Clinical Review

Principles and Practice of Antibiotic Therapy for Cellulitis

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Abstract

Cellulitis is a common medical emergency. Investigations often fail to establish the specific microbial aetiology and there are few data to support common choices of antibiotic therapy used to treat cellulitis. Potentially unusual pathogens can be predicted from the epidemiological circumstances at presentation, while empirical treatment choices must be based on an understanding of the underlying pharmacokinetic and pharmacodynamic principles that govern antibiotic-microbe interactions. Animal models have established conditions that predict treatment success, taking into account confounding factors such as bacterial inoculum size. Synergistic combinations of antibiotics can improve outcome in difficult cases.

Keywords

Cellulitis, infection, antibiotics, pharmacodynamic.

Key Points

1. Most cases of cellulitis are caused by Beta-haemolytic streptococci or Staphylococcus aureus.
2. Combinations of intravenous benzylpenicillin and flucloxacillin are appropriate for patients requiring in-patient treatment.
3. Daily outpatient treatment with intravenous ceftriaxone is effective and may reduce the need for hospital admission, where facilities permit.
4. Clindamycin or vancomycin should be considered for patients with documented severe penicillin allergy.

Introduction

Cellulitis is a common medical emergency and accounts for 2.7% of acute general medical admissions to hospital.[1] Diagnosis is often straightforward, and recent reviews have discussed differential diagnosis in more difficult cases.[2] This review focuses on the antibiotic management of patients with cellulitis.

Pathogenesis

The skin is a highly effective barrier, which protects against infection by virtue of its physical characteristics, anti-microbial secretions and resident microbial flora of low virulence. Any disruption to this barrier gives pathogenic bacteria potential access to deeper skin structures and may result in infection. *Cellulitis* describes severe infection that extends beyond the dermis, deep into subcutaneous tissues and often occurs following minor skin trauma. It is more common in those with fungal foot infections and abnormalities of venous or lymphatic drainage. The area is clearly demarcated, hot, red and painful and spreads rapidly via the lymphatics to produce regional lymph-node involvement and systemic symptoms. Severe cellulitis may result in vesiculation and tissue necrosis.

Factors that determine the severity of presentation in cellulitis are poorly understood. Large tissue inocula of bacteria have been proposed as potential explanations for poor response to antibiotic therapy; however, there is poor correlation between tissue density of infecting bacteria and severity of presentation. It is often difficult to isolate bacteria from severe cellulitis caused by ß-haemolytic streptococci and toxin mediated tissue damage may be important. Host susceptibility factors may also be important in determining severity. The role of cellular immunity is not known. However, cellulitis developing in neutropaenic patients is often severe and responds poorly to antibiotic therapy. Humoral immunity appears to afford no protection. A mouse model of cellulitis showed no protective effect of anti-M surface-protein antibodies resulting from previous Group G streptococcal infection.[3]

Schemes to quantify severity in cellulitis are not well developed. Assessment of simple measures, which include determining underlying risk factors, the percentage of limb inflammation and the presence or absence of regional lymphadenopathy, vesiculation and systemic toxicity will aid stratification of cases and will help to guide initial therapy, predict likely duration of therapy and allow better comparison of outcomes.

Aetiology

Recognising the depth of skin structures involved in skin infection is important in assessing severity and may help to identify the specific pathogen. *Impetigo* affects superficial epidermal layers producing thin walled bullae that easily rupture to produce superficial ulceration and crusting exudates. *Staphylococcus aureus* accounts for 70-80% of

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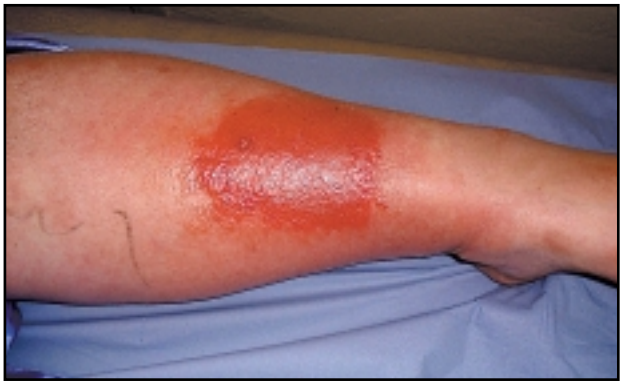

