Antibacterial Agents

134

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Key Points

- Dermatologists should be familiar with the current epidemiology of skin and soft tissue infections (SSTIs), including the prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) clones.
- Penicillin remains the drug of choice for streptococcal infections such as erysipelas and cellulitis.
- MRSA strains should be considered resistant to all β-lactams, with the exception of ceftaroline.
- For MRSA strains, appropriate oral antibacterial agents may be trimethoprim/sulfamethoxazole, minocycline, clindamycin, or the oxazolidinones, depending on the susceptibility profile of the pathogen.
- When *Pseudomonas* is a likely or proven pathogen, antipseudomonal quinolones are the only appropriate oral agents, if the pathogen is susceptible.
- For complicated SSTIs, source control (i.e., surgical drainage) should always be considered.

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Introduction

Dermatologists have been identified as the providers that prescribe the highest number of oral antibiotics in the United States, with most frequent indications being acne, rosacea, hidradenitis suppurativa, skin and soft tissue infections (SSTI), cysts, and pre-operative antimicrobial prophylaxis. Given that antibiotic exposure is associated with adverse events and emergence of antimicrobial resistance, the contemporary dermatologist should be familiar with the risks associated with the use of antibiotics and learn how to use these precious drugs judiciously, in terms of correct indication, dosage, and duration. Additionally, alternative non-antibiotic treatments of chronic dermatologic conditions should be evaluated and preferred, if appropriate, and the role of source control (i.e., surgical drainage for purulent infections) carefully considered.

Furthermore, the contemporary dermatologist should be aware of the current epidemiology of SSTIs. Over the past 20 years, there has been a global increase in the burden of staphylococcal SSTIs due to the increase in dissemination of

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specific clones of methicillin-resistant *Staphylococcus aureus* (MRSA), which are genetically and epidemiologically distinct from hospital-acquired clones, designated community-acquired MRSA (CA-MRSA). These clones carry smaller staphylococcal chromosomal cassette *mec* (SCC*mec*) elements, mostly type IV or V, frequently carry genes for virulence determinants such as Panton-Valentine leucocidin (PVL) and remain susceptible to many non-β-lactam classes of antimicrobial agents including many oral agents (clindamycin, minocycline, trimethoprim/sulfamethoxazole, fusidic acid, etc.), although multidrug resistance among CA-MRSA is increasing. Also, they typically affect groups lacking risk factors for exposure to health-care system. The modern dermatologist should be able to recognize and adequately treat this pathogen. For patients with prior exposure to health care and with immune deficiencies, multidrug resistant Gram-negative bacteria may be anticipated, mandating the use of newer, often parenteral antibiotics. In this chapter, the reader will find an overview of established and new antibacterial agents that can be used in the treatment of SSTIs. New antibacterials were selected on the basis of an approved indication for SSTI. The Food and Drug Administration (FDA) has introduced the definition of Acute Bacterial Skin and Soft Structure Infection (ABSSSI) in 2013 in the regulations for approval of new antibiotics for SSTIs. ABSSSI is defined as a bacterial infection of the skin with a lesion size area of at least 75 cm^2, with variable clinical presentations and is intended to be used as a means of homogenization of patient's entry criteria across clinical trials. In addition, early assessment of clinical response was established as the new primary endpoint for relevant trials: at least 20% reduction in lesion size at 48–72 h compared with baseline.

Antibacterial Agents

Penicillin G

Today this is still the drug of choice for streptococcal infections such as erysipelas and cellulitis, as well as for anthrax and *Erysipelothrix* infection (soft tissue and/or systemic infection after exposure to domestic or marine animals and seafood). Depending on the severity of the infection it is given either orally as penicillin V, in case of impetigo (1.5 million IU every 6 h, on empty stomach [at least for an hour]) or parenterally as i.v. penicillin G (3–4 million IU every 4–6 h, over 30 min). Oral penicillin (1.5 million IU every 12 h on empty stomach) or i.m. benzathine penicillin G (2.4 million IU every 20 days) given for a period of 12–18 months is effective as prophylaxis for recurrent cellulitis (for patients with a history of two or more episodes). Penicillins remain the drugs of choice for syphilis: benzathine penicillin (2.4 million IU i.m. once) is the preferred regimen for primary syphilis.

The major side effects of penicillins in general are hypersensitivity reactions, which range in severity from rash to anaphylactic shock and death. While allergic rash reactions occur in 4–7/1000 penicillin treatment courses, immediate anaphylactic reactions occur mostly with penicillin G from 0 to 1 h postadministration and are expressed as urticaria, angioedema, laryngeal edema, bronchospasm, and shock. They occur in 4/100,000 penicillin treatment courses with fatalities reported once in every 32,000–100,000 treatment courses. Late allergic reactions observed after 72 h of β-lactam administration are manifested by morbilliform rash, Stevens-Johnson syndrome, exfoliative dermatitis, drug fever, serum sickness, neutropenia, thrombocytopenia, hemolytic anemia, interstitial nephritis, vasculitis, pruritus, and contact dermatitis.

The detection of anaphylactic reactions to penicillin requires skin testing using minor antigenic determinants, a test not available in several countries. However, a negative result when testing with the major antigenic determinants, available commercially as the Pre-pen test, does not exclude the possibility of an anaphylactoid reaction, while skin testing with diluted penicillin G is very dangerous in individuals prone to express an anaphylactoid reaction. Therefore, whenever the appropriate tests are not available, a careful history of any potential for previous allergic reactions should be noted. In cases of an immediate

reaction, adrenaline solution (1:1000) should be given i.m. and repeated every 15 min until recovery, followed by corticosteroids.

Antistaphylococcal Penicillins

Oxacillin, dicloxacillin, cloxacillin, flucloxacillin, and nafcillin, either orally at a dose of 1 g every 8 h for mild infections or parentally at a dose of 3 g every 6–8 h for serious infections, are still the drugs of choice for staphylococcal infections. However, it should be seriously considered that 20–50% of *S. aureus* strains are now resistant to them (MRSA). Interestingly, such infections, although mostly hospital acquired, are also encountered in the community (CA-MRSA). Therefore, susceptibility tests, at least in serious infections, are required. It should be pointed out that MRSA strains are resistant to any type of β-lactam antibiotic including the inhibitor combinations, the cephalosporins, and the carbapenems, with the notable exception of ceftaroline.

The remaining group of penicillins, i.e., aminopenicillins (ampicillin and amoxicillin), carboxypenicillins (carbenicillin and ticarcillin), ureidopenicillins (mezlocillin, azlocillin, piperacillin) as well as the β-lactam group of monobactams (aztreonam) and carbapenems, will not be included since they are out of the scope of this handbook.

β-Lactamase Inhibitors

These compounds, which are by themselves weak antibiotics, are potent inhibitors of many plasmid-mediated, and of some chromosomal, β-lactamases, produced by *S. aureus* and several Enterobacterales. Three derivatives are in clinical use, clavulanic acid, sulbactam, and tazobactam. These restore the antibacterial activity of amoxicillin and ticarcillin (when combined with clavulanic acid), ampicillin (combined with sulbactam), piperacillin, and cefoperazone (combined with tazobactam) against Gram-positive cocci, including staphylococci (but not MRSA strains) and several common Gram-negative species. Ticarcillin and piperacillin combinations are also active against *Pseudomonas aeruginosa*.

