

Review Article

A review of antibiotics in dermatology

抗生素在皮膚科中的應用

KSC Fung 馮秀珍

Antibiotics refer to the natural occurring microbial products, synthetic and semi-synthetic products with antimicrobial activities useful in treating infections. The choice of antibiotics will be based on clinical evidence with regard to the agent's activity, efficacy, safety and cost. Non-essential use should be avoided because of their potential for selection of resistant organisms and are of public health concern. This article explores the mechanism of action, spectrum of activity, clinical application, adverse effects and drug-drug interactions for selective antibiotics commonly employed in dermatological practice.

抗生素是具有對抗微生物作用並且可用於治療感染的物質，它可以由微生物自然地產生，亦可以由人工合成或半合成而取得。抗生素的使用可以根據它們的抗菌性、抗菌效能、安全性以及價格來選用。應該避免不必要地使用抗生素，以免抗藥菌群出現並影響公眾健康。本文對在皮膚科診治中常用的抗生素進行討論，詳述其作用原理、抗菌譜、臨床作用、不良反應以及藥物之間的互相作用。

Keywords: Antibiotics, dermatology, review

關鍵詞：抗生素，皮膚科，綜述

Introduction

Antibiotics originally refer only to naturally occurring microbial products that suppress the growth of micro-organisms. Now it also covers those antimicrobial agents manufactured synthetically or semi-synthetically. During the past

decades, new macrolides and fluoroquinolones, extended spectrum penicillins and cephalosporins have been developed. New uses and new derivatives of many old antibiotics are continuously introduced into the market; many of them are merely expensive alternatives to existing equally effective drugs. Indiscriminate use of antibiotics not only increases the cost, but also significantly contributes to the development of resistant organisms. The most important pathogens in dermatological practice include *Staphylococcus aureus*, β -haemolytic streptococci, *Pseudomonas aeruginosa* and the causative agents of sexually transmitted diseases. Most antibiotics against these organisms can be classified according to

Department of Microbiology, Prince of Wales Hospital, Hong Kong

KSC Fung, FRCPA, FHKAM(Path)

Correspondence to: Dr. KSC Fung

Department of Microbiology, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

the main target sites for antibacterial action. Those commonly used are agents inhibiting the synthesis of bacterial cell wall, protein and nucleic acids. Choices of antibiotics for some common dermatologic infections are shown in Table 1.¹

Inhibitions of cell wall synthesis

The beta-lactams are bactericidal drugs that block the formation of bacterial peptidoglycan cell wall and activate cell autolysis.² The penicillins and cephalosporins are the major classes widely used in dermatological practice.

Penicillins

Spectrum of activity

The penicillins have wide spectrum of antibacterial activity, low toxicity, good efficacy and are relatively inexpensive. Natural penicillins include aqueous penicillin G, penicillin V, and benzathine penicillin G. They are active against *Treponema pallidum*, streptococci and a very small percentage of staphylococci causing cellulitis, impetigo and blistering distal dactylitis. Penicillin G and penicillin V are also useful against agents causing actinomycosis, Lyme disease, erysipeloid, meningococcaemia and infected dogs or cat bites.

