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Review

Diagnosis and management of skin and soft-tissue infections (SSTI). A literature review and consensus statement: an update

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Skin and soft-tissue infections (SSTIs) are among the most common bacterial infections, posing considerable diagnostic and therapeutic challenges. Fourteen members of the Italian Society of Infectious Diseases, after a careful review of the most recent literature using Medline database and their own clinical experience, updated a previous paper published in 2011 by preparing a draught manuscript of the statements. The manuscript was successively reviewed by all members and ultimately re-formulated the present manuscript during a full day consensus meeting. The microbiological and clinical aspects together with diagnostic features were considered for necrotizing and not necrotizing SSTIs in the light of the most recent guidelines and evidences published in the last five years. The antimicrobial therapy was considered as well – both empirical and targeted to methicillin-resistant *Staphylococcus aureus* and/or other pathogens, also taking into account the epidemiological and bacterial resistance data and the availability of new antibacterial agents.

Keywords: Skin and soft-tissue infections (SSTIs), Acute bacterial skin and skin-structure infection (ABSSSI), Antibiotics

Introduction

Skin and soft-tissue infections (SSTIs) are among the most common bacterial infections, accounting for ~10% of hospital admissions for infections in the USA.[1] SSTIs are clinical entities of variable presentation, aetiology and severity that involve microbial invasion of the layers of the skin and underlying soft tissues, ranging from mild to serious life-threatening infections.[2]

Their incidence has increased because of the ageing of the general population and the increased number of critically ill patients and their treatment has become more challenging because of the increasing emergence.[2]

The purpose of this study was to update a previous paper published in 2011 on diagnosis and treatment of SSTI following the same methodology.[3]

Fourteen members of the Italian Society of Infectious Diseases prepared the manuscript following an in-depth review of the most recent (last five years) current literature using the MEDLINE database and aimed to provide an insight into these complex issues and, when applicable, their personal insight from their own clinical experience. The expert panel met via email to prepare, discuss and revise the paper. The manuscript was successively reviewed by all members and ultimately re-formulated

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Table 1 Classification of SSTIs

Not necrotizing infections	Necrotizing infections
Impetigo	Pyomiositis
Furunculous and carbuncles	Necrotizing fasciitis
Animal and human bites	Clostridial myonecrosis
Infected pressure ulcers	Fournier's Gangrene
ABSSSI:	
• Erysipela	
• Cellulitis	
• Surgical infections	
• Cutaneous abscess	

as the present manuscript during a full day face-to-face consensus meeting.

Definitions and classifications

SSTIs represent a heterogeneous array of disorders.[2,4] Several classifications have been proposed, but as yet none is universally accepted. Every scheme organizes SSTI on the basis of a specific variable, such as anatomical localization, aetiological agent, skin extension, progression rate, clinical presentation and severity.[3]

Each of them has its own usefulness, but in general what the clinician expects from classifications is to be driven towards the most appropriate management of the condition. On this basis, the Infectious Diseases Society of America (IDSA) classification has been the most useful and practical guidance to date by adopting three different distinctions: (i) skin extension: uncomplicated typically superficial infections (uSSTI), and complicated infections (cSSTI) usually with deep involvement; (ii) rate of progression: acute and chronic wound infections; and (iii) tissue necrosis: necrotizing and non-necrotizing infections.[5] Recently, the U.S. Food and Drug Administration (FDA) has introduced the new definition of acute bacterial skin and skin-structure infection (ABSSSI)[6] to more closely define complicated soft-tissue infection for the purposes of registration trials. ABSSSIs include cellulitis/erysipelas, wound infections and major cutaneous abscesses. Thus, an ABSSSI is defined as a bacterial infection of the skin with a lesion size area of $\geq$75 cm^2 (lesion size measured by the area of redness, oedema or induration).

In the present paper, we decided to consider not necrotizing and necrotizing infections as the main criteria to classify SSTIs to deal with Table 1.[7–9]

Microbiological diagnosis and aetiology

Even though microbiological data do not play a role in the choice of initial empiric therapy, the need for aetiological tests depends on several factors, including type of infection; severity of the clinical condition and the underlying patient condition.[10] For common and simple SSTIs (cellulitis or small subcutaneous abscess) cultures are not necessary, on the contrary when complicated SSTIs are associated with exudates or with abscesses, specimens have to be collected and sent rapidly to microbiology laboratory with detailed information.[11] Cultures and microscopic examination of cutaneous aspirates or biopsies have to be considered in immunosuppressed patients, injuries contaminated with soil or animal bites.[5,12] Cultures of superficial swab are usually unreliable for the microbiological assessment of SSTI as the results of superficial techniques do not reflect the aetiological pathogen in case of deep tissue infections because of the presence of commensal micro-organisms, against which there is no need for antibiotic therapy, on wound surface.[13] Quantitative cultures could provide the threshold to distinguish commensal microbiota from clinically significant bacterial growth. But for quantitative cultures, tissue sample processing is challenging and traditional swabs yield a reduced amount of the actual bacterial burden, therefore numerous prospective studies contradict the usefulness of quantitative cultures.[14] Traditional bacterial culture is associated with delay in the results, molecular technologies instead can represent a suitable time-saving alternative. PCR-based techniques do not appear to be more sensitive than cultures, in particular for cellulitis,[15] but molecular techniques seem to be very useful for the diagnosis of SSTI sustained by *Staphylococcus aureus*, potentially providing crucial information for the choice of appropriate antibiotic regimen, such as the rapid detection of Panton–Valentine leucocidin-encoding genes from pus samples[16] or the identification of cryptic resistances which could be not identified by classical microbiological approaches.[17]

Ray et al. report that during the three-year study period from 2009 to 2011, 376,262 individuals experienced 471,550 SSTI episodes, of which 23% were cultured.[18] Among cultured episodes, 54% were pathogen-positive. *S. aureus* was isolated in 81% of pathogen-positive specimens, of which nearly half (46%) were MRSA. The rate of clinically diagnosed SSTIs in this population was 496 per 10,000 person-years. After adjusting for age group, gender, race/ethnicity and diabetes, Asians and Hispanics were at reduced risk of SSTIs compared to Whites, while diabetics were at substantially higher risk compared to non-diabetics. There were strong age group by race/ethnicity interactions, with African-Americans aged 18 to <50 years being disproportionately at risk for SSTIs compared to persons in that age group belonging to other race/ethnicity groups. Compared to Whites, *S. aureus* isolates of African-Americans and Hispanics were more likely to be MRSA (Odds Ratio (OR): 1.79, Confidence Interval (CI): 1.67 to 1.92, and, OR: 1.24, CI: 1.18 to 1.31, respectively), while isolates from Asians were less likely to be MRSA (OR: 0.73, CI: 0.68 to 0.78).

Imaging studies

Imaging studies are sometimes required to establish the diagnosis of SSTI. Plain Radiography may be useful to detect the presence of gas in the soft tissues, suggesting a necrotizing infection, and to reveal a possible underlying osteomyelitis even though it could have low accuracy in

diagnosing an osteomyelitis or a PJI if the lesion is close to a prosthetic implant.[19]

Computed Tomography (CT) scans can help to assess the extent of the infectious process, to guide fluid aspiration and to reveal the presence of foreign objects or even small fluid-air collections in the soft tissues.[19,20] Magnetic Resonance Imaging (MRI) is considered the investigation of choice for SSTI because of its great soft tissue contrast. MRI is particularly helpful in differentiating cellulitis from pus and abscess formation. Moreover, MRI provides better accuracy than CT in detecting necrosis, inflammatory oedema and muscular fascia involvement but its use is limited because too expensive.[20,21] Though MRI is considered the most accurate test for SSTI, many recent studies reported that Ultrasonography (US) has important advantages over other imaging studies, including MRI. First, US is a highly sensitive technique for SSTI diagnosis, providing useful information to differentiate cellulitis from abscess therefore preventing more expensive imaging studies and unnecessary harmful procedures like incision and drainage. Moreover, US is easy, rapid, has no side effects, no high costs and it can be performed even in patients with contraindications to MRI.[21,22] Recent studies reported that US can even suggest the aetiological pathogen: several sonographic features are associated with MRSA infection.[23] US can also be a guidance for diagnostic and therapeutic aspiration in order to avoid complications.[24] Radionuclide scanning studies generally lack of specificity in the acute situation but the development of hybrid techniques (such as single photon emission tomography [SPECT]/CT and positron emission tomography [PET]/MRI) may increase specificity of nuclear medicine imaging techniques.[24,25]

