Skin and Soft Tissue Infections

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KEYWORDS

• Skin and soft tissue infection • Skin and skin structure infection
• Necrotizing soft tissue infection • Necrotizing fasciitis

Skin and soft tissue infections (SSTIs) are a common cause of hospitalization, disability, and antibiotic therapy. Less severe infections are typically managed without the need for surgical intervention or the involvement of surgeons. SSTI may be more severe and invasive, however, placing patients at risk of soft tissue loss, limb amputation, and death. Recognition of the extent, depth, and severity of the skin and soft tissue infection is paramount if appropriate and timely therapeutic intervention is to be achieved. For more severe necrotizing infections, rapid and aggressive surgical debridement, appropriate antibiotic therapy, and supportive critical care management may be required.

TERMINOLOGY AND DEFINITIONS

A variety of terms are applied to infections of the skin and underlying soft tissue structures. For the purpose of therapeutic clinical trials, the Food and Drug Administration (FDA) uses the term ''skin and skin structure infections.''[1] The FDA specifically excludes necrotizing deep space infections from clinical trials, however, excluding infections involving the fascial planes and muscle and those infections with the greatest likelihood of adverse outcome.

Additionally, skin and skin structure infections are classified by the FDA as either ''uncomplicated'' or ''complicated.'' Uncomplicated skin and skin structure infections are defined as those that respond to either a simple course of antibiotics alone or simple drainage alone and include superficial cellulitis, folliculitis, furunculosis, simple abscesses, and minor wound infections.[1–3] Complicated skin and skin structure infections are defined as those that involve the invasion of deeper tissues or require significant surgical intervention or occur in the presence of a significant underlying disease state that complicates the response to therapy. These infections include complicated abscesses, infected burn wounds, infected ulcers, infections in diabetics, and deep space wound infections.[1]

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With the exception of cases of minor cellulitis that may occur at incision sites, SSTI that require intervention by surgeons include both complicated skin and skin structure infections and necrotizing soft tissue infections (NSTI). NSTIs by definition include the presence of devitalized or necrotic tissue as part of their pathophysiology. The presence of devitalized or necrotic tissue not only provides growth medium for bacteria but also precludes the delivery of host cellular and humoral defense mechanisms and antimicrobial agents. NSTIs may involve the dermal and subcutaneous layers (necrotizing cellulitis); fascia (necrotizing fasciitis); the muscle (pyomyositis and myonecrosis); or any combination of these.[3]

The author prefers the inclusive term "skin and soft tissue infection" to include uncomplicated, nonnecrotizing complicated, and necrotizing infections that may involve skin, subcutaneous tissues, fascia, or muscle. At presentation, the depth, severity, and specific tissues involved are frequently uncertain and at times difficult to establish. Additionally, the definitions of the various categories of these infections are indistinct and overlapping. This article discusses the diagnosis and management of complicated SSTI and NSTI.

NONNECROTIZING SKIN AND SOFT TISSUE INFECTIONS

SSTI may occur with a wide variety of clinical presentations and in numerous clinical settings, with diverse etiologic processes, and with varying severities. Numerous bacteria may be involved in SSTI, with the likelihood of individual pathogens being altered by factors including the inciting disease process and the clinical presentation and setting. Most SSTI infections are generally mild to moderate in severity and include simple cellulitis, folliculitis, furunculosis, and minor trauma-related wound infections.[2,3] Antibiotic therapy for most complicated SSTI is typically initiated empirically, hours to days before appropriate culture and sensitivity data are available. Selection of appropriate antibiotic therapy is based on knowledge of the likely pathogens involved in the particular infection episode.

Overall, *Staphylococcus aureus* is the most common pathogen isolated from SSTI, isolated in roughly one quarter to one half of all infections.[2,4,5] The most frequent pathogens identified in the SENTRY Antimicrobial Surveillance Program for the United States and Canada for SSTI collected from participating medical centers in five provinces in Canada and 32 states within the United States between 1998 and 2004 are provided in **Table 1**.[5] A total of 5837 pathogens tested represent 50 consecutive cultures collected from hospitalized patients in participating centers determined to be significant causes of pyogenic soft tissue infections. These cultures include both SSTI and surgical site infections and community-acquired and nosocomial infections. These results represent mainly complicated infections. These data may underrepresent the total frequency of β-hemolytic streptococci in SSTI because superficial cellulitis may not require hospital admission and adequate cultures are difficult to obtain even in severe cases of β-hemolytic streptococcal infections. A slightly different frequency distribution of pathogens in SSTI is provided through analysis of culture data from hospitalized patients in 584 hospitals in North America and Europe during 2001 obtained through the Surveillance Network.[2] The most frequent pathogens within this study in order of frequency are *S aureus*, *Enterococcus* spp, coagulase-negative staphylococcal species, *Escherichia coli*, and *Pseudomonas aeruginosa*. Again, streptococcal species were rarely isolated, representing only 1% to 2% of all isolates.

Antibiotic resistance among isolates from SSTI has increased significantly over time. **Fig. 1** demonstrates the percentage of individual pathogens that were classified

Table 1
Rank order of bacterial pathogens producing skin and soft tissue infections in North America for the years 1998 to 2004

Rank	Pathogen	Total Isolates	% of Isolates
1	*Staphylococcus aureus*	2602	44.6
2	*Pseudomonas aeruginosa*	648	11.1
3	*Enterococcus* spp	542	9.3
4	*Escherichia coli*	422	7.2
5	*Enterobacter* spp	282	4.8
6	*Klebsiella* spp	248	4.2
7	β-*Streptococcus*	237	4.1
8	*Proteus mirabilis*	166	2.8
9	Coagulase-negative *Staphylococcus*	161	2.8
10	*Serratia* spp	125	2.1

Data from Moet GJ, Jones RN, Biedenbach DJ, et al. Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: report from the SENTRY antimicrobial surveillance program (1998–2004). Diagn Microbiol Infect Dis 2007;57:7–13.

as resistant in the SENTRY program between 1998 and 2004.[5] During that time period there has been a rise in methicillin resistance among *S aureus* (from 26.2%–47.4%); vancomycin resistance among enterococcus (from 8.6%–14.8%); extended-spectrum β-lactamase production among *Klebsiella* spp (from 4.9%–16.3%) and *E coli* (from 3.5%–12.8%); and multidrug resistant (nonsusceptible to members of four drug classes) *P aeruginosa* (from 1.3%–3.9%). The increase in methicillin-resistant *S aureus* (MRSA) in part represents the changing epidemiology of community-acquired soft tissue infections because of recent dramatic increases in the incidence of community-acquired MRSA (CA-MRSA) SSTI. In many locations within the United States, CA-MRSA is now the single most frequent pathogen isolated from SSTI.[6–9]

