A guide to antibiotic resistance in bacterial skin infections

G Perera,*† R Hay‡
†Department of Dermatology, King’s College Hospital, Denmark Hill, Camberwell, London, SE5 9RS and ‡Faculty of Medicine & Health Sciences, Queen’s University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast, BT9 7BL, Northern Ireland, *Corresponding author: Department of Dermatology, King’s College Hospital, Denmark Hill Camberwell, London, SE5 9RS, tel. +44 (0) 20 7737 4000; fax +44 (0) 20 7346 3616; E-mail: gayathriperera@aol.com

ABSTRACT
The emergence of bacterial resistance to commonly used antibiotics is not new. In this review we have tried to cover the ever increasing problems facing the treatment and containment of bacterial skin infections. We have tried to give an overview of the varied mechanisms by which bacteria gain and spread antimicrobial resistance, whilst dealing with the patterns of resistance exhibited by some of the commonly encountered organisms. Where there is evidence, we have formulated an approach on how to tackle antibiotic resistance. Where there is a lack of evidence we have formulated what we perceive to be appropriate guidelines.

Key words: Antibiotics, bacteria, infection, MRSA, resistance, streptococcus

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Introduction
Dermatological infections need to be categorized in order to target successful therapy. A primary infection is the result of an organism invading intact skin, while secondary infection is superimposed upon an underlying dermatosis. A tertiary infection, in this context, can be considered as a cutaneous manifestation of a systemic disease process. The latter may occur as a result of immunosuppression.

When considering bacterial infections involving the skin, it is important to differentiate as to whether the bacterium isolated on culture is a pathogen, colonizer of an abnormal skin surface, or part of the normal skin flora, prior to initiation of antimicrobial therapy. This informs not only the appropriate choice of topical, systemic or dual therapy, but also helps define therapeutic goals. It is important to define at the initiation of therapy as to whether complete eradication of skin bacteria is desired and indeed realistic, whilst treating the acute infection. If eradication is not the goal, then there should be a predetermined duration of therapy so as to minimize the development of antimicrobial resistance associated with the prolonged use of antibiotic therapy.

Over the last 50 years, since the wide availability of antibiotics, well-known and predictable sensitivity patterns have changed requiring susceptibility testing (e.g. *Streptococcus pneumoniae* and penicillin, tetracycline, erythromycin). The ability of bacteria to develop resistance to antimicrobials has also long been recognized and this has led to a continuing quest by the pharmaceutical industry for newer, more potent antibiotics. The scientific community appears to be falling behind in this race, between bacterial adaptability and drug discovery, and multiply resistant strains are ever increasing. For the moment, the emergence of such tenacious organisms is primarily a problem of hospitals, and there is a compelling requirement for hospital physicians to rationalize the use of antimicrobial therapies.

Dermatologists are only too aware of the difficulty of treating those patients with an underlying dermatosis and bacterial colonization of the skin. The current resistance patterns of the commonly encountered bacteria in dermatology will be reviewed in this paper, and where available the recommended antimicrobial therapy or appropriate approach to dealing with the infection will be discussed. The evidence for many of the regimens suggested or discussed are not firmly established and are presented as the authors attempt to suggest a helpful approach to dealing with particular issues. The main reason for lack of evidence is that clinical trials designed to answer many of the issues raised simply have yet to be carried out. The mechanisms and diagnosis of skin infections as well as tropical dermatology is beyond the scope of this review.

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Selection criteria for antimicrobial therapy

The approach to antibiotic selection should be based on a number of different considerations such as patient factors, the pharmacokinetics of the chosen antibiotic, bacterial profile and the antibiotic sensitivity pattern.

Patient factors

When considering patient profile, the identification of predisposing factors for infection must be considered. The alteration of normal skin flora, existence of underlying chronic dermatoses, the use of corticosteroid therapy, a state of immunodeficiency or malnutrition, underlying vascular insufficiency, the existence of a foreign body (whether surgical or accidental), skin trauma and underlying systemic disease all have to be evaluated when selecting the appropriate antimicrobial therapy.

Pharmacokinetic and pharmacological factors

Pharmacodynamics such as bactericidal and intrinsic activity against pathogenic strains and β-lactamase stability need to be addressed. The antimicrobial agent should barely alter the composition of normal flora and there should be little potential for the development of resistance. Ideally, there has to be good bioavailability, rapid intestinal absorption and good tissue penetration.

Resident skin flora are characterized by their attachment to the skin surface and adnexal structures, existence in low numbers and exhibition of low virulence. It is important to be familiar with bacteria that are common pathogens found in the skin and those that are uncommon when considering the clinical significance of bacteria isolated from the skin or blood cultures (Table 1).

Bacterial profile

In order to manage the infection effectively, the virulence of the organism and overall pattern of behaviour need to be understood. For example, it is well known that *Staphylococcus aureus* has a predilection for abnormal heart valves and bone.

Endocarditis and osteomyelitis need to be considered as potential complications of *S. aureus* skin infection in patients who are immunocompromised or in those who continue to exhibit features of infection despite successful treatment of the deep skin infection.

Choice of antibiotics and resistance patterns

Isolation of an organism in blood cultures or skin swabs requires sensitivity patterns to the antibiotics normally used against these bacteria. The gold standard antimicrobial is one that is able to target the pathogenic organism only. *In vitro* resistance patterns are based on the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) of an antibiotic against an organism. A low MIC and a high MBC imply that the antibiotic is bacteriostatic, inhibiting growth but not killing the organism. Translation of laboratory studies into the *in vivo* situation does not always correlate. This may be because the MIC/MBC ratio can be exceeded by larger doses of the antibiotic than those tested for in the *in vitro* assays. This is often the case with what appears to be penicillin-resistant *S. pneumoniae*. Administration of a large dose of penicillin in this situation can sometimes arrest ongoing infection.