Table 1. Antibiotic choices for skin infections*

Pathogens	Diseases	Preferred antibiotics	Alternatives
<i>Actinomyces israelii</i>	Actinomycosis	Penicillin V	Clindamycin
<i>Bacillus anthracis</i>	Anthrax	Penicillin G, ciprofloxacin	Erythromycin, doxycycline
<i>Borrelia burgdorferi</i>	Lyme disease	Doxycycline, amoxicillin	Erythromycin, cefuroxime
<i>Calymmatobacterium granulomatis</i>	Granuloma inguinale	Doxycycline	Trimethoprim-sulfamethoxazole
<i>Chlamydia trachomatis</i>	Non-gonococcal urethritis, cervicitis	Doxycycline, azithromycin	Erythromycin
<i>Clostridium perfringens</i>	Gas gangrene	Penicillin G	Clindamycin
<i>Haemophilus ducreyi</i>	Chancroid	Erythromycin, ceftriaxone	Azithromycin, fluoroquinolone
<i>Neisseria gonorrhoeae</i>	Gonorrhoea	Ceftriaxone, ceftibuten	Spectinomycin, fluoroquinolone
<i>Pasteurella multocida</i>	Dogs or cat bites	Penicillin	Amoxicillin-clavulanate, doxycycline
<i>Propionibacterium acnes</i>	Acne	Doxycycline	Erythromycin, clindamycin
<i>Staphylococcus aureus</i>	Impetigo, ecthyma, blistering distal dactylitis	Cloxacillin	First generation cephalosporin, clindamycin
<i>Streptococcus pyogenes</i>	Cellulitis, impetigo, blistering distal dactylitis	Penicillin V	First generation cephalosporin, erythromycin, clindamycin
<i>Treponema pallidum</i>	Syphilis	Penicillin G	Doxycycline, ceftriaxone, erythromycin
<i>Vibrio vulnificus</i>	Wound or bacteraemia with skin lesions	Doxycycline	Cefotaxime, ciprofloxacin

* Modified from reference 1

Benzathine penicillin is primarily indicated for treatment of syphilis, streptococcal cellulitis and prophylaxis against recurrent streptococcal infections.

Bacteria such as *Staphylococcus aureus* and *Neisseria gonorrhoeae* produce beta-lactamase enzymes that inactivate beta-lactam agents. Nafcillin, dicloxacillin and cloxacillin are penicillinase-resistant penicillins (PRP) with useful activity against staphylococci, and to a less extent, streptococci. Therefore, a combination of penicillin and PRP is commonly employed in treating skin and soft tissue infections. The penicillin binding proteins of methicillin-resistant *Staphylococcus aureus* (MRSA) have decreased affinity to PRP,³ requiring the use of vancomycin for treatment.

The aminopenicillins (ampicillin, amoxicillin), carboxypenicillins (carbenicillin, ticarcillin) and the ureidopenicillins (mezlocillin, piperacillin) were developed for their gram-negative antimicrobial activity. They have little use in dermatological practice but are associated with drug rashes. By inhibiting beta-lactamases, beta-lactamase inhibitors (clavulanic acid, sulbactam, or tazobactam) extend the antibacterial spectra of penicillins to cover *S. aureus*, a certain proportion of gram-negative bacteria and anaerobes.⁴ Amoxicillin-clavulanic acid and ampicillin-sulbactam have been shown to be effective in the treatment of skin or soft tissue infections and animal or human bites.

Adverse reactions and drug interactions

Hypersensitivity reactions to penicillin are estimated to occur in 3 to 10% of the general population. Cross-reactivity among all classes of penicillins is high. The risk of anaphylactic reactions is roughly 1 in 10,000 treatment courses, usually begin within 30 minutes after administration, and 10% of cases are fatal.⁵ Gastrointestinal side effects may manifest as nausea, vomiting, abdominal pain, diarrhoea or even *Clostridium difficile* enterocolitis. Mild to serious neurologic adverse reactions may rarely

occur, particularly if given in large intravenous doses to renal impaired patients. Rare reactions such as haemolytic anaemia, granulocytopenia, thrombocytopenia, hepatotoxicity, interstitial nephritis and renal failure have been reported.

Cephalosporins

Spectrum of activity

The cephalosporins are classified into generations. The first generation cephalosporins (cefazolin, cephalexin) provide good coverage against streptococci and methicillin-sensitive staphylococci, and are very useful for treatment of community acquired skin and soft tissue infections. Second-generation agents (cefuroxime, cefaclor) have variable activity against staphylococci but are more active against selected gram-negative organisms. Third-generation compounds are the most active against gram-negative organisms, agents such as ceftazidime are active against *P. aeruginosa*. Ceftriaxone, cefixime and ceftibuten are highly effective and well tolerated as a single-dose therapy for treatment of uncomplicated gonorrhoea.^{6,7} Their cure rate compares favourably with each other; cefixime and ceftibuten are also well absorbed orally. Cefepime is a fourth-generation agent with extended spectrum of activity against both gram-positive and gram-negative organisms (including *Pseudomonas*) and is useful in treating complicated nosocomial skin and soft tissue infections.⁸