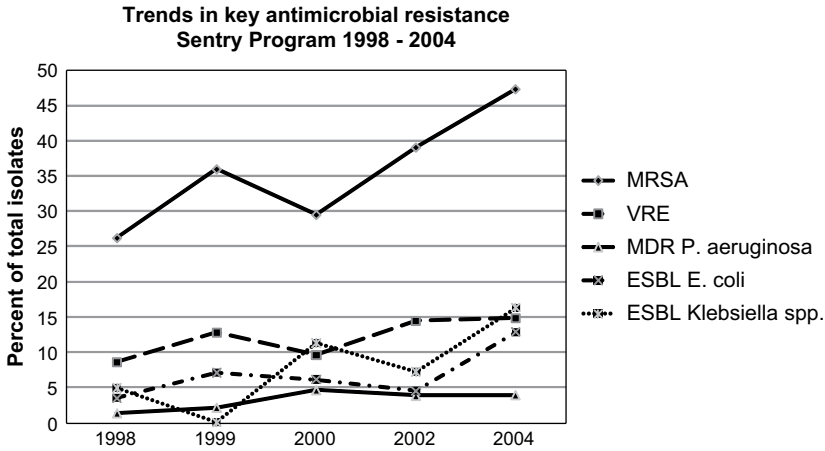

Fig. 1. Trends in key antimicrobial resistance Sentry Program 1998–2004. ESBL, extended spectrum β-lactamase; MDR, multidrug resistance; MRSA, methicillin-resistant *S aureus*; VRE, vancomycin-resistant enterococci.

Community-Acquired Methicillin-Resistant Staphylococcus Aureus Skin and Soft Tissue Infections

Staphylococcus aureus has consistently been the most common pathogen isolated from SSTI over the past decade or more.[5,10] Rapidly changing epidemiology now places CA-MRSA as one of the most common SSTI pathogens.[6–9] Historically, SSTIs caused by MRSA have generally been associated with nosocomial or chronic wound settings (hospital-acquired MRSA [HA-MRSA]), particularly when previous antibiotic selection pressure is present. Until recently, staphylococcal infections acquired outside of the health care setting have been frequently methicillin-sensitive and responsive to a wide range of antibiotics. As early as 1981, however, MRSA has been reported in community outbreaks in patients with and without risk factors for MRSA. These organisms have been called community-acquired or community-associated MRSA. Outbreaks have been reported in otherwise healthy Alaskan natives, children, inmates in correctional facilities, institutionalized adults with developmental disabilities, nursing homes, and athletes.[6] Most CA-MRSA infections are SSTI, although they may be associated with respiratory, bloodstream, and urinary tract infections.

CA-MRSA is more commonly associated with SSTI than HA-MRSA.[9,11] This association is likely related to the virulence factor Panton-Valentine leukocidin. This dermonecrotic cytotoxin may be carried by either methicillin-sensitive or methicillin-resistant strains of *S aureus,* but it is more commonly produced by certain clonal strains of CA-MRSA, particularly the USA 300 clone.[11,12] Enterotoxins and superantigens, such as toxic shock toxin–1, may also be produced by CA-MRSA and contribute to its virulence. Although most SSTI caused by CA-MRSA are associated with skin findings, such as furuncles and abscesses, they may also be associated with more serious findings, such as necrotizing fasciitis, invasive infections, toxic shock, and necrotizing pneumonia.[11,12]

CA-MRSA SSTI may involve previously healthy skin in an otherwise healthy adult. Patients may frequently believe that they have been bitten by a spider because of the character of the local wound involvement (a small central dark area surrounded by a firm indurated abscess and a variable degree of cellulitis). Although most cases of CA-MRSA SSTI may be considered uncomplicated infections, the toxin-related pathogenicity of CA-MRSA complicates the evaluation of depth and extent of tissue involvement in these infections and the possibility of an unsuspected necrotizing infection should be ruled out if unclear.

CA-MRSA isolates frequently have a different antibiotic susceptibility profile than HA-MRSA, although local patterns may be quite variable.[6–9,12] HA-MRSA is usually resistant to at least three β-lactam antibiotics and is usually susceptible to vancomycin, sulfamethoxazole, and nitrofurantoin. CA-MRSA is more likely to be susceptible to clindamycin and has varying susceptibility to tetracycline, fluoroquinolone, and erythromycin and vancomycin.[11]

Treatment of Nonnecrotizing Skin and Soft Tissue Infections

Most SSTIs treated by surgeons are classified as complicated infections and are more frequently severe in nature relative to those treated by nonsurgeons or treated on an outpatient basis. Uncomplicated skin and subcutaneous abscesses respond well to incision and drainage with appropriate wound care and do not require antibiotics.[13] Classification of an SSTI as uncomplicated is not always clear-cut, particularly with the involvement of CA-MRSA. The extent of the abscess must be appropriately evaluated during drainage to rule out underlying soft tissue involvement. Additionally, significant erythema, tenderness, or the presence of any systemic signs of infection

should alert the clinician to the likelihood of a more complicated infection. More extensive cases of folliculitis and furunculosis may require treatment with antibiotics if the process is diffuse, has significant surrounding erythema, or the presence of fever.[2,3]

Nonnecrotizing cellulitis

Nonnecrotizing cellulitis by definition involves only the dermal layers and responds to antibiotic therapy without debridement. The term ''nonnecrotizing cellulitis'' incorporates two clinical entities, erysipelas and cellulitis, which are diffusely spreading skin infections not associated with underlying suppurative foci. The term ''cellulitis'' is frequently interchangeable with the term ''erysipelas,'' and the latter term is frequently preferred in Europe. A fine distinction exists, however, between erysipelas and cellulitis. Erysipelas has two classic features of this skin infection: a clear line of demarcation between involved and uninvolved tissue, and lesions raised above the surrounding normal skin.[3] Cellulitis involves deeper layers of the dermis and subcutaneous tissue and has less distinctive features than erysipelas but both involve rapidly spreading areas of edema, erythema, and heat and may be accompanied by lymphangitis.[14] Establishing that the clinical signs and symptoms are indeed related to nonnecrotizing cellulitis or erysipelas rather than an underlying necrotizing infection is paramount but frequently inaccurate. Most cases of necrotizing fasciitis originally have an admitting diagnosis of cellulitis.[15–17] Several clinical and laboratory findings strongly suggest the presence of a necrotizing infection (see later) but careful clinical judgment is mandatory.

Nonnecrotizing cellulitis and erysipelas are most commonly caused by β-hemolytic streptococci (usually group A) but may also be caused by other streptococcal species.[14] In specific clinical situations, other bacterial species may cause a spreading, nonnecrotizing cellulitis, such as *Haemophilus influenzae* in children and pneumococcal cellulitis in the limbs of patients with altered immunity. Rarely, *S aureus* may be involved but these infections usually are more suppurative and less diffuse. Superficial, nonnecrotizing infections caused by certain strains of group A streptococci may also be associated with streptococcal toxic shock syndrome characterized by the rapid progression of septic shock and organ failure.[18]

Nonnecrotizing cellulitis and erysipelas generally arise when organisms enter through breaches in the skin. A number of predisposing factors for these infections broadly includes conditions involving alterations in integrity of the skin (ie, dermatoses, fungal infections, ulcerations); alterations in lymphatic and venous drainage (ie, saphenous vein harvest, lymph node dissections); alterations in vascularity of the skin; and alteration of host defenses (eg, diabetes mellitus).[19] Antibiotic therapy is most commonly based on empiric diagnosis established by clinical findings because cultures are most frequently negative. Blood cultures are positive in less than 5% of cases and positive results from either needle aspiration or punch biopsy range from less than or equal to 5% to 40%.

