Are there any reasons to change our behavior in necrotizing fasciitis with the advent of new antibiotics?

Francesco Menichetti, Simone Giuliano, and Simona Fortunato

Purpose of review
The treatment of necrotizing fasciitis requires a multifaceted approach, consisting of surgical source control with immediate surgical debridement along with life support, clinical monitoring, and antimicrobial therapy. Many drugs are now available for the treatment of this life-threatening infectious disease, and the purpose of this review is to provide the reader with an updated overview of the newest therapeutic options.

Recent findings
Because most necrotizing soft tissue infections are polymicrobial, broad-spectrum coverage is advisable. Acceptable monotherapy regimens include piperacillin-tazobactam or a carbapenem. However, drugs such as ceftolozane–tazobactam, ceftazidime–avibactam in association with an antianaerobic agent (metronidazole or clindamycin) are currently available as valuable alternatives. The new cephalosporins active against methicillin-resistant *Staphylococcus aureus* (MRSA), ceftaroline, and ceftobiprole share similar antibacterial activity against Gram-positive cocci, and they might be considered as an alternative to nonbetalactam anti-MRSA agents for necrotizing fasciitis management. Two new long-acting lypoglycopeptides – oritavancin and dalbavancin – share the indications for acute bacterial skin and skin structure infections and had similar activity against Gram-positive cocci including MRSA and streptococci.

Summary
Carbapenem-sparing agents are particularly suitable for antimicrobial stewardship strategy. The new long-acting lypoglycopeptides are very effective in treating necrotizing fasciitis and are uttermost attractive for patients requiring short hospital stays and early discharge.

Keywords
ceftazidime–avibactam, ceftobiprole, ceftolozane–tazobactam, dalbavancin, necrotizing fasciitis, oritavancin, tedizolid

INTRODUCTION

Because of different types of prognosis and therapeutic options, it is helpful to distinguish the various skin and soft tissue infections that can be best classified anatomically (Fig. 1) [1]. The common superficial pyodermas do not extend beyond the skin (epidermis and dermis) and include erysipelas, impetigo, folliculitis, ecthyma, furunculosis, and carbunculosis [2,3]. Cellulitis is a skin infection that is located more deeply than erysipelas. Necrotizing fasciitis primarily involves superficial fascia, subcutaneous fat (which contains vascular structures and nerves), and deep fascia. Myonecrosis (clostridial or nonclostridial) refers to a condition resulting in rapid necrosis of muscle, with delayed involvement of overlying skin and soft tissues [2].

Necrotizing fasciitis is an uncommon soft tissue infection, usually caused by toxin-producing virulent bacteria, and it is characterized by widespread fascial necrosis with relative sparing of skin and underlying muscle. It is often associated with severe systemic toxicity and is usually rapidly fatal unless promptly recognized and aggressively treated with surgical intervention and broad-spectrum intravenous antimicrobials.

CLASSIFICATION AND CAUSE

A few distinct necrotizing fasciitis syndromes should be recognized.

Infectious Disease Unit, Cisanello Hospital, Pisa, Italy

Correspondence to Prof Francesco Menichetti, Infectious Disease Unit, Cisanello Hospital, Pisa, Italy. E-mail: menichettifrancesco@gmail.com

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KEY POINTS

- The treatment of necrotizing fasciitis requires a multifaceted approach consisting of surgical source control with immediate surgical debridement along with life support, monitoring, and antimicrobial therapy.
- Drugs such as ceftolozane–tazobactam, ceftazidime–avibactam, and ceftobiprole might be employed in the setting of a carbapenem-sparing strategy.
- Ceftobiprole and ceftaroline are active against MRSA, and they can be used in types I and II necrotizing fasciitis.
- Dalbavancin, Oritavancin, and Tedizolid are very effective agents against Gram-positive cocci, including MRSA and streptococci.

Type I necrotizing fasciitis is a polymicrobial synergistic infection and occurs in a variety of settings that allow aerobic and anaerobic pathogens in combination to access the fascial plane between subcutaneous fat and the underlying musculature [4].

