Complicated skin and soft tissue infection

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Skin and soft tissue infections (SSTIs) are common, and complicated SSTIs (cSSTIs) are the more extreme end of this clinical spectrum, encompassing a range of clinical presentations such as deep-seated infection, a requirement for surgical intervention, the presence of systemic signs of sepsis, the presence of complicating co-morbidities, accompanying neutropenia, accompanying ischaemia, tissue necrosis, burns and bites. *Staphylococcus aureus* is the commonest cause of SSTI across all continents, although its epidemiology in terms of causative strains and antibiotic susceptibility can no longer be predicted with accuracy. The epidemiology of community-acquired and healthcare-acquired strains is constantly shifting and this presents challenges in the choice of empirical antibiotic therapy. Toxin production, particularly with Panton–Valentine leucocidin, may complicate the presentation still further. Polymicrobial infection with Gram-positive and Gram-negative organisms and anaerobes may occur in infections approximating the rectum or genital tract and in diabetic foot infections and burns.

Successful management of cSSTI involves prompt recognition, timely surgical debridement or drainage, resuscitation if required and appropriate antibiotic therapy. The mainstays of treatment are the penicillins, cephalosporins, clindamycin and co-trimoxazole. β-Lactam/β-lactamase inhibitor combinations are indicated for polymicrobial infection. A range of new agents for the treatment of methicillin-resistant *S. aureus* infections have compared favourably with the glycopeptides and some have distinct pharmacokinetic advantages. These include linezolid, daptomycin and tigecycline. The latter and fluoroquinolones with enhanced anti-Gram-positive activity such as moxifloxacin are better suited for polymicrobial infection.

Keywords: antibiotic treatment, MRSA, PVL, linezolid, daptomycin, tigecycline, moxifloxacin

Introduction

Skin and soft tissue infections (SSTIs) are ubiquitous and the most common of infections, suffered by everyone at some point to a lesser or greater degree and encountered by all doctors. SSTIs reflect inflammatory microbial invasion of the epidermis, dermis and subcutaneous tissues. Indeed, the classical signs of inflammation were described in SSTI by Celsus in the first century as calor, rubor, tumor and dolor (heat, redness, swelling and pain). To these four signs is often added a fifth—fluor (discharge). The skin is the largest organ of the body and, with the underlying soft tissue, which includes the fat layers, fascia and muscle, represents the majority of the tissue in the body. It acts as a tough, flexible, structural barrier to invasion.[1]

The skin is colonized with an indigenous microbial flora, which typically consists of a variety of species of staphylococci, corynebacteria, propionibacteria and yeasts, in numbers that may vary from a few hundred to many thousands per square centimetre in the moister areas such as the groin and axillae.[1] The normal flora may act as a competitive inhibitor of pathogenic microbes. Breaks in the skin, such as leg ulcers, burns and surgical or traumatic wounds, allow colonization with a broader range

of bacteria. Colonization of ulcers does not usually result in inflammation, but occasionally infection of the surrounding tissues may result from lateral spread of the colonizing organisms. Clinically, it is important to distinguish between colonization, which does not require antibiotic treatment, and infection, which might.[2] Antibiotic stewardship and appropriate use of these therapeutic agents is so important to bacterial ecology and future public health that all physicians must consider in every case of SSTI whether antibiotics are clinically indicated.[3] Colonization of skin surfaces or broken skin should never require systemic antibiotics, although it would appear from a major survey on the practice of managing methicillin-resistant *Staphylococcus aureus* (MRSA) infection in Europe that a significant proportion of practitioners treat MRSA-colonized ulcers with systemic antibiotics.[4]

Direct infection of the skin occurs by invasion of the epidermis, usually after damage to the skin, and infection may affect any anatomical layer (Table 1). Microbial disease of the skin may also occur by haematogenous spread of bacteria (e.g. meningococcal rash or rickettsial macules in tick typhus) or viruses (measles or chickenpox for instance), or by toxin-mediated damage from an infection elsewhere in the body (such as staphylococcal scalded skin syndrome or streptococcal scarlet

fever). Table 2 gives examples of skin manifestations of systemic disease.