The treatment options for erysipelas and cellulitis have not been established through randomized, prospective studies but significant clinical practice has established standards of therapy. For cases of erysipelas and cellulitis caused by streptococci, penicillin given parentally (for severe infection) is the agent of choice.[3] Other regimens include antistaphylococcal penicillins, cefazolin, and ceftriaxone.[14] Teatment failures with β-lactam antibiotics do occur, however, despite in vitro microbial sensitivity to the agents used.[20,21] The mechanism of failure is believed to involve the failure of bacterial killing by cell wall–inhibiting agents when high numbers of bacteria in the static phase lead to decreased expression of penicillin-binding proteins.[21,22] Protein synthesis–inhibitory agents, such as macrolide and lincoamine antibiotics, may be as effective

and potentially superior in certain settings.[20,21] Clindamycin either alone or in combination with a cell wall–inhibiting agent was found to be more effective than cell wall–inhibiting agents alone in a retrospective analysis of pediatric group A streptococcal infection.[21] Roxithromycin proved to be equivalent to penicillin for the treatment of erysipelas in a randomized, multicenter trial.[23] Increasing macrolide resistance among streptococci introduces concern for these agents, however, and local sensitivity patterns should be considered when using these agents alone for the treatment of complicated group A streptococcal infections.[21] Additionally, because clindamycin has been demonstrated to reduce exotoxin and superantigen production by pathogenic strains of group A streptococci, the drug is frequently used as an adjunct in the treatment of streptococcal toxic shock syndrome.[20] The most effective antibiotic regimen in this setting has not been established, however, in prospective studies. If methicillin-sensitive *S aureus* is suspected, the treatment of choice is a penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin for non–methicillin-resistant staphylococcal infections.[3,14] The recent dramatic increase in CA-MRSA makes the empiric treatment of staphylococcal infections with β-lactam antibiotics problematic, however, and other agents should be considered unless the risk of resistant staphylococcus is low (see later).[8,12]

Complicated skin and soft tissue infections

Complicated SSTIs may involve a variety of pathogens. They may involve only a single pathogen but are frequently polymicrobial in origin and may involve a number of organisms.[4,5,24–26] Initiating pathogens often vary on the originating site of the infection. Gram-positive aerobic pathogens are isolated in over 50% of all complicated abscesses and necrotizing infections and depending on the source of origin, anaerobes, *Pseudomonas* spp, gram-negative Enterobacteriaceae, and clostridial species may commonly be present. An accurate clinical history and examination should suggest the underlying etiology and direct empiric therapy. Complicated skin and subcutaneous abscesses are typically well circumscribed or walled off and respond to incision and drainage with adjuvant antibiotic therapy. Inadequate resolution should prompt consideration of further drainage, resistant pathogens, or host immune failure. During incision and drainage, appropriate examination must be undertaken to ensure that all loculations have been identified and that occult involvement of fascia or deeper tissue spaces is not involved. Certain areas, such as the perineum and perirectal space, may have deep space involvement that is very difficult to identify and CT imaging should be considered preoperatively to rule out occult, deep soft tissue involvement.

Empiric antibiotic therapy should be directed toward the likely pathogens involved. For polymicrobial infections, several classes of agents or combinations of agents provide adequate antibiotic coverage. Broad-spectrum agents with coverage of gram-positive, gram-negative, and anaerobic pathogens may be required depending on clinical setting. In nosocomial settings, coverage of resistant pathogens encountered locally should also be considered. De-escalation therapy should be considered and based on culture results. Given the high frequency of MRSA, this pathogen should be empirically covered unless specific data indicate otherwise. No randomized studies are available for the treatment of SSTI specifically caused by CA-MRSA. Sensitivity patterns are usually used to direct available options. A number of oral agents have been used for less severe infections treated as an outpatient.[11] In the patient with a simple abscess suspected to be caused by MRSA, incision and drainage of the abscess should be performed. The use of antibiotics as an adjunct to incision and

drainage may be considered, particularly for those with significant cellulitis, and should be directed against MRSA. Although historically cultures of abscesses were not often obtained for simple SSTI, the increase in CA-MRSA prevalence suggests that this may be more clinically useful, particularly if there is no response to presumed adequate therapy. If CA-MRSA is suspected and the patient can be treated as an outpatient, oral antibiotics, such as clindamycin, tetracycline, trimethoprim-sulfamethoxazole, erythromycin, and some quinolones, may be used. Other oral agents, such as linezolid, an oxazolidinone antibiotic that inhibits bacterial protein translation at the initial phase of protein synthesis, have been shown in randomized trials to be efficacious for MRSA.[27,28]

Complicated SSTI requiring hospital admission usually requires initiation of intravenous broad-spectrum antibiotics. Again, no randomized studies exist specifically for the treatment of CA-MRSA and therapeutic options are extrapolated from other studies of soft tissue infections caused by MRSA. Although vancomycin has been the gold standard, one randomized study demonstrated superiority of linezolid in the treatment of complicated SSTI (88.6% versus 66.9% cured for linezolid versus vancomycin; $P<.001$).[28] Additionally, linezolid has been shown to inhibit toxin production in vitro providing theoretic advantage.[29] Other newer agents with activity against MRSA tested in randomized trials of complicated skin and skin structure infections include quinupristin-dalfopristin, daptomycin, and tigecycline.[6,30] Although each is approved for the treatment of complicated skin and skin structure infections, the randomized studies to evaluate the efficacy of these agents contained too few MRSA to draw conclusions for recommendations. Quinupristin-dalfopristin is a combination of two streptogramins that inhibit protein synthesis but requires central intravenous administration and has significant side effects, daptomycin is a lipopeptide with bactericidal activity against gram-positive pathogens including MRSA, and tigecycline is a broad-spectrum glycylcycline antibiotic with activity against gram-positives including MRSA.[31] New agents currently being studied but not yet approved include dalbavancin, telavancin, and ceftobiprole. Another anti-MRSA cephalosporin, ceftaroline, has been shown to be effective in phase II trials and is currently undergoing further study.