Clavulanic acid and sulbactam bind primarily to plasmid-encoded β-lactamases, while tazobactam binds also to chromosomally encoded enzymes, produced mainly by *Klebsiella* and *Bacteroides* species.

The pharmacokinetics of clavulanic acid and sulbactam in humans are similar to those of amoxicillin and ampicillin. They are both available in oral and parenteral formulations with a weight ratio of inhibitor to the relevant β-lactam of 1:5 and 1:2, respectively. When clavulanic acid is combined with ticarcillin the ratio is 1:25 and for tazobactam-piperacillin is 1:8. With the exception of clavulanic acid, the excretion of which is influenced in renal failure (and therefore amoxicillin plus clavulanic acid should not be administered in patients with renal insufficiency), the dose of the remaining combinations should be reduced proportionally to the decrease of the relevant β-lactam dose. Tissue kinetics of the inhibitors are compatible with those of the combined β-lactam.

Clavulanic acid plus amoxicillin is given in adults orally at a dose of 1 g every 12 h, while i.v. at a dose of 1.2 g every 6 h. An oral extended release (XR) formulation is available, which is administered at a dose of 1.25 g every 12 h. Sulbactam plus ampicillin is given orally at a dose of 3.75 g every 8 h, and i.v. at a dose of 3 g every 6–8 h. Clavulanic acid plus ticarcillin is given only i.v. at a dose of 3.2 g every 4 h or 5.2 g every 6 h while tazobactam plus piperacillin is given at a dose of 3.375 g every 6 h or 4.5 g every 6 h (depending on the available formulation).

As with any β-lactam antibiotic, allergic reactions are the main threat and they are mainly attributed to the combined β-lactam and very seldom to the inhibitor itself. Diarrhea with the oral compounds exceeds in some series 10% of the treated cases.

Because of their very wide spectrum of activity, which disturbs gastrointestinal tract flora and destroys colonization resistance, the inhibitors should not be given for the common streptococcal or staphylococcal infections, taking also into consideration that MRSA strains are, by defini-

tion, resistant. On the contrary, when SSTIs are likely to be polymicrobial such as surgical site infections of the abdominal wall, or in proximity to the genital tract or rectum, diabetic foot infections and human or animal bites, β-lactam/β-lactamase inhibitor combinations should be among the preferred treatment options.

Cephalosporins

Based on their in vitro activity and their stability to β-lactamases, cephalosporins are divided into four generations (Table 134.1). They represent broad-spectrum antibiotics, the first and second generation being more potent against the Gram-positive cocci, the third and fourth against the nosocomial Gram-negatives, including the various Enterobacterales and *P. aeruginosa.* Also, the fourth generation has greater coverage against Gram-positive organisms than the third-generation agents.

Cephalothin, cephradine, cefazolin, cefoxanide, and cefamandole possess the highest activity against staphylococci; cefoxitin and cefotetan are the only ones active against *Bacteroides fragilis* but acquired resistance is increasing. Ceftazidime is the most potent against *P. aeruginosa.* The latter compound, however, is practically not active against streptococci and staphylococci. None of the first-, second-, third-, or fourth-generation agents is active against methicillin-resistant staphylococci. Ceftriaxone (250 mg i.m. single dose) remains the preferred treatment for uncomplicated gonococcal infections.

The pharmacokinetic properties of the parenteral compounds differ in that the half-life ($t_{½}$) can range from 30 min to 8 h, mandating the frequency of administration (Table 134.1). Based on the much lower minimal inhibitory concentrations (MICs) for Gram-negative bacteria as well as the addition of different side-chains at position 3 of their nucleus, which modifies their kinetic properties, third- and fourth-generation cephalosporins in comparison with earlier compounds, have kinetics which are particularly advantageous when treating infections in the cerebrospinal fluid or the prostatic and bone tissues.

Table 134.1 Classification of cephalosporins with half-lives and daily dosage schedules

Generic name	Half-life (h)	Daily dosage regimen and route of **administration**
First generation		
Cefazolin	1.8	1 g every 8 h i.v. or i.m.
Cephradine	0.7	0.5 g every 6 h orally or 1–2 g every 4–6 h i.v.
Cephalexin	0.9	0.5–1 g every 6 h orally
Cefadroxil	1.2	0.5–1 g every 12 horally
Second *generation*		
Cefamandole	0.8	2 g every 4–6 h i.v.
Cefoxitin	0–8	2 g every 4–6 h i.v,
Cefuroxime	1.3	1.5 g every 6–8 h i.v.
Cefotetan	3.5	2–3 g every 12 h i.v.
Ceforanide	3.0	1–2 g every 12 h i.v.
Cefuroxime axetil	1.3	0.25–0.5 g every 12 h orally
Cefaclor	0.8	0.5–1 g every 8 h orally
Cefprozil	1.2	0.5–1 g every 8 h orally
Loracarbef	1.1	0.4 g every 12 h orally
Third generation		
Cefotaxime	1.0	2 g every 6–8 h i.v.
Ceftriaxone	8.0	2 g every 12-24 h i.v.
Ceftazidime	1.8	2 g every 8 h i.v.
Ceftizoxime	1.7	2 g every 8–12 h i.v.
Cefoperazone	2.0	2 g every 8–12. h i.v
Cefixime	3.7	0.4 g every 24 h orally
Gefpodoxim eproxetil	2.2	0.4 g every 12 h orally
Cefetamet	2.2	0.5 g every 12 h orally
Ceftidoren pivoxil	1.6	0.4 g every 12 h orally
Ceftibuten	2.5	0.2 g every 12 h orally
Fourth generation		
Cefepime	2.1	1–2 g every 8–12 h i.v.
Cefpirome	1.0	1–2 g every 8–12 h i.v.
Anti-MRSA		
Ceftaroline fosamil	2.6	0.6 g every 12 h i.v.
Ceftobiprole	3.0	0.5 g every 8–12 h i.v.

Adverse effects associated with the cephalosporins are similar to those from other β-lactams and concern mainly allergic reactions. However, anaphylaxis/angioedema reactions are rare relative to the frequency of 0.04% associated with penicillin. Allergic cross-reactions with the penicillins are expected at a range of <7%. Hematological reactions and coagulation abnormalities (hypoprothrombinemia) have been rarely reported, while gastrointestinal reactions, antibiotic-associated diarrhea including pseudo-

membranous colitis occur at a frequency of 1–7%.

Like the β-lactam/β-lactamase inhibitor combinations, cephalosporins should not be given for common SSTIs since their broad spectrum of activity disturbs the normal flora, facilitating colonization with enterococci and fungi. Additionally, cephalosporin use favors selection of resistant clones, especially Gram-negative species producing extended-spectrum β-lactamases (ESBLs) in normal floras. Furthermore, these agents do not provide coverage against MRSA, so if this pathogen is a concern, empiric coverage with another active agent is recommended pending culture results. The appropriate dosage regimens for adults are shown in Table 134.1.