Figure 1. Typical picture of erysipelas. ASO titre was elevated. She responded to 2 days iv ceftriaxone as an outpatient followed by 14 days oral amoxycillin.

infections with ß-haemolytic streptococci accounting for the remainder.[4] *Erysipelas* involves the epidermis, dermis and variable amounts of subcutaneous fat and is characterised by a well-demarcated acute skin lesion with a hard raised leading edge (Figure 1). Erysipelas is almost exclusively caused by ß-haemolytic streptococci of groups A, G and C, but the specific aetiology can usually be confirmed only by specialised immunofluorescent staining of biopsy specimens or by serological tests.[5] *Furunculosis* describes subcutaneous abscesses relating to sebaceous glands or hair follicles and is usually due to *S. aureus* infection. *Pseudomonas aeruginosa* may cause a similar infection in those recently exposed to poorly chlorinated swimming pool water.

Wound infections producing cellulitis are characterised by the mode of injury, including surgery, trauma, bites, scratches and ischaemic ulceration. They may have polymicrobial aetiology.[6] Surgical wound infections are most commonly caused by *S. aureus*. Cellulitis associated with traumatic wounds is often caused by similar pathogens to primary skin infection; however, the specific epidemiological circumstances in which the wound is received may provide clues to identify unusual potential pathogens (Table 1). Puncture wounds to the foot are often infected by *Pseudomonas aeruginosa*, particularly when penetrating sports footwear. Cellulitis resulting from trauma occurring in water may be due to Gram-negative organisms including *Aeromonas hydrophila* and *Vibrio vulnificus*. Animal bites and scratches often become infected, commonly with *Pasteurella multocida* and oral anaerobes. In addition, up to 25% of human bites, particularly those associated with clenched fist injuries become infected with *Eikenella corrodens*.

Clinical infection	Common pathogens
Impetigo	*Staphylococcus aureus*
Erysipelas	β-haemolytic streptococci
Cellulitis	β-haemolytic streptococci, *Staphylococcus aureus*
Furuncles/ folliculitis	*Staphylococcus aureus, Pseudomonas aeruginosa*
Animal bite/ scratch	*Pasteurella multocida, Staphylococcus aureus,* oral anaerobes
Human bite	*Eikenella corrodens,* oral anaerobes
Fresh water injury	*Aeromonas hydrophila*
Salt water injury	*Vibrio vulnificus*
Puncture wound to foot	*Pseudomonas aeruginosa*
Diabetic foot ulcer	*Staphylococcus aureus,* microaerophilic and β-haemolytic streptococci, anaerobes. Polymicrobial infection

Table 1. Common pathogens causing skin infection in specific epidemiological circumstances.

Cellulitis starting in the groin or peri-anal area may have polymicrobial aetiology often including *S. aureus*, microaerophilic streptococci and sometimes Gram-negative bowel flora, including anaerobes. Diabetic foot ulcers and ischaemic pressure ulcers often contain similar flora.

Identifying the pathogen

It is often not possible to establish the specific microbial aetiology of cellulitis (Figure 2). Cultures of intact skin are usually unrewarding, isolating colonising skin flora only. Broken skin may be additionally colonised by coliforms, particularly if cultures are performed after antibiotic therapy has been commenced. A convincing pathogen is isolated in approximately 30% of cases. Cultures are particularly useful in identifying unusual pathogens that may be associated with specific epidemiological circumstances. Blood cultures have a low yield even in the presence of systemic toxicity and their value in managing cellulitis has been challenged.[7]

Aspiration of subcutaneous fluid from the centre or leading edge of the cellulitic area, or injection of sterile saline followed by aspiration, yields a pathogen in less than 25% of cases, although aspiration of subcutaneous collections of pus may be positive in up to 40% of cases.[8,9] Aspiration is best reserved for cellulitis occurring in the context of unusual epidemiological circumstances, or where conventional treatment is failing. Aspiration cultures yield more *S. aureus* than would be expected for unselected cases of cellulitis. This may reflect the greater likelihood of abscess formation or a higher tissue inoculum occurring with *S. aureus* infection.

Serological investigation of cellulitis by detecting serum antibodies to streptolysin O toxin is often helpful in identifying Group A, C and G, but not Group B ß-haemolytic streptococcal infection and has a sensitivity of approximately 60%.[5,10] Serological tests to detect anti-staphylococcal antibodies are less sensitive and are rarely of help.