Bacterial resistance

Mechanisms (Table 2)

Bacterial resistance can occur through many mechanisms. The mechanism depends on the site and mode of action of the antibiotic. Resistance can be categorized as intrinsic or acquired. In the former, the target site is lost, absent or bypassed, as with vancomycin resistance in Gram-negative organisms. Acquired resistance occurs via host adaptability, where genetic material can encode inactivating enzymes, alter the target site, and exclude the antibiotic from the target site. The bacterium can produce large quantities of antibiotic-inactivating enzymes and can either surround itself with these, as is seen with β-lactamase from *S. aureus*, or have small amounts in the periplasmic space, as with Gram-negative bacteria.
Alteration of the target site can be structural, preventing antibiotic binding, or functional, bypassing the targeted metabolic pathway. This is seen with sulphonamide- and methicillin-resistant *S. aureus*. Exclusion of an antibiotic occurs via a porin, a protein structure that is embedded in the outer lipid membrane of Gram-negative bacteria. Molecular weight and size are the determinants of what passes in and out of the cell. The genetic elements encoding these proteins can undergo spontaneous permeability mutations that have the ability to exclude one or more antibiotics. *Pseudomonas aeruginosa* has two lipid membranes and also produces β-lactamase, hence exhibits more resistance than other coliforms. Efflux resistance is an energy-dependent mechanism by which a drug can be extruded from the bacterial cell. This is seen with the tetracyclines, macrodides and fluoroquinolones.

### Acquisition of resistance

The most adaptable mechanism available to a bacterium is the ability to exchange genetic material within its species and with different species. It can transfer nonfatal chromosomal mutations directly on to progeny and also to other bacteria. Alternatively, plasmids can be passed from one bacterium to another or between different species of bacteria. Plasmids are covalently closed circles of double-stranded DNA, which are autonomous replicating genetic elements. Each plasmid has its own origin of replication and behaves in some ways like a miniature version of the chromosome. The great advantage of a plasmid is that its genes do not code for proteins essential for normal cell growth and are therefore free to mutate when in contact with an antibiotic. Transfer of resistance genes can occur via conjugation between cells requiring physical contact, or through transduction, relying on the transfer of genetic material by a bacterium-specific bacteriophage (virus). Plasmids also enable transposons to replicate. Transposons are large segments of DNA that are readily transferred from one DNA molecule to another. The segments can contain many genes for antibiotic resistance. The transposition occurs between one self-replicating molecule of DNA (e.g. the chromosome) and another (e.g. a plasmid). The reverse can occur as can transposition from one plasmid to another. Transposition is replicative but transposons cannot replicate in isolation. They only survive when integrated into the DNA of a chromosome or plasmid. A single plasmid is therefore able to incorporate genes for resistance to a variety of unrelated antibiotics from other plasmids or from the chromosome.

Another genetic structure implicated in the acquisition of bacterial resistance is the integron, described as one or more gene cassettes located at a specific site. Most gene cassettes encode antibiotic-resistant determinants but antiseptic-resistant genes have also been described. Integrons seem to have a major role in the spread of multidrug resistance in Gram-negative bacteria but integrons in Gram-positive bacteria have also recently been described.

### Staphylococcal infections

**Coagulase-negative staphylococci**

*Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus saprophyticus* (perineum), *Staphylococcus capitis* (sebum-rich areas), and *Staphylococcus auricularis* (ear canal) are all Gram-positive micrococcae that belong to the coagulase-negative staphylococci (CNS). Very rarely do they cause disease in immunocompetent patients, and as such, they do not require directed antimicrobial therapy. When isolated from a well patient, with a dermatosis, each usually represents contamination of blood culture medium. They become implicated in disease when there is an underlying dermatosis, immunodeficiency, or prolonged systemic disease such as that encountered in the ICU or HDU setting or in a patient who is systemically unwell. *S. epidermidis* is a well-known culprit in endocarditis and septicemia, especially in the immunocompromised. Where there is bacterial resistance to numerous antibiotics, this is easily transferred to *S. aureus*.

**Staphylococcus aureus**

This Gram-positive coagulase-positive micrococcus is the most common and notorious of the staphylococcal family to be isolated from skin and skin adnexal infections. It is a pathogenic organism, which does not reside on normal skin flora. The majority of skin infections due to *S. aureus* can easily be treated with local wound care and a short course of oral antibiotics (Table 3). Where the clinical situation indicates, the antibiotics can be either enteral or parenteral. The skin of atopic dermatitis patients is more frequently colonized with *S. aureus* than that of normal controls. As the severity of lesions increases there appears to be an increase in the numbers of *S. aureus* isolated.

<table>
<thead>
<tr>
<th>Resistance mechanisms</th>
<th>Decreased binding to receptor</th>
<th>Bacterial inactivating enzymes</th>
<th>Decreased permeability of bacteria</th>
<th>Efflux resistance/active transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>β-lactamases</td>
<td>chloramphenicol</td>
<td>tetracycline</td>
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<tr>
<td>glycopeptides</td>
<td>aminoglycosides</td>
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<tr>
<td>fusidic acid</td>
<td>quinolones</td>
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<td>fluoroquinolones</td>
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</table>

Fusidic acid

Fusidic acid belongs to the fusidanes, which have molecular structures similar to corticosteroids without the steroid-like effects. It is able to achieve a high penetration and concentration at the site of infection, and is highly effective against *S. aureus*. Many guidelines suggest fusidic acid as first line in the treatment of superficial skin infections and infected eczema, as the main bacterial culprit is *S. aureus*.

Topical fusidic acid and mupirocin appear to be equally effective in cases of primary cutaneous infections. Both ointments appear to be effective against Gram-positive, Gram-negative or a combination of these organisms. The only adverse effect was that of greasiness, which was higher in the mupirocin group.

Randomized trials have demonstrated the existence of resistance to topical fusidicin and oral fusidic acid. Recent studies from Yorkshire and Bristol have further highlighted this concern over growing fucidin resistance. The West Yorkshire study found that 50% of fusidic acid-resistant strains were from dermatology patients exposed to topical fucidin in the 6 months prior to the study. The Bristol study found a doubling of fusidic acid resistance in methicillin-susceptible *S. aureus* over a 4-year period.