NECROTIZING SKIN AND SOFT TISSUE INFECTIONS

NSTI are discussed separately because of (1) the increased severity; (2) the variation of pathogens relative to nonnecrotizing infections; (3) the difficulty and importance of establishing an early diagnosis; and (4) the impact of early, aggressive surgical debridement on outcome. NSTIs are serious infections, producing progressive tissue destruction with significant potential for soft tissue and limb loss and mortality. Despite advances in therapy over the past three decades, the mortality from NSTI remains significant. The overall published mortality in 67 studies of NSTI including 3302 patients between 1980 and 2008 (**Table 2**) is 23.5%.[4,15,16,24,32–94] Although the mortality has trended down slightly in published studies (27.8% mortality for studies from 1980–1999 versus 21.7% mortality since 1999), it still remains greater than 20%. NSTI may involve any combination of dermis, subcutaneous tissue, fascia, or muscle. Notably, each of these layers has varying degrees of intrinsic resistance to infectious processes. Blood supply to the fascia is typically more tenuous than that of muscle or healthy skin making the fascia more vulnerable to infectious processes. Additionally, the propensity for fluid to collect between involved fascia and adjacent tissues further weakens fascial immune function by altering host clearance of pathogens by decreasing phagocytic function. Necrotizing fasciitis is more common than necrotizing

Table 2
Outcome of necrotizing fasciitis

Authors	Year	Number of Cases	Percent Mortality	Authors	Year	Number of Cases	Percent Mortality
Casali[41]	1980	12	33	Gallup[54]	2002	23	13
Kaiser[61]	1981	20	40	Fustes-Morales[53]	2002	39	18
Freeman[51]	1981	14	29	Childers[44]	2002	163	28
Oh[73]	1982	28	36	Wong[16]	2003	89	21
Rouse[78]	1982	27	73	Tilou[85]	2004	46	17
Majeski[68]	1983	30	33	Qazi[77]	2004	25	24
Walker[88]	1983	8	38	Catena[42]	2004	11	64
Miller[71]	1983	15	27	Wilkinson[92]	2004	44	14
Adinolfi[33]	1983	11	27	Escobar[48]	2005	42	12
Spirnak[80]	1984	20	45	Kao[62]	2005	59	12
Stamenkovic[81]	1984	19	42	Legbo[65]	2005	24	17
Barzilai[37]	1985	11	36	Cheng[43]	2005	17	65
Pessa[76]	1985	33	33	Taviloglu[83]	2005	98	35
Freishlag[52]	1985	21	35	Endorf[47]	2005	65	17
Gozal[56]	1986	16	12	Tiu[86]	2005	48	29
Sudarsky[82]	1987	33	6	Anaya[34]	2005	166	17
Clayton[46]	1990	57	18	Bakleh[36]	2005	81	20
Asfar[35]	1991	10	30	Liu[67]	2005	87	33
Anaya[99]	1991	14	43	Kwan[63]	2006	36	36
Ward[91], Wang[90]	1992	18	33	Ozalay[74]	2006	22	14
Francis[49]	1993	25	24	Ogilvie[72]	2006	150	9
Chow[45]	1993	12	25	Yilmaziar[94]	2007	67	49
Brown[40]	1994	54	35	Lee[64]	2007	74	15
McHenry[69]	1995	65	29	Yaghoubian[93]	2007	124	17
Bosshardt[24]	1996	45	27	Peer[75]	2007	38	21
Elliot[4]	1996	198	25	Golger[55]	2007	99	20
Bilton[38]	1998	68	21	Tsai[87]	2007	32	31
Adant[32]	1998	7	14	Hefny[59]	2007	11	18
Hsiao[60]	1998	34	27	Miller[70]	2008	11	36
Haywood[58]	1999	20	20	Lui[66]	2008	118	22
Brandt[39]	2000	37	24	Frazee[50]	2008	122	16
Wall[89]	2000	21	29	Hsiao[15]	2008	128	19
Theis[84]	2002	13	31	Gunter[57]	2008	52	10
Singh[79]	2002	75	27	Total (N = 67 studies)		3302	23.5

processes involving other soft tissue layers because infection can spread widely across the fascial planes with minimal involvement of surrounding skin or muscle.

The pathogens involved in NSTIs differ somewhat from those isolated from nonnecrotizing infections, particularly those NSTIs that are rapidly progressive. In an analysis of 198 consecutive patients with necrotizing SSTI, Elliot and coworkers[4] documented a significant increase in the frequency of rapidly growing, virulent

pathogens, particularly streptococcal and clostridial species (**Table 3**). In contrast to findings of the SENTRY program, which predominately includes nonnecrotizing, complicated SSTI, streptococcal species were the most commonly isolated organisms, occurring in greater than 50% of those patients in whom only one pathogen was isolated in this study. Streptococcal species were also the most frequent pathogens isolated from 707 patients included in six separate studies on NSTI, being isolated in 39.2% of patients, followed by *S aureus*, which was isolated from 30.1% of patients.[4,15,16,34,44,67] Most patients with necrotizing infections have polymicrobial infections with an average of 4.4 organisms isolated per infection in the study by Elliot and coworkers.[4] Such polymicrobial necrotizing infections arise from a number of inciting events including perirectal infection and Fournier's gangrene, trauma, intravenous drug abuse, chronic diabetic ulcerations, and surgical site infections.[4] An accurate clinical history and examination should be undertaken to identify the likely source and to identify the polymicrobial nature of these infections. Although these polymicrobial infections can spread widely and become both limb- and life-threatening, they tend to be much more indolent than infections caused by a fairly limited number of highly virulent pathogens. Such highly virulent pathogens may cause very rapidly spreading necrotizing infections in an immunologically intact host through production of exotoxins that contribute significantly to their pathogenicity. Such pathogens most commonly include *Streptococcus pyogenes* (group A β-hemolytic streptococcus), group B *Streptococcus*, CA-MRSA, and *Clostridium* spp. Other highly virulent species that can cause rapidly progressive NSTI with specific environmental exposures include *Pasteurella* spp (animal bites); *Vibrio* spp (shell fish or salt water exposure); and *Aeromonas hydrophila* (contaminated fresh water exposures).[95]

Table 3
Microbiologic organisms recovered from original wounds

Organism	N	n	%
Aerobic			
Streptococci	182	83	45.6
Enterococci	182	61	33.5
Staphylococci	182	64	35.2
Escherichia coli	182	57	31.3
Proteus sp	182	38	20.9
Other gram-negative rods[a]	182	76	41.8
Anaerobic			
Peptostreptococci	131	45	34.4
Bacteroides species	128	70	54.7
Clostridium perfringens	129	12	9.3
Other clostridial species	128	17	13.3
Other anaerobic species	128	27	21.1
Fungal species	171	9	5.3

N, number of cultures obtained; n, number of isolates.

[a]Including (in order of prevalence) *Klebsiella* spp, *Enterobacter* spp, *Pseudomonas*, *Acinetobacter* spp, *Eikenella corrodens*, *Citrobacterfreundii*.

Data from Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections: risk factors for mortality and strategies for management. Ann Surg 1996;224:672–83.