A variant of necrotizing fasciitis type I is saltwater necrotizing fasciitis, in which an apparently minor skin wound is contaminated with saltwater-containing *Vibrio* species [1,5▪▪]. *Vibrio vulnificus* is a cause of necrotizing fasciitis in patients with exposure to warm coastal water (particularly in the Gulf of Mexico), with penetrating injuries from seafood or ingestion of uncooked/undercooked seafood. *Once identified in culture, V. vulnificus is best treated with doxycycline and ceftriaxone or cefotaxime* [5▪▪]. *Aeromonas hydrophila* necrotizing fasciitis occurs after exposure of wounds to fresh or brackish water or contaminated soil. Leech use can also result in *A. hydrophila* infections. *Treatment is typically doxycycline PLUS ciprofloxacin, though ciprofloxacin resistance has been reported; this means that empiric cefepime may be employed while awaiting susceptibility testing* [5▪▪].

Type II necrotizing fasciitis is monomicrobial and is classically caused by group A *Streptococcus pyogenes*, but *Staphylococcus aureus* may also be identified as the etiologic agent.

Surgical control of infection is particularly important because diffusion of antimicrobials into affected tissues is limited due to significant tissue edema, necrosis, inflammation, and thromboses of penetrating blood vessel [6]. These conditions determine an environment that is particularly suitable for anaerobic bacterial proliferation in type I necrotizing fasciitis. In addition, bacteria can invade blood vessel walls and result in direct vascular injury that worsens tissue perfusion. In type II necrotizing fasciitis, streptococcal superantigens result in cytokine

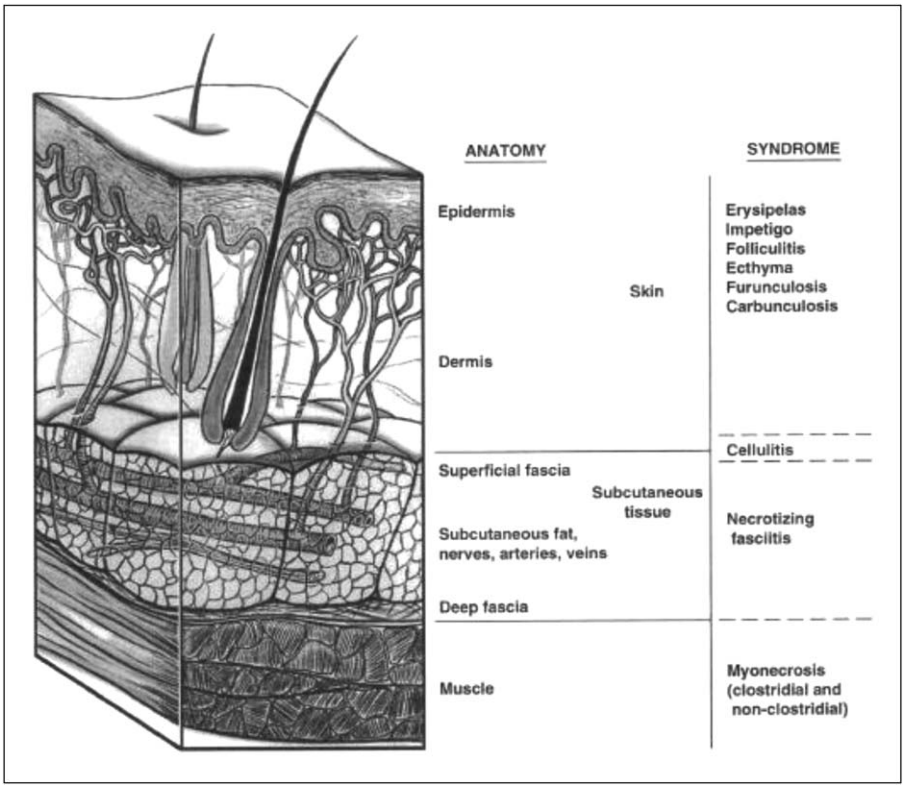

FIGURE 1. Anatomic and clinical classification of self-tissue infection.

cascade that cause systemic vasodilation and inflammation, leading to tissue hypoxia that precludes effective antimicrobial concentrations in tissue [5▪▪].

The number and types of organisms in necrotizing fasciitis tend to depend on the site of infection. Abdominal and perineal infections, particularly in a postsurgical background, tend to be polymicrobial and grow enteric pathogens [6–8].

The importance of early surgical debridement and collection of material for bacterial cultures, in combination with broad spectrum antimicrobial treatment implementation as the first line of therapy, should be stressed [9,10].