SSTIs are best classified according to the anatomical site of infection (Table 1). Alternatively, they may be classified according to their microbial aetiology or by severity.[5] The practice guidelines of the Infectious Diseases Society of America (IDSA) for the diagnosis and management of skin and soft tissue infections[6] classifies SSTIs into five categories, comprising superficial, uncomplicated infection (includes impetigo, erysipelas and cellulitis), necrotizing infection, infections associated with bites and animal contact, surgical site infections and infections in the immunocompromised host. By contrast, Eron et al.[7] classify these infections according to the severity of local and systemic signs, thereby developing a system that guides the clinical management and treatment decisions for patients with SSTIs. They divide patients with SSTIs into four classes based on the criteria shown in Table 3.

Definitions

Complicated SSTIs (cSSTIs), which are the focus of this review, are a somewhat false distinction as they represent the more severe end of the spectrum of all SSTI, including everything apart from the superficial, uncomplicated infection in the IDSA guidelines,[6] or Class 2 onwards in the Eron classification.[7]

cSSTIs therefore represent a heterogeneous package of disorders: from otherwise healthy people with severe infection to patients with major co-morbidities and relatively minor infection; patients with extensive cellulitis and systemic symptoms who can be managed with antibiotics alone to patients with necrotizing limb-threatening infection that requires life-saving surgery; diabetic foot infections to cutaneous anthrax in an intravenous drug user. It is a very mixed clinical group with even greater variation in the aetiology.

In the USA, the Food and Drug Administration (FDA) issues guidance to the pharmaceutical industry with regard to developing the protocols for trials in this clinical area,[8] and it is largely through clinical trials that the concept of cSSTI has evolved. Licensing of most new antibiotics follows the successful demonstration in clinical trials of their efficacy for treatment of cSSTIs. The FDA guidance regards infections that can be treated by surgical incision alone, such as cases of isolated (meaning one solitary area of infection) furunculosis or folliculitis, as uncomplicated infections that should not be included in clinical trials. In contrast, the complicated category includes infections either involving deeper soft tissue or those requiring significant surgical intervention, such as infected ulcers, burns and major abscesses or a significant underlying disease state that complicates the response to treatment. Superficial infections or abscesses in an anatomical site such as the rectal area, where the risk of

Table 1. Types of infection affecting skin and soft tissue structures

Anatomical structure	Infection	Microbial cause
Epithelium	varicella	varicella zoster virus
	measles	measles virus
Keratin layer	ringworm	dermatophyte fungi (*Microsporum*, *Epidermophyton*, *Trichophyton*)
Epidermis	impetigo	*Streptococcus pyogenes*
		S. aureus
Dermis	erisipelas	*S. pyogenes*
Hair follicles	folliculitis, boils, carbuncles	*S. aureus*
Sebum glands	acne	*Propionibacterium acnes*
Subcutaneous fat	cellulitis	β-haemolytic streptococci
Fascia	necrotizing fasciitis	*S. pyogenes* or mixed anaerobic infection
Muscle	myositis	toxigenic strains of *S. aureus*
	gangrene	*C. perfringens*

Table 2. Examples of systemic infections causing skin manifestations

Pathogen	Disease	Skin manifestation
Varicella zoster virus	chickenpox	vesicles
S. aureus	toxic shock syndrome	rash and desquamation
	scalded skin syndrome	
Streptococcus pyogenes	scarlet fever	erythematous rash
Neisseria meningitidis	meningococcal sepsis	non-blanching petechiae or haemorrhagic rash
Salmonella typhi	enteric fever, typhoid	rose spots
P. aeruginosa	septicaemia	ecthyma gangrenosum
Rickettsia conorii	African tick typhus	macular rash
Cryptococcus neoformans	cryptococcosis	papule on face or trunk

anaerobic or Gram-negative pathogen involvement is higher, should be considered complicated infections.

SSTIs accompanied by signs and symptoms of systemic toxicity such as fever, hypothermia, tachycardia (>100 beats/min) and hypotension (systolic blood pressure <90 or 20 mmHg below baseline) can be classified as complicated.[6,7] In addition, infection in patients likely to require admission to hospital to stabilize their clinical condition and prevent progression of the disease can likewise be classified as cSSTIs. Initial investigations should include blood cultures, full blood count and measurement of C-reactive protein, creatinine, bicarbonate and creatine phosphokinase levels. Soft tissue cultures should be done where possible. If there is evidence of rapid spread of infection an early surgical review is essential to assess the requirement for debridement and drainage.[6,7] Sepsis accompanying SSTI requires prompt diagnosis and treatment.[9]

Aetiology and epidemiology

Common pathogens

The vast majority of SSTIs are caused by *S. aureus*[10] and β-haemolytic streptococci, usually Lancefield groups A, C and G, with group B occurring in diabetics and the elderly.[5,6] Clinically, the microbial aetiology can often be predicted with some accuracy in uncomplicated SSTI. Localized pus-producing lesions such as boils, abscesses, carbuncles and localized wound sepsis are usually staphylococcal, while rapidly spreading infections such as erysipelas, lymphangitis or cellulitis are usually caused by β-haemolytic streptococci.

