SKIN AND SOFT TISSUE INFECTIONS

Abdul Ghafur, PS Shareek, Chennai

INTRODUCTION

“Suffered by everyone at least once in life time, most common infection, and challenge to a physician in his day to day practice but unfortunately the most misdiagnosed and mismanaged these days. This is how we can define skin and soft tissue infections (SSTI) in the modern era. Added to this, the arsenal of weapons carried by pathogens has changed dramatically over decades.”

This quote depicts the importance of early diagnosis and correct management of the broad spectrum of SSTI, ranging from simple boils to life threatening necrotising fasciitis. In this article we try to provide a brief description of various SSTIs and their management.

SSTIs can be defined as an inflammatory microbial invasion of the epidermis, dermis and subcutaneous tissues. The presence of bacteria over the skin surface or even on an ulcer doesn’t mean that this microbe is responsible for the pathology. Unless there are signs of inflammation over the skin surface, result of wound swab culture should be viewed with suspicion and all efforts should be undertaken to differentiate pathogen from a colonizer before hunting for the sensitivity pattern and commencing on a lengthy antibiotic regimen. Colonization doesn’t warrant antibiotics as a rule but infections may need it. Over use of antibiotics is a global problem, even in countries with good antibiotic stewardship policies. An excellent review article by Dryden on soft tissue infections, highlights the usage of antibiotics to treat MRSA colonization rather than infection.

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. Direct infection of skin occurs by invasion of epidermis usually by a breach in the skin. Hematogenous spread of microbes also results in SSTI. Bacterial dissemination of Meningococcus and rickettsia can affect skin. Measles and chicken pox are well known pathogens affecting skin. Staphylococcal scalded skin syndrome and streptococcal scarlet fever are typical examples of toxin mediated skin damages.

CLASSIFICATION

There is no scarcity on the availability of various classifications of SSTI and despite all the advances in modern medicine, managing severe types of these infections are still difficult. SSTI may be classified according to the layer of infection, severity of infection and microbiologic etiology. Easiest of these is the classification based on the layer of involvement (Table 1).

The practice guidelines of the Infectious Diseases Society of America (IDSA) for the diagnosis and management of skin and soft tissue infections 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. Eron classification, based on the severity of local and systemic signs is also useful (Table 2). The advantage of this classification is that it guides the clinical management and treatment decisions for patients with SSTIs more efficiently when compared with the previous ones.

WHAT IS COMPLICATED SSTI?

Complicated SSTI [cSSTI] represents more severe types of SSTI. Healthy people with unhealthy wounds, immunocompromised patients with even healthy wounds, patients with extensive cellulitis
and systemic symptoms, patients with necrotizing limb-threatening infection that requires life-saving surgery and diabetic foot infections fall into this category. Infections in areas where rate of complication is more as in perianal region can also be classified as cSSTI. 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

IMPETIGO

Impetigo is an initially vesicular, later crusted, superficial infection of the skin. Though previously it was most often caused by Even though Group A streptococcus was the commonest cause of this entity, now days Staphylococcus has become the number one offender.7,8 Increasing prevalence of MRSA as a cause of impetigo is indeed worrying.9 Nasal colonization can act as a source of Staphylococcal impetigo.10

CLINICAL FINDINGS

Streptococcal impetigo starts on exposed surfaces appearing as small vesicles that pustulate rapidly and ruptures readily. This purulent discharge dries and forms the characteristic golden yellow, stuck on, crusts. Pruritus is common and scratching of lesions results in spreading of infection. Healing generally occurs without scarring.

Laboratory findings

Gram stain may show gram positive cocci and culture of the exudates may grow Staph aureus, streptococci or both. Assays of streptococcal antibodies are not useful in the diagnosis and treatment of impetigo, but positivity may indicate recent streptococcal infection in patients suspected of having post streptococcal glomerulonephritis. The antistreptolysin O response is weak in patients with streptococcal impetigo, as skin lipids suppress Streptolysin O response, but anti–DNAase B levels are consistently elevated.11-13

Treatment

Penicillin was the drug of choice for treating impetigo at a time when Streptococci were the commonest cause of impetigo. This antibiotic is no longer advisable now days, with staphylococcosis becoming the predominant cause. Penicillinase resistant penicillin or a cephalosporin may be better treatment choice currently to treat impetigo. Erythromycin or a newer macrolide is used for penicillin allergic patients. Cotrimoxazole, doxycycline and clindamycin has good activity against CA MRSA.14 Topical antibiotic mupirocin may be used when lesions are limited in number, but increasing mupirocin resistance is a concern.15 Retapamulin is a recently approved topical agent. Fusidic acid is another topical agent especially in pediatric population.