SITE OF INFECTION

Although it can occur in any region of the body, necrotizing fasciitis most commonly occurs in the abdominal wall, extremities, and perineum [3,6,7,11–13]. Introduction of pathogens into the subcutaneous space can occur through any disruption of the overlying skin, such as a cut, abrasion, laceration, contusion, bite, injection, or surgical incision. Reported causes of soft tissue injury leading to necrotizing fasciitis include blunt or penetrating trauma, postoperative complications, cutaneous infections or ulcers, illicit IV or subcutaneous drug injections, perirectal abscesses, animal or insect bites, incarcerated hernias, subcutaneous insulin injection, colocutaneous fistula, renal calculi, and idiopathic causes. In addition to direct inoculation of the subcutaneous tissues from a superficial site, hematogenous spread from a distant site of infection can probably occur [7,12–21].

When necrotizing fasciitis involves the male genitalia, it is known as Fournier's gangrene. Some authors expand the definition of Fournier's gangrene to include necrotizing fasciitis of the perineal region in both men and women [8,22]. The most common causes of necrotizing fasciitis of the male genitalia are genitourinary infections and trauma.

Necrotizing fasciitis of the head and neck is rare. Cases can be separated into two groups: those originating from the scalp or periorbital region and those originating from the face or neck [1]. Blunt or penetrating trauma is the most common cause of scalp involvement, whereas the cause of periorbital involvement is usually trauma, eyelid infection, or pruritus [23,24].

EPIDEMIOLOGY AND MORTALITY

In Europe, rates of necrotizing fasciitis vary widely based on region (0.18–15.5 per 100 000) and seem to be increasing over time. In a cohort study of a Texas inpatient population with diagnosis of necrotizing fasciitis during the years 2001–2010, 12 172 necrotizing fasciitis hospitalizations were identified, with ICU admission in 50.3%. A rising incidence of necrotizing fasciitis between 2001–2002 and 2009–2010 [5.9 versus 7.6 per 100 000 ($P < 0.0001$)] was documented. Hospital mortality (9.3%) remained unchanged during study period [25▪].

In another patient series, 19.3% of patients (290/1504) with a diagnosis of necrotizing fasciitis died in hospital. Prognostic factors for mortality in necrotizing fasciitis patients included being woman; age 60 years; or having chronic heart disease, cirrhosis, skin necrosis, pulse rate more than 130/min, SBP less than 90 mmHg, and serum creatinine more than 1.6 mg/dl [26].

CLINICAL CLUES AND DIAGNOSIS

Even though the classic teaching for necrotizing fasciitis is pain out of proportion at physical examination, it is important to remember that superficial nerves may undergo necrosis, resulting in anesthesia of affected areas. Due to the severity of illness and altered sensorium, clinical history may be difficult to obtain, and the diagnosis of necrotizing skin and skin structure infection still relies on a high index of suspicion.

Clinical and biochemical parameters that are associated with an increased likelihood of necrotizing infection are listed in Table 1.

Wong *et al.* [27] created a laboratory risk score for necrotizing fasciitis (LRINEC). The score can be employed to risk stratify patients presenting with signs of cellulitis and can be a useful tool to

Table 1. Clinical and biochemical parameters that are associated with an increased likelihood of necrotizing infection

Clinical parameters	Laboratory parameters
Pain out of proportion to examination	Serum sodium <135 mmol/l
Bullae	White blood cell count >15 400 cells/μl
Tenderness beyond area of erythema	Renal failure
Crepitus	Progressive lactic acidosis
Cutaneous anesthesia	
Cellulitis refractory to antibiotic therapy	
Rapid progression of cellulitis	
Dusky appearance of skin	
Systemic toxicity	

determine the likelihood of necrotizing fasciitis. It uses six different parameters: C-reactive protein (CRP, >150 mg/l – 4 points), total white cell count (<15 × 106/μl – 0 points, 15–25 – 1 point, >25 – 2 points), hemoglobin (>13.5 g/dl – 0 points, 11–13.5 – 1 point, <11 – 2 points), sodium (<135 mmol/l – 2 points), creatinine (>141 mmol/l – 2 points), and glucose (>10 mmol/l – 1 point). A score of 6 or more indicates a high probability of necrotizing fasciitis. Recently, a modification of the score (pain out of proportion, when present, along with elevated CRP) led to a clear improvement of LRINEC diagnostic accuracy with a higher positive predictive value without losing specificity (Table 2) [28▪▪].