Bacteria associated with SSTIs in hospitalized patients have been recorded over some years in the SENTRY Antimicrobial Surveillance Program database (Figure 1).[11] The predominant

Table 3. Classification of SSTI according to the severity of local and systemic signs, and associated management[7]

| Category	Clinical features	Management
Class 1	SSTI but no signs or symptoms of systemic toxicity or co-morbidities	drainage (if required) and oral antibiotics as outpatient
Class 2	either systemically unwell or systemically well but with co-morbidity (e.g. diabetes) that may complicate or delay resolution	oral or outpatient intravenous antibiotic therapy; may require short period of observation in hospital
Class 3	toxic and unwell (fever, tachycardia, tachypnoea and/or hypotension)	likely to require inpatient treatment with parenteral antibiotics
Class 4	sepsis syndrome and life-threatening infection (e.g. necrotizing fasciitis)	likely to require admission to ICU, urgent surgical assessment and treatment with parenteral antibiotics

ICU, intensive care unit.
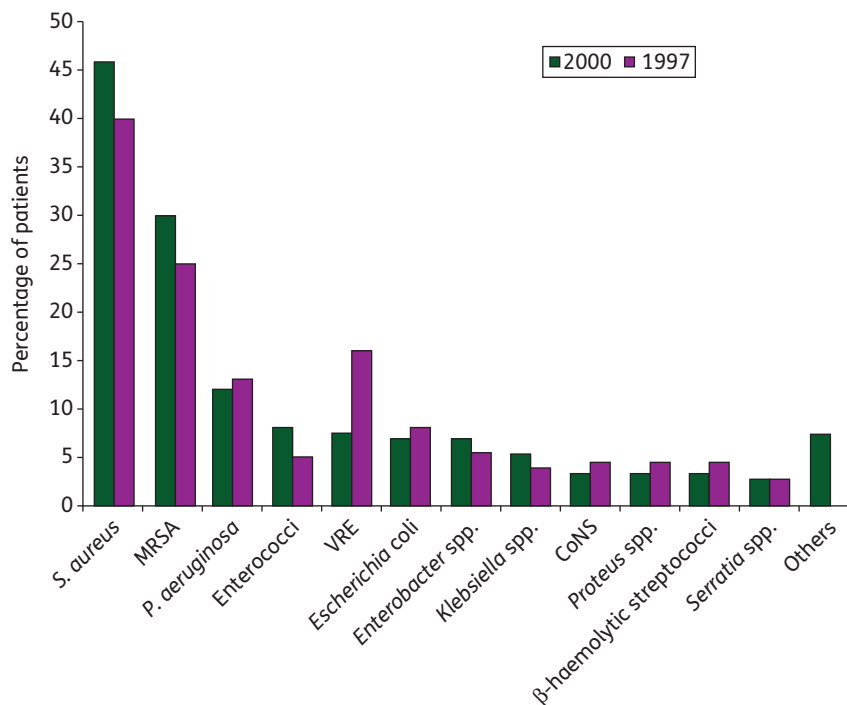
Figure 1. Frequency of pathogens isolated from SSTIs among hospitalized patients in the SENTRY Antimicrobial Surveillance Programs.[11] Adapted from Dryden MS. *Int J Antimicrob Agents* 2009; **34** Suppl 1: S2–7.[2]

pathogens included *S. aureus* (ranked first in all geographical regions), *Pseudomonas aeruginosa*, *Escherichia coli* and *Enterococcus* spp. The broad range of bacterial species reflects the fact that this group of patients is hospitalized and that it is a laboratory-based survey without direct clinical assessment of the relevance of the isolate to the clinical condition. As a result some of the isolates reported may not necessarily have been the causative pathogens. Gram-negative and anaerobic bacteria are more common in association with surgical site infections of the abdominal wall or infections of the soft tissue in the anal and perineal region. Polymicrobial infections involving both Gram-positive and Gram-negative organisms occur particularly where tissue vascular perfusion is compromised, such as diabetic foot infection or infection of ischaemic or venous ulcers. Chronic infections, especially in patients previously treated with antibiotics, are likely to be polymicrobial with Gram-negative and obligate anaerobic pathogens found alongside Gram-positive organisms. Such infections with Gram-positive and Gram-negative microbes clearly require broad-spectrum antibiotic treatment.