Antibiotic Therapy

There are few data to support common choices of antibiotic therapy used to treat cellulitis. The majority of published trials are manufacturer-sponsored studies, designed to support licensing of new antibiotics and powered to show equivalence with older agents, which are often used singly in low doses (Table 2).[11-17] Comparing trials is difficult, because most suffer from a lack of common definitions of severity, use heterogeneous patient groups, particularly in hospital studies and may include vague endpoints to define cure, using subjective terms

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Antibiotic	Days Tx	% failure	Type of Study	No. patients	Year
Linezolid iv then oral 600mg 12h	14	11.4	DBRCT[10]	298 inpatients	2000
Oxacillin iv 2g 6h then dicloxacillin oral 500mg 6h	14	14.2		302 inpatients	
Dirithromycin oral 500mg once-daily	5	17	DBRCT[11]	220 outpatients	2000
Erythromycin oral 250mg 6h	7	19.2		219 outpatients	
Ceftriaxone iv 2g once-daily + 1g probenecid	2.5	7.3	DBRCT[12]	96 outpatients	1996
Cefazolin 1v 2g once-daily + 1g probenecid	2.8	8.2		98 outpatients	
Teicoplanin iv 12mg/kg then 6mg/kg once-daily	9.2	0	RCT + open label[13]	26 inpatients	1994
Teicoplanin im 12mg/kg then 6mg/kg once daily	8.4	4.5		22 inpatients	
Cefazolin iv 1g 8h	8.2	7		28 inpatients	
Imipenem iv 500mg 12h	9	2.7	Open label[14]	74 inpatients	1991
Ofloxacin oral 400mg 12h	12	2	SBRCT[15]	43 inpatients	1989
Cefotaxime iv 2g 8h	12.3	2		50 inpatients	
Clindamycin oral 150mg 6h	4	5	Retrospective[16]	15000 outpatients	1980

Table 2. Summary of selected trials of antibiotic therapy for cellulitis.
Abbreviations: DBRCT and SBRCT, double and single blind randomised controlled trial.

such as 'clinical improvement'. Microbiological cure rates are generally high (> 85%) when a specific pathogen is isolated, and where isolating a resistant pathogen results in exclusion from the trial. However, clinical cure rates on an intention-to-treat basis are usually lower, where a specific microbial diagnosis is often not made.

Because of the lack of useful trial data, selection of empirical antibiotic treatment choices must often be based on an understanding of the underlying pharmacokinetic and pharmacodynamic principles that govern antibiotic-microbe interactions.

Principles of antibiotic therapy

Successful eradication of a pathogen from the site of infection is determined by the local concentration of free drug present relative to the minimum concentration of drug required to inhibit (MIC) or kill (MBC) the infecting pathogen. The majority of antibiotics used to treat cellulitis exhibit time-dependent bacterial killing, whereby the rate of killing does not increase once a threshold concentration is achieved (often 4-times MIC). Treatment success is predicted by the time the antibiotic concentration is maintained above the MIC of the pathogen. Animal models indicate that time above MIC of >40% correlates with cure.[18] Lower tissue concentrations of antibiotic may inhibit but not kill bacteria.

For pathogens reported by *in-vitro* sensitivity testing to be resistant to an antibiotic, tissue drug concentrations that predict successful therapy are unlikely to be achieved. For pathogens determined to be sensitive *in-vitro*, antibiotic dosing strategies should be aimed at maintaining a drug concentration above MIC, bearing in mind the following points. First, many antibiotics that are active against the bacterial cell wall, in particular penicillins and cephalosporins, exhibit an inoculum effect *in-vitro*, whereby the MIC of a given pathogen increases proportionally to the number of bacteria tested, due to some bacteria reaching a slow-growth or stationary phase. *In-vitro* antibiotic sensitivity testing is performed in a highly standardised manner, using a bacterial inoculum of $2x10^5$ cfu/ml. Quantitative culture of material from soft-tissue infection yields up to $3x10^8$ cfu/ml of Gram-positive bacteria. Testing using a pathophysiologically correct inoculum results in a substantial rise in penicillin MICs against *S. aureus*.[19] Second, individuals with a significant systemic inflammatory response to cellulitis may have a widespread increase in vascular permeability resulting in an increased volume of distribution and lower than predicted serum levels for a given antibiotic dose, which may result in a lower than expected tissue concentration of antibiotic at the site of active infection. This provides a theoretical basis for using large frequent doses of