Due to unacceptably low sensitivity, imaging findings cannot rule out necrotizing fasciitis. The diagnostic delay that ensues might be responsible for poor outcomes. However, in patients that are clinically stable, MRI may be helpful in distinguishing necrotizing infection from nonnecrotizing infection [5▪▪].

MANAGEMENT OF NECROTIZING FASCIITIS

A recent survey conducted in 100 European ICUs highlights significant heterogeneity in terms of organization of care, treatment strategies, and adherence to the most recent guidelines. Two major and modifiable prognostic factors (delayed diagnosis of necrotizing soft tissue infection and lack of priority access to the operating room) appear responsible for increasing the time to first surgical debridement [29].

Prolonged time from presentation to first surgical intervention is associated with increased mortality [30]. Delay in diagnosis of necrotizing soft tissue infections is felt to be one of the highest impact risk factor for surgery deferral [29]. Source control of infection is paramount, and serial surgical debridements are generally required. The frequency and number of debridements vary on the basis of aggressiveness of infection, but generally patients should return to the operating room for debridement every 24–48 h until there is no evidence of progression of skin and soft tissue necrosis [5▪▪]. Wound dressing change should be carried out at least daily to look for evidence of ongoing infection (e.g., bullae, devitalized tissue, and spreading erythema) that would require repeat debridement [5▪▪]. In addition to wound appearance, clinical deterioration, measured by the increased need for intensive care support, or laboratory parameters suggestive of worsening infection (e.g., progressive renal failure, increasing leukocytosis, and increasing lactate) should prompt to repeat debridement [5▪▪].

In all cases of necrotizing soft tissue infections, one of the goals of surgery should be to seek out portals of entry for bacteria that could have established the infection, either from indwelling devices or the external environment/foreign bodies or other organs (e.g., gastrointestinal or genitourinary systems) [5▪▪]. Together with serial surgical debridements, vacuum-assisted closure of wounds is considered a useful contribution to healing [5▪▪]. For cases of necrotizing infection involving the perineum or other sites with potential for stool contamination, temporary colostomy may be required to assist in wound healing. Rates of amputation necrotizing fasciitis of lower extremity depend on comorbidities and vary from 15 to 72%, with diabetes being a strong risk factor for amputation [31]. Although potentially life-saving, it is important to recognize that amputation, among other factors, may be associated with significant functional limitations after discharge.

Table 2. Modified LRINEC score with clinical symptoms

Laboratory parameters		
C-reactive protein	>150 mg/dl	4 points
White cell count	$<15 \times 10^6$/μl	0 point
	$15–25 \times 10^6$/μl	1 point
	$>25 \times 10^6$/μl	2 points
Erythrocyte count	$<4 \times 10^6$/μl	1 point
Hemoglobin	>13.5 g/dl	0 point
	11–13.5 g/dl	1 point
	<11 g/dl	2 points
Creatinine	<135 mmol/l	2 points
Fibrinogen levels	>750 mg/dl	2 points
Clinical parameters		
Pain	Mild/none	0 point
	Intermediate	1 point
	Strong	2 points
Fever	≤37.5 °C	0 point
	37.6–37.9 °C	1 point
	≥38.0 °C	2 points
Tachycardia	>100 heart beats/min	1 point
Signs of acute renal injury	No	0 point
	Yes	1 point

Score results: ≥8 strong suspicion for necrotizing fasciitis; 6–7 suspicion; ≤5 no suspicion. Reproduced from [28▪▪].

ANTIMICROBIAL THERAPY

In the face of the new sepsis definitions, a prudent approach would be to define skin and soft tissue infection (SSTI) as severe if the patient meets either

of the following criteria: ICU patients with an acute change in sequential organ failure assessment (SOFA) score at least 2 points due to infection, non-ICU patients matching two-third quick SOFA criteria (altered mental status, SBP $\leq$ 100 mmHg, or respiratory rate $\geq$22/min) [32]. Necrotizing SSTI should always be classified as severe.