Diagnosis of Necrotizing Skin and Soft Tissue Infections

Early diagnosis of the presence of a necrotizing soft tissue infection is critical if optimal outcomes are to be achieved. Distinguishing a NSTI that necessitates surgical debridement from a nonnecrotizing cellulitis that responds solely to antibiotic therapy, however, can be difficult. Patients with NSTI have the diagnosis established on admission well less than 50% of the time.[15–17] Most patients are admitted with the diagnosis of cellulitis and a smaller number with the diagnosis of abscess. Unfortunately, any delay in diagnosis is potentially catastrophic, because the concomitant delay in appropriate surgical therapy has been shown to increase mortality.[4,24,26,38,69] Certain features of the disease presentation facilitate the detection of a necrotizing process. Pain, erythema, warmth, and swelling are present in most cases but are not specific to necrotizing infections and may not be universally present.[15,16] Several ''hard'' clinical signs are very specific to NSTI but occur late in the course. These include (1) the presence of bullae, (2) skin ecchymosis that precedes skin necrosis, (3) presence of gas in the tissues by examination or radiographic evaluation, and (4) cutaneous anesthesia. Although these findings are strongly suggestive of a necrotizing infection and should prompt immediate surgical exploration, these signs are present in the minority of cases (7%–44%).[16,69,93] Other clinical signs that are suggestive but less specific include (5) pain that is disproportionate to examination, (6) edema that extends beyond skin erythema, (7) systemic toxicity, and (8) progression of infection despite antibiotic therapy. The presence of gas in tissue by plain radiograph is more sensitive than detecting crepitance by physical examination.[69] CT scanning and MRI also assist in detecting the severe infections. These imaging techniques may detect fluid along fascial planes, edema within tissues, and gas not seen on plain radiographic evaluation. Notably, neither fluid nor edema is specific for the presence of necrotizing infection, and the sensitivity and specificity of these modalities have not been established.

Laboratory values may be useful to aid in the early diagnosis of NSTI. Two studies have examined the predictive value of standard laboratory tests to improve the diagnostic accuracy. In a study by Wall and colleagues,[89] 21 patients with necrotizing fasciitis were matched with 21 patients with nonnecrotizing infections. By multivariate analysis admission white blood cell count of greater than 14×10^9/L, serum sodium of less than 135 mmol/L, and blood-urea-nitrogen of greater than 15 mg/dL all discriminated necrotizing from nonnecrotizing infection with acceptable predictive ability. The small numbers of patients, however, limits the power required to evaluate a number of parameters of interest in this setting. More recently, Wong and colleagues[17] evaluated the predictive capability of various laboratory parameters in a larger population of patients (89 patients with NSTI, 225 with cellulitis or abscess). By multivariate analysis, they created the Laboratory Risk Indicator for Necrotizing Fasciitis score, which can classify patients as low, intermediate, and high risk for NSTI (**Tables 4** and **5**). This score should be applied to those patients without ''hard'' signs of necrotizing infection or in whom the diagnosis is uncertain. It use, however, has not been prospectively validated in other cohorts. The use of full-thickness biopsy and frozen section has been advocated but neither has been adequately evaluated or widely adopted.[81] If the presence of a necrotizing infection cannot be excluded, surgical exploration is indicated.

Therapeutic Approach for Necrotizing Infections

Aggressive and timely resuscitation, timely administration of appropriate antibiotic therapy, certain adjunctive therapies, and timely surgical debridement all may be required for optimal outcome. Of these interventions, surgical intervention is the mainstay of treatment. A number of studies demonstrate that time to first debridement

Table 4
Laboratory Risk Indicator for Necrotizing Fasciitis score

Value	Score, Points
C-reactive protein, mg/L	
<150	0
>150	4
WBC count, cells/mm3	
<15	0
15–25	1
>25	2
Hemoglobin level, g/dL	
>13.5	0
11–13.5	1
<11	2
Sodium level, mmol/L	
≥135	0
<135	2
Creatinine level, mg/dL	
≤1.6	0
>1.6	2
Glucose level, mg/dL	
≤180	0
>180	1

Data from Wong CH, Khin LW, Heng KS, et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004;32:1535–41.

and adequacy of first debridement are important and alterable predictors of survival.[4,24,38,44,52,67–69,78,82,89] Unfortunately, definitions for delayed or inadequate initial therapy were not clearly described by the authors. In most studies, a delay in surgical debridement of greater than 24 hours after admission is associated with a significant increase in mortality. Surgical drainage and debridement at the earliest possible time, however, almost certainly improves outcome. In a recent report of 52 patients with NSTI managed by a dedicated acute care surgery service with in-house faculty, the median time from diagnosis to operative debridement was 8.6 hours with an overall mortality of 9.6%.[57] This mortality rate compares favorably with the combined published mortality rate in 67 studies since 1980 that is 23.5% (see **Table 2**). These data suggest that early recognition and adequate surgical management could reduce mortality to less than 10%.

Surgical Therapy for Necrotizing Infections

Surgical drainage and debridement of involved tissues is the mainstay of therapy in NSTI. No randomized studies or significant case series are available, however, to direct the actual surgical approach. Although retrospective reviews identify adequate and early surgical debridement as predictors of survival, they do not report quantifiable methods of defining adequate debridement.[4,24,38,44,52,67–69,78,82,89] Several issues should be considered: (1) determining the extent of resection, (2) full-thickness versus fascial excision for necrotizing fasciitis, (3) serial wound examination and

Table 5
Probability of necrotizing soft-tissue infection based on Laboratory Risk Indicator for Necrotizing Fasciitis score categories

Risk Category	Points by Score	Probability
Low	≤ 5	<50%
Intermediate	6–7	50%–75%
High	≥ 8	>75%

Data from Wong CH, Khin LW, Heng KS, et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004;32:1535–41; and Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: diagnosis and management. Clin Infect Dis 2007;44:705–10.

debridement, and (4) diverting colostomy versus other methods of control of the fecal stream for perineal and scrotal infectious processes. The determination of extent of resection is most commonly based on clinical judgment and the gross appearance of tissues involved. Fascial layers, skin, subcutaneous fat, and muscle may each be involved in the infectious process with their involvement varying depending on the clinical setting, bacteriology, and inciting insult. The most common clinical entity is necrotizing fasciitis with involvement and spread along the fascial planes, frequently with little involvement of surrounding tissues. The ability to separate fascia easily from the normally adherent surrounding tissue strongly suggests involvement with infection.[26,69,82] In elderly and critically ill patients with extensive edema, however, the ease of separation can be difficult to distinguish from noninfected fascia and the previous necrotizing infection still requires considerable clinical judgment. For skin, fat, and muscle involvement, the lack of inflammation and purulence and the presence of normal bleeding at the line of incision are commonly used to determine adequacy of debridement. Additionally, muscle should demonstrate contractility. For fasciitis without involvement of surrounding tissues, debridement and drainage of involved fascia through a series of parallel incisions without resection of overlying tissue may be successful and preserve overlying tissues.[96] If surrounding tissues are involved, however, full-thickness excision is required.

