sensitivity analyses excluding high risk-of-bias studies (by QUADAS-2 criteria) for accuracy of physical examination, imaging and LRINEC for diagnosis of NSTI are depicted in eTable 10 and eFigures 5–7; http://links.lww.com/SLA/B411. Only CT with fascial gas, LRINEC $\geq$6, and LRINEC $\geq$8 had at least 3 included studies for meta-analysis. In the sensitivity analysis, CT had a pooled sensitivity and specificity of 93.3% (95% CI 48.7%–99.5%) and 93.1% (95% CI 80.9%–98.2%), respectively. LRINEC $\geq$6 had a sensitivity of 62.6% (95% CI 43.7%–78.3%) and specificity of 78.7% (95% CI 67.0%–87.1%), while LRINEC $\geq$8 had a sensitivity of 32.4% (95% CI 22.0%–45.1%) and specificity of 93.9% (95% CI 80.9%–98.2%).

DISCUSSION

We performed a systematic review and meta-analysis to evaluate the accuracy of physical examination findings, imaging, and LRINEC score in diagnosis of NSTI among adult patients with suspected NSTI. Given the clinical implications of delayed or missed NSTI diagnosis, and that waiting for imaging or laboratory results may delay time to definitive surgical management,[1,2] it is important to gain an understanding of the diagnostic accuracy of these tests in order to appropriately weigh the risks and benefits of using them. Taken together, this study comprehensively summarizes the available

literature and synthesizes the best available assessment of these various tools for diagnosis of NSTI.

NSTI is classically described as a clinical diagnosis based on patient risk factors and so-called pathognomonic physical examination features.[2] However, as this review illustrates, this dogma is not founded in high-quality evidence. We were unable to identify any historical risk factors suitable for meta-analysis, noting mixed findings for diabetes, immunocompromised status and intravenous drug use based on descriptive tests of association. Classic physical manifestations of NSTI may include a variety of findings,[1] however the available literature only allowed for meta-analysis of fever, hemorrhagic bullae, and hypotension. We found that all 3 physical examination findings had poor sensitivity for diagnosis of NSTI. In many cases, the development of physical signs such as hemorrhagic bullae or hypotension and shock appear to be evidence of more advanced disease.[43] Therefore, their absence should not be individually used to rule out the disease. This point is highlighted by examining the effect of these physical examination features in deriving post-test probability of NSTI from physician-determined pre-test probability (eTable 11; http://links.lww.com/SLA/B411). For example, a patient with a pre-test probability of NSTI of 50% but with absence of fever, hemorrhagic bullae, or hypotension, still retains a post-test probability of 41.3%, 43.9%, and 44.7%, respectively. Such patients should still undergo further testing or immediate surgical consultation.[44] It is important to note that in the clinical context, it is often not a single physical examination finding that is used to make the diagnosis, but rather a combination of findings. Unfortunately, such combinations were not evaluated in the available literature.

Imaging modalities are commonly used for diagnosis of NSTI. Plain radiography is readily available at most centers, and can often be obtained at the bedside. We found that plain radiography had poor sensitivity for diagnosis of NSTI, and therefore should not be used to rule out the diagnosis. In comparison, presence of fascial gas on contrast CT had far superior sensitivity and specificity than plain radiography. While the presence of fascial gas on CT was associated with a sensitivity of 88.5%, this finding had a specificity of 93.3% for NSTI. We performed a sensitivity analysis and pragmatically broadened acceptable CT criteria to include more subtle signs of NSTI (including fascial edema and enhancement), which increased the sensitivity to 94.3%, but decreased the specificity to 76.6%. The effects of these CT findings on physician derived pre-test probability of NSTI are depicted in eTable 10; http://links.lww.com/SLA/B411. In a patient with an equivocal pre-test probability of NSTI of 50%, the presence of fascial gas increases the probability to 93%, while the absence of fascial enhancement, edema or gas decreases the probability to less than 7%. The pragmatic approach of pooling studies with varying CT criteria for NSTI resulted in more heterogeneity of test specificity, as demonstrated by the wider confidence intervals for the pooled specificity estimate. This illustrates the importance of not simply accepting "positive" or "negative" CTs for NSTI at face value, but rather understanding that much like the physical examination, CT findings encompass a variety of specific components with a range of potential diagnostic utility. In fact, these findings may highlight the need for universal reporting checklists for CT requests querying the possibility of NSTI. Importantly, not all hospitals have access to CT imaging, and even if available, CT imaging may delay definitive surgical management. Therefore, despite the relatively strong accuracy of CT in diagnosis of NSTI, surgical consultation and intervention should never be delayed, particularly in cases of severe systemic illness. Diagnostic accuracy of Magnetic Resonance Imaging (MRI) was not evaluated in enough studies for meta-analysis, but existing work suggests that MRI can recognize subtle signs of NSTI, potentially allowing for earlier diagnosis.[27] However, the lack of availability of MRI in many centers may limit its practical utility, and since it may result in significant delay to surgical intervention, its use in the diagnosis of NSTI cannot be recommended at present. Point-of-care ultrasound, a newer bedside diagnostic modality, is available in many centers, and may play a role in NSTI diagnosis in the future; however, no data currently exists.[45] Future research investigating the accuracy of point-of-care ultrasound in diagnosis of NSTI is warranted, given the ubiquitous availability of this modality, and its ability to be used without significant delay to surgical consultation.

Finally, we evaluated the diagnostic accuracy of the LRINEC score,[10] which has become the most widely used clinical decision instrument for the diagnosis of NSTI.[1,2] We found that a LRINEC score $\geq$6 ("moderate" risk of NSTI) was poorly sensitive for diagnosis of NSTI, and only moderately specific. These performance characteristics are markedly worse than reported in the external validation population of the original study.[10] A LRINEC score $\geq$ 8 ("high" risk of NSTI) increased the specificity, but at the cost of substantially decreased sensitivity. Recognizing the limitations in sensitivity of the LRINEC score is extremely important, as computation of the score requires laboratory values, and therefore can delay definitive surgical management and result in worse outcomes.[5] A low LRINEC score (<6) does not significantly reduce post-test probability of NSTI in a patient with moderate risk of the diagnosis (eTable 13; http://links.lww.com/SLA/B411), as a patient with a pre-test probability of 50% but a LRINEC <6 still retains a 27.3% risk of NSTI. While the LRINEC score itself was associated with poor diagnostic accuracy, it is possible that individual elements of the score (such as WBC or sodium) may have better individual accuracy on their own. This represents an important avenue for future research.

This review was performed using a comprehensive search with clear inclusion and exclusion criteria, and it synthesizes the best available evaluation of the available assessments for diagnosis of NSTI. Limitations of this review relate primarily to the quality and heterogeneity of included studies. First, many included studies did not mention whether the diagnostic tests (namely the LRINEC score) were interpreted by individuals who were blinded to knowledge of the final diagnosis. Five of the included studies were case-control design, which represents a potential high risk-of-bias.

With regard to clinical heterogeneity, 3 articles specifically looked at cervical NSTI, which may represent a distinct subtype whose findings may not be extended to all types of NSTI. Unfortunately, none of the other studies evaluated diagnostic accuracy of affected body site, or total body surface area, which are known indicators of prognosis in patients with NSTI.[8] We did perform a sensitivity analysis removing high risk-of-bias studies, which did not substantially alter the conclusions. Finally, we sought to include studies that differentiated NSTI from control patients with clinical suspicion of NSTI, and as a result, there was variability in inclusion criteria between studies, with many of them including relatively "high-risk" patients (i.e. undergoing imaging or surgery to rule out NSTI), and only a minority including all consecutive patients presenting with a skin and soft tissue infection. Therefore, these studies may be biased towards prioritizing tests that are more strongly associated with severe or late disease, as opposed to tests that would be more useful for screening. Tests derived and evaluated in high-risk settings do not necessarily project their performance in low-risk settings.

This review demonstrates that the vast majority of diagnostic accuracy literature for NSTI is based on CT or LRINEC findings of high-risk populations. However, the determination of the patient's "pre-test probability" (in other words, identifying those that are "high risk") is based upon the clinician's assessment of history and physical examination findings, which are demonstrably scarce in evidence. Defining the appropriate population in which to apply the

LRINEC or CT is challenging, as reflected by the varying study definitions (and resultant variation in NSTI prevalence across studies) in this review.

CONCLUSIONS

Our systematic review found that individual physical examination signs (fever, hemorrhagic bullae, and hypotension) were poorly sensitive for diagnosis of NSTI. CT had superior sensitivity and specificity to plain radiography in diagnosing NSTI, but may not be readily available in all centers, and may not be suitable for unstable patients. Finally, the LRINEC score was poorly sensitive for diagnosis of NSTI, suggesting that a low score is not sufficient to rule out the diagnosis.

ACKNOWLEDGMENTS

The authors thank Dr. Stefan Leichtle (Virginia Commonwealth University) for providing data for our meta-analysis.

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Infectious Diseases in Obstetrics and Gynecology 1:16–22 (1993)

Necrotizing Fasciitis: A Review of Management Guidelines in a Large Obstetrics and Gynecology Teaching Hospital

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ABSTRACT

Necrotizing fasciitis is a severe, life-threatening soft tissue infection that results in rapid and progressive destruction of the superficial fascia and subcutaneous tissue. Because of its varied clinical presentation and bacteriological make-up, it has been labelled with many other names such as acute streptococcal gangrene, gangrenous erysipelas, necrotizing erysipelas, hospital gangrene, and acute dermal gangrene. Although described by Hippocrates and Galen, it has received increasing attention in obstetrical and gynecological literature only within the last 20 years. This review includes two recent cases successfully managed at Parkland Memorial Hospital, Dallas, Texas. The first patient was a 50 year old, morbidly obese, diabetic woman who presented with a small, painful lesion on the vulva. After failing triple antibiotic therapy with ampicillin, clindamycin, and gentamicin, the diagnosis of necrotizing fasciitis of the vulva was made, and she was taken to the operating room for extensive excision. She was discharged home on hospital day 29. The second patient was a 65 year old, obese, diabetic woman with risk factors for atherosclerosis who had a wound separation after an abdominal hysterectomy. Two days later a loss of resistance to probing was noted in the subcutaneous tissue. Necrotizing fasciitis was suspected, and she was taken to the operating room for resection. The patient was discharged home on hospital day 27. The mortality rate after diagnosis of necrotizing fasciitis has been reported to be 30% to 60%. We review the literature and outline the guidelines used in a large Ob/Gyn teaching hospital to minimize the adverse outcome. Lectures on soft-tissue infections are included on a regular basis. The high-risk factors of age over 50, diabetes, and atherosclerosis are emphasized. The need for early diagnosis and surgical treatment within 48 hours is stressed, and any suspicious lesions or wound complications are reported to experienced senior house officers and staff. We use two recent cases to highlight the diagnostic clues and management strategies for this often fatal polymicrobial infection. © 1993 Wiley-Liss, Inc.

KEY WORDS

Soft tissue infections, gynecologic infections, obstetrical infections

CASE REPORTS

Case 1

A 50 year old white woman (G_2P_2) originally presented to the Parkland Memorial Hospital Ob/Gyn Emergency Room complaining of a painful "boil on my vagina." She had a 1 cm follicular abscess on the left vulva at the intertriginous fold that would rub against her thigh as she walked. She denied fever, chills, or other systemic symptoms. Her past medical history was significant for a total abdominal hysterectomy with bilateral salpingo-oophorectomy and appendectomy in 1963, a ventral hernia repair in 1970, and a 20-year history of adult onset diabetes mellitus controlled with glyburide 7.5 mg daily. Her serum glucose was 128 mg/dl. She had a 22 pack/year history of smoking and denied the use of alcohol. Physical examination revealed a morbidly obese (327 pounds) woman who was generally healthy, other than her present-

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Clinical Study

Received July 10, 1992
Accepted December 15, 1992

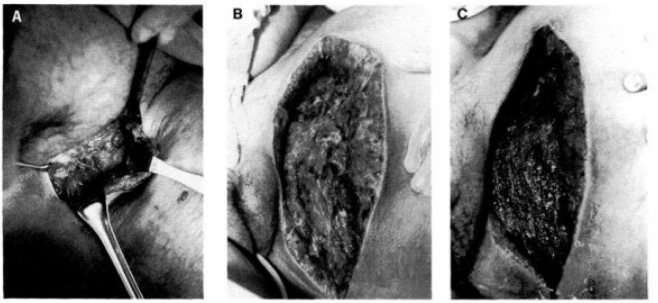

Fig. 1. Photographs of the vulvar area from case 1. **A:** Large area of involvement developed in 24 hours and was extensively débrided. **B:** Continued tissue necrosis and loss of resistance to probing was noted at 36 hours and required repeat excision. **C:** Granulation tissue and healing of wound bed 14 days after original surgery.

ing complaint. The abscess was needle aspirated, and the patient was sent home on oral dicloxacillin 500 mg q6h.

The following day, she returned to the emergency room complaining of increased pain and redness in the left groin area and subjective fever. Exam was significant for a temperature of 38°C, blood pressure 138/78, heart rate 88, respiratory rate 20. The left vulva was slightly edematous and erythematous. The left groin had an 8 × 10 cm erythematous area that extended down the inner thigh and was warm and tender to the touch. She had no clubbing or cyanosis of her extremities, nor did she have any pelvic masses or tenderness. She was alert and oriented and had a normal neurological exam.

She was admitted to the hospital and placed on intravenous ampicillin (2 mg IV q4h), gentamicin (1 mg/kg IV q8h), and clindamycin (900 mg IV q8h). Laboratory evaluation revealed an elevated white blood cell count of 17,400/mm^3 and a glucose of 168 mg/dl. The next day the area of inflammation had extended to 20 cm down the left inner thigh, and foul-smelling purulent material exuded from the aspirated lesion. The patient was taken to the operating room where exploration of the groin area revealed multiple loculated abscess cavities extending from the left groin superior to the inguinal ligament and inferior to the femoral triangle and containing foul-smelling yellow-greenish pus. This material was sent for gram stain and aerobic and anaerobic cultures. Blood was sent for *Clostridium* toxin and aerobic and anaerobic cultures. The involved area was dissected underneath the subcutaneous tissue to the inferior margin of the left vulva (Fig. 1A). The necrotic tissue was excised to the point of bleeding with no loss of resistance to probing, and the area was irrigated with 6 liters of saline and packed.

Post-operatively, she was managed with subcutaneous insulin to maintain tight glucose control. Deep vein thrombosis (DVT) prophylaxis with a pneumatic compression hose on both legs and subcutaneous heparin 5,000 units twice daily was initiated in the operating room and continued postoperatively. Wound debridement and cleaning with one-quarter strength Dakin's solution (163 ml sodium hypochlorite 5.25% plus 0.325$_g$ sodium bicarbonate in 3,637 ml water) were performed twice daily, and sterile gauze was used for packing the wound. After 36 hours, further necrosis of the wound edges was apparent. She was again taken to surgery, where blunt probing revealed loss of tissue resistance superiorlaterally close to the margin of the inguinal ligaments as well as medially past the inferior margin of the vulva and inner thigh (Fig. 1B). The skin, superficial fascia, and subcutaneous tissue of the areas were excised to the point of bleeding and no loss of resistance to probing.

Hemostasis was attained, and the wound was packed with sterile gauze.

Ampicillin, clindamycin, and gentamicin were continued, as were sliding scale insulin, DVT prophylaxis, and twice daily wound débridement and dressing changes. Aztreonam (2 g IV q6h) was substituted to reduce the risk of renal toxicity, which was significant in this patient. When no further signs of infection were present in the wound bed, one-quarter strength Dakin's solution was deleted, and sterile saline was substituted for wound care. The wound was cleaned with Biolex spray (a dilute aloe vera solution) and gel to promote granulation. Antibiotics were stopped after 10 additional days, after she had been afebrile for 48 hours. By this time, the wound was granulating well (Fig. 1C).

Aerobic cultures demonstrated both gram-negative (*E. coli, Klebsiella pneumoniae*) and gram-positive rods (*Corynebacterium* sp). Anaerobic cultures showed gram-negative rods (*Bacteroides* sp). Blood cultures and *Clostridium* toxin assay were negative. Pathological examination revealed necrotic skin with abscess and underlying fat necrosis. The patient was discharged home on hospital day 25 on twice daily dressing changes, and was followed with weekly visits for 6 weeks. She was doing well at her 6-month follow-up.

Case 2

A 65 year old black woman ($G_7P_5A_2$) was admitted to Parkland Memorial Hospital for a hysterectomy after fractional dilatation and curettage revealed dysfunctional endometrium with cellular atypia. Because of her significant medical problems including hypertension, coronary artery disease, non-insulin dependent diabetes mellitus, degenerative joint disease, and a history of a mild stroke, she was evaluated by the medicine department consult staff and cleared for surgery. She had a 30 pack/year history of smoking and denied alcohol use. Physical examination revealed an obese (235 pounds) woman, blood pressure 150/90, heart rate 90, respiratory rate 20, temperature 37°C. She underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy without complication. Pathology revealed multiple leiomyomata and no gross endometrial tumor.

On post-operative day 1 (POD 1), she had a maximum temperature of 38.5°C. Her incision was draining a small amount of serosanguineous fluid but did not look infected. On POD 2 she had a maximum temperature of 38.5°C, which was attributed to pulmonary atelectasis. She quickly defervesced and remained afebrile. On POD 4, a slight serosanguineous discharge was noted with wound separation apparent on probing. Her staples were removed to allow drainage, and the wound was packed with saline-moistened sterile gauze covered with dry sterile dressing and changed twice daily.

She remained afebrile until POD 6, when her temperature spiked to 38.4°C. At this time, her bandages contained greenish purulence, and the wound edges were necrotic and foul-smelling. When the wound was probed, loss of resistance of the subcutaneous tissue superficial to the rectal fascia extended 6 cm bilaterally. Only minimal skin erythema was present, but the wound margins were anesthetic. Importantly, the patient maintained normal bowel function, and her fluid balance and electrolytes were well controlled. Necrotizing fasciitis was suspected, and the patient was placed on IV ampicillin (2 g IV q4h), gentamicin (1 mg/kg IV q8h), and clindamycin (900 mg IV q8h) and taken to the operating room that same day. The areas of necrosis were excised to the point at which no loss of resistance was encountered and brisk capillary bleeding was evident. Tissue was sent for aerobic and anaerobic cultures. The wound was irrigated with 3 liters of saline and packed with sterile gauze.

Post-operatively, she was maintained with careful fluid management, and her triple antibiotics were continued. The wound was debrided and cleaned with one-quarter strength Dakin's solutin twice daily. The patient defervesced after 6 days, and granulation tissue became apparent. Hydrotherapy in a whirlpool bath was begun at this time. The wound occasionally required sharp débridement of necrotic debris, but otherwise it continued to granulate well. The wound culture revealed *Proteus mirabilis*. Pathology showed marked acute and chronic inflammation, necrosis, ulceration, and organizing fat necrosis. The patient was discharged 27 days after her admission on twice daily dressing changes and weekly follow-up in clinic for 6 weeks. She was doing well 4 months post-operatively.

DISCUSSION

One of the earliest descriptions of hospital gangrene was written in 1871 by Joseph Jones, a Con-

TABLE 1. Risk factors for necrotizing fasciitis

Age over 50[a]
Arteriosclerosis[a]
Diabetes[a]
Obesity
Smoking
Previous radiation
Operative trauma

[a]Major risk factors.

federate Army surgeon: "a purple or blue spot is first perceived that is sometimes raised, and contains serum below. The skin in the affected spot may melt away in 24 hours, whilst a deep blue and purple, almost black, areola surrounding the dead mass, spreads rapidly in an ever increasing circle. This is witnessed most generally in the worst and fatal cases."[4] The first large series was published by Meleney in 1924.[5] He studied 20 cases in China from which he cultured hemolytic streptococci and hence called the disease hemolytic streptococcal gangrene. The term *necrotizing fasciitis* was coined in 1952 by Wilson.[6] The first vulvar cases were described in 1972 by Roberts.[7]

The exact incidence of necrotizing fasciitis is not known, but fortunately it is uncommon. It has been described in all ages and in almost every site of the body. It is most commonly found in the lower extremities, followed by the upper extremities, abdomen, perineum, groin, back, and buttocks.[2,8] The initiating event is usually a minor penetrating injury and involves a surgical site less than half the time. In Rea's series of 44 patients with necrotizing fasciitis, 80% of the cases originated outside the hospital with minor injuries such as abrasions, cuts, bruises, boils, and insect bites, and only 20% were post-surgical infections.[2] In eight of the cases, no specific initiating factor could be found.

Those at highest risk of necrotizing fasciitis are those whose repair mechanisms are compromised due to peripheral vascular damage. The most common risk factors are summarizd in Table 1. The most frequent predisposing risk factors are advanced age followed closely by arteriosclerosis and diabetes. Rea first noticed the association of these factors with necrotizing fasciitis in 1970.[2] Of 44 cases studied, 45.5% were over age 50, 22.2% had arteriosclerosis, and 18.2% had diabetes.[2] In Roberts and Hester's and Roberts's collective cases of 22 patients with necrotizing fasciitis of the vulva, 68.1% were over age 50, and all but one, or 95.5%, were diabetic.[7,9] He did not comment on patients with arteriosclerosis. Other factors thought to predispose to necrotizing fasciitis are hypertension, vascular disease, obesity, renal failure, immunosuppression, a history of radiation therapy, and operative trauma.[10,11]

Necrotizing fasciitis is often misdiagnosed as cellulitis or a simple abscess because of the misleading symptoms and signs of its victims. Early skin changes include erythema, tenderness, and edema extending beyond the area of erythema.[1] These are usually accompanied by fever, malaise, and other systemic toxic signs. Early on, the skin may be intact.[11] Late signs include a purple or bluish discoloration, vesicles filled with red-black fluid, crepitance, cutaneous anesthesia, and necrosis. Once these late signs appear, however, the area of underlying destruction is usually large, and severe systemic toxicity develops.

The pathognomonic sign present in 100% of the cases is subcutaneous and superficial fascial necrosis.[2] Classically, this extends along fascial planes beyond the area of skin involvement. When blunt dissection with a probe or even a finger is carried out, the superficial tissue is sheared away without resistance. Wilson admonished that when undermining of this nature is demonstrated, the patient should receive immediate surgical therapy.[6]

The bacterial etiology of necrotizing fasciitis is polymicrobial (Table 2). In Meleney's series of 20 in 1924, the predominant organism was the hemolytic streptococcus, which was present in all cases.[5] Staphylococci was found in only 10%. Wilson, in contrast, reported in 1952 that 88% of his cases were infected with staphylococci.[6] Rea showed that streptococci and staphylococci were present in equal proportions, representing 43% each among his cases.[2] The majority of his cases grew out more than one organism, however. In a recent series by Stephenson the organisms most currently found were anaerobic *Peptostreptococcus* and *Bacteroides*.[12] These differences are most likely attributed to the improved techniques for culturing anaerobic organisms in recent years. Other bacteria reported to be involved include *E. coli*, *K. pneumoniae*, *Enterobacter*, *Peptococcus*, and *Pseudomonas*.[11] *Vibrio* sp. can be seen in wounds exposed to sea water.[13] *Clostridium* sp. are found less commonly in necrotizing fasciitis, even in those cases with subcutane-

TABLE 2. Polymicrobial etiology of necrotizing fasciitis

Aerobes	Anaerobes
Gram-positive	
Cocci	
Group A, B, D streptococci[a]	*Peptostreptococcus* sp.[a]
Other α- and γ-streptococci	*Peptococcus* sp.[a]
Staphylococcus aureus[a]	
Staphylococcus epidermidis	
Rods	
Lactobacilli	*Clostridium* sp.
Diphtheroids	*Propionibacterium* sp.
	Eubacterium sp.
Gram-negative	
Cocci	
Neisseria gonorrhoeae	*Veillonella* sp.
Rods	
E. coli[a]	*Bacteroides fragilis* group[a]
Klebsiella pneumoniae[a]	Other *Bacteroides* sp.
Enterobacter sp.[a]	*Fusobacterium* sp.
P. mirabilis	
Pseudomonas aeruginosa[a]	

[a]Most common isolates.

TABLE 3. Diagnostic clues for necrotizing fasciitis

Cellulitis that fails to respond to antibiotic therapy
Edema beyond the area of erythema
Development of ecchymosis or vesicles over an area of cellulitis
Presence of gas in the tissue as demonstrated by palpation (crepitus)

ous emphysema. Subcutaneous emphysema is thought to occur by aerobic and anaerobic bacteria synergistically forming hydrogen and nitrogen gas.[1] Gas formation is mostly associated with *E. coli*, microaerophilic *Streptococcus*, and *Bacteroides* sp.[13]

Diagnosis of necrotizing fasciitis can be difficult and is often made after the disease is widespread. A high clinical suspicion must be maintained to enable early and accurate diagnosis. Important diagnostic clues that lead to high suspicion for necrotizing fasciitis are listed in Table 3. Fisher emphasized the importance of radiological studies to demonstrate soft-tissue gas.[14] He showed that while crepitus was found in 29% of patients with necrotizing fasciitis, soft-tissue gas was found by x-ray in 100%. Fisher also gave six clinical criteria to satisfy the diagnosis of necrotizing fasciitis: 1) extensive necrosis of supeficial fascia with widespread undermining of surrounding tissue; 2) moderate to severe systemic toxic reaction with altered mental status; 3) absence of muscle involvement (vs. the prominent myonecrosis seen in certain clostridial infections and synergistic necrotizing cellulitis); 4) failure to demonstrate clostridia in wound and blood cultures; 5) absence of major vascular occlusion; and 6) pathological examination of débrided tissue showing intense leukocyte infiltration, focal necrosis of fascia and surrounding tissue, and thrombosis of the microvasculature.[14] Although clostridial species are typically not present in necrotizing fasciitis, it is important to rule out the presence of this pathogen in the wound, as this may mean the deep fascia and muscle are involved (clostridial myonecrosis). At surgery, a frozen section can aid in this diagnosis. Classically, necrotizing fasciitis shows necrosis of the superficial fascia and subcutaneous tissue with an intense polymorphonuclear infiltration and presence of multiple microorganisms on gram stain.[11,13] A clostridial infection will be remarkable for the absence of an inflammatory infiltrate and the presence of many gram-positive rods.[13] If the latter is the case, close inspection of the deep fascia and underlying muscle is warranted. Stephenson et al.[12] reported the presence of *Clostridium tetani* in one patient with necrotizing fasciitis of the vulva but indicated that no myonecrosis was present, as has been reported in cases with *Clostridium perfringens*.

Once suspicion is high for necrotizing fasciitis, the patient should be taken to the operating room for exploration and surgical débridement. Brewer and Meleney are credited with the first two successful surgical treatments of necrotizing fasciitis, then called progressive gangrenous infection of the skin and subcutaneous tissues, which occurred in and around abdominal incisions for operative care of acute perforative appendicitis.[15] In one case, an incision was made circumferentially around the infected area, down to the deep fascia, and the wound was packed. The enclosed area sloughed, but there was no progression of disease, so the wound ultimately granulated closed. The other case was successfully treated with excision of involved tissue to viable margins.

If inspection shows the characteristic skin ecchymosis, it is likely that the area of undermining is great. It is important, however, to incise and débride the entire extent of disease, until there is no further loss of resistance to blunt probing and until the tissue bleeds easily when cut. As Wilson stated, "to postpone surgery and use massive doses of antibiotics is ineffective and, in addition, the incision

which must eventually be made must then be more extensive in a sicker patient."[6] In such a patient, the post-operative care should be in an intensive care unit in isolation, much like that of a burn victim. Insensible fluid losses will be great, and the prospect of hypovolemia with hemoconcentration is high.[13] Aggressive fluid and electrolyte management is important, along with periodic blood transfusions to correct anemia due to red cell destruction. Broad spectrum antibiotics (i.e., ampicillin, gentamicin, clindamycin) should be used until the identity and sensitivities of pathogens are known. We have found twice daily dressing changes and wound débridement to be sufficient for wound care. The wound is cleaned in this manner with 3% hydrogen peroxide or one-quarter strength Dakin's solution, and packed with sterile gauze. When the old dressings no longer have a foul odor, saline can be substituted for one-quarter strength Dakin's solution for wound cleaning. We also use Biolex gel (an aloe vera-containing gel) to promote wound healing.

Hyperbaric oxygen treatments have been cited as reducing edema, halting progression of tissue necrosis, and decreasing mortality, especially among wounds infected with clostridia.[13,16] Split-thickness skin grafting is an option for re-epithelializing large areas after adequate granulation. Fortunately, in our cases the extent of the disease was not so severe as to require disfiguring surgery, and the wounds were able to granulate in completely.

Mortality rates for necrotizing fasciitis are generally quoted as 30–60%,[8] and antibiotics have not significantly changed this.[2] Death is usually immediately attributed to overwhelming sepsis, complications of diabetes (ketoacidosis), vascular insufficiency, and hemodynamic collapse.[3,8] Not only do old age and diabetes seem to be the most important predisposing factors for necrotizing fasciitis, but they are also the two leading factors for a grave prognosis.[3] Rea showed the mortality rate in patients over 50 years of age to be 67%, while that in diabetics to be 63%.[2] Roberts and Hester and Roberts had a mortality rate from his cases of 47% and 38%, respectively.[7,9] Stephenson reported a 62% mortality in patients over age 50 and a 55% mortality rate in diabetic patients.[12] Significantly, all of the fatalities had one or both of these significant high-risk factors. The most important factors for survival are rapid diagnosis, and rapid and adequate surgical treatment. Rea once again stresses this fact by showing that the average time from onset of disease to diagnosis and treatment of those who lived was 4 days, while that of those who died was 7 days.[2] Stephenson found that 48 hours was a more significant time frame, after which the mortality rate was 75%.[12] The mortality rate in Wilson's collection was only 8.7%; this low number may be attributed in part to the expertise of the house officers in the teaching program at Parkland Memorial Hospital, who had been trained to recognize the clinical manifestations of the disease.[6]

SUMMARY

We have presented two cases of necrotizing fasciitis recently managed at a large Ob/Gyn residency training program. We have reviewed the patients' histories, risk factors, signs and symptoms, bacteriology, pathology, therapy, and mortality factors associated with this life-threatening disease process. Our patients were both in a high mortality risk category for necrotizing fasciitis in that both were over 50 years old, had diabetes, and were obese. One patient had documented arteriosclerosis, and the other had risk factors for it (obesity, smoking, and diabetes). Despite these high risk factors, both of these patients did well. We agree with Wilson that high suspicion and prompt action on the part of the house officers involved in the care of these women were the keys to their successful outcome.[6] Some of the general guidelines for the management of necrotizing fasciitis at Parkland Memorial Hospital are listed in Table 4. In the first case, the main clinical clue was the failure of the presumed cellulitis to respond to antibiotics. In the second, it was the loss of tissue resistance to blunt probing. Both were taken to surgery within 3 days of the presenting problem.

The first case showed the typical polymicrobial nature of necrotizing fasciitis, whereas in the second only one organism (*P. mirabilis*) was cultured. This may be due to the perioperative broad spectrum antibiotic prophylaxis given to this patient at the time of her hysterectomy.

Necrotizing fasciitis can occur in any surgical or nonsurgical insult. In the recent Ob/Gyn literature alone, there are cases reported from episiotomy, mini-laparotomy, diagnostic laparoscopy, and suprapubic catheter placement.[16–19] There are also reports of patients without an obvious original nidus of infection, or patients on standard treatment

TABLE 4. Guidelines for managing necrotizing fasciitis at PMH

1. Patients with suspicious lesions in the vulvar, groin, or thigh region with high-risk factors for necrotizing fasciitis are admitted for observation
2. Patients with presumed cellulitis who fail to respond to IV antibiotics are taken to surgery for wound exploration
3. Post-operative patients who have high-risk factors for necrotizing fasciitis and have wound separation with loss of tissue resistance are started on IV antibiotics and taken to the operating room for exploration
4. Junior house officers notify senior house officers and faculty experienced in the care of necrotizing fasciitis about any suspicious lesions or wound complications
5. Lectures on soft-tissue infections are included on a regular basis for residents and medical students
6. Wound care is managed by the same upper level resident on any service, and additional débridement and/or return to the operating room is performed as needed
7. Survival depends on early recognition and immediate surgical débridement to healthy tissue margins
   - Remove all indurated, edematous, crepitant tissue
   - Incise tissue to margins that bleed easily
   - Change wound dressings frequently
   - Initiate broad spectrum antibiotics

regimens such as radiotherapy, chemotherapy, and anti-inflammatory drugs.[20–22]

It is often said that anyone who uses a certain kind of intervention or therapy should be prepared to deal with the consequences of that intervention or therapy. Among the surgical specialties, obstetricians and gynecologists frequently deal with heavily contaminated body areas; therefore, knowledge of surgical complications is imperative, especially one as life-threatening as necrotizing fasciitis.