There may be prolonged use of topical fusidicin in people with atopic eczema. It is true that 90% of atopic eczema sufferers are colonized by *S. aureus*; however, the risk of atopic children developing MRSA infection in the future remains a growing and real concern. The resistance level to fucidin is low at present, most likely due to its unique molecular structure and therefore is less likely to share resistance mechanisms with other antibiotics. Prolonged treatment with fusidic acid on human skin, and is highly effective against *S. aureus*.

Prolonged treatment with fusidic acid ointment should be avoided, even in the community setting. Short-term use of fusidic acid, over a 2-week period, has not been found to increase resistance.

**Systemic treatment of MRSA infections**

A definitive microbiological diagnosis of invasive MRSA infection should be obtained prior to initiating potentially toxic and expensive therapies. There should be a concerted effort to obtain specimens likely to yield a positive microbiological identification. Swabs from pus and open wounds, urine samples, bronchial washings and blood cultures are essential. Sputum samples are on the whole unreliable and not indicative of systemic infection. If there is a collection of pus, whether internally or in the deeper cutis, then antimicrobial therapy alone is insufficient. Both antibiotic and surgical intervention to drain the pus is required. The usual treatment recommended for severe MRSA infections is intravenous vancomycin or teicoplanin. The incidence of severe cutaneous infections with MRSA is low.

**A new cutaneous syndrome with MRSA**

Neonatal toxic shock syndrome-like exanthematous disease (NTED) is a new neonatal entity describing toxic shock
Vancomycin and resistance

It is important that the patient receives adequate doses of vancomycin but that adverse effects are minimized. Monitoring serum levels is an essential undertaking when prescribing vancomycin. Initially, the third dose and subsequent weekly or twice-weekly levels need to be taken. Desirable trough levels are 5–10 mg/L and levels of 10–12 mg/L are considered as early signs of accumulation and an indication for dose modification. In some studies the mortality of patients with MRSA bacteraemia treated with vancomycin is higher than when patients have bacteraemia due to methicillin-sensitive *S. aureus* (MSSA) treated with other antibiotics. Delay in the initiation of appropriate MRSA therapy has been shown to be a significant mortality risk factor. Reports from Japan, USA and Eastern Europe have shown low-level vancomycin resistance in MRSA. Although these isolates did not carry the vancomycin resistance genes described in enterococci, it is a worrying development. There are no strict guidelines as regards those patients infected with vancomycin-resistant MRSA. It is advisable to limit the number of healthcare workers in contact with the patient, and extend the period of combination antimicrobial therapy.

Vancomycin intermediate resistant *Staphylococcus aureus* (VISA)

MRSA with reduced sensitivity to vancomycin has been reported from many countries. It is unclear from the emerging results whether resistance is evolving in different genetic backgrounds or in a single clone. If the former proves to be the case then it may mean that MRSA infections may become even more difficult to treat.

Glycopeptide intermediate resistant *Staphylococcus aureus* (GISA)

Since many VISA isolates also have been resistant to teicoplanin, the term glycopeptide-intermediate *S. aureus* (GISA) is more appropriate. The frequency of GISA isolates appears to be extremely low; to date, only 10 GISA infections have been reported worldwide. However, heterogeneous resistance to glycopeptides (h-GISA) have been reported in Japan, Europe and Thailand. These h-GISA strains showed vancomycin MICs ranging from 1 to 4 mg/L, but had subpopulations that could grow on agar plates containing 4–8 mg/L, which may represent the first step in the development of GISA strains. Although GISA isolates have shown resistance to many antimicrobials, all GISA isolates remain susceptible to cotrimoxazole and some of them to other common antimicrobials. Currently, there are no recommended therapy guidelines for GISA infections, although in recent studies, several new drugs have shown promising activity against GISA strains. In addition, synergy between glycopeptides and beta-lactams against GISA strains was observed in some *in vivo* and *in vitro* studies. Specific MRSA/GISA control programmes, rational antibiotic policies, including the reduction of glycopeptide use, and rapid laboratory detection of GISA and h-GISA strains are the key measures in preventing the spread of these strains.

One of the main problems encountered when managing patients with underlying dermatoses and an MRSA infection is difficulty with venous access as well as continued skin sloughing. In these situations, oral anti-MRSA agents prove to be of value. The newer oxazolidinones (linezolid) are options, but resistance is developing, once again due to inappropriate and prolonged use.

Linezolid

Linezolid is a novel synthetic antibacterial that was approved for use as an antibacterial in April 2001. It was licensed for use against vancomycin-resistant enterococci (VRE) in Japan. It has a wide range of antibacterial activity against Gram-positive bacteria. These properties are similar to those of vancomycin but it also has properties against drug-resistant bacteria including VRE and MRSA. Linezolid’s action means that it does not have cross-resistance to drug-resistant bacteria and development of resistance is slow. Linezolid is rapidly absorbed following oral administration and bioavailability, when compared with intravenous administration, is almost 100%. However, there may be reversible marrow suppression in susceptible individuals and haematological parameters need to be monitored for anaemia, neutropenia and thrombocytopenia. The regime is for twice daily administration in those patients who have either VRE or where long-term MRSA therapy is required, for instance in patients in whom venous access is almost impossible or where it proves to be a potential for further sepsis.

Recently, linezolid-resistant *Enterococcus faecalis* and *Enterococcus faecium* were reported from an Austrian ITU. Isolates were found to be related to linezolid-sensitive isolates from the same patient. This was apparently the first case report of emerging linezolid-resistance in isolates that were sensitive to vancomycin. When using linezolid, ensure that the duration of therapy is predetermined and if there does not appear to be clinical effect then linezolid must be stopped to prevent resistance build-up.