ERYSipelAS

This is a superficial infection of skin, with prominent lymphatic involvement. It is commonly caused by group A streptococcus.

Clinical findings

Erysipelas is more common in infants, young children and older adults. Lower extremities are affected more, though rarely face may also get involved in 5-20% of patients. Bacteria enter through skin ulcers, local trauma, psoriasis or eczema or fungal infections. Predisposing factors include lymphoedema, venous stasis, obesity, paraparesis, diabetes mellitus, alcohol abuse and nephrotic syndrome. Erysipelas is painful lesion with a bright red, edematous, indurated appearance with an advancing raising and sharply demarcated borders. Presence of fever is a usual finding. Cellulitis, abscess and necrotizing fasciitis are not uncommon complications.16

Laboratory findings

Leucocytosis is common. Cultures are usually sterile.

<table>
<thead>
<tr>
<th>Anatomy</th>
<th>Infection</th>
<th>Microbial cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelium</td>
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<td></td>
<td>Gangrene</td>
<td>Clostridium perfringens</td>
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Table 1: Types of infection affecting skin and soft tissue structures

<table>
<thead>
<tr>
<th>Count</th>
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Table 2 : Eron classification.5

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<th>Category</th>
<th>Clinical features</th>
<th>Management</th>
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<tr>
<td>Class 1</td>
<td>SSTI but no signs or symptoms of systemic toxicity or co-morbidities</td>
<td>Drainage (if required) and oral antibiotics as outpatient</td>
</tr>
<tr>
<td>Class 2</td>
<td>Either systemically unwell or Oral or outpatient intravenous systemically well but with antibiotic therapy; may require short period of observation in hospital</td>
<td>Likely to require inpatient treatment with parenteral antibiotics</td>
</tr>
<tr>
<td>Class 3</td>
<td>Toxic and unwell (fever, tachycardia, tachypnoea and/or hypotension)</td>
<td>Likely to require admission to ICU, urgent surgical assessment and treatment with parenteral antibiotics</td>
</tr>
<tr>
<td>Class 4</td>
<td>Sepsis syndrome and life threatening infection</td>
<td>Likely to require admission to ICU, urgent surgical assessment and treatment with parenteral antibiotics</td>
</tr>
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Skin and Soft Tissue Infections

Skin and Soft Tissue Infections
easily from the surface of skin lesions.

Treatment
Mild cases can be treated with oral penicillin (500 mg every 6 hourly). Erythromycin (250 mg -500 mg orally every 6 hourly) can also be used, but resistant isolates are reported. Severe cases need parenteral crystalline penicillin at a dose of 2000000 units every 6 hrly. Presence of bullous erysipelas or if associated cellulitis is cannot be ruled out penicillinase resistant penicillin (cloxacillin) or a first generation cephalosporin should be used. Recurrence of erysipelas may be prevented by prolonged use of oral penicillin.¹⁷

CELLULITIS

Introduction
Cellulitis is an acute spreading infection that involves subcutaneous tissue, most commonly caused by group a streptococcus and staph aureus. Trauma and underlying skin lesion can lead to the development of cellulitis. Bacteraemia can rarely be the cause of cellulitis. Cellulitis may also develop due to the spread of adjacent infections like osteomyelitis.

Clinical findings
Clinically rapidly intensifying pain and redness is a common presentation. Fever and lymphadenopathy may be present. The borders in cellulitis are not well demarcated. Bacteraemia, thrombophlebitis, especially in older people, and local abscess formation may develop. Though group A streptococci and staphylococcus are the most common organisms rarely organisms like H influenza, pneumococcus may also cause cellulitis. Acutely presenting and rapidly progressing lesions are due to most commonly with streptococcus and vice versa is true for staph aureus. This is a useful clue for the physician when selecting the antimicrobial.