ACKNOWLEDGMENTS

The authors acknowledge the many hours of medical care provided to these patients by the following physicians: Deborah Lenart, M.D., Stacy Travis, M.D., and Michael Bevers, M.D. We appreciate the skillful manuscript preparation by Ms. Maria McFarland.

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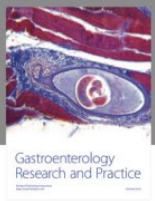

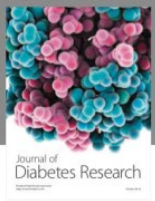

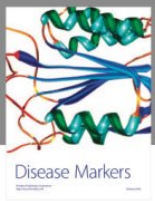

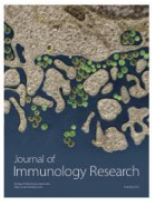

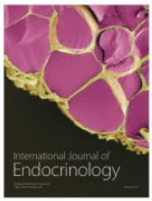

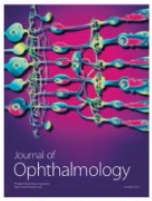

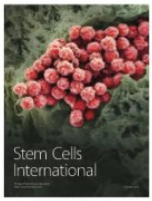

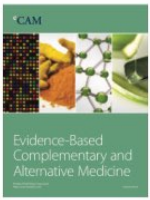

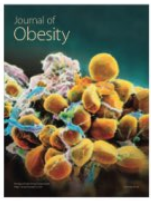

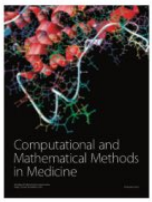

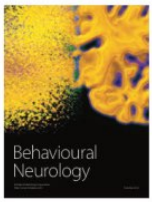

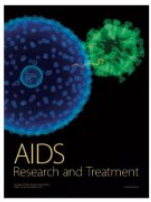

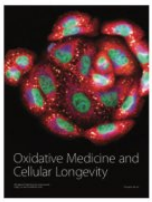

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Original article

Necrotizing fasciitis: eight-year experience and literature review

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ARTICLE INFO

Article history:
Received 1 July 2013
Accepted 20 August 2013
Available online 22 November 2013

Keywords:
Necrotizing fasciitis
Comorbidity
Debridement
Antibiotics

ABSTRACT

Objectives: To describe clinical, laboratory, microbiological features, and outcomes of necrotizing fasciitis.

Methods: From January 1, 2004 to December 31, 2011, 115 patients (79 males, 36 females) diagnosed with necrotizing fasciitis were admitted to Mackay Memorial Hospital in Taitung. Demographic data, clinical features, location of infection, type of comorbidities, microbiology and laboratory results, and outcomes of patients were retrospectively analyzed.

Results: Among 115 cases, 91 survived (79.1%) and 24 died (20.9%). There were 67 males (73.6%) and 24 females (26.4%) with a median age of 54 years (inter-quartile ranges, 44.0–68.0 years) in the survival group; and 12 males (50%) and 12 females (50%) with a median age of 61 years (inter-quartile ranges, 55.5–71.5 years) in the non-surviving group. The most common symptoms were local swelling/erythema, fever, pain/tenderness in 92 (80%), 87 (76%) and 84 (73%) patients, respectively. The most common comorbidies were liver cirrhosis in 54 patients (47%) and diabetes mellitus in 45 patients (39%). A single organism was identified in 70 patients (61%), multiple pathogens were isolated in 20 patients (17%), and no microorganism was identified in 30 patients (26%). The significant risk factors were gender, hospital length of stay, and albumin level.

Discussion: Necrotizing fasciitis, although not common, can cause notable rates of morbidity and mortality. It is important to have a high index of suspicion and increase awareness in view of the paucity of specific cutaneous findings early in the course of the disease. Prompt diagnosis and early operative debridement with adequate antibiotics are vital.

Introduction

Necrotizing fasciitis is a rapidly progressive infectious disease that primarily involves the fascia and subcutaneous tissue. It is an uncommon but life threatening infection. It can affect all parts of body and the lower extremities are the most common sites of infection.[1–3] The predisposing conditions are diabetes mellitus, liver cirrhosis, alcoholism, hypertension, chronic renal insufficiency, and malignancy. Prompt diagnosis and early treatment with adequate antibiotic with or without surgical intervention are vital because of high mortality. We

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1413-8670
http://dx.doi.org/10.1016/j.bjid.2013.08.003

herein describe clinical, laboratory, microbiological features, and outcomes of 115 patients diagnosed with necrotizing fasciitis during a consecutive eight-year period and review the relevant literature.

Patients and methods

We retrospectively reviewed all necrotizing fasciitis cases at Mackay Memorial Hospital, Taitung from January 1, 2004 to December 31, 2011. Demographic data, clinical features, site of infection, type of comorbidities, microbiological and laboratory findings and outcomes were analyzed. The severity of liver cirrhosis was classified according to the Child–Pugh score. Diagnosis was made by operation and based on lack of resistance to blunt dissection of the normally adherent fascia, presence of necrotic fascia, and purulent discharge with a foul fish-water odor. Histopathological findings of surgical specimens typically show neutrophils and bacterial clumps infiltration between collagen bundles with focal necrosis were used to confirm the diagnosis when available. Blood and pus cultures were obtained at the time of first operative debridement. The number of operative debridement, the need for amputation, the duration of hospitalization, and in-hospital mortality rate were also documented.

The continuous variables, presented as medians and inter-quartile ranges (IQR, the range between the 25th and 75th percentile) due to the small sample size, were compared between surviving and non-surviving groups by the Mann–Whitney *U* test. Likewise the categorical variables were expressed by count and percentage and compared using the Yate's continuity correction or Fisher's exact test. To investigate the independent factors associated with death, simple and multiple logistic regression models were performed. All significant factors on univariate analyses were considered for the initial multivariate models. The final multiple logistic regression model was determined using the backward selection technique, wherein variables that did not improve model fit at $p < 0.1$ were discarded; however, the potential confounders such as age and gender were always forced in all multivariate models for adjustment. Moreover, multicollinearity was also evaluated by variance inflationary factor (VIF). Variables with VIF > 5 were then considered to have multicollinearity with other covariates and would be excluded from the multivariate analyses. The statistical analyses were performed with SAS software version 9.2 (SAS Institute Inc., Cary, NC). A two-sided p-value < 0.05 was considered as statistically significant.

Results

Clinical findings

Out of 115 cases of necrotizing fasciitis enrolled 91 survived (79.1%) and 24 died (20.9%). There were 67 males (73.6%) and 24 females (26.4%) with a median age of 54 years (IQR, 44.0–68.0 years) in the surviving group; and 12 males (50%) and 12 females (50%) with a median age of 61years (IQR, 55.5–71.5 years) in the non-surviving group, respectively. Table 1 summarizes the clinical features of patients. The most common comorbidity was liver cirrhosis in 54 patients (47%) and diabetes mellitus in 45 patients (39%). Among the 54 patients with liver cirrhosis, 33 patients were chronic alcohol abusers, nine had chronic hepatitis B and 16 had chronic hepatitis C. Eight patients had no comorbidity. Local swelling/erythema, fever, pain/tenderness were the most common clinical features at presentation in 92 (80%), 87 (76%) and 84 (73%), respectively.

Table 1 – Clinical features of the 115 necrotizing fasciitis patients.

Clinical features	No. of patients (% of total)
Local swelling/erythema	92 (80%)
Fever	87 (76%)
Pain/tenderness	84 (73%)
Tachycardia	43 (37%)
Shortness of breath	32 (28%)
Shock	30 (26%)
Bullous lesion	25 (22%)
Consciousness change	7 (6%)
Crepitus	7 (6%)

Site of infection

The infection involved the head and neck in four cases (3%), the upper limb in 15 cases (13%), the trunk in 15 cases (13%), the lower limb in 70 cases (61%), bilateral lower limb in four cases (3%) and the perineum and scrotum in 11 cases (10%), as shown in Table 2.

Laboratory findings

An initial blood count revealed leukocytosis (total white count $>12 \times 10^3/\mu L$) in 60 of the 115 patients (52%), leucopenia (total white count $<4 \times 10^3/\mu L$) in nine of 115 patients (8%) and thrombocytopenia (platelet count $>150 \times 10^3/\mu L$) in 46 of the 115 patients (40%). Hemoglobin <10 mg/dL is observed in 42 of the 115 patients (37%). Prothrombin and activated partial thromboplastin time (>12 s and >36 s, respectively) were prolonged in 64 (56%) and 44 (38%) of the 115 patients respectively. Acute renal failure was diagnosed in 26 (23%) of the 115 patients but serum sodium and potassium remained normal in most cases. In 74 cases (64%), serum albumin level was below 3 g/dL, of whom 18 (16%) were Child–Pugh class C.

Table 2 – Anatomical sites involved with necrotizing fasciitis.

Anatomical location	Number of cases (%)
Head and neck	4 (3%)
Upper limb	15 (13%)
Right	8 (7%)
Left	7 (6%)
Lower limb	70 (61%)
Right	28 (24%)
Left	38 (33%)
Bilateral	4 (3%)
Perineum and scrotum	11 (10%)
Trunk	15 (13%)

Table 3 – Microorgansims isolated in patients with necrotizing fasciitis.

Microorganisms	Total (*n* = 115)	Survival (*n* = 91)	Nonsurvival (*n* = 24)	Mortality rate of pathogen (%)
Gram positive	60 (52.2%)	49 (53.8%)	11 (45.8%)	18.3%
MRSA	13 (11.3%)	10 (11%)	3 (12.5%)	23%
MSSA	12 (10.4%)	11 (12.1%)	1 (4.2%)	8.3%
CoNS	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Group A *Streptococcus*	14 (12.1%)	9 (9.9%)	5 (20.8%)	35.7%
Group B *Streptococcus*	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Group D *Streptococcus*	2 (1.7%)	1 (1.1%)	1 (4.2%)	50%
Non-group ABD *Streptococcus*	6 (5.2%)	6 (6.6%)	0 (0%)	0%
α-Hemolysis *Streptococcus*	4 (3.5%)	3 (3.3%)	1 (4.2%)	25%
Enterococcus	7 (6.1%)	7 (7.7%)	0 (0%)	0%
Gram negative	57 (49.6%)	42 (46.2%)	12 (50%)	21.1%
Escherichia coli	11 (9.6%)	10 (11%)	1 (4.2%)	9.1%
Klebsiella pneumonia	7 (6.1%)	5 (5.5%)	2 (8.3%)	28.6%
Enterobacter species	4 (3.5%)	4 (4.4%)	0 (0%)	0%
Serratia marcescens	3 (2.6%)	3 (3.3%)	0 (0%)	0%
Citrobacter freundii	3 (2.6%)	2 (2.2%)	1 (4.2%)	33.3%
Proteus mirabilis	7 (6.1%)	7 (7.7%)	0 (0%)	0%
Aeromonas hydrophila	7 (6.1%)	2 (2.2%)	5 (20.8%)	71.4%
Vibrio vulnificus	2 (1.7%)	0 (0%)	2 (8.3%)	100%
Morganella	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Pseudomonas aeroginosa	5 (4.3%)	4 (4.4%)	1 (4.2%)	20%
Salmonella group B	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Shewanella putrefaciens	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Acinetobacter species	2 (1.7%)	2 (2.2%)	0 (0%)	0%
Anaerobes	3 (2.6%)	2 (2.2%)	1 (4.2%)	33.3%
Provetella dentiola	1 (0.9%)	1 (1.1%)	0 (0%)	0%
Bacteroides fragilis	2 (1.7%)	1 (1.1%)	1 (4.2%)	50%

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; CoNS, coagulase negative *Staphylococcus*.

Microbiological findings

Isolated microorganisms are summarized in Table 3. A single organism was identified in 70 patients (61%) and multiple pathogens were isolated in 20 patients (17%) and no organism was identified in 30 patients (26%). The most common Gram positive bacteria were group A *Streptococcus*, followed by methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA). *Escherichia coli* was isolated in 11 patients and it was the most common Gram negative bacteria. *Aeromonas hydrophila* was isolated in seven patients and five patients (71%) died. *Vibrio vulnificus* was identified in two patients and both have expired. Blood culture was positive in 33 patients (29%): seven among group A *Streptococcus* and in five cases of *Aeromonas hydrophila*.

Treatment

Surgical debridement and amputation were performed in 102 patients and 8 patients, respectively. Five patients were not operated on. Two patients were too critical to be operated at the time of visit to the emergency department and the family refused operation in three patients due to old age and multiple comorbidities. All patients of *Aeromonas hydrophila* and *Vibrio vulnificus* infection received surgical intervention immediately but five of seven *Aeromonas hydrophila* patients and all *Vibrio vulnificus* patients died. One, two and three and above three surgical debridement were performed in 31, 33, 35 patients respectively. The mean hospitalization time was 24.5 days (SD 16.29 days).

Clinical outcome and factors predictive of death

Of the 115 patients, 24 (20.9%) died and 91 (79.1%) survived. Baseline comparisons between surviving and non-surviving patients with necrotizing fasciitis are shown in Table 4. There were significant differences in age, gender, hospital days, peptic ulcer disease, hemoglobin, platelet, prothrombin time, activated partial thromboplastin time, and all biochemistry tests. The non-surviving group was older, had higher prothrombin time, activated partial thromboplastin time, and glucose, creatinine, aspartate aminotransferase and alanine aminotransferase serum levels (all $p \leq 0.046$); additionally, this group had shorter length of hospital stay, and lower hemoglobin, platelet and albumin levels (all $p < 0.001$). The percentage of peptic ulcer disease was higher in the non-surviving group (58.3%) than in the survival group (30.8%, $p = 0.024$).

Risk factors associated with death are listed in Table 5. In univariate analysis, gender, hospital days, diabetic mellitus, peptic ulcer disease, hemoglobin, platelet, prothrombin time, activated partial thromboplastin time, glucose, creatinine, aspartate aminotransferase, alanine aminotransferase and albumin were significant predictors of death (all $p \leq 0.034$). In multivariate analysis, after adjusting for age and gender, which were forced in the model for controlling for potential confounding effect, the significant risk factors were gender,

Table 4 – Summary of baseline characteristics by outcome.

	Survival ($n=91$)	Death ($n=24$)	p-Value
Demographics			
Age (years)[a]	54.0 (44.0, 68.0)	61.0 (55.5, 71.5)	0.046*
Gender[b]			0.049*
Female	24 (26.4)	12 (50.0)	
Male	67 (73.6)	12 (50.0)	
Hospital days (days)	23.0 (15.0, 35.0)	11.5 (4.0, 25.5)	0.001*
Comorbidities[b]			
Diabetes mellitus	31 (34.1)	14 (58.3)	0.053
Hypertension	25 (27.5)	8 (33.3)	0.756
Liver cirrhosis	42 (46.2)	12 (50.0)	0.916
Cardiovascular disease	20 (22.0)	9 (37.5)	0.196
Chronic renal disease	26 (28.6)	12 (50.0)	0.082
Malignancy	6 (6.6)	2 (8.3)	0.672
Peptic ulce disease	28 (30.8)	14 (58.3)	0.024*
Gout	16 (17.6)	2 (8.3)	0.356
Hematology[a]			
HB (g/dL)	11.9 (9.5, 13.1)	9.9 (8.6, 10.8)	0.001*
WBC ($10^3/\mu L$)	13.9 (9.8, 22.2)	14.2 (9.7, 21.3)	0.682
PLT ($10^3/\mu L$)	243.0 (146.0, 332.0)	78.0 (48.0, 110.0)	<0.001*
PT (s)	12.0 (11.0, 12.9)	14.5 (12.9, 16.6)	<0.001*
APTT (s)	33.1 (29.8, 36.0)	49.4 (39.4, 59.4)	<0.001*
Biochemistry[a]			
GLU (mg/dL)	120.0 (100.0, 174.0)	280.0 (198.5, 382.0)	<0.001*
Cr (mg/dL)	1.3 (0.9, 2.4)	3.6 (2.5, 4.4)	<0.001*
AST (IU/L)	35.0 (19.0, 53.0)	130.5 (38.0, 161.5)	<0.001*
ALT (IU/L)	24.0 (14.0, 36.0)	98.5 (20.0, 125.5)	<0.001*
Albumin (g/dL)	2.8 (2.3, 3.1)	1.7 (1.2, 2.0)	<0.001*

HB, hemoglobin; WBC, white cell count; PLT, platelet; PT, prothrombin time; APTT, activated partial thromboplastin time; GLU, glucose; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a] The continuous data were presented as median (IQR), and compared between different groups by Mann–Whitney *U* test.

[b] The categorical variables were expressed by counts and percentages, and compared between different groups by the Yate's continuity correction or the Fisher's exact test, as appropriate.

* Indicated a significant difference between survival and death.

hospital days and albumin (both $p \leq 0.032$). Controlling for age, hospital days and albumin, males had a lower risk of dying than females (OR = 0.18, 95% CI: 0.04–0.86, $p = 0.032$); controlling for age, gender and albumin, for every one day increase in hospital stay, death OR decreased by 0.91 (95% CI: 0.85–0.97, $p = 0.004$); controlling for age, gender and hospital stay, for every one g/dL increase in albumin, death OR decreased by 0.05 (95% CI: 0.01–0.18, $p < 0.001$).

The comparisons between survival and death in necrotizing fasciitis patients with liver cirrhosis were shown in Table 6. There were significant differences in initial Child–Pugh class between survival and death ($p < 0.001$). The percentage of class C was higher in the non-surviving group (83.3%) than in the survival group (19.0%, $p < 0.001$).

Discussion

The term necrotizing fasciitis was introduced by Wilson in 1952 when he observed a rapid progressive inflammation and necrosis of subcutaneous tissue, superficial fascia, and superficial part of the deep fascia with variable presence of cutaneous gangrene. It has been divided into distinct groups on the basis of microbiological cultures. Type 1 infections are polymicrobial infections that are usually caused by non-group A streptococcus, other aerobic and anaerobic microorganisms. Type 2 infections are usually caused by *Streptococcus pyogenes* alone or with *Staphylococci*.[4–7]

Patients usually present with the triad of pain, swelling, and fever. Tenderness, erythema, and fever are common signs of early necrotizing fasciitis. In our study, local swelling/erythema, fever, pain/tenderness were noted in 92 patients (80%), 87 patients (76%), 84 patients (73%), respectively. It is important to recognize the early stage, which can present with minimal cutaneous manifestations, making prompt diagnosis difficult. Pain out of proportion at the physical examination is the most consistent feature noted at the time of presentation. An apparent cellulitis that does not respond to appropriate antibiotic therapy should raise suspicion of necrotizing fasciitis especially in patients who have an underlying disease. The presence of bullae filled with serous fluid is an important diagnostic clue and should raise the suspicion of this condition. As the infection progresses, the skin characteristically becomes more erythematous, painful and swollen with indistinct borders. The skin develops a violaceous hue, may become necrotic with bullae formation and eventually appears hemorrhagic and gangrenous lesion. But

Table 5 – Univariate and multivariate logistic regression models for the event of death.

	Univariate			Multivariate		
	OR	(95% CI)	p-Value	Adjusted OR	(95% CI)	p-Value
Age (years)	1.03	(1.00, 1.07)	0.060	1.04	(0.99, 1.09)	0.164
Gender (male)	0.36	(0.14, 0.90)	0.030*	0.18	(0.04, 0.86)	0.032*
Hospital days (day)	0.94	(0.89, 0.98)	0.003*	0.91	(0.85, 0.97)	0.004*
Diabetes mellitus	2.71	(1.08, 6.80)	0.034*			
Hypertension	1.32	(0.50, 3.47)	0.573			
Liver cirrhosis	1.17	(0.47, 2.87)	0.737			
CV dis	2.13	(0.81, 5.58)	0.124			
Chronic renal dis	2.50	(1.00, 6.28)	0.051			
Malignancy	1.29	(0.24, 6.83)	0.766			
Peptic ulcer disease	3.15	(1.25, 7.95)	0.015*			
Gout	0.43	(0.09, 2.00)	0.279			
HB (g/dL)	0.69	(0.54, 0.86)	0.001*			
WBC ($10^3/\mu L$)	0.98	(0.93, 1.04)	0.594			
PLT ($10^3/\mu L$)	0.98	(0.98, 0.99)	<0.001*			
PT (s)	1.31	(1.11, 1.55)	0.002*			
APTT (s)	1.23	(1.13, 1.34)	<0.001*			
GLU (mg/dL)	1.01	(1.00, 1.01)	<0.001*			
Cr (mg/dL)	3.24	(2.00, 5.26)	<0.001*			
AST (IU/L)	1.03	(1.02, 1.04)	<0.001*			
ALT (IU/L)	1.04	(1.02, 1.06)	<0.001*			
Albumin (g/dL)	0.06	(0.02, 0.19)	<0.001*	0.05	(0.01, 0.18)	<0.001*

HB, hemoglobin; WBC, white cell count; PLT, platelet; PT, prothrombin time; APTT, activated partial thromboplastin time; GLU, glucose; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TB, total bilirubin; DB, direct bilirubin.

* Indicates a significant association with the event of death.

large hemorrhagic bullae, skin necrosis, fluctuance, crepitus and sensory and motor deficits are late signs of necrotizing fasciitis. It is crucial to be alert to these characteristics because the earlier diagnosis of necrotizing fasciitis is made the better outcome and fewer complications will ensue. In our study, 25 patients (22%) had bullae and seven patients (6%) were noted with crepitus.[8,9]

Necrotizing fasciitis develops not only in the extremities but also in head and neck, trunk, perineum and scrotum. Infections of the head and neck region are associated with high mortality. Mao et al.[10] previously reported the poorer survival of patients with thoracic extension (60%) when compared to those without thoracic extension (100%). In our study all patients with head and neck infections have not extended to thorax and no one has died. It might have been due to the alertness of poor outcomes associated with infections of the cranio-cervical region and a more aggressive treatment was implemented in these patients.

Table 6 – Summary of characteristics by outcome (survival or death) in necrotizing fasciitis patients with liver cirrhosis.

	Survival (n = 42)	Death (n = 12)	p-Value
Demographics			
Alcoholism	25 (59.5)	8 (66.7)	0.747
Disease			
Initial Child–Pugh class			<0.001*
A and B	34 (81.0)	2 (16.7)	
C	8 (19.0)	10 (83.3)	
Hepatitis B	7 (16.7)	2 (16.7)	1.000
Hepatitis C	13 (31.0)	3 (25.0)	1.000

The categorical variables were expressed by counts and percentages, and compared between different groups by the Fisher's exact test, as appropriate.

* Indicated a significant difference between survival and death.

Alcohol consumption compromises the integrity of natural barriers to infection in the mouth and decrease saliva flow, resulting in an increased concentration of bacteria which predisposed to cervical necrotizing fasciitis. Although the involvement of extemities is often secondary to trauma, illicit drug use or insect bite, necrotizing fasciitis often develops without any obvious portal of entry in liver cirrhotic patients. Moreover, liver cirrhotic patients usually have chronic edema of the lower limbs, which may predispose them to minor trauma, resulting in an entry port of bacteria. On the other hand, bacteremia may first occur via the intestinal–portal route, because liver cirrhosis weakens the barrier to the passage of bacteria from the intestine to the systemic circulation. Bacteria in the bloodstream may subsequently seed in the edematous soft tissue of lower limbs and then cause infection.[11,12] In our study, necrotizing fasciitis in extremities, trunk and perineum occurred in 85 patients (74%), 15 patients (13%), and 11 patients (10%) respectively. It is consistent with other studies.

Some laboratory findings are common in necrotizing fasciitis, but are by no means diagnostic. Anemia, hypoalbuminemia, altered coagulation profile and elevated white cell count were common. In 74 cases (64%), serum albumin level was below 3 g/dL, which is probably due to associated malnutrition, compromised liver function due to alcoholism, hepatitis B, C, and the effect of bacterial toxins. Hemoglobin < 10 mg/dL was noted in 42 of the 115 patients (37%) because the red mass was frequently diminished by

thrombosis, echymoses, sequestration by the reticuloendothelial system and hemolysis. Production of red cells by the bone marrow was often depressed by infection and toxemia in these patients. The association of thrombocytopenia, altered coagulative profile and elevated creatinine level with higher mortality found in our study is similar to previously reported articles. It may be due to disseminated intravascular coagulation and toxic shock syndrome. In multivariate analysis, negative prognostic factors for survival were gender, decrease albumin level and decreased length of hospitalization time. It might be due to critical initial presentation with fulminant clinical evolution. Survivors were healthy enough to tolerate further debridement and this increased the length of hospitalization time as found in our series.[13–15]

Although it is rare, its mortality rate remains high. The etiology is still not fully understood and cannot be identified in many cases. However, it may result from prior history of trauma and certain conditions such as immunosuppression, diabetes mellitus, malignancy, drug abuse and chronic renal disease. Diabetes mellitus is the most common predisposing factor for necrotizing fasciitis and longer hospitalization and higher mortality have been reported. In our study, a higher mortality rate of 58.3% was noted in diabetic patients compared to non-diabetic patients. Hypertensive disease may result in impaired immunity by causing microvascular injury leading to impaired tissue oxygenation and antimicrobial delivery. A mortality rate of 33.3% was found in our hypertensive patients. The percentage of peptic ulcer disease was higher among non-surviving group (58.3%) than in survival group (30.8%).

Group A *Streptococcus* and *S. aureus* were the predominant pathogens causing necrotizing fasciitis in the USA and Europe. However, monomicrobial Gram negative aerobic pathogens such as *E. coli*, *A. hydrophila*, *V. vulnificus* were the most frequently isolated microorganisms in Asia. In our series, monomicrobial infections were found in 70 (61%) of 115 patients and polymicrobial infections were found in 20 (17%) of 115 patients. In our study, *Vibrio* spp. and *Aeromonas* spp. were not uncommonly detected as the causative organisms, in contrast to other studies. Two patients had Vibrio infection and seven patients had *Aeromonas* infection. One possible reason for this finding is that *Vibrio* spp. and *Aeromonas* spp. are natural inhabitants of seawater, and they are the two common causative pathogens of disseminated bacteremia in patients with liver cirrhosis, and chronic hepatitis. In our study, seven patients had *Aeromonas* infection and four of them had liver cirrhosis, chronic hepatitis. Two patients had *Vibrio* infection all had liver cirrhosis and chronic hepatitis. While clinical isolates of *A. hydrophila* are susceptible to a wide range of antimicrobial agents, they are universally resistant to penicillin, ampicillin, carbenicillin, erythromycin, streptomycin, cefazolin, and clindamycin, and are susceptible to chloramphenicol, ciprofloxacin, co-trimoxazole, aminoglycosides, and third generation cephalosporins. Antibiotic resistance in *Aeromonas* species poses a potential problem in antibiotic therapy. Intravenous administration of gentamycin or a fluoroquinolone such as ciprofloxacin is recommended for treatment of serious *Aeromonas* infections, with broad-spectrum penicillins and cefazolin being avoided as first choice agents, particularly for invasive infections. Since in many cases streptococcal or staphylococcal soft tissue infections will be suspected, empirical therapy directed against these organisms most often included penicillin-based antibiotics such as cloxacillin or cefazolin, to which *A. hydrophila* is intrinsically resistant. The possibility of *A. hydrophila* infection should be considered when confronted clinically by Gram negative bacilli in purulent exudates and soft tissue swabs. Only then can truly effective antibiotic treatment be provided. Tetracycline and third-generation cephalosporins have been the suggested treatment for *Vibrio* spp. Once *Vibrio* infection is suspected, appropriate effective early initiation of antibiotic treatment is important because it significantly improves mortality in *Vibrio* infection.[16–21]

Plain X-rays of involved area may show evidence of soft tissue air. In equivocal cases, Computerized Tomography and Magnetic Resonance Imaging are helpful in defining the presence and extent of infection. Although it cannot be overemphasized, these have been used primarily for patients in whom the diagnosis is doubtful. However, the extent of debridement is determined by physical findings at the time of surgery and not by Computerized Tomography findings.

Fournier's gangrene, a necrotizing fasciitis of the perineal, genital and perianal region was first described by Baurienne in 1764. Fournier's gangrene has a high death rate ranging from 15 to 50%, and is an acute urological emergency.[22,23] In our series, 11 patients were diagnosed Fournier's gangrene and only three patients survived (27%).

It has been reported to have a mortality rate of 34% (range 6–76%) in necrotizing fasciitis patients and a review involving affection of upper extremities found a mortality rate of 35.7%. Our mortality rate was 20.9%. Death usually occurred as a result of bacterial infection with septic shock, disseminated intravascular coagulation, and/or multiple organ failure. So, early recognition of necrotizing fasciitis followed by appropriate antibiotic therapy with or without surgical intervention is necessary to reduce mortality.[24,25]

Conclusion

Despite being a relatively uncommon infection, the present retrospective study highlights that necrotizing fasciitis can be the cause of notable morbidity and mortality among immunocompromised persons. *Aeromonas hydrophila* and *Vibrio vulnificus* infection may be frequently overlooked as the cause of skin and soft tissue infection. The rapid onset of cellulitis in the setting of soft tissue trauma should alert the clinician to the possibility of these two organisms intrinsically resistant to common antibiotics used for cellulitis. Therefore, it is important to have a high index of suspicion and increase awareness at initial presentation. Delayed diagnosis and treatment with adequate antibiotics were crucial for patient survival. Outcomes depend on the promptness of diagnosis, surgical treatment and management of post operative complications.

Conflicts of interest

The authors declare no conflicts of interest.

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Necrotizing Surgical Infection and Necrotizing Fasciitis in Obstetric and Gynecologic Patients

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ABSTRACT: Necrotizing fasciitis (NF) is a rapidly progressive disease characterized by extensive necrosis of the skin, fascia, and subcutaneous tissue, with sparing of the underlying muscle. Diabetes mellitus, Bartholin's gland abscess, and recent surgical procedures (including episiotomy) are factors often found in obstetric and gynecologic patients. Mortality in this group of patients is higher than in the general surgical population. Death is usually due to overwhelming sepsis, renal and respiratory failure, and multiple organ failure. The infections are usually polymicrobial, with α-hemolytic streptococci, gram-negative coliforms, and anaerobic bacteria. Lower survival has been reported in large series when the groin is involved or when the general nutritional state is poor. From October 1988 to August 1990, we treated five patients with necrotizing fasciitis. Certain important characteristics of such patients have not been discussed in the obstetric and gynecologic literature. Nutritional status, with special emphasis on total protein, albumin, and the effects of alcoholism, has a significant impact on mortality. Nutritional support of these patients may improve survival. To limit the impact of secondary infections, surgical approaches should be modified by the anatomic location of the initial lesions. More frequent debriding in the operating room and early fecal diversion are recommended.

NECROTIZING FASCIITIS (NF) is a rare, clinical syndrome characterized by extensive necrosis of the superficial fascia and subcutaneous tissues, with concomitant thrombosis of the cutaneous microcirculation. It is accompanied by severe systemic toxicity. NF was first recognized more than a century ago.[1] Wilson,[2] in 1952, was the first to cite the term "necrotizing fasciitis" and observed that no specific pathogenic organism was involved. NF was first reported in the obstetric and gynecologic literature in 1972.[3]

In most cases, minor trauma or surgical procedures are the initiating event. The most common presenting symptom is moderate to severe pain at the site, with pain often disproportionate to the physical findings. Bacteriologically, these infections are characterized as caused by synergistic combinations of aerobic and anaerobic bacteria. NF can affect any part of the body, but the extremities, abdomen, groin, and perineum are the most commonly involved.[3] Risk factors for NF are multiple and include diabetes,[4] intravenous drug use,[5] immunosuppression,[6] renal failure,[7] radiotherapy,[8] obesity, hypertension with arteriosclerosis,[9] malnutrition,[5] advanced age,[10] and operative trauma.

The diagnosis of NF is difficult to make and is often delayed. Mortality from NF is also high, with a reported range of 8.3% to 73.0%.[11,12] Janevicius et al[13] reported an average mortality of 38%. In contrast, the mortality rate from severe necrotizing infections of the perineal and pelvic areas is reported to be up to two times higher; in diabetics, the mortality may be six times higher.[14] Indeed, the mortality rate from severe necrotizing skin and wound infections in obstetric and gynecologic patients is greater than 33% in most series.[4,15,16]

Most of the reports in the obstetric and gynecologic literature have evolved from either the uniqueness of the presentation or the predisposing factors leading to the diagnosis. Few reports have discussed management beyond the need for early surgical debridement and antibiotic therapy for control of spreading infection in healthy tissues. During the past 3 years we have managed five cases of necrotizing fasciitis at the Medical College of Georgia Hospital. The purpose of this article is to present our recent experience and suggest a unified approach to obstetric and gynecologic patients with necrotizing infections in the 1990s.