Daptomycin

The increasing incidence of serious infections caused by antibiotic-resistant Gram-positive bacteria has led to the development of new spectrum-specific agents of which daptomycin is one. It is the first member of a new class of antibacterials called cyclic...
lipopeptides. Daptomycin has rapid, concentration-dependent bactericidal activity against most clinically significant Gram-positive pathogens, including vancomycin-resistant enterococci, methicillin-resistant S. aureus, and vancomycin-intermediate and vancomycin-resistant S. aureus. This cyclic lipopeptide has a unique mechanism of action and exhibits a relatively prolonged concentration-dependent post-antibiotic effect in vitro. In September 2003 the US FDA approved daptomycin for the treatment of complicated skin and skin-structure infections. It has a once-daily dosing, and an excellent safety profile with, so far, low potential for resistance. 56

Treatment of carriers

Hospital staff and inpatients are important sources of MRSA. Hand washing and strict infection control guidelines are required. Eradication should be attempted in all medical and ancillary personnel and in those patients whose main complaint is non-dermatological. 57

Nasal carriage

The most effective topical treatment for nasal colonization is mupirocin in a paraffin base (‘Bactroban Nasal’), applied to the anterior nares three times daily for 5 days. 58 There is an increasing resistance to mupirocin, secondary to prolonged and frequent use for eradication. 59 There should be at least a 1-month hiatus before mupirocin is repeated for skin eradication. 60 Naseptin cream (0.1% chlorhexidine and 0.5% neomycin) is less effective but may reduce the number of organisms in the nose, and is particularly useful if there is mupirocin resistance. 61 Systemic therapy with rifampicin can be considered in exceptional circumstances if the benefit outweighs the risk of side-effects. It should never be used alone as this increases the risk of resistance. 62 The combination that is preferred is that with sodium fusidate, ciprofloxacin or trimethoprim.

Intact skin

Skin adjacent to carriage sites is frequently contaminated with S. aureus, which can easily be transferred to the environment on skin scales. Daily bathing for three consecutive days with chlorhexidine, hexachlorophane or povidone-iodine detergents have been shown to produce a progressive reduction in skin flora. 63 Concentrates are also available to use in the bath (Savlon, Ster-Zac Bath concentrate) but are less effective in reducing colonization than direct application. These all have some activity against staphylococci. If there is an irritant contact dermatitis then eradication should be stopped.

Ster-Zac powder (hexachlorophane powder) is an effective anti-staphylococcal agent that is useful in infants and in the groins and axillae of adults. This should not be applied to broken skin. 64

The combination of 2% topical mupirocin with 4% aqueous chlorhexidine has been used to decolonize patients in medical wards and care institutions. In observational studies, clearance has been achieved but recurrence of colonization can exceed 40% only a couple of months later. 65

Those patients in whom eradication was attempted were those in long-term care facilities or in hospital for a prolonged period of time. This was also a group that was unlike that encountered in a dermatological setting. Eradication of MRSA from intact skin is achievable, whereas those patients with chronic dermatoses will develop resistance readily when exposed to these eradication therapies. 66

Approach to tackling MRSA in the dermatology patient

1 Selective screening for MRSA in high-risk patients has similar sensitivity and is more cost-effective than a systematic approach of blanket screening every patient in hospital. 67
2 Identification of independent risk factors predicting MRSA infection of hospital patients (e.g. Inpatient transfer, ITU/HDU transfer, etc.). 68
3 Treat acute sepsis and bacteraemias once antibiotic sensitivity pattern is known. 69
4 Isolate carriers in side rooms
5 Strict infection control measures need to be implemented and the infection control team needs to supervise and ensure adherence to national and local policies. 70
6 Antibiotic prescribing needs to be monitored by consultants and pharmacy.
7 A specified time period needs to be predetermined prior to initiation of therapy.
8 If there is no clinical improvement after an appropriate length of time, then stop therapy, reculture and await sensitivity patterns.
9 Burns patients (those with large areas of denuded skin fall into this category) need to be isolated but cutaneous clearance is almost impossible and therefore eradication should not be commenced. It is more appropriate for strict infection control and for the patient to be managed in a self-contained burns unit whenever possible.
10 Surveillance programmes of the resistance patterns of the bacteria (from the local hospital microbiology laboratory as well as national patterns from PHLS laboratory) on skin wound flora are very important. 71
11 Assessment as to whether trying to control MRSA causes more problems than it solves is vital at the outset of treatment. 72
12 Wound dressings may prove very important in combating antibiotic resistance build up and in the battle against pathogens in dermatologically affected patients. 73 CombiDERM, Allevyn hydrocellular, Tegaderma and Tielle, underwent an 11-day challenge period with MRSA, E. faecalis and P. aeruginosa. Except for Tielle, the other three
The best approach when dealing with NF, in addition to tissue debridement, is combination antibiotic therapy, with the patient nursed under barrier conditions, in isolation, and whenever possible, in a surgical intensive care unit. The best antibiotic regime would be ampicillin and gentamicin with or without Gram-negative cover with either clindamycin or metronidazole. In patients with MRSA, vancomycin is the treatment of choice.\textsuperscript{73}

**Antibiotic resistance patterns of streptococci**

**Erythromycin**

Once the gold standard antimicrobial agent against uncomplicated skin infections, widespread resistance has relegated erythromycin from being the first choice in the treatment of deep-seated streptococcal infection. Europe appears to have higher levels of resistance than the USA.\textsuperscript{76–79} The resistance to erythromycin is increasing and therefore it should not be used as first line for deeper tissue infections.

**Penicillin**

The majority of streptococci are sensitive to penicillin. What appears to be moderate resistance to penicillin \textit{in vitro} can be overcome by higher doses of penicillin both \textit{in vitro} and \textit{in vivo}. This apparent \textit{in vitro} resistance may be the result of using different susceptibility testing kits that have different concentrations of penicillin and is not an accurate representation of therapeutic concentrations \textit{in vivo}.