As a general rule, all severe SSTI, including necrotizing cellulitis, should be treated empirically with broad-spectrum antibiotics directed against typical pathogens, specifically methicillin-resistant *S. aureus* (MRSA), resistant Gram-negatives, and anaerobes. However, when selecting empiric therapy, all practitioners should consider local bacterial susceptibilities as these can vary significantly from institution to institution. Risk factors for mixed Gram-positive and Gram-negative SSTI include admission to the ICU, residence in a nursing home, and SSTI other than an abscess [33]. *Reasonable empiric therapies meeting these criteria include vancomycin or linezolid PLUS piperacillin/tazobactam or meropenem or imipenem, or cefepime PLUS metronidazole. De-escalation of antibiotic therapy should be based on clinical improvement and cultured pathogens from blood or surgical specimens. Once patients have improved and are ready for discharge, switching to oral antibiotic therapy is possible, though nonadherence to prescribed antibiotics is common and is a risk factor for treatment failure.*

Empiric antibiotic therapy for necrotizing fasciitis can be employed until wound culture isolates are identified. Because most necrotizing soft tissue infections are polymicrobial, broad-spectrum coverage is advisable. Acceptable monotherapy regimens include a carbapenem or piperacillin/tazobactam. However, an optimal choice in the management of necrotizing fasciitis has been the association of ampicillin/sulbactam plus clindamycin.

The new anti–Gram-negative antibiotics, ceftolozane/tazobactam and ceftazidime/avibactam, in combination with an antianaerobic agent (metronidazole or clindamycin) can be considered as a potential alternative to meropenem, for a carbapenem-sparing strategy.

Ceftazidime/avibactam is active against extended spectrum beta-lactamase (ESBL) and carbapenemase (including Klebsiella pneumoniae carbapenemase carbapenemases) producing Gram-negative bacilli but it lacks activity against metallo-beta lactamases [34▪▪]. Ceftolozane/tazobactam is a new antibiotic active against ESBL-producing enterobacteriaceae and MDR strains of *Pseudomonas aeruginosa*, including strains resistant to meropenem and ceftazidime [35▪▪].

For necrotizing fasciitis caused by group A streptococci, high-dose penicillin, and clindamycin appear to be the treatment of choice. Clindamycin inhibits M protein and exotoxin synthesis by group A beta-haemolytic streptococcus.

Alternative options in patients with risk factors or documented infections due to either community-acquired or hospital-acquired-MRSA are represented by vancomycin, teicoplanin, daptomycin, and linezolid. Of note, daptomycin can be particularly useful in the management of necrotizing fasciitis because it exhibits a rapid and concentration-dependent bactericidal activity and reduces macrophage inflammatory response to *S. aureus* by diminishing release of proinflammatory bacterial components [36].

There are several new anti–Gram-positive antimicrobial agents potentially useful for severe SSSI, including necrotizing fasciitis. The new anti-MRSA cephalosporins, Ceftaroline (Allergan, Parsippany, NJ, USA) and Ceftobiprole (Basilea Pharmaceutica, Basel, Switzerland), share similar antibacterial activity against Gram-positive cocci (including MRSA and streptococci). Ceftobiprole also shows some activity against selected strains of *P. aeruginosa* [37]. Ceftaroline has been registered for acute bacterial skin and skin structure infections (ABSSSI) and might be considered as an alternative to nonbeta lactam anti-MRSA agents [38▪▪,39▪▪,40▪].

A novel oxazolidinone, Tedizolid (Merck, Whitehouse Station, NJ, USA), binds to the bacterial 50S ribosomal subunit to inhibit protein synthesis, resulting in broad in-vitro activity against Gram-positive pathogens, including MRSA and strains resistant to vancomycin or linezolid [41]. Tedizolid turned out to be noninferior to linezolid in the management of skin and skin structure infections [42▪▪]. Noninferiority was achieved with a 6-day once-daily intravenous or oral regimen, and fewer low platelet counts and gastrointestinal side effects were reported than with linezolid. All these results align perfectly with antimicrobial stewardship principles [42▪▪].

Two new long-acting lypoglycopeptides, Oritavancin (The Medicine Company, Parsippany, NJ, USA) and Dalbavancin (Durata Therapeutics, Chicago, IL, USA), share the indications for ABSSSI and have similar activity against Gram-positive cocci including MRSA and streptococci [5▪▪]. Used as single-dose regimens of 1200 and 1500 mg, respectively [43▪▪,44▪▪], they show rapid bactericidal activity and very long half-life persisting for about 2 weeks. These agents are particularly attractive in patients requiring short hospital stay or having limitations for vascular access. Their specific role in necrotizing cellulitis, including necrotizing fasciitis, should be evaluated but they might be a potential alternative to glycopeptides and daptomycin.