Antibiotics and surgical drainage are the basis of treatment for staphylococcal infections, but the emergence of strains with resistance to multiple agents has complicated the choice of empirical therapy. It is therefore important that a local knowledge of the epidemiology and susceptibility of pathogens guides the development of antibiotic guidelines for empirical treatment. Methicillin resistance was first detected in *S. aureus* in 1961,[12] shortly after the agent was introduced clinically, and over the last four decades there has been a global epidemic of MRSA.[13,14] Considerable variation in the resistance rates of *S. aureus* to methicillin (or oxacillin) has been noted between countries and continents, with the highest rates in North America (35.9%), followed by Latin America (29.4%) and Europe (22.8%).[11] Although these figures probably reflect hospital-acquired infection there has undoubtedly been an increase in true community-acquired MRSA (CA-MRSA) infection in parts of North America[15,16] and this trend may now be shifting to Europe.[17] In parts of North America this increase in CA-MRSA represents a major change in the epidemiology of staphylococcal infections.[15,18] In Texas, the majority of patients hospitalized with community-associated *S. aureus* infections had MRSA, most of which involved an SSTI. In a Californian clinic 83% of 837 positive cultures from SSTIs were *S. aureus* and of these 76% were MRSA.[19] In a study of 422 patients with SSTIs presenting at emergency rooms across the USA, 59% (range 20%–74%) of the cases were due to CA-MRSA.[20]

Having recurrent infections, being a child, a member of the armed forces, an athlete or an injecting drug user are recognized risk factors for infection with CA-MRSA in the USA;[21] similar risk factors are apparent in Europe as well.[22–26] CA-MRSA infection occurs in younger patients and has a significant association with SSTI,[22] while hospital attendance, surgery, dialysis, diabetes, indwelling devices and residence in a long-term care facility were risks associated with hospital-acquired (HA)-MRSA.[16,21] However, no clinical profile could reliably exclude MRSA.[23] In the Netherlands, people in contact with pigs have a higher risk of MRSA carriage than the general population,[24] but by and large, with the exception of a few small outbreaks,[20–26] CA-MRSA remains focal and contained within Europe in 2010. Should this change, which is likely, European infection doctors believe that empirical therapy for community SSTI would have to be changed.[4]

Although a number of criteria have been proposed to predict the likelihood of infection with CA-MRSA,[16,17] epidemiological and clinical criteria are rarely sufficient to distinguish accurately between MRSA and methicillin-susceptible *S. aureus* (MSSA) infection at initial presentation.[27] The boundaries between HA-MRSA and CA-MRSA are becoming blurred due to the movement of patients and infections between hospitals and the community.[28] Nosocomial outbreaks of CA-MRSA following the admission of colonized or infected patients have occurred.[29] In the USA, it is becoming increasingly difficult to distinguish between CA-MRSA and HA-MRSA on clinical and epidemiological grounds.[21,27] Since HA-MRSA and CA-MRSA strains are often genotypically and phenotypically different, the microbiological characteristics of the isolates may help to distinguish between the two types of infection.[16,23,29] For example, CA-MRSA may be susceptible to a wider range of antibiotics (Table 4).[23]

Antibiotic resistance is not limited to methicillin (Table 4). However, staphylococcal resistance to glycopeptides remains rare,[30] although rising MICs of glycopeptides may affect the efficacy of these agents.[31] Resistance in strains of MRSA to the more recently licensed anti-MRSA antibiotics linezolid, daptomycin and tigecycline also remains remarkably uncommon. The evolution of strains causing SSTI and serious infection is rarely static and strains of apparently susceptible (at least phenotypically susceptible) but *mecA* gene-positive *S. aureus* have emerged to challenge diagnostic laboratories and clinicians.[32] Selection pressure and microbial evolution are rarely predictable!