Ceftaroline

Ceftaroline fosamil is the prodrug of the active metabolite, ceftaroline. Ceftaroline is a novel agent that belongs to the antimicrobial class of cephalosporins. Because of its unique spectrum of activity, which includes MRSA, it has been described in the literature as a "fifth-generation" cephalosporin.

Like other β-lactams, ceftaroline exerts its rapid bactericidal effect by binding to key penicillin-binding proteins (PBPs). It has a high affinity against MRSA PBP 2A and against penicillin-resistant *Streptococcus pneumoniae* PBPs.

Ceftaroline has a broad-spectrum activity against Gram-positive and Gram-negative organisms including *S. pneumoniae*, *S. aureus* (methicillin-resistant as well as vancomycin-intermediate and -resistant isolates), *Streptococcus pyogenes* and other Streptococci and Gram-negative species (*Haemophilus influenzae, Moraxella catarrhalis,* and Enterobacterales non-ESBL-producers).

Ceftaroline fosamil is dosed at 600 mg i.v. every 12 h (infusion over 1 h) in adults. Dosage adjustment is necessary in patients with moderate to severe renal impairment. Ceftaroline is well tolerated. The most common adverse events reported in clinical trials were diarrhea, nausea, and headache. The most common adverse event leading to discontinuation of ceftaroline was hypersensitivity (0.3% of patients).

Ceftaroline fosamil has been approved for the treatment of acute SSTIs and community-acquired pneumonia. In cases where coverage for MRSA is necessary but *Pseudomonas* and *Acinetobacter* are not among the possible pathogens, ceftaroline is an attractive option because of its favorable safety and tolerability profile.

Aminoglycosides

They are represented by tobramycin, netilmicin, amikacin, and isepamicin for systemic use, neomycin for topical application, and gentamicin for both. It should be pointed out that all aminoglycosides are inactive against streptococci as well as against anaerobes, while despite their in vitro activity, they do not behave as bactericidal agents against staphylococci. However, after combination in vitro with antistaphylococcal penicillins and/or rifampicin they exhibit a synergistic result. Therefore, the dermatologist at least for the common streptococcal or staphylococcal infections should not prescribe any aminoglycoside either systemically or locally, as solutions or as ointments. Aminoglycosides are by definition ototoxic and nephrotoxic agents. Local application facilitates development of resistance among the Gram-negatives and particularly in *P. aeruginosa* strains (which serve as colonizers and future pathogens) since the exposed skin area favors transfer of resistance genes. It should also be considered that various non-antimicrobial ointment ingredients are capable of inducing allergic skin reactions aggravating inflammatory signs.

Tetracyclines

The tetracyclines currently in use for systemic administration are the short-acting compound, tetracycline ($t_{½}$, 8–9 h) and the long-acting derivatives, doxycycline and minocycline ($t_{½}$, 16–18 h).

Tetracycline should be administered on an empty stomach to increase absorption while doxycycline and minocycline are absorbed almost completely, achieving high serum levels with relatively small doses. Despite their broad spectrum of activity covering both Gram-positive and several Gram-negative aerobic and anaerobic species, acquired resistance has emerged both among *S. pyogenes* and among *S. aureus strains*. In particular, minocycline is the most effective against *S. aureus,* including both MRSA and CA-MRSA strains.

The long-acting tetracyclines are lipophilic and they are diffused in many tissues and fluids. However, they all cross the placenta. They concentrate in fetal bone and teeth causing hypoplasia of the enamel with subsequent permanent grey-brown to yellow discoloration of the teeth and depression of skeletal growth in premature infants. Therefore, tetracyclines should not be given during pregnancy, at the breastfeeding period or to children up to the age of 8 years when tooth enamel is being formed. Tetracyclines may cause photosensitivity reactions, gastrointestinal tract disturbances, and hepatotoxicity. Vertigo is a side effect unique to minocycline, usually beginning on the second or third day of therapy and it is more frequently observed in women than in men.

Food in general decreases the absorption of tetracyclines, while all form inactive complexes with divalent or trivalent cations. Therefore, tetracyclines should not be given simultaneously with calcium, magnesium, and aluminum in antacids, milk, or iron-containing compounds. Also, they should not be prescribed in pre-existing renal or hepatic insufficiency.

Tetracycline is given at a dose of 500 mg every 6 h. Minocycline is given at a loading oral dose of 200 mg followed by a daily dose of 100 mg every 12 h and doxycycline at a dose of 100 mg every 12 h. Doxycycline or minocycline have been proposed by the Infectious Diseases Society of America (IDSA) guidelines as one of the options for empirical treatment of SSTIs caused by CA-MRSA in outpatients. In cases where coverage for both β-hemolytic streptococci and CA-MRSA is desirable, combination with a β-lactam is recommended.

Tigecycline

Tigecycline is the first member of a new class of broad-spectrum antibiotics, the glycylcyclines. It is a derivative of minocycline, designed to avoid both *tetK* (tetracycline-specific efflux-mediated) resistance and *tetM* (target modification) class resistance to tetracyclines. It inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit but with a five times higher affinity than that for the tetracyclines. Tigecycline exhibits a bacteriostatic activity. Its antimicrobial spectrum includes staphylococci (both methicillin-susceptible and -resistant isolates), streptococci, enterococci (both vancomycin-susceptible and -resistant isolates), multidrug resistant Enterobacterales (with the exception of *Proteus, Providencia,* and *Morganella* spp.), *Acinetobacter* spp. as well as anaerobes. It is not active against *P. aeruginosa*. Tigecycline is administered at a loading dose of 100 mg i.v. the first day, followed by 50 mg every 12 h from the second day on. No dose adjustment is required in renal impairment and in moderate hepatic impairment while a 50% reduction of the daily dose is required in case of severe hepatic impairment.

Tigecycline has been approved for the treatment of complicated SSTI (cSSTI) by susceptible pathogens. Monotherapy with tigecycline could be a choice when a broad-spectrum antimicrobial coverage is indicated (for polymicrobial or mixed infections) provided that *P. aeruginosa* is not among the causative bacteria. Tigecycline has not been approved for the treatment of diabetic foot infection. Clinicians should add an antipseudomonal agent to empirical regimens in patients with risk factors for pseudomonal infections. A concern is that tigecycline has not been evaluated in randomized trials for the treatment of severely ill patients. The bacteriostatic action of the drug and the limitations of its PK/PD characteristics, mainly a low achievable Cmax, create concerns about its use in the case of bacteremic and septic patients.

Tigecycline is in general well tolerated. Frequently observed side effects are of gastrointestinal origin (nausea, vomiting) but the most serious ones consist of a decrease in fibrinogen

and a reversible coagulopathy and thrombocytopenia.