Non necrotizing infections

Impetigo

Impetigo is a highly contagious bacterial infection of the superficial layers of the epidermis. Impetigo predominantly affects children and it is one of the most common SSTI in children worldwide.[26,27] A recent estimate of global burden disease reveals that more than 162 million children suffer from impetigo at any one time,[28] most of them are in low- and low-middle-income countries because of the presence of several predisposing factors such as tropical or subtropical climates, overcrowding and poor hygiene.[29] Epidemiological studies indicate that the bacterial aetiology of impetigo varies according to time and region: in tropical contexts group A beta-haemolytic streptococcus (GABHS) still represents the dominant reported pathogen, but in temperate climates *S. aureus* has largely replaced GABHS during recent decades, becoming the most prevalent aetiological agent of impetigo in United States and Europe.[29,30] Moreover, of particular concern is the rising role of CA-MRSA as impetigo's aetiological agent reported by several studies worldwide.[31–33] The aetiology also varies according to the clinical presentation; there are two forms of disease: non-bullous and bullous impetigo. Non-bullous impetigo is the most common, representing more than 70% of all cases. The typical lesion is a thin-walled vesicle which easily breaks, leaving a characteristic honey-coloured crust, that frequently involves the extremities and the skin of face (e.g. nares, perioral region). Bullous impetigo is characterized by fragile, flaccid bullae with purulent content leaving a brown crust and a peripheral collarette after its rupture. The lesions occur most commonly on the trunk, axilla and intertriginous areas.[34,35] Non-bullous impetigo is caused by both *S. aureus* and GABHS whilst bullous lesions are associated with group II *S. aureus*, often phage type 71, which is able to produce the extracellular exfoliative exotoxins exfoliatins A and B.[36]

Erysipela

Erysipelas is a superficial, brilliant red, oedematous, painful infection of the skin, with induration, well-defined margins and rapid progression. Streptococci are the primary cause of erysipelas. Most facial infections are attributed to GABHS, with an increasing percentage of lower extremity infections being caused by non-GABHS. The role of *S. aureus*, and specifically MRSA, remains controversial.[3]

As reported by Raya et al. in 2014, 996 episodes in 841 hospitalized patients with any diagnosis of SSTIs were analysed in Spain.[37] Cellulitis/erysipela (66.7%) was the most frequently diagnosed condition, with 77% of all SSTIs being community acquired, and the majority of patients had comorbidities, mainly diabetes (33%) and heart failure (17.7%). The most frequent isolated microorganism was *S. aureus* (35.1%), in 19 (12.9%) cases with methicillin-resistance (MRSA), 84.2% of them were nosocomial or health-care acquired.

Cutaneous abscess, furuncles and carbuncles

A cutaneous abscess is a localized collection of pus within the dermis and deeper skin tissues. Cutaneous abscesses are typically caused by bacteria that represent the normal regional skin flora of the involved area.[4,9,38] Methicillin-Resistant *S. aureus*, especially CA-MRSA

USA300, is now the most common cause of cutaneous abscesses in the United States in patients presenting to an emergency department.[39]

Emergency department visits increased by 30% between 1996 and 2005, but the number of abscesses more than doubled.[40]

Furuncles (or boils) are deep infections of the hair follicle leading to small abscesses formation in subcutaneous tissue. Carbuncles are clusters of multiple furuncles, extending into the subcutaneous fat. These infections can occur anywhere on hairy skin but they are common on the neck, breasts, face and buttocks. Furuncles and carbuncles are usually caused by *S. aureus* infection.[9,38]

Table 2 Comparison of health care associated (HA-MRSA), community-associated methicillin-resistant (CA-MRSA) and community-associated susceptible (CA-MSSA) Staphylococcus aureus characteristics

Characteristic	HA-MRSA	CA-MRSA	CA-MSSA
SCC[1] *mec* type	I–II–III	IV–VI	None
Panton-Valentine leukocidin	NO	Common	Rare
Prevalence of lineage	Classic hospital clones	ST8 (USA 300), ST80 (Europe), ST30 (Australia)	Heterogeneous
Age	Adults Elderly	Young adults	Newborn Young adults
Health care exposure	Frequent	Rare	Rare
Comorbitities	Often present	Few	Few
Antibiotic susceptibility	Methicillin resistant	Methicillin resistant	Almost all antibiotic classes

[1]SCC, staphylococcal chromosome cassette

Frequently carbuncle occurs in diabetic persons. Outbreaks of furunculosis caused by *S. aureus* have been described.[41,42]

The severity of purulent SSTIs (such as abscesses, furuncles and carbuncles) depends largely on the toxigenic profile of the micro-organism and the immune status of the host.

Although clinicians are currently concerned primarily with infections sustained by CA-MRSA, methicillin-susceptible *S. aureus* (CA-MSSA) PVL producing in adults can present with similar epidemiologic and clinical characteristics without significant statistical differences[43]; reports involving CA-MSSA infections in newborn, have been described.[44,45]

Factors facilitating the spread of infection include crowding, frequent skin-to-skin contact between individuals, participation in activities that result in compromised skin surfaces, sharing of personal items that may become contaminated with wound drainage, and challenges in maintaining personal cleanliness and hygiene. Limited access to health care and frequent antibiotic exposure may also facilitate spread of infection in some settings.[46]

In Table 2 are compared the health care-associated methicillin resistant (HA-MRSA), community-associated methicillin-resistant (CA-MRSA) and susceptible (CA-MSSA) *Staphylococcus aureus* characteristics.

Animal and human bites

Animal bites account for 1% of all emergency department visits in the United States and more than $50 million in health care costs per year. Most animal bites are from a dog, usually one known to the victim. Most dog bite victims are children.[47]

Rothe et al. report that 30,000–50,000 injuries are caused by bites in Germany every year, dog and cat bites being more common, human bites relatively rare. Twenty-five per cent of the victims are under age 6, and 34% are aged 6–17. In small children, most bite wounds are on the head and neck; in older children and adolescents, most are on the limbs. Bite injuries range from trivial ones needing no medical intervention to major soft-tissue defects with the loss of functionally important structures.[48]

The predominant pathogens in these wounds are part of the normal oral flora of the biting animal, along with human skin organisms and occasional secondary invaders (e.g. *S. aureus* and GABHS). *Pasteurella multocida* is usually found in approximately 50–70% of dog and cat bite wounds.[3] *Capnocytophaga canimorsus* can cause bacteremia and fatal sepsis after animal bites, especially in patients with hepatic disease.[3] *Staphylococcus* spp. and *Streptococcus* spp. are found in 40% of bites from both types of animals. *Bacteroides* spp., *Fusobacterium* spp., *Porphyromonas* spp., *Prevotella heparinolytica*, *Proprionibacteria*, and peptostreptococci are common anaerobes isolated from both dog and cat bite wounds. *Actinobacillus* spp. has been found in horse and sheep bite wounds.[3] The most common organisms found in infected human bites are *Streptococcus anginosus*, *S. aureus*, *Eikenella corrodens*, *Fusobacterium* spp., *Prevotella* spp. and *Porphyromonas* spp.[3] In a multicentre prospective study of 50 patients with infected human bites, the median number of isolates per wound culture was 4 (3 aerobes and 1 anaerobe); aerobes and anaerobes were isolated from 54% of wounds, aerobes alone were isolated from 44%, and anaerobes alone were isolated from 2%. In addition, transmission of hepatitis B and C, as well as HIV infection, has also been documented through human bites.[3]

Cellulitis

Cellulitis is an acute spreading infection of the skin, involving the subcutaneous tissues. As already reported in a previous paragraph, cellulitis has been recently classified as an Acute Bacterial Skin and Skin Structure Infection (ABSSSI) together with erysipela, surgical site infections and major abscesses.[6]