It is important that the inoculum effect is understood in order to explain the apparent lack of clinical efficacy of penicillin in fulminant streptococcal infection. Eagle, in 1952, demonstrated this in an experimental murine model. He used a large inoculum of \textit{Staphylococcus pyogenes} to establish fulminant infection before initiating therapy. This had the effect of appearing to lower the clinical efficacy of penicillin.\textsuperscript{80} The inoculum effect on penicillin appears to be the result of bacteria entering a slower phase of growth becoming therefore less susceptible to the action of cell-wall synthesis antagonists such as the β-lactams, like penicillin and the cephalosporins. The effect of the inoculum is not the same for clindamycin or erythromycin. Clindamycin was still as effective whereas erythromycin efficacy was reduced to an intermediate level. Clindamycin is an antimicrobial agent with very good bioavailability, after oral administration\textsuperscript{81} and in many cases should be used as the first line in antimicrobial therapy for systemic or deep-seated soft tissue infections with \textit{S. pyogenes}.

However, even after taking into account the ‘Eagle effect’ there is a real and increasing resistance of streptococcal species to penicillin.\textsuperscript{82} Change in the prescribing patterns can have an effect on the resistance rates. This is quite evident when antibiotic consumption is kept to a shorter duration.\textsuperscript{83}

The PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) surveillance study,

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<th>Table 4</th>
<th>Cutaneous disease caused by streptococci</th>
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<td><strong>Primary infections</strong></td>
<td>Impetigo</td>
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<tr>
<td><strong>Secondary infections</strong></td>
<td>Eczema</td>
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<tr>
<td><strong>Toxin-induced damage</strong></td>
<td>Scarlet fever</td>
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<tr>
<td><strong>Allergic hypersensitivity</strong></td>
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<tr>
<td><strong>Contribution to dermatosis</strong></td>
<td>Psoriasis</td>
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</table>
between 1999 and 2000, produced some interesting information about the resistance patterns among isolates of S. pneumoniae. The group collected 3362 pneumococcal isolates from 69 centres in 25 countries. Overall resistance to penicillin was 22.1% with the highest incidence in isolates from Asia (53.4%), France (46.2%) and Spain (42.1%). Erythromycin resistance occurred in 31.1% of isolates overall, with highest rates found in Asia (79.6%), France (57.6%), Hungary (55.6%) and Italy (42.9%).

There was an interesting geographical variation in the prevalence of penicillin G (Netherlands 0%; S Korea 71.5%) and erythromycin (Sweden 4.7%; S Korea 87.6%) resistance. Asia had the highest prevalence of overall resistance with only 8 out of 19 antimicrobials having high activity against pneumococcal isolates. These eight included coamoxiclav, linezolid, vancomycin, teicoplanin, quinupristin/dalfopristin, levofloxacin, moxifloxacin and telithromycin. There were clear rates of resistance to clarithromycin, azithromycin, cotrimoxazole, and tetracycline, in the majority of countries submitting pneumococcal isolates. Resistance to fluoroquinolones remains low with 14.3% of 70 isolates from Hong Kong exhibiting resistance. At the moment, resistance is limited to clonal spread but care must be taken to limit that spread of resistance.

### Acne

**Propionibacterium acnes**

Propionibacteria (P. acnes, P. granulosum and P. avidum) are the only anaerobic organisms that are part of the resident skin flora. P. acnes is the most common and is found in almost all adults. These bacteria normally reside within the sebaceous follicle and share their environment with Malassezia, staphylococci and streptococci.

**Propionibacterium acnes** has for a long time been associated with acne vulgaris. Although it is widely accepted that its presence does not explain the pathophysiology of acne vulgaris, the hypothesis that P. acnes has an important role to play, especially in the development of inflammatory lesions, has been given much credence by the fact that there is clinical improvement in skin lesions when treated with topical and systemic antibiotics. Unfortunately, as elsewhere in dermatology, the resistance to frequently used antibiotics in acne is increasing and this is leading to treatment failure with previously successful therapies. This is mainly due to the inappropriate length of therapy rather than choice of antibiotic.

The emergence of resistance to the common and frequently used erythromycin, doxycycline and clindamycin has meant that therapy now has to be targeted depending on previous exposure to and duration of antibiotic therapy. New therapies need to be initiated with a view to limiting therapy to shorter periods of time to prevent emergence of resistance. The availability of the topical and systemic retinoids enables the use of antibiotics to be kept to a bare minimum and antibiotic ‘holidays’ to be given.

Resistance has a major influence on therapeutic options, for treatment can continue for months or even years and thus a selective advantage is exerted on resistant bacteria. This resistance is not only exhibited by P. acnes, but also by the cutaneous coagulate-negative staphylococci, S. aureus in the nares, streptococci in the oropharynx and enterococci in the gut. This is due to the fact that systemic antibiotics select for the overgrowth of resistant bacteria at all body sites that support a resident commensal flora. Furthermore, it is well established now that there is transfer of resistance within resident flora from treated patients to close untreated contacts.

### Erythromycin combination preparations

Monotherapy with erythromycin is no longer advocated. The combination of erythromycin-containing compounds is clinically effective in those patients with erythromycin-resistant propionibacteria. For instance, Benzamycin gel (erythromycin and benzoyl peroxide) has been shown to have comparable efficacy to double-strength Isotrexin (erythromycin and isotretinoin).

Although clindamycin resistance is increasing, it is nowhere near the levels of erythromycin resistance, and can be used for limited amounts of time. A recent study, although small numbers were evaluated, indicated that benzoyl peroxide was more adept at suppressing the follicular population of P. acnes than topical clindamycin. Even if resistance to tetracycline exists, it is less likely to be transferred to minocycline than to doxycycline.