Unusual pathogens

With most community-acquired SSTIs being caused by staphylococci and streptococci it is easy to ignore more unusual causes. Clinical history and risk factors are important when considering such cases (Table 5). Of particular importance is the presence of underlying disease, previous hospital admissions, animal contact and bite history, injecting drug use and travel. For example, a history of travel with water contact may hint at a diagnosis of an infection with a *Vibrio* spp.[33] (which will not be

Table 4. Examples of characteristics of CA-MRSA and HA-MRSA from US strains[23]

Characteristic	CA-MRSA	HA-MRSA
Susceptibility to CHL	usually S	often R
Susceptibility to CLI	usually S	usually R
Susceptibility to ERY	usually R	usually R
Susceptibility to FLQ	usually S	usually R
Susceptibility to SXT	usually S	usually S
SCCmec type	IV	II
Lineage	USA 300, USA 400	USA 100, USA 200
Toxin production	more	fewer
PVL production	common	rare
Healthcare exposure	less common	more common

S, susceptible; R, resistant; CHL, chloramphenicol; CLI, clindamycin; ERY, erythromycin; FLQ, fluoroquinolones; SXT, cotrimoxazole.

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Table 5. Risk factors for SSTIs caused by specific pathogens

Risk factor	Characteristic pathogens
Recurrent hospital admissions	MRSA
Contact sports, recurrent boils/ abscesses, visit to certain States in the USA	MRSA or MSSA producing PVL
Diabetes	*S. aureus* (MRSA and MSSA), Group β-haemolytic streptococci, anaerobes, Gram-negative bacilli
Neutropenia	Gram-negative bacilli, *P. aeruginosa*
Bite wounds	
human	human oral flora
cat	*Pasteurella multocida*
dog	*Capnocytophaga canimorsus*
rat	*Streptobacillus moniliformis* (also consider tetanus and rabies)
Animal contact	*Campylobacter* spp. dermatophyte infection *Bartonella henselae* *Francisella tularensis* *Bacillus anthracis* *Yersinia pestis*
Water exposure (sea, estuarine, rivers)	*Vibrio* spp. *Aeromonas hydrophila* *Mycobacterium marinum* *P. aeruginosa*
Reptile contact	*Salmonella* spp.
Injecting drug use	MRSA *Clostridium botulinum* *Clostridium tetani*
Travel	leishmaniasis cutaneous larva migrans myiasis
tropical Africa	*Cordylobia anthropophaga*
tropical America	*Dermatobia hominis*

adequately treated by empirical antibiotics active against staphylococci and streptococci), while tick bites could suggest rickettsial or borrelia infection. A drug user with an abscess at an injection site is most likely to have a staphylococcal infection, but unusual bacteria such as *Clostridium botulinum* or *Bacillus anthracis* may also be involved.[34] Organisms other than staphylococci or β-haemolytic streptococci may be the cause of SSTIs in patients who have had contact with a dog[35] or have recently returned from adventurous travel in the tropics.[36] It is also important to remember that bacteria are not the only microbes implicated in SSTIs and, in certain circumstances, it is important to consider viral, fungal, protozoal and arthropod causes (Table 5).

Although there is considerable debate over the value of microbiological culture in the management of SSTIs, there can be no doubt that the rise in multiply resistant bacteria and the possibility of unusual causes of SSTI increase the importance of diagnostic microbiology and antibiotic susceptibility testing for epidemiological purposes and the surveillance of antimicrobial resistance.[37] Furthermore, microbiological analysis can help to promote appropriate antibiotic prescribing,[38] and laboratory analysis accompanied by good clinical microbiology support should increasingly be used to promote good antibiotic stewardship.[39] For microbiological diagnosis, pus or tissue samples have the greatest sensitivity[6] and swabs of open, infected wounds can provide valuable diagnostic information if collected before the commencement of antibiotics. Whereas aspiration of the leading edge of cellulitis with a needle is often advocated in North America, this practice is rarely carried out in the UK and is generally deemed too invasive in enclosed cellulitis. Blood cultures should be collected where there are signs of systemic sepsis, such as a raised temperature, tachycardia, hypotension or confusion.

Necrotizing infection

This medico-surgical emergency is a life-threatening, invasive, soft tissue infection caused by aggressive, usually gas-forming bacteria, which primarily involves the superficial fascia and extends rapidly along subcutaneous tissue planes with relative sparing of skin and underlying muscle. Clinical presentation includes fever, signs of systemic toxicity and pain out of proportion to the clinical findings.[40] Paucity of cutaneous findings early in the course of the disease can make diagnosis challenging and confirmation of the diagnosis is often made after surgical debridement. Delay in diagnosis and/or treatment correlates with a poor outcome, leading to sepsis and/or multiple organ failure.[6,7] Plain radiographs, CT or magnetic resonance imaging may help to diagnose necrotizing fasciitis. Prompt surgical debridement, intravenous antibiotics, fluid and electrolyte management, and analgesia are the mainstays of therapy. Adjuvant treatments such as hyperbaric oxygen therapy and intravenous immunoglobulins are sometimes advocated.[6]