In a large European multicentre study Garau et ala analysed a population of patients diagnosed with complicated (c)SSTI hospitalized between December 2010 and January 2011 reporting that cellulitis was the most frequent diagnosis accounting for 59% of the total,[49] most often caused by GABHS or *S. aureus*. Streptococci cause diffuse, rapidly spreading infection; staphylococcal cellulitis is typically more localized. Isolation of MRSA is steadily increasing. Bacterial strains are increasingly resistant to other standard

antibiotic treatments, including erythromycin. Patients with cytotoxic therapy induced granulocytopenia, such as those affected by haematologic malignancies or bone marrow transplant recipients, may develop 'ecthyma gangraenosum' cellulitis due to haematogenous seeding of *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, as well as other bacteria and fungi. Similarly, patients who are immunocompromised after solid organ transplantation may develop cellulitis due to infection with unusual organisms, including Gram-negative bacilli (e.g. *Pseudomonas* spp., *Proteus* spp., *Serratia* spp., *Enterobacter* spp., *Citrobacter* spp.), anaerobes, other opportunistic pathogens (e.g. *Helicobacter cinaedi*, *Fusarium* spp.), mycobacteria, and fungi (e.g. *Cryptococcus* spp., *Histoplasma, Nocardia spp*).[3]

Surgical site infections

Surgical site infections (SSIs) remain a major source of illness and a potential cause of death in the surgical patient.[50]

The frequency of SSIs is clearly related to the category of operation and they are classified as being either incisional or organ/space. Incisional SSIs are further divided into those involving only skin and subcutaneous tissue (superficial incisional SSI) and those involving deeper soft tissues of the incision (deep incisional SSI).[3] The results recently obtained by Martin et al. by a systematic review and meta-analysis support the consideration of diabetes as an independent risk factor for SSIs for multiple surgical.[51]

The pathogens isolated from infections differ, primarily depending on the type of surgical procedure. In clean surgical procedures, *S. aureus* from the exogenous environment or the patient's skin flora is the usual cause of infection. According to data from the National Nosocomial Infections Surveillance System (NNIS), in the last years an important increase in the rate of MRSA in SSIs has been observed worldwide.[52]

Sganga et al. have recently reported that the risk factors associated with MRSA SSIs identified by the Delphi method were: patients from long-term staying care facilities, recent hospitalization (within the preceding 30 days), Charlson score >5 points, chronic obstructive pulmonary disease and thoracic surgery, antibiotic therapy with beta-lactams (especially cephalosporins and carbapenems) and/or quinolones in the preceding 30 days, age 75 years or older, current duration of hospitalization >16 days, and surgery with prosthesis implantation.[53]

Infected pressure ulcers

Pressure ulcers, also known as bedsores, decubitus ulcers and pressure injuries, are localized areas of injury to the skin or the underlying tissue, or both. They represent a frequent disease especially in those elderly defined as 'frail' with chronic co-morbidity.[3]

Clinical examination often underestimates the degree of deep-tissue involvement, and its findings are inadequate for the detection of associated osteomyelitis. Microbiological data, if obtained from deep-tissue biopsy, are useful for directing antimicrobial therapy, but they are insufficient as the sole criterion for the diagnosis of infection. Imaging studies, such as computed tomography and magnetic resonance imaging, are useful, but bone biopsy and histopathological evaluation remain the 'gold standard' for the detection of osteomyelitis.[54]

Tissue necrosis, and wound width and depth represent a significant predisposing factors to colonization and consequently to infection. When infection occurs, it is typically polymicrobial and includes aerobes (*S. aureus*, *Enterococcus* spp., *Proteus mirabilis*, *Escherichia coli*. *Pseudomonas* spp.) and anaerobes (*Peptococcus* spp, *Bacteroides fragilis*, *Clostridium perfringens*).[3]

Recurrent non necrotizing skin and soft-tissue infections

Recurrence of infection is a common and challenging complication of SSTI. Three clinical syndromes are frequently associated with recurrence, especially when specific risk factors are present: cellulitis (mainly erysipelas or associated with lymphangitis), furunculosis and alterations of skin structures like pilonidal sinus or bartholinitis[55,56] (Table 3). Recurrent cellulitis is a common clinical scenario, considering that about 22–49% of patients with cellulitis report at least 1 previous episode of cellulitis. Recurrences were reported in approximately 14% of patients within 1 year and in 45% of cases within 3 years and, usually, tend to occur in the same body area.[57] The main aetiological agent is considered *Streptococcus pyogenes,* but in these patients it is crucial the analysis of predisposing risk factors: lower extremities oedema, obesity, eczema, venous insufficiency, diabetes and immunosuppressive status are considered the more important features associated with recurrent infection.[5] In particular, in patients with end-stage heart failure or who underwent oncological surgery (like breast cancer), a lymphangitis is an additional risk factor for recurrence. Moreover, it is also plausible that each recurrent episode of cellulitis might result in a further damage to the lymphatic system, implementing a vicious circle.[58]

Necrotizing infections

Pyomyositis

Pyomyositis is a primary infection of skeletal muscle not arising from contiguous infection, presumably haematogenous in origin, and often associated with abscess formation.[3]

Muscle histology and its culture remain the gold standard for diagnosis. However, among noninvasive methods, MR imaging is highly sensitive and can image large areas of the body and detect subclinical involvement.[59]

The main pathogen in approximately 70% of the cases is *S. aureus*, often producing Panton-Valentine leukocidin and enterotoxins.[60] Other potential aetiological agents

Table 3 Recurrent skin and soft-tissue infections

Syndrome	Risk factors	Usual involved body areas	Body areas of recurrence	Aetiology	Prophylactic therapy after standard therapy for acute infection
Cellulitis (mainly erysipelas and lymphangitis)	*Main risk factors:* Lower extremities oedema, Oncological surgery with lymphonodes removal, Radiatiation therapy *Other comorbidities:* Obesity Eczema Diabetes Immunosuppressive status	Lower extremities	Areas of first infection	*Streptococcus pyogenes*	Benzathine Penicillin G
Furunculosis	Nasal colonization Recurrent skin trauma Suboptimal hygiene Familiary spread	Everywhere	Body areas different from initial ones	*Staphylococcus aureus* (PVL+ strains CA-MRSA USA 300 clone as additional risk factors for recurrence)	Nasal decolonization with mupirocin Chlorhexidine gluconate Doxycycline or Minocycline +/– Rifampin Clindamycin
Alterations of skin structures	Genetic predisposition (pilonidal cysts) Sedentary work Anatomic predisposing alterations	Sacrococcygeal (pilonidal cyst) and vaginal (bartholinitis) areas	Areas of first infection	Gram-negative anaerobic rods *Staphylococcus aureus*	Surgery

include *Streptococcus* spp., Gram-negative bacteria, and *Mycobacterium tuberculosis*. Anaerobic bacteria such as *Bacteroides fragilis*, *Fusobacterium* spp., *Clostridium* spp. and *Peptostreptococcus* spp. have also been recovered in studies where proper methods for their isolation were employed.[3]

Necrotizing fasciitis

A number of diseases have been described that share pathophysiological and clinical features of necrotizing fasciitis (NF), thus generating some confusion in their classification. For this reason, many authors nowadays prefer to encompass all necrotizing infections of the subcutaneous and muscular tissues under the term 'necrotizing soft-tissue infections' (NSTIs).[3]

Necrotizing fasciitis is anyway 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%).

The diagnosis and severity of the infection can be appropriately defined with laboratory-based scoring systems, such as the laboratory and clinical risk indicator for necrotizing fasciitis score (LRINEC score system) which has been recently modified by Borschitz et al.[61]

NF is classified into three types, depending on microbiological findings. Most cases are polymicrobial, classed as type 1. *S. aureus* (including MRSA) and GABHS, alone or in synergism, are frequently the initiating infecting bacteria (type 2). However, other aerobic and anaerobic pathogens may be present, including *Bacteroides* spp., *Clostridium* spp., *Peptostreptococcus* spp., *Enterobacteriaceae*, *Proteus* spp., *Pseudomonas* spp., and *Klebsiella pneumoniae*. *B. fragilis* is usually noted as part of a mixed flora in combination with *Escherichia coli*. *B. fragilis* does not directly cause these infections, but it does play a part in reducing immune function.[3,62] Some cases of necrotizing fasciitis can be caused by *Vibrio vulnificus*. This organism is seen more often in patients with chronic liver dysfunction, and it often follows the consumption of raw seafood or trauma involving salt water. Another rare cause of necrotizing fasciitis occurring after exposure of wounds to fresh or brackish water or contaminated soil or leech use is represented by *Aeromonas hydrophila*.[63] All the last are classified as type 3.