Necrotizing infections have the potential for rapid and continued progression despite surgical debridement. Frequent re-evaluation of the wound should be undertaken. Many authors recommend return to the operating room within 24 hours to ensure adequacy of debridement and lack of progression,[26,38,69] and the average number of operative procedures is typically three to four per patient.[4,24,38,69,82] Prevention of heavy and recurrent contamination of dressings may be problematic in patients with perineal, perianal, or scrotal involvement. When fecal soilage of dressings is problematic, diverting colostomy is recommended.[97] Recently, the development of a specifically designed rectal system to control the fecal stream has been used successfully to avoid diverting colostomy.[98] In summary, the surgical management of necrotizing soft tissues continues to be driven by clinical experience and expertise. Early and adequate surgical debridement is linked to improved outcomes but remain poorly defined.

Antibiotic Therapy for Necrotizing Infections

As with surgical therapy, very limited prospective data exist to guide antibiotic therapy for necrotizing infections. As indicated earlier, FDA guidelines for the study of soft tissue infections exclude patients with these more severe infections from prospective trials.[1] Most randomized studies evaluating complicated skin and skin structure infections

report clinical success rates ranging from 75% to 90% or greater, depending on the study population and analysis group. Typically, mortality for the populations included in these studies is well less than 1%. Because studies examining the outcome of NSTI identify mortality rates of 6% to greater than 70% (see **Table 2**), there may be little applicability of the data from randomized studies of complicated skin and skin structure infections to treatment of severe necrotizing infections. The current recommendations are garnered from limited data on seriously ill patients available from prospective studies of patients with complicated skin and skin structure infections; prospective studies of clinical problems involving similar pathogens (eg, intra-abdominal infection trials); and interpretation of current sensitivity patterns of the pathogens most typically involved in these infections. Because most of these infections are mixed infections and may involve aerobic and anaerobic gram-negative and gram-positive pathogens, broad antibiotic coverage of these pathogens is indicated in most cases. The clinical presentation and physical findings, along with the rapidity with which the pathologic process evolves, should alert the practitioner to the potential presence of specific, highly virulent pathogens, such as group A streptococci, *Clostridium* spp, and *Vibrio* spp, as discussed next. If such pathogens are suspected, then antibiotic therapy should be altered accordingly.

For most complicated and NSTI, a number of single-agent or combination regimens that provide anaerobic, gram-positive, and enteric gram-negative coverage may be effective. Several single-agent regimens have been evaluated in prospective, randomized trials of complicated skin and skin structure infections including imipenem-cilastatin, meropenem, ertapenem, piperacillin-tazobactam, ticarcillin-clavulanate, levofloxacin, and tigecycline. Ampicillin-sulbactam has been shown to be effective in complicated skin and skin structure infections; however, recent increases in resistance among gram-negative rods introduce concern about selecting this as a single agent. Numerous combination regimens are recommended by different sources, but have not been studied rigorously. These combinations typically include penicillins or cephalosporins with either an aminoglycoside or fluoroquinolone and an anaerobic agent, such as clindamycin or metronidazole. There are inadequate data comparing regimens to support the use of any one antimicrobial regimen over another for the treatment of these severe infections. For nonrapidly progressive soft tissue infections, use of one of the single agents or combination regimens noted previously, along with an anti-MRSA drug if suspicion of this pathogen is present, is the general recommendation.

Antibiotic Therapy for Necrotizing Skin and Soft Tissue Infections Caused by Highly Virulent Pathogens

As noted previously, some pathogens, such as *S pyogenes* (group A β-hemolytic streptococcus), group B *Streptococcus*, CA-MRSA, *Clostridium* spp, *Pasteurella* spp, *Vibrio* spp, and *A hydrophila*, can cause rapidly progressive soft tissue infections, even in intact hosts.[4,12,15,34,95] These pathogens generally produce a variety of exotoxins that contribute to their rapid growth and tissue invasion. The rapidity of clinical deterioration and high mortality for this group of necrotizing infections warrants special consideration. Although no prospective studies examine antibiotic efficacy in these settings, animal and retrospective human data support the use of protein synthesis–inhibiting antibiotics in combination with cell wall–active agents, particularly if toxin production is important pathogenically or if a high inoculum is present. The choice of protein synthesis–inhibiting agent should be based on the known or predicted sensitivity of the organisms to the agents considered. Recommended agents include clindamycin (if resistance is not of concern) or linezolid for gram-positive infections (*Streptococcu*s,

CA-MRSA, and *Clostridium* spp), and members of the tetracycline class for the gram-negative pathogens *Vibrio* spp and *Aeromonas* spp.

REFERENCES

1. Guidance for Industry: Uncomplicated and complicated skin and skin structure infections: developing antimicrobial drugs treatment. US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 1998. Available at: http://www.fda.gov/CDER/guidance/2566dft.pdf. Accessed October 17, 2008.
2. Jones ME, Karlowsky JA, Draghi DC, et al. Epidemiology and antibiotic susceptibility of bacteria causing skin and soft tissue infections in the USA and Europe: a guide to appropriate antimicrobial therapy. Int J Antimicrob Agents 2003;22:406–19.
3. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 2005;41:1373–406.
4. Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections: risk factors for mortality and strategies for management. Ann Surg 1996;224:672–83.
5. Moet GJ, Jones RN, Biedenbach DJ, et al. Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: report from the SENTRY antimicrobial surveillance program (1998–2004). Diagn Microbiol Infect Dis 2007;57:7–13.
6. Deresinski S. Methicillin-resistant *Staphylococcus aureus*: an evolutionary, epidemiologic, and therapeutic odyssey. Clin Infect Dis 2005;40:562–73.
7. Fridkin SK, Hageman JC, Morrison M, et al. Methicillin-resistant *Staphylococcus aureus* disease in three communities. N Engl J Med 2005;352:1436–44.
8. King MD, Humphrey BJ, Wang YF, et al. Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* USA 300 clone as the predominant cause of skin and soft-tissue infections. Ann Intern Med. 2006;144:309–17.
9. Moran GJ, Amii RN, Abrahamian FM, et al. Methicillin-resistant *Staphylococcus aureus* in community-acquired skin infections. Emerg Infect Dis 2005;11:928–30.
10. Doern GV, Jones RN, Pfaller MA, et al. Bacterial pathogens isolated from patients with skin and soft tissue infections: frequency of occurrence and antimicrobial susceptibility patterns from the sentry antimicrobial surveillance program (United States and Canada, 1997). Sentry Study Group (North America). Diagn Microbiol Infect Dis 1999;34:65–72.
11. Naimi TS, LeDell KH, Como-Sabetti K, et al. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. JAMA 2003;290:2976–84.
12. Miller LG, Perdreau-Remington F, Rieg G, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. N Engl J Med 2005;352:1445–53.
13. Llera JL, Levy RC. Treatment of cutaneous abscess: a double-blind clinical study. Ann Emerg Med 1985;14:15–9.
14. Swartz MN. Clinical practice. Cellulitis. N Engl J Med 2004;350:904–12.
15. Hsiao CT, Weng HH, Yuan YD, et al. Predictors of mortality in patients with necrotizing fasciitis. Am J Ethics Med 2008;26:170–5.
16. Wong CH, Chang HC, Pasupathy S, et al. Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am 2003; 85-A:1454–60.