Omadacycline

Omadacycline is a novel tetracycline derivative acting through inhibition of protein synthesis by binding the 30S unit of the bacterial ribosome. Its structure offers protection against the most common mechanisms of resistance which inactivated previous members of the class, namely, efflux pumps and ribosomal protection. Omadacycline possesses a large spectrum of in vitro activity, including Gram-positives, Gram-negatives, anaerobes, and intracellular organisms. It exhibits good activity against *S. aureus* (including MRSA), streptococci, vancomycin-susceptible and vancomycin-resistant enterococci, covering a great array of pathogens causing ABSSSI.

Omadacycline has a long plasma half-life permitting once daily dosing and a low protein binding of 20%. It is available in both i.v. and oral formulation, allowing a convenient switch to oral treatment. The recommended dose scheme is 100 mg once daily for the i.v. formulation and 300 mg once daily for the oral one. No adjustment is needed for impaired renal or hepatic function. As all members of the tetracycline class, omadacycline is subject to some dietary restrictions: the oral formulation must be taken with water on an empty stomach with at least 4 h of fasting before and 2 h of fasting after its congestion. Clinicians should caution the patients to avoid medications or foods with polyvalent cations up to 4 h after administration of omadacycline.

OASIS-1 and OASIS-2 were the two Phase III, double-blind, multicenter, registrational trials in which omadacycline was compared to linezolid in the treatment of adult patients with ABSSSI. The OASIS-1 trial compared the i.v formulations of both drugs; omadacycline was given 100 mg twice daily on day 1 and then 100 mg once daily. In both arms there was an optional transition to oral treatment on day 3. OASIS-2 used oral only formulations, employing a loading dose of 450 mg on day 1 and 2 followed by 300 mg once daily for omadacycline. Linezolid was given in standard doses in both trials. The total duration was 7–14 days. A great proportion of patients (61%) in both studies were illicit drug users. Omadacycline established noninferiority to linezolid for the primary endpoint of early clinical response. Clinical success rates were similar across groups of pathogens, however, in the OASIS-1, success rates were lower for omadacycline for *S. pyogenes* (72.7% omadacycline vs. 88.9% linezolid) although this was reversed in OASIS-2 (69% omadacycline vs. 56.3% linezolid). Treatment emergent adverse events were most common with omadacycline compared to linezolid and particularly during the loading phase of OASIS-2 trial. The most common adverse events in the OASIS trials were nausea (21.9% vs. 8.7%) and vomiting (11.4% vs. 3.9%).

Omadacycline was FDA approved in 2018 for the treatment of ABSSSI and community-acquired pneumonia; European application was withdrawn in November 2019.

Macrolides and Clindamycin

The macrolides (erythromycin, roxithromycin, azithromycin, and clarithromycin) and the lincosamides (lincomycin and clindamycin) although chemically unrelated they have similar properties. Among the macrolides, clarithromycin possesses the most potent in vitro action against group A streptococci and methicillin-susceptible staphylococci (MSSA) strains followed by erythromycin, while azithromycin is two- to fourfold less active than erythromycin. However, cross-resistance among macrolides and lincosamides is usually the rule. It is a matter of concern that resistance rates of *S. pyogenes* to erythromycin have been increasing. MRSA strains are almost always resistant to macrolides. Lincomycin or clindamycin resistance has been reported in 20–85% of MRSA strains including 50% of erythromycin-resistant strains. Clindamycin resistance among erythromycin-resistant strains could be inducible and it may be overlooked if the laboratory does not perform a special test, called "D test." However,

cross-resistance of *S. aureus* between lincomycin and clindamycin is complete. Clindamycin activity against streptococci is more potent than lincomycin but similar to that of erythromycin.

With the exception of azithromycin, which is better absorbed without food, all others can be taken with food. Half-lives are 1.4 h for erythromycin, 3–7 h for clarithromycin, >70 h for azithromycin, and >2.5 h for the lincosamides. Therefore, erythromycin should be administered at doses of 500 mg every 8 h orally or i.v., clarithromycin at 500 mg every 12 h orally or i.v., azithromycin at 500 mg every 24 h orally or i.v., lincomycin at 600 mg every 8 h i.v. or i.m., and clindamycin at 600 mg every 8 h i.v. or orally. With the exception of CSF, all have good tissue penetration and all are selectively concentrated in the neutrophils and the macrophages. A dose adjustment is required for erythromycin and clarithromycin in patients with renal impairment.

Macrolides in general are well tolerated. Their main adverse reactions concern the gastrointestinal tract, more with erythromycin and much less with clarithromycin and azithromycin. However, with lincosamides, diarrhea occurs in up to 20% of patients, while 1.9–10% of clindamycin-treated patients will suffer from the complication of pseudomembranous colitis caused by toxin-producing *Clostridioides difficile.*

Macrolides and lincosamides can be used as alternatives to penicillin, particularly in β-lactam allergic patients when streptococci and MSSA are the potential pathogens. However, macrolides should not be used alone in the treatment of deep-seated staphylococcal infections because of the fear for the emergence of resistance during therapy. Clindamycin has been proposed by the IDSA guidelines as one of the options for empirical treatment of SSTIs caused by CA-MRSA. It can be used as monotherapy when coverage for both CA-MRSA and β-hemolytic streptococci is needed. An advantage of clindamycin is that it suppresses toxin production in toxin-producing strains of *S. aureus* or streptococci, which could be responsible for serious complications in the setting of SSTIs (necrotizing fasciitis, toxic shock syndrome, etc.).

Streptogramins

Synercid

Synercid is a combination of two semisynthetic streptogramin molecules, quinupristin (a group B or type I streptogramin) and dalfopristin (a group A or type II streptogramin) in a 30:70 ratio (w/w). The combination has synergistic antibacterial activity in vitro against a wide range of Gram-positive organisms, including methicillin-resistant and glycopeptide-intermediate strains of staphylococci (GISA), penicillin and macrolide-resistant strains of streptococci, multidrug-resistant and vancomycin-resistant strains *of E. faecium,* while it is intrinsically inactive against *E. faecalis.* It is also active against *S. pneumoniae, M. catarrhalis,* pathogenic *Neisseria* spp., and Gram-positive anaerobes such as *Clostridium* and *Peptostreptococcus* spp. Synercid exerts its activity through inhibition of protein synthesis. It is bactericidal against staphylococci and pneumococci and bacteriostatic against enterococci. The recommended dose is 7.5 mg/kg every 8 h or every 12 h for SSTIs, infused over 60 min. A dose reduction is required for patients with hepatic cirrhosis or severe renal insufficiency. The drug combination is a potent inhibitor of the cytochrome P450 enzymes, exhibiting clinically important interactions with many other drugs such as antihistamines, antiretroviral agents, antineoplastic agents, benzodiazepines, calcium channel blockers, cholesterol-lowering agents, gastrointestinal motility agents, immunosuppressive agents, steroids, as Synercid enhances their activity.

It is approved for the treatment of cSSTIs and as a salvage therapy for invasive *E. faecium* and MRSA infections in the setting of vancomycin treatment failure. The most common adverse effects are arthralgia, myalgia, gastrointestinal disturbances, rash, headache, generalized pain and pruritus and increased conjugated bilirubinemia. Peripheral venous irritation is common and can be minimized by infusion via a central venous route.