Clostridial myonecrosis

Life-threatening soft tissue infections caused by Clostridium species have been described in the medical literature for hundreds of years largely because of their fulminant nature, distinctive clinical presentations and complex management issues.

Clostridial myonecrosis (gas gangrene) refers to a rapidly progressive, life-threatening, toxaemic infection of skeletal muscle caused by clostridial species (principally *Clostridium perfringens*). *C. perfringens* is the most common *Clostridium* spp. causing the infection. *Clostridium septicum* and other species (*Clostridium novyi, Clostridium bifermentans, Clostridium histolyticum* and *Clostridium fallaxf*) have also been recovered.[3] Spontaneous development of clostridial myonecrosis is described (most commonly produced by *C. septicum*), propagated mainly from the colon in patients with neoplasia and in poor health [190]. Patients often complain of a sudden onset of pain at the site of trauma or the surgical wound, which rapidly increases in severity and extends beyond the original borders of the wound. The skin initially becomes edematous and tense; its pale appearance progresses to a magenta hue. Haemorrhagic bullae are common, as is a thin, watery, foul-smelling discharge.

Similarly, over the last 15 years there has been increased recognition of a toxic shock-like syndrome associated with Clostridium sordellii in black tar heroin addicts, in women undergoing childbirth or other gynaecologic procedures including medically-induced abortion. Like their cousins *Clostridium tetani* and *Clostridium botulinum*, the pathogenesis of these clostridial infections is largely the consequence of potent exotoxin production.[64]

Fournier's gangrene

Fournier's gangrene (FG) is a polymicrobial necrotizing fasciitis of the perineal, perianal or genital areas, characterized by obliterative endarteritis of the subcutaneous arteries, resulting in gangrene of the subcutaneous tissue and the overlying skin.[65] It is a sporadic disease with an estimated incidence of 1.6 cases per 100,000 males and a case fatality rate between 7 and 20%.[66]

Predisposing factors are peripheral vascular disease, hypertension, renal insufficiency, trauma, diabetes mellitus, alcoholism, malnutrition, smoking, obesity, immunocompromised status,

intravenous drug abuse, malignancy and spinal cord injury; elderly patients with poor self-care and poor nutritional status are more susceptible to infection than general population. FG has an identifiable local cause in approximately 95% of cases and the most common initial port of entry is local trauma or extension of a urinary tract or a perianal infection; anorectal pathologies (perianal/ischiorectal abscess, recent haemorrhoidectomy, rectal injury, perianal fistula and sigmoid colon and rectum carcinoma), are the most common local causes in both males and females.[67]

The onset of symptoms tends to occur over a 2–7-day period; although initially FG could present as indolent cellulitis near the portal of entry, it can rapidly progress to swelling, dramatic pain, fever and signs and symptoms of sepsis. To assess the disease severity a specific score, the Fournier's Gangrene Severity Index (FGSI) has been introduced and validated since 1995. Like LRINEC score for necrotizing fasciitis, FGSI was obtained by combining clinical signs (temperature, heart and respiratory rates) and laboratory parameters (haematocrit and leukocyte count, serum sodium, potassium, creatinine and bicarbonate). Each parameter is given 0 to 4 points, and FGSI is calculated by adding the points of each parameter. A score greater than 9 is considered sensitive indicator of mortality, with a 75% probability of death.[68]

A wide range of micro-organisms can be involved: typical perineal commensals like Enterobacteriaceae, Bacteroides, *Staphylococcus* spp, and *Streptococcus* spp are the most frequent, but also non fermentative Gram-negative bacilli, anaerobes and fungi are reported as causative agents.

Surgical debridement, early broad-spectrum antibiotics in doses high enough to reach an effective concentration in the infected tissues and appropriate resuscitative measures are the mainstays of treatment.

Principles of clinical pharmacology for SSTIs

On the basis of their different patterns of bactericidal activity, we can divide antibiotics into two major groups: time-dependent or concentration-dependent drugs. Antibiotics such as fluoroquinolones, semi-synthetic macrolides, aminoglycosides, daptomycin and the new lipo-glycopeptides dalbavancin and oritavancin display maximal bactericidal activity when their concentrations are high (high Cmax/MIC or AUC/MIC ratio), even if they are maintained for a relatively short time, and are considered concentration-dependent drugs. Therefore, in order to maximize the exposure these drugs are generally administered at high doses and long intervals (i.e. one single daily dose or no more than two daily doses). On the other hand, antibiotics such as beta-lactams, carbapenems, natural macrolides, glycopeptides, linezolid and tigecycline show time-dependent activity and the free drug concentrations should be maintained above the MIC for the specific pathogen at the infection site for a relatively prolonged time in order to optimize exposure.[69,70]

Moreover we have to remember that for hydrophilic antibiotics only a fraction of the plasma concentration may diffuse into tissue, and the penetration may be even reduced in the presence of co-morbidities such as diabetes (Table 4).[71–89] Consequently, in some clinical circumstances, optimal treatment of SSTIs might require a more aggressive dosing schedule. For time-dependent drugs the application of prolonged or continuous infusion may be helpful, while for concentration-dependent antibiotics higher doses might be effective.[69–91] On the contrary, lipophilic agents may achieve tissue concentrations higher than in plasma and their penetration into the interstitial fluid of soft tissues is usually high and often unaffected by the underlying pathophysiological status (Table 4).[71–89] Therefore, for these drugs a standard dosing approach might be successful in the majority of case.[69–91]

Indeed, the application of pharmacokinetic/pharmacodynamic (PK/PD) principles to these patients has been shown to be of help in optimizing antimicrobial therapy in terms of clinical success and minimal toxicity. Evidence is now accumulating (both experimentally and clinically) that the application of PK/PD principles can also help control antimicrobial resistance by avoiding the exposure of micro-organisms to antimicrobial doses that exert selective pressure rather than eradicate them.[69,90,92]

Non necrotizing infections: therapy

Impetigo

Impetigo (both bullous or non bullous) can be usually treated with topical or oral antimicrobials.

Topical therapy can be performed with either mupirocin or retapamulin, chlortetracycline twice daily for five days. Oral therapy can be a seven-day regimen with an agent active against *Staphylococcus aureus* unless cultures

Table 4 Tissue penetration (skin and skin structures) of antimicrobial drugs (alphabetical order)

Antibiotic	Administration route	Penetration (T/P)%	Method	Reference
Amoxicillin/clavulanic acid	IV	40	CB	69
Amoxicillin/clavulanic acid	PO	76	CB	69
Ampicillin/sulbactam	IV	42	T	69
Cefazolin	IV	11	W	69
Cephalexin	PO	59	CB	69
Cefepime	IV	134	CB	69
Ceftaroline		No data		
Ceftriaxone	IV	53	SB	69
Ceftriaxone	IV	92	SB	70
Ciprofloxacin	PO	57–80	SB	69
Ciprofloxacin	PO	118–121	SB	71
Clindamycin	PO	9	W	69
Clindamycin	PO	24–82	W	72
Dalbavancin	IV	59.6	CB	73
Daptomycin	IV	19–68	CB	69,74
Doxicicline	PO	47	SB	69
Ertapenem	IV	61	SB	75
Gentamicin	IM	31	W	69
Imipenem/cilastatin	IV	30–47	MD	69
Imipenem/cilastatin	IV	51–54	SB	76
Levofloxacin	IV	103	MD	77
Linezolid	IV/OS	104		78
Meropenem	IV	87	SB	69
Oritavancin		No data		
Oxacillin*	IV	19	SB	69
Oxacillin*	IV	11–16	MD	79
Oxacillin**	IV	56	CB	69
Penicillin G	IM	17	W	69
Piperacillin	IV	100	SB	80
Piperacillin/tazobactam	IV	35	CB	69
Rifampin	PO	20	SB	69
Tedizolid	PO	110–120	MD	81
Teicoplanin	IV	49	SB	82
Teicoplanin	IV	63–77	CB	69,83
Teicoplanin	IV	24	W	84
Telavancin	IV	40	CB	85
Tigecycline	IV	74	CB	86
TMP/SMX	PO	37/55	SB	69
Vancomycin	IV	10–30	MD	87

Notes: IM = intramuscular; IV = intravenous; PO = per os
Techniques: CB = cantharidine blisters; SB = suction blister; T = threads; W = skin window; MD = microdialysis
*Data were obtained using cloxacillin
**Data were obtained using flucloxacillin

yield streptococci alone (when oral penicillin is the recommended agent).