Infections caused by toxin-producing bacteria

Strains of *S. aureus* and β-haemolytic streptococci can produce a variety of toxins that may both potentiate their virulence and affect the soft tissues.[41,42] Panton–Valentine leucocidin (PVL) appears to be a marker for severity and recurrence.[20,43,44] Epidermal loss may occur in staphylococcal infections in which there is production of exfoliatin (scalded skin syndrome toxin) or toxic shock syndrome toxin (TSST). In one recent study,[45] 100 *S. aureus* isolates from diverse cases of SSTI were characterized. Virulence factors, including PVL, were detected and the isolates were assigned to clonal groups. Thirty isolates were positive for the gene encoding PVL. Only three PVL-positive MRSA isolates were found, two of which belonged to European clone ST80-MRSA IV and one to USA 300 strain ST8-MRSA IV. The remaining methicillin-susceptible PVL-positive isolates belonged to a variety of different multilocus sequence types. In a large, prospective study of patients with MRSA infection in North America, strains from community-acquired infections, which were most likely to be of the skin and soft tissues, were particularly likely to express exotoxins, especially PVL.[46] Other studies have reported a high incidence of PVL production among strains of CA-MRSA.[20,43,44]

The use of antimicrobials effective against MRSA that also decrease exotoxin production, such as clindamycin and linezolid, is theoretically desirable. Clindamycin decreases the production of TSST-1 by 95% in stationary phase cultures[41] and stops the normal peak of α-toxin production during the late exponential phase of growth.[46] Clindamycin and linezolid both markedly suppress PVL production as staphylococci approach the stationary phase, to the extent that there may be no PVL detectable 12 h after exposure to the antibiotic.[46] Flucloxacillin is bactericidal, but the low, subinhibitory concentrations achievable *in vivo* in necrotic tissue may further augment PVL toxin and α-haemolysin production.[46] Subinhibitory concentrations of clindamycin, linezolid and fusidic acid all induce a concentration-dependent decrease in PVL concentration, whereas low concentrations of oxacillin increase the concentration of PVL up to threefold.[47] The severity of streptococcal infections may also be influenced by the expression of superantigens and virulence factor enzymes.[48]

Infections associated with bites

This review will focus on a brief discussion of aggressive mammals, including humans, and the infections their bites cause. However, there are a good many non-vertebrates and indeed other vertebrates willing to cause trauma and transmit infection. It might be imagined that the least of a victim's problems after a shark attack would be infection but this is not necessarily the case.[49] Snake bites can be more than venomous with *Aeromonas* spp. causing infection[50] and damage of a limb by a crocodilian can also lead to infection.[51]

Human bites can result in serious soft tissue infection. Isolates implicated in human bite infections include *Streptococcus anginosus* (52%), *S. aureus* (30%), *Eikenella corrodens* (30%), *Fusobacterium nucleatum* (32%) and *Prevotella melaninogenica* (22%). *Candida* spp. are found in 8% of SSTIs. *Fusobacterium* spp., *Peptostreptococcus* spp. and *Candida* spp. are isolated more frequently from occlusional bites than from clenched-fist injuries.[52] Infections related to dog bites are often polymicrobial, predominantly involving *Pasteurella* and *Bacteroides* spp.[53] Infected bites presenting <12 h after injury are particularly likely to be infected with *Pasteurella* spp., whereas those presenting >24 h after the event are likely to be infected predominantly with staphylococci or anaerobes. It is important to seek a history of animal contact when *Pasteurella* is isolated.[35] The unusually named *Capnocytophaga canimorsus* (dysgonic fermenter type 2 or DF2) causes septicaemia that is often mistaken for fulminant meningococcal disease. Infection usually follows a trivial bite in patients with asplenia or cirrhosis. Typically, Gram-negative bacilli are seen within polymorphs on peripheral blood films. *Capnocytophaga* is susceptible to penicillin and ciprofloxacin/moxifloxacin.[52,53] Clinical infection may result from incorrect management at the time of primary care and erythromycin or flucloxacillin must never be used alone in the prophylaxis of bite wounds. In one small study, 70% of patients with *Pasteurella multocida* infections had received inadequate or incorrect antibiotics, usually flucloxacillin or erythromycin.[54]

Other considerations in animal bites and contact are rabies, tetanus and infections with unusual organisms of high pathogenicity, such as *Francisella tularensis* or *Bacillus anthracis*.[6]

Travel

A history of travel is important in the assessment of SSTIs. Although the common causes of SSTI—streptococci and staphylococci—are also common in travellers, unusual microbial causes of infection may present in this group.[36] Such infections may be unresponsive to conventional empirical treatment,[33] as in the case of *Vibrio* spp. infection in those exposed to sea and estuarine waters (Table 5). Travel history should be sought and diagnostic microbiology performed. Unusual or non-bacterial infections may present a diagnostic challenge in travellers. Rashes in travellers may be associated with a range of infections, such as primary Lyme disease (erythema chronicum migrans) caused by *Borrelia burgdorferi*; serpiginous tracks caused by hookworm larvae (cutaneous larva migrans); and rickettsial infection, of which the most common presenting in UK travellers is African tick typhus (*Rickettsia conorii*) causing a widespread maculopapular rash associated with systemic symptoms. Persistent ulcers may be caused by atypical mycobacteria or protozoa such as *Leishmania* spp. Enlarging, fluctuant and largely painless abscesses may be caused by arthropod maggot infestation, such as *Cordylobia anthropophaga* from tropical Africa or *Dermatobia hominis* from tropical America. All of these infections or infestations may require specialist medical referral to make the diagnosis and initiate appropriate treatment.

Soft tissue infection in immunocompromised hosts

SSTIs in immunocompromised hosts can be challenging as they can be caused by unusual and diverse organisms.[55] Such infections may progress rapidly to become life threatening and are difficult to eradicate with antibiotics alone in the absence of an intact immune system. Surgical review and follow-up are often advisable. Establishing a diagnosis and performing susceptibility testing is crucial,[6] because many infections are hospital acquired and increasing resistance among both Gram-positive and Gram-negative bacteria makes empirical treatment regimens difficult, if not dangerous. In addition, fungal infections such as cryptococcosis or histoplasmosis may present with cutaneous findings.

Treatment

The management of cSSTIs normally involves a combination of surgical debridement or drainage and empirical antibiotic therapy. The antibiotic management of cSSTIs is well reviewed in the published guidelines.[5–7,17] The main choice of antibiotic depends on the clinical presentation. In probable Gram-positive infection where MRSA is not suspected, penicillins, antistaphylococcal penicillins, cephalosporins, clindamycin or co-trimoxazole are indicated.[6] Where infection is likely to be polymicrobial such as surgical site infections of the abdominal wall, or in proximity to the genital tract or rectum, diabetic foot infections and bites, antibiotic treatment must cover the broad range of pathogens seen in these cSSTIs. Such treatment may include β-lactam/β-lactamase inhibitor combinations, fluoroquinolones with enhanced Gram-positive activity such as moxifloxacin, co-trimoxazole or tigecycline.[2,6] Diabetic foot infections in particular require proper wound care and

early surgical intervention as well as aggressive appropriate antibiotic therapy.

The mainstay of treatment for serious MRSA infections has until recently been the glycopeptides vancomycin and teicoplanin. However, concern about the gradual development of resistance and concerns about efficacy[30,31] have turned attention to the development of new agents active against Gram-positive bacteria. Those that have been licensed for treating cSSTI are linezolid, daptomycin and tigecycline. The range of oral antibiotics used to treat MRSA infections is very wide across Europe,[4] and the choice seems to depend on local susceptibility and personal experience, because there are no comparative trials to support the use of specific older agents. The only new oral agent is linezolid. There is, however, evidence to show that agents such as co-trimoxazole and tetracycline, which are cheap and reasonably well tolerated, have good efficacy against MRSA[56] and the rate of therapeutic failure is low.[57] Clindamycin may also be clinically effective[58] but the rates of resistance may be high and inducible resistance needs to be excluded with the 'D' test.

Newer antibiotics are finding a place in the treatment of cSSTI caused by more resistant strains and indeed many of the randomized clinical trials in cSSTI have been industry sponsored. All these trials have been designed specifically for licensing purposes and therefore have only been powered to show non-inferiority. Linezolid has been available for 10 years now and is well established as an effective agent in cSSTI,[59–63] with the added advantages of early intravenous-to-oral switch with the oral preparation having 100% bioavailability and excellent tissue penetration.[61,64,65] Linezolid use is also associated with significant reduction in the requirement for intravenous treatment and with the length of hospital stay.[63] That study also showed a numerical but not statistically significant superiority of linezolid over vancomycin in the per-protocol group and a significant superiority at the end of study in the modified intention-to-treat group, and this is despite the study being powered for non-inferiority. These efficacy data are supported by a meta-analysis suggesting that linezolid may indeed be superior to the glycopeptides.[66]

Tigecycline is as effective as vancomycin[67,68] and has a broader range of activity, covering infections caused not only by resistant Gram-positive bacteria but also by many multiply resistant Gram-negative organisms including those producing extended spectrum β-lactamases. It is recommended for polymicrobial infection that may include MRSA and for necrotizing fasciitis.[69] It is only available as an intravenous formulation.