Laboratory findings
Neutrophil leucocytosis is a common finding. Cultures of needle aspirates are routinely not recommended because of low sensitivities. Aspiration is recommended only if we suspect unusual pathogens, presence of abscess formation or failed antimicrobial therapy. Blood cultures are usually negative, even though Staph aureus or a Group A streptococcus may be positive.

Treatment
Streptococcus cellulitis responds to β lactam. Penicillinase resistant penicillin or a first or second generation cephalosporin may be used if MRSA is less likely. Strong suspicion of MRSA needs vancomycin (1gm twice daily) or linezolid 600 mg twice daily.¹⁸ Daptomycin is another option and can be given once a day. Step down to oral antibiotics is possible after settling of fever and improvement in the skin lesions. Oral agents can be tried in the outset in mild cases of cellulitis. Immobilization and elevation of involved limbs will be useful. Chronic suppressive usage of antibiotics may be necessary in cases of recurrent cellulitis.

GANGRENOUS CELLULITIS

This is a rapidly progressive cellulitis with extensive necrosis of skin and subcutaneous tissues. They can be divided into

A. Necrotizing fasciitis
B. Gas gangrene
C. Progressive bacterial synergistic gangrene
D. Gangrenous cellulitis in immunocompromised host

Necrotizing fasciitis

Introduction
Necrotizing fasciitis is a term that describes a disease condition of rapidly spreading infection, usually located in fascial planes of connective tissue that results in tissue necrosis. Any part of the body may be affected. Group A beta-hemolytic streptococci (Streptococcus pyogenes) is the number one culprit, but any other bacteria, either alone or together (polymicrobial) can cause this disease. Occasionally, even fungus can cause necrotizing fasciitis.
Necrotising fasciitis can be divided into two forms. Type 1 necrotizing fasciitis is polymicrobial. Type 2 is caused by Group A streptococcus alone or in combination with other organism especially staphylococcus. Necrotizing fasciitis can affect any part of the body but is most common on the legs. Abdominal wall, perianal and groin areas and postoperative wounds are the other areas usually affected. Organisms gain entry through areas of trauma, surgery and ulcers. Diabetes mellitus and alcoholism can increase the risk for necrotizing fasciitis and parenteral drug abuse is other common risk factors (Fig. 1).

Clinical findings
The affected area is erythematous, swollen, without sharp margins, hot, very tender, and painful in the early stage. Within 3 to 5 days after onset, skin breakdown with bullae developing to cutaneous gangrene. High grade fever is common. The involved areas become non tender at this stage and this feature helps in identifying necrotizing fasciitis. Subcutaneous gas is often present in the polymicrobial form of necrotizing fasciitis especially in diabetics.

Laboratory findings
Leucocytosis is commonly seen. Gram-stain of the exudates or the tissue can help in early identification of the possible pathogen or pathogens. Blood cultures are frequently positive.

Treatment
It is extremely important to diagnose this condition at a very early stage to reduce the morbidity and mortality, as this condition has a rapid clinical course. The overall mortality rate for this condition varies from 24-34%. Immediate surgical debridement is an essential part of the management. The antibiotic choice depends on the local resistance pattern in the community and health care settings. For group A streptococcal necrotizing fasciitis, penicillin or plus clindamycin can be used. Empirical broad spectrum antibiotics should be used initially until cultures are back. Gram positives, gram negative aerobes and anaerobes should be kept in mind.

Fourniers gangrene
Fourniers gangrene is the necrotizing fasciitis of genitalia, which usually affects scrotum but may spread to lower abdominal wall and perianal area. Local trauma, diabetes and perineal infections are predisposing factors.

Gas gangrene
Introduction
Gas gangrene is a rapidly progressive myonecrosis which can be life threatening. It is usually caused by clostridia, especially clostridium perfringens. This condition usually follows muscle injury, but rarely can be seen in post operative patients as well. Muscle injury and contamination with soil or foreign material containing spores of clostridium perfringens is the key initiating factor of this condition. Non traumatic clostridial myonecrosis is usually caused by Clostridium septicum species can cause non traumatic clostridial myonecrosis.