Because *S. aureus* isolates from impetigo are usually methicillin susceptible, penicillinase-resistant penicillins or first-generation cephalosporins are good options. When MRSA is suspected or confirmed, doxycycline, minocycline, clindamycin or sulphamethoxazole-trimethoprim (SMX-TMP) can be used.

However, it is unclear if oral antibiotics are superior to topical antibiotics for people with extensive impetigo. Thus, the decision of how to treat impetigo still depends on the number of lesions, their location and the need to limit the spread of infection to other individuals.[5,93–95]

Furuncles and carbuncles

Chronic furunculosis is difficult to treat and there are no convincing data to recommend a specific therapeutic strategy.

For small furuncles, warm compresses to promote drainage are usually sufficient treatment. Larger furuncles, all carbuncles and all abscesses require incision and drainage.

The role of ancillary antimicrobial therapy with anti-staphylococcal drugs in the treatment of furuncles and carbuncles is unclear. If used, empiric antibiotic therapy for furuncles and carbuncles should include drugs with anti MRSA activity in areas of high MRSA prevalence.

Furuncles frequently recur and can be prevented by applying liquid soap containing chlorhexidine gluconate with isopropyl alcohol. In addition, a 1–2 months course of low-dose oral clindamycin (150 mg daily) can be an approach to prevention of recurrent staphylococcal skin infections.

The application of mupirocin for treatment of staphylococcal carriers reduces the incidence of nasal colonization, which in turn reduces the risk of skin infection.[5,93,96]

Animal and human bites: therapy

Prophylactic antibiotics are recommended only for wounds that are considered at high risk of infection in view of their type and location, the species of the biting animal, and the characteristics of the patient. Bite wounds should be cleaned, copiously irrigated with normal saline using a 20-mL or larger syringe or a 20-gauge catheter attached to the syringe. The wound should be explored for tendon or bone involvement and possible foreign bodies.

In 2014, IDSA guidelines[5] about management and therapy of SSTI reported the role of a pre-emptive antibiotic therapy. Animal and human bites that completely penetrate the epidermal layer, as well as bites that involve joints or cartilaginous structures, merit antibiotic prophylaxis with amoxicillin/clavulanate or ampicillin/sulbactam. Treatment is mandatory in a particular setting of patients to prevent life-threatening and/or fulminant infections secondary to animal bites, especially dog and cat bites. Clinical manifestations include meningitis, septic shock, gangrene, pneumonia and disseminated purpura. An early pre-emptive therapy for at least 3–5 days was recommended for (1) immunocompromised patients; (2) asplenic; (3) end-stage liver disease. Aetiology is mainly due to gram-negative bacteria, such *Capnocytophaga canimorsus* and *Pasteurella multocida,* and antibiotic treatment should include parenteral beta-lactam/beta-lactamase inhibitors (principally piperacillin/tazobactam) or carbapenems, ceftriaxone (if present meningitis), also in association with clindamycin.[5]

Cutaneous abscesses

Primary management of cutaneous abscesses should be incision and drainage as highlighted also on IDSA guidelines (strong recommendation).[5] Incision, evacuation of pus and debris, and probing of the cavity to break up loculations provides effective treatment of cutaneous abscesses. A randomized trial comparing incision and drainage of cutaneous abscesses to ultrasonographically guided needle aspiration of the abscesses showed that aspiration was successful in only 25% of cases overall and in <10% with MRSA infections.[97]

In general, antibiotic therapy is not indicated for localized abscesses in patients with presumably normal host defences and lesions <5 cm diameter. Recent studies showed similar outcomes in patients treated with effective antibiotics and those treated with ineffective antibiotics after incision and drainage.[3] The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based on the presence or absence of clinical symptoms such as temperature >38 °C or <36 °C, tachypnea >24 breaths per minute, tachycardia > 90 beats per minute, or white blood cell count >12000 or <400 cells/μL (moderate).[5] An antibiotic active against MRSA is recommended for patients who are immunocompromised and for patients who present with multiple lesions, a large surrounding area of cellulitis, systemic toxicity or lymphangitis.[3]

In geographic areas with a high prevalence of community-associated MRSA (CA-MRSA), a variety of oral agents, such TMP-SMX, clindamycin, tetracyclines (doxycycline and minocycline), linezolid, rifampin, fusidic acid and occasionally, fluoroquinolones (usually in combination with rifampin) have been used in the outpatient setting.[3] A recent randomized clinical trial conducted in five U.S. Emergency Department showed that TMP-SMX administered twice daily for seven days was superior to placebo in outpatient with uncomplicated abscesses that were previously drained.[98] For more serious infections requiring hospitalization, a variety of parenteral agents are available, including vancomycin, teicoplanin, daptomycin, linezolid, tigecycline and telavancin (only in US).[3] More recently new drugs have been approved for ABSSSI and have an important activity against MRSA, especially dalbavancin and tedizolid.

Tedizolid was non inferior to linezolid for an early clinical response evaluated 48–72 h after the beginning of therapy.[7] In ESTABLISH 1 and 2 studies, tedizolid was successfully used to treat ABSSSIs, of whom 20% were cutaneous abscess.[99]

Dalbavancin was recently approved by FDA and EMA with a two dose regimen of 1000 mg followed one week later by 500 mg administered intravenously over 30 min. The DISCOVER 1 and DISCOVER 2 studies showed that once weekly intravenous dalbavancin was non inferior to twice daily vancomycin followed by oral linezolid.[100] One of the strengths of dalbavacin is the prolonged half life which lead the possibility of a single, 1500 mg iv administration.[101]

The main features of anti-MRSA antibiotics for treatment of SSTI, the antibiotic of choice for treatment of ABSSI (erysipelas, cellulitis, cutaneous abscess and surgical infections) and dosages of the main antibiotics used for treatment of SSTIs are reported in Tables 5–7.

Erysipelas

Cases of erysipelas in an adult may be treated with oral or parenteral beta-lactams according to severity of infection.[3,99] Among the oral beta-lactams demonstrating good clinical efficacy are included cefprozil, cefpodoxime proxetil, cefuroxime axetil, cephalexin, cefadroxil and beta-lactam/beta-lactamase inhibitor combinations such as amoxicillin-clavulanate. Fluoroquinolones and clindamycin are also effective as treatment of uncomplicated SSTIs due to susceptible organisms.[3,99] In an acutely ill patient, intravenous administration of a penicillinase-resistant penicillin, a first-generation cephalosporin, or beta-lactam/beta-lactamase inactivator combinations such as amoxicillin-clavulanate is warranted. Recently, some data suggest that daptomycin and linezolid are effective treatments for uncomplicated SSTIs. Finally, treatment of predisposing factors and long-term antimicrobial prophylaxis may be useful to reduce recurrences in selected patients.[3] A recent metanalysis evaluating the role of treatment with a macrolide or lincosamide compared to beta-lactams in patients with cellulitis or erysipelas showed that therapy with these drugs had a similar efficacy and incidence of adverse effects as treatment with a beta-lactam.[56]

Non-inferiority trials have confirmed that novel antibiotics such as linezolid, daptomycin, tigecycline, telavancin and ceftaroline have efficacy comparable to vancomycin with or without aztreonam in SSTIs, including erysipelas and cellulitis due to MRSA.[102–105] There are no specifically designed randomized controlled trials with teicoplanin in

Table 5 Empirical treatment of ABSSI

Antibiotic	Dosage	Route of administration	Frequency of administration	Time of infusion	Duration of therapy	Advantages
Dalbavancin	1000 mg once followed by 500 mg after one week or 1500 mg one dose	intravenous	Once a week or once in all	Over 30 min	One week	Early discharge
Tedizolid	200 mg	Intravenous/oral	Once a day	Over 60 min	Six days	Early switch
Ceftaroline	600 mg	Intravenous	Twice a day	Over 60 min	5–14 days	Tolerability