Adverse reactions and drug interactions

Around 1 to 3% of patients who receive cephalosporins will develop mild, self-limiting maculopapular rash. Gastrointestinal complaints such as nausea, vomiting or diarrhoea may occur. Fever, serum sickness, candidal vulvovaginitis, blood eosinophilia are occasional complications. Cross-reactivity to cephalosporins may occur in 3 to 5% of penicillin-allergic patients. The manifestations are usually mild, but will be of particular concern with severe or immediate hypersensitivity reactions to penicillins.⁹

Cephalosporins are useful to treat streptococcal and staphylococcal infections for patients with non-life-threatening reactions to penicillin.

Inhibitors of protein synthesis

Commonly used by dermatologists, the tetracyclines, macrolides and lincosamides inhibit bacterial protein synthesis by binding to the ribosomes. Tetracyclines act on the 30S subunits. Macrolides and lincosamides act on the 50S subunits and resistance to one confers resistance to the other group.

Tetracyclines

Spectrum of activity

Tetracycline and the longer acting doxycycline and minocycline are commonly used in dermatology. Different tetracyclines differ mainly in their pharmacological properties rather than in their antibacterial spectra. They are bacteriostatic broad spectrum antibiotics inhibiting aerobic and anaerobic bacteria.¹⁰ Tetracyclines are valuable in treating agents causing acne vulgaris, chlamydial infections, granuloma inguinale, *Vibrio vulnificus* infections, dogs or cat bites, mycoplasma and rickettsial infections, anthrax, syphilis, Lyme disease, ehrlichiosis and some protozoal and mycobacterial infections. However, widespread resistance to tetracyclines has occurred in staphylococci and streptococci. Minocycline is useful for treating sensitive strains of MRSA, in particular when vancomycin is not considered appropriate.¹¹ *Mycobacterium marinum* is susceptible to minocycline, whereas other mycobacteria such as *M. fortuitum* and *M. chelonae* are more susceptible to doxycycline.

Adverse reactions and drug interactions

Tetracyclines are contraindicated in pregnancy and in children because of their association with dental staining and interference with bone growth. Doxycycline has less gastrointestinal side effects and requires less frequent dosing. It is excreted

primarily via biliary tract and is preferred for patients with impaired renal function. Absorption may be impaired by food, particularly milk products, and by cations like calcium, aluminium and iron. Photosensitivity and phototoxicity may occur with some tetracyclines. Tetracyclines may interact with digoxin causing digitalis toxicity. Minocycline and amitriptyline given together may accelerate cutaneous pigmentation. Serum levels of doxycycline will be influenced by co-administration of cytochrome P-450 enzymes inducers or inhibitors.

Macrolides

Spectrum of activity

Important members of these bacteriostatic drugs include erythromycin and the new macrolides, clarithromycin and azithromycin. Clarithromycin and azithromycin are better tolerated, more stable and have improved pharmacokinetics that allow shorter dosing schedules. Azithromycin has the additional advantage of shorter treatment regimens, improved tolerance and potentially improving compliance. Erythromycin is commonly used for treatment of streptococcal infections in patients allergic to penicillin. All three macrolides are active against β -haemolytic streptococci and some methicillin-sensitive *S. aureus*. However, the emergence of resistance amongst these organisms gradually limits their clinical usefulness. They have good activity against *Chlamydia*, *Mycoplasma* species, *Treponema pallidum*, *Haemophilis ducreyi* and *Ureaplasma urealyticum*. Clarithromycin and azithromycin are more active than erythromycin against some non-tuberculous mycobacteria, *Haemophilis influenzae* and *Chlamydia trachomatis*. Clarithromycin is as effective and safe as cefadroxil and erythromycin for treating skin/skin structure infections.¹² Azithromycin has longer half-life, allows single-dose therapy in the treatment of uncomplicated chlamydial genital infection¹³ and gonorrhoea.¹⁴