17. Wong CH, Khin LW, Heng KS, et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004;32:1535–41.
18. Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. The Working Group on Severe Streptococcal Infections. JAMA 1993;269:390–1.
19. Dupuy A, Benchikhi H, Roujeau JC, et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. BMJ 1999;318:1591–4.
20. Mascini EM, Jansze M, Schouls LM, et al. Penicillin and clindamycin differentially inhibit the production of pyrogenic exotoxins A and B by group A streptococci. Int J Antimicrob Agents 2001;18:395–8.
21. Zimbelman J, Palmer A, Todd J. Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive *Streptococcus pyogenes* infection. Pediatr Infect Dis J 1999;18:1096–100.
22. Stevens DL, Gibbons AE, Bergstrom R, et al. The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. J Infect Dis 1988;158:23–8.
23. Bernard P, Plantin P, Roger H, et al. Roxithromycin versus penicillin in the treatment of erysipelas in adults: a comparative study. Br J Dermatol 1992;127:155–9.
24. Bosshardt TL, Henderson VJ, Organ CH Jr. Necrotizing soft-tissue infections. Arch Surg 1996;131:846–52.
25. Brook I, Frazier EH. Aerobic and anaerobic bacteriology of wounds and cutaneous abscesses. Arch Surg 1990;125:1445–51.
26. Green RJ, Dafoe DC, Raffin TA. Necrotizing fasciitis. Chest 1996;110:219–29.
27. Stevens DL, Herr D, Lampiris H, et al. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Clin Infect Dis 2002;34:1481–90.
28. Weigelt J, Itani K, Stevens D, et al. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrobial Agents Chemother 2005;49:2260–6.
29. Stevens DL, Wallace RJ, Hamilton SM, et al. Successful treatment of staphylococcal toxic shock syndrome with linezolid: a case report and in vitro evaluation of the production of toxic shock syndrome toxin type 1 in the presence of antibiotics. Clin Infect Dis 2006;42:729–30.
30. Ellis-Grosse EJ, Babinchak T, Dartois N, et al. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. Clin Infect Dis 2005;5(41 Suppl):S341–53.
31. Raghavan M, Linden PK. Newer treatment options for skin and soft tissue infections. Drugs 2004;64:1621–42.
32. Adant JP, Bluth F, Fissette J. Necrotizing fasciitis: a life-threatening infection. Acta Chir Belg 1998;98:102–6.
33. Adinolfi MF, Voros DC, Moustoukas NM, et al. Severe systemic sepsis resulting from neglected perineal infections. South Med J 1983;76:746–9.
34. Anaya DA, McMahon K, Nathens AB, et al. Predictors of mortality and limb loss in necrotizing soft tissue infections. Arch Surg 2005;140:151–7.
35. Asfar SK, Baraka A, Juma T, et al. Necrotizing fasciitis. Br J Surg 1991;78:838–40.
36. Bakleh M, Wold LE, Mandrekar JN, et al. Correlation of histopathologic findings with clinical outcome in necrotizing fasciitis. Clin Infect Dis 2005;40:410–4.
37. Barzilai A, Zaaroor M, Toledano C. Necrotizing fasciitis: early awareness and principles of treatment. Isr J Med Sci 1985;21:127–32.

38. Bilton BD, Zibari GB, McMillan RW, et al. Aggressive surgical management of necrotizing fasciitis serves to decrease mortality: a retrospective study. Am Surg 1998;64:397–400.
39. Brandt MM, Corpron CA, Wahl WL. Necrotizing soft tissue infections: a surgical disease. Am Surg 2000;66:967–70.
40. Brown DR, Davis NL, Lepawsky M, et al. A multicenter review of the treatment of major truncal necrotizing infections with and without hyperbaric oxygen therapy. Am J Surg 1994;167:485–9.
41. Casali RE, Tucker WE, Petrino RA, et al. Postoperative necrotizing fasciitis of the abdominal wall. Am J Surg 1980;140:787–90.
42. Catena F, La Donna M, Ansaloni L, et al. Necrotizing fasciitis: a dramatic surgical emergency. Eur J Emerg Med 2004;11:44–8.
43. Cheng NC, Tai HC, Tang YB, et al. Necrotising fasciitis: clinical features in patients with liver cirrhosis. Br J Plast Surg 2005;58:702–7.
44. Childers BJ, Potyondy LD, Nachreiner R, et al. Necrotizing fasciitis: a fourteen-year retrospective study of 163 consecutive patients. Am Surg 2002;68:109–16.
45. Chow LWC, Ong C, Damien JCP, et al. Necrotizing fasciitis revisited. Contemp Surg 1993;42:181–4.
46. Clayton MD, Fowler JE Jr, Sharifi R, et al. Causes, presentation and survival of fifty-seven patients with necrotizing fasciitis of the male genitalia. Surg Gynecol Obstet 1990;170:49–55.
47. Endorf FW, Supple KG, Gamelli RL. The evolving characteristics and care of necrotizing soft-tissue infections. Burns 2005;31:269–73.
48. Escobar SJ, Slade JB Jr, Hunt TK, et al. Adjuvant hyperbaric oxygen therapy (HBO_2) for treatment of necrotizing fasciitis reduces mortality and amputation rate. Undersea Hyperb Med 2005;32:437–43.
49. Francis KR, Lamaute HR, Davis JM, et al. Implications of risk factors in necrotizing fasciitis. Am Surg 1993;59:304–8.
50. Frazee BW, Fee C, Lynn J, et al. Community-acquired necrotizing soft tissue infections: a review of 122 cases presenting to a single emergency department over 12 years. J Emerg Med 2008;34:139–46.
51. Freeman HP, Oluwole SF, Ganepola GA, et al. Necrotizing fasciitis. Am J Surg 1981;142:377–83.
52. Freischlag JA, Ajalat G, Busuttil RW. Treatment of necrotizing soft tissue infections. the need for a new approach. Am J Surg 1985;149:751–5.
53. Fustes-Morales A, Gutierrez-Castrellon P, Duran-Mckinster C, et al. Necrotizing fasciitis: report of 39 pediatric cases. Arch Dermatol 2002;138:893–9.
54. Gallup DG, Freedman MA, Meguiar RV, et al. Necrotizing fasciitis in gynecologic and obstetric patients: a surgical emergency. Am J Obstet Gynecol 2002;187:305–10.
55. Golger A, Ching S, Goldsmith CH, et al. Mortality in patients with necrotizing fasciitis. Plast Reconstr Surg 2007;119:1803–7.
56. Gozal D, Ziser A, Shupak A, et al. Necrotizing fasciitis. Arch Surg 1986;121:233–5.
57. Gunter OL, Guillamondegui OD, May AK, et al. Improved outcome in necrotizing fasciitis; an Emergency General Surgery Service Experience. Presented at the 27th Annual Meeting of the Surgical Infection Society, Toronto. 2007.
58. Haywood CT, McGeer A, Low DE. Clinical experience with 20 cases of group A streptococcus necrotizing fasciitis and myonecrosis: 1995 to 1997. Plast Reconstr Surg 1999;103:1567–73.

59. Hefny AF, Eid HO, Al Hussona M, et al. Necrotizing fasciitis: a challenging diagnosis. Eur J Emerg Med 2007;14:50–2.
60. Hsiao GH, Chang CH, Hsiao CW, et al. Necrotizing soft tissue infections: surgical or conservative treatment? Dermatol Surg 1998;24:243–7.
61. Kaiser RE, Cerra FB. Progressive necrotizing surgical infections: a unified approach. J Trauma 1981;21:349–55.
62. Kao LS, Knight MT, Lally KP, et al. The impact of diabetes in patients with necrotizing soft tissue infections. Surg Infect (Larchmt) 2005;6:427–38.
63. Kwan MK, Saw A, Chee EK, et al. Necrotizing fasciitis of the lower limb: an outcome study of surgical treatment. Med J Malaysia 2006;61(Suppl A):17–20.
64. Lee TC, Carrick MM, Scott BG, et al. Incidence and clinical characteristics of methicillin-resistant *Staphylococcus aureus* necrotizing fasciitis in a large urban hospital. Am J Surg 2007;194:809–12.
65. Legbo JN, Shehu BB. Necrotizing fasciitis: a comparative analysis of 56 cases. J Natl Med Assoc 2005;97:1692–7.
66. Liu BM, Chung KJ, Chen CH, et al. Risk factors for the outcome of cirrhotic patients with soft tissue infections. J Clin Gastroenterol 2008;42:312–6.
67. Liu YM, Chi CY, Ho MW, et al. Microbiology and factors affecting mortality in necrotizing fasciitis. J Microbiol Immunol Infect 2005;38:430–5.
68. Majeski JA, Alexander JW. Early diagnosis, nutritional support, and immediate extensive debridement improve survival in necrotizing fasciitis. Am J Surg 1983;145:784–7.
69. McHenry CR, Piotrowski JJ, Petrinic D, et al. Determinants of mortality for necrotizing soft-tissue infections. Ann Surg 1995;221:558–63.
70. Miller AT, Saadai P, Greenstein A, et al. Postprocedural necrotizing fasciitis: a 10-year retrospective review. Am Surg 2008;74:405–9.
71. Miller JD. The importance of early diagnosis and surgical treatment of necrotizing fasciitis. Surg Gynecol Obstet 1983;157:197–200.
72. Ogilvie CM, Miclau T. Necrotizing soft tissue infections of the extremities and back. Clin Orthop Relat Res 2006;447:179–86.
73. Oh C, Lee C, Jacobson JH. Necrotizing fasciitis of perineum. Surgery 1982;91: 49–51.
74. Ozalay M, Ozkoc G, Akpinar S, et al. Necrotizing soft-tissue infection of a limb: clinical presentation and factors related to mortality. Foot Ankle Int 2006;27: 598–605.
75. Peer SM, Rodrigues G, Kumar S, et al. A clinicopathological study of necrotizing fasciitis: an institutional experience. J Coll Physicians Surg Pak 2007;17: 257–60.
76. Pessa ME, Howard RJ. Necrotizing fasciitis. Surg Gynecol Obstet 1985;161: 357–61.
77. Qazi SA, Mohammed AA, Saber EI, et al. Necrotizing fasciitis: role of early surgical intervention. Saudi Med J 2004;25:890–4.
78. Rouse TM, Malangoni MA, Schulte WJ. Necrotizing fasciitis: a preventable disaster. Surgery 1982;92:765–70.
79. Singh G, Sinha SK, Adhikary S, et al. Necrotising infections of soft tissues: a clinical profile. Eur J Surg 2002;168:366–71.
80. Spirnak JP, Resnick MI, Hampel N, et al. Fournier's gangrene: report of 20 patients. J Urol 1984;131:289–91.
81. Stamenkovic I, Lew PD. Early recognition of potentially fatal necrotizing fasciitis: the use of frozen-section biopsy. N Engl J Med 1984;310:1689–93.

82. Sudarsky LA, Laschinger JC, Coppa GF, et al. Improved results from a standardized approach in treating patients with necrotizing fasciitis. Ann Surg 1987;206: 661–5.
83. Taviloglu K, Cabioglu N, Cagatay A, et al. Idiopathic necrotizing fasciitis: risk factors and strategies for management. Am Surg 2005;71:315–20.
84. Theis JC, Rietveld J, Danesh-Clough T. Severe necrotising soft tissue infections in orthopaedic surgery. J Orthop Surg (Hong Kong) 2002;10:108–13.
85. Tillou A, St Hill CR, Brown C, et al. Necrotizing soft tissue infections: improved outcomes with modern care. Am Surg 2004;70:841–4.
86. Tiu A, Martin R, Vanniasingham P, et al. Necrotizing fasciitis: analysis of 48 cases in South Auckland, New Zealand. ANZ J Surg 2005;75:32–4.
87. Tsai YH, Hsu RW, Huang TJ, et al. Necrotizing soft-tissue infections and sepsis caused by *Vibrio vulnificus* compared with those caused by *Aeromonas* species. J Bone Joint Surg Am 2007;89:631–6.
88. Walker M, Hall M Jr. Necrotizing fasciitis: the Howard University Hospital experience. J Natl Med Assoc 1983;75:159–63.
89. Wall DB, de Virgilio C, Black S, et al. Objective criteria may assist in distinguishing necrotizing fasciitis from nonnecrotizing soft tissue infection. Am J Surg 2000; 179:17–21.
90. Wang KC, Shih CH. Necrotizing fasciitis of the extremities. J Trauma 1992;32: 179–82.
91. Ward RG, Walsh MS. Necrotizing fasciitis: 10 years' experience in a district general hospital. Br J Surg 1991;78:488–9.
92. Wilkinson D, Doolette D. Hyperbaric oxygen treatment and survival from necrotizing soft tissue infection. Arch Surg 2004;139:1339–45.
93. Yaghoubian A, de Virgilio C, Dauphine C, et al. Use of admission serum lactate and sodium levels to predict mortality in necrotizing soft-tissue infections. Arch Surg 2007;142:840–6.
94. Yilmazlar T, Ozturk E, Alsoy A, et al. Necrotizing soft tissue infections: APACHE II score, dissemination, and survival. World J Surg 2007;31:1858–62.
95. Vinh DC, Embil JM. Rapidly progressive soft tissue infections. Lancet Infect Dis 2005;5:501–13.
96. Nichols RL, Florman S. Clinical presentations of soft-tissue infections and surgical site infections. Clin Infect Dis 2001;33(Suppl 2):S84–93.
97. Eke N. Fournier's gangrene: a review of 1726 cases. Br J Surg 2000;87:718–28.
98. Echols J, Friedman B, Mullins R, et al. Initial experience with a new system for the control and containment of fecal output for the protection of patients in a large burn center. Chest 2004;126:862S.
99. Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: diagnosis and management. Clin Infect Dis 2007;44:705–10.