Clinical findings
Pain is the earliest symptom, with rapidly increasing severity progressing to signs of toxicity and shock. Foul smelling serosanguinous discharge from the wound is a feature. Crepitus is usually present. The area later turns into greenish black cutaneous necrosis.

Lab findings
Leucocytosis is a common feature, blood culture usually negative. Gram stain usually shows gram positive bacilli without spores. Presence of spore favours clostridium septicum. Anaerobic culture turns positive in as early as 6 hours time, with the growth as fast as the clinical progress. X ray of the area may show evidence of gas in muscles and fascial planes.

Treatment
Emergency surgical exploration is a must. Combination of crystalline penicillin and clindamycin are the drugs of choice. Hyperbaric oxygen has been tried with conflicting results.

Progressive bacterial synergistic gangrene
This develops as a complication of laparotomy wounds or colostomy sites or as a chronic ulcer n the extremity, appearing as a painful erythematous area, which later ulcerates, progressing to gangrene. Staph aureus or streptococci are the causative organisms.

Gangrenous cellulitis in immunocompromised patients
In an immunocompromised host, even unusual pathogens like fungi can produce severe cellulitis progressing to gangrene. Gram negative bacteria like pseudomonas and fungi like mucormycosis can produce life threatening infections in these patients. Cryptococcosis and histoplasmosis can also produce skin lesions.

CA MRSA (COMMUNITY-ACQUIRED MRSA)
MRSA infections have already turned into a menace in hospitals across the globe. In Indian hospitals the MDR Gram negative saga has masked the importance of MRSA, with multiple antibiotics available against MRSA, at a time when the pipeline of Gram negative antibiotics is drying up. Now there are increasing case reports of community acquired MRSA infection even in India, while this problem has turned to a routine problem in countries like USA.

What do we mean by community acquired MRSA (CAMRSA)?
CA-MRSA is entirely different from the MRSA circulating
in hospitals (e MRSA/HA-MRSA). CA-MRSA is not due to spread of hospital strains to community. They belong to a different molecular class with different characteristics. CDC Population-Based Surveillance Definition of cMRSA is; MRSA culture positivity in outpatient setting or 14-48 hours of hospitalization AND Patient lacks risk factors for healthcare-associated MRSA, like Hospitalization, Surgery, Long-term care Dialysis Indwelling devices, history of MRSA positivity.

Salient differentiating features of CAMRSA are the acquisition of infection in community setting, especially young otherwise healthy individuals, while HA-MRSA is acquired in hospital setting in patients with co-morbidities. CA-MRSA has SCC mec IV-V cassette and in USA they belong to clone USA 300 and USA 400. CA-MRSA carry PVL (Pantone Valentine Leucocidin) gene, producing PVL toxin, which is an important virulent factor of CA-MRSA. PVL may be produced by some strains of MSSA as well. PVL producing MSSA and MRSA infections usually present as recurrent boils, especially in close groups like family members, contact sports team members. Severe soft tissue infections, rapidly progressive necrotizing pneumonia and severe arthritis are well known manifestations of these bacteria.

Reports of community acquired MRSA cases started appearing almost a decade ago in various countries in USA the prevalence of CA-MRSA has increased rapidly over the last 10 years. Incidence of CAMRSA rose to 76% of isolates in Houston and 63%-72% of isolates in Atlanta. USA 300 clone of CA MRSA has become the most predominant one in USA, accounting for 90%-99% of cases. CA-MRSA caused an increasing percentage of hospital onset bacteraemias between 2000 and 2006 in Chicago (increasing from 24% to 49%). Mathematical models predict that within the next few years, so-called community-associated strains will become the predominant strains in hospitals throughout the USA. In a 2010 Indian study rate of CA MRSA was 9.6%. Another big study from Mumbai revealed increasing prevalence of CAMRSA in India. 54% of MRSA isolates were community acquired. This interesting study by the Mumbai team should be an eye opener on the possible extends of CA MRSA in the resistance marathon.