Adverse reactions and drug interactions

The most common side effects are gastrointestinal:

nausea, vomiting, diarrhoea, abdominal pain, anorexia. Deranged liver functions and eosinophilia occasionally occurred. By interfering with the hepatic cytochrome P-450 enzyme system, erythromycin and clarithromycin can increase the blood levels of theophylline, warfarin, triazolam, carbamazepine, and cyclosporine.¹⁵ Co-administration with astemizole, terfenadine may cause ventricular arrhythmia and should be avoided. Human studies have shown that azithromycin gives fewer drug-drug interactions than the other two macrolides.

Lincosamides

Spectrum of activity

Clindamycin provides bacteriostatic coverage for gram-positive cocci including streptococci and most *Staphylococcus aureus*, and is active against most anaerobes including *Propionibacterium* and *Actinomyces species*. Enterobacteriaceae, *Pseudomonas spp.* and *Acinetobacter spp.* are intrinsically resistant to clindamycin. It is useful for treatment of acne vulgaris, rosacea,^{16,17} and necrotising fasciitis. Clindamycin is an alternative to penicillin for streptococcal or staphylococcal infections in allergic patients. It is also alternative to metronidazole for the treatment of bacterial vaginosis.¹⁸

Adverse reactions and drug interactions

Diarrhoea is a common side effect of clindamycin therapy. The reported incidence of clindamycin associated *Clostridium difficile* colitis varies between 0.01% and 10%.¹⁹ and its uses are therefore restricted. Clindamycin, chloramphenicol and the macrolides should not be used concurrently because they have similar activities and competitively inhibit each other.

Inhibitors of nucleic acid synthesis

Fluoroquinolones

The fluoroquinolones inhibit DNA gyrase, an essential enzyme involved in the stability

of bacterial DNA.²⁰ Commonly used fluoroquinolones such as ciprofloxacin and ofloxacin are rapidly absorbed in the oral form with high bioavailability.

Spectrum of activity

They are broad-spectrum bactericidal agents covering both gram-negative and gram-positive organisms. They are active against *Staphylococcus aureus*, less likely for MRSA, and are not reliable for streptococci. They are also effective for *Bartonella henselae*, *Rickettsia spp.* and mycobacterial spp. such as *M. tuberculosis*, *M. xenopi* and *M. fortuitum*. Ciprofloxacin remains the most potent quinolone against *Pseudomonas aeruginosa*. In the treatment of sexually transmitted infections, they are active against *Haemophilus ducreyi* and sensitive strains of *Neisseria gonorrhoeae*. Ofloxacin or its more active counterpart, levofloxacin, cover both chlamydia and gonorrhoea and is useful for pelvic inflammatory disease. The quinolones have no activity against some important pathogens such as *Nocardia asteroides*, *Ureaplasma urealyticum* and treponemes.

Adverse reactions and drug interactions

The frequency of gastrointestinal upset is about 5%. Allergic reactions such as rash, urticaria, and photosensitivity occur in 1 to 2% of patients. Reduce exposure to sunlight and use of sunscreen is advised. They caused chondrocyte toxicity and impaired cartilage development in experimental studies;^{21,22} and should be avoided in pregnant, nursing women and children. They are sometimes associated with dizziness, headache, insomnia, deranged liver function and prolong QT interval. Interference with urine screening of porphyrins by ofloxacin, giving false-positive diagnosis of porphyria was reported.²³ Absorption can be interfered by co-ingestion with food, sucralfate and cations such as aluminium, magnesium, iron, or calcium. Ciprofloxacin can inhibit theophylline and caffeine metabolism. It also inhibits gamma-aminobutyric acid, potentially causing seizures when administered with some nonsteroidal anti-inflammatory drugs.