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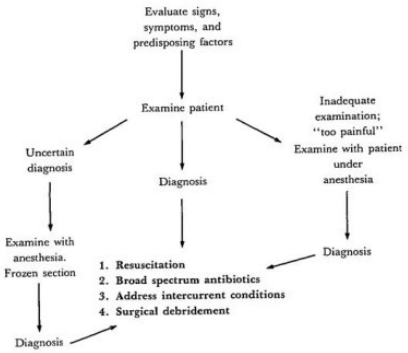

FIGURE 1. Algorithm for diagnosis of necrotizing infections.

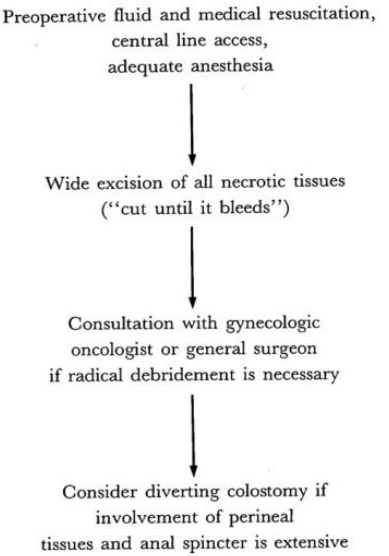

FIGURE 2. Proposed operative management of necrotizing infections.

CASE REPORTS

Case 1. A 47-year-old white woman (gravida 3, para 3) had spontaneous rupture of a left perianal abscess 2 days before admission. Her medical history was significant for alcohol abuse, alcoholic hepatitis, and malnutrition (weight 10% below ideal body weight and serum albumin value of 0.9 g/dL). Gynecologic history was significant for multiple episodes of left-sided Bartholin's gland abscesses. Admitting diagnosis was ruptured left vulvoperineal abscess with cellulitis complicated by lactic acidosis. The following morning, the wound was noted to have a gray discharge, necrotic edges, and a putrid odor. Presumptive diagnosis at that time was NF, and treatment with broad spectrum antibiotics was initiated.

At operation, necrotic tissue was found to involve the perineum, left vulva, and left anterior portion of the abdominal wall. The disease extended into the vulva and ischiorectal fossa superior to the rectum. After extensive dissection of the vulva, perineum, ischiorectal fossa, and superficial anterior abdominal wall, the wound was left open and packed with wet to dry saline dressings. On the first postoperative day, radiologic findings and pulmonary artery catheter pressures were consistent with adult respiratory distress syndrome (ARDS), and there were signs of worsening sepsis. Total parenteral nutrition was initiated. The patient's clinical condition did not allow reexploration. Her course was further complicated by systemic candidiasis on day 7. Her pulmonary status continued to decline and multisystem organ failure developed. Despite aggressive resuscitative measures, the patient became hypotensive and died on postoperative day 33.

Case 2. A 41-year-old woman (gravida 1, para 1) with massive obesity was admitted to a local hospital because of an abscess in the groin. An incision and drainage of the suprapubic abscess was done, and cultures obtained at surgery grew multiple organisms. The patient's condition worsened, and she was transferred to the Medical College of Georgia Hospital 4 days postoperatively. Examination on admission revealed a 6 cm necrotic ulcer at the surgical site extending into the left lower quadrant. Additionally, she was noted to have hyperglycemia, lactic acidosis, hypernatremia, hyperchloremia, and hypoalbuminemia. Preoperative resuscitation consisted of broad spectrum antibiotics, an insulin infusion, and intravenous fluid administration. After medical stabilization, exploratory operation revealed necrotic tissue involving the perineum, vulva, left groin, and entire left abdominal wall. Radical debridement of the vulva and necrotic abdominal wall tissue left an abdominal surgical defect measuring 40 x 30 cm. No ischiorectal fossa involvement was noted. The wound was left open and packed with wet to dry saline dressings.

Postoperatively, the patient was taken to the intensive care unit and given ventilatory support for 36 hours. Because her clinical condition rapidly improved, the wound was not reexplored. Parenteral hyperalimentation was begun in the early postoperative period to correct depressed prealbumin and transferrin levels and was discontinued when the patient tolerated oral feedings on postoperative day 5. Antibiotic therapy was discontinued on postoperative day 10. By day 12, the albumin level was normal (3.1 mg/dL). On day 31, with good healing and improvement in nutritional parameters, skin grafting by plastic surgery was done. She was discharged on postoperative day 50 and has done well.

Case 3. A 44-year-old woman (gravida 1, para 1) was found to have inoperable squamous cell carcinoma of the vulva in May 1990. Primary treatment consisted of external beam radiotherapy (4640 cGy) with concomitant 5-fluorouracil and cisplatin chemotherapy. Past medical history was significant for obesity, chronic obstructive pulmonary disease (COPD) due to cigarette abuse, and hypertension. An intestinal bypass had been done in 1973. In 1986 she had laser ablation of extensive perineal condyloma acuminatum.

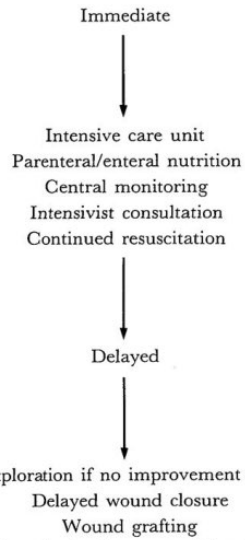

FIGURE 3. Proposed postoperative management of necrotizing infections.

In August 1990 she had an uncomplicated secondary radical excision of the residual vulvar carcinoma. On postoperative day 31, she complained of pain and wound drainage. Examination revealed extensive vulvar necrosis. She was admitted to the hospital for wound care and broad spectrum antibiotic therapy. On day 60 she had acute worsening of her condition and became febrile with altered mental status. Operation showed extensive necrosis of the vulva extending into the pubic symphysis and the adjacent abdominal wall. Exploration of the space of Retzius revealed extension into both obturator fossae. Radical debridement included partial pubic symphyseotomy, and the wound was left open. Cultures grew mixed flora. Total parenteral nutrition was begun on postoperative day 1. The postoperative course was complicated by prolonged intubation necessitated by the COPD. After extubation, the patient continued to receive wound care, parenteral nutrition, and conservative treatment and was discharged home on day 25 with a suprapubic catheter for a urethrovesicocutaneous fistula. The wound spontaneously closed after 11 months and the patient continues to do well.

Case 4. A 64-year-old black woman with non-insulin-dependent diabetes (NIDDM) and hypertension was admitted to the general surgical service with a history of multiple episodes of bartholinitis. Physical examination showed erythema extending to the right gluteal area. Initially, the general surgical service drained an extensive vulvar abscess. On postoperative day 3 the gynecology service was consulted, and a diagnosis of possible NF was made. Examination revealed extensive erythema of the right buttock extending to the right labia and mons pubis, with extensive necrosis and wound drainage. The patient was transferred to the gynecology service for care.

After broad spectrum antibiotic therapy was started, extensive surgical debridement of the right vulva, buttock, and ischiorectal fossa was done in addition to drainage of a paravaginal abscess. In the early postoperative period the patient was hypotensive and was treated with dopamine and norepinephrine bitartrate (Levophed). Early signs of a coagulopathy were treated with fresh frozen plasma. Total parenteral nutrition was begun on the first postoperative day. The wound was left open and packed with wet to dry saline dressings. Three days after the second procedure, additional debridement was done, with a prophylactic colostomy to prevent fecal soilage in the deep perineal area.

On day 16 she was transferred to the ward, where conservative wound management was continued. On day 20, a serum potassium value of 7.1 mg/dL prompted treatment with oral sodium polystyrene sulfonate (Kayexalate). Before any clinical effect of the medication, she aspirated vomitus and had a respiratory arrest. After cardiopulmonary resuscitation, the patient was responsive only to deep pain. Dialysis was begun for acute renal failure. After several episodes of hypotension, candidal sepsis was diagnosed and antifungal therapy was initiated. Despite all measures, the patient died the following day.

Case 5. A 59-year-old nulligravida with a history of end-stage renal disease necessitating hemodialysis, insulin-dependent diabetes, hypertension, coronary artery disease, and rheumatoid arthritis was admitted to the internal medicine service in July 1990 for evaluation of fever. Examination revealed a Bartholin's gland abscess. Two days later, on the advice of the general surgery service, the gynecology service was consulted. The diagnosis of NF was made, with physical findings of crepitus, erythema, and pain out of proportion for findings in the left perineum.

Broad spectrum antibiotic therapy was begun, followed by extensive debridement of the left vulva, buttock, groin, ischiorectal fossa, and upper aspect of the thigh. Total parenteral nutrition was begun on postoperative day 1. On day 6, the primary dissection was closed with skin flaps. Medical therapy during the postoperative course included dialysis and nutritional support. She was discharged home on day 29 and has continued to do well.

DISCUSSION

Four types of necrotizing surgical infections have been previously described: necrotizing fasciitis, clostridial cellulitis, clostridial myonecrosis, and synergistic necrotizing cellulitis.[11,17] A high mortality rate continues to be reported. Synopsis of necrotizing infections is listed in the Table.[11,18] The variations in these syndromes may make differentiation difficult even for experienced physicians. What is probably more important is to recognize an ongoing necrotizing process and the necessity for emergency treatment and debridement.

Review of the medical literature on NF suggests that, above all, early diagnosis and adequate debridement is critical to overall survival.[10,12] Sudarsky et al[5] suggested that morbidity and mortality are greater if operation is delayed more than 12 hours, even with broad spectrum antibiotic coverage. Since most teaching hospitals have only a few cases per year of NF, lack of experience lead-

TABLE. Synopsis of Necrotizing Surgical Infections*

	Necrotizing Fasciitis	*Synergistic Necrotizing Cellulitis*	*Clostridial Myonecrosis*	*Clostridial Cellulitis*
Predisposing Factors	Diabetes, trauma, peripheral vascular disease, immunodeficiency	Diabetes, perineal involvement, peripheral vascular disease, renal disease	Trauma, contamination	Trauma
Bacteriology	Aerobe-anaerobe	Aerobe-anaerobe	Clostridia, mixed gram-positive and gram-negative organisms	Clostridia, mixed gram-positive and gram-negative organisms
Tissue Involvement	Skin through muscle	Skin through muscle	Muscle to skin	Subcutaneous fissures
Systemic Toxicity	Moderate to severe	Severe	Severe	Mild
Pathologic Findings	Intense leukocytic infiltration, focal necrosis of fascia, thrombosis of microvasculature	Dense leukophilic infiltration and edema of dermis and superficial muscle	Dense leukophilic infiltration of dermis with hyaline necrosis of muscle and gas formation	Dense leukophilic infiltration of dermis with necrosis of vessels and sweat glands
Onset/Progression	Hours-days/rapid	Days/rapid	Hours-days/rapid	3 to 5 days/moderate
Clinical Findings	Red-purple color, blebs, edema, hypoesthesias, fever	"Dishwater" pus or edema, crepitus, fever, blebs, necrosis	"Bronze" erysipelas, sickly sweet odor, fever, crepitus, necrosis, tan color	Fever, crepitus, blebs, necrosis, red-brown fluid, edema, extreme wound pain

*Adapted from Kaiser and Cerra[11] and Fisher et al.[18]

ing to delay in early diagnosis remains common. In all five of our cases, surgical exploration was delayed by lack of recognition and experience. Three techniques may facilitate earlier recognition of NF. The first is adequate exploration of the wound, using general anesthesia if necessary. The second is the use of frozen section biopsy of necrotic tissue to facilitate diagnosis, as reported by Stamenkovic et al.[19] The third is to engender a high index of suspicion in physicians treating patients with known risk factors for NF by continued emphasis in the literature and teaching programs.

Diabetes, previous radiation therapy, advanced age, vascular disease, immunosuppression, and chronic renal disease place patients at risk for the development of NF. These underlying conditions undoubtedly contribute to the poor outcomes that have been reported in the literature.[10] The anatomic site of the necrotizing infection is also a prognosticator for patient survival. Perineal and perianal involvement have been uniformly associated with poor patient outcome.[4,7,17]

A regimen of broad spectrum antibiotics, aggressive surgical debridement, aggressive perioperative resuscitation, and nutritional support has been recommended for patients with NF.[5,11] All of our patients had significant delays in diagnosis and all had at least two serious chronic medical conditions at time of diagnosis of NF. Additionally, 80% (4/5) had deep perineal/perianal involvement. Despite this, we were able to salvage 60% (3/5) of our patients (40% mortality rate) by aggressive perioperative and postoperative management with intensive care support and parenteral nutrition. Recent reports on NF in the medical literature have recommended broad spectrum antibiotics and aggressive perioperative resuscitation, including invasive monitoring and nutritional support.[5,11,17] We agree with this management, as it seems to have improved survival in other patients with NF.[5,11,17]

Early wound closure has been recommended as an adjunct for postoperative care in patients with NF because of the difficulties in preventing infection and managing large open wounds.[5,17] We were able to use delayed primary closure in one patient, which significantly shortened the hospital course. Skin grafting was necessary in one other patient. The third survivor's wound healed by secondary intention, necessitated by previous extensive irradiation. The use of skin grafting and delayed wound closure have been described.[5,17] Amniotic membranes and Vicryl mesh have been used for wound coverage in case reports in the obstetric and gynecologic literature.[20,21]

Chronic fecal soiling of perineal/perianal wounds is an important factor to consider in compromised hosts. Adinolfi et al[22] reported a series of patients with NF in the perineal/perianal areas treated with diverting colostomy; the mortality rate was only 27%. Only one case in which treatment of NF included diverting colostomy has been reported in a gynecologic patient.[9] We believe

colostomy was important in Case 4, despite the patient's death from pulmonary aspiration. In retrospect, a prophylactic colostomy should have been done in patient No. 1, whose recurrent sepsis might have been due to continued fecal soilage. Unfortunately, her medical condition precluded another operative procedure. To facilitate wound care and decrease secondary infection, prophylactic colostomy should be considered in patients with deep perineal/perianal involvement.

On the basis of our experience and that reported in the literature, we propose a series of algorithms to aid in the diagnosis and treatment of NF. The decision algorithm for diagnosis, presented in Figure 1, emphasizes the importance of evaluating the signs and symptoms of NF and assessing medical risk factors. Without this assessment, diagnosis and treatment are likely to be delayed, jeopardizing survival. Figure 2 emphasizes the importance of radical debridement of the wound with consideration of diverting colostomy if the perianal area or sphincter area are involved. Intensive care and support are outlined in Figure 3. We believe aggressive reexploration is indicated anytime there is not rapid clinical improvement or wound healing. Delayed wound closure (or grafting) is also helpful in reducing sepsis.

In summary, NF requires aggressive early intervention and modern adjuvant therapy in intensive care, nutritional support, and plastic surgery techniques.

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ARTÍCULO ORIGINAL

Guía de Práctica Clínica para el Diagnóstico y Manejo de las Infecciones de Piel y Tejidos Blandos en Colombia

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Resumen

Las infecciones de piel y tejidos blandos (IPTB) representan la tercera causa de consulta por enfermedad infecciosas a los servicios médicos, después de las infecciones respiratorias y urinarias. Se presenta una guía de práctica clínica (GPC) con 38 recomendaciones basadas en la evidencia, graduadas bajo el sistema SIGN, para el diagnóstico y tratamiento de pacientes adultos con IPTB en el contexto colombiano, posterior a un proceso de adaptación de GPC publicadas y la búsqueda sistemática y síntesis de literatura para la actualización de la evidencia científica. Además, se realizó un consenso de expertos para la evaluación de las potenciales barreras para la implementación de las recomendaciones y la evaluación del grado de recomendación en el contexto local.

Palabras claves (DeCS): Enfermedades Cutáneas Infecciosas, Absceso, Celulitis, Fascitis Necrosante, Piomiositis, *Staphylococcus aureus*.

Clinical Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections in Colombia

Abstract

Skin and soft tissue infections (SSTI) represent the third leading cause of infectious disease consultation for medical services after respiratory and urinary tract infections. This document generates a clinical practice guideline with 38 recommendations based on evidence, graduated under the SIGN system for the diagnosis and treatment for SSTI infections in adult patients in Colombia, following a process of adaptation of guidelines published, and the systematic search and synthesis of literature for the updating of scientific evidence. In addition, a consensus of experts was made for the evaluation of the potential barriers for the implementation of the recommendations and the evaluation of the degree of recommendation in the local context.

Key words (MeSH): Skin Diseases, Infectious; Abscess; Cellulitis; Fasciitis, Necrotizing; Pyomyositis, Staphylococcal skin infections.

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Recibido: 30/11/2018; Aceptado: 06/04/2019

Cómo citar este artículo: S. Valderrama-Beltrán, *et al.* Guía de Práctica Clínica para el Diagnóstico y Manejo de las Infecciones de Piel y Tejidos Blandos en Colombia. Infectio 2019; 23(4): 318-346

Introducción

La infección de piel y tejidos blandos (IPTB) constituye una de las causas principales de consulta a nivel mundial, precedida únicamente por las infecciones de tracto respiratorio (ITR) y las infecciones urinarias (IVU)[1]. Juntos, estos tres grupos conforman cerca del 71,8% de visitas a los departamentos de urgencias de los EE.UU para el periodo 2006-2010 (19,1% ITR, 12,6% IVU y 11,1% IPTB). En nuestro medio se ha reportado que 2,7% de los pacientes consultaron al primer nivel por una durante el 2014[2]. Datos aportados por la encuesta médica ambulatoria nacional y la encuesta médica hospitalaria nacional en los EE.UU han demostrado que las visitas por IPTB aumentaron en un 50% entre 1997 y 2004[3]. El aumento en la presentación de IPTB puede estar relacionada al envejecimiento de la población, el mayor número de comorbilidades, los estados de inmunosupresión y el uso indiscriminado de antibióticos[4].

Las IPTB, como su nombre lo indica, son infecciones que afectan cualquier capa de la piel, fascia o músculo (5). El programa de vigilancia antimicrobiana "SENTRY" ha reportado la etiología de las IPTB en Norteamérica, Latinoamérica y Europa de 1998 a 2004, encontrando como principal causa al *Staphylococcus aureus*[6]. La resistencia reportada a *S. aureus* para ese momento fue de 23 al 36%, sin embargo, la resistencia de este microorganismo en Norteamérica y el norte de Latinoamérica ha aumentado de manera importante en los últimos años; desde 2004 se ha descrito la epidemia de *S. aureus* meticilino resistente adquirido en la comunidad (SAMR-AC) en estas regiones, atribuido a la propagación del clon USA 300 (reconocido como la principal causa de IPTB en estos países)[7-9]. En Colombia, la prevalencia global de SAMR se ha reportado entre 45 a 51% en infecciones invasivas en pacientes de hospitales de cuarto nivel[10,11], sin embargo, en el registro multicéntrico de pacientes hospitalizados con IPTB entre 2009 y 2016 realizado en 11 instituciones a lo largo del país, se documentaron 1134 casos, con 706 cultivos, de los cuales el 37% correspondieron a *S. aureus*, siendo el 68,7% microorganismos tipo SAMR[12].

Se calcula que de 16 a 34,1% de los pacientes con IPTB reciben un tratamiento inicial inapropiado, definido como un espectro antimicrobiano inadecuado, o una duración inadecuada del tratamiento; lo que se relaciona con un incremento en la estancia hospitalaria (1,39-5,4 días adicionales), aumento de los costos e incluso mayor riesgo de mortalidad (OR 2,91; IC 95%: 2,34– 3,62)[13,14]. Por las razones anteriores se justificó la construcción de una guía de IPTB en Colombia.

Objetivos y alcance de la guía

Objetivo de la guía:
Generar recomendaciones para el diagnóstico y tratamiento de las infecciones de piel y tejidos blandos (IPTB) en el contexto colombiano.

Aspectos clínicos abordados por la guía
La guía se enfoca en el diagnóstico y tratamiento de personas adultas con IPTB entre las cuales se abordan las siguientes (ver definiciones, anexo 1): IPTB purulenta, IPTB no purulenta, e IPTB necrosante.

Se excluyen de la guía los aspectos relacionados con el pie diabético, infecciones del sitio operatorio (ISO) incisionales superficiales y profundas, infecciones virales, asociadas a mordeduras o relacionadas a quemaduras e infecciones en inmunosuprimidos. Tampoco se tuvo en cuenta la población pediátrica.

Pacientes diana
La guía está construida para el abordaje de pacientes adultos (de 18 años o más) , con origen en la comunidad o en el hospital que consultan a los servicios de salud ambulatorios u hospitalarios.

Usuarios diana
La guía está construida para orientar la práctica clínica de los profesionales de la salud en el ámbito asistencial, en consulta externa y en hospitalización. Los usuarios de la guía incluyen médicos generales o especialistas con formación en infectología, medicina familiar, medicina interna, dermatología, urgencias, cirugía general, o cirugía plástica. También se propone para profesiones de la salud que apoyan actividades de diagnóstico o atención de pacientes con los diagnósticos anotados como enfermería, bacteriología o microbiología, entre otros.

Metodología de desarrollo de la guía de práctica clínica
El desarrollo de la GPC para el diagnóstico y tratamiento de las IPTB se llevó a cabo siguiendo una metodología específica propuesta para la adaptación de guías de práctica clínica. Esta metodología incluye la búsqueda sistemática, tamización y evaluación de la calidad de guías de práctica clínica publicadas por otras sociedades científicas o servicios de salud, la búsqueda sistemática y síntesis de literatura para la respuesta de preguntas clínicas adicionales y para la actualización de la evidencia científica de algunas recomendaciones, la evaluación de las potenciales barreras para la implementación de las recomendaciones contenidas en la guía y la evaluación del grado de recomendación en el contexto local; a través de un consenso de expertos.

Equipo de desarrollo de la guía (EDG) y participantes en el consenso
El equipo de desarrollo de la guía es parte de la Asociación Colombiana de Infectología (Capítulo Central) con formación en enfermedades infecciosas de adultos y metodología en el desarrollo de guías de práctica clínica (SLVB, JAC, CAAM, JLCA, MACF). Se convocó a médicos especialistas en enfermedades infecciosas, microbiólogos y representantes de la Sociedad Colombiana de Cirugía y la Asociación Colombiana de Medicina Interna. El grupo de consenso quedó integrado por médicos con especialidad en las diferentes áreas y microbiólogos.

Revisión de la literatura

Fuentes consultadas y resultados iniciales de la búsqueda

Para la realización de la búsqueda bibliográfica se contó con la colaboración de una documentalista independiente, quien realizó una búsqueda sistemática en diversas fuentes, según una estrategia diseñada previamente. La búsqueda de la literatura estuvo restringida a referencias en idioma español e inglés, sin límites en fecha de publicación. Se realizó búsqueda de la literatura en bases de datos especializadas: Guidelines International Network, Agency for Healthcare Research and Quality/ National Guidelines Clearinghouse, CMA Infobase: Clinical Practice Guidelines, Catálogo de Guías de Práctica Clínica en el Sistema Nacional de Salud, National Institute for Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (NICE), American College of Physicians (ACP). Para la búsqueda en bases de datos se utilizaron los siguientes descriptores o palabras claves ajustados a los distintos buscadores: Skin Diseases, Infectious; Cellulitis; Erysipelas; Abscess; Skin Soft tissue infection. La búsqueda se realizó en los siguientes buscadores o bases de datos: PubMed (Medline, Biblioteca del Congreso de los Estados Unidos), Science Direct, Scopus, Embase, Lilacs.

El proceso de búsqueda arrojó como resultado 19 archivos de los cuales se eliminaron 8 por falta de coincidencia con el tema de interés.

Tamización y evaluación de las guías identificadas

Una vez terminada la búsqueda en las bases de datos anteriormente mencionadas, se procedió a la eliminación de duplicados, aplicación de criterios de inclusión y finalmente aplicación de la escala de evaluación de utilidad de la guía. Se tuvieron en cuenta los siguientes criterios de inclusión: humanos, adultos (edad ≥18 años), sin límite en año de publicación, idioma español o inglés. Se excluyeron aquellos con diagnóstico de infección de sitio operatorio y pie diabético. También se excluyeron guías de prevención, paliación, y rehabilitación.

Con el objetivo de asegurar la calidad de los documentos rescatados, se usó la escala de tamizaje propuesta por el Instituto de evaluación de tecnologías IETS[15]. La evaluación de cribado se realizó por parte de experto clínico y metodológico. La evaluación de tamización se aplicó a 11 documentos o GPC, cada evaluador desarrollo el proceso de manera individual e independiente; diligenciando una evaluación para cada documento. Una vez se tuvieron los formatos de tamizaje diligenciados se digitó la información en una base de datos construida en el software de análisis de datos SPSS 20, Inc. Chicago, USA® para la posterior estimación del índice de acuerdo de Kappa de Cohen.

Para la evaluación de las guías se ha utilizado la herramienta propuesta por parte del Ministerio de Salud y Protección Social, en la reglamentación para la habilitación de las instituciones prestadoras de servicios de salud; la metodología AGREE II, esta es una herramienta que evalúa el rigor metodológico y la transparencia con la cual se elabora una guía[15]. Para la evaluación con esta metodología se usó un instrumento que consta de 23 ítems agrupados en 6 dominios que, en resumen, dan cuenta la calidad de la guía, y dos ítems de evaluación global de la guía.

Documentos seleccionados

A través de la metodología descrita se escogieron dos guías de práctica clínica: Las guías coreanas: Clinical Guidelines for the Antibiotic Treatment for Community-Acquired Skin and Soft Tissue Infection[16]; y Las guías de la Sociedad Americana de Enfermedades Infecciosas (IDSA, por sus siglas en inglés): Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America[17].

Preguntas adicionales y estrategia de búsqueda

Esta fase incluyó además la búsqueda complementaria de literatura de actualización a las recomendaciones, y la solución a preguntas clínicas que no estaban resueltas en las guías seccionadas para la adaptación. Se evaluó la pertinencia, las barreras de implementación y la actualización de evidencia científica.

Para el desarrollo de esta tarea se usó la escala propuesta por el Scottish Intercollegiate Guidelines Network (SIGN) (18) ilustrada en la tabla 1.

Desarrollo del consenso

Consenso Delphi en tiempo real. En un segundo momento, y con base en los resultados de la revisión sistemática, se desarrolló un consenso Delphi en tiempo real[19–21]. El grupo desarrollador formuló las preguntas que fueron puestas a consideración del grupo de expertos como la base de las recomendaciones. Conforme a las indicaciones de RAND/UCLA, se utilizó una escala ordinal de nueve categorías para calificar cada una de las recomendaciones formuladas. Teniendo en cuenta esto, cada una de las preguntas propuestas se calificó como recomendada (apropiada), contraindicada (inapropiada) o dentro de un nivel de incertidumbre, de acuerdo con el valor de la mediana de las respuestas de los expertos. Además, se presentó la información del grado de acuerdo (consenso) con los resultados de los rangos de respuesta a cada una de las preguntas. Esta calificación fue basada en el método descriptivo propuesto por Sánchez y colaboradores[22]. Finalmente, si después de tres rondas no existió consenso, se estableció que no se alcanzó el mismo y no se realizó ninguna recomendación. Al final, se enunciaron las recomendaciones según los resultados del consenso.

Fuerza de Recomendaciones

Dependiendo del valor de la mediana estimado de las votaciones entregadas por los participantes en la reunión de consenso; puede calificarse el grado de la recomendación, de la siguiente manera: i. Si la mediana se ubica en la zona de la escala 7 a 9 se considera que la recomendación es ade-

cuada, indicada o de primera línea. ii. Cuando la mediana se ubica en la zona de la escala 1 a 3 se toma la recomendación como no indicada o no recomendada. iii. Si la mediana se encuentra en la zona 4 a 6 no es posible plantear afirmaciones sobre qué tan adecuada o indicada es la recomendación. (ver Tabla 1.)

Procedimiento de difusión y actualización de la guía

Siendo la primera edición de la guía y con el fin de alcanzar el máximo grado de cumplimiento de los objetivos de esta GPC, así como contribuir a alcanzar los mayores niveles de calidad en la práctica asistencial en torno a las IPTB se publica en la revista Infectio (órgano de difusión de la Asociación Colombiana de Infectología) para su difusión con el objetivo de facilitar su acceso a los profesionales de la salud implicados. La participación de miembros de diferentes ramas de la medicina y sociedades científicas en sus diferentes niveles permitió al equipo de desarrollo tener en cuenta las posibles barreras organizativas potenciales que la aplicación de las recomendaciones de esta guía podía presentar, lo cual ha sido valorado a la hora de determinar las formas de implantación y difusión de esta guía. Se propone actualizar la presente guía en un plazo no mayor de 5 años.

Tabla 1. Escala de evaluación de artículos utilizados para la generación de recomendaciones.

Nivel de Evidencia	Tipos de estudio
1++	Meta-análisis de gran calidad, revisiones sistemáticas de ensayos clínicos aleatorizados o ensayos clínicos aleatorizados con muy bajo riesgo de sesgos.
1+	Meta-análisis bien realizados, revisiones sistemáticas de ensayos clínicos aleatorizados o ensayos clínicos aleatorizados con bajo riesgo de sesgos.
1-	Meta-análisis, revisiones sistemáticas de ensayos clínicos aleatorizados o ensayos clínicos aleatorizados con alto riesgo de sesgos.
2++	Revisiones sistemáticas de alta calidad de estudios de cohortes o de casos y controles, o Estudios de cohortes o de casos y controles de alta calidad, con muy bajo riesgo de confusión, sesgos o azar y una alta probabilidad de que la relación sea causal.
2+	Estudios de cohortes o de casos y controles bien realizados, con bajo riesgo de confusión, sesgos o azar y una moderada probabilidad de que la relación sea causal.
2-	Estudios de cohortes o de casos y controles con alto riesgo de confusión, sesgos o azar y una significante probabilidad de que la relación no sea causal.
3	Estudios no analíticos (observaciones clínicas y series de casos).
4	Opiniones de expertos.

Tomado y adaptado de sistema SIGN (Scottish Intercollegiate Guidelines Network (SIGN)[19].

Microbiología de las infecciones de piel y tejidos blandos

Los microorganismos causantes de infecciones de piel y tejidos blandos (IPTB) provienen principalmente del ambiente, de la microbiota corporal, y de las mucosas.

La gran mayoría de estas infecciones tanto agudas como crónicas son causadas por *S. aureus* y *Streptococcus pyogenes*, aunque es posible que estén en menor proporción estreptococos del grupo B, C y G. Otros agentes importantes, aunque considerablemente menos frecuentes, son *Enterococcus spp., Bacillus anthracis*, bacilos gram negativos como enterobacterias y *Pseudomonas aeruginosa*; y anaerobios como *Bacteroides spp, Peptostreptococcus spp,* y *Clostridium spp*[4].

S. pyogenes ha sido reportado como causa de la cuarta parte de los casos de celulitis difusa (con un factor de virulencia importante más que su capacidad de resistencia)[23], mientras *que S. aureus, P. aeruginosa, Enterococcus,* y *E. coli* son predominantemente aislados en pacientes hospitalizados[6].

S. aureus es el germen que en los últimos años ha causado gran impacto debido al aumento de infecciones ocasionadas por cepas resistentes a meticilina, tanto asociado al cuidado de la salud (SAMR-AH) como a la comunidad (SAMR-AC). Este último catalogado por varios estudios como el principal responsable de IPTB, ocasionando hasta el 59 % de los casos en la comunidad y en el hospital, mientras que *S. aureus* sensible se mantiene, pero en baja frecuencia[4,24]. En la tabla 2, se describen los agentes más frecuentemente involucrados en las IPTB así como sus factores de riesgo[6,23,25–29]. Para mayor información de la microbiología de IPTB ver Anexo 1.

Preguntas y evidencia

El resumen ejecutivo de las recomendaciones se puede revisar en la tabla 3 y las dosis recomendadas de antimicrobianos en la tabla 4. Las definiciones de las IPTB en el anexo 2.

¿Cuál es la mejor estrategia para el diagnóstico de impétigo y ectima?

1. Se recomienda basar el diagnóstico de impétigo y ectima en los hallazgos clínicos.
   Se recomienda realizar tinción de Gram y cultivo de secreción purulenta o exudado en los casos en que se quiera identificar S. aureus o estreptococo beta-hemolítico por interés epidemiológico

El impétigo es una infección superficial de la piel, que generalmente afecta a niños menores de 5 años, pero puede presentarse en cualquier momento de la vida. Existen en general dos tipos de impétigo: buloso (IB) y no buloso (INB). La forma más común de presentación del impétigo es el INB (70% de los casos), que es causado principalmente por *S. aureus o Streptococcus pyogenes*, y generalmente se puede observar en extremidades y rostro[16,17,30,31].