TREATMENT OF CA MRSA
Unlike HA MRSA, community acquired type is mostly not multidrug resistant, being sensitive to many oral antibiotics like cotrimoxazole, doxycycline and clindamycin. Can be used in most outpatient setting.

UK practice recommendations gives emphasis to combination therapy in managing CAMRSA. They include rifampicin and sodium fusidate, doxycycline; rifampicin and trimethoprim or linezolid, rifampicin+trimethoprim; or linezolid. Glycopeptides or daptomycin may be used in moderately severe infections especially in the outpatient settings. Linezolid is another alternative in this context.

Panton valentine toxin (PVL)
Panton valentine toxin (PVL) is a γ hemolysin toxin seen in staph aureus which was first isolated in 1932 by Panton and valentine. Prevalence of PVL gene varies among strains of Staph aureus and MRSA. Presence of PVL in MSSA and HA MRSA is less common, while majority of CAMRSA in USA produce PVL. Other studies have reported a high incidence of PVL production among strains of CA-MRSA. There have been case reports of PVL producing strains from India also. The first Indian case report of PVL producing CA MRSA was in a pediatric patient from Chennai in 2009. In an excellent study from Mumbai 64% of MRSA were PVL producers and 67% of the isolates from SSTIs were PVL producers.

The choice of antibiotic selection is extremely important while treating PVL producing MSSA or MRSA. Betalactam antibiotics even though active against MSSA will trigger release of toxins further contribute to the pathogenesis. Clindamycin and linezolid are active against MRSA and also suppress toxin production. Flucloxacillin is bactericidal, but the low sub inhibitory concentrations achievable in vivo in necrotic tissue may further augment PVL toxin. Sub-inhibitory concentrations of clindamycin, linezolid and fusidic acid induce a concentration dependent decrease in PVL production, whereas low concentrations of oxacillin increase the concentration of PVL up to threefold.

Antibiotics used in SSTI

Introduction
Complicated skin and soft tissue infections caused by wide spectrum of bacteria, especially at an era of increasing resistance and new virulence factors makes empirical antibiotic section a real challenge. The predominance of Gram positives over the Gram negatives as the cause of cSSTI is in fact a solace at a time when the Gram negative pipeline is getting drier and the Gram positive one is still flowing at full velocity and vigour. The appearance of CA MRSA has changed the scenario of antibiotic management of CSSTI, forcing us to choose antibiotics which can suppress toxins, even for MSSA; rather than blindly choosing beta lactam agents.

Cotrimoxazole
Cotrimoxazole has reemerged as a good antibiotic choice for mild to moderate soft tissue infections due to CA MRSA. Almost 90-100% of isolates are sensitive to cotrimoxazole in western studies. History of sulph allergy should carefully be ruled out before starting this drug. Hyperkalaemia is another side effect especially in elderly and patients already on ACE inhibitors and ARB group of drugs.
Clindamycin

Clindamycin has very good ant staphylococcal activity with good soft tissue penetration and toxin suppressing activity, making this drug a good choice for treating soft tissue infections. Even though clindamycin resistance is common in HAMRSA, it usually works well with CA MRSA, as these isolates retain their sensitivity to clindamycin. MRSA isolates resistant to erythromycin must have a D test done in the laboratory and if positive, clindamycin should be avoided, as therapeutic failure can occur.

Daptomycin

Daptomycin is a cyclic lipopeptide and is approved for treatment of cSSTIs. Daptomycin is bactericidal drug acting on the cell membrane of the bacteria. Daptomycin is active against MRSA, glycopeptide- and linezolid-resistant S. aureus and vancomycin-resistant enterococcal species. It has good activity during the stationary phase growth of bacteria as against the β lactams and has a good post antibiotic effect against staph aureus. Daptomycin is highly protein bound and renally excreted. Elevation in creatinine phosphokinase (CPK) and associated myopathy is a well reported complication of daptomycin, uncommon with the once a day dosing pattern. CPK level should be monitored at least once a week during daptomycin therapy. Development of eosinophilic pneumonias is another but uncommon complication. This drug is not licensed in children. It is pregnancy category B. Daptomycin is non inferior to vancomycin for the treatment of cSSTI.