The sulfonamides and trimethoprim

Both sulfonamides and trimethoprim are bacteriostatic drugs inhibiting bacterial folic acid synthesis.²⁴ Trimethoprim-sulfamethoxazole (TMP-SMX) combination improves the antibacterial spectrum and decreases the resistance rate.

Spectrum of activity

TMP-SMX covers both gram-negative and gram-positive organisms such as staphylococci (including methicillin-resistant strains), *Haemophilus influenzae*, *Salmonella typhi* but increasing resistance is a concern. TMP-SMX is mainly used to treat urinary tract infections, *Pneumocystis carinii* pneumonia, shigellosis and respiratory tract infections. For dermatological use, it is useful for treatment of nocardiosis and some forms of Wegener's granulomatosis.^{25,26} It is also effective in the treatment of acne. However, it should not be used as first line drug because of the potential serious adverse effects such as hypersensitivity reactions and Stevens-Johnson syndrome. Trimethoprim alone has also been found to be useful in the treatment of inflammatory acne, with the principal adverse effect being a drug eruption that usually resolved rapidly upon cessation of drug. Skin and soft tissue infections due to staphylococci and streptococci should preferably be treated with other more reliable agents.

Adverse reactions and drug interactions

TMP-SMX can cause gastrointestinal side effects; hypersensitivity reactions such as fever or rashes may occur in 3 to 5% of patients. Aseptic meningitis and meningoencephalitis, or even severe adverse effects including Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anaemia and fulminant hepatic necrosis have rarely been seen. Stevens-Johnson syndrome is more likely to be associated with the sulfonamide component and no cases were recorded for trimethoprim alone. TMP-SMX can cause haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. It acts as folate

inhibitors and should be avoided in megaloblastic anaemia, pregnancy and during breastfeeding. TMP-SMX may increase the serum concentration of warfarin, phenytoin, oral hypoglycaemic agents and methotrexate to toxic levels.²⁷

Other useful antibiotics

Metronidazole

Reduced metronidazole interferes with DNA structure and inhibit nucleic acid synthesis. Metronidazole is an anti-anaerobe and an anti-protozoal agent but is ineffective against aerobic bacteria. It is useful in treating bacterial vaginosis, trichomonas vaginitis and anaerobic infections except actinomycosis and acne vulgaris.²⁸ Side effects include gastrointestinal complaints, metallic taste, dizziness, headache and disulfiram-like effect with alcohol. Metronidazole can cause neurological complications^{28,29} in patients with history of central nervous system disorders.

Glycopeptides

The antibacterial activity of vancomycin and teicoplanin is essentially restricted to gram-positive organisms, notably staphylococci and streptococci.³⁰ They are particular useful in the management of MRSA infections and in treating severe infections caused by susceptible organisms in patients with penicillin allergy. However, vancomycin-resistant *S. aureus* has recently been reported.

Oxazolidinones

Linezolid is a completely new synthetic agent active against all the clinically important gram-positive bacteria, including multiple resistant strains.³¹ It has good bioavailability by both oral and intravenous routes and dose adjustment in patients with renal impairment is not required. The drug has a good safety profile and useful in treating a variety of skin and soft tissue infections.

Topical antibiotics

Topical antibiotics are used primarily for mild to moderate superficial infections and for the prevention of recurrences in carriers of *Staphylococcus aureus*. They are also useful as prophylaxis following minor dermatological and cosmetic procedures to prevent postoperative wound infections. Comparing with systemic therapy, it has lower risk of systemic side effects and emergence of resistance in the gut microflora, higher concentration at the infection site and the overall usage of less drug. Development of contact allergy and bacterial resistance are potential adverse reactions. Commonly used topical antibiotics include tetracycline, macrolide, lincosamide, fusidic acid, chloramphenicol and mupirocin. Tetracycline, erythromycin and clindamycin are useful for the treatment of mild to moderate acne vulgaris. It was shown that tetracycline and erythromycin have additional anti-inflammatory effects that allow inhibition of neutrophilic chemotactic factors.³² Fusidic acid and tetracycline are suitable for treating skin infections caused by gram-positive cocci. Mupirocin is effective in eradicating nasal carriage and local treatment of *Staphylococcus aureus* (including MRSA). In order to prevent development of bacterial resistance, prolonged use of topical antibiotics has to be restricted.