El ectima es una infección más profunda que el impétigo, sus lesiones son ulceradas en sacabocado y cubiertas por costras verde-amarillentas que se extienden en la dermis, con bordes elevados y eritematosos, usualmente con cicatriz como secuela. Su etiología principal es por estreptococos o *S. aureus*, incluso podría ser polimicrobiana en algunos casos. Las lesiones suelen ser múltiples y se ubican principalmente en miembros inferiores[31,32]. El diagnóstico del impétigo es clínico y las decisiones de tratamiento rara vez pueden basarse en los resultados de hisopados o tinciones.

En caso de existir exudado o material purulento, se podría tomar una muestra y realizar Gram y cultivo[16,33] sin embargo hay que tener en cuenta que estos resultados microbiológicos no diferencian claramente entre colonización e infección, las muestras usualmente no son tomadas correctamente y pueden ser no representativas[34]. En caso de definir realizar Gram y cultivo, el resultado de éste, en ningún caso debe retrasar el inicio del tratamiento empírico.

¿Cuál es la mejor estrategia para el tratamiento de impétigo y ectima?

2. El impétigo (buloso y no buloso) puede ser tratado con antibiótico tópico u oral, sin embargo, la terapia oral está recomendada para paciente con múltiples lesiones (más de 5), o en brotes epidémicos de glomerulonefrits (GMN) postestreptocócica para disminuir la transmisión de la enfermedad.
3. El tratamiento tópico de impétigo no buloso o buloso debe ser con mupirocina, ácido fusídico, retapamulina 2 veces al dia por 5 días..
4. El tratamiento para ectima debe ser oral.
5. Se recomienda que el tratamiento oral en casos de ectima o impétigo se realice con un antibiótico activo contra SAMR a menos que se tenga un cultivo que evidencie SAMS o Streptococcus β hemolíticos del grupo A, con una duración de 7 días.
   a. Se recomienda realizar el tratamiento empírico con trimetoprim/sulfametoxazol o clindamicina.
   b. Si la infección es por SAMS se recomienda cefalexina o dicloxacilina.
   c. Si la infección es por estreptococo beta hemolítico del grupo A se recomienda penicilina oral o cefalexina.

El antibiótico empírico que se seleccione para el manejo de impétigo debe permitir el adecuado cubrimiento tanto de *Streptococcus spp*., como *S. aureus*[16]. El impétigo es en principio, autorresolutivo, en los casos en que la infección es leve y no hay comorbilidades en el paciente puede no requerir un tratamiento específico[35].

En una revisión de Cochrane de 2016 se evaluaron diferentes intervenciones terapéuticas del impétigo[36], 26 tratamientos orales y 24 tópicos, incluyendo placebo (5.708 participantes). El manejo tópico con mupirocina y ácido fusídico fue igualmente efectivo en comparación con la terapia oral cuando la enfermedad no es extensa, al igual que Retapamulina que también ha mostrado efectividad. En Colombia hay una barrera de acceso a este último por no tenerla disponible en el mercado. En los estudios comparando antibióticos orales, penicilina fue inferior a eritromicina en dos estudios con 79 participantes (riesgo relativo (RR) 1.29, intervalo de confianza (IC) 95%: 1.07 a 1.56), y a cloxacilina en 2 estudios con 166 participantes (RR 1.59, IC 95%:1,21 a 2,08), por lo que la penicilina oral como manejo empírico no es adecuada para el impétigo. Se da la recomendación de manejo empírico con trimetoprim sulfametoxazol o clindamicina cuando se requiera manejo oral, basados en la epidemiología local. Remedios naturales como árbol de té, oliva, ajo y aceite de coco se han utilizado con algo de éxito, sin embargo, la evidencia es insuficiente para recomendarlos de manera rutinaria[34,37].

Por recomendación de expertos para pacientes con enfermedad extensa, ectima y en brotes epidémicos de glomerulonefrits (GMN) postestreptocócica se recomienda la terapia oral, con el objetivo de disminuir la transmisión de la infección[16,17].

¿Cuál es la mejor estrategia para el diagnóstico de IPTB purulenta?

6. Realizar tinción de Gram y cultivo de secreción purulenta.
7. Se recomienda utilizar la ecografía de piel y tejidos blandos como una herramienta para diagnosticar abscesos cuando existan dudas del diagnóstico después de la valoración clínica.

Las infecciones purulentas incluyen forúnculos, carbunclos y abscesos. *S. aureus* es el agente etiológico más frecuente en los dos primeros. Los microorganismos que se encuentran con más frecuencia en abscesos son *S. aureus y Streptococcus* β- hemolítico. Los anaerobios que predominan son cocos Gram positivos, bacilos Gram negativos (incluyendo *Bacteroides fragilis, Prevotella y Porphyromonas spp*) y *Fusobacterium spp*. Las infecciones por anaerobios son relevantes a nivel vulvovaginal, glúteos, perirrectal, dedos y cabeza, mientras que las infecciones por aerobios son prevalentes en cuello, manos, piernas y tronco.

La realización de tinción de Gram y el cultivo del pus recolectado del tejido infectado en forúnculos y carbunclos puede ayudar en la elección del antibiótico correcto, sin embargo, en casos típicos el manejo empírico puede iniciarse sin confirmación microbiológica[16,17,38,39]. En los abscesos, la realización de punción y aspirado siempre debería ejecutarse. En caso de no existir colección susceptible de drenaje, la mejor muestra es una biopsia pequeña de piel o tejido blando después de desinfección superficial y retiro del material necrótico[40].

Varios estudios a nivel internacional y nacional han evidenciado el aumento de cepas de *S. aureus* meticilino resistente como causante de infecciones purulentas. Un estudio observacional y multicéntrico de 2014, realizado en EE.UU investigó el impacto de la realización de un test de reacción en cadena de la polimerasa (de sus siglas en inglés, PCR) para

SAMR con resultados en 1 hora, en la prescripción de antibióticos en IPTB: a pesar de tener un disminución teórica de 58% a 6,5% en los pacientes identificados como infectados por cepas resistentes, el uso de antibióticos con espectro contra SAMR no disminuyó de manera estadísticamente significativa[41]. Lo anterior sugiere que en la actualidad no es claro el beneficio de estas pruebas diagnósticas en la toma de decisiones en IPTB, y antes de implementarlas se debe evaluar el costo-efectividad en nuestro medio.

Ecografía en el diagnóstico de IPTB purulenta: A pesar que el diagnóstico de absceso es explícito en la mayoría de los casos, pueden existir dudas diagnósticas ya sea por una presentación atípica o por la sospecha clínica de orígenes alternos al infeccioso (como el tumoral), en dichas ocasiones puede requerirse una imagen, como la ecografía de tejidos blandos[38].

En la ecografía, los abscesos suelen verse esféricos u ovoides, acompañados de bordes irregulares, centros hipo ecoicos e hiperemia periférica[42]. En una revisión sistemática publicada en 2017 se midió la precisión diagnóstica de la ecografía para la identificación de abscesos cutáneos en pacientes con IPTB en los departamentos de urgencias, se incluyeron 8 estudios, y se reportó una sensibilidad de 96,2% (IC 95%: 91,1 a 98,4) y especificidad de 82,9% (IC 95%: 60,4 a 93,9). Dada la limitación de ser operador-dependiente, es recomendable contar con personal entrenado en ecografía musculoesquelética que permita mejorar el rendimiento diagnóstico de la prueba[42-44].

Además de ayudar en el diagnóstico de abscesos, también se evidenció que la realización de la ecografía permitía cambios en el manejo terapéutico (realizar o no un drenaje) en 14 a 56% de los casos revisados. En el estudio de Tayal et al, se evidenció una tasa de error de 30 a 50% en drenar los abscesos basándose únicamente en los hallazgos clínicos, independiente de la probabilidad pretest[45,46].

¿Cuál es la mejor estrategia para el tratamiento de IPTB purulenta ?

8. Se recomienda la incisión y drenaje para absceso, carbúnculo, forúnculos grandes (más de 2cm) y quiste epidermoide infectado.
9. Para pacientes con IPTB purulenta asociada a signos de respuesta inflamatoria sistémica, inmunosupresión, absceso de más de cinco centímetros, absceso con celulitis extensa, o recurrente al manejo con incisión y drenaje, se recomienda el inicio de antibiótico oral contra SAMR en adición a la incisión y drenaje.
10. Para el manejo antibiótico empírico de IPTB purulenta se recomiendan las siguientes alternativas terapéuticas:

- Para el manejo ambulatorio: TMP SMX o clindamicina oral por 5 a 7 días, alternativa linezolid 600 mg oral cada 12 horas.
- Para el manejo hospitalario: Vancomicina, como alternativa: linezolid endovenoso, daptomicina, clindamicina endovenosa, tigeciclina o ceftarolina, **(se recomienda que estas dos últimas opciones sean consultadas con un especialista en infectología o avaladas por el comité de infecciones)** por 7 a 14 días.

A pesar de reconocer que el mejor tratamiento es incisión y drenaje, cerca de un 85,1% de pacientes recibe terapia antibiótica posterior al procedimiento, incluso de forma ambulatoria[47]. El principal factor relacionado con la adición de antibiótico a IPTB parece ser un eritema mayor a 2 cms (OR, 4.52; IC 95%, 1,39-14,75), sin embargo, la mayor parte de estos pacientes pudieron ser manejados ambulatoriamente (94%), sugiriendo que se trataba de infecciones purulentas leves[48].

A pesar de tener pautas recomendadas en las diferentes guías internacionales para el uso de terapia antibiótica en abscesos posterior a IPTB, actualmente existe la controversia del uso de ésta en todos los casos. Un metaanálisis de 2013 que incluyó 12 estudios y se concentró principalmente en las infecciones por SAMR, no encontró beneficio de manejo antibiótico en todos los casos[49], adicionalmente en un estudio retrospectivo y multicéntrico publicado en JAMA por Paydar y col., no se encontró diferencia en la resolución del cuadro clínico en pacientes que recibieron antibióticos discordantes al microorganismo hallado, versus pacientes con antibiótico dirigido[50]. A pesar de esta evidencia en contra, recientemente dos estudios apoyan el uso de antimicrobianos en todos los pacientes con IPTB purulenta, en 2016 Talan et al, realizó un estudio con 1247 pacientes, en los que se evidenció que la cura clínica entre el día 7 a 14 de tratamiento ocurría en el 80,5% de los casos de TMP/SMX y 73,6% en el grupo placebo (p= 0,005))[51]. Daum y colaboradores en 2017, con 786 sujetos incluidos en su estudio, que difiere del anterior en que sólo incluyo abscesos menores de 5 centímetros, reporta una cura clínica entre el día 17 a 20 en el 83% de los pacientes con clindamicina, 82% con TMP/SMX y 69% en el grupo placebo (p < 0,001), sin embargo, se observó una relativa alta frecuencia de diarrea en los que recibieron clindamicina[52].

Dados los datos presentados previamente, se identifican como ventajas para brindar el tratamiento a todos los pacientes, una mayor respuesta clínica, disminución de las recaídas y de la transmisión de SAMR entre contactos en casa, sin embargo, la magnitud del efecto benéfico es baja y se debe tener en cuenta el riesgo de eventos adversos, especialmente en pacientes con IPTB leves, y el riesgo de inducción de resistencia bacteriana. Teniendo en cuenta el balance de beneficios y efectos adversos se mantuvo la recomendación internacional de ofrecer tratamiento a los pacientes con IPTB purulenta asociada a SIRS, inmunosupresión, abscesos de más de 5 cms, con celulitis extensa, o recurrente al manejo con incisión y drenaje[16,17]. Ahora bien, en pacientes que requieran manejo antimicrobiano, siempre deben recibir cubrimiento de SAMR. En Colombia un registro multicéntrico en pacientes con IPTB[53], evidenció como agente etiológico principal al SAMR en infecciones purulentas, en un 57% de los casos el tratamiento empírico fue inadecuado, demostrando la baja cobertura de este microorganismo en el manejo.

Para el manejo de IPTB purulenta de pacientes que requieren hospitalización en una revisión de Cochrane 2016 con estudios de alto riesgo de sesgo se evaluó el uso de linezolid vs

vancomicina[54], se identificaron 9 estudios aleatorizados con un total de 3144 participantes. Linezolid mostró mayores tasas de curación clínica (RR 1,09, IC 95% 1,03-1,16), mayores tasas de cura bacteriológica (RR 1,17, IC 95%, 1,04-1,32), sin diferencias en mortalidad comparado a vancomicina (RR 1,44, 95% CI 0,75 to 2,80). Los autores anotan que se presenta la evidencia con alto riesgo de sesgos. Por tal motivo el grupo desarrollador de la guía considera que, dada la falta de evidencia adecuada, y teniendo en cuenta los costos, se recomienda el uso de vancomicina como primera línea y el de linezolid como alternativa, sin embargo, se requieren estudios de farmacoeconomía en nuestro medio. Otras alternativas para el manejo de pacientes con IPTB purulenta que requieren hospitalización son clindamicina, daptomicina, tigeciclina y ceftarolina, **recordando siempre que la escogencia de estos últimos antimicrobianos, deberá estar supeditada al visto bueno del médico especialista o el comité de infecciones institucional**.

De los medicamentos mencionados previamente, clindamicina oral, linezolid oral, daptomicina, ceftarolina y tigeciclina se encuentra por fuera del Plan Obligatorio de Salud y requieren prescripción por Mipres (Mi prescripción) lo cual podría limitar su uso en la comunidad. Linezolid también tiene una fuerte barrera de acceso económica por el costo de las tabletas en el mercado

La duración recomendada del antibiótico posterior a la incisión y drenaje, para pacientes que se pueden manejar ambulatoriamente es de 5 a 10 días y para pacientes que requieren el inicio de manejo hospitalario de 7 a 14 días[16,17].

¿Cuál es la mejor estrategia para el diagnóstico de IPTB para erisipela y celulitis?

11. Se recomienda la realización de hemocultivos, aspirados, o biopsia de piel para diagnóstico de erisipela o celulitis, en pacientes que se encuentren en quimioterapia activa, tengan neutropenia, inmunodeficiencia celular severa, o por interés epidemiológico.

No hay una prueba de oro que permita confirmar el diagnóstico de estas infecciones, y debido a que son no purulentas, la mayor parte de las veces basta con el examen físico y los datos epidemiológicos locales para diagnosticarlas; aunque no todo eritema siempre corresponderá a celulitis/erisipela. En países europeos, erisipela y celulitis pueden ser sinónimos, sin embargo, en América, aunque significan espectros de la misma enfermedad, se sigue utilizando la clasificación según profundidad del compromiso cutáneo. Cuando existe una lesión con eritema, calor y unos bordes que permiten diferenciar clínicamente entre el tejido sano y el tejido afectado, con compromiso de los vasos linfáticos, se diagnóstica una erisipela, en los casos en que estos bordes no son nítidos se considera una celulitis[55,56].

La presentación clínica de estas dos entidades tiene un rango amplio de diagnósticos diferenciales (la dermatitis por estasis, ulceras, gota, falla cardiaca y trombosis venosa profunda, TVP)[55]. En un estudio de pacientes hospitalizados, hasta un 30% estaban mal diagnosticados con celulitis, y algunos reportes han demostrado que cuando hay una segunda revisión por parte de dermatólogos, hasta un 74% de los pacientes diagnosticados con celulitis tienen otros diagnósticos[56,57].

En Colombia, según el registro multicéntrico de infecciones de piel y tejidos blandos, la celulitis representó el tipo más común de infección (50%), con datos similares a los españoles[58]. La mayoría de las pacientes no evidenciaron signos de respuesta inflamatoria sistémica (SIRS). De aquellos pacientes con complicaciones, la principal fue la abscedación de una celulitis[16].

La solicitud rutinaria de hemograma y reactantes de fase aguda no es mandatoria, y puede tener resultados inespecíficos, algunos estudios han reportado la utilidad de procalcitonina para establecer diagnósticos diferenciales (principalmente TVP), gravedad de la infección y como factor pronóstico, sin embargo, los estudios realizados hasta el momento no tienen adecuado poder y no se recomienda su uso de rutina[59,60].

Los hemocultivos no se deben realizar en todos los pacientes por su baja sensibilidad (positividad entre 0-24%)[23,59]. Tampoco se recomienda otro tipo de cultivos del área afectada, como cultivos de hisopados superficiales, que tienen bajo rendimiento y especificidad, e incluso de cultivos profundos por aspirado o biopsia de piel por su baja sensibilidad (cercana al 15%), sin impactar en el manejo del paciente[23,61,62]. Recientemente, escalas capaces de predecir la presencia de bacteriemia en este tipo de infecciones han sido estudiadas, como ALT 70 (puntaje > 5, con sensibilidad 61.3%, especificidad 70,9%) y la escala de predicción de bacteriemia en celulitis (área bajo la curva 0,865 (95 % CI, 0,804-0,926), sin embargo, faltan estudios de validación[81,82]. En pacientes inmunosuprimidos, en quimioterapia, neutropénicos la realización de hemocultivos, y cultivos profundos por aspirado o biopsia de piel pueden estar recomendados[16,17].

Por último, el uso de pruebas moleculares como reacción en cadena de la polimerasa (PCR) para detectar 16 S rRNA DNA, no mejoró sustancialmente la frecuencia de detección bacteriana y los aislamientos no difieren mucho de los encontrados con los cultivos por biopsia, no obstante, podrían tener alguna utilidad en infecciones polimicrobianas, y en pacientes con infecciones severas, donde la identificación de ciertos microorganismos pueden producir cambios en el tratamiento[63].

La mayoría de las veces, el diagnóstico por medio de imágenes no es necesario, sin embargo, en los casos en los que se sospeche compromiso osteoarticular o probabilidad de infección necrosante, la realización de imágenes diagnósticas, podría ser de ayuda[16,17,64].

Cuál es la mejor estrategia para el tratamiento de erisipela y celulitis?

12. Los antibióticos recomendados para el manejo oral de erisipela o celulitis de primera línea son cefalexina, como alternativa clindamicina, amoxicilina /clavulanato o TMP SMX.

13. Los antibióticos recomendados para el manejo intravenoso de erisipela o celulitis son la oxacilina, cefazolina, ampicilina sulbactam o clindamicina, y como alternativa amoxicilina/clavulanato,
14. Para pacientes en los que la celulitis se asocia con trauma penetrante, infección previa o colonización por SAMR, uso de drogas intravenosas, celulitis abscedadas, o inmunosupresión se debe administrar un antimicrobiano efectivo contra SAMR y estreptococos.
15. La duración recomendada de antimicrobiano es 5 días, pero el tratamiento podrá ser extendido si la infección no ha mejorado en este periodo de tiempo.

Recomendación de buena práctica: La elevación de área afectada y el manejo de factores predisponentes como el edema, o alteraciones dermatológicas subyacentes están recomendados.

En celulitis de miembros inferiores, el clínico debe examinar y tratar las fisuras de espacios interdigitales que permitan erradicar la colonización con patógenos y reducir la incidencia de recurrencia.

Se estima que la celulitis contribuye con el 0,04% de la carga mundial total de morbilidad[65]. Debido a que los principales agentes etiológicos de la erisipela y celultitis son el *estreptococo b* hemolítico del grupo A y *S. aureus*, este último especialmente meticilino sensible, la prescripción de antibióticos que cubran estos microorganismos es recomendable. El reporte de intervenciones en celulitis y erisipela de Cochrane 2010, incluyó 25 ensayos clínicos, evaluó betalactámicos, macrólidos, lincosamidas y estreptograminas[58], la evidencia no fue suficiente para recomendar una monoterapia sobre la otra. La selección de un antimicrobiano comparado a otro dependerá de un menor espectro, mayor biodisponibilidad (en el caso de los antimicrobianos orales), menos efectos adversos y disponibilidad en el plan obligatorio de salud[16,17]. Dentro de las opciones orales más recomendadas están cefalexina, amoxicilina/clavulanato, clindamicina o TMP/SMX, y dentro de las intravenosas: oxacilina, cefazolina, ampicilina sulbactam, clindamicina o amoxicilina clavulanato. En infecciones no complicadas, se recomienda un régimen de 5 días de antimicrobiano, se puede prolongar la terapia si no existe la respuesta clínica esperada[16,17,66].

Las fallas en el tratamiento de erisipela y celulitis, definidas como la recurrencia de la infección que requiere hospitalización o la falla al tratamiento inicial que requiere un cambio en el manejo antimicrobiano se han descrito en 12 a 29% de los pacientes[13]. Los siguientes factores se han relacionado: fiebre al momento del triaje (temperatura > 38°C), úlceras crónicas en miembros inferiores, edema o linfedema crónico, celulitis previa en la misma área, y celulitis en el sitio de una herida. En otro estudio, los pacientes mayores a 65 años también tenían un mayor riesgo de falla terapéutica, con riesgos aún mayores por cada 10 años en incremento de edad. Las fallas terapéuticas aumentan los días de estancia hospitalaria, la recurrencia (75%) y la probabilidad de muerte[13,67,68]. Por tal motivo se deben tener en cuenta estos factores de riesgo para definir el manejo antimicrobiano apropiado, la vía de administración y la duración de la terapia.

Otra consideración que se debe realizar es definir si pacientes con celulitis o erisipela requieren cubrimiento para SAMR. En un estudio multicéntrico, aleatorizado, doble ciego realizado en los EE. UU. en el 2017, se intentó determinar si la combinación de cefalexina con TMP/SMX era más efectiva para tratar una celulitis que la cefalexina sola, la combinación empírica de tratamiento no logró desenlaces superiores a la monoterapia, y una proporción similar de SAMR fue encontrada dentro de las fallas terapéuticas de cada grupo[69], con lo que se concluye que este tipo de cubrimiento no es necesario en todos los pacientes, y la monoterapia con betalactámicos o lincosamidas continúa siendo la elección. Sin embargo, varios autores recomiendan el cubrimiento empírico para cepas SAMR en los siguientes escenarios: pacientes con celulitis asociada con trauma penetrante, infección previa o colonización por SAMR, uso de drogas intravenosas, celulitis abscedadas, o inmunosupresión, por tener mayor riesgo de infección por este microorganismo[16,17].

Por otro lado, TMP/SMX es un antibiótico con uso recomendado para IPTB por SAMR, la creencia de su inefectividad contra *Streptococcus pyogenes*, por estudios retrospectivos, ha limitado su uso. Una revisión sistemática de la literatura en 2017 demostró que comparado con la clindamicina tiene una tasa de cura clínica similar (78% Vs 80%), 10 a 14 días después de completar la terapia[65]. Aunque TMP/SMX o clindamicina no han sido comparados en un estudio cabeza a cabeza con los betalactámicos, la alta tasa de éxito terapéutico encontrada por Miller et al, sugieren que cualquiera: betalactámicos, clindamicina o TMP/SMX son efectivos para el manejo de celulitis o erisipela[70].

En cuanto al uso de clindamicina oral y amoxicilina clavulanato, éstas no están incluidas en el plan de beneficios del sistema de salud de Colombia y requieren realización de "mi prescripción" (MiPres) lo cual podría limitar su uso.

¿Cuál es la mejor estrategia para el diagnóstico de IPTB necrosante?

16. La fascitis necrosante debe sospecharse cuando se presenta cualquiera de los siguientes síntomas o signos: (1) dolor importante inconsistente con los hallazgos en el examen físico, (2) deterioro clínico rápidamente progresivo, (3) SIRS, (4) ampollas, (5) edema a tensión (6) equimosis o piel necrótica, (7) crepitación palpable, (8) hipoestesia localizada en piel.
17. Se recomienda que el uso de escalas o procedimientos diagnósticos no retrase el inicio de tratamiento en pacientes con alta sospecha clínica.
18. En pacientes con duda clínica, se recomienda usar la escala de LRINEC modificado para orientar la decisión del manejo quirúrgico.

19. En pacientes con duda diagnóstica, se recomienda el uso de ecografía, TAC o RM según disponibilidad
20. El signo clínico principal intraoperatorio para diagnosticar IPTB necrosante es el aspecto macroscópico del tejido celular subcutáneo y la fascia.
21. Para el diagnóstico bacteriológico se recomienda realizar Gram y cultivo de tejido profundo intraoperatorio y hemocultivos.

Dentro de las infecciones necrosantes podemos encontrar la fascitis necrosante (FN), gangrena bacteriana sinergística progresiva, celulitis necrosante sinergística, gangrena estreptocócica, mionecrosis clostridial y celulitis no clostridial anaeróbica, sin embargo, la diferencia entre este espectro de enfermedades es sutil y el abordaje diagnóstico y terapéutico similar[71] La FN es una infección inusual, devastadora y rápidamente fatal que involucra la grasa de tejido celular subcutáneo y las capas profundas de fascia, caracterizada macroscópicamente por un tejido desvitalizado, falta de resistencia, sangrado fácil, la presencia de un exudado blanco grisáceo y la ausencia de pus. Las infecciones necrosantes pueden ser resultado de traumatismos obvios, así como rupturas no evidentes de piel o mucosa, no obstante, hasta un 20% son idiopáticas[72].

Existen varias clasificaciones de FN, la más aceptada la divide en dos. La fascitis tipo I de origen polimicrobiano, usualmente visto en pacientes ancianos o con comorbilidades basales (diabetes mellitus, episiotomías, fisuras rectales, cirugías urológicas, ginecológicas o colónicas). Son variaciones de este tipo de infecciones: la celulitis necrosante sinergística y la celulitis no clostridial anaeróbica[72,73]. Las infecciones necrosantes tipo II son monomicrobianas, con mayor presencia de organismos Gram positivos, principalmente estreptococos del grupo A, seguido por SAMR. Los pacientes que las padecen suelen ser de cualquier edad y pueden tener o no factores predisponentes, usualmente afecta los miembros inferiores (dos terceras partes de los pacientes). En los últimos años, dada la variedad de microorganismos causantes, se ha propuesto extender la clasificación a Grupo III (por Gram negativos: *Aeromonas* y *Vibrio vulnificus*) y grupo IV (fúngica)[72].

El reto en este tipo de infecciones es un diagnóstico temprano, la sospecha clínica elevada continúa siendo esencial para cualquier paciente que se presente al servicio de urgencias. La identificación diagnóstica tardía ocurre en 85 al 100% de los casos por la falta de especificidad de la sintomatología inicial de la enfermedad[74]. Los hallazgos clínicos que sugieren este diagnóstico son: 1) dolor importante, que es desproporcionado con respecto al compromiso de la piel (signo temprano, se presenta en 73 a 98% de los casos); 2) tejido duro y con consistencia de madera a la palpación del tejido subcutáneo, que se extiende más allá del área de compromiso de piel; 3) compromiso sistémico, a menudo con alteración del estado mental; 4) edema o sensibilidad en piel que se extiende más allá del eritema cutáneo; 5) crepitación, que indica gas en los tejidos; 6) lesiones bullosas; 7) necrosis de la piel o equimosis, y 8) falta de respuesta a la terapia antibiótica inicial[17].

Goh y colaboradores en una revisión sistemática identificaron como los tres signos más tempranos de fascitis necrosante: hinchazón (80.8%), dolor (79%) y eritema (70.7%)[75]. El rash equimótico, la epidermólisis necrosis tisular, y el choque séptico, hallazgos que se han descrito como "signos duros" de fascitis por Wang y colaboradores[75], aunque son más específicos de enfermedad necrosante, corresponden a un estado avanzado, tardío, con pocas posibilidades terapéuticas y pronósticas[76]. La presencia de crépitos al examen físico, si bien es reconocido como un signo de alarma, solo se presenta en el 13 a 31% de los casos de infecciones necrosantes[70,73,77–79]. En un estudio reciente de casos y controles, los factores capaces de diferenciar fascitis de celulitis incluían antecedente reciente de cirugía, dolor desproporcionado, hipotensión, necrosis de la piel y bullas hemorrágicas[63].

Desde hace varios años se ha considerado la implementación de escalas diagnósticas que permitan realizar la identificación oportuna de estas infecciones. Wall y colaboradores demostraron por medio de un análisis de regresión logística que leucocitos mayores a 15.4 x 10(9)/L y sodio menor a 135 mmol/L al ingreso, con una sensibilidad de 90% y especificidad de 76%, pueden distinguir fascitis necrosante de celulitis[72,80]. Por esto, la ausencia de estos hallazgos puede disminuir la probabilidad de este diagnóstico, pero desafortunadamente su presencia no es tan útil para confirmarlo.

Wong et at, construyó una escala predictiva denominada "Indicadores de Laboratorio de riesgo para Fascitis necrosante" (LRINEC, de sus siglas en inglés) en un estudio descriptivo analítico comparando paraclínicos de pacientes con infecciones necrosante profundas contra infecciones superficiales como celulitis. Las variables seleccionadas por la regresión logística fueron: glicemia, creatinina, sodio sérico, hemoglobina, proteína C reactiva (PCR) y leucocitos; el valor de la escala varía de 0 a 13 y clasifica el riesgo de fascitis en leve, moderado y severo. Un puntaje mayor a 6 fue asociado con una sensibilidad de 68.2% (IC 95% 51.4% - 81.3%) y especificidad de 84.8% (IC 95% 75.8% - 90.9%) para el diagnóstico de FN. Esta escala no tiene utilidad cuando los signos clínicos de fascitis son evidentes, y las conductas clínicas se deben tomar inmediatamente, su utilidad radica en reconocer tempranamente los casos de fascitis en los que los signos clínicos no son suficientes y una intervención temprana mejorará los resultados de los pacientes[72,73,81].

Estudios posteriores han mostrado pobre reproducibilidad de los resultados obtenidos por Wong. En un estudio asiático se encontró una curva ROC (de las siglas en inglés: "Receiver Operating Characteristic") menor a 0,5[86], la variabilidad en especificidad y sensibilidad reportada en diferentes estudios para la escala es amplia[72,73,81,82], y puede deberse en gran parte a la población en la cual se ha implementado. Esta herramienta puede perder cerca del 20% de los pacientes

que están cursando con una verdadera infección necrosante según lo evidenciado en un estudio de pacientes en el departamento de urgencias de los EE.UU[83]. Otra debilidad de la escala LRINEC es no considerar ningún factor clínico como edad, comorbilidades, y otros parámetros séricos (como lactato), los cuales podrían mejorar su rendimiento diagnóstico. En conclusión, mientras que un LRINEC alto aumenta la sospecha diagnóstica, un puntaje bajo no puede excluirla.

En el 2015 Borschitz y colaboradores, demostraron que los valores de proteína C reactiva son más relevantes de lo pensado y que los niveles de sodio sérico y glucosa tienen menor importancia, así realizaron variaciones del LRINEC demostrando que al ajustar los valores de proteína C reactiva (150 mg/l: 4 puntos y 100 mg/L: 2 puntos), intercambiar sodio y glucosa por conteo de eritrocitos y agregar niveles de fibrinógeno, así como agregar parámetros clínicos, específicamente el nivel de dolor, fiebre, taquicardia, y lesión renal aguda, se optimiza la escala predictiva, reportando una sensibilidad del 83% y una especificidad del 90% para los pacientes con sospecha fuerte (valor mas de 8). Una vez se obtiene el puntaje, es posible clasificar a los pacientes en 3 grupos: "sospecha fuerte", "sospechoso" y "no signos de infección necrosante"[74].

El uso de imágenes diagnósticas no es mandatorio en pacientes con sospecha de FN, usualmente consumen más tiempo que la realización del resto de paraclínicos y pueden retardar o fallar en el diagnóstico de infección necrosante, sin embargo, pueden ser de ayuda en el grupo de pacientes en que persiste la sospecha diagnóstica a pesar de la aplicación de las escalas predictivas[16,17]. En la radiografía la presencia de gas en el tejido blando representa el único signo específico de necrosis, pero es visto en un número limitado de pacientes, especialmente con infecciones por estreptococos del grupo A; por lo demás, la radiografía no evidencia hallazgos específicos; la TAC contrastada puede funcionar mejor que la radiografía (sensibilidad 80%). La ausencia de realce de la fascia junto con evidencia del compromiso de ésta, suelen tener mayor especificidad para infecciones necrosante que la visualización de aire o edema[84-86].

La resonancia magnética ha demostrado ser superior a las dos anteriores, los hallazgos sugestivos de FN incluyen la disminución de la intensidad de tejidos blandos en T1, la presencia de un aumento en la captación de la señal de T2 y áreas focales carentes de realce en la fascia profunda; tiene sensibilidad y especificidad entre 90 y 100%, y 50 y 85%, respectivamente[16,17,85,86]. Malghem y colaboradores, reportaron que el engrosamiento leve de la fascia intermuscular en el diagnóstico de FN tiene un significado limitado, ya que en algunos casos podría estar relacionado con celulitis o con compromisos no infecciosos de la misma, por lo que la especificidad puede estar sobreestimada[87].