Table 6 Main features of anti-MRSA antibiotics

Antibiotics	Action	Route of administration	Aderse events	Advantages	Concerns
Trimethoprim-sulphamethoxazole	Cidal	Oral/parenteral	Leukopenia, thrombocytopenia, granulocytopenia, anaemia, hypersensitivity, mild gastrointestinal upset	Most commonly used agent for the outpatient treatment of CA-MRSA infections	The release of thymidine from pus and dead tissue may explain the limited efficacy, thus, drainage is mandatory; lack of activity against group A streptococcal infections, *in vitro* antagonism with rifampin combination; concerning if bacteraemia present in who have staphylococcal infections compared vancomycin, uncertain dosage (2 or 1 double-strength tablets twice daily)
Clindamycin	Slow cidal	Oral/parenteral	Diarrhoea and pseudomembranous colitis	Inhibit toxin production	Resistance is increasing
Doxicycline and Minocycline	Static	Mainly oral	Nausea, vomiting, vestibular effects (headedness, loss of balance, dizziness and tinnitus)	Useful for mixed infections possibly including MRSA	Emerging resistance
Fusidic acid	Static	Oral/parenteral	Thrombophlebitis, jaundice, mild gastrointestinal upset	Inhibit toxin production	Not available in Italy; rapid development of resistance in monotherapy
Rifampin	Cidal	Mainly oral	Turning bodily fluids red, pill oesophagitis, hepatotoxicity, nephrotoxicity (most commonly interstitial nephritis)	Penetrate biofilms and kill organisms in the sessile phaseof growth	Rapid development of resistance in monotherapy, drug interactions
Vancomycin and teicoplanin	Cidal	Only parenteral	Thrombophlebitis, nephrotoxicity, red man syndrome, thrombocytopenia.	Backbone of MRSA infections	MIC increase, routine monitoring, continuous- or intermittent infusion
Linezolid	Static	Oral/parenteral	Thrombocytopenia, anaemia, peripheral and optical neuropathy	High bioavailability, inhibits toxin production	Toxicity risk in prolonged therapy
Daptomycin	Cidal	Only parenteral	CPK level elevation	Penetrates biofilms and kills organismsin the sessile phase of growth	Emerging resistance with low dose in foreign body-related infections
Tigecycline	Static	Only parenteral	Nausea and vomiting	Useful for mixed infections possibly including MRSA	Low serum levels, concern if bacteraemia present
Ceftaroline	Cidal	Only parenteral	As per cephalosporins	Beta-lactam with anti MRSA activity	Beta-lactam with low activity against Gram negatives
Dalbavancin	Cidal	Only parenteral	Nausea and diarrhoea	Early discharge	Long half life in case of adverse events
Tedizolid		Oral/parenteral	Much lower than linezolid	Early switch	Adverse events and emerging resistance of the class

Table 7 Dosage of antibiotics used in the treatment of skin and soft tissue infections

	Dosage	
Antibiotic	Parenteral	Oral
Amoxicillin/clavulanate	2.2 mg/6–8 h	1 g/8 h
Ampicillin/sulbactam	1.5–3.0 g/ 6–8 h	–
Cefazolin	1–2 g/8 h	–
Cephalexin	–	0.5–1 g/6–8 h
Cefepime	2 g/8 h	–
Ceftaroline	600 mg/12 h	–
Ceftriaxone	2 g/24 h	–
Ciprofloxacin	400 mg/8–12 h	500–750 mg/12 h
Clindamycin	600 mg/6–8 h	300–450 mg/6–8 h
Dalbavancin	1000 mg once followed by 500 mg after one week or 1500 mg one dose	
Daptomycin	6–8 mg/kg/ 24 h**	–
Doxicycline	–	200 mg/12 h
Ertapenem	1–2 g/24 h	–
Gentamicin	3–5 mg/kg/24 h	–
Imipenem/cilastatin	0,5–1 g/6–8 h	–
Levofloxacin	500 mg/12–24 h	500 mg/12–24 h
Linezolid	600 mg/12 h	600 mg/12 h
Meropenem	0.5–1 g/6–8 h	–
Minocycline	–	200 mg/12 h
Metronidazole	500 mg/8 h	500 mg/8 h
Moxifloxacin	–	400 mg/24 h
Oxacillin	2 g/ 4 h	–
Penicillin G	2–4 MU/4–6 h	–
Piperacillin/tazobactam	4/0.5 mg/6–8 h	–
Rifampin	600/12–24 h	600/12 or 24 h
Tedizolid	200 mg/24 h	200 mg/24 h
Teicoplanin	6–12 mg/kg/24 h*	–
Tigecycline	50 mg/12 h**	–
Trimethoprim-sulphamethoxazole	160/800 mg/8–12 h	160/800 mg/8–12 h
Vancomycin	30 mg/kg/24 h	–

*6–12 mg/kg /12 h on day 1; **Start: 100 mg first dose.
**Approved at the dosage of 4 mg/kg/24 h, it is currently used at higher dosages.

MRSA cSSTIs, although efficacy has been reported in several retrospective and prospective studies.[106]

The main features of anti-MRSA antibiotics for treatment of SSTI, the antibiotic of choice for treatment of ABSSI (erysipelas, cellulitis, cutaneous abscess and surgical infections) and dosages of the main antibiotics used for treatment of SSTIs are reported in Tables 5–7.

Cellulitis

Treatment should begin promptly with agents effective against the typical Gram-positive pathogens, especially streptococci.[5] If the cellulitis is very early and mild and no significant co-morbidities are present, oral beta-lactams might be sufficient in areas where CA-MRSA is not prevalent.[3] Other available options are macrolides and lincosamides, however resistance to erythromycin and clindamycin are increasing. Fluoroquinolones have been approved for the treatment of most uncomplicated cellulitis but are not adequate for treatment of MRSA infections.[3] For more severe infections, parenteral route is the first choice. Cefazolin is a reasonable choice for an adult.[3] Vancomycin plus either piperacillin-tazobactam or imipenem-meropenem is recommended as a reasonable empiric regimen for severe infections (strong, moderate) as suggested by IDSA guidelines. The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period (strong, high).[5]

If additional bacterial species are likely to be involved in cellulitis after unusual exposures such as human or animal bites, initial therapy might involve beta-lactam/beta-lactamase inactivator combinations such as ampicillin/sulbactam or amoxicillin/clavulanate.[3] In the setting of cellulitis where abrasion or laceration occurred after salt water exposure, where *V. vulnificus* might be the pathogen, treatment with cefotaxime plus doxycycline is effective.[3]

In immunocompromised patients, the combination of a third-generation cephalosporin and doxycycline or minocycline is the better choice in antimicrobial treatment of *V. vulnificus* septicemic patients with haemorrhagic bullous necrotic cutaneous lesion.[3] Fluoroquinolones as single agents are a good oral alternative.[3] Similarly, in the setting of cellulitis after an abrasion or laceration occurring with fresh water exposure, where *Aeromonas hydrophila* might be involved, treatment with ciprofloxacin (along with an antimicrobial targeted to the common pathogens) is indicated; alternatively, a combination of ceftazidime plus gentamicin may be used.[3] Working as a butcher, fish or clam handler, or veterinarian is a risk factor for infection with *Erysipelothrix rusiopathiae* which can be confused with streptococci. While it is usually susceptibile to penicillin, it is intrinsically resistant to glycopeptides.[3] For mild infections, oral amoxicillin is a good choice. For more serious infections, parenteral beta-lactams such as penicillin is effective.[3] For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere in the body, nasal colonization with MRSA, injection drug use, purulent drainage, vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended (strong, moderate).[5]

If MRSA is suspected (both HA – [hospital-acquired] and CA-MRSA), glycopeptides and new antimicrobial options, including linezolid, daptomycin, telavancin (only US) and tigecycline, are available agents.[3] If coverage for both streptococci and MRSA is desired for oral therapy, options include clindamycin alone or the combination of either SMX-TMP or doxycycline with a beta-lactam (e.g. penicillin, cephalexin, or amoxicillin).[1] Dalbavancin and tedizolid also can be administered in the setting of ABSSSIs.