### Minocycline

Minocycline is a tetracycline antibiotic that is commonly used in the treatment of moderate to severe acne. It is more convenient for patients as there is a once daily dose and can be taken with food. It is, however, more expensive and has a more adverse side-effect profile than the other tetracyclines. Although widely used by general practitioners and dermatologists there does not appear to be a consensus concerning the risk and benefits of this antibiotic. The Cochrane Database Systematic Reviews undertook the task of evaluating the evidence on the clinical efficacy of minocycline in the treatment of inflammatory acne vulgaris. The results revealed that the trials with minocycline were generally small and of poor quality, and lacked the gold standard randomized controlled trials. It was shown to be as effective as other tetracyclines, but there was lack of evidence to suggest superiority over other tetracyclines.

### Authors recommendations for the use of antibiotics in the treatment of acne

1. **Do not be too hasty to prescribe** antibiotics and do so only if topical therapy with adapalene or retinoids have failed.
2. **Limit time period** to a maximum of 4–6 months with oral antibiotics, and 3–4 months for topical. If there is no response at this time then prolonged therapy is unlikely to prove clinically effective.
3. **If further therapy is required** re-use previously successful antibiotic to limit cross-resistance.
Table 5 Cutaneous infections caused by Corynebacteria

<table>
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<tr>
<th>Organism and disease</th>
<th>Cutaneous manifestation</th>
<th>Location manifestations</th>
<th>Systemic</th>
<th>Diagnosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. diphtheriae</em></td>
<td>Non-healing, painful ulcer</td>
<td>Legs, feet, hands</td>
<td>Myocarditis</td>
<td>Methylene blue smears of the membrane</td>
<td>Antitoxin im/iv Erythromycin 2 g/day or Penicillin G im 600 000 U/day or Rifampicin 600 mg/day and Debridement of necrotic eschar</td>
</tr>
<tr>
<td><em>Cutaneous diphtheria</em></td>
<td>Grey pseudo-membrane</td>
<td>Axillae, groin</td>
<td>Demyelination Renal tubular necrosis Pharyngitis</td>
<td>Culture in special agar</td>
<td></td>
</tr>
<tr>
<td><em>C. minutissimum</em></td>
<td>Brown/red lesions</td>
<td>Axillae, groin</td>
<td>Asymptomatic</td>
<td>Wood's lamp-coral-red Special culture</td>
<td></td>
</tr>
<tr>
<td><em>Erythrasma</em></td>
<td>Confluent with faint scale</td>
<td>Vulval areas, Web spaces</td>
<td></td>
<td>Erythromycin 250 mg qds for 2 weeks +/- topical erythromycin or fusidic acid</td>
<td></td>
</tr>
<tr>
<td><em>C. tenuis</em></td>
<td>Thickening and encrustation of hair shaft, offensive odour, red stain</td>
<td>Axillary hair, pubic hair</td>
<td></td>
<td>Remove hair Topical erythromycin or clindamycin Antiperspirant Germicides</td>
<td></td>
</tr>
<tr>
<td><em>Trichomycosis axillaris</em></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>C. spp.</em></td>
<td>Shallow depressions, pits, boggy macerated tissue</td>
<td>Soles and toes, rarely palms</td>
<td>Foul smelling odour No systemic effects</td>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td><em>Pitted keratolysis</em></td>
<td></td>
<td></td>
<td></td>
<td>Dry area Topical benzoyl peroxide + Topical erythromycin or clindamycin</td>
<td></td>
</tr>
</tbody>
</table>

4 Use benzoyl peroxide for a week after systemic therapy to eliminate resistant cutaneous flora.
5 Do not swap one antibiotic for another too easily.
6 Avoid using dissimilar topical and systemic antibiotics at the same time.
7 Encourage compliance and patient education regards antibiotic use and resistance.

Uncommon infections

Corynebacteria

These are Gram-positive anaerobic bacilli which when viewed under Wood’s lamp exhibit coral-red fluorescence due to the porphyrin that they carry. The organisms have special growth requirements and are very difficult to culture. There are four main cutaneous infections caused by Corynebacteria: cutaneous diphtheria, erythrasma, trichomycosis axillaries and pitted keratolysis (Table 5).

The true extent of microbial resistance appears to be limited to erythromycin and tetracycline. Sensitivity to doxycycline and minocycline appeared preserved in a study of 160 bacterial isolates.98 Interestingly, there appeared to be a predilection of erythromycin- and tetracycline-resistant organisms to toe web spaces when compared to the axillae.

Pseudomonas infections

*Pseudomonas aeruginosa* is an organism found in the soil and fresh water. It gains cutaneous entry through hair follicles or breaks in the skin. There are many bacterial serotypes. The serotype O:11 appears to be the commonest freshwater isolate and possibly more invasive than the others. Pseudomonas folliculitis is a community acquired skin infection, which arises from bacterial colonization of the hair follicles. Outbreaks have been associated with prolonged water exposure, excessive number of bathers in a small area, and inadequate pool care. *P. aeruginosa* is resistant to most antibiotics and as this eruption clears spontaneously within 2–10 days it very rarely warrants systemic therapy.99,100 In cases with associated mastitis, persistent infections or in the immunocompromised, then oral ciprofloxacin can be used.

Resistance rates of *P. aeruginosa* to ciprofloxacin, ceftazidime, gentamicin, imipenem and piperacillin/tazobactam were found to be between 4% and 7% in a recent study of antimicrobial susceptibility of the pathogens of bacteraemia in the UK and Ireland 2001–02.101 Among the newly licensed and development agents, there was no resistance to linezolid in Gram-positive organisms.

Levoﬂoxacin and sparﬂoxacin have been shown to have improved Gram-positive activity compared with the older fluoroquinolones. Sparﬂoxacin has greater anaerobic activity than levoﬂoxacin, which has greater activity than ciprofloxacin or ofloxacin. However, as a class, the quinolones do have safety issues concerning their use. Amongst the variety of side-effects, phototoxicity and CNS disturbances are commonly reported.