Drug	% Oral bioavailability	Cmax (mg/l)	T1/2 (h)	Protein binding (%)	MIC GAS	MIC MSSA
Benzylpenicillin 1.2g iv	-	60.0	0.5	60	0.01	-
Penicillin V 500mg oral	60	4.0	0.6	80	0.02	-
Amoxycillin 500mg oral	75	10.0	1.0	20	0.01	-
Flucloxacillin 1g iv	-	50.0	2.0	95	0.1	0.25
Ceftriaxone 1g iv	-	123.0	6.0	90	0.25	2.0
Teicoplanin 400mg iv	-	40.0	33	90	0.1	0.5
Flucoxacillin 500mg oral	50	15.0	2.0	95	0.1	0.25
Cephalexin 500mg oral	95	20.0	0.9	20	0.4	2.0
Erythromycin 500mg oral	30	2.4	2.0	75	0.25	0.5
Clarithromycin 500mg oral	55	1.7	3.5	70	0.12	0.25
Clindamycin 300mg oral	90	4.0	2.5	95	0.04	0.1

Table 3. Pharmacokinetic properties of antibiotics commonly used to treat cellulitis. Treatment success is predicted when free drug concentration exceeds MIC of pathogen for more than 40% of the time.
Abbreviations: C_{max} - maximum serum concentration;
T1/2 serum elimination half-life;
MIC minimum inhibitory concentration;
GAS group A *Streptococcus*;
MSSA methicillin-sensitive *Staphylococcus aureus*.

intravenous antibiotics for the initial treatment of cellulitis.

Oral agents will be as effective as intravenous agents if they are capable of maintaining the free antibiotic concentration above the MIC of the pathogen for >40% of the dose interval (Table 3). Tissue antibiotic concentrations will be lower with agents that have poor oral bioavailability, or are given in significantly lower doses than intravenous equivalents and may fail to meet the conditions for cure in the initial stages of treatment. Following partial therapy with intravenous agents, when the inoculum of pathogen will be significantly reduced and increased vascular permeability will be restricted to the local area of infection, switching to oral agents is more likely to be successful.

Choice of antibiotic

For the majority of cases of cellulitis, antibiotic treatment is empirical and should be aimed at eradicating ß-haemolytic streptococci and *S. aureus*. A combination of benzyl-penicillin and flucloxacillin is a common narrow-spectrum choice. Penicillin resistance in Group A, C and G streptococci has not yet been described, despite over 50 years of use and the vast majority of community-acquired *S. aureus* isolates are still sensitive to flucloxacillin. Cephalosporins may be used in documented minor allergy to penicillins, but clindamycin, or vancomycin should be used in severe allergy. Clindamycin is preferable to erythromycin, particularly in an outpatient setting, having better oral bioavailability and a higher success rate in mild infection. Oral erythromycin therapy for 7days was associated with 44% gastrointestinal side-effects, compared to 1% taking clindamycin for 4 days.[12,17] *Clostridium difficile* infection has not occurred in over 2 years of use of clindamycin in an outpatient cellulitis clinic in Southampton. Newer macrolides cause less gastro-intestinal upset, but may have significantly contributed to the increase in macrolide resistance seen since their introduction and widespread use. Macrolide resistance shows considerable variation between countries, but was detected in 11.8% of UK streptococcal isolates in 1997 and predicts resistance to clindamycin.[20]

Methicillin resistant *Staphylococcus aureus* (MRSA) infection should be considered in those who are already colonised or who develop soft-tissue infection in hospital. Vancomycin is a conventional treatment choice, but requires prolonged infusion to be given safely and requires monitoring to ensure adequate but not toxic serum levels. Teicoplanin is an effective and possibly less toxic alternative, but is expensive. Oral trimethoprim or minocycline, combined with rifampicin have been used to treat MRSA cellulitis of mild to moderate severity and achieve anecdotal success rates comparable to other agents. Clearance of MRSA colonisation using such regimes achieves 53-91% success rates.[21,22] New agents with significant activity against resistant Gram-positive bacteria, including linezolid and quinupristin-dalfopristin are also effective in treating MRSA cellulitis. Quinupristin-dalfopristin can only be given by via a large vein and is limited to hospital use. Linezolid, however, has excellent oral bioavailability and achieves high soft-tissue concentrations. Linezolid is expensive, but is cost-effective if drug-acquisition costs can be offset against hotel costs for those who would otherwise remain in hospital to receive intravenous therapy.

Cellulitis resulting from animal and human bites is often polymicrobial in nature. A broad-spectrum antibiotic such as co-amoxiclav that covers anaerobes and ß-lactamase producing organisms as well as *S. aureus* and streptococci is indicated. In cases of penicillin allergy, doxycycline plus metronidazole is a suitable alternative, or clindamycin plus ciprofloxacin for more severe infection. Addition of ciprofloxacin should also be considered to cover Gram-negative pathogens that cause cellulitis acquired following contact with water.[23]

Outpatient parenteral antibiotic therapy

Many patients with cellulitis are admitted to hospital solely to receive intravenous antibiotics. Up to 80% of such patients may be suitable for outpatient management using antibiotics such as ceftriaxone or teicoplanin, which have sufficiently long half-lives to allow once-daily dosing in a clinic. Considerable experience has been developed managing cellulitis in this way, which is as effective as conventional therapy.[24] In general, patient satisfaction with OPAT is extremely high compared with the experience of hospital admission (Figure 3).

Duration of antibiotic therapy

The duration of antibiotic therapy necessary to treat cellulitis will vary considerably between individual cases and must be guided by initial severity and the speed of response to therapy. Serial CRP measurements may help clinical assessment, but there is a lack of evidence on which to base decision-making. Published data on duration of therapy for specific antibiotics are difficult to compare due to a lack of common definitions of severity. Mild infection involving superficial skin structures usually responds to up to 7 days of oral antibiotics. Infection involving deeper skin structures, which is severe enough to require admission to hospital, usually responds to treatment of between 10-21 days. A published audit from one unit showed that intravenous antibiotics were continued for an average of 2.4 days[25] reflecting standard UK practice of switching early to oral antibiotics.

Failure to respond to antibiotic therapy

The majority of cellulitis responds rapidly to appropriate intravenous antibiotics. In approximately 10% of cases response to initial therapy is poor. In these circumstances review of the diagnosis should be made and consideration given to the possibility of unusual pathogens or abscess formation. In most instances however, no additional information is forthcoming and consideration should be given to optimising antibiotic dosing and tissue penetration, or adding additional antibiotics for synergistic effect. Glycopeptides, such as vancomycin and teicoplanin, are large polar molecules and have relatively poor penetration into tissue. Careful attention to dosing is necessary to ensure therapeutic drug levels are achieved.

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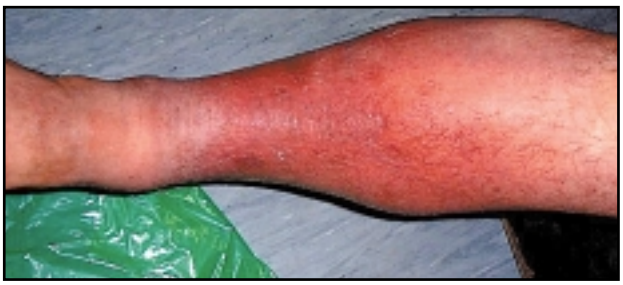

Figure 2. Cellulitis secondary to tinea pedis infection of toes. No pathogen was identified. He responded to 4 days iv followed by 21 days oral antibiotic therapy.

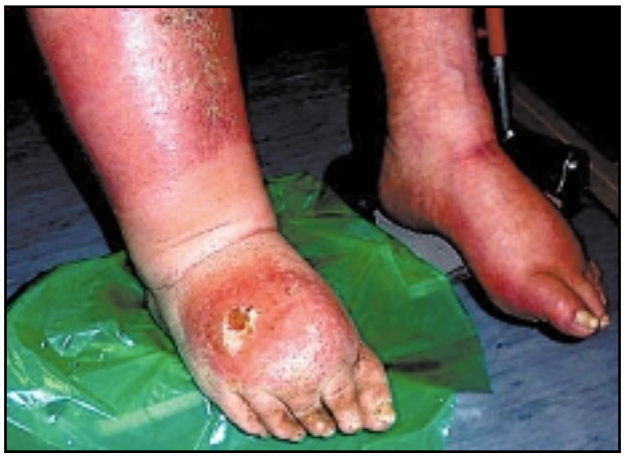

Figure 3. Infected ischaemic ulcer with surrounding cellulitis. Staphylococcus aureus was isolated from the ulcer. She responded to 5 days iv ceftriaxone as an outpatient followed by 21 days oral clindamycin.

Flucloxacillin is highly protein-bound and adequate tissue concentrations of free drug may not be achieved at conventional doses, particularly if a large bacterial inoculum is present.

Cell-wall-active antibiotics, including ß-lactams and glycopeptides, act preferentially against rapidly dividing and easily accessible organisms. Synergistic combination with other antibiotics may be useful against slowly dividing, less accessible organisms, or where large inocula of bacteria are present. Gentamicin renders nearly all ß-haemolytic streptococci and *S. aureus* hypersensitive to killing by penicillins and this effect persists at sub-inhibitory concentrations. Rifampicin has excellent penetration to less accessible sites and may act preferentially on slower dividing organisms. Clindamycin also has good tissue penetration. It acts by inhibition of protein synthesis, thereby switching off bacterial toxin production and has immunomodulatory effects to enhance macrophage function. It is particularly useful in severe streptococcal cellulitis.

Assessing need for surgical intervention

Severe cellulitis may progress rapidly to necrotising infection, which is life-threatening and mandates early surgical assessment and intervention. Necrotising infection is characterised by progressive inflammation and necrosis of skin, subcutaneous fat, fascia and muscle. Tissue damage results from a combination of pressure necrosis of infected areas contained by fascia, vascular thrombosis and direct effects of bacterial toxins. The lower limbs and perineal area are most often affected, but necrotising infection may occur in other areas with pre-existing tissue damage. Diabetes is a common underlying condition.

Distinguishing severe cellulitis that will respond to aggressive antibiotic therapy alone from necrotising infection that requires early and aggressive surgical debridement of necrotic tissue in addition to antibiotic therapy is often a difficult diagnostic challenge. Repeated assessment is necessary in all suspected cases. Severe local pain often heralds vascular thrombosis, while detection of crepitus by palpation or by radiography indicates the formation of gas in affected soft tissues, resulting from bacterial metabolism and tissue destruction. Bullous lesions may also develop on overlying skin. A systemic inflammatory response is usual. Objective criteria that may assist in distinguishing necrotising from non-necrotising soft-tissue infection include marked leucocytosis and renal impairment on admission.[26,27]

Infection is often polymicrobial, particularly when involving the groin and bacteria isolated may include ß-haemolytic streptococci, *S. aureus*, enterococci, Enterobacteriaceae, Pseudomonas sp. and a variety of anaerobes. Initial antibiotic therapy should be sufficiently broad spectrum to cover likely pathogens until results of tissue culture are available, using agents such as piperacillin/tazobactam or imipenem. Adding gentamicin may produce synergy and adding clindamycin is of value in suppressing bacterial toxin production.[28]

Conclusions

It is often not possible to establish the specific microbial aetiology of cellulitis and selection of antibiotic therapy must often be based on an understanding of the epidemiology of infection and the underlying pharmacokinetic and pharmacodynamic principles that govern antibiotic-microbe interactions. There is a lack of useful trial data to provide an evidence-base to inform treatment choices and duration of therapy. Empirical antibiotic treatment of cellulitis should be effective against ß-haemolytic streptococci and *Staphylococcus aureus*.

References

1. Pearse RM, Mitra AV, Heymann TD. What the SHO really does. *J R Coll Physicians Lond* 1999; **33**: 553-556.
2. Cox NH. Management of lower leg cellulitis. *Clin Med JRCPL* 2002; **2**: 23-27.
3. Gaviria JM, Bisno AL. An experimental model of group G streptococcal soft-tissue infections. Studies of acquired immunity. *Adv Exp Med Biol* 1997; **418**: 813-815.
4. Swartz M. Skin and Soft tissue infections. Mandell GL, Bennett JE Dolin R editors: Mandell, Douglas and Bennett's principles and practice of infectious disease, 5th edition, Churchill Livingstone, Philadelphia 2000; p 1037-1057.
5. Bernard P, Bedame C, Mournier M *et al*; Streptococcal cause of erysipelas and cellulitis in adults. *Arch Dermatol* 1989; **125**: 779-783.
6. Calandra GB, Norden C, Nelson JD et al. Evaluation of new anti-infective

drugs for the treatment of selected infections on the skin and skin structure. *Clin Infect Dis* 1992; **1992**: S148-S154.