For CA-MRSA, some recommended oral agents are clindamycin, tetracyclines, TMP-SMX, rifampin, fusidic acid (the last two in combination therapy), linezolid, tedizolid and dalbavancin and occasionally, fluoroquinolones.[3]

Finally, in patients with recurrent episodes of cellulitis (despite support stockings and good skin hygiene), with predisposing condition such as oedema, obesity, eczema, venous insufficiency, administration of prophylactic antibiotics, such as oral penicillin or erythromycin bid for 4–52 weeks, or intramuscular benzathine penicillin every 2–4 weeks, should be considered in patients who have 3–4 episodes of cellulitis per year despite attempts to treat or control predisposing factors (weak, moderate).[1] This programme should be continued so long as the predisposing factors persist (strong, moderate).[5]

As anticipated, new antibiotics such as tedizolid, dalbavancin and tigecycline have recently been introduced as options to treat SSTIs, including MRSA cellulitis.

Tedizolid, a novel oxazolidinone with Gram-positive activity including MRSA, is promising because it can be administered daily in oral or intravenous forms, and dalbavancin, a second-generation lipoglycopeptide that covers MRSA, can be administered as infrequently as once weekly. Given the limited use of these agents to date, they should be considered as needed on a case-by-case basis.[100]

In severe non purulent cellulitis, when MRSA aetiology is suspected, tigecycline might be a successful option, although the IDSA guidelines did not recommended at all this drug as an effective treatment despite the favourable results reported by clinical trials and real life experiences.[5,102]

Ceftobiprole medocaril is currently under investigation in phase III trials for the use in cSSTIs. The efficacy of ceftobiprole for the treatment of cSSTIs has been assessed in two large phase III trials by Noel et al. with promising results.[105,106] Ceftobiprole shares many characteristics with ceftaroline, such as the mechanism of action, the spectrum of activity and the tolerability profile, although only approved for CAP and HAP, excluding VAP in Italy.[107,108]

The main features of anti-MRSA antibiotics for treatment of SSTI, the antibiotic of choice for treatment of ABSSI (erysipelas, cellulitis, cutaneous abscess and surgical infections) and dosages of the main antibiotics used for treatment of SSTIs are reported in Tables 5–7.

Surgical site infections

For early SSI without systemic signs, incision and drainage (I&D) remain the most important aspects of therapy. Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with I&D may be beneficial for surgical site infections associated with a significant systemic response. Antibiotic treatment recommendations are based on the site of operation. Where the prevalence of methicillin resistance is high, an antibiotic with activity against MRSA is mandatory. Glycopeptides, both vancomycin and teicoplanin, remain the gold standard of therapy for serious MRSA infections.[3] However, there is great controversy over the current utility of these agents, the backbone of treatment for MRSA infections.[3] There is a growing body of evidence indicating that the glycopeptide minimum inhibitory concentration (MIC) has real impact on patient outcomes.[3] Between 2000 and 2006, in a single centre in the USA, patient samples from debridement of SSTIs revealed that there was a significant increase in the overall incidence of MRSA, leading to greater use of empirical vancomycin. Over the same period the proportion of MRSA isolates with a MIC of <0.5 mg/mL decreased from 100% in 2003 to only 62% in 2006, at which time 31% of isolates had a MIC = 2 mg/mL (165). However, the evidence that this phenomenon is causing serious problems in cSSTIs is not clear (166). Newer antibiotics with activity against MRSA have been introduced: linezolid, daptomycin, telavancin, tigecycline, ceftaroline, dalbavancin and tedizolid. Linezolid is an alternative to glycopeptides in the management of serious cSSTIs due to Gram-positive pathogens.

Whereas prospective randomized clinical trials comparing the two agents have shown non-inferiority, an open-label study revealed that in a subset of patients infected with MRsA vancomycin achieved significantly lower cure rates (~67%) than linezolid.[3] However, some recent studies showed that linezolid was more effective than vancomycin in the treatment of cSSTIs due to MRSA.[3] in addition, drugs that inhibit toxin production (linezolid and clindamycin) as opposed to acting on the cell wall (beta-lactams, glycopeptides) may, at least on theoretical grounds, be preferred for this subset of patients as an agent acting on the cell wall may promote toxin release.[3] Finally, the possible superiority of linezolid in patients with proven complicated MRSA infection and in SSTIs, along with its availability as an oral agent with a high bioavailability, may also facilitate early hospital discharge and provide another cost effective alternative where appropriate.[3]

Daptomycin 4 mg/kg i.v. every 24 h for 7–14 days was compared with conventional antibiotics (ssP or vancomycin) in two randomized, international trials involving 1092 patients with complicated SSTIs. Among 902 clinically evaluable patients, clinical success rates were 83.4% and 84.2% for the daptomycin- and comparator-treated groups, respectively. Among patients successfully treated with i.v. daptomycin, 63% required only 4–7 days of therapy, compared with 33% of comparator treated patients ($p < 0.0001$).[3] In a subsequent open-label study of daptomycin compared with vancomycin in patients prospectively evaluated with cSSTIs at risk of MRSA, a higher proportion of patients treated with daptomycin had complete resolution of infection (77%) than those treated with vancomycin (42%); the resolution of signs was quicker and the duration of intravenous therapy was shorter 170. More recently, Bliziotis et al. performed a meta-analysis to compare rates effectiveness and toxicity of daptomycin with that of other antimicrobials for the treatment of SSTIs. The authors found that no statistically significant difference between daptomycin and comparators regarding clinical success in clinically evaluable, intention-to-treat population, MRSA-infected patients, and those with cSSTIs. Two

studies reported that significantly fewer patients with cSSTIs required prolonged treatment in the daptomycin arm and that clinical cure was faster than with comparators. No difference between the compared regimens was found in other outcomes.[3] The safety and efficacy of tigecycline versus vancomycin/aztreonam were determined in two phase 3, double-blind studies in hospitalized adults with complicated SSTIs. Clinical responses to tigecycline and vancomycin/aztreonam at test-of-cure evaluation were similar: 79.7 vs. 81.9% as were the responses of the clinically evaluable population: 86.5 vs. 88.6%.[125] Of note, the FDA and EMA have recently given a warning on the use of tigecycline in the treatment of severe infections, including cSSTIs.

Among the new drugs, ceftaroline is a novel option in the treatment of SSI due to MRSA or when risk factors for MRSA are high with a dosage of 600 mg q12 h.[5] Two multicentre, double-blind randomized clinical trials, CANVAS 1 and 2, evaluated the efficacy of ceftaroline compared to patients treated with vancomycin plus aztreonam in complicated SSTIs. Ceftaroline was non-inferior and had a low incidence of serious adverse event.[103,104]

Tedizolid and dalbavancin are also effective treatments including those caused by MRSA and were approved by the U.S. FDA in June 2014. Two randomized, double-blinded, phase-III trials (ESTABLISH-1 and ESTABLISH-2) demonstrated that a 6-day course of tedizolid was statistically non inferior to a 10-day course of linezolid for the treatment of cSSTIs. The major advantages of tedizolid over linezolid are the lower risk of myelotoxicity *a*nd drug-drug interactions.[109,110]

Despite the favourable results reported by clinical trials in 2010 the U.S. FDA issued a warning regarding an increased risk of mortality associated with tigecycline use in the treatment of severe infections.[109] Real-life studies, however, have subsequently demonstrated that tigecycline used alone or in combination provides good clinical outcomes in patients with cSSTIs, even when a high severity of illness is present.[111,112,113]

Moreover, low mortality rates have been observed in patients with cSSTIs treated with tigecycline and a secondary analysis of clinical trials assessing the association of baseline factors (including antibiotic treatment) with clinical failure and mortality in patients with cSSTIs showed that tigecycline was not a significant risk factor for clinical failure. Nowadays, because of the progressive increase in antimicrobial resistance and the lack of therapeutic options, tigecycline plays an important role for the empirical and targeted treatment of cSSTIs among patients with polymicrobial infections or high suspicion for multidrug-resistant pathogens, including complicated infections.[114]

The main features of anti-MRSA antibiotics for treatment of SSTI, the antibiotic of choice for treatment of ABSSSIs (erysipelas, cellulitis, cutaneous abscess and surgical infections) and dosages of the main antibiotics used for treatment of SSTIs are reported in Tables 4, 5 and 7.