Se han realizado varios estudios sobre la capacidad de la ultrasonografía en identificar infecciones necrosante, los hallazgos compatibles son engrosamiento fascial difuso, colecciones de fluidos anormales a lo largo del plano fascial e irregularidad de la fascia, se ha documentado una sensibilidad aproximada de 88,2%, y especificidad de 93,3%. La portabilidad y la rapidez en realización de US en los departamentos de urgencias, son ventajas de esta imagen, especialmente en instituciones con limitación para acceder a una resonancia magnética[86,88].

Otra herramienta diagnóstica a tener en cuenta, no menos importante de las previamente expuestas, es la realización de una biopsia de piel y fascia, que se puede realizar mediante una incisión exploratoria pequeña en el área con mayor compromiso o después de desbridamiento, en la que se tengan en cuenta: los hallazgos macroscópicos, la biopsia por congelación (los principales hallazgos son la presencia de neutrófilos, vasculitis y trombosis en la fascia), y la solicitud de Gram y cultivo. En descripciones de casos estos procedimientos se han relacionado con un manejo más oportuno y menor mortalidad, sin embargo, se debe recordar que la biopsia por congelación puede tener falsos negativos[16,17,89-91].

El resultado del Gram y cultivo de la biopsia de tejido profundo es esencial para el diagnóstico microbiológico de FN. Por otro lado, la toma de hemocultivos en pacientes con sospecha de FN es mandatoria, sus resultados, junto a los cultivos de tejidos, permitirán posteriormente el ajuste del antibiótico[89].

¿Cuál es la mejor estrategia para el tratamiento de IPTB necrosante?

22. Para los pacientes con alta sospecha diagnóstica de IPTB necrosante, se recomienda manejo quirúrgico.
23. El tratamiento antibiótico empírico debe ser de amplio espectro debido a que la etiología puede ser polimicrobiana, incluyendo el cubrimiento de SAMR. En nuestro medio se recomienda: vancomicina con cefepime o piperacilina/tazobactam más clindamicina endovenosa. Se recomienda remplazar vancomicina por linezolid endovenoso en pacientes con falla renal.
24. En caso de pacientes con compromiso de función hepática o cirrosis, ingesta reciente de comida de mar o contacto con agua salada, la terapia combinada con cefalosporina de tercera o cuarta generación y doxiciclina debe ser usada por sospecha de *Vibrio vulnificus*.
25. Para paciente con factores de riesgo para infección por *Aeromonas* spp. se recomienda el uso de cefepime, o quinolona más doxiciclina.
26. Una vez se cuenta con aislamiento microbiológico se debe ajustar la terapia antibiótica a un espectro más estrecho basado en la susceptibilidad del cultivo.
27. El uso de penicilina más clindamicina se recomienda para tratamiento en aquellos pacientes que tienen infección confirmada por *S. pyogenes*.

El manejo de las IPTB necrosantes radica en 4 puntos fundamentales: diagnóstico temprano, reanimación hemodinámica, desbridamiento de la lesión (siendo este último de gran relevancia para asegurar control de foco) y administración de antibióticos de amplio espectro[92].

El estado hemodinámico de estos pacientes suele estar gravemente comprometido, no solo por la generación de respuesta inflamatoria sistémica con la vasodilatación subsecuente, sino por grados variables de deshidratación dada la pérdida de la integridad de la piel. En el momento en que una infección necrosante sea sospechada, se debe iniciar una resucitación hídrica intensiva para optimizar el volumen intravascular, mantener perfusión de órganos, oxigenación de tejidos y limitar los efectos adversos de la hipotensión[93,94].

El manejo quirúrgico inicial con lavado y desbridamiento tiene un gran impacto en los desenlaces, y nunca debe ser retrasado a la espera de la estabilización hemodinámica previa a la inducción con anestésicos, porque el control del estado de choque no ocurrirá hasta no haber removido el tejido necrótico e infectado, y en ninguna circunstancia se debe llevar a un cierre primario de la lesión[95].

Una vez el paciente es manejado quirúrgicamente necesitará revisiones cada 6 a 24 horas, según el contexto clínico, con el objetivo de evaluar la progresión de la infección y la necesidad de aumentar la extensión de desbridamiento. En un estudio hasta el 64% de los pacientes requieren múltiples intervenciones[95].

Wall y colaboradores, recomendaron la admisión inmediata de pacientes con "signos duros" al quirófano (que incluye la presencia de bulas, equimosis que precede la necrosis, presencia de gas en el tejido al examen físico o por evaluación radiológica y anestesia cutánea), independiente de los hallazgos de laboratorio[96]. Una demora de 12 horas podría ser fatal dependiendo del progreso de la lesión. Múltiples estudios han demostrado el aumento en mortalidad con demoras en manejo quirúrgico hasta de 24 horas (9 veces más riesgo de muerte en 2 estudios)[70,78,97–100]. En caso de no tener una alta sospecha diagnóstica, previo al manejo quirúrgico deberán realizarse estudios imagenológicos y de laboratorio, sin diferir esto, el inicio de antibioticoterapia.

Los casos esporádicos y la dificultad en diagnóstico temprano han limitado la realización de estudios de tratamiento aleatorizados, por lo que la terapia antibiótica debe guiarse por epidemiología y el reporte de la tinción de Gram inicial. Teniendo en cuenta que las infecciones pueden ser polimicrobianas y que tienen mal pronóstico, el uso de terapia empírica de amplio espectro es la opción más adecuada.

La estrategia antibiótica inicial debe ser endovenosa dado el compromiso general que impactará la farmacocinética y la farmacodinamia de los medicamentos; se recomienda cubrir Gram negativos, incluyendo *P. aeruginosa*, Gram positivos incluyendo SAMR y anaerobios. Algunos autores recomiendan la adición de clindamicina empíricamente en la terapia de combinación considerando la alta frecuencia de infección por *S. pyogenes* como agente causante, el efecto "Eagle" (un fenómeno observado en el laboratorio, sin evidencia en ensayos clínicos, en que la acción del antimicrobiano no está afectada por el estado de crecimiento bacteriano), y por la capacidad de la clindamicina de inhibir la síntesis de la proteína M y su efecto perpetuador del choque[94,96,98,101]. Para el cubrimiento de microorganismos específicos según los cultivos, se puede ajustar el tratamiento a dosis altas de penicilina o ampicilina para *Clostridium spp, Streptococcus spp y Peptostreptococcus spp.* y metronidazol o clindamicina para el cubrimiento de anaerobios como *Bacteroides spp, Fusobacterium spp, y Peptostreptococcus spp*.

En caso de sospechar infección por gérmenes distintos a los comunes, deberán tenerse en cuenta los factores de riesgo descritos. La infección por *Vibrio vulnificus* debe ser altamente sospechada en pacientes con enfermedad hepática crónica (especialmente en cirrosis alcohólica o infección por virus de hepatitis B o C). Los estudios han demostrado que la ingesta de alcohol diaria puede aumentar el riesgo de infección por este microorganismo. Otros factores de riesgo adicionales son las inmunodeficiencias, enfermedad renal terminal (principalmente los que reciben dosis parenteral de hierro), desórdenes gastrointestinales (cirugía, úlceras, aclorhidria), diabetes mellitus y desórdenes hematológicos (talasemias, hemocromatosis)[101–104]. Los hombres están más predispuestos por varias razones entre las que figuran factores ocupacionales y recreacionales (con exposición a peces y mariscos), mayor nivel sérico de hierro y mayores tasas de alcoholismo. Otro factor de riesgo relevante es la ingesta o exposición a comida cruda de mar o actividades que involucran agua salada, especialmente en la primavera y el verano en países con estaciones (104). En los EE. UU, los individuos susceptibles a este microorganismo corresponden al 7 a 16% de la población adulta. Menos del 5% de los pacientes con aislamientos para este germen no tienen los factores de riesgo descritos y corresponden a "personas sanas"[87]. Las IPTB por *V. vulnificus*, representa solo un 30% del espectro de enfermedades que este germen puede causar (sepsis e infección gastrointestinal, son las otras), con un 8% de mortalidad atribuible[101,104].

Las fascitis necrosantes por *V. vulnificus* suelen ser más severas y rápidamente progresivas, dentro de los factores pronósticos se encuentra el nivel de leucocitos segmentados, el conteo de bandas, los niveles de albúmina, la hipotensión (<90 mm Hg) y trombocitopenia (<80,000 cel/mm3) (103). Los estudios demuestran que el LRINEC como puntaje predictor en este microorganismo es inadecuado para el diagnóstico temprano[82]. Los CDC (Centers for Disease Control and Prevention - Centros de control y prevención de enfermedades, por sus siglas en inglés) y las guías internacionales como la coreana y la americana, recomiendan una cefalosporina de 3 generación (ceftriaxona en nuestro medio) más doxiciclina como manejo empírico.

Otro microorganismo de relevancia es *Aeromonas hydrophila*, un bacilo Gram negativo que se encuentra en aguas cálidas, frescas y salobres en todo el mundo. La infección por este microorganismo ocurre usualmente posterior a heridas de inmersión como mordeduras por lagartos, serpientes o

peces. Por lo general se encuentran en las extremidades o en regiones corporales expuestas a la inmersión. Estas especies son resistentes a penicilinas y cefalosporinas de primera generación, por lo cual adicional al manejo quirúrgico es recomendable utilizar cefepime en el esquema antimicrobiano, quinolonas o TMP SMX al manejo, hasta obtener un aislamiento final[104].

El uso empírico de antifúngicos no es esencial, pero puede adicionarse cuando exista evidencia visual o crecimiento en sangre o en cultivos de elementos fúngicos como *Candida spp* o *Mucorales spp*.[16,17,85].

Se han estudiado intervenciones adicionales de manejo, y entre ellas las dos principales son el uso de inmunoglobulina endovenosa (IgIV) y la aplicación de oxígeno hiperbárico[16,17,85]. El mecanismo propuesto para la efectividad de la IgIV radica en su unión a los superantígenos circulantes y su posterior inactivación. Estudios retrospectivos demostraron algún tipo de respuesta, pero los ensayos aleatorizados terminaron por comprobar que no existe beneficio en supervivencia o costo efectividad. En 2017 el estudio danés INSTICTC (por sus siglas en inglés), aleatorizado, no encontró beneficio en función física o supervivencia a los 6 meses[105].

El oxígeno hiperbárico ha sido propuesto posterior a una intervención quirúrgica, con la racionalidad del aumento en la concentración de O2 disuelto en los tejidos que rodean al músculo o la fascia y su probable efecto bactericida en microorganismos anaerobios. No obstante, la limitación de cámaras hiperbáricas ha impedido estudios adicionales, por lo que su uso no es recomendado y no existe la evidencia suficiente[106].

Cuál es la mejor estrategia para el diagnóstico de piomiositis?

28. Realizar cultivos de secreción purulenta y hemocultivos para obtener aislamiento microbiológico.
29. Se recomienda la resonancia magnética para el diagnóstico de piomiositis. La tomografía y la ecografía se recomiendan como alternativa para el diagnóstico.

La piomiositis es una infección purulenta de los grandes grupos musculares estriados con formación de uno o más abscesos en las capas musculares profundas[107]. Se han identificado varios factores de riesgo que predisponen a esta infección, siendo todos comunes a la disrupción de la piel y a alteraciones en los mecanismos de defensa del huésped (VIH/Sida, diabetes, desnutrición, neoplasias, enfermedades autoinmunes, hepatopatías crónicas, uso de drogas IV, uso de esteroides). En un estudio argentino fue posible identificar algún factor predisponente en la mayoría de los casos, siendo el más frecuentemente identificado la infección por VIH en el 60%[107,108]. Cerca del 50% de los pacientes acusan haber sufrido un trauma contundente o antecedente de ejercicio intenso[106].

Dentro de los grupos musculares más comúnmente afectados, se encuentran la cintura pelviana y los miembros inferiores (cuádriceps 26 %, iliopsoas 14%, gemelos y psoas), sin embargo, el tronco, los brazos y la espina también pueden verse afectados, además puede identificarse un compromiso uni o multifocal. El primero fue más frecuente (59%) en el estudio de Méndez y colaboradores[107]). Hasta en el 40% el compromiso puede ser secuencial o simultáneo[108,109].

Fisiológicamente hay identificación de tres estadios[106]. En el estadio I, la siembra bacteriana a nivel muscular ocurre, causando edema y dolor, sin embargo, dado que los músculos afectados son muy profundos, la aponeurosis muscular y la fascia pueden retardar transitoriamente el compromiso del tejido celular subcutáneo y la piel junto con los signos inflamatorios superficiales, los estudios han demostrado que existe una demora en el diagnóstico cercano a los 10 días (93). En el estadio II o supurativo, que ocurre 10 a 20 día posterior a la lesión, hay formación de colecciones y aunque la mayor parte de los pacientes son reconocidos en este periodo, no hay signos clínicos obvios de absceso o afección muscular propiamente dicha. Se deben realizar estudios para descartar diagnósticos diferenciales como trombosis venosa profunda, hematomas, sarcoma, tromboflebitis, artritis séptica y osteomielitis. Si la enfermedad progresa, es posible identificar un estadio II cuando hay disfunción multiorgánica y sepsis[106-108].

La mayoría de los pacientes presentan clínicamente fiebre y mialgias, asociadas a músculos que se palpan "leñosos" y hallazgos paraclínicos específicos dentro de los que se encuentra una leucocitosis moderada con desviación a la izquierda, elevación de la velocidad de sedimentación globular (VSG) y PCR, y enzimas musculares normales (algunas veces pueden elevarse)[87]. Los hemocultivos son positivos en el 5 a 30% de los casos, y de estos hasta un 75% son positivos para *S. aureus*, seguido de estreptococos del grupo A, y neumococo, aunque los bacilos Gram negativos vienen en aumento (30%)[16,17,106-108]. Un estudio colombiano mostró en 132 pacientes con piomiositis que más del 95% tenían cultivo positivo para *S. aureus*[110].

Las diferentes técnicas radiológicas ayudan no solo al diagnóstico sino ofrecen un abordaje terapéutico mediante drenaje. La punción guiada por ecografía es un procedimiento útil para el diagnóstico temprano, descartar otros diagnósticos y mejorar la sintomatología del paciente. Dada la facilidad para su realización en los departamentos de urgencias, está recomendada. Es capaz de identificar el tejido perimuscular y la presencia de colecciones (hipoecoicas), con realce posterior. Por ecografía los abscesos no poseen flujo interno y son compresibles manualmente, lo cual la diferencia de otras masas apreciadas en tejidos blandos[106,108].

La tomografía computarizada permite evaluar todos los planos de la lesión, y es útil en identificar el compromiso muscular profundo como en el caso del psoas, en que la ecografía no es suficiente. Por medio de la adición de medio de contraste es posible presencial un anillo de realce en las áreas necróticas del músculo viable[101,108].

La prueba de oro es la resonancia magnética (RM), permite visualizar la extensión total de la infección y la localización exacta de la misma, así como el compromiso de estructuras adyacentes (articulación, hueso, etc); es el método más sensible para detectar cambios inflamatorios en la fase supurativa temprana, por lo que ayuda en el diagnóstico precoz. Sin embargo, su realización está limitada por los costos y el acceso en nuestro medio[93,106–108].

La falla en disponer de un diagnóstico temprano, la falta de sospecha clínica y el manejo quirúrgico retrasado o incompleto, puede ocasionar un diagnóstico y manejo tardío, con el riesgo de secuelas como cicatrices musculares, debilidad residual y mortalidad en el 0.5% a 2.5% de los casos[108].

¿Cuál es la mejor estrategia para el para el tratamiento de piomiositis?

30. El manejo con vancomicina se recomienda como terapia empírica inicial.
    * El linezolid es una alternativa en pacientes con falla renal aguda.
31. Cefazolina u oxacilina se recomiendan en el tratamiento de piomiositis por SAMS.
32. Se recomienda realizar un drenaje temprano del material purulento.
33. Se deben realizar imágenes de control en pacientes con bacteriemia persistente para identificar focos no drenados de infección.
34. Los antibióticos deben ser administrados vía endovenosa inicialmente, pero una vez exista mejoría clínica se podrá realizar cambio a manejo oral siempre y cuando no exista evidencia de endocarditis o absceso metastásico.
    Se recomienda una duración de la terapia antimicrobiana de 2 a 3 semanas.

La opción terapéutica de la piomiositis usualmente va de la mano con el estadio en el cual haya sido diagnosticado el paciente. El diagnóstico temprano de piomiositis puede agilizar el uso de antibióticos parenterales que impidan la evolución de la infección y la formación de abscesos[93]. En los estadios iniciales, dada la ausencia de colecciones francas en las imágenes diagnósticas, es posible iniciar manejo antibiótico empírico guiado por epidemiología local y según los factores de riesgo del individuo. En Colombia, dada la prevalencia de SAMR, se recomienda el inicio con cubrimiento de amplio espectro con vancomicina. El uso de linezolid es una alternativa en pacientes con función renal alterada. El cubrimiento para Gram negativos actualmente sólo se recomienda para pacientes inmunosuprimidos o con trauma penetrante al músculo[16,17].

Si bien la duración de la terapia no ha sido establecida, por lo general varía entre 2 a 6 semanas dependiendo de la gravedad de la infección y la respuesta clínica que presente el paciente. Habrá también que tener en cuenta las comorbilidades, el estado de inmunidad del individuo, el número de colecciones identificadas, la extensión de las mismas y la imposibilidad para drenaje completo, para estos casos un periodo de antibiótico más largo podría ser considerado[16,17,93].
En caso de evidenciar formación de abscesos, el manejo adecuado como previamente fue discutido, es la incisión y el drenaje. Dado que la mayoría de pacientes son diagnosticados cuando una colección ya ha sido formada (estadio II y III), el drenaje seguido de la administración de antimicrobiano endovenoso permanece como el manejo de elección[16,17].

Hace varios años el drenaje se realizaba por técnica abierta en salas de cirugía, sin embargo, recientemente el desarrollo de las técnicas radiológicas ha permitido la realización de punciones percutáneas guiadas por TAC o ecografía y la opción quirúrgica se desplaza a alternativa cuando no es posible lograr un drenaje completo por los métodos de radiología intervencionista[93].

En caso de que exista una respuesta clínica desfavorable, a pesar de adecuado cubrimiento antimicrobiano, se debe considerar la toma de imágenes de control (RM o TAC) para descartar la presencia de complicaciones o la persistencia de colecciones.

¿Cuales son los factores de riesgo para IPTB por microorganismos Gram negativos?

35. Se recomienda la administración de tratamiento para el cubrimiento de Gram negativos en pacientes con IPTB con relación a compromiso de las estructuras del tracto genitourinario, gastrointestinal, región perineal, inmunosupresión, úlceras, infección necrosante, infección adquirida en el hospital o contacto con agua dulce o salada.

Si bien la causa principal de IPTB a nivel internacional está representada por los microorganismos Gram positivos, también existe un porcentaje, no despreciable, de infecciones causadas por bacilos Gram negativos. De la correcta identificación de estos potenciales casos dependerá un tratamiento empírico adecuado, las infecciones por microorganismos Gram negativos son infrecuentes y tienen un espectro más grave de enfermedad[94].

Es común ver este tipo de microorganismos no sólo en condiciones de inmunocompromiso, como trasplante de órgano y neutropenia, sino también en cirrosis, VIH, uso de drogas endovenosas, diabetes mellitus, uso previo de antibióticos (fluoroquinolonas y carbapenémicos) y hospitalizaciones prolongadas con requerimiento de estancia en UCI[102,111,112].

Los bacilos Gram negativos más comúnmente identificados suelen ser *Escherichia coli y Klebsiella pneumoniae,* no obstante, otros como *Serratia spp., Pseudomonas spp., Capnocytophaga spp.,* y *Vibrio spp.* también han sido aislados[113]. En un es-

tudio realizado por Chang et al en Taiwan 2008, se reportó *K. pneumoniae* como etiología de IPTB en extremidades en cerca del 17% de los casos con predominio en hombres (OR 11,5, IC 95% 1,1-116,8, p = 0,039), cirrosis hepática (aOR 12,5, IC 95% 2,0-79,1, p = 0,007), neoplasias malignas y alcoholismo.

También se han descrito las siguientes relaciones: *Stenotrophomonas maltophilia* en IPTB de pacientes críticamente enfermos de la UCI o en traumas durante la cosecha de maíz, *Burkholderia spp.* en IPTB de soldados con heridas de inmersión, *Pseudomonas spp, Aeromonas spp.*, y *Vibrio spp.* en relación a exposición acuática, *Acinetobacter spp.* durante catástrofes naturales y heridas de guerra, y *K. pneumoniae* en malignidades hematológicas[113].

En el registro multicéntrico colombiano de infecciones de piel y tejidos blandos[100] el 17,7% de los casos fueron atribuibles a gérmenes Gram negativos. Los microorganismos aislados con mayor frecuencia fueron *E. coli* (8%), *P. aeruginosa* (6%), *K. pneumoniae* (4%), *Proteus mirabilis* (4%), y otras enterobacterias (6%). Los factores de riesgo identificados fueron: infección necrosante (P< 0,01), infección del sitio operatorio (P< 0,01), pie diabético (P< 0,01), úlceras por presión (P< 0,01), infección perineal (P< 0.01), infección adquirida en el hospital (P= 0,02), pacientes con edad entre 45 a 64 años, comparado a pacientes de 15 a 45 años (P= 0,017), e inmunosupresión (P= 0,019).

¿Cuándo se debe hospitalizar un paciente con IPTB para lograr una mayor curación clínica?

36. Se recomienda hospitalizar a un paciente con IPTB no purulenta o purulenta si presenta sepsis, comorbilidad no controlada, sospecha de infección necrosante, sospecha de miembro en riesgo, si requiere soporte social para garantizar el tratamiento, inmunosupresión o tratamiento fallido
37. Se recomienda dar egreso para continuar con manejo ambulatorio oral en un paciente con IPTB cuyas comorbilidades se encuentren controladas, tenga un manejo antimicrobiano definido, una evolución clínica favorable, tolere la vía oral y se garantice el suministro del medicamento.

Del abordaje inicial que se le brinde al paciente, dependerá el éxito de las intervenciones ofrecidas en reducir la morbimortalidad, por lo anterior se ha propuesto un abordaje dependiente de la gravedad de infección para establecer el sitio y el tipo de manejo a ofrecer. El tratamiento básicamente puede ser oral o parenteral, recordando siempre que el tratamiento empírico, dependiente de epidemiología local y de los microorganismos que se sospechan, debe ofrecerse en el menor tiempo posible dado que la primera dosis de antibiótico siempre es la más importante[24].

Los estudios realizados hasta la actualidad continúan evidenciando un mayor número de hospitalización del necesario, según las cifras de infecciones no complicadas[26,114]. Factores socioeconómicos, inseguridad del tratante o exigencia del paciente juegan roles importantes en la decisión final de la ubicación del enfermo.

Shrock reportó como factores para manejo hospitalario el sexo femenino y la presencia de leucocitosis mayor de 15.000 cel/mm^3[115], sin embargo, estudios adicionales como el de Sabbaj et al encontró como único factor predisponente para hospitalización, la presencia de fiebre[115]. Se ha demostrado que solo un porcentaje bajo de pacientes con IPTB presentan fiebre en el momento de ingreso a urgencias[116]. Otras pruebas como el lactato elevado podrían representar un marcador válido para el manejo hospitalario como subrogado de una alteración metabólica subyacente, pero no todos los pacientes tienen indicación clínica de solicitud de este laboratorio al ingreso[117].

La guía americana para el manejo de IPTB del 2014 (IDSA) propone una clasificación dependiente de gravedad, basada en un esquema propuesto por Eron et al en 2003 capaz de dividir a los pacientes en infección leve, moderada o severa dependiendo de su estabilidad clínica, factores de riesgo y comorbilidades[118–120]. Sin embargo, ha sido criticada por ser poco práctica, y por el grado de subjetividad sobre el estado clínico del paciente. En el año 2014 Tiwari y Lal, realizaron un estudio que permitía evaluar el rol de la estratificación por gravedad en el abordaje terapéutico y el pronóstico, plantean cuatro clases de infección: Clase 1, los pacientes no presentan signos o síntomas de toxicidad sistémica o presencia de comorbilidad que pueda complicar el tratamiento, y usualmente es posible manejarla ambulatoriamente de forma oral o tópica[119,120]. En la infección clase 2 los pacientes lucen enfermos, pero las comorbilidades se encuentran estables (por lo general tienen mas de 1 comorbilidad que puede prolongar el tratamiento o complicar el cuadro clínico general). Algunos de estos pacientes mejoran con terapia oral, otros requieren una vigilancia intrahospitalaria corta, y no hay forma de predecir el comportamiento de estos pacientes, por lo que la terapia endovenosa podrá ser preferida inicialmente al menos por un breve periodo de tiempo y posteriormente manejar en hospitalización en casa[119,120]. En la clase 3, el paciente puede tener una apariencia que sugiere sepsis (alteración de estado de conciencia, taquicardia, taquipnea o hipotensión) o alguna comorbilidad no controlada que interfiera con la respuesta al antimicrobiano. Estos pacientes usualmente requieren manejo intrahospitalario y parenteral, pero presentan respuesta clínica rápida favorable que permite en pocos días el cambio de vía de administración o el manejo ambulatorio[119,120]. En la clase 4 el paciente está en sepsis o con una infección potencialmente fatal como las infecciones necrosante y siempre deberán ser manejados de forma hospitalaria, para terapia médica y quirúrgica, en la mayoría de los casos[119,120].

Nathwani et al, han propuesto una serie de criterios que permiten establecer la posibilidad de cambio a un manejo oral; todos los criterios deben ser cumplidos: manejo endovenoso

mayor a 24 horas, infección clínicamente estable o mejoría clínica, afebril, leucocitos entre 4000 y 12000/L, ausencia de taquicardia, tensión arterial sistólica ≥ 100, tolerancia a la vía oral, microorganismo susceptible al manejo actual (si hay disponibilidad de cultivos)[121]. La mejoría clínica (documentada con una reducción mayor al 20% del tamaño de la lesión) así como la tolerancia a la vía oral deben estar aseguradas previas al egreso, el mismo espectro antibiótico usado parenteralmente puede ser cambiado a vía oral[122-125].

Puntos de buena práctica

¿Cuáles son los puntos claves en la atención de un paciente con IPTB?

Considerar los siguientes puntos para definir la necesidad de hospitalización del paciente: comorbilidades, presentación clínica, sitio de la lesión, tamaño de la lesión, signos de infección necrosante, condiciones sociales y red de apoyo[126].

- Presencia de comorbilidades que impacten la progresión y la respuesta clínica de IPTB: inmunocompromiso, enfermedad hepática o renal, enfermedad vascular, asplenia o neuropatía.
- La presentación de fiebre (mayor a 40 grados o menor a 35ºC), hipotensión, taquicardia (más de 100/min) o alteración del estado de conciencia, todos estos como representación de sepsis y posible compromiso profundo de la infección
- Sitio de la lesión: compromiso de mano o cabeza representan gravedad
- Tamaño de la lesión cualquier infección con compromiso mayor al 9% de área corporal total debe ser considerada como severa.
- Presencia de signos o síntomas específicos: bulas, hemorragias, dolor desproporcionado, crepito, anestesia, progresión rápida.
- Condiciones sociales y emocionales: pacientes sin red social de apoyo, psicológicamente inestables, con riesgo de no adherencia a la terapia o incapaces de seguir órdenes, no obstante, deberá evaluarse la pertinencia de manejo endovenoso vs oral durante la hospitalización (127).

Ajustes en el tratamiento: La mejoría clínica debe ser evidente entre las 48 y 72 horas posterior al inicio del antibiótico. En ese tiempo los médicos deberán realizar una nueva evaluación completa del contexto clínico del paciente en miras a efectuar ajustes terapéuticos, según los cultivos (si ha sido posible su realización) o el juicio clínico[117,121,125,126]. El desescalonamiento antibiótico, el cambio de endovenoso a vía oral, la hospitalización domiciliaria, la realización de procedimientos quirúrgicos o el egreso, deben ser considerados. El ajuste del manejo deberá realizarse con los aislamientos finales de cultivos siempre que estén disponibles, para permitir el ajuste terapéutico con un espectro de cubrimiento más estrecho al originalmente colocado.

Otra estrategia propuesta es el manejo de pacientes en hospitalización domiciliaria, que permite la administración de antibióticos parenterales en el domicilio del paciente. Un estudio controlado y aleatorizado que comparó el uso de medicación intravenosa en el hospital vs en casa para el manejo de celulitis no encontró diferencias en los desenlaces, y evidenció mayor grado de satisfacción del paciente con el manejo domiciliario[119]. Los programas de hospitalización domiciliaria han demostrado un alto porcentaje de éxito (87% en el Reino Unido) y solo 7% de eventos adversos y 6% de readmisiones[123].

Egreso: La estrategia más útil en términos de costo/efectividad, es un egreso temprano, aunque no hay recomendaciones formales respecto a esto, y su implementación va en paralelo con la posibilidad de cambio de manejo a vía oral.[114,121,128,129]. El mejor candidato a esta estrategia será el paciente que cumpla con las siguientes indicaciones:

- Cumplir con todos los criterios para cambio de antibiótico a vía oral
- No tener razones adicionales de estancia hospitalaria distintos a la infección
- Estado de conciencia estable
- Comorbilidades estables
- Situación social estable
- Plan de duración final del antibiótico posterior a egreso
- Seguimiento clínico
- Educación frente al cuidado de heridas
- Control glicémico estable en caso de DM

Ver Algoritmo para el tratamiento de paciente con IPTB (*figura 1*)

Agradecimientos: Al Dr. Gilberto Montoya por la revisión al consenso y sus sabias sugerencias.

SVB ha realizado conferencias financiadas por Pfizer, y Merck Sharp and Dhome, JAC ha realizado conferencias financiadas por Pfizer, MSD, Becton Dickinson. CAA ha realizado conferencias financiadas por Pfizer, y Merck Sharp and Dhome, JVOP ha realizado conferencias financiadas por Pfizer, y Merck Sharp and Dhome. IBM ha realizado conferencias financiadas por Pfizer, y Merck Sharp and Dhome.

MAC, FG, JLC, CC, SMG, JYR, AMG no declaran conflictos de interés

Todos los autores han leído y aprobado el manuscrito, y cumplen con los requisitos de autoría.

Este consenso ha recibido financiación por parte de Pfizer, GSK y Lafracol.

Tabla 2. Agentes más frecuentemente involucrados en las IPTB y factores de riesgo.