Table 3. Drugs available for the treatment of necrotizing fasciitis with potential advantages and limitations

Ceftazidime–Avibactam	Activity against AmpC-producing, ESBL-producing, and carbapenemase-producing Gram-negative bacteria	No activity against anaerobes and MBL-producing bacteria
Ceftolozane–Tazobactam	Activity against AmpC-producing and ESBL-producing Gram-negative bacteria; activity against ceftazidime-nonsusceptible and meropenem-nonsusceptible *P. aeruginosa* strains (MICs not affected by efflux pump overexpression and porin loss of function)	No activity against anaerobes and MBL-producing and carbapenemase-producing bacteria
Ceftobibrole	Activity against MRSA and *P. aeruginosa*	No activity against ESBL-producing, MBL-producing, and carbapenemase-producing bacteria; with the exception of efficacy demonstrated *in vitro* against AmpC overproducing strains, activity against *P. aeruginosa* is comparable with that of ceftazidime
Ceftaroline	Activity against MRSA	Activity against Gram-negative bacteria comparable with that of ceftriaxone; no efficacy against *P. aeruginosa*; inactivated by AmpC and ESBL
Daptomycin	High bactericidal activity against MSSA and MRSA; reduces *S. aureus* release of proinflammatory components	No activity against Gram-negative bacteria
Dalbavancin	High bactericidal activity against MSSA and MRSA; long half-life allows for 2-weekly dosing	No activity against Gram-negative bacteria
Oritavancin	High bactericidal activity against MSSA and MRSA; long half-life allows for 2-weekly dosing	No activity against Gram-negative bacteria
Tedizolid	Broad in-vitro activity against Gram-positive pathogens, including MRSA and strains resistant to vancomycin or linezolid; fewer toxic effects compared with linezolid	No activity against Gram-negative bacteria

MBL, metallo-beta lactamase; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 4. Suggested regimens for different types of necrotizing fasciitis

Type of infection	Therapy
Necrotizing fasciitis by mixed pathogens	Ampicillin/sulbactam plus clindamycin and ciprofloxacin OR Piperacillin/tazobactam or carbapenems OR Fluoroquinlonones or third-generation Cephalosporins or **ceftazidime/avibactam** or **ceftolozane/tazobactam** or **ceftobiprole** aminoglycosides plus antianaerobic agent[a]
Necrotizing fasciitis by GABHS	Penicillin plus clindamycin OR Glycopeptides or linezolid or **tedizolid** or **ceftobiprole** or tigecycline or **daptomycin** or **dalbavancin**
Necrotizing fasciitis by *S. aureus*	*MSSA*: oxacillin or first-generation cephalosporin *MRSA*: glycopeptides or linezolid or **tedizolid** or tigecycline or **daptomycin** or **ceftaroline** or **ceftobiprole** or **dalbavancin**

GABHS, group A beta-haemolytic streptococcus.
Drugs displayed as bold text are new antibiotics.
[a]Metronidazole or clindamycin.

A summary of relative advantages and drawbacks of drugs potentially available for the treatment of necrotizing fasciitis is showed in Table 3.

Improved survival was documented with the administration of intravenous immunoglobulins for treating streptococcal [45] and staphylococcal [46] TSS, often complicating necrotizing fasciitis, and their use is based upon a potential benefit related to the binding of Gram-positive organism exotoxins. The role of hyperbaric oxygen in the treatment of necrotizing fasciitis remains controversial.

Due to the relative rarity, heterogeneity of microbiologic causes, and severity of disease, no clinical trials are available to guide duration of therapy, though guidelines based on expert opinions suggest continuation of therapy directed against cultured organisms for at least 48–72 h after patients are clinically stable and require no further operative interventions. Table 4 lists suggested antimicrobial regimens for different types of necrotizing fasciitis.

CONCLUSION

Necrotizing fasciitis is a potentially life-threatening condition requiring a multifaceted therapeutic approach consisting of surgical source control with immediate surgical debridement along with life

support, monitoring, and antimicrobial therapy. Many new drugs are now available for the treatment of this infectious disease. Some of these new molecules have the potential of reducing carbapenem use. Other novel drugs with strong activity against Gram-positive cocci might increase cure rates and reduce length of hospital stay.

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Conflicts of interest

There are no conflicts of interest.

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