Daptomycin has rapid concentration-dependent bactericidal activity against Gram-positive pathogens.[70] Its tissue penetration supports its use in the treatment of cSSTI and daptomycin has been shown to be non-inferior to vancomycin and semi-synthetic penicillins. The registration studies included 1092 patients between the ages of 18 and 85 years with a cSSTI that was due, at least in part, to Gram-positive organisms and required hospitalization and parenteral antimicrobial therapy for at least 96 h.[71]

Moxifloxacin is probably the most effective fluoroquinolone with extended Gram-positive activity on the basis of *in vitro* activity.[72] The IDSA guidelines recommend fluoroquinolones for the treatment of infections that are likely to be polymicrobial,[6] including surgical wound infections involving the abdominal wall, perineum and genital tract. Both animal and human bite infections with their specific and unusual pathogens can also be effectively treated with moxifloxacin. The characteristics of fluoroquinolones in general may explain their demonstrated efficacy in the treatment of cSSTIs. These include a broad spectrum of activity, rapid bactericidal action and adequate tissue concentrations at skin and deep tissue sites. Specifically, moxifloxacin has broad-spectrum activity *in vitro* against all common pathogens implicated in both uncomplicated and complicated SSTIs.[73] Indeed, cSSTI was the first non-respiratory indication for moxifloxacin and the first step towards moving it from the category of a respiratory fluoroquinolone and placing it as a broad-spectrum antibiotic for a range of organisms and conditions. Moxifloxacin has excellent pharmacokinetics and tissue penetration, can be delivered via both intravenous and oral routes allowing a seamless switch and is particularly suitable as monotherapy for infections that are likely to be polymicrobial. The RELIEF study[74,75] demonstrated its efficacy in comparison with intravenous piperacillin/tazobactam and oral co-amoxiclav in a wide range of cSSTIs including deep-seated abscess, diabetic foot infection,[75,76] infected ischaemic ulcers and surgical site infections. Moxifloxacin has good activity against Gram-positive organisms such as *S. aureus* and streptococci with the MIC_{90} values for MSSA ranging from 0.25 to 1.0 mg/L.[77,78] However, while some strains of CA-MRSA are susceptible to fluoroquinolones, many strains are resistant. Moxifloxacin may, therefore, be a treatment option for infection caused by susceptible strains of MRSA, which may be more common in community-acquired infections.[23,79] Given the unpredictability of fluoroquinolone activity against MRSA, the use of fluoroquinolones should be reserved for definitive treatment once antibiotic susceptibilities are known. The RELIEF study demonstrated efficacy of moxifloxacin in cSSTI caused by strains of MRSA even though the MIC_{90} was 2 mg/L.[74,75] Moxifloxacin is also active against Enterobacteriaceae and anaerobes (e.g. *Peptostreptococcus* spp., *Clostridium perfringens*, *Clostridium* spp. and *Bacteroides fragilis*), but has relatively poor activity against *Pseudomonas* spp. Moxifloxacin also has good *in vitro* activity against other pathogens isolated from patients with either animal or human bite infections (e.g. *P. multocida*, coagulase-negative *Staphylococcus* spp., *Prevotella* spp., *Fusobacterium* spp. and *E. corrodens*), and the causes of more exotic cSSTIs, such as *B. anthracis*, *Yersinia pestis*, *Vibrio* spp. and *F. tularensis*.[6,39]

Other promising agents for cSSTI, such as dalbavancin with its exceptionally long half-life, ceftobiprole with broad-spectrum activity including MRSA, and iclaprim (a trimethoprim derivative), have all met with major obstacles in the licensing process. They may be important therapeutic options if these barriers can be overcome.

Conclusions

cSSTIs represent a very varied group of clinical conditions. Of primary clinical and epidemiological interest are those infections caused by *S. aureus* whose predominant causative strains appear to be becoming more resistant and more pathogenic. This convergence of antimicrobial resistance and enhanced virulence requires vigilant epidemiology and creativity in the development of therapeutic options.

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