	Entidad	Localización	Característica / Factor de riesgo asociado	Agente Etiológico
Infecciones superficiales	Impétigo	Epidermis	Costroso- húmedo, principalmente localización facial	*S. pyogenes*
			Ampolloso- localizadas o diseminadas	*S. aureus*
	Ectima	Epidermis y dermis		*S. aureus- SAMR*
	Foliculitis	Folículo piloso superficial		
	Forúnculos	Folículos piloso profundo		
	Carbunclos	Dermis		
	Erisipela	Dermis		***Streptococcus pyogenes*** Estreptococos grupo B, C y G *S.aureus* (ocasional)
	Abscesos	Tejido celular subcutáneo	Recurrencia	***S.aureus.* SAMR** *Streptococcus spp, anaerobios*
	Celulitis común	Tejido celular subcutáneo	No asociados a puerta de entrada concreta	*Estreptococos β-hemolíticos*
			Asociada a forúnculos, abscesos y traumatismos	***S. aureus*- SAMR**
Infecciones Profundas	Celulitis severa	Tejido celular subcutáneo	Uso de drogas inyectadas	***S. aureus*- SAMR** *Streptococcus spp Clostridium botulinum*
			Linfedema crónico	*Streptococcus spp*
			Secundaria a heridas traumáticas sucias o quirúrgicas	*Clostridium perfringens* Otras especies de *Clostridium spp*
			Heridas en agua fresca	*Aeromonas hydrophila*
			Herida con agua salada	*Vibrio vulnificus*
	Fascitis necrosante	Fascia		**Polimicrobiana** -Aerobios: *Streptococcus, Staphylococcus aureus* Bacilos gram negativos -Anaerobios: *Peptostreptococcus, Bacteroides, Clostridium spp* **Monomicrobiana:** *S.aureus S. pyogenes*
	Mionecrosis	Músculo	Gangrena gaseosa	Clostridium spp *Clostridium perfringes*
	Piomiosistis		Antecedentes de colonización, infección, hospitalización previa	***S. aureus*** **SAMR** (90%) *S. pyogenes S. pneumoniae* Enterobacterias
	Infección de úlceras por presión			*S. aureus* Enterobacterias *P. aeruginosa* Anaerobios

Tabla 3. Resumen de recomendaciones

Pregunta	Recomendación	Nivel de evidencia	Grado de Recomendación (mediana)	
Cuál es la mejor estrategia para el diagnóstico de impétigo y ectima?	1. Se recomienda basar el diagnóstico de impétigo y ectima en los hallazgos clínicos. Se recomienda realizar tinción de Gram y cultivo de secreción purulenta o exudado en los casos en que se quiera identificar *S. aureus* o estreptococo beta- hemolítico por interés epidemiológico.	1++	Adecuada	9
Cuál es la mejor estrategia para el tratamiento de impétigo y ectima?	2. El impétigo (buloso y no buloso) puede ser tratado con antibiótico tópico u oral, sin embargo, la terapia oral está recomendada para paciente con múltiples lesiones (más de 5), o en brotes epidémicos de glomerulonefrits (GMN) postestreptocócica para disminuir la transmisión de la enfermedad.	1++	Adecuada	8,5
	3. El tratamiento tópico del impétigo no buloso o buloso debe ser con mupirocina, ácido fusídico o retapamulina 2 veces al día por 5 días. Barrera de acceso: Retapamulina es un antibiótico tópico que no esta comercializado en Colombia.	1++	Adecuada	9
	4. El tratamiento para ectima debe ser oral.	1++	Adecuada	9
	5. Se recomienda que el tratamiento oral en casos de ectima o impétigo se realice con un antibiótico activo contra SAMR a menos que se tenga un cultivo que evidencie SAMS o Streptococcus β hemolíticos del grupo A, con una duración de 7 días. a. Se recomienda realizar el tratamiento empírico con trimetoprim/sulfametoxazol o clindamicina. b. Si la infección es por SAMS se recomienda cefalexina o dicloxacilina. c. Si la infección es por estreptococo beta hemolítico del grupo A se recomienda penicilina oral o cefalexina.	1++	Adecuada	9
¿Cuál es la mejor estrategia para el diagnóstico de IPTB purulenta?	6. Realizar tinción de Gram y cultivo de secreción purulenta.	1++	Adecuada	8
	7. Se recomienda utilizar la ecografía de piel y tejidos blandos como una herramienta para diagnosticar abscesos cuando existan dudas del diagnóstico después de la valoración clínica.	1++	Adecuada	9
¿Cuál es la mejor estrategia para el tratamiento de IPTB purulenta?	8. Se recomienda la incisión y drenaje para absceso, carbúnculo, forúnculos grandes (más de 2cm) y quiste epidermoide infectado	2+	Adecuada	9
	9. Para pacientes con IPTB purulenta asociada a signos de respuesta inflamatoria sistémica, o inmunosupresión, o absceso de más de cinco centímetros, o absceso con celulitis extensa, o recurrente al manejo con incisión y drenaje, se recomienda el inicio de antibiótico oral contra SAMR en adición a la incisión y drenaje.	2+	Adecuada	8
	10. Para el manejo antibiótico empírico de IPTB purulenta se recomiendan las siguientes alternativas terapéuticas: • Para el manejo ambulatorio: TMP SMX o clindamicina oral por 5 a 7 días, alternativa linezolid 600mg oral cada 12 horas. • Para el manejo hospitalario: vancomicina, como alternativa: linezolid endovenoso, daptomicina, clindamicina endovenosa, tigeciclina o ceftarolina, por 7 a 14 días	1++	Adecuada	8,5
¿Cuál es la mejor estrategia para el diagnóstico de IPTB para erisipela y celulitis?	11. Se recomienda la realización de hemocultivos, aspirados, o biopsia de piel para diagnóstico de erisipela o celulitis, en pacientes que se encuentren en quimioterapia activa, tengan neutropenia, inmunodeficiencia celular severa, o por interés epidemiológico.	1++	Adecuada	9
¿Cuál es la mejor strategia para el tratamiento de erisipela y celulitis?	12. Los antibióticos recomendados para el manejo oral de erisipela o celulitis son de primera línea cefalexina, como alternativa clindamicina, amoxicilina/clavulanato o TMP SMX.	1++	Adecuada	9
	13. Los antibióticos recomendados para el manejo intravenoso de erisipela o celulitis son la oxacilina, cefazolina, ampicilina sulbactam o clindamicina, como alternativa amoxicilina/clavulanato,	1++	Adecuada	9

Pregunta	Recomendación	Nivel de evidencia	Grado de Recomendación (mediana)	
	14. Para pacientes en los que la celulitis se asocia con trauma penetrante, infección previa o colonización por SAMR, uso de drogas intravenosas, celulitis abscedadas, inmunosupresión se debe administrar un antimicrobiano efectivo contra SAMR y estreptococos.	1++	Adecuada	9
	15. La duración recomendada de antimicrobiano es 5 días, pero el tratamiento podrá ser extendido si la infección no ha mejorado en este periodo de tiempo. Grado de recomendación fuerte, nivel de evidencia alto.	1++	Adecuada	
¿Cuál es la mejor estrategia para el diagnóstico de IPTB necrosante?	16. La fascitis necrosante debe sospecharse cuando se presentan cualquiera de los siguientes síntomas o signos: (1) dolor severo inconsistente con los hallazgos en el examen físico, (2) deterioro clínico rápidamente progresivo, (3) SIRS, (4) ampollas, (5)edema a tensión (6)equimosis o piel necrótica, (7) crepitación palpable, (8) hipoestesia localizada en piel.	1++	Adecuada	8
	17. Se recomienda que el uso de escalas o procedimientos diagnósticos no retrase el inicio de tratamiento en pacientes con alta sospecha clínica	1++	Adecuada	9
	18. En pacientes con duda clínica, se recomienda usar la escala de LRINEC modificado para orientar la decisión del manejo quirúrgico	1++	Adecuada	9
	19. En pacientes con duda diagnóstica, se recomienda el uso de ecografía, TAC o RM según disponibilidad	1++	Adecuada	8
	20. El signo clínico principal intraoperatorio para diagnosticar IPTB necrosante es el aspecto macroscópico del tejido celular subcutáneo y la fascia.	1++	Adecuada	9
	21. Para el diagnóstico bacteriológico se recomienda realizar Gram y cultivo de tejido profundo intraoperatorio y hemocultivos.	1++	Adecuada	9
¿Cuál es la mejor estrategia para el tratamiento de IPTB necrosante?	22. Para los pacientes con alta sospecha diagnóstica de IPTB necrosante, se recomienda manejo quirúrgico	1++	Adecuada	8
	23. El tratamiento antibiótico empírico debe ser de amplio espectro endovenoso, debido a que la etiología puede ser polimicrobiana, incluyendo el cubrimiento de SAMR, en nuestro medio se recomienda: vancomicina con cefepime o piperacilina/tazobactam más clindamicina endovenosa. Se recomienda remplazar vancomicina por linezolid endovenoso en pacientes con falla renal.	1++	Adecuada	8
	24. En caso de pacientes con compromiso de función hepática o cirrosis, ingesta reciente de comida de mar o contacto con agua salada, la terapia combinada con cefalosporina de tercera o cuarta generación y doxiciclina debe ser usada por sospecha de Vibrio vulnificus.	1++	Adecuada	9
	25. Para paciente con factores de riesgo para infección por Aeromonas spp. se recomienda el uso de cefepime, o quinolona más doxicilcina	1++	Adecuada	9
	26. Una vez se cuenta con aislamiento microbiológico se debe ajustar la terapia antibiótica a un espectro más estrecho basado en la susceptibilidad del cultivo.	1++	Adecuada	8
	27. El uso de penicilina más clindamicina se recomienda para tratamiento en aquellos pacientes que tienen infección confirmada por Streptococcus B hemolítico del grupo A	1++	Adecuada	7
Cuál es la mejor estrategia para el diagnóstico de piomiositis?	28. Realizar cultivos de secreción purulenta y hemocultivos para obtener aislamiento microbiológico.	1++	Adecuada	9
	29. Se recomienda la resonancia magnética para el diagnóstico de piomiositis. La tomografía y la ecografía se recomienda como alternativa para el diagnóstico.	2+	Adecuada	8
¿Cuál es la mejor estrategia para el para el tratamiento de piomiositis?	30. El manejo con vancomicina se *recomienda como terapia empírica inicial.* *El linezolid es una alternativa en pacientes con falla renal aguda	1++	Adecuada	9

Pregunta	Recomendación	Nivel de evidencia	Grado de Recomendación (mediana)	
	31. Cefazolina o oxacilina se recomiendan en el tratamiento de piomiositis por SAMS.	1++	Adecuada	9
	32. Se recomienda realizar un drenaje temprano del material purulento.	1++	Adecuada	9
	33. Se deben realizar imágenes de control en pacientes con bacteriemia persistente para identificar focos no drenados de infección.	1++	Adecuada	9
	34. Los antibióticos deben ser administrados vía endovenosa inicialmente, pero una vez exista mejoría clínica se podrá realizar cambio a manejo oral siempre y cuando no exista evidencia de endocarditis o absceso metastásico.	1++	Adecuada	9
¿Cuales son los factores de riesgo para IPTB por microorganismo Gram negativos?	35. Se recomienda la administración de tratamiento para el cubrimiento de Gram negativos en pacientes con IPTB en relación a compromiso de las estructuras del tracto genitourinario, gastrointestinal, región perineal, inmunosupresión, úlceras, infección necrosante, infección adquirida en el hospital o contacto con agua dulce o salada.	1+	Adecuada	9
¿Cuándo se debe hospitalizar un paciente con IPTB para lograr una mayor curación clínica?	36. Se recomienda hospitalizar a un paciente con IPTB no purulenta o purulenta si presenta sepsis, comorbilidad no controlada, sospecha de infección necrosante, sospecha de miembro en riesgo, si requiere soporte social para garantizar el tratamiento, inmunosupresión o tratamiento fallido	1+	Adecuada	8
	37. Se recomienda dar egreso para continuar con manejo ambulatorio oral en un paciente con IPTB cuyas comorbilidades se encuentren controladas, tenga un manejo antimicrobiano definido, una evolución clínica favorable, tolere la vía oral y se garantice el suministro del medicamento.	1+	Adecuada	9

Tabla 4. Dosis de antimicrobianos para el manejo de IPTB

Tipo de terapia	Antibiótico	Dosis	Intervalo de dosificación	Ajuste en Falla renal
ORAL	Amoxacilina/ clavulanato	875/125 mg 500/125 mg	Cada 12 h Cada 8 h	TFG 10-50: 250-500 mg c/12 h TFG <10: 250-500 mg c/24 h
	Cefalexina	500 mg - 1 g	Cada 6 h	TFG 10-50: 500 mg c/12 h TFG<10: 150 mg c/12 h
	Clindamicina	300 mg	Cada 8 h	No requiere ajuste renal
	Dicloxacilina	500 mg	Cada 6 h	No requiere ajuste renal. Dar una dosis despues de hemodialisis
	Doxicilina	100 mg	Cada 12 h	No requiere ajuste renal.
	Linzezolid	600 mg	Cada 1 2h	No requiere ajuste renal.
	Trimetoprim/ sulfametoxazol	160/800 mg (tableta)	1 a 2 tabletas cada 12 h	TFG 30-90: 5-20 mg/kg/d TFG 10-29: 5-10 mg/kg/dia, c/12 h TFG<10: No recomendada
INTRAVENOSA	Cefazolina	1- 2 g	Cada 8 h	TFG 10-50: 1-2 g c/12 h TFG <10: 1-2g c/24-48 h
	Clindamicina	600 a 900 mg IV c/8h	Cada 8 h	No requiere ajuste renal
	Daptomicina	6–10 mg/kg/d	Cada 24 h	TFG < 30 c/ 48 horas
	Linzezolid	600 mg	Cada 12 h	No requiere ajuste renal.
	Oxacilina	2 g	Cada 4 h	No requiere ajuste de dosis renal
	Trimetoprim/ sulfametoxazol	8-10 mg/kg/d	Cada 6 a 12 h	TFG 30 - 90: 5 - 20 mg/kg/d TFG 10-29: 5-10 mg/kg/d, c/12h TFG<10: No recomendada
	Vancomicina	15 – 20 mg/Kg/dosis	Cada 12 h	TFG10-50: c/24-96 h Hemodialisis/CAPD 7,5 mg/Kg, c/2-3d

d: día; g: gramo; h: hora; TFG: tasa de filtración glomerular;

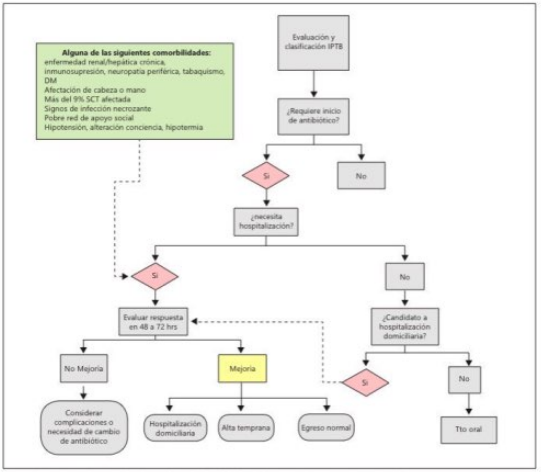

Figura 1. Algoritmo para la decisión del manejo hospitalario en pacientes con IPTB

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ANEXO 1

Microbiología de las infecciones de piel y tejidos blandos (iptb)

S. pyogenes y S. aureus en IPTB

Las cepas de *S. pyogenes* que causan el impétigo presentan patrones de genotipo *emm* diferentes a las cepas asociadas con amigdalitis y faringitis, por lo que se pueden dividir en 3 grupos clínicos y ecológicamente relevantes[1]; los patrones de genotipos *emm AC* tienen una gran predilección por causar infecciones de garganta, las cepas del patrón *emm D* por causar impétigo[1], mientras que las de patrón *E* causan infecciones en ambos sitios[2]. Otra característica que los diferencia es su apetencia de unión por los queratinocitos[3].

A pesar del paso del tiempo, la sensibilidad de *S. pyogenes* a la penicilina continúa siendo representativa (la prueba de susceptibilidad no es necesaria de acuerdo a la CLSI -- Clinical and Laboratory Standards Institute) no obstante, el aumento de tolerancia al antibiótico.

Staphylococus aureus ha desarrollado resistencia a prácticamente todas las clases de antibióticos disponibles, incluyendo agentes inhibidores de pared como β-lactámicos y glicopéptidos; inhibidores ribosomales como macrólido-lincosamida, estreptogramina B (MLSB), aminoglucósidos, tetraciclinas, ácido fusídico y las nuevas oxazolidinonas; inhibidores de la ARN polimerasa como la rifampicina; bloquedores de la ADN girasa como las quinolonas, y a los nuevos antibióticos lipopeptidos y a las nuevas móleculas anti SAMR. Lo anterior ha obligado ala realización de pruebas susceptibilidad siempre que se detecte este microorganismo (CLSI 2018).

La resistencia a los beta-lactámicos (SAMR) es la más importante por su impacto sobre las opciones de tratamiento. Esta resistencia está mediada genéticamente por la presencia del gen *mec*A y su distribución se ha relacionado con la circulación de clones específicos en nuestro país. Hasta el año 2005 los clones de SAMR estaban relacionados a la exposición en el hospital (clones Chileno y Pediátrico). Sin embargo, a partir del año 2005 se ha documentado la aparición de clones de SAMR en la comunidad. La diferencia fundamental es que estos últimos tienen menores perfiles de resistencia a varias clases de antimicrobianos, es decir, que aunque tienen resistencia a los beta-lactámicos (excepto a la recientemente introducida ceftarolina), la frecuencia de resistencia a otros antibióticos útiles como clindamicina, trimetoprim/sulfametoxazol, doxiciclina o rifampicina es baja (usualmente por debajo del 10%). Estos clones se han diseminado de la comunidad a los hospitales, remplazando los clones antiguamente circulantes, haciendo imposible predecir la resistencia con base en el sitio de origen de la infección (comunidad vs. Asociado a la atención de salud), la gravedad de la infección o su aspecto clínico[4].

Características microbiológcas y susceptiblidad del S. pyogenes.

Streptococcus pyogenes es un patógeno versátil, en parte debido a la cantidad de factores de virulencia que posee. Desde los años 80´s se reportaron cambios en la epidemiología de las infecciones causadas por este microorganismo y la severidad de estas. La falta de una vacuna autorizada y la posibilidad de adquisición de resistencia a penicilina, ha aumentado la preocupación sobre esta bacteria[5].

S. pyogenes es un coco gram positivo, inmóvil, β-*hemolítico*, no formador de esporas, anaeróbio facultativo, catalasa negativa y de acuerdo a la estructura de hidratos de carbono descrita por Lancefield para la tipificación de las cepas β-hemolíticas, pertenece al grupo A. Son nutricionalmente exigentes, generalmente se cultivan en medios ricos, como el sangre y se incuban a una atmósfera del 5% al 10% de dióxido de carbono. Después de una incubación a 35 °C a 37 °C por 18 a 24 horas, se observan colonias grises de 1 a 2 mm de diámetro rodeadas de una zona de hemólisis completa (β-hemolisis).

Puede ser diferenciado de otros estreptococos *β-hemolíticos* por su sensibilidad a bacitracina, la cual sumada a la detección del antígeno de Lancefield brinda gran especificidad para la identificación de *S. pyogenes*, dado que otras cepas de estreptococo β-hemolíticas que pueden contener el antígeno grupo A son resistentes[6].

Actualmente el diagnóstico de laboratorio de *S. pyogenes* continúa basándose en el cultivo a partir de muestras clínicas en agar sangre (hemólisis de la colonia), con la consecuente confirmación de especie (puede realizarse con pruebas comerciales rápidas para la detección del antígeno de Lancefield o sistemas automatizados de identificación bioquímica completa).

Los ensayos de anticuerpos anti-estreptolisina O (ASO) no tienen valor en el diagnóstico y manejo del impétigo, ya que la respuesta es débil, presumiblemente porque la actividad de la respuesta es inhibida por lípidos de la piel (colesterol)[2].

Sistemas moleculares de tipificación, se basan en el gen emm que codifica para la proteína M. Se reconocen más de 234 tipos de emm y un gran número de variantes alélicas[7]. No obstante, la caracterización molecular de este microorganismo no esta indicada en la práctica clínica.

Por su parte los macrólidos, incluyendo eritromicina, claritromicina, y azitromicina, se consideran buenas alternativas en pacientes con alergia a la penicilina[8]. Sin embargo, en los últimos años el aumento del uso de estos antibiótico, ha conducido al reporte de la resistencia en EE.UU y Europa[9], por lo que la evaluación de las pruebas de susceptibilidad son obligatorias para estos antibióticos.

Las pruebas de susceptibilidad para los macrólidos se pueden realizar usando eritromicina, ya que predice la resistencia a otros miembros de esta familia de antibióticos. Para detectar la resistencia inducible a la clindamicina en S. pyogenes, CLSI recomienda el ensayo de difusion de doble disco[10].

Además de los antibióticos MLS (Macrólidos, Lincosamidas y estreptograminas), *S. pyogenes* también puede adquirir resistencia a la familia de las tetraciclinas. Numerosos aislados clínicos son co-resistentes a MLS y las tetraciclinas, ya que ambos determinantes de la resistencia se encuentran en los mismos elementos genéticos móviles. La resistencia de alto nivel a los aminoglucósidos sigue siendo rara, mientras que a glicopéptidos aún no se ha reportado susceptibilidad reducida[10].

Evolución de S. aureus en Colombia

S. aureus es un coco Gram positivo, que pertenece al género *Staphylococcus*, mide entre 0,5 a 1 micras de diámetro, es inmóvil, aerobio y anaerobio facultativo, no forma esporas y generalmente no posee cápsula. En medios de cultivo como el agar sangre, su crecimiento se observa entre las 18-24h, a 34-37ºC, produciendo colonias blancas que tienden a adoptar un color amarillo dorado con el paso del tiempo y generalmente son beta hemolíticas. Las variantes de morfología pequeña pueden requerir períodos de crecimiento prolongados, y las placas deben mantenerse de 2 a 3 días para detectarlos[11].

Una variedad de pruebas fenotípicas se emplea para identificación de *S. aureus*, entre las cuales se encuentran: crecimiento a altas concentraciones de NaCl, fermentación de manitol, producción de catalasa, coagulasa y DNAsa. La prueba de coagulasa en tubo es la prueba estándar de oro para discriminar *S. aureus* de las demás especies de su género agrupadas como *Staphylococcus Coagulasa* negativos (CoNS)[11,12].

Pruebas de identificación fenotípica rápida incluyen la prueba de coagulasa en placa que detectan el factor *cumpling*, sin embargo, hasta el 15% de los aislamientos de *S. aureus* pueden ser negativos. Otras pruebas de aglutinación en latex que evalúan el factor *cumpling*, la proteína A y otros determinantes superficie han mostrado buena sensibilidad, pero son menos específicos debido a reactividad cruzada con varios CoNS[13].

Para la susceptibilidad antimicrobiana en *S. aureus*, se emplean varias metodologías. El método de difusión del disco, en el cual la evaluación de susceptibilidad a oxacilina se debe realizar con el disco de cefoxitin de 30 µg , ya que ha demostrado ser un mejor inductor de la resistencia a la meticilina[14]. Así mismo, varios plataformas automatizadas comerciales son empleadas como el Vitek® 2, Phoenix™ BD o MicroScan.

Debido a que los métodos fenotípicos consumen mucho tiempo, donde los resultados de identificación y susceptibilidad son disponibles aproximadamente a las 48 h, se ha estimulado el desarrollo de metodologías moleculares, que pueden mejorar el procesamiento tradicional del laboratorio o pueden reemplazar completamente las técnicas basadas en el cultivo. Entre estas metodologías se encuentra la identificación de especie basada en ácidos nucleicos empleando PCR que amplifican el ARN ribosomal 16S o genes específicos de especie como el gen *nuc*.

Otra metodología recientemente implementada es el MALDI-TOF, que identifica colonias bacterianas mediante el análisis de la composición proteica de la célula bacteriana y permiten la identificación en cuestión de minutos[13].

Para la detección molecular de la susceptibilidad a meticilina se emplea el gen *mec*A, que codifica para la proteína PBP 2A, que tiene baja afinidad por la penicilina (PBP2A). Sin embargo, *mec*A puede estar presente en CoNS resistentes a meticilina, por lo tanto, se debe realizar la identificación de especie simultáneamente.

La presión de los antibióticos ha favorecido la evolución genética del *S. aureus*, con la consecuente aparición de cepas con diferentes determinantes de virulencia y patrones variables de susceptibilidad, que difieren no solo epidemiológicamente sino también en los tipos de infecciones que producen; así, se reportan cepas, de *S. aureus* sensibles a meticilina (SAMS), resistentes a meticilina asociadas a la atención en salud (SAMR-AH), resistente a meticilina asociadas a la comunidad (SAMR-CA).

SAMS ocasiona un número importante de infecciones en piel, se aísla comúnmente en pacientes con infecciones asociadas a la comunidad, son más heterogéneos en comparación con SAMS (11,15). Entre los linajes genéticos observados en SAMS, se encuentran con mayor frecuencia complejos clonales comunes a los reportados en SAMR como: CC5, CC8, CC22, CC30 y el CC45. Así mismo, se reportan otros complejos clonales como: CC7, CC9, CC12, CC15, CC25, CC51 y CC101[15,16].

Por su parte SAMR, se observaron por primera vez en Inglaterra en 1961[15], desde entonces, las cepas de SAMR se diseminaron gradualmente en hospitales de todo el mundo, y se caracterizaban por presentar resistencia no solo a meticilina sino a múltiples antibióticos no β-lactámicos (aminoglicósidos, macrólidos, lincosamidas y estreptograminas) como característica albergaban principalmente los SCCmec tipo I,II,II (17,18) En SAMR-AH se han descrito varios clones epidémicos a nivel mundial, entre los cuales se encuentran, el clon Arcaico (CC8-ST 250-SCCmec I), clon Ibérico (CC8-ST 247-SCCmec I), Brasilero (CC8-ST 239- SCCmec III), Pediátrico (CC5-ST 5-SCCme-IV), NewYork /Japón (CC5-ST 5- SCCmec II y EMRSA-15 (CC 22-ST 22- SCCmec IV). Cambios en el tiempo en la presencia de estos clones se han observado en países, regiones e incluso dentro de hospitales.

En los años 90 aparecieron los primeros informes de SAMR-AC; que fueron reportados con mayor frecuencia en niños y adultos jóvenes sin factores de riesgo. Se caracterizan por presentar bajos niveles de resistencia a antibióticos no β-lactámicos y pertenecen principalmente al CC 8, CC1 y CC30 y portan el SCCmec tipo IV ó V, además presentan factores de virulencia como la leucocidina de Panton-Valentine-PVL, relacionada con la producción de infecciones purulentas con tendencia a la necrosis[9,19]. En América del Norte (NA), la epidemia de SAMR-AC se atribuye ampliamente al clon designado como USA300, perteneciente al CC8 (20). Recientemente, en el ámbito hospitalario SAMR-AC ha comenzado a reemplazar las cepas tradicionales SAMR-AH, especialmente en regiones, donde la prevalencia de SAMR-AC es alta[21].

En Colombia el primer estudio publicado de caracterización molecular de SAMR, se realizó entre los años 1996 y 1998, con muestras de hospitales de Bogotá y Manizales[22]. En este trabajo, se encontró que todos los aislados pertenecían al "Clon Pediátrico", de forma interesante este clon presentaba resistencia a múltiples medicamentos y se aisló en pacientes de todas las edades. En el año 2005, Cruz et al[23] evaluaron cepas de SAMR recolectadas entre el 1996 y el 2003, provenientes de hospitales de Bogotá y Cali, estos autores no detectaron el "Clon pediátrico", solo encontraron el denominado "Clon Chileno", lo cual indicaba un cambio en la población genética de SAMR. Álvarez et al[24]. realizaron en el 2006 el primer reporte de SAMR-AC en Colombia; posteriormente Reyes et al en 2009 (25) y Alvarez et al. en (26), reportaron la diseminación del clon USA 300 (ST8-MRSA-IV) causando infecciones asociadas a la atención en salud en población adulta, y posteriormente se describe la importancia de este clon en población pediátrica[27].

En 2012, Jiménez et al., evidenciaron que las cepas de SAMR tradicionalmente asociadas a comunidad portadoras del SCCmec IVc, pvl positivas, con perfil de resistencia a oxacilina ó a oxacilina y tetraciclina, estaban llegando a ser predominantes en los hospitales de Medellín y estaban desplazando clones característicos asociados al hospital, como el Clon Chileno. En este estudio no se detectó el clon pediátrico, lo que demostraba un cambio en las poblaciones de SAMR en esta región, adicionalmente, se observaron mínimas diferencias en las características clínico- epidemiológicas entre las infecciones ocasionadas por SAMS y SAMR[4,28,29].

En este año tambien, se reportó la diseminación en varios paises de latinoamérica de la variante latinoamericana de USA 300, "USA 300-LV"[30] que se diferencia del prototipo de cepas USA 300-0114, en que alberga el SCCmec IVc en lugar del IVa, carece del elemento ACME, y con frecuencia es resistente a tetraciclina. Posteriores análisis filogenéticos de SAMR USA300 y USA300-LV revelaron que los dos linajes genéticos están estrechamente relacionados[31].

Recientemente, Escobar et al reportan la emergencia y diseminación en el país de un nuevo clon de SAMR-AC denominado COL 923 no relacionado con el USA300 y el USA300-LV. Este clon porta el SCCmec IVa, no presenta el ACME (Elemento catabólico de arginina) y presenta resistencia al menos a un antibiótico no β-lactámico y alta frecuencia de resistencia a macrólidos y tetraciclina. Fué descrito inicialmente en población pediátrica pero posteriormente se describió en adultos y en varias ciudades del país[32,33]. Los estudios realizados hasta la fecha en el país muestran la constante evolución o reemplazamiento clonal de *S.aureus*, y resaltan la importancia de su vigilancia.

ANEXO 2

Definiciones

***Infecciones de piel y tejidos blandos*[34–37]:**
son las infecciones que comprometen cualquiera de las tres capas de la piel, fascia o músculo, afectan cualquier tipo de huésped, y pueden ser manejadas de manera ambulatoria u hospitalaria.

Infecciones purulentas
Absceso cutáneo: presencia de colección de material purulento dentro de la dermis o en capas subyacentes.

Forúnculo: consisten en infecciones locales de folículos pilosos que penetran hacia tejidos subcutáneos y dan origen a nódulos inflamados con pústulas en la superficie. Afectan principalmente el cuello, rostro, axilas, ingles y muslos. Cuando se cuenta con varias unidades foliculares afectadas recibe el nombre de ántrax[38].

Carbúnculo: infección que se extiende a los quistes pilares para formar nódulos inflamatorios llenos con material purulento[34,35].

Piomiositis: infección aguda que infiltra el músculo, lo cual conlleva a formación de abscesos a este nivel

Las infecciones se clasifican de acuerdo a su gravedad en[39,40]
- Leve: No presenta signos de respuesta inflamatoria sistémica. Individuo afebril y sin comorbilidades conocidas.
- Moderada: presencia de signos clínicos de infección purulenta más signos de respuesta inflamatoria sistémica, o al menos una comorbilidad no controlada. También incluye a los pacientes con inmunosupresión.
- Grave: infección con riesgo potencial de pérdida de extremidad o mortalidad, definida por la presencia de sepsis.

***Infecciones no purulentas*[41]**
Impétigo: infección bacteriana que ocurre en la epidermis, y se manifiesta clínicamente de dos formas: buloso y no buloso. El impétigo no buloso, se caracteriza por la presencia de vesículas que rápidamente se transforman en pústulas que se ulceran fácilmente, con formación de un exudado purulento y formación de costras amarillentas. El impétigo buloso consta de vesículas que se transforman a bulas no elásticas con contenido claro, que una vez se ulcera producen una costra café.

Ectima: infección de piel, que afecta a la piel con una mayor profundidad que el impétigo y ocasiona lesiones ulceradas con costras amarillas y grises que se extienden a la dermis. Tiene bordes delimitados, elevados y eritematosos. Por lo general, producen cicatriz.

Erisipela: infección bacteriana aguda, no purulenta, de la parte superior de la dermis, con una definición evidente clínicamente entre el tejido sano y el tejido afectado, con compromiso de los vasos linfáticos. Causada principalmente por streptococcus Beta hemolítico (Streptococcus pyogenes) del grupo A, pero tambien grupo B, C o G pueden aislarse, y por lo general existe una lesión cutánea, pequeña y a veces imperceptible, como factor predisponente (tiña interdigital, erosiones en eczema, excoriaciones)[42].

Celulitis: La celulitis es una infección de la parte inferior de la dermis y tejido celular subcutáneo, con bordes poco definidos. La etiología principal es similar a la erisipela, *S. pyogenes* y *S. aureus* con variaciones locales[36,40].

Se clasifican en
- Leve: celulitis y erisipela
- Moderada: celulitis y erisipela con signos de respuesta inflamatoria sistémica o en paciente inmunocomprometido, o con signos clínicos de infección profunda como bullas, dolor intenso, hipotensión o disfunción de órgano

***Infección necrotizante*[30,41]**
Infección con necrosis o rápidamente progresiva. Implican riesgo de amputaciones o mortalidad si el tratamiento no es oportuno. Existen varias definiciones en la literatura médica que puede sobreponerse o que hacen referencia a escenarios específicos. Por definición, las infecciones necrotizantes se clasifican únicamente como complicadas.

Estas definiciones antiguas incluyen los términos de fascitis necrotizante, mionecrosis (clostridial o no), celulitis gangrenosa, celulitis anaerobia, entre otras

1. **Fascitis necrotizante:** Infección necrótica de piel y tejidos blandos, que invade la fascia que recubre el compartimiento muscular,
   a. Tipo I polimicrobiana
   b. Tipo II monomicrobiana
2. **Mionecrosis clostridial (Gangrena gaseosa):** infección toxémica, rápidamente progresiva y fatal, que involucra al músculo esquelético por infección por *Clostridium spp*., principalmente *C. perfringens*. Es secundaria generalmente a lesión muscular y su contaminación o posterior a cirugía. También hay causas no traumáticas, usualmente por *C. septicum*, como complicación de bacteriemia y traslocación en mucosa digestiva (adenocarcinoma o una complicación de la colitis neutropénica).
3. **Celulitis gangrenosa (gangrena infecciosa):** es una celulitis rápidamente progresiva, con necrosis extensa de los tejidos subcutáneos y la piel. Se pueden distinguir diversos síndromes clínicos diferenciados dependiendo del microorganismo causante específico, la localización anatómica de la infección y las condiciones predisponentes. Entre estos cuadros clinicos están: 1) fascitis necrotizante 2) gangrena gaseosa (mionecrosis clostridial) y celulitis anaerobia; 3) gangrena sinérgica bacteriana progresiva; 4) celulitis necrotizante sinérgica, flemón perineal y ba-

lanitis gangrenosa; 5) celulitis gangrenosa en un paciente inmunosuprimido, y 6) áreas muy localizadas de necrosis cutánea como complicación de una celulitis convencional.