Lyme disease

Lyme disease is a vector-borne illness caused by the spirochaete *Borrelia burgdorferi*. The vector is the *Ixodes* species of ticks, and it is the nymphal form that causes infection in humans. The incidence is highest in the USA, Europe, Far East Asia and Australia, especially among woodland habitats. The animal reservoir for the vectors is deer, dogs, horses and cattle and the incubation period varies from 7 to 10 days after tick bite up to 1 month. There is also a seasonal variation with a higher incidence in the summer and autumn.
Clinical manifestations
A nonspecific prodrome of fever, chills, myalgia and headaches may be the initial clinical symptoms, which appear approximately 7–10 days after the initial tick bite. Of the cutaneous manifestations, 30–80% suffer from the pathognomonic rash of erythema chronicum migrans, at the site of the bite. Several days after this initial lesion approximately 50% of patients will develop multiple annular lesions unrelated to the site of the bite. Additional cutaneous lesions include a malar rash, urticaria or conjunctivitis. The erythema migrans rash, annular lesions and symptoms of the prodrome tend to resolve between 3 and 4 weeks.

Therapy
In uncomplicated disease, oral antibiotic therapy with doxycycline is the gold standard treatment. Amoxicillin is safer in children as it does not cause dental staining. In the presence of allergies, oral cefuroxime or azithromycin can be used. Cutaneous disease responds within 10 days of treatment. In complicated disease, such as with cranial nerve involvement, intravenous penicillin or third-generation cephalosporins can be used.

Resistance to aminoglycosides, fluoroquinolones and rifampicin is increasing. Erythromycin resistance is increased by pre-exposure to the antibiotic and appears to be directly related to the inoculum size. It is prudent to initiate empirical antimicrobial therapy whilst awaiting antibiotic sensitivity. There is no evidence to suggest that antimicrobial prophylaxis is warranted in those patients who have been bitten by a deer tick but who have no clinical symptoms of Lyme disease.

Mycobacterial infections
Tuberculous mycobacterial skin infections
Mycobacterium tuberculosis of the human, bovine and rarely avian type causes cutaneous tuberculosis. The 1970s public health regimens implemented in the developed world led to a rapid decrease in the number of affected individuals. By the mid-1980s, there was a resurgence of tuberculosis most likely as a result of simultaneous events coinciding. Events such as the relaxation of strict public health systems, the increase in the number of immigrants from endemic areas, increased international travel, the increase in the number of homeless people, the increase in poverty and lower standards of living, the emergence of an increasing HIV-positive population and also lack of clinical suspicion leading to delayed diagnoses, and hence, untreated index cases being free to infect contacts.

The simplest way of thinking about cutaneous tuberculosis is to classify it according to exogenous or endogenous infections. Exogenous infection occurs as a result of direct inoculation via broken skin and results in primary inoculation tuberculosis and tuberculosis verrucosa cutis. Endogenous infection occurs as a result of tuberculous infection elsewhere in the body. This group includes lupus vulgaris, scrofuloderma, tuberculosis orificialis, miliary tuberculosis of the skin and tuberculous gummas.

Treatment
Chemotherapy is the mainstay of treatment for rapid cure but the spread of the disease and possible resistant strains is a growing problem. The basic principles of therapy apply to any infection with M. tuberculosis. Prior to initiation of antimicrobials consider:
1. Minimum treatment period of 6 months
2. Never with a single drug
3. If compliance is an issue, then directly observed therapy (DOT) may be required
4. Anticipation of drug interactions if there is simultaneous ingestion of other medication
5. Patient education and contact tracing
6. Chemotherapy is the same for pulmonary and extra-pulmonary disease.

The duration of therapy is between 6 and 9 months. The longer 18–24 months regime has been linked to higher failure rates due to patient compliance issues and also an increased cost:benefit ratio.

Low cost, low toxicity and highly effective first line agents in previously untreated cases include isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol, thiacetazone and p-aminosalicylic acid (PAS). Second line agents are used in those patients who have received previous treatment with first line agents and have relapsed, or those with multiple drug resistance to the first line agents. These agents tend to be less effective, require longer duration of therapy, and tend to be more expensive. The second line agents include ethionamide, prothionamide, cycloserine, kanamycin, capreomycin and viomycin.

There is considerable controversy about the optimal duration of therapy for tuberculosis among HIV-infected patients. The main danger is the apparently higher rate of recurrence in individuals treated for 6 months. It is thought that this recurrence rate can be decreased by longer treatment course of between 9 and 12 months. If DOT and response to therapy can be monitored then a 6-month course appears to be as effective.

American Thoracic Society/Centre for Disease Control Guidelines
1. 6-month regime for adults:
   Phase 1: 2 months with triple therapy
   Isoniazid + Rifampicin + 3rd drug
   (Ethambutol/Pyrazinamide/Streptomycin)
   Phase 2: 4 months with dual therapy
   Isoniazid + Rifampicin
2. 6-month regime for infants/children/adolescents:
   Phase 1 can be supplemented with the third drug choice if resistance is identified, otherwise 6 months of dual therapy.
3 9-month regime in pregnancy
   Phase 1: 2 months of triple therapy
      Isoniazid + Rifampicin + Ethambutol (DO NOT use Streptomycin or Pyrazinamide)
      Phase 2: 4 months of dual therapy
      Isoniazid + Rifampicin
4 9–12 month regime in the immunosuppressed individual
   Phase 1: 3–4 months of triple therapy
      Isoniazid + Rifampicin + 3rd drug
      (Ethambutol/Pyrazinamide/Streptomycin)
   Phase 2: 6–8 month dual therapy
      Isoniazid + Rifampicin
5 12–18 month regimes in drug-resistant individuals
   Ethambutol + Pyrazinamide + Amikacin + Ciprofloxacin or Ofloxacin
   Doses:
   Isoniazid 5 mg/kg
   Rifampicin 10 mg/kg
   Pyrazinamide 30 mg/kg
   Ethambutol 25 mg/kg (15 mg/kg in children)
   Streptomycin 15 mg/kg
   Thioacetazone 2.5 mg/kg
   Amikacin 15 mg/kg im or
   Ciprofloxacin 500–1000 mg four times a day
   Ofloxacin 400–800 mg four times a day

Nontuberculous mycobacterial infections
These are slender, nonmotile, acid-fast bacilli that are present in a variety of environments. They are varied in number and present cutaneously in as many ways. The nontuberculous or atypical mycobacteria include Mycobacterium marinum, Mycobacterium ulcerans, Mycobacterium kansaii, Mycobacterium scrofulaceum, Mycobacterium avium-intracellulare, Mycobacterium haemophilum, Mycobacterium fortuitum and Mycobacterium chelonae (Table 6).