Quinolones

The fluoroquinolones are represented by norfloxacin, ciprofloxacin, ofloxacin, moxifloxacin, levofloxacin, and prulifloxacin. Delafloxacin is the most recent addition to this class and will be discussed in the end of the chapter. They represent fluorine- and piperazinyl-substituted derivatives of the original nalidixic acid structure, which is a 1, 8-naphthyridine. They are characterized by a broad spectrum of activity and good tolerability. Most are available for oral and parenteral use and possess similar bioavailability for both routes. Despite their broad spectrum of activity, the abovementioned fluoroquinolones (with the exception of moxifloxacin) are not active against streptococci, anaerobes, and MSSA, while their activity against MRSA is considered as borderline. Therefore, there is no absolute indication for their use in common dermatological infections. However, whenever *P. aeruginosa* is implicated, ciprofloxacin is an option because it is the only orally available antimicrobial agent with antipseudomonal activity. Furthermore, norfloxacin and prulifloxacin have no indication for SSTIs.

Ciprofloxacin is administered at a dose of 500–750 mg every 12 h p.o. or 600 mg every 12 h i.v. A formulation of extended release (XR) is also available and it is given at a dose of 500 or 1000 mg every 24 h. Ofloxacin is administered at a dose of 400 mg every 12 h p.o. or i.v. and levofloxacin at 500–750 mg every 24 h p.o. or i.v. A dose adjustment is needed for ciprofloxacin and levofloxacin in patients with renal impairment.

The most important but rare adverse effects of the abovementioned quinolones include QTc interval prolongation, central nervous system (CNS) excitatory symptoms, glucose dysregulation, hepatotoxicity, hypersensitivity, phototoxicity, peripheral neuropathy, and tendonitis. Also, quinolones have been associated with *C. difficile*-associated diarrhea.

Moxifloxacin exhibits an improved spectrum of activity, which includes Gram-positive, Gram-negative, aerobic and anaerobic bacteria as well as intracellular pathogens. As with other quinolones, moxifloxacin acts by binding to and inhibiting bacterial topoisomerases (i.e., topoisomerase II and IV), exhibiting a bactericidal effect. It is very active against streptococci, pneumococci, irrespective of β-lactam or macrolide-resistance and against MSSA. It has a more variable activity against MRSA strains. It is also active against Enterobacterales but not against *P. aeruginosa.* Its spectrum also includes several species of anaerobes: *Clostridia, Fusobacteria, Prevotella, Porphyromonas, Peptostreptococci, Propiobacterium,* and *B. fragilis.* Moxifloxacin has good in vitro activity against pathogens isolated from patients with animal or human bite infections as well as pathogens that cause less common cSSTIs, such as *Bacillus anthracis, Yersinia pestis, Vibrio* spp. and *Fransicella tularensis.*

It is administered orally at a dose of 400 mg once daily. It has a favorable pharmacokinetic profile with advantageous tissue penetration at skin and soft tissue sites. It is metabolized by conjugation to inactive metabolites and it is excreted by both renal and hepatic routes, reducing the potential for drug accumulation in patients with renal or liver impairment.

The most common, adverse events are gastrointestinal disturbances. In contrast to some other fluoroquinolones, it appears to have a low propensity for photosensitivity and CNS toxicity. As it is not metabolized by the cytochrome P450 pathway, it shows no interactions with methylxanthines, ranitidine, oral anticoagulants, or contraceptives. Its bioavailability is reduced by the coadministration of antacids, sucralfate, or iron preparations but not by food.

It is licensed for the indication of respiratory tract infections, as well as for the treatment of mixed aerobic and anaerobic SSTIs from susceptible pathogens. The IDSA guidelines recommend fluoroquinolones for the treatment of infections that are likely to be polymicrobial, including surgical wound infections involving the abdominal wall, perineum and genital tract as well as animal and human bite infections. Fluoroquinolones (apart from delafloxacin) should not be used for treatment of skin and soft tissue infections due to MRSA because resistance may develop during therapy.

Delafloxacin is a new quinolone with a broad spectrum of in vitro activity encompassing both Gram-positive pathogens (including MRSA) and Gram-negative bacteria (including quinolone-resistant *Escherichia coli* and *K. pneumoniae)*, while maintaining activity against anaerobic bacteria. It shows a greater in vitro activity against both quinolone-susceptible and quinolone-resistant Gram-positive cocci (including MSSA, MRSA, CoNS, *S. pyogenes*, and enterococci) compared to the other members of the class. As far as Gram-negative pathogens are concerned, delafloxacin showed increased activity against quinolone-resistant strains of *P. aeruginosa*.

Delafloxacin can be given as i.v. or as oral administration and has the potential to be used in sequential therapy with the oral formulation. The recommended dosage for ABSSSI is: 300 mg i.v. q12h for 5–14 days, or 300 mg i.v. q12h, then switch to a 450-mg tablet po q12h for 5–14 days, 450 mg po q12h for 5–14 days. Renal clearance is significantly affected by renal impairment. A dosage reduction is recommended in patients with impaired creatinine clearance, according to the following scheme: (1) i.v. formulation; CrCl 15–29 mL/min: 200 mg IV q12h OR 200 mg IV q12h, then switch to 450 mg PO q12h. CrCl<15 mL/min: not recommended (2) oral formulation; CrCl 15–89 mL/min: No dosage adjustment needed. CrCl<15 mL/min: not recommended. No dose adjustment is required in patients with hepatic impairment.

Nausea and diarrhea are the most common adverse events that have been reported in registrational trials; no effect in QTc was reported. A lower risk for *C. difficile* diarrhea may exist, since delafloxacin is in vitro active against this anaerobic pathogen. No tendon injury or CNS-related adverse effects have been reported so far with delafloxacin.

Delafloxacin possesses some characteristics that distinguish it from previous members of the quinolone class. Due to its weak acidic character, delafloxacin exhibits enhanced activity in low pH environments including inflammatory cells and infected tissues; this offers a great advantage for the treatment of biofilm-associated infections, abscesses, skin and urinary infections. In addition, it is capable of dual target binding (gyrase and topoisomerase IV) which allows for a broader spectrum of antimicrobial activity against Gram-positive and Gram-negative bacteria. Coverage against P. aeruginosa is another important asset. It is a mild CYP3A4 inducer, therefore drug–drug interactions are rare. This large spectrum antimicrobial profile makes it a perfect candidate for empirical treatment of ABSSSI, including patients with risk factors for polymicrobial infections. A favorable safety profile was shown in clinical trials, denoting the potential for prolonged treatment where necessary.

Randomized controlled trials have shown similar efficacy to the comparators (vancomycin, linezolid, and tigecycline) in the treatment of ABSSSI against heterogeneous bacterial populations. Delafloxacin was Food and Drug Administration (FDA) approved in 2017 for ABSSI. European Medicines Agency (EMA) approval was granted in 2019.