- **Celulitis necrotizante sinérgica (gangrena cutánea anaerobia por Gramnegativos, mionecrosis anaerobia no clostrídica sinérgica):** es una variante de la fascitis necrotizante, con una afectación destacada de la piel y los músculos y del tejido subcutáneo y las fascias. Algunos casos de gangrena de Fournier que se extienden a la pared abdominal son ejemplos de esta infección. Existe toxicidad sistémica; alrededor del 50% de los pacientes presentan bacteriemia.
- **Gangrena de fournier:** Una forma de fascitis necrotizante que aparece alrededor de los genitales masculinos y el periné en ambos sexos, también conocida como gangrena idiopática del escroto, gangrena escrotal estreptocócica y flemón perineal. Puede quedar limitada al escroto o extenderse y afectar al periné, el pene o la pared abdominal. Las bacterias infecciosas probablemente atraviesan la fascia de Buck del pene y se extienden a lo largo de la túnica dartos del escroto y el pene, la fascia de Colles del periné y la fascia de Scarpa de la pared anterior del abdomen. Las bacterias anaerobias desempeñan un papel destacado y contribuyen al mal olor típico que se asocia a esta forma de fascitis necrotizante.
- **Celulitis anaerobia clostridial:** infección clostrídica necrotizante del tejido subcutáneo desvitalizado. La fascia profunda no está afectada de manera apreciable y no suele existir miositis asociada. La formación de gas es habitual y con frecuencia extensa. La celulitis anaerobia es varias veces más habitual que la gangrena gaseosa en las heridas de guerra.
- **Celulitis anaerobia no clostridial:** Un cuadro clínico muy similar al de la celulitis anaerobia clostrídica puede estar producido por la infección con varias bacterias anaerobias no formadoras de esporas (p. ej., varias especies de *Bacteroides, Peptoestreptococos, Peptococos,* bien de forma aislada o como infecciones mixtas)[28]. Las bacterias anaerobias pueden encontrarse conjuntamente con especies facultativas (bacilos coliformes, varios estreptococos, estafilococos) en una infección mixta. *E. coli, Klebsiella spp., Aeromonas spp.* y quizá otras bacterias facultativas han causado infecciones de los tejidos blandos productoras de gas.

Otras definiciones

Inmunosupresión: Para efectos del presente documento se considera inmunosupresión en pacientes con infección por VIH y un recuento de linfocitos T CD4 inferior a 200 por mm3, cáncer activo, quimioterapia, neutropenia (recuento de neutrófilos inferior a 500 células por ml), enfermedades autoinmunes activas como el lupus eritematoso sistémico o la artritis reumatoide, o recibir medicamentos que pueden incluir los siguientes (aunque no está limitado a estos): prednisona o equivalentes a una dosis diaria superior a 20mg, azatioprina, ciclosporina, micofenolato, sirolimus, everolimus, ciclofosfamida, rituximab, inhibidores de la acción del factor de necrosis tumoral o interleuquina[35].

Falla renal: Para efectos del presente documento se acepta la clasificación de falla renal de KDIGO 2017 (estructuralidad, tasa de filtracion glomerular < 89 ml/min/1.73 m2 y presencia de albuminuria).

Choque séptico: Situación en la cual las anormalidades de la circulación, celulares y del metabolismo subyacentes son lo suficientemente profundas como para aumentar sustancialmente la mortalidad. Se identifica clínicamente por la necesidad de vasopresores para mantener una tensión arterial media ≥ 65 mmHg y por presentar un lactato sérico ≥ 2 mmol/l (18 mg/dl) en ausencia de hipovolemia. Esta situación refleja tasas de mortalidad superiores al 40 %.

Sepsis: toda disfuncion de órgano que amenaza la vida por una disregulación de la respuesta del húesped a la infección y que amerita detección temprana

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SHEA/IDSA PRACTICE RECOMMENDATION

Strategies to Prevent Surgical Site Infections in Acute Care Hospitals: 2014 Update

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PURPOSE

Previously published guidelines are available that provide comprehensive recommendations for detecting and preventing healthcare-associated infections (HAIs). The intent of this document is to highlight practical recommendations in a concise format designed to assist acute care hospitals in implementing and prioritizing their surgical site infection (SSI) prevention efforts. This document updates "Strategies to Prevent Surgical Site Infections in Acute Care Hospitals,"[1] published in 2008. This expert guidance document is sponsored by the Society for Healthcare Epidemiology of America (SHEA) and is the product of a collaborative effort led by SHEA, the Infectious Diseases Society of America (IDSA), the American Hospital Association (AHA), the Association for Professionals in Infection Control and Epidemiology (APIC), and The Joint Commission, with major contributions from representatives of a number of organizations and societies with content expertise. The list of endorsing and supporting organizations is presented in the introduction to the 2014 updates.[2]

SECTION 1: RATIONALE AND STATEMENTS OF CONCERN

I. SSIs are common complications in acute care facilities
   A. SSIs occur in 2%–5% of patients undergoing inpatient surgery.[3,4]
   B. Approximately 160,000–300,000 SSIs occur each year in the United States.[5,6]
   C. SSI is now the most common and most costly HAI.[7-9]

II. Outcomes associated with SSI
   A. Up to 60% of SSIs have been estimated to be preventable by using evidence-based guidelines.[10,11]
   B. SSIs account for 20% of all HAIs in hospitalized patients.[12]
   C. Each SSI is associated with approximately 7–11 additional postoperative hospital-days.[3,9,13,14]
   D. Patients with an SSI have a 2–11-times higher risk of death compared with operative patients without an SSI.[15,16]
      1. Seventy-seven percent of deaths in patients with SSI are directly attributable to SSI.[17]
   E. Attributable costs of SSI vary depending on the type of operative procedure and the type of infecting pathogen.[14,16,18-25]
      1. SSIs are believed to account for $3.5 billion to $10 billion annually in healthcare expenditures using the CPI (consumer price index for inpatient hospital services with all cost estimates adjusted for 2007 dollars).[6]

SECTION 2: BACKGROUND—STRATEGIES TO DETECT SSI

I. Surveillance definitions
   A. The Centers for Disease Control and Prevention's (CDC's) National Healthcare Safety Network (NHSN) definitions for SSI are widely used for public reporting, interfacility comparison, and pay-for-performance comparisons.[26]
   B. SSIs are classified (Figure 1) as follows:
      1. Superficial incisional (involving only skin or subcutaneous tissue of the incision).

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Received February 12, 2014; accepted February 17, 2014; electronically published May 5, 2014.
Infect Control Hosp Epidemiol 2014;35(6):605-627
 0899-823X/2014/3506-0001$15.00. DOI: 10.1086/676022

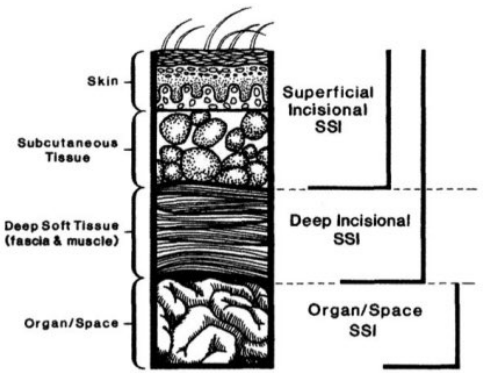

FIGURE 1. Centers for Disease Control and Prevention's National Healthcare Safety Network classification for surgical site infection (SSI).[215]

2. Deep incisional (involving fascia and/or muscular layers).
   a. Deep incision primary (DIP)—SSI identified in a primary incision in a patient who has had an operation with 1 or more incisions.
   b. Deep incision secondary (DIS)—SSI identified in a secondary incision in a patient who has had an operation with more than 1 incision.
3. Organ/space (involving any part of the body opened or manipulated during the procedure, excluding skin incision, fascia, or muscle layers).

II. Methods for surveillance of SSI

A. The direct method with daily observation of the surgical site by the physician, physician extender, registered nurse, or infection prevention and control (IPC) professional starting 24–48 hours postoperatively is the most accurate method of surveillance.[13,27-29]
   1. While the direct method is used as the gold standard for studies, it is rarely used in practice because of its resource utilization requirements and impracticality.

B. The indirect method of SSI surveillance consists of a combination of the following:
   1. Review of microbiology reports and patient medical records.
   2. Surgeon and/or patient surveys.
   3. Screening for readmission and/or return to the operating room.
   4. Other information, such as coded diagnoses, coded procedures, operative reports, or antimicrobials ordered.

C. The indirect method of SSI surveillance is less time-consuming and can be readily performed by IPC personnel during surveillance rounds.

D. The indirect method of SSI surveillance is both reliable (sensitivity, 84%–89%) and specific (specificity, 99.8%) compared with the gold standard of direct surveillance.[30,31] Components of the indirect methods that were associated with highest sensitivities included review of nursing notes, *International Classification of Diseases, Ninth Revision* codes, and antimicrobials used.

E. Indirect methods for SSI surveillance are not reliable for surveillance of superficial incisional infections, particularly those occurring postdischarge.[32]

F. Automated data systems can be used to broaden SSI surveillance.
   1. SSI surveillance can be expanded by utilizing hospital databases that include administrative claims data (including diagnosis and procedure codes), antimicrobial-days, readmission to the hospital, and return to the operating room and/or by implementing a system that imports automated microbiologic culture data, surgical procedure data, and general demographic information into a single surveillance database.[33-35]
   2. These methods improve the sensitivity of indirect surveillance for detection of SSI and reduce the effort of the infection preventionist.[33]
   3. Medicare claims data can be used to enhance traditional surveillance methods for SSI and to identify hospitals with unusually high or low rates of SSI.[36,37]
   4. Use of administrative data can increase the efficiency of SSI reporting and validation.[38]

III. Postdischarge surveillance

A. Over the past 3 decades, advances in medical technology and changes in payment arrangements have increasingly shifted performance of surgical procedures from

the acute care setting to the ambulatory (free-standing or hospital-affiliated) outpatient care setting.[39-41]

B. Concurrently, postoperative hospital length of stay has steadily declined.[42] These trends highlight the increasing importance of postdischarge surveillance, without which SSI rates will be underestimated[43] and opportunities for improvements in healthcare delivery, patient safety, and SSI prevention will be missed.

C. The proportion of SSIs detected through postdischarge surveillance can vary by surveillance method, operative setting, type of SSI, and surgical procedure.
   1. No standardized or reliable method for postdischarge surveillance has been established.[34,44-48] Postdischarge surveillance based on surgeon and patient questionnaire results have been shown to have poor sensitivity and specificity.[44,49-51]
   2. The ambulatory care setting represents a challenge because patients do not return to it for routine postoperative care or for management of complications.[41] Research is needed to better understand how definitions and postdischarge surveillance protocols developed for the acute care setting can be translated to the ambulatory care setting.
   3. Superficial incisional SSIs are most commonly detected and managed in the outpatient setting. In contrast, deep incisional and organ/space infections typically require readmission to the hospital for management.[52]
   4. In the Netherlands, the proportion of deep SSIs identified after discharge from the hospital ranged from 6% for colon resections to 88% for knee arthroplasties.[43] The differences between these procedures could be explained by potential differences in both wound contamination class and the duration of postdischarge surveillance (30 days versus 1 year for an implant-related procedure). A pilot study in general surgery reported that 10.5% of SSIs following colon procedures were identified after discharge from the hospital.[52]
   5. By improving completeness of reporting, the overall institutional SSI rate typically increases after postdischarge surveillance methods are implemented regardless of which method is used.[43,44,53]
      a. To improve interfacility comparisons and minimize potential bias introduced by differences in postdischarge surveillance methods, national public reporting focuses on nonsuperficial incisional SSIs detected during hospitalization for the index procedure or after discharge and requiring readmission for management.[41,54,55]

SECTION 3: BACKGROUND—STRATEGIES TO PREVENT SSI

I. Summary of existing guidelines, recommendations, and requirements

A. CDC and Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines
   1. The most recently published guideline for prevention of SSIs was released in 1999 by Mangram et al.[17] The CDC and HICPAC are currently working on an updated version of the guideline with a projected publication date in mid-2014.

B. National Institute for Health and Clinical Excellence (NICE)—United Kingdom
   1. NICE published guidelines for the prevention and treatment of SSI in 2008.[56]

C. Surgical Infection Prevention (SIP) Project
   1. The Centers for Medicare & Medicaid Services (CMS) created the SIP project in 2002.
      a. After review of published guidelines, an expert panel identified 3 performance measures for quality improvement related to antimicrobial prophylaxis:[57,58]
         i. Delivery of intravenous antimicrobial prophylaxis within 1 hour before incision (2 hours are allowed for the administration of vancomycin and fluoroquinolones).
         ii. Use of an antimicrobial prophylactic agent consistent with published guidelines.
         iii. Discontinuation of the prophylactic antimicrobial agent within 24 hours after surgery (discontinuation within 48 hours is allowable for cardiothoracic procedures in adult patients).
      b. The SIP project focused on 7 procedures: abdominal hysterectomy, vaginal hysterectomy, hip arthroplasty, knee arthroplasty, cardiac surgery, vascular surgery, and colorectal surgery.
      c. Many hospitals that implemented and improved compliance with SIP performance measures decreased their rates of SSI.[59]

D. Surgical Care Improvement Project (SCIP)
   1. The SCIP, a multiagency collaboration created in 2003, is an extension of SIP.
   2. In addition to the 3 performance measures of SIP, the SCIP also focuses on 3 additional evidence-supported process measures to prevent SSIs and expanded the types of operations eligible for the performance measures.[58]
      a. Proper hair removal: no hair removal, although hair removal with clippers or the depilatory method is considered appropriate. Use of razors is considered inappropriate with exception of use on the scrotal area or on the scalp after a traumatic head injury. Because of near-universal compliance with this performance measure, CMS retired the measure in 2012.
      b. Controlling blood glucose during the immediate postoperative period for cardiac surgery patients: controlled 6 AM blood glucose (200 mg/dL or lower) on postoperative days 1 and 2, with the procedure day being postoperative day 0. In 2014,

this measure will be revised to assess glucose control (180 mg/dL or lower) in cardiac surgery patients in the time frame of 18–24 hours after anesthesia end time.[60,61]

c. Maintenance of perioperative normothermia in surgical patients who have anesthesia duration of at least 60 minutes.

E. Institute for Healthcare Improvement (IHI)

1. The IHI created a nationwide quality improvement project to improve outcomes in hospitalized patients.[62,63]
2. The IHI recommends the same 6 preventive measures recommended by the SCIP and has included these in the 100,000 and 5 Million Lives Campaigns.[62,63]

F. The Joint Commission National Patient Safety Goals

1. The Joint Commission's National Patient Safety Goal 07.05.01 includes several evidence-based practices for prevention of SSI.[64]

G. Federal requirements

1. CMS

a. In accordance with the Deficit Reduction Act of 2005, hospitals that are paid by Medicare under the Acute Care Inpatient Prospective Payment System receive their full Medicare annual payment update only if they submit required quality measure information to CMS.

b. CMS now requires hospitals to submit data on 7 SCIP measures as a part of the Hospital Inpatient Quality Reporting (IQR) system.[65] Three of these measures focus on prevention of SSI (antimicrobial prophylaxis provided within 1 hour of incision, antimicrobial selection, and cardiac surgery perioperative glucose control). In addition, CMS now requires hospitals to report SSI rates for patients undergoing abdominal hysterectomy and colorectal surgery through NHSN.[65]

c. Actual rates of performance on SCIP measures now impacts hospital payment under the Value-Based Purchasing (VBP) program. Current benchmarks identified for the VBP score that is used to modify a hospital's base operating diagnosis-related group payment are at or near 100%.[65,66]

II. Infrastructure requirements

A. Trained personnel

1. Infection preventionists must (1) be specifically trained in methods of SSI surveillance, (2) have knowledge of and the ability to prospectively apply the CDC/NHSN definitions for SSI, (3) possess basic computer and mathematical skills, and (4) be adept at providing feedback and education to healthcare personnel when appropriate.[17]

B. Education

1. Regularly provide education to surgeons and perioperative personnel through continuing education activities directed at minimizing perioperative SSI risk through implementation of recommended process measures.

a. Several educational components can be combined into concise, efficient, and effective recommendations that are easily understood and remembered.[67]

b. Provide education regarding the outcomes associated with SSI, risks for SSI, and methods to reduce risk to all patients, patients' families, surgeons, and perioperative personnel.

c. Education for patients and patients' families is an effective method to reduce risk associated with intrinsic patient-related SSI risk factors.[68,69]

C. Computer-assisted decision support and automated reminders

1. Several institutions have successfully employed computer-assisted decision support methodology to improve the rate of appropriate administration of antimicrobial prophylaxis (including redosing during prolonged cases).[70-73]
2. Computer-assisted decision support, however, is potentially expensive, can be time-consuming to implement, and in a single study was reported to initially increase the rate of adverse drug reactions.[74]
3. Institutions must appropriately validate computer-assisted decision support systems after implementation.

D. Utilization of automated data

1. Install information technology infrastructure to facilitate data transfer, receipt, and organization to aid with tracking of process and outcome measures.

SECTION 4: RECOMMENDED STRATEGIES FOR SSI PREVENTION

Recommendations are categorized as either (1) basic practices that should be adopted by all acute care hospitals or (2) special approaches that can be considered for use in locations and/or populations within hospitals when HAIs are not controlled by use of basic practices. Basic practices include recommendations where the potential to impact HAI risk clearly outweighs the potential for undesirable effects. Special approaches include recommendations where the intervention is likely to reduce HAI risk but where there is concern about the risks for undesirable outcomes resulting from the intervention, where the quality of evidence is low, or where evidence supports the impact of the intervention in select settings (eg, during outbreaks) or for select patient populations. Hospitals can prioritize their efforts by initially focusing on implementation of the prevention approaches listed as basic practices. If HAI surveillance or other risk assessments suggest that there are ongoing opportunities for improvement, hospitals should then consider adopting some or all of the prevention approaches listed as special approaches. These can be implemented in specific locations or patient populations or can be implemented hospital-wide, depending on outcome data, risk assessment, and/or local requirements. Each infec-

TABLE 1. Grading of the Quality of Evidence

Grade	Definition
I. High	Highly confident that the true effect lies close to that of the estimated size and direction of the effect. Evidence is rated as high quality when there is a wide range of studies with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval.
II. Moderate	The true effect is likely to be close to the estimated size and direction of the effect, but there is a possibility that it is substantially different. Evidence is rated as moderate quality when there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide.
III. Low	The true effect may be substantially different from the estimated size and direction of the effect. Evidence is rated as low quality when supporting studies have major flaws, there is important variation between studies, the confidence interval of the summary estimate is very wide, or there are no rigorous studies, only expert consensus.

NOTE. Based on Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)[234] and the Canadian Task Force on Preventive Health Care.[235]

tion prevention recommendation is given a quality-of-evidence grade (see Table 1).

I. Basic practices for preventing SSI: recommended for all acute care hospitals
   1. Administer antimicrobial prophylaxis according to evidence-based standards and guidelines (quality of evidence: I).[17,75,76]
      a. Begin administration within 1 hour before incision to maximize tissue concentration.[57,58] Administering agent closer than 1 hour is effective, and some studies show superior efficacy for administration between 0 and 30 minutes prior to incision compared with administration between 30 and 60 minutes.[77,78]
         i. Two hours are allowed for the administration of vancomycin and fluoroquinolones.
         ii. Many experts believe that antimicrobials should be infused prior to inflation of tourniquets in procedures using "bloodless" techniques, although data are insufficient to support this recommendation.[79,80]
      b. Select appropriate agents on the basis of the surgical procedure, the most common pathogens causing SSIs for a specific procedure, and published recommendations.[76]
      c. Discontinue agent within 24 hours after surgery.[76]
         i. Although guidelines suggest stopping the antimicrobial agent within 24 hours of surgery, there is no evidence that agents given after closure contribute to efficacy, and they do contribute to increased resistance[81,82] and the risk of *Clostridium difficile* disease.[83]
      d. Adjust dosing on the basis of patient weight;[76] for example:
         i. Use 30 mg/kg for pediatric patients, 2 g of cefazolin for patients weighing 80 kg or more, and 3 g for patients weighing 120 kg or more.
         ii. Vancomycin should be dosed at 15 mg/kg.
         iii. Gentamicin should be dosed at 5 mg/kg for adult patients and 2.5 mg/kg for pediatric patients.
            (a) For morbidly obese patients receiving gentamicin, the weight used for dose calculation should be the ideal weight plus 40% of the excess weight.
      e. Redose prophylactic antimicrobial agents for long procedures and in cases with excessive blood loss during the procedure.[76]
         i. Prophylactic antimicrobials should be redosed at intervals of 2 half-lives (measured from time the preoperative dose was administered) in cases that exceed this time.
      f. Use a combination of parenteral antimicrobial agents and oral antimicrobials to reduce the risk of SSI following colorectal procedures.[84-91]
         i. The additional SSI reduction achieved with mechanical bowel preparation has not been studied, but the data supporting use of oral antimicrobials have all been generated in combination with mechanical bowel preparation.
         ii. Mechanical bowel preparation without oral antimicrobials does not decrease the risk of SSI.[92]
   2. Do not remove hair at the operative site unless the presence of hair will interfere with the operation. Do not use razors (quality of evidence: II).[17,93]
      a. If hair removal is necessary, remove hair outside the operating room using clippers or a depilatory agent.
   3. Control blood glucose during the immediate postoperative period for cardiac surgery patients[38] (quality of evidence: I) and noncardiac surgery patients[94-98] (quality of evidence: II).
      a. Maintain postoperative blood glucose of 180 mg/dL or lower.
         i. The recommendation of maintaining postoperative blood glucose less than 200 mg/dL at 6 AM on postoperative days 1 and 2 is being replaced. In 2014, this measure will be revised in the SCIP to assess

glucose control (180 mg/dL or lower) in cardiac surgery patients in the time frame of 18–24 hours after anesthesia end time. Several societies, experts, and the National Quality Forum support this new recommendation.[60,61,99,100]

b. Intensive postoperative glucose control (targeting levels less than 110 mg/dL) has not been shown to reduce the risk of SSI and may actually lead to higher rates of adverse outcomes, including stroke and death.[101]

4. Maintain normothermia (temperature of 35.5°C or more) during the perioperative period (quality of evidence: I).
   a. Even mild degrees of hypothermia can increase SSI rates. Hypothermia may directly impair neutrophil function or impair it indirectly by triggering subcutaneous vasoconstriction and subsequent tissue hypoxia. In addition, hypothermia may increase blood loss, leading to wound hematomas or need for transfusion, both of which can increase rates of SSI.[102]
   b. Randomized controlled trials have shown the benefits of both preoperative and intraoperative warming to reduce SSI rates and to reduce intraoperative blood loss.[103-105]
5. Optimize tissue oxygenation by administering supplemental oxygen during and immediately following surgical procedures involving mechanical ventilation (quality of evidence: I).
   a. Supplemental oxygen is most effective when combined with additional strategies to improve tissue oxygenation, including maintenance of normothermia and appropriate volume replacement. The available evidence is in patients undergoing surgery with general anesthesia using mechanical ventilation.[106-108]
      i. Seven randomized clinical trials have been published comparing 80% with 30%–35% FiO_2 (4 with nitrogen[106-109] and 3 with nitrous oxide[110-112]) in patients undergoing general anesthesia with intraoperative mechanical ventilation and postoperative oxygen delivered for 2–6 hours via a nonrebreathing mask.
      ii. Three trials in patients undergoing elective colorectal resection[106,107,111] and 1 each in open appendectomy[108] and total gastrectomy with esophagojejunal anastomosis[112] reported an approximate 40% decrease in the rate of SSI. Three of the studies reported protocols that included maintenance of perioperative normothermia and liberal fluid replacement.[106-108]
      iii. Two trials in mixed surgical populations undergoing emergency or elective laparotomy for gastrointestinal, gynecologic, or urologic procedures reported different results.[109,110]
         (a) The large multicenter trial that restricted perioperative fluid replacement reported no difference.[109] A follow-up study performed in this population noted that patients undergoing cancer surgery who received 80% FiO_2 had higher rates of mortality than patients undergoing cancer surgery who received 30% FiO_2.[113]
         (b) The smaller trial without standardized protocols for perioperative normothermia or volume replacement reported an increase in SSIs.[110] In this study, the 80% FiO_2 group had a significantly higher proportion of patients with high body mass index (more than 30), higher blood loss, more crystalloid infused, and longer operations. This group also had 5 patients who remained intubated postoperatively (vs 1 in the 35% group). Postoperative intubation was predictive of SSI.
   b. A meta-analysis of 5 of the above-referenced studies concluded that perioperative supplemental oxygen led to a relative risk (RR) reduction of 25% for SSI.[114]
6. Use alcohol-containing preoperative skin preparatory agents if no contraindication exists (quality of evidence: I).
   a. Alcohol is highly bactericidal and effective for preoperative skin antisepsis but does not have persistent activity when used alone. Rapid, persistent, and cumulative antisepsis can be achieved by combining alcohol with chlorhexidine gluconate or an iodophor.[115]
      i. Alcohol is contraindicated for certain procedures, including procedures in which the preparatory agent may pool or not dry (eg, involving hair) due to fire risk. Alcohol may also be contraindicated for procedures involving mucosa, cornea, or ear.
   b. The most effective disinfectant to combine with alcohol is unclear.
      i. A recent trial of 849 patients undergoing clean-contaminated surgery randomized patients to preoperative skin antisepsis with chlorhexidine-alcohol or povidone-iodine.[116] The overall rate of SSI was significantly lower in the chlorhexidine-alcohol group than in the povidone-iodine group (9.5% vs 16% [$P = .004$]; RR, 0.59 [95% confidence interval (CI), 0.41–0.85]).
      ii. In contrast, a single-center study compared povidone-iodine followed by isopropyl alcohol versus chlorhexidine-alcohol versus iodine-alcohol using a sequential implementation design.[117] General surgical patients who received skin antisepsis with iodine-alcohol had the lowest rates of SSI (3.9 per 100 procedures), compared with 6.4 per 100 procedures for patients who received povidone-iodine followed by alcohol and 7.1 per 100 procedures for patients who received chlorhexidine-alcohol.
      iii. In the absence of alcohol, chlorhexidine gluconate may have advantages over povidone-iodine, in-

cluding longer residual activity and activity in the presence of blood or serum.[118,119]

iv. These disinfectants are not interchangeable. Follow the manufacturers' instructions to ensure correct application.

7. Use impervious plastic wound protectors for gastrointestinal and biliary tract surgery (quality of evidence: I).
   a. A wound protector is a plastic sheath that lines a wound and can facilitate retraction of an incision during surgery without the need for additional mechanical retractors.
   b. A recent meta-analysis of 6 randomized clinical trials in 1,008 patients reported that use of a plastic wound protectors was associated with a 45% decrease in SSIs.[120]
      i. There was a nonsignificant trend toward greater protective effect using a dual-ring protector compared with a single-ring protector.
8. Use a checklist based on the World Health Organization (WHO) checklist to ensure compliance with best practices to improve surgical patient safety (quality of evidence: I).
   a. The WHO checklist is a 19-item surgical safety checklist to improve adherence with best practices.
   b. A multicenter quasi-experimental study conducted in 8 countries demonstrated that use of the WHO checklist led to lower rates of surgical complications, including SSI and death.[121]
   c. These findings have been confirmed in subsequent single-center and multicenter quasi-experimental studies.[122,123]
9. Perform surveillance for SSI (quality of evidence: II).
   a. Identify high-risk, high-volume operative procedures to be targeted for SSI surveillance on the basis of a risk assessment of patient populations, operative procedures performed, and available SSI surveillance data.
   b. Identify, collect, store, and analyze data needed for the surveillance program.[17]
      i. Develop a database for storing, managing, and accessing data collected on SSIs.
      ii. Implement a system for collecting data needed to identify SSIs. Data are required from surgical and microbiological databases. Obtain the following data from surgical databases: patient name, medical record number, date, type of procedure, surgeons, anesthesiologists, incision time, wound class, ASA score, closure time, and presence of an SSI. Ideally, these data are supplemented with process data, including prophylactic agent and dose and time(s) of administration of prophylactic agent. For patients diagnosed with an SSI, necessary microbiological data include type of SSI, infecting organism and antimicrobial susceptibilities, and date of infection. More detailed surgical and patient information may be useful for some procedures, including use of general anesthesia, emergency or trauma-related surgery, body mass index, and diagnosis of diabetes.
      iii. Prepare periodic SSI reports (time frame will depend on hospital needs and volume of targeted procedures).
      iv. Collect denominator data on all patients undergoing targeted procedures in order to calculate SSI rates for each type of procedure.[67]
      v. Identify trends (eg, in SSI rates and pathogens causing SSIs).
   c. Use updated CDC NHSN definitions for SSI.[26]
   d. Perform indirect surveillance for targeted procedures.[30,31,124,125]
   e. Perform postoperative surveillance for 30 days; extend the postoperative surveillance period to 90 days for certain procedure categories.[26]
      i. Procedures that require 90-day surveillance are determined by specific procedure codes.
   f. Surveillance should be performed on patients readmitted to the hospital.
      i. If an SSI is diagnosed at your institution but the surgical procedure was performed elsewhere, notify the hospital where the original procedure was performed.
   g. Develop a system for routine review and interpretation of SSI rates to detect significant increases or outbreaks and to identify areas where additional resources might be needed to improve SSI rates.[125] If increased rates are identified, determine the number of potentially preventable infections that occurred, defined as the number of SSIs that occurred during a procedure in which less than 100% of recommended practices and processes were completed.
10. Increase the efficiency of surveillance through utilization of automated data (quality of evidence: II).
    a. Implement a method to electronically transfer microbiology and operative data, including process measures when available, to IPC personnel to facilitate denominator data acquisition and calculation of SSI rates for various procedures.
    b. If information technology and infrastructure resources are available, develop automated methods for detection of SSIs utilizing automated data for readmissions, diagnosis and procedure codes, microbiology results, and antimicrobial dispensing.[35,126-129]
    c. Implementation of automated surveillance may improve the sensitivity of surveillance.
11. Provide ongoing feedback of SSI rates to surgical and perioperative personnel and leadership (quality of evidence: II).
    a. Routinely audit and provide confidential feedback on SSI rates and adherence to process measures to in-

dividual surgeons, the surgical division and/or department chiefs, and hospital leadership.[17,130]
   i. For each type of procedure performed, provide risk-adjusted rates of SSI.
   ii. Anonymously benchmark procedure-specific risk-adjusted rates of SSI among peer surgeons.
12. Measure and provide feedback to providers regarding rates of compliance with process measures (quality of evidence: III).[58]
   a. Routinely provide feedback to surgical staff, perioperative personnel, and leadership regarding compliance with targeted process measures.
13. Educate surgeons and perioperative personnel about SSI prevention (quality of evidence: III).
   a. Include risk factors, outcomes associated with SSI, local epidemiology (eg, SSI rates by procedure, rate of methicillin-resistant *Staphylococcus aureus* [MRSA] infection in a facility), and basic prevention measures.
14. Educate patients and their families about SSI prevention as appropriate (quality of evidence: III).
   a. Provide instructions and information to patients prior to surgery describing strategies for reducing SSI risk. Specifically provide preprinted materials to patients.[131]
   b. Examples of printed materials for patients are available from the following websites:
      i. *JAMA* patient page: wound infections (from the *Journal of the American Medical Association*; available at http://jama.ama-assn.org/cgi/reprint/294/16/2122).
      ii. SCIP's tips for safer surgery (available at https://www.premierinc.com/safety/topics/scip/downloads/consumer-tips.pdf).
      iii. Frequently asked questions about SSIs (available from SHEA at http://www.shea-online.org/Assets/files/patient%20guides/NNL_SSI.pdf).
      iv. SSI: resources for patients and healthcare providers (available from the CDC at http://www.cdc.gov/hai/ssi/ssi.html).
15. Implement policies and practices aimed at reducing the risk of SSI that align with evidence-based standards (eg, CDC, Association for periOperative Registered Nurses, and professional organization guidelines; quality of evidence: II).[17,58,132]
   a. The pathogenesis and likelihood of developing an SSI involves a complex relationship among the following:
      i. Microbial characteristics (eg, degree of contamination, virulence of pathogen);
      ii. Patient characteristics (eg, immune status, comorbid conditions); and
      iii. Surgical characteristics (eg, type of procedure, introduction of foreign material, amount of damage to tissues).[133]
   b. Risk factors for SSI can be separated into intrinsic patient-related characteristics and extrinsic procedure-related characteristics. Implement policies and practices to reducing modifiable risk factors (Table 2), including the following:
      i. Optimal preparation and disinfection of the operative site and the hands of the surgical team members.
      ii. Adherence to hand hygiene, including nonsurgeon members of the operating team.[134]
      iii. Reduce unnecessary traffic in operating rooms.[135,136]
      iv. Appropriate care and maintenance of operating rooms, including appropriate air handling and optimal cleaning and disinfection of equipment and the environment.[17]

II. Special approaches for preventing SSI

Standard infection control methods of outbreak investigation are recommended for use in locations and/or populations within the hospital with unacceptably high SSI rates despite implementation of the basic SSI prevention strategies listed above.