7. Gottehrer PB, Raveh D, Schlesinger Y *el al*; Cost-effectiveness of blood cultures for adult patients with cellulitis. *Clin Infect Dis* 1999; **29**: 1483-1488.
8. Newell PM, Norden CW. Value of needle aspiration in bacteriologic diagnosis of cellulitis in adults. *J Clin Microbiol* 1988; **26**: 401-404.
9. Sigurdsson AF, Gudmundsson S. The etiology of bacterial cellulitis as determined by fine needle-aspiration. *Scand J Infect Dis* 1989; **21**: 537-542.
10. Cox NH, Colver GB, Paterson WD. Management and morbidity of cellulitis of the leg. *J R Soc Med* 1998; **91**: 634-637.
11. Stevens DL, Smith LG, Bruss JB *et al*; Randomised comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. *Antimicrob Agent Chemother* 2000; **44**: 3408-3413.
12. Wasilewski MM, Wilson MG, Sides GD *et al*; Comparative efficacy of 5 days of dirithromycin and 7 days of erythromycin in skin and soft tissue infections. *J Antimicrob Chemother* 2000; **46**: 255-262.
13. Brown GB, Chamberlain R, Goulding J *et al*; Ceftriaxone vesus cefazolin with probenecid for severe skin and soft tissue infections. *J Emerg Med* 1996; **14**: 547-551.
14. Chirurgi VA, Edelstein H Oster SE *et al*; Randomised comparison of trail of teicoplanin IV, teicoplanin IM, and cefazolin therapy for skin and soft tissue infections caused by Gram positive bacteria. *South Med J* 1994; **87**: 875-880.
15. Sexton DJ Wlodaver CG, Tobey LE *et al*; Twice-daily intramuscular imipenem/cilastatin in the treatment of skin and soft tissue infections. *Drugs* 1991; **42**: 51-56.
16. Gentry LO, Rodriguez-Gomez G, Zeluff BJ *et al*; A comparative evaluation of oral ofloxacin versus intravenous cefotaxime therapy for serious skin and skin structure infections. *Am J Med* 1989; **87**: 57S-60S.
17. Wilson DH. Clindamycin in the treatment of soft tissue infections: a review of 15019 patients. *Br J Surg* 1980; **67**: 93-96.
18. Craig WA. Pharmacodynamics of antimicrobials:general concepts and applications. Nightingale CH, Murakawa T, Ambrose PG editors: Antimicrobial pharmacodynamics in theory and clinical practice. Marcel Dekker, New York 2002; p 1-22.
19. Konig C, Simmen HP, Blaser J. Bacterial concentrations in pus and infected peritoneal fluid – implications for bactericidal activity of antibiotics. *J Antimicrob Chemother* 1998; **42**: 227-232.
20. www.phls.co.uk/facts/streppn.htm.
21. Darouiche R, Wright C, Hamil R *et al*; Eradication of colonisation by methicillin-resistant Staphylococcus aureus by using oral minocycline-rifampin and topical mupirocin. *Antimicrob Agents Chemother* 1991; **35**: 1612-1615.
22. Walsh TJ, Standiford HC, Reboli AC *et al*; Randomized double-blind trial of rifampin with either novobiocin or trimethoprim-sulfamethoxazole against methicillin-resistant Staphylococcus aureus colonisation: prevention of antimicrobial resistance and effect of host factors on outcome. *Antimicrob Agents Chemother* 1993; **37**: 1334-1342.
23. Reed KC, Crowell MC, Castro MD *et al*; Skin and soft-tissue infections after injury in the ocean: culture methods and antibiotic therapy for marine bacteria. *Mil Med* 1999; **164**: 198-201.
24. HG Deery II. Outpatient parenteral anti-infective therapy for skin and soft-tissue infections. *Infect Dis Clin N Am* 1998; **12**: 935-949.
25. Nathwani D, Moitra S, Dunbar J *et al*; Skin and soft-tissue infections: development of a collaborative management plan between community and hospital care. *Int J Clin Pract* 1998; **52**: 456-460.
26. Nichols RL, Florman S. Clinical presentations of soft-tissue infection and surgical site infections. *Clin Infect Dis* 2001; **33**(suppl 2): S84-93.
27. Wall DB, de Virgilo C, Black S *et al*; Objective criteria may assist in distinguishing necrotising fasciitis from nonnecrotising soft tissue infection. *Am J Surg* 2000; **179**: 17-21.
28. File TM, Tan JS. Treatment of skin and soft-tissue infections. *Am J Surg* 1995; **169**: 272S-33S.