The reader has to keep always in mind the cautionary warnings that have been issued by the FDA and the EMA from 2018 onwards, against the use of members of the quinolone class, when other treatment options are available. The warnings were based on accumulating data for irreversible peripheral neuropathy, aortic aneurysms and dissection of aortic aneurysms, risks for mental health, serious blood sugar disturbances and tendon ruptures. Elderly patients, as well as patients with organ transplantation, chronic kidney disease and those under corticosteroid treatment are at greater risk to tendon injuries, therefore the EMA recommends quinolone use with caution in these patient groups. Product label changes and boxed warnings were implemented accordingly.

Rifampin

Primarily used for tuberculosis, rifampin has also very promising bactericidal activity against staphylococci, including a high percentage of MRSA strains. However, it should never be administered as a single agent, because staphylococci will rapidly develop resistance in vivo even

after the first dose. To protect against this, rifampin should be combined with another agent possessing antistaphylococcal activity, like trimethoprim-sulfamethoxazole, a fluoroquinolone, a glycopeptide, or daptomycin. It should not be given empirically but only in cases where MRSA strains have been isolated and their susceptibility to rifampin has been confirmed. As an extremely lipophilic substance, rifampin penetrates well into all body tissues and stains brightly red almost all body excretions.

It is given in adults as a daily dose of 600 mg plus 300 mg orally or i.v. on empty stomach (at least 1 h before meals). Rifampin may cause hepatotoxicity, and drug interactions because it is one of the most potent inducers of intestinal and hepatic microsomal enzymes leading to decreased serum $t_{½}$ for several compounds, among which digoxin, dicumarol anticoagulants, prednisone, ketoconazole, and oral contraceptives, requiring dosage adjustments for the latter drugs or therapeutic drug monitoring or even drug discontinuation.

Fusidic Acid

This antibiotic, despite its advantageous properties, is not available in the USA. It is mainly active in vitro and in vivo against staphylococci, including a high percentage of MRSA strains. Fusidic acid possesses excellent tissue kinetics and has a $t_{½}$ of 14 h. With the exception of self-limited hepatotoxicity, fusidic acid is safe and well tolerated by the oral route. The i.v. formulation should be given by slow infusion (3–4 h) to avoid chemical irritation of veins and subsequent thrombophlebitis. It is administered at a dose of 500 mg every 8 h orally or i.v. Topical use of fusidic acid in the form of gauzes or ointments should be avoided since it is rapidly followed by emergence of resistance in staphylococci colonizing the skin.

Trimethoprim/Sulfamethoxazole

The combination acts synergistically against Enterobacterales and staphylococci since trimethoprim potentates the sulfonamide activity by the sequential inhibition of folic acid synthesis. It is given at a dose of 980 mg every 8–12 h p.o. or i.v., with a dose adjustment in case of renal impairment. The most important side effects are attributed to the sulfonamide component and include acute hemolysis related to glucose-6-phosphate dehydrogenase deficiency, hematologic toxicity (leukopenia, thrombocytopenia, or pancytopenia), hypersensitivity reactions and erythema multiforme often expressed as Stevens-Johnson syndrome. The combination has bactericidal activity against staphylococci. It has proven to be in vitro active against 95–100% of CA-MRSA strains and although clinical studies for its efficacy in the treatment of staphylococcal infections are limited, the IDSA guidelines recommend it as one of the options for empirical treatment of SSTIs caused by CA-MRSA in outpatients. The good tissue penetration, the availability of oral formulation, and the low cost make trimethoprim/sulfamethoxazole an attractive alternative to newer more expensive drugs or drugs that require intravenous administration. Nevertheless, it should be avoided as monotherapy in cellulitis because it has poor activity vs. *S. pyogenes*.

Iclaprim

Iclaprim is a diaminopyrimidine which acts by selectively inhibiting the bacterial dihydrofolate reductase (DHFR), similarly to trimethoprim.

Compared to its ancestor, iclaprim has demonstrated an 8- to 32-fold more potent in vitro activity for all Gram-positive isolates with a rapid bactericidal in activity. Along with its pharmacokinetic properties (large volume of distribution and high concentrations in the skin compartment), iclaprim stands out as an ideal candidate for the treatment of ABSSSI.

The spectrum of in vitro activity includes also MRSA isolates that are nonsusceptible to daptomycin, linezolid, or vancomycin, against which iclaprim has demonstrated relatively low MICs.

REVIVE-1 and REVIVE-2 were the two double-blind, multicenter registrational trials of iclaprim given as an 80 mg fixed IV dose infused

over 2 h every 12 h, vs. vancomycin in patients with ABSSSI. Noninferiority was demonstrated in both trials for the primary endpoint of early clinical response.

Iclaprim approval from the FDA is pending.

Glycopeptides, Lipopeptides, and Glycolipopeptides

This group is represented by vancomycin and teicoplanin. They bind with high affinity to the D-Ala-D-Ala C-terminus of late peptidoglycan precursors and prevent reactions of cell-wall synthesis in Gram-positive bacteria. Glycopeptides are active against staphylococci, including methicillin-resistant strains, streptococci, enterococci, *Corynebacterium* spp., and *B. anthracis*. They are also active against Gram-positive anaerobes including *Clostridium* spp. However, some *S. haemolyticus* and *S. epidermidis* strains are resistant.

Vancomycin is administered i.v. at a dose of 15–20 mg/kg/dose every 8–12 h. Therapeutic drug monitoring is recommended, and trough levels should not be lower than 15 mg/L for a successful clinical outcome. Teicoplanin has an extremely prolonged $t_{½}$ (30–180 h), therefore it is given both i.v and i.m. at a dose of 8–10 mg/kg twice daily for the first day and once daily afterwards.

For decades, vancomycin has been the standard therapy for patients with serious infections due to MRSA. In addition, vancomycin is the antibiotic most extensively studied in clinical trials involving patients with SSTIs and it is recommended by the IDSA guidelines as one of the treatment options for patients with cSSTIs due to MRSA. However, its efficacy has come into question, with concerns over its slow bactericidal activity, the emergence of resistant or heteroresistant strains, and the MIC "creep" among susceptible strains. The rate of treatment failure is high in infections caused by MRSA with MIC >1 mg/L. In this case and particularly for severe infections, antistaphylococcal agents other than the glycopeptides are recommended. Vancomycin kills staphylococci more slowly than do β-lactams in vitro and is clearly inferior to β-lactams for methicillin-sensitive *S. aureus* infections. Only in cases of serious allergy to β-lactams could the glycopeptides replace them for MSSA infections.

Rapid or bolus administration of vancomycin can cause flushing and hypotension; the so-called "red-man" or "red-neck" syndrome, which is not an allergic reaction. Therefore, vancomycin should always be given over a 30–60 min infusion. Vancomycin is also ototoxic and potentially nephrotoxic particularly when combined with aminoglycosides or diuretics, while drug fever is the most frequent side effect. Teicoplanin is well tolerated; it does not require slow infusion but ototoxicity, nephrotoxicity (microscopic hematuria), thrombocytopenia, and drug fever may be encountered. Allergic cross-reactions are not anticipated between the two agents.

Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic that disrupts cell membrane function via calcium-dependent binding, resulting in rapid bactericidal activity in a concentration-dependent fashion. It is active against Gram-positive cocci and Gram-positive bacteria including MRSA as well as staphylococci with reduced susceptibility to the glycopeptides.

Daptomycin is administered intravenously at the dose of at least 6 mg/kg/dose once daily, which could be safely increased to 8–10 mg/kg/dose once daily in patients with serious infections such as bacteremia or infective endocarditis. No dose adjustment is needed for patients with a mild renal insufficiency whereas for patients with a CL_{CR} of <30 mL/min including patients in hemodialysis, administration of the same dose every 48 h is recommended.

It is approved for the treatment of *S. aureus* bacteremia, right-sided infective endocarditis, and cSSTI. It should not be used for the treatment of pneumonia, because its activity is inhibited by pulmonary surfactant. Consequently, daptomycin is one of the preferred treatment options in patients with cSSTI caused by MRSA and a high

risk or evidence for bacteremia. Furthermore, the once daily regimen and the advantageous safety profile make daptomycin an attractive option for outpatient treatment in cases where no appropriate oral regimen is available.

The most serious side effects consist of creatinine phosphokinase (CPK) elevations with or without symptoms. Patients should be observed for development of muscle pain or weakness and have weekly CPK levels determined, with more frequent monitoring in those with renal insufficiency or who are receiving concomitant statin therapy. Nevertheless, this is rarely treatment limiting. Treatment discontinuation is required in case of symptomatic myopathy with an increase >5 times ULN or 1000 units/L or in asymptomatic patients with a CPK ≥10 times ULN. Also, case reports of daptomycin-induced eosinophilic pneumonia have been described.

It should be noted that non-susceptible isolates have emerged during therapy in clinical trials, leading to treatment failure.

Telavancin

Telavancin is a lipoglycopeptide derivative of vancomycin. It has a dual mechanism of action; it is a potent inhibitor of peptidoglycan synthesis, with a tenfold greater activity than vancomycin but also triggers rapid concentration-dependent dissipation of cell membrane potential, which results in membrane pores and leakage of cytoplasmic adenosine triphosphate and potassium ions. This second mode of action is specific for bacterial membranes and appears to contribute to the more rapid bactericidal activity of telavancin, compared with vancomycin.

Telavancin is consistently active against *S. aureus,* including methicillin-resistant, vancomycin-intermediate, linezolid-resistant and daptomycin-nonsusceptible strains, against coagulase-negative staphylococci, streptococci, vancomycin-susceptible enterococci as well as *Clostridium* spp.

The drug is usually administered intravenously at 10 mg/kg every 24 h. It is excreted by the kidneys, and thus, dosage adjustments are required in cases of renal failure. Clinical trials have demonstrated non-inferiority, compared with vancomycin, in the treatment of cSSTIs and pneumonia but it is currently approved by the FDA for the treatment of cSSTIs only. The IDSA guidelines for the treatment of MRSA infections recommended telavancin as one of the first line options (AI) for the empirical therapy of cSSTI in hospitalized patients. The once daily dose makes it useful for patients who warrant parenteral therapy but do not otherwise require inpatient management. Telavancin is associated with higher rates of nephrotoxicity, altered taste, nausea, and vomiting but lesser rates of pruritus and infusion-related events, compared with vancomycin. Telavancin might be an alternative to vancomycin in cases of difficult-to-treat MRSA infections. The potent antistaphylococcal activity of telavancin should be weighed against the potential for nephrotoxicity.

Dalbavancin

Dalbavancin is a lipoglycopeptide similar to vancomycin. It exerts a bactericidal mode of action through inhibition of cross-linking of the peptidoglycan in the bacterial cell wall. The spectrum of antimicrobial activity includes the majority of Gram-positive microorganisms including common causes of ABSSSI: *S. aureus* (including MRSA, VISA and MSSA), *S. pyogenes, S. agalactiae* and *S. anginosus* group. Enterococci are also susceptible, except forvanA-type VRE.

Dalbavancin possesses a lipophilic side chain, which provides extensive protein binding (93–98%), and a long plasma half-life of 8–14 days. It was initially approved as a two-dose series of 1000 mg IV of dalbavancin on day one, followed by 500 mg a week later; soon approval was gained as a single dose of 1500 mg. Renal impairment warrants dose adjustments according to the scheme: ClCr less than 30 mL/min (dalbavancin 1125 mg as single dose or 750 mg as first dose, followed by 375 mg a week later); in end stage renal disease (ESRD) under intermittent hemodialysis, it can be administered without dose adjustment. It exhibits no significant interaction with

P450 isoenzymes, precluding no drug–drug interactions through this pathway. In the registrational trials of ABSSSIs DISCOVER-1 and DISCOVER-2, dalbavancin was compared to vancomycin IV with an optional switch to PO linezolid for a total of 10–14 days and demonstrated non-inferiority with a comparable rate of treatment-emergent adverse events of 12.3% vs. 13.7% respectively in the pooled analysis. The most common side effects with dalbavancin are nausea, diarrhea, and headache. These side effects were generally of mild or moderate severity.

Dalbavancin offers the advantage of a parenteral treatment either in the outpatient or the inpatient setting with early discharge. The increased acquisition cost should thereby be balanced against the reduced length of stay or even the averted hospital admission.

Dalbavancin was FDA and EMA approved for ABSSSI in 2014 and 2015 respectively.

Oritavancin

Oritavancin is another novel lipoglycopeptide that is licensed for the treatment of ABSSSI as a single dose of 1200 mg i.v. infused over 3 h. The antibacterial spectrum is similar to that of dalbavancin, including a large array of Gram-positive organisms. VRE are included in its spectrum (vanA-type and vanB), as well as VRSA. Again, its lipophilic side chain provides stability in membrane anchoring and a very long plasma half-life of 393 h. Oritavancin possesses a large volume of distribution and a high protein bounding. There is no need of dose adjustments in renal impairment, because a very small fraction of the drug is excreted in the urine. Oritavancin is not removed during hemodialysis.

Oritavancin was found noninferior to vancomycin, when tested in the treatment of ABSSSI in the registrational studies SOLO-1 and SOLO-2 as a single dose of 1200 mg, vs. 7–10 days of i.v. use of the comparator. No difference was found in the treatment emergent adverse event in the pooled analysis of the studies, however, in the vancomycin group almost the rate of hypersensitivity reactions was almost double (7.7% vs. 14.1%). Duration of the adverse events was similar between the comparator arms.

Oritavancin was FDA and EMA approved for ABSSSI in 2014 and 2015, respectively.

Long acting lipoglycopeptides have completely changed the landscape of treatment of skin and soft structure infections. The possibility to discharge early the patients, apart from profound cost savings in terms of hospitalization costs, allows for a shorter exposure to the healthcare environment thereby minimizing the risk of health-care-acquired infections. This is important for patients of productive age but also for incapacitated elderly patients. Furthermore, single dosing provides a convenient solution for illicit drug users who suffer very commonly from severe and frequently bacteremic infections by MRSA including their skin; as an alternative to receiving a single dose parenteral course with either oritavancin or dalbavancin, they could be discharged on a central venous catheter with obvious challenges.

For both long acting lipoglycopeptides, clinicians should maintain caution about the possible emergence of antimicrobial resistance.

Oxazolidinones

Linezolid

Linezolid is the first member of the oxazolidinone class of synthetic antibacterial agents to be introduced into clinical practice. It has a unique mechanism of action: it inhibits protein synthesis by interfering with initiation complex formation. Cross-resistance with other inhibitors of protein synthesis (i.e., macrolides, streptogramins, aminoglycosides, fusidic acid, tetracyclines, chloramphenicol) has not been observed since the oxazolidinones act early in translation, inhibiting this process at a different stage.

Linezolid inhibits most Gram positive organisms such as staphylococci, including methicillin-resistant, glycopeptide-intermediate (GISA) or glycopeptides-resistant (GRSA) strains, *Streptococcus* spp. including macrolide-resistant

strains, E. *faecium* and *E. faecalis*, including vancomycin-resistant strains, pneumococci including penicillin-resistant strains, Bacillus spp., Corynebacterium spp., Erysipelothrix spp. Anaerobes such as C*lostridium* spp., *Propionibacterium acnes*, *Bacteroides* spp., *Fusobacterium* spp. are also susceptible to linezolid whereas Enterobacteriaceae and *P. aeruginosa* are not. It has bacteriostatic activity against staphylococci and enterococci.

Linezolid is available for both oral and i.v. administration at the same dose of 600 mg every 12 h. It is rapidly and completely absorbed after oral administration with a bioavailability of approximately 100%, not influenced by the presence of food. It has an elimination $t_{½}$ of 5–7 h and is excreted by both renal and non-renal routes. No dose adjustment is required for renal or liver impairment.

Linezolid is approved for adults and children for the treatment of SSTI and nosocomial pneumonia due to MRSA. It has been demonstrated to be superior to vancomycin for the treatment of cSSTI caused by MRSA on the basis of a phase 4 clinical trial. For serious SSTI, such as necrotizing fasciitis or infections by CA-MRSA producing Panton Valentine Leucocidin, linezolid may be particularly useful because of its ability to impair toxin production.

Long-term linezolid use (>14 days) is limited by hematologic toxicity (thrombocytopenia occurring more frequently than anemia and neutropenia), peripheral and optic neuropathy (with vision loss) and lactic acidosis. Although myelosuppression and optic neuropathy are generally reversible, peripheral neuropathy is not always reversible. Linezolid is a weak, nonselective, reversible inhibitor of monoamine oxidase and has been associated with serotonin syndrome in patients taking concurrent selective serotonin receptor inhibitors (SSRIs). For this reason, treatment with SSRIs should be discontinued during therapy with linezolid.

Linezolid offers the possibility of early switch to oral therapy and, consequently, early discharge, which may be of possible economic advantage, particularly in the field of cSSTI.

Tedizolid

Tedizolid is a novel oxazolidinone. Similarly to linezolid, it acts by interacting with the 23S rRNA component of the 50S ribosomal unit to inhibit protein synthesis. Its antibacterial spectrum provides excellent coverage against Gram-positive organisms such as *Streptococcus* spp., *Staphylococcus* spp., and *Enterococcus* spp. including MRSA, VISA, VRE. Isolates of VRE exhibiting resistance to daptomycin and linezolid may be susceptible to tedizolid, as well as and some MRSA isolates resistant to linezolid.

Tedizolid exists in i.v. and oral formulation with excellent bioavailability, offering the possibility of switch to oral treatment. It is administered as a single daily dose of 200 mg (i.v. or orally). No dose adjustments are needed in renal or hepatic impairment; the drug is not absorbed through hemodialysis.

The most common adverse effects reported from registrational trials were nausea, vomiting, and diarrhea. Overall, it has a better tolerability profile compared to linezolid, with considerably lower probability for myelotoxicity and optic and peripheral neuropathy and less drug–drug interactions including serotoninergic syndrome.

Tedizolid was approved for use in ABSSSI (FDA approval 2014, EMA approval 2015). In two Phase III studies of ABSSSI (ESTABLISH-1 and -2), a 6-day course with tedizolid was significantly non-inferior to a 10-day linezolid course for the primary endpoint of early clinical response. Thrombocytopenia was observed in 2.3% vs. 4.9% and 9% vs. 13% in ESTABLISH-1 and ESTABLISH-2, respectively; however, tedizolid was given for 6 and linezolid for 10 days. Further postmarketing data are needed to ascertain the safety and tolerability of tedizolid, particularly in complicated infections which may require more prolonged treatment.

In conclusion, tedizolid offers the possibility of a short course (6 days) of treatment of ABSSSI, against a large spectrum of Gram-positive pathogens including those resistant to linezolid, with an excellent tolerability and safety profile. Switch from i.v. to oral treatment is an additional advantage.

Locally Applied Treatments

Mupirocin

Mupirocin is a locally applied agent, which is bactericidal against streptococci and staphylococci both MSSA and MRSA at concentrations achieved by topical administration (20,000 mg/mL with the 2% formulation) after 24–36 h exposure. Its weak in vitro activity against normal skin flora, e.g., *Corynebacterium*, *Propionibacterium* and *Micrococcus* spp., is advantageous because it preserves the skin's natural defense against infection. Unfortunately, prolonged courses of mupirocin for chronic skin infections can lead to development of resistant staphylococci. Therefore, mupirocin should not be used for long-term therapy.

Mupirocin is used for localized impetigo and folliculitis with clinical and bacteriological cure rates of 85–100% and 80–95%, respectively and it is recommended for this indication by the IDSA. However, in cases of widespread impetigo, systemic therapy is preferable. It is also effective in the therapy of secondarily infected eczema, lacerations, burns, and leg ulcers. Intranasal application of mupirocin (one-half of the ointment from the single-use 1 g tube into each nostril twice daily for 5–10 days in combination with a skin antiseptic, e.g., chlorhexidine body wash) is indicated for select patients who have recurrent *S. aureus* infection or warrant preoperative decolonization. No substantial toxicity in humans has been reported.

Retapamulin

Retapamulin is a topical antibiotic labeled for use of impetigo caused by MRSA and *S. pyogenes*. It belongs to a new class of antibiotics called pleuromutilins. Retapamulin has a bacteriostatic mechanism of action similar to that of macrolides and clindamycin.

Retapamulin is effective in the treatment of impetigo in patients older than 9 months of age. Controlled studies show a clinical success rate of 86 vs. 52% with retapamulin ointment vs. placebo after 7 days. A 5-day course of retapamulin is equally effective as a 10-day course of oral cephalexin in the treatment of secondarily infected dermatitis and traumatic lesions of the skin.

Retapamulin is administered as a 1% ointment, twice a day for 5 days for localized impetigo. It is safe and well tolerated and represents an effective alternative to topical mupirocin. However, it is not indicated for nasal MRSA decontamination.

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