TIGECYCLINE

Tigecycline belongs to the group glycycline. It inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit but with a five times higher affinity than that for the tetracyclines. It can overcome the normal tetracycline resistance mechanisms and other bacterial resistance mechanisms like ESBLs. Tigecycline was shown to be noninferior to combination vancomycin-aztreonam regimens and exhibited higher clinical success rates for cSSTI. Tigecycline use has been associated with higher all cause mortality rates, though it was not statistically significant, FDA has issued a warning. No dosage adjustment of tigecycline is necessary in patients with renal insufficiency or mild to moderate hepatic impairment and the aged population, although in patients with severe hepatic impairment, the initial dose should be 100 mg, followed by a reduced maintenance dose of 25 mg every 12 hrs.

Televancin

Telavancin is a novel parenteral lipoglycopeptide. It inhibits cell wall synthesis. Telavancin is used in settings of MRSA, VISA, and VRSA. It is pregnancy category C. Nephrotoxicity was more commonly reported among individuals treated with telavancin than among those treated with vancomycin. So monitoring of renal functional tests is mandatory when using this drug.

Tetracyclines

Tetracyclines are a good option for treating mild to moderate MRSA soft tissue infection, even though increasing resistance is concern. Tetracyclines are pregnancy category D and are not recommended for children <8 years of age because of the potential for tooth enamel discoloration and decreased bone growth.

Vancomycin

Vancomycin is probably the most commonly used drug used for treating MRSA infections. Emergence of resistance and “the MIC creep” is a serious issue to be kept in mind while choosing this drug. Tissue penetration is highly variable and depends upon the degree of inflammation. Vancomycin is considered pregnancy category C.

Linezolid

Linezolid is a synthetic oxazolidinone and inhibits protein synthesis at the 50S ribosome. Linezolid has 100% oral bioavailability. Parenteral therapy is indicated only if gastrointestinal absorption is compromised. Linezolid resistance is rare, but has been reported. Long-term use can produce hematologic toxicity, commonly thrombocytopenia though anemia and neutropenia is also seen. Peripheral and optic neuropathy and lactic acidosis are the other side effects seen with use of linezolid. Although myelosuppression is generally reversible, peripheral and optic neuropathy are not reversible or are only partially reversible. Linezolid has been associated with serotonin syndrome in patients taking concurrent selective serotonin-receptor inhibitors. Linezolid causes less bone marrow suppression in children than in adults. It is considered pregnancy category C.

SOLVE THE PROBLEMS!

1. A 22 year old man presents with multiple boils on thigh with abscess, severe pneumonia and arthritis. Which one of the following drugs should be avoided?
   A. daptomycin
   B. cephalexin
   C. clindamycin
   D. linezolid

2. 30 year old male patient admitted with severe sepsis and cSSTI. Which of the following should be avoided in this scenario?
   A. linezolid
   B. tigecycline
C. daptomycin
D. daptomycin+clindamycin

3. One of the following is not true about linezolid.
   A. it has 100% oral bioavailability.
   B. peripheral neuropathy is completely reversible.
   C. thrombocytopenia is the most common hematological abnormality.
   D. hematological abnormalities are less common in children

4. The drug which is associated with eosinophilic pneumonia
   A. linezolid
   B. daptomycin
   C. clindamycin
   D. none of the above

5. D test is done on MRSA isolates to predict the resistance of which antibiotic?
   A. clindamycin
   B. doxycycline
   C. linezolid
   D. daptomycin

ANSWERS
1. B: Cephalexin
   This scenario is very suggestive of CAMRSA/CA MSSA PVL toxin producing infection. Toxin suppressing antibiotics should be used and Beta lactam antibiotics should be avoided as these drugs can increase toxin production.

2. B: Tigecycline. Tigecycline is not reliable for treatment of bacteremia due to inadequate concentration of this drug in blood. In severe sepsis bacteremia should be anticipated.

3. B: Linezolid induced thrombocytopenia is not always reversible.

4. B: Daptomycin

5. A: If D test is positive clindamycin therapy may fail. This test should be performed if clindamycin is used in MRSA infection.

REFERENCES


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