1. Screen for *S. aureus* and decolonize surgical patients with an antistaphylococcal agent in the preoperative setting for high-risk procedures, including some orthopedic and cardiothoracic procedures (quality of evidence: II).
   a. Screening for *S. aureus* refers to the practice of attempting to identify patients colonized with methicillin-susceptible *S. aureus* (MSSA) and/or MRSA. Decolonization refers to the practice of treating patients with known *S. aureus* colonization with antimicrobial and/or antiseptic agents to eliminate *S. aureus* colonization.
      i. There is no standardized approach to either screening or decolonizing. Most clinicians attempt to decolonize surgical patients with a combination of chlorhexidine gluconate applied to the skin and nasal mupirocin.
   b. A Cochrane review concluded that mupirocin alone may be effective, particularly in certain groups, including orthopedic and cardiothoracic patients.[137] Several nonrandomized trials corroborate this conclusion.[138-140]
   c. Clinical practice guidelines from the American Society of Health-System Pharmacists recommend giving mupirocin intranasally to all patients with documented *S. aureus* colonization for orthopedic procedures, including total joint replacement and hip fracture repair, and cardiac procedures.[76]
   d. Some trials demonstrate that preoperative screening for *S. aureus*, coupled with intranasal mupirocin and chlorhexidine bathing is effective in reducing SSI for some patients.
      i. For example, a randomized, double-blind, placebo-controlled, multicenter trial that evaluated rapid identification of *S. aureus* nasal carriers followed

TABLE 2. Selected Risk Factors for and Recommendations to Prevent Surgical Site Infections (SSIs)

Risk factor	Recommendation	Quality of evidence
Intrinsic, patient related (preoperative)		
Unmodifiable		
Age	No formal recommendation. Relationship to increased risk of SSI may be secondary to comorbidities or immunosenescence.[216-218]	NA
History of radiation	No formal recommendation. Prior irradiation at the surgical site increases the risk of SSI, likely due to tissue damage and wound ischemia.[219]	NA
History of SSTIs	No formal recommendation. History of a prior skin infection may be a marker for inherent differences in host immune function.[220]	NA
Modifiable		
Glucose control	Control serum blood glucose levels for all surgical patients, including patients without diabetes.[17] For patients with diabetes mellitus, reduce glycosylated hemoglobin A1c levels to less than 7% before surgery, if possible.[94]	I
Obesity	Increase dosing of prophylactic antimicrobial agent for morbidly obese patients.[76,221]	I
Smoking cessation	Encourage smoking cessation within 30 days of procedure.[17,222-226]	I
Immunosuppressive medications	Avoid immune-suppressive medications in perioperative period, if possible.	III
Hypoalbuminemia	No formal recommendation. Although a noted risk factor,[227] do not delay surgery for use of TPN.	NA
Extrinsic, procedure related (perioperative)		
Preparation of patient		
Hair removal	Do not remove unless hair will interfere with the operation.[17] If hair removal is necessary, remove outside the OR by clipping. Do not use razors.	II
Preoperative infections	Identify and treat infections (eg, urinary tract infection) remote to the surgical site prior to elective surgery.[17] Do not routinely treat colonization or contamination.	II
Operative characteristics		
Surgical scrub (surgical team members' hands and forearms)	Use appropriate antiseptic agent to perform preoperative surgical scrub.[17,228] For most products, scrub the hands and forearms for 2–5 minutes.	II
Skin preparation	Wash and clean skin around incision site. Use a dual agent skin preparation containing alcohol, unless contraindications exist.[17]	I
Antimicrobial prophylaxis	Administer only when indicated.[17]	I
Timing	Administer within 1 hour of incision to maximize tissue concentration[76,a]	I
Blood transfusion	Blood transfusions increase the risk of SSI by decreasing macrophage function. Reduce blood loss and need for blood transfusion to the greatest extent possible.[229-231]	II
Choice of prophylactic agent	Select appropriate agents on the basis of surgical procedure, most common pathogens causing SSIs for a specific procedure, and published recommendations.[76]	I
Duration of prophylaxis	Stop agent within 24 hours after the procedure for all procedures.[76]	II
Surgeon skill/technique	Handle tissue carefully and eradicate dead space.[17]	III
Appropriate gloving	All members of the operative team should double glove and change gloves when perforation is noted.[208]	III
Asepsis	Adhere to standard principles of OR asepsis.[17]	III
Operative time	No formal recommendation in most recent guidelines. Minimize as much as possible without sacrificing surgical technique and aseptic practice.	I
OR characteristics		
Ventilation	Follow American Institute of Architects' recommendations for proper air handling in the OR.[17,232]	III
Traffic	Minimize OR traffic.[17,135,136]	III
Environmental surfaces	Use an EPA-approved hospital disinfectant to clean visibly soiled or contaminated surfaces and equipment.[17]	III
Sterilization of surgical equipment	Sterilize all surgical equipment according to published guidelines.[233] Minimize the use of immediate-use steam sterilization.[17]	II

NOTE. EPA, Environmental Protection Agency; NA, not applicable; OR, operating room; SSTI, skin and soft-tissue infection; TPN, total parenteral nutrition.

[a] Vancomycin and fluoroquinolones can be given 2 hours prior to incision.

by decolonization was associated with a greater than 2-fold reduction in the risk for postoperative infection due to *S. aureus* and an almost 5-fold reduction in risk for deep incisional SSI due to *S. aureus*.[141]
   (a) This study was performed in a setting with high baseline rates of SSI and in the absence of MRSA.
e. In contrast, other trials have failed to demonstrate a benefit.
   i. A prospective, interventional cohort study with a crossover design involving 21,000 patients concluded that universal, rapid screening for MRSA at admission coupled with decolonization of carriers did not reduce the rate of SSI due to MRSA.[142]
   ii. A double-blind randomized controlled trial involving more than 4,000 patients showed that intranasal application of mupirocin, which was not coupled with chlorhexidine bathing, did not significantly reduce the *S. aureus* SSI rate.[143]
      (a) In a secondary analysis of these data, the use of intranasal mupirocin was associated with an overall decreased rate of nosocomial *S. aureus* infections among the *S. aureus* carriers.
f. A recently published meta-analysis of 17 studies concluded that decolonization strategies prevent gram-positive SSIs, *S. aureus* SSIs, and MRSA SSIs, although there was significant heterogeneity among the trials.[144]
g. Factors that impact the decision to implement screening for *S. aureus* and decolonization include adherence to basic SSI prevention strategies, baseline rate of SSI due to *S. aureus*, individual patient risk factors for acquiring SSI due to *S. aureus*, availability of resources to implement the protocol, and ability to follow-up on protocol parameters (eg, laboratory results) and adherence.
h. Routine preoperative decolonization with mupirocin without screening is not currently recommended.
   i. Mupirocin resistance has been documented.[145]

2. Perform antiseptic wound lavage (quality of evidence: II).
   a. Wound lavage is a common practice, although the solution used for lavage differs among surgeons.[146]
   b. Several groups have evaluated whether dilute povidone-iodine lavage of the surgical wound can decrease the risk of SSI. A meta-analysis published in 2010 evaluated 24 randomized controlled trials and concluded that lavage with dilute povidone-iodine decreased the risk of SSI compared with nonantiseptic lavage (RR, 0.64 [95% CI, 0.51–0.82]).[147]
3. Perform an SSI risk assessment (quality of evidence: III).
   a. Convene a multidisciplinary team (eg, surgical leadership, hospital administration, quality management services, and infection control) to identify gaps, improve performance, measure compliance, assess impact of interventions, and provide feedback.[148]
   b. Determine baseline SSI rates by surgical specialty, procedure, and/or surgeon to better target your evaluation and interventions.
4. Observe and review operating room personnel and the environment of care in the operating room (quality of evidence: III).
   a. Perform direct observation audits of operating room personnel to assess operating room processes and practices to identify infection control lapses, including but not limited to adherence to process measures (antimicrobial prophylaxis choice, timing and duration protocols, hair removal, etc), surgical hand antisepsis, patient skin preparation, operative technique, surgical attire (wearing and/or laundering outside the operating room), and level of operating room traffic.[149-153] Perform remediation when breaches of standards are identified.
      i. Operating room personnel should include surgeons, surgical technologists, anesthesiologists, circulating nurses, residents, medical students, trainees, and device manufacturer representatives.[149]
   b. Perform direct-observation audits of environmental cleaning practices in the operating room, instrument processing (sterilization), and storage facilities.
      i. Review instrument processing and flash sterilization logs.
      ii. Review maintenance records for operating room heating, ventilation, and air conditioning system, including results of temperature and relative humidity testing, and test for maintenance of positive air pressure in the operating room(s).
   c. Provide feedback and review infection control measures with operating room and environmental personnel.
5. Observe and review practices in the postanesthesia care unit, surgical intensive care unit, and/or surgical ward (quality of evidence: II).
   a. Perform direct observation audits of hand hygiene practices among all personnel with direct patient contact.[151]
   b. Evaluate wound care practices.[154]
   c. Perform direct observation audits of environmental cleaning practices.
   d. Provide feedback and review infection control measures with staff in these postoperative care settings.

III. Approaches that should not be considered a routine part of SSI prevention
1. Do not routinely use vancomycin for antimicrobial prophylaxis (quality of evidence: II).[75,76,155]
   a. Vancomycin should not routinely be used for antimicrobial prophylaxis, but it can be an appropriate agent for specific scenarios. Reserve vancomycin for specific clinical circumstances, such as a proven outbreak of SSI due to MRSA; high endemic rates of SSI due to MRSA; targeted high-risk patients who are at

increased risk for SSI due to MRSA (including cardiothoracic surgical patients and elderly patients with diabetes); and high-risk surgical procedures in which an implant is placed.[156]

i. No definitions for high endemic rates of SSI due to MRSA have been established.[157]

ii. Studies of the efficacy of vancomycin prophylaxis were published prior to the emergence of community-acquired MRSA.

b. Two meta-analyses of studies comparing glycopeptides to β-lactam antimicrobial prophylaxis concluded that there was no difference in rates of SSI between the 2 antimicrobial prophylaxis regimens.[144,158]

c. A meta-analysis of 6 studies concluded that prophylaxis with a glycopeptide and a second agent was protective against SSI due to gram-positive organisms compared with prophylaxis with a β-lactam alone.[144] Of note, the 2 randomized controlled trials included in the meta-analysis combined a glycopeptide with non-β-lactam antibiotic(s). Thus, no study has prospectively analyzed the effect of providing both glycopeptides and β-lactam antimicrobials for preoperative antimicrobial prophylaxis. As vancomycin does not have activity against gram-negative pathogens and appears to have less activity against MSSA than β-lactam agents, many experts recommend adding vancomycin to standard antimicrobial prophylaxis for the specific clinical circumstances described above.[76,157-159]

2. Do not routinely delay surgery to provide parenteral nutrition (quality of evidence: I).

a. Preoperative administration of total parenteral nutrition has not been shown to reduce the risk of SSI in prospective randomized controlled trials and may increase the risk of SSI.[160,161]

b. Individual trials comparing enteral and parenteral perioperative nutrition and "immunomodulating" diets containing arginine and/or glutamine with "standard" control diets tend to have very small numbers and fail to show significant differences. Two recent meta-analyses, however, demonstrate reduction in postoperative infectious complication in patients receiving enteral diets containing glutamine and/or arginine administered either before or after the surgical procedure.[162,163]

3. Do not routinely use antiseptic-impregnated sutures as a strategy to prevent SSIs (quality of evidence: II).

a. Human volunteer studies involving foreign bodies have demonstrated that the presence of surgical sutures decreases the inoculum required to cause an SSI from 10^6 to 10^2 organisms.[164]

b. Some trials have shown that surgical wound closure with triclosan-coated polygactin 910 antimicrobial sutures may decrease the risk of SSI compared with standard sutures. For example, a recent randomized controlled trial of 410 colorectal surgeries concluded that the rate of SSI decreased more than 50% (9.3% in the control group vs 4.3% among cases; $P = .05$).[165]

c. In contrast, a recent systematic review and meta-analysis evaluated 7 randomized clinical trials and concluded that neither rates of SSI (odds ratio [OR], 0.77 [95% CI, 0.4–1.51]; $P = .45$) nor rates of wound dehiscence (OR, 1.07 [95% CI, 0.21–5.43]; $P = .93$) were statistically different compared with controls.[166] In addition, one small study raised concern about higher rates of wound dehiscence while using these sutures.[167]

d. The impact of routine use of antiseptic-impregnated sutures on development of resistance to antiseptics is unknown.

4. Do not routinely use antiseptic drapes as a strategy to prevent SSIs (quality of evidence: I).

a. An incise drape is an adhesive film that covers the surgical incision site to minimize bacterial wound contamination due to endogenous flora. These drapes can be impregnated with antiseptic chemicals, such as iodophors.

b. A 2007 Cochrane review of 5 trials concluded that nonantiseptic incise drapes were associated with a higher risk of SSI compared with no incise drape (RR, 1.23 [95% CI, 1.02–1.48]),[168] although this association may have been caused by one specific study.[169] Two trials (abdominal and cardiac surgical patients) compared iodophor-impregnated drapes to no drapes.[170,171] While wound contamination was decreased in one trial,[170] neither trial demonstrated that iodophor-impregnated drapes decreased the rate of SSI. A nonrandomized retrospective study similarly concluded that impregnated drapes do not prevent SSIs after hernia repair.[172]

IV. Unresolved issues

1. Preoperative bathing with chlorhexidine-containing products.

a. Preoperative bathing with agents such as chlorhexidine has been shown to reduce bacterial colonization of the skin.[173] Several studies have examined the utility of preoperative showers, but none has definitively proven that they decrease SSI risk. A Cochrane review evaluated the evidence for preoperative bathing or showering with antiseptics for SSI prevention.[174] Six randomized controlled trials evaluating the use of 4% chlorhexidine gluconate were included in the analysis, with no clear evidence of benefit noted. It should be noted that several of these studies had methodological limitations and were conducted several years ago. Thus, the role of preoperative bathing in SSI prevention is still uncertain.

i. To gain the maximum antiseptic effect of chlorhexidine, adequate levels of CHG must be achieved and maintained on the skin. Typically, adequate levels are achieved by allowing CHG to dry com-

pletely. New strategies for preoperative bathing with chlorhexidine, such as preimpregnated cloths, have shown promise,[175,176] but data are currently insufficient to support this approach.

2. Preoperative intranasal and pharyngeal chlorhexidine treatment for patients undergoing cardiothoracic procedures.
   a. Although data from a randomized controlled trial exist to support the use of chlorhexidine nasal cream combined with 0.12% chlorhexidine gluconate mouthwash,[177] chlorhexidine nasal cream is neither approved by the Food and Drug Administration (FDA) nor commercially available in the United States.
3. Use of gentamicin-collagen sponges.
   a. Gentamicin-collagen sponges have been evaluated as a way to decrease SSI among colorectal and cardiac surgical patients.
      i. Colorectal surgical patients. Several single-center randomized trials have demonstrated that gentamicin-collagen sponges decrease the risk of SSI following colorectal procedures.[178-180] The rate of SSI was higher with the sponge, however, in a recent large, multicenter randomized clinical trial.[181]
      ii. Cardiothoracic surgical patients. Four randomized controlled trials have evaluated the use of gentamicin-collagen sponges in cardiothoracic surgery. Three of these trials demonstrated a decrease in SSIs,[182-184] and one showed no difference.[185] A recent meta-analysis combining these trials concluded that the risk of deep sternal wound infection was significantly lower in patients who received a gentamicin-collagen sponge than in patients who did not (RR, 0.62 [95% CI, 0.39–0.97]) despite significant heterogeneity among the trials.[186]
   b. Gentamicin-collagen sponges are not currently approved by the FDA for use in the United States.
4. Use of bundles to ensure compliance with best practices.
   a. Bundles have been promoted as methods to improve adherence to best practices.
   b. Although generally favorable, the use of bundles for the prevention of SSI has led to mixed results, depending on which components are included.[59,187,188]
   c. Thus, there is no consensus on the components of an effective bundle to prevent SSIs.

SECTION 5: PERFORMANCE MEASURES

I. Internal reporting

These performance measures are intended to support internal hospital quality improvement efforts and do not necessarily address external reporting needs. The process and outcome measures suggested here are derived from published guidelines, other relevant literature, and the opinion of the authors. Report process and outcome measures to senior hospital leadership, nursing leadership, and clinicians who care for patients at risk for SSI.

A. Process measures
   1. Compliance with antimicrobial prophylaxis guidelines.
      a. Measure the percentage of procedures in which antimicrobial prophylaxis was appropriately provided. Appropriateness includes (1) correct type of agent, (2) start of administration of the agent within 1 hour of incision (2 hours allowed for vancomycin and fluoroquinolones), and (3) discontinuation of the agent within 24 hours after surgery.
         i. Numerator: number of patients who appropriately received antimicrobial prophylaxis.
         ii. Denominator: total number of selected operations performed.
         iii. Multiply by 100 so that the measure is expressed as a percentage.
   2. Compliance with hair removal guidelines.
      a. Measure the percentage of procedures for which hair removal is appropriately performed (ie, clipping, use of a depilatory or no hair removal is performed rather than use of razor).
         i. Numerator: number of patients with appropriate perioperative hair removal.
         ii. Denominator: total number of selected operations performed.
         iii. Multiply by 100 so that the measure is expressed as a percentage.
   3. Compliance with perioperative glucose control guidelines.
      a. Measure the percentage of procedures for which serum glucose is 180 mg/dL or lower within 18–24 hours after anesthesia end time for all cardiac surgery patients.[60,61,100]
         i. Numerator: number of patients with appropriately maintained serum glucose (180 mg/dL or lower) in the time frame of 18–24 hours after anesthesia end time following cardiac surgery.
         ii. Denominator: total number of cardiac procedures performed.
         iii. Multiply by 100 so that the measure is expressed as a percentage.

B. Outcome measures
   1. SSI rate
      a. Use NHSN definitions and risk adjustment methods for SSI (available at http://www.cdc.gov/nhsn/acute-care-hospital/ssi/index.html).
         i. Numerator: number of patients with an SSI following selected operations.
         ii. Denominator: total number of selected operations performed.
         iii. Multiply by 100 so that the measure is expressed as the number of SSIs per 100 procedures.
         iv. Rates of SSI can be risk adjusted using one of 2 methods: stratification using the NHSN risk

index[133] or calculation of the standardized infection ratio (SIR).[189] NHSN now promotes the use of SIR over the NHSN risk index for improved risk adjustment potential,[190] and SIR is preferentially used for the national public reporting outcome measure within NHSN.

(a) The NHSN risk index is an operation- and patient-specific prospectively applied risk score that predicts SSIs.[191] This risk index includes 3 predictors of increased risk of SSI: (1) estimators of wound microbial contamination, (2) duration of operation, and (3) markers for host susceptibility.[42]

(b) SIR is the ratio of the observed number of SSIs (O) that occurred compared with the expected number for a surgeon performing a specific type of procedure (E; eg, SIR = O/E).[189] The expected number of SSIs can be obtained by multiplying the number of operations done by the surgeon in each procedure risk category by the NHSN rate for the same procedure risk category and dividing by 100. Values that exceed 1.0 indicate that more SSIs occurred than expected. Importantly, SIR can only be calculated if the number of expected HAIs is ≥ 1. Thus, this approach may be more difficult for small surgical programs or if few procedures are performed for any one procedure type.[192]

(c) Risk adjustment using logistic regression and the SIR method generally provides better risk-adjustment than the basic risk index.[190,193]

II. External reporting

There are many challenges in providing useful information to consumers and other stakeholders while preventing unintended adverse consequences of public reporting of HAIs.[194] Recommendations and requirements for public reporting of HAIs have been provided by HICPAC,[195] the Healthcare-Associated Infection Working Group of the Joint Public Policy Committee,[54] the National Quality Forum,[55] and CMS.[196] The following is an example of an external performance measure that is currently required by some healthcare stakeholders and regulators.

A. Process measures

1. Compliance with CMS antimicrobial prophylaxis guidelines (see the section above on internal reporting in "Section 5: Performance Measures").
   a. Measure the percentage of procedures in which antimicrobial prophylaxis was appropriately provided. Appropriateness includes correct type of agent, administration of the agent within 1 hour of incision (2 hours are allowed for vancomycin and fluoroquinolones), and discontinuation of the agent within 24 hours after surgery (48 hours for cardiothoracic procedures).[197]
2. Compliance with the CMS guideline for control of postoperative blood glucose in cardiac surgery patients.
   a. Measure the percentage of procedures in which postoperative blood glucose was appropriately controlled in cardiac surgery patients.

B. Federal and state requirements

1. Federal requirements
   a. The CMS published a final rule in the *Federal Register* on August 18, 2011, that includes SSI reporting via the CDC's NHSN in the CMS Hospital IQR program requirements for 2012.[196] More specifically, the rule announced a reporting requirement for SSI data for inpatient abdominal hysterectomy and inpatient colon procedures beginning with surgical procedures performed on January 1, 2012.[198]
   b. The requirements for SSI reporting to NHSN for the IQR program do not preempt or supersede state mandates for SSI reporting to NHSN (ie, hospitals in states with an SSI reporting mandate must abide by their state's requirements, even if they are more extensive than the requirements for this CMS program). NHSN users reporting SSI data to the system must adhere to the definitions and reporting requirements for SSIs as specified in the NHSN Patient Safety Component Protocol Manual.[198] For more information, see http://www.cdc.gov/nhsn/acute-care-hospital/ssi/index.html.
2. State requirements and collaboratives
   a. *State requirements.* Hospitals in states that have mandatory SSI reporting requirements must collect and report the data required by the state. For information on state requirements, check with your state or local health department.
   b. *State collaboratives.* Currently 27 states have implemented voluntary SSI collaboratives. For more information on state collaboratives for SSI, see http://www.cdc.gov/hai/stateplans/states-w-SSI-collaborative.html.
3. External quality initiatives
   a. Several external quality initiatives focused on SSI prevention are ongoing. The benefits in participation in these external quality initiatives is unknown but may include improvement in the culture of safety and patient outcomes, including decreased rates of SSI. For additional information, see the following:
      i. http://www.ahrq.gov/qual/haify11.htm#projects
      ii. http://www.ihi.org/Engage/Initiatives/Completed/ProjectJOINTS/Pages/default.aspx

TABLE 3. Fundamental Elements of Accountability for Healthcare-Associated Infection Prevention

Senior management is responsible for ensuring that the healthcare system supports an infection prevention and control (IPC) program that effectively prevents healthcare-associated infections (HAIs) and the transmission of epidemiologically important pathogens
Senior management is accountable for ensuring that an adequate number of trained personnel are assigned to the IPC program and adequate staffing of other departments that play a key role in HAI prevention (eg, environmental services)
Senior management is accountable for ensuring that healthcare personnel, including licensed and nonlicensed personnel, are adequately trained and competent to perform their job responsibilities
Direct healthcare providers (such as physicians, nurses, aides, and therapists) and ancillary personnel (such as environmental service and equipment processing personnel) are responsible for ensuring that appropriate IPC practices are used at all times (including hand hygiene, standard and isolation precautions, and cleaning and disinfection of equipment and the environment)
Senior and unit leaders are responsible for holding personnel accountable for their actions
IPC leadership is responsible for ensuring that an active program to identify HAIs is implemented, that HAI data are analyzed and regularly provided to those who can use the information to improve the quality of care (eg, unit staff, clinicians, and hospital administrators), and that evidence-based practices are incorporated into the program
Senior and unit leaders are accountable for ensuring that appropriate training and educational programs to prevent HAIs are developed and provided to personnel, patients, and families
Personnel from the IPC program, the laboratory, and information technology departments are responsible for ensuring that systems are in place to support the surveillance program

SECTION 6: EXAMPLES OF IMPLEMENTATION STRATEGIES

Accountability is an essential principle for preventing HAIs. It provides the necessary translational link between science and implementation. Without clear accountability, scientifically based implementation strategies will be used in an inconsistent and fragmented way, decreasing their effectiveness in preventing HAIs. Accountability begins with the chief executive officer and other senior leaders who provide the imperative for HAI prevention, thereby making HAI prevention an organizational priority. Senior leadership is accountable for providing adequate resources needed for effective implementation of an HAI prevention program. These resources include necessary personnel (clinical and nonclinical), education, and equipment (Table 3).

The following information identifies implementation strategies that can be used as part of a program to prevent and reduce the risk for SSI. The implementation strategies are organized under 4 concepts: engage, educate, execute, and evaluate.[199]

I. Engage

In the engagement phase, there needs to be clear and effective communication pertaining to the reasons why the SSI implementation strategies are important for patient care. Engagement of senior leadership, physician champions, infection preventionists, and multidisciplinary teams are examples of strategies necessary for initial implementation of a program to reduce SSIs. The following implementation strategies are described in the literature as being essential for the engagement process.

A. *Obtaining support for SSI reduction from senior leadership.* Senior leadership support is an important factor contributing to SSI rate decreases. Senior leadership is also critical for sustaining improvements over time. Senior leadership can include but is not limited to the hospital's board, president, chief operating officer, chief medical officer, and chief nursing officer.[148,200-203]

B. *Obtaining highly engaged physicians as champions.* Medical and surgical staff engagement is critical for SSI prevention activities and to champion SSI prevention throughout the hospital. Examples include a physician leading an SSI prevention multidisciplinary team and a physician champion who provides education on strategies to reduce SSIs to other physicians and staff.[202,203]

C. *Use of multidisciplinary teams.* Numerous studies and literature address the effectiveness of multidisciplinary teams to plan, develop, implement, and evaluate efforts to reduce SSIs. The key components of the team include preoperative, intraoperative, and postoperative management of the patient. Teams should include nursing, pharmacy, and physician champions.[148,200,204-207]

D. *Adopting evidence-based practices and guidelines.* Several studies in the literature focus on the need for hospitals to adopt evidence-based practices and guidelines in an effort to decrease the risk of SSIs. The literature stresses that, although evidence-based interventions can reduce the number of SSIs and improve patient outcomes, implementation of these practices nationally occurs less frequently than is desirable.[10,148,203,208-210]

E. *Focus on a culture of safety.* The literature supports the need for a culture of safety to successfully implement a program focusing on reducing SSIs. A culture of safety focuses on teamwork, technical processes, and promoting accountability for preventing SSIs throughout the continuum of care.[136,200,202]

II. Educate

Education pertaining to practices to prevent SSIs is es-

sential for senior leadership, physicians, nurses, and patients and families. The following implementation strategies describe the types of education that can impact SSI rates and who should be the focus of educational efforts.

A. *Aligned and coordinated SSI education for licensed independent practitioners and staff.* Multidisciplinary education for licensed independent practitioners (physicians and midlevel practitioners) and other practitioner staff (registered nurses) must be aligned and coordinated. The content of the education focuses on the continuum of the patient's care and execution of evidence-based practices to prevent SSIs.[202,203]

B. *One-to-one education of the surgeon when an SSI issue is identified.* Provide one-to-one education when surgeons have elevated SSI rates and/or when appropriate preventive processes are not being adhered to. This education may be conducted by another surgeon, infection preventionist, quality office, or other qualified individuals. The education should be nonconfrontational with an emphasis on understanding variation in practice rather than judgment. If lack of adherence to evidence-based practices is identified, then an action plan must be developed.[203]

C. *Education for senior leadership that describes the value and benefits of SSI reduction.* Provide education to executive leadership regarding the value of reducing SSIs, including patient and fiscal outcomes.[131]

D. *Education for the surgical team on safety science.* Provide education to licensed independent practitioners and staff involved in the care of surgical patients on the science of safety, including the principles of safe system design.[200]

E. *Specific SSI education for patients and families.* Patient education for reducing SSIs is a major priority for any hospital focused on preventing SSIs. Education strategies such as presurgical classes, television education, and one-to-one education with the patient and family have been used successfully. Educational materials should be provided in multiple languages on the basis of the population served.[131,202,203]

III. Execute

In the execution phase, the focus is on implementation strategies to reduce barriers and improve adherence with evidence-based practices and reduce the risk of SSIs, including (*a*) standardization of care processes, (*b*) creating redundancy or independent checks, and (*c*) learning from defects when an SSI occurs. As noted above, no consensus exists on the components of an effective bundle to prevent SSIs. Thus, individual hospitals must identify local deficits and create their own bundle.

A. *Use a quality improvement methodology.* Use of quality improvement methodology for designing and implementing a program leads to reduced rates of SSIs. Quality improvement methodologies include Lean Six Sigma, the Comprehensive Unit-Based Safety Program, and the Plan-Do-Check-Act model. Various performance improvement (PI) tools have been used, including dashboards, scorecards, and histograms, to display data.[149,200,203,207,211]

B. *Differentiate between adult and pediatric populations.* Pediatric-focused evidence-based practices for reducing SSIs are lacking. Clinical interventions designed for the adult population cannot necessarily be transferred to the pediatric population. Hospital and pediatric surgeons must determine whether adult evidence-based interventions can be safely used with the pediatric population.[203]

C. *Use of information technologies (IT).* IT innovations can be used to simplify and standardize clinical documentation. IT and the electronic medical record can also be used for electronic surveillance, electronic prompts, automatic stops for prophylactic antibiotic orders, and education. Education can be delivered to patients, families, and healthcare workers through different media, including the Internet and television.[148,202,203,212]

D. *Participation in a collaborative.* Numerous studies have reported that participation in a collaborative can help reduce SSI rates in participating organizations. Collaboratives provide a mechanism for organizations to

1. Utilize valid data, such as with the American College of Surgeons National Surgical Quality Improvement Program;[213]
2. Identify increased morbidity and mortality through comparisons to peer hospitals on a national basis;[213] and
3. Learn through the collaboration process.[161,202,203,205,207,209,213,214]

E. *Use of preoperative/postoperative order sets.* Standardized order sets can be developed on the basis of evidence-based practices. The order sets should be approved by the medical staff and updated when the evidence-based practices change. The development of order sets is a labor-intensive process necessitating skills and expertise of several disciplines, including surgery, anesthesia, nursing, and pharmacy. All relevant disciplines should be educated in the use of the order sets.[148,202,203]

F. *Acting on identified SSI issues.* When issues suspected of increasing the risk of SSI are identified, the hospital should take action to resolve the identified issues. Several hospitals conduct root-cause analyses with a multidisciplinary team to identify the cause of the issues and any lack of adherence in the evidence-based practices.[149,202-204]

G. *Establish a protocol for preoperative testing.* Establish a protocol for procedure-specific preoperative testing to detect medical conditions that increase the risk of SSI. The protocol should focus on nutritional counseling if indicated, smoking cessation if indicated, preadmission infections, and reconciling medications with adjustments prior to surgery if indicated.[202] If high-risk pa-

tients are identified through screening, alerts should be added to electronic medical records to ensure that all members of the perioperative team are aware of the high-risk condition(s).

IV. Evaluate

In the evaluation phase, the focus is on the use of measurement and evaluation tools to determine the effectiveness of implementation strategies in the prevention of SSIs.

A. *Use of performance improvement tools.* Various PI tools can be used. PI tools include dashboards, scorecards, or histograms to display data. Additional PI tools can include root-cause analysis and failure modes and effects analysis.[148,202,203]

B. *Direct observation of evidence-based practices.* As part of a hospital's SSI improvement activities, trained observers (eg, infection preventionists, educators, nurses, and physicians) should observe surgery to assure that evidence-based practices have been implemented in the operating room. Direct observation can also be conducted for hand hygiene and surgical hand antisepsis technique. This activity is used to educate and reinforce evidence-based practices with the operating room practitioners.[136,149,203,214]

C. *Longitudinal evaluation of SSI rates and compliance rates.* Track the success of the SSI reduction program by evaluating SSI rates over time (ie, before, during, and after the program). If specific practices or processes are identified for improvement, evaluate the compliance with evidence-based practices related to these practices and processes. Feed these data evaluations back to frontline staff.

ACKNOWLEDGMENTS

Disclaimer. S.I.B.-T.—The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Potential conflicts of interest. E.P.D. reports serving as an advisor/consultant for Merck, Baxter, Ortho-McNeil, Targanta, Rib-X, Affinium, 3M, Schering-Plough, Astellas, CareFusion, Durata, Pfizer, and Applied Medical and receiving grant support from Tetraphase. L.G. reports receiving honoraria from Premier, CareFusion, and *Infection Control Today.* K.S.K. reports receiving grant support and serving as an advisor/consultant for Sage Products. D.J.A., K.P., D.W.B., S.I.B.-T., A.-C.N., L.L.M., L.S., and D.S.Y. report no relevant conflicts of interest.

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