Systemic antibiotic prophylaxis

Indications for antibiotic prophylaxis in dermatology are few. In recurrent skin infections, oral clindamycin, penicillin or erythromycin can be used depending on the causative agents. The expected infection rate following dermatological surgery without chemoprophylaxis is about 5% and the infections are usually mild. Systemic antibiotic prophylaxis is usually not required. Deep and extensive surgery involving mucosal surface may warrant preoperative antibiotics. A single dose of intravenous cefazolin 1 g will be adequate. Antibiotic prophylaxis is justified in patients with abnormal heart valves or implanted prostheses

undergoing surgery of infected tissue. A single dose of antibiotic (oral or parenteral) given one hour before the procedure is usually adequate. Appropriate choices include first generation cephalosporin (cefazolin, cephalexin), penicillinase-resistant penicillin (cloxacillin, nafcillin), or clindamycin in penicillin-allergic patients.

Antibiotic resistance

The importance of antibiotic resistance in dermatological practice is increasing. In dermatological patients the most important resistance problems are found among staphylococci, streptococci, *Propionibacterium acne* and *Neisseria gonorrhoeae*. Over 95% of *Staphylococcus aureus* strains have developed resistance to penicillin, and MRSA is in the rising trend. MRSA are often resistant also to erythromycin, tetracycline, gentamicin and quinolones. Increasing resistance of erythromycin and tetracycline has been reported for *Streptococcus pyogenes*. It is estimated that one in four acne patients harbours *Propionibacterium acnes* strains resistant to tetracycline, erythromycin, and clindamycin. An alarming trend toward antibiotic resistance was observed in hospitalised dermatology patients.³³ In Hong Kong, the IMPACT (Interhospital Multi-disciplinary Programme on Antimicrobial Chemotherapy) provides information on local antimicrobial resistance in hospital. Whereas the Department of Health set up a sentinel surveillance system to monitor the resistance patterns in the community.³⁴ Comparing the resistance pattern of 1999 with that of 2000, Penicillin-resistance in *Streptococcus pneumoniae* rose from 0% to 10%. *Streptococcus pyogenes* showed increased resistance to co-trimoxazole (0% Vs 21%) and erythromycin (8% Vs 22%). Tetracycline resistance remained relatively stable at 16%. For *Staphylococcus aureus*, methicillin-resistance rose from 0% to 15%. This might represent an over-estimation by including some strains of MRSA from patients recently discharged from hospitals.³⁴ Another local study revealed that

all (n=496) beta-haemolytic streptococci (group A, C and G) tested remained uniformly susceptible to penicillin. The overall resistance rate to erythromycin, cotrimoxazole and tetracycline were 25.6%, 6.5% and 65.3%.³⁵ Approximately half of the erythromycin-resistant isolates in Hong Kong are susceptible to clindamycin, indicating that clindamycin may be an alternative for treating patients who are allergic to penicillin. For *Neisseria gonorrhoeae*, fluoroquinolone resistance is being identified more frequently. Local testing of fluoroquinolone-resistant *Neisseria gonorrhoeae* showed that 81.2%, 89.9%, and 78.3% were resistant to penicillin, tetracycline and both, respectively.³⁶ High-level quinolone-resistance occurs in 14.5% of the quinolone-resistant strains and all remained fully susceptible to spectinomycin and ceftriaxone.

Conclusion

The choice of antibiotic depends on the clinical setting, patient factors and local susceptibility patterns. Antibiotics should be restricted for essential uses to avoid emergence of bacterial resistance. The agent that is most active, least costly and has a narrow spectrum of activity is preferred. Inexpensive, generic preparations of penicillins, first-generation cephalosporins, tetracyclines and the macrolides are usually adequate for most of the commonly encountered dermatologic infections.

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