Recurrent non necrotizing infections: therapy

In this setting of patients with one or more episodes of recurrent cellulitis, it was demonstrated the efficacy of benzathine penicillin G in preventing recurrence of infection, but the protective effect diminished progressively once drug therapy was stopped.[115]

Low-dose prophylactic penicillin given for a period of 12 months could reduce significantly the risk of recurrence over a 3-year period.

Management of recurrent furunculosis is considered a public health problem related to nasal colonization by *Staphylococcus aureus*; prophylaxis of infective episodes involves several measures, considering that infection might recur in different body areas: antibiotic treatment, general skin care (using antibacterial soap and water with a careful hand washing if contact with lesions), care of clothing, and care of dressings (covering lesions to prevent autoinoculation). Nasal decolonization of MRSA is the most important measure to prevent infection: intranasal application of a 2% mupirocin twice daily for five days can eliminate *S. aureus* carriage.[116]

Other strategies for patients and their household members are based on application of 4% chlorhexidine gluconate solution to all body parts (excluding face, open wounds, and mucous membranes) followed by rinse with water daily for 5 days.[117]

Antibiotic therapy for approximately seven days is based on oral rifampin, but such therapy can lead to rapid selection of rifampin-resistant strains. Association with doxycycline or minocycline is preferable. Finally, oral therapy with clindamycin for 10 days is considered an alternative option.

Among infections of particular skin structures, pilonidal cysts usually occur in young men, with a role for genetic predisposition, or people who sit for prolonged periods of time (for example in sedentary works); infection of the cyst should be drained through a small incision or removed surgically with complete resolution of infection; however, complications such as sacrococcygeal or lumbar osteomyelitis with epidural abscess and a life-threatening myonecrosis after excision have been reported.[118]

Of importance, there are no data about a standard antibiotic therapy or prophylaxis that however should cover aerobic Gram-negative bacilli and *S. aureus* (i.e. amoxicillin-clavulanate).[10]

Another example of these kinds of infections is abscesses of the Bartholini gland. Combined therapy of antibiotic therapy (i.e. amoxicillin-clavulanate) and marsupialization, a surgical procedure in which Bartholini cyst remains permanently opened, has been associated with lower rate of recurrence but not definitive elimination of risk of recurrence.[119]

Necrotizing infections: therapy

Pyomyositis

Treatment consists of antibiotic therapy combined with incision and drainage of the abscess.[3] The beta-lactam class of antibiotics is frequently used for the treatment of pyomyositis. Antibiotic therapy includes SSP, first-generation cephalosporins and beta-lactam/beta-lactamase inactivator combinations such as amoxicillin-clavulanate.[3] However, myositis secondary to MRSA has also been described.[3] Therefore, empirical therapy might include a glycopeptide or another agent which covers MRSA such as ceftaroline and/or daptomycin or dalbavancin.[106,120–124]

Other antimicrobials, such as aztreonam, fluoroquinolones, aminoglycosides or later generation cephalosporins, alone or in combination, have also been used with good results.[3]

Clostridial myonecrosis

Antibiotic therapy has traditionally consisted of high-dose intravenous penicillin. Currently, clindamycin is often added to penicillin on the basis that the combination of penicillin with clindamycin has been shown to provide greater efficacy than either agent alone.[3]

Hyperbaric oxygen has been reported to reduce associated tissue loss and mortality; however, the mainstay of treatment is surgical debridement, and this should never be delayed while arrangements for hyperbaric oxygen treatments are made.[3]

Necrotizing fasciitis

Once the diagnosis of necrotizing fasciitis is confirmed, the treatment is initiated without delay.[125,126] Because of the complexity of this disease, a team approach that should include a surgeon, an infectious disease specialist and a pathologist/microbiologist is recommended. Haemodynamic parameters should be closely monitored, and aggressive resuscitation initiated immediately if needed to maintain haemodynamic stability. The treatment for necrotizing fasciitis involves the principles of treatment for any kind of surgical infection: source control, antimicrobial therapy, support and monitoring.[3] Immediate surgical debridement is mandatory because a prompt surgery ensures a higher likelihood of survival. A regimen of surgical debridement is continued until tissue necrosis ceases and the growth of fresh viable tissue is observed. In addition, early surgical treatment may minimize tissue loss, eliminating the need for amputation of the infected extremity.[3] If a limb or organ is involved, amputation may be necessary because of irreversible necrosis and gangrene or because of overwhelming toxicity, which occasionally occurs. Empiric antibiotics should be started immediately. Initial antimicrobial therapy should be broad-based, to cover aerobic Gram-positive and Gram-negative organisms and anaerobes. A foul smell in the lesion strongly suggests the presence of anaerobic organisms. The maximum doses of the antibiotics should be used, with consideration of the patient's weight and liver and renal status. Empiric antibiotic therapy can be employed until wound culture isolates are identified. 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 and ciprofloxacin.[3] Possible other regimens include a combination of penicillin G and an aminoglycoside (if renal function permits), as well as clindamycin (to cover streptococci, staphylococci, Gram-negative bacilli, and anaerobes). In addition, clindamycin inhibits M protein and exotoxin synthesis by GABHS.[3] The association of a third-generation cephalosporin or ceftazidime/avibactam with an anti-anaerobic agent (metronidazole or clindamycin) can be a useful option.[104,124] For necrotizing fasciitis caused by GABHS, high-dose penicillin and clindamycin appear to be the treatment of choice.[3] Glycopeptides, linezolid, tigecycline, and daptomycin and dalbavancin[91] are alternative options in patients with risk factors for MRSA infections. Of note, daptomycin can be useful in the management of necrotizing fasciitis because exhibits a rapid and concentration-dependent bactericidal activity against a broad spectrum of Gram-positive pathogens including MRSA. Improved survival was documented with the administration of intravenous immunoglobulin for treating

Table 8 Antibiotic treatment of necrotizing infections by aetiology

Type of infecton	Therapy
Necrotizing fasciitis by mixed pathogens	Ampicillin/sulbactam plus Clindamycin and Ciprofloxacin or Piperacillin/tazobactam or carbapenems or fluoroquinolonones or third-generation cephalosporins or Ceftazidime/avibactam or aminoglycosides plus anti-anaerobic agent*
Necrotizing fasciitis by GABHS	Penicillin plus Clindamycin or glycopeptides or Linezolid or Tigecycline or Daptomycin or Dalbavancin
Nectrotizing fasctitis by *S. aureus*	Oxacillin or first-generation cephalosporin or glycopeptides or Linezolid or Tigecycline or Daptomycin or Ceftaroline or Dalbavancin
Clostridial myonecrosis	Penicillin plus Clindamycin

Table 9 Empirical antibiotic treatment of necrotizing infection

Necrotizing fasciitis	Antibiotic choice
Synergistic (aerobic and anaerobic pathogens)	Imipenem Meropenem Piperacillin/tazobactam
Penicillin allergy (skin rash only)	Cefepime + Metronidazole
Penicillin allergy (anaphylaxis)	Ciprofloxacin + Metronidazole
If *Staphylococcus aureus* is suspected	Add: Vancomycin or Daptomycin
New anti-staph alternatives	Dalbavancin Ceftaroline

streptococcal[127] and staphylococcal SSTIs, and their use is based upon a potential benefit and is related to binding of Gram-positive organism exotoxins[3] (Tables 8 and 9).

Well-controlled, randomized clinical trials demonstrating a statistically significant benefit of hyperbaric oxygen are lacking, however, and consequently its use as an adjunctive therapy for necrotizing fasciitis remains controversial.[3,128]

Conclusions

SSTIs have become one of the major causes for ambulatory physical visit, especially in the Emergency Room, and the number of hospitalizations substantially increased in the last few years. *S. aureus* is the most common cause of SSTIs worldwide with high percentage of MRSA in some part of the word including CA-MRSA.

While no substantial change and/or innovation has been proposed in the last five years for the general approach to the diagnosis of SSTIs, the recent approval by FDA in USA and EMA in Europe of new antibacterial anti-staphylococcal agents (including MRSA) for empirical treatment of ABSSSIs will probably change significantly the therapeutic approach to these infections.

These new drugs (dalbavancin and tedizolid) suitable for early discharge and early switch from parenteral to oral treatment will change the management of these infections with a considerable reduction of hospitalization costs and related risks.[129–133]

Disclosure statement

No potential conflict of interest was reported by the authors.

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