Resistance pattern
The emergence of resistant mycobacteria indicates selection of mutant variants within a susceptible bacterial population. It remains unclear whether antimycobacterial drugs act as selective agents or whether they influence the rate of appearance of resistant mutants. For instance, there appeared to be a dose effect of *M. avium* resistance to clarithromycin when pre-exposed to the drug. However, there was less resistance when used in combination with either ethambutol or rifabutin.111 This effect appears to be due to the bacteriostatic effect of rifabutin on clarithromycin-resistant species.

If there is clinical failure with the appropriate regime then it is worthwhile testing the mycobacteria for resistance. For those strains that exhibit resistance to the first line antituberculous regimes then second line drugs need to be substituted.

Conclusion
This is by no means a complete and all encompassing review of antimicrobial resistance in dermatology. What this review hopes to achieve is a broader understanding and a collective awareness of our role as clinicians in the curtailment of antibacterial resistance. We as dermatologists should take as much responsibility for the prevention of global antimicrobial resistance as the rest of the medical profession. When attempting to deal with dermatological patients with skin infections it is important to establish an antibiotic policy at both local and national level.

Local guidelines have to cater for the prevalent resistance patterns for that area. Clinicians should work closely with the microbiology departments of the hospitals and when required with the Public Health Laboratories. Access to rapid diagnostic methods and resistance patterns is vital for our understanding, patient management and the choice of the appropriate antibiotic for the appropriate length of time. Strengthening appropriate clinical trial data for practice in the treatment of infection is an important goal for the future.

References
<table>
<thead>
<tr>
<th>Organism</th>
<th>Habitat</th>
<th>Cutaneous features</th>
<th>Extra-cutaneous features</th>
<th>Diagnosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. marinum (fish tank granuloma)</td>
<td>Fresh water</td>
<td>Purple – plaques – nodules sites of trauma</td>
<td>Tenosynovitis</td>
<td>History</td>
<td>Trimethoprim-sulfamethoxazole or Minocycline or Doxycycline or Clarithromycin or Ethambutol + Rifampicin</td>
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<tr>
<td></td>
<td>Salt water</td>
<td></td>
<td></td>
<td>Culture organism</td>
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<td></td>
<td>Beaches</td>
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<td></td>
<td>Swimming pools</td>
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<tr>
<td></td>
<td>Fish tanks</td>
<td></td>
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<tr>
<td>M. kanasii</td>
<td>Lungs</td>
<td>Papules – Pustules sporotrichoid verrucose nodules cellulitis</td>
<td>Pulmonary disease</td>
<td>Microbial culture</td>
<td>Isoniazid + Rifampicin + Ethambutol</td>
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<tr>
<td></td>
<td>Tap water</td>
<td></td>
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<td></td>
<td>Ice machine</td>
<td></td>
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<tr>
<td>M. ulcerans (Buruli ulcer)</td>
<td>Near bodies of water</td>
<td>Sites of microtrauma – solitary – painless, – enlarging, – ulcerating nodules</td>
<td>Rarely have systemic symptoms</td>
<td>Histology</td>
<td>Wide surgical excision and debridement +/- skin grafting</td>
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<tr>
<td></td>
<td>(tropical or temperate rainforests)</td>
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<td></td>
<td>Australia, Africa, Mexico, Malaysia</td>
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<tr>
<td>M. scrofulaceum</td>
<td>Water</td>
<td>Subcutaneous ulcerating nodules Abscesses</td>
<td>Unilateral lymphadenitis Pulmonary infection</td>
<td>Culture organism</td>
<td>Isoniazid + Rifampicin +/- surgical excision of localized lesion Clarithromycin or Ethambutol or Clarithromycin + Rifabutin + Ethambutol +/- Streptomycin for 3 months</td>
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<td></td>
<td>Soil</td>
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<td></td>
<td>Dairy products</td>
<td></td>
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<tr>
<td>M. avium-intracellulare (MAI)</td>
<td>Environ</td>
<td>Subcutaneous nodules + abscesses</td>
<td>Pulmonary disease Panniculitis Lymphadenitis Synovitis Fasciitis Osteomyelitis Disseminated disease</td>
<td>Culture organism</td>
<td>Clarithromycin + Ethambutol or Clarithromycin + Rifabutin + Ethambutol +/- Streptomycin for 3 months</td>
</tr>
<tr>
<td>M. haemophilum</td>
<td>Cities close to oceans Environ</td>
<td>Nodules Papules Plaques Abscesses</td>
<td>Septic arthritis Osteomyelitis Lymphadenitis Pneumonia CNS disease Meningitis Endocarditis Keratitis Osteomyelitis Hepatitis Mediastinitis Disseminated disease</td>
<td>Histology</td>
<td>Rifampicin + Clarithromycin +/- Amikacin</td>
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<td></td>
<td>Soil dust water</td>
<td></td>
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<td>Culture organism</td>
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<td>Dust</td>
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<td>Water</td>
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<td>Milk</td>
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<td></td>
<td>Marine life</td>
<td></td>
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<tr>
<td>M. chelonei</td>
<td>Uncertain</td>
<td>Nodules Abscesses Cellulitis Catheter associated</td>
<td>Osteomyelitis</td>
<td>Culture organism</td>
<td>Surgical debridement + Amikacin + Ciprofloxacin + Sulphonamides or Amikacin + Cefotaxine/Imipenem or Doxycycline or Clarithromycin</td>
</tr>
</tbody>
</table>


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