Novel antibiotic treatment for skin and soft tissue infection

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Purpose of review
Acute bacterial skin and skin structure infection (ABSSSI) is a common and significant indication for antibiotic treatment. The microbial aetiology is becoming more resistant to available antibiotics and the treatment of patients is additionally challenged by extremes of age, obesity, diabetes and other co-morbidities. This review examines recent antimicrobial developments.

Recent findings
In many parts of the world, multidrug-resistant (MDR) staphylococci are the predominant cause of ABSSSI in both the community and in hospital. Increasing resistance in Gram-negative organisms presents problems in the management of surgical-site infections. Most new antibiotics have been developed to treat MDR Gram-positive bacteria and there are few agents to treat infections caused by MDR Gram-negative pathogens.

Summary
A number of novel agents are available clinically, with other agents of related chemical structure under development. There are no entirely new classes of antibiotics. Maintaining the efficacy of antimicrobial treatment require effective antibiotic stewardship, good infection prevention and the development of further new antibiotics.

Keywords
antibiotics, multidrug resistance, skin and soft tissue infection

INTRODUCTION

Novel antibiotics are required because antibiotic resistance is a major global health hazard. Without novel antibiotics, the further development of medical technology and the future of medical treatment may be at risk unless solutions to global antibiotic resistance are found. Multiresistant organisms are rapidly becoming ubiquitous, selected by uncontrolled antibiotic use and spread by poor infection prevention and public sanitation, and are quietly colonizing the global population. Antibiotics are a finite resource and are life-saving in sepsis [1]. Their overuse is caused by diagnostic limitations, which mean that antibiotics are given to patients who have no infection or a viral infection [2]. Empirical treatment is often very broad, de-escalation rarely occurs and the duration often too long [3,4]. Antibiotic stewardship programmes attempt to address these issues [2]. The solutions to this major problem seem simple but are difficult to achieve [4,5]. Better stewardship would reduce selection pressure; good infection control and improved public hygiene would mean fewer infections and less transmission and less need to use antibiotics; improved diagnostics would mean lower requirement for empirical therapy; and finally reinvigoration of antibiotic discovery would mean greater choice for managing multidrug-resistant (MDR) [6▪▪] infections. The British Society of Antimicrobial Chemotherapy has launched Antibiotic Action (www.antibioticaction.com) and the Infectious Diseases Society of America (IDSA) the 10 × '20 initiative to promote novel drug discovery [7].

Soft tissue infections, now called acute bacterial skin and skin structure infections (ABSSSIs) are common in every medical specialty and are encountered by everyone at some point. ABSSSIs are inflammatory microbial invasions of the epidermis, dermis and subcutaneous tissues, presenting with various combinations of heat, redness, swelling and pain. The skin is the largest organ in the body and, with

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KEY POINTS

- Skin and soft tissue infections are increasingly challenging to manage.
- Patients with ABSSSI may be elderly or have multiple comorbidities.
- Mild ABSSSI is often overtreated and severe ABSSSI undertreated.
- There is convergence of resistance and pathogenicity in causes of ABSSSI, particularly in *S. aureus*.
- Novel antibiotics with narrow Gram-positive spectrum are linezolid, daptomycin, oritavancin and tedizolid.
- Novel antibiotics with broader spectrum to include Gram-negative organisms are tigecycline, ceftaroline and moxifloxacin.

the underlying soft tissue that includes the fat layers, fascia and muscle, represents the majority of the tissue in the body [8]. Normally, the skin is colonized with an endogenous flora, a variety of species of staphylococci, corynebacteria, propionibacteria and yeasts in numbers that may vary from a few hundred to many thousands per centimetre [2] in the moister areas such as the groin and axillae [8]. The normal flora may act as a competitive inhibitor of pathogenic microbes. Breaks in the skin, such as leg ulcers, burns and surgical or traumatic wounds, allow colonization with a broader range of bacteria. Colonization of ulcers does not usually result in inflammation, but occasionally infection of the surrounding tissues may progress from mere colonization. Clinically, it is important to distinguish between colonization, which does not require antibiotic treatment, and infection, which might [9]. Antibiotic stewardship and appropriate use of this important group of drugs are so important to bacterial ecology and future public health that all physicians must consider in every case whether antibiotics are clinically indicated [10]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is probably the most common world-wide cause of ABSSSI [11,12] and this may have become more widespread because of selection pressure from antibiotic use. Colonization of skin surfaces or broken skin should never require systemic antibiotics, although it would appear from a major survey on the practice of managing MRSA infection in Europe that a significant proportion of practitioners treat MRSA colonized ulcers with systemic antibiotics [13].

Clinical management of ABSSSI is achieved using a combination of surgical, supportive and antimicrobial therapies [14,15]. Cutaneous abscess is dealt with primarily by incision and drainage, with antibiotics indicated for patients who do not respond to these initial interventions. Antibiotics are also indicated when there is more extensive disease or the abscess is in an area that is difficult to drain, for rapid progression of infection, and where there are signs of systemic illness, comorbidities or immunosuppression [15]. The antibiotic management of ABSSSI is well reviewed in the published guidelines [10,16–18]. The main choice of antibiotic depends on the clinical presentation. In likely Gram-positive infection wherein MRSA is not suspected, penicillins, antistaphylococcal penicillins, cephalosporins, clindamycin or cotrimoxazole are indicated [10,16].

Where infection is 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 (DFIs) and bites, antibiotic treatment must cover the broad range of pathogens seen in these ABSSSI. Such treatment may include β-lactam-β-lactamase inhibitors and fluoroquinolones with enhanced Gram-positive activity such as moxifloxacin, cotrimoxazole, tigecycline or ceftaroline [10,16–18]. DFIs in particular require proper wound care and early surgical intervention as well as aggressive appropriate antibiotic therapy.

ANTIBIOTIC DEVELOPMENT

A number of novel agents have been developed in recent years to supplement the paucity of agents available for the treatment of multiresistant microbes and many of these new antibiotics have been trialled in ABSSSI (Table 1). This review covers those agents that have reached at least phase III trials. The mainstay of treating serious resistant Gram-positive infections has until recently been the glycopeptides, vancomycin and teicoplanin. However, concern about the gradual development of resistance and concerns about efficacy [19,20] have turned attention to the development of new agents active against Gram-positive bacteria, linezolid and daptomycin, and those with both Gram-positive and Gram-negative activity, tigecycline, ceftaroline and moxifloxacin. Other agents are as yet unlicensed and under development.

Of the new antibiotics, only linezolid is available as an oral administration. The range of oral antibiotics used to treat MRSA infections is very wide across Europe [13], and the choice seems to depend on local susceptibility and personal experience because there are no comparative trials to support the use of specific older agents. There is, however, evidence to show that agents such as co-trimoxazole, which are cheap and reasonably well tolerated,

Table 1. Antibiotics currently or soon to be clinically available which are active in ABSSSI cause by MDR bacteria

Class	Agent	Dose	Route	Spectrum	Indications	Comments
Glycopeptides	Vancomycin	1–1.5 g bd; 15 mg/kg	i.v.	Gm+	MDR-Gm+ infections	Concern over MIC creep and resistance. Avoid rapid infusion. Renal toxicity and levels
	Teicoplanin	400 mg bd, od; 6–10 mg/kg	i.v.	Gm+	MDR-Gm+ infections	By injection or infusion. Similar issues as with vancomycin
	Oritavancin	1200 mg od	i.v.	Gm+ inc VRE	ABSSSI	Similar safety profile to vanc, excreted unchanged in urine & faeces. Dose change not necessary in renal impairment
	Dalbavancin		i.v.	Gm+		Once weekly dosing
Oxazolidinones	Linezolid	600 mg bd	i.v./p.o.	Gm+	ABSSSI, CAP	Dose change not necessary in renal impairment. Marrow toxicity and nephropathy. Useful for IV oral switch
	Tedizolid	200 mg og	i.v./p.o.	Gm+	ABSSSI	Possibly fewer adverse events than linezolid
Glycylcycline	Tigecycline	100 mg, then 50 mg bd	i.v.	Gm+, Gm−	ABSSSI, IAI	Does not cover *Pseudomonas* and some *Proteus* spp
Lipopeptide	Daptomycin	4–6 mg/kg	i.v.	Gm+	ABSSSI, right endocarditis	Check creatinine kinase (and INR if required) before treatment
Fluoroquinolones	Moxifloxacin	400 mg od	i.v./p.o.	Gm+, Gm−	ABSSSI, CAP, PID, DFI	Will not cover quinolone-resistant MRSA
Beta-lactams	Ceftaroline	600 mg bd	i.v.	Gm+, Gm−	ABSSSI, CAP	First β-lactam with anti-MRSA activity, possible more rapid early clinical response. No ESBL, *Pseudomonas* spp. cover

ABSSSI, acute bacterial skin and skin structure infection; bd, 12 hourly; CAP, community-acquired pneumonia; DFI, diabetic foot infection; ESBL, extended-spectrum β-lactamase; Gm−, Gram-negative bacteria; Gm+, Gram-positive bacteria; IAI, intra-abdominal infection; i.v., intravenous; INR, measurement of clotting; MDR, multidrug resistant; MIC, minimum inhibitory concentration; od, once daily; p.o., orally; PID, pelvic inflammatory disease.

have good efficacy against MRSA [21] and the rate of therapeutic failure is low [22]. Clindamycin may also be clinically effective, but the rates of resistance may be high and inducible resistance needs to be excluded with the 'D' test [23].

For the treatment of ABSSSI, noninferiority trials have confirmed that linezolid, daptomycin, tigecycline, telavancin and ceftaroline all demonstrate efficacy comparable with that of vancomycin with or without aztreonam [24–29].

LIPOGLYCOPEPTIDES

The glycopeptides, vancomycin and teicoplanin, have been the gold standard treatment for MDR Gram positives for decades. Most new compounds are compared against them. Glycopeptides attach to the bacterial cell membrane surface, and those with a lipophilic side chain, the lipoglycopeptides, are believed to attach with greater affinity. Dalbavancin has been shown to be noninferior to linezolid in the treatment of ABSSSI and it has a particularly long half life with once weekly dosing [30].

Oritavancin is an investigational intravenous lipoglycopeptide antibiotic administered as a single dose for ABSSSI caused by Gram-positive pathogens. Oritavancin exerts potent activity against Gram-positive bacteria via three mechanisms of action: inhibition of cell wall synthesis at two distinct steps (transglycosylation and transpeptidation) and perturbation of cell membrane integrity [31,32] resulting in rapid, concentration-dependent bactericidal activity [33]. Oritavancin has an extended Gram-positive spectrum that includes methicillin-susceptible *S. aureus* and MRSA, group A and B streptococci, and both vancomycin-susceptible enterococci and vancomycin-resistant enterococci [34–36]. The pharmacokinetic/pharmacodynamic profile of oritavancin, including concentration-dependent killing and a long half-life, allows for a unique single-dose treatment [37–39]. Additionally, oritavancin is excreted unchanged in both urine and faeces; therefore, no dosage adjustment is required for renal or hepatic impairment [40].

The results of two large, identical, global, randomized, well-controlled clinical trials (SOLO I and SOLO II) in 1959 patients demonstrated that a single 1200 mg intravenous (IV) dose of oritavancin is noninferior to 7–10 days of intravenous vancomycin (1 g or 15 mg/kg twice daily) using a prespecified noninferiority margin of 10%. The studies demonstrated noninferiority for the primary efficacy outcome at

early clinical evaluation (ECE) at 48–72 h [41] and the secondary efficacy outcome of investigator-assessed clinical cure at the post-therapy evaluation, 7–14 days after the end of treatment [42]. Non-inferiority was also demonstrated for the clinically relevant endpoint of 20% or more reduction in lesion size from baseline at ECE. The phase III studies evaluated 405 patients with documented MRSA infections. Efficacy was similar in MRSA patients to that observed in the overall population for all endpoints.

The safety of oritavancin has been characterized in over 3000 subjects treated throughout the development programme, which includes a total of 23 completed clinical studies. Throughout these studies, intravenous oritavancin was administered to 2479 patients with ABSSSI, 113 patients with bacteraemia, 410 healthy subjects and 40 subjects with hepatic impairment.

The phase III SOLO studies, which included a long-term safety follow-up (60 days), demonstrated that a single 1200-mg dose of oritavancin was well tolerated and has a similar safety profile to 7–10 days of vancomycin treatment. A single effective 1200-mg dose of oritavancin has the potential to improve the treatment of ABSSSI, ensuring treatment compliance and reducing the economic burden on the healthcare system [43].

OXAZOLIDINONES

The oxazolidinones are the most recent entirely novel class of antibiotics. Their mode of action is to bind the 50S bacterial ribosomal subunit and inhibit protein transcription. Linezolid has been the only oxazolidinone in clinical use since its launch at the turn of the millenium. It is well established as an effective agent in ABSSSI [22,23,29,44,45]. Linezolid also has the added advantages of early intravenous to oral switch with the oral preparation having 100% bioavailability and excellent tissue penetration [28,46]. Much clinical research data has been published on the pharmacokinetics, efficacy, safety and health economic outcomes of linezolid. Linezolid use is associated with significant reduction in the requirement for intravenous treatment and with the length of hospital stay [47,48]. This study has shown a numerical but not significant superiority of linezolid over vancomycin in the per-protocol group and a significant superiority at the end of study in the modified intention to treat group. These efficacy data are supported by a meta-analysis suggesting that linezolid may indeed be superior to the glycopeptides [49].

Linezolid is well absorbed, with a bioavailability of approximately 100% in healthy volunteers [50]. This characteristic is a major benefit, allowing this agent to be used early intravenously then switched to oral, or indeed even to commence treatment of infection with oral therapy. After oral doses of 600 mg, steady-state peak serum concentrations (Cmax) are 15–27 mg/l and are reached 0.5–2 h after administration [51–56]. Linezolid penetration through the skin was found to be 104% of the serum concentration [51]. The mean fluid : plasma ratios for sweat and saliva were 0.55 : 1 and 1.2 : 1, respectively. A number of studies have shown better clearance of staphylococci from skin sites with linezolid as opposed to a comparator (vancomycin and teicoplanin), at least in the short term, supporting good soft tissue drug penetration [50]. In patients with diabetic foot infections, penetration of linezolid at the standard dose and frequency into inflamed areas of tissue gave tissue : plasma ratios of just over 100% with a mean concentration of 9.6 mg/g, greater than those predicted to be effective against most strains of methicillin-resistant staphylococci and other Gram-positive pathogens [56]. The microdialysis technique has been used to collect serial samples of interstitial fluid from inflamed subcutaneous adipose tissue and metatarsal bone 0–8 h postdose in diabetic patients [57]. In a recent study, mean peak concentrations of free linezolid in plasma, healthy subcutis, inflamed subcutis and cancellous bone were found to be $16.6 + 3.0$, $15.5 + 2.5$, $15.8 + 2.8$ and $15.1 + 4.1$ mg/l, respectively. These concentrations are 4–30 times the minimum inhibitory concentration (MIC) of potential Gram-positive pathogens. The degree of tissue penetration as expressed by the ratio of the AUC of free linezolid from 0–12 h (fAUC0–12) in tissue to the fAUC0–12 in plasma was $1.32 + 0.09$, $1.12 + 0.22$ and $1.09 + 0.11$ for healthy subcutis, inflamed subcutis and bone, respectively. This demonstrates the excellent antibiotic penetration of infected soft tissue and bone and little difference in drug concentrations between healthy and inflamed tissue. These data support the use of the standard dose of linezolid in the treatment of diabetic patients suffering from bacterial foot infections, including those complicated by osteomyelitis [58].

The high oral bioavailability of linezolid permits either early intravenous to oral switch or outpatient oral therapy in its entirety, a highly attractive option for patients with complex soft tissue infections who are not critically ill and for reducing healthcare costs [59▪,60].

Two molecular derivatives, torezolid and radezolid, have been shown to be active against linezolid-resistant staphylococci [60,61]. Phase III trials have not yet commenced for radezolid.

Tedizolid (TR-700) is the active moiety of the prodrug tedizolid phosphate in oral and intravenous formulations for the treatment of ABSSSI. The pharmacokinetic/pharmacodynamic profile of tedizolid allows once-daily dosing and the 91.7% oral bioavailability [62] allows intravenous/oral sequential therapy. Tedizolid has an improved monoamine oxidase inhibitory profile suggesting a safety advantage over linezolid [63]. Tedizolid is active against almost all clinically relevant bacteria including vancomycin and linezolid-resistant pathogens [64], and it is 4–32 fold more potent than linezolid [65,66]. As the first trials under the 2010 FDA draft guidance for the development of systemic drugs to treat ABSSSIs [67], the two randomized, multicentre, double-blind phase III trials [ESTABLISH-1 (oral only) and ESTABLISH-2 (intravenous/oral)] were designed and conducted to examine the efficacy and safety of 6-day tedizolid vs. 10-day linezolid in patients with ABSSSIs. The results of the two phase III trials have shown that a 6-day course of tedizolid 200 mg once a day was statistically noninferior to a 10-day course of linezolid 600 mg twice daily for both early and sustained clinical responses in patients with ABSSSIs [68,69]. Additionally, tedizolid was generally well tolerated, with fewer gastrointestinal adverse events and less impact on haematology parameters [68,69].

TIGECYCLINE

Tigecycline, a glycylcycline antibiotic, is a broad-spectrum antibiotic, approved in the United States and Europe for the treatment of patients with ABSSSI and complicated intra-abdominal infections (cIAIs). Tigecycline is as effective as vancomycin [70,71] and has a broader range of activity, covering infections caused not only by resistant Gram-positive bacteria but also by many multiply resistant Gram-negative microbes including many extended-spectrum β-lactamase producers. It is recommended for polymicrobial infection, which may include MRSA, and for necrotizing fasciitis [72,73]. It is only available as intravenous preparation. In-vitro studies have shown that tigecycline has good activity against multiple skin pathogens including Gram-positive bacteria (such as *Enterococcus* spp., *S. aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus*), Gram-negative bacteria (such as *Escherichia coli, Klebsiella* spp., *and Enterobacter* spp.), anaerobes, and antibiotic-resistant pathogens, such as MRSA, methicillin-resistant *S. epidermidis*, and vancomycin-resistant *Enterococcus* [72,74–76]. Tigecycline has a large volume of distribution and achieves high concentrations in tissues and low concentrations in serum [73]. A recent study examining the penetration of tigecycline into skin and soft tissue in patients with complicated skin and soft tissue infections (cSSTIs) showed that concentrations of tigecycline were higher in skin and soft tissue than in serum at each of three time intervals: 2–4 h, 5–7 h, and 8–10 h, with mean tissue : serum ratios of 3.8 (range 0.7–5.5), 5.2 (range 0.8–7.1) and 2.8 (range 0.8–8.8), respectively [77].

Tigecycline has been used extensively across Europe for ABSSSI and cIAI. This 'real-life' experience has now been published. In this study, tigecycline tended to be used as second-line or rescue therapy in sicker patients and often in combination. In these challenging clinical conditions, the antibiotic performed well and therapeutic success was high [78▪]. The role of this agent in ABSSSI has been suggested for patients with co-morbidities, those more likely to be colonized with resistant bacteria and with polymicrobial infection.

Novel glycylcyclines, omadacycline (PTK-0796) and eravacycline (TP-434) are in early development.

DAPTOMYCIN

Daptomycin is a cyclic lipopeptide antibiotic, approved in Europe for the treatment of cSSTIs in 2006 and for the treatment of right-sided infective endocarditis (RIE) due to *S. aureus* and *S. aureus* bacteraemia when associated with RIE or with cSSTI in 2007. By mid 2010, daptomycin had been used to treat an estimated one million patients with serious Gram-positive infections worldwide [79]. Daptomycin has rapid concentration-dependent bactericidal activity against Gram-positive pathogens [80,81]. Its tissue penetration supports its use in the treatment of ABSSSI, and daptomycin was shown to be 'non-inferior' to vancomycin and semisynthethic penicillins [26]. The registration studies included 1092 patients between the ages of 18 and 85 years with a complicated skin and skin structure infection (ABSSSI) that was due, at least in part, to Gram-positive organisms that required hospitalization and parenteral antimicrobial therapy for at least 96 h [82,83]. It is suitable for patients suspected to be bacteraemic and with endocarditis.

In recent years, clinical experience data with daptomycin have been captured in a prospective observational study [81]. Daptomycin treatment was documented in 1127 patients with diverse infections, including cSSTIs (33%), bacteraemia (22%), endocarditis (12%) and osteomyelitis (6%). It was used empirically, before microbiological results became available, in 53% of patients. *S. aureus* was the most common pathogen (34%), with 52% of isolates resistant to methicillin; coagulase-negative staphylococci and enterococci were also frequent, with 22% of *Enterococcus faecium* isolates resistant to

vancomycin. Daptomycin was used as first-line therapy in 302 (27%) patients. When used second line, the most common reasons for discontinuation of previous antibiotic were treatment failure and toxicity or intolerance. The use of concomitant antibiotics was reported in 65% of patients. Most frequent doses were 6 (47%) and 4 mg/kg (32%). The median duration of daptomycin therapy was 10 days (range 1–246 days) in the inpatient setting and 13 days (range 2–189 days) in the outpatient setting. The overall clinical success rate was 79%, with a clinical failure rate of less than 10% for all infection types. Low failure rates were observed in first and second-line therapy (6% and 8%, respectively). Daptomycin demonstrated a favourable safety and tolerability profile regardless of treatment duration.

FLUOROQUINOLONES

Moxifloxacin is a fluoroquinolone with enhanced Gram-positive activity. Moxifloxacin is probably the most effective fluoroquinolone with extended Gram-positive activity [84] on the basis of in-vitro activity and its performance in clinical trials described. The IDSA guidelines [7] recommend fluoroquinolones for the treatment of infections that are likely to be polymicrobial. These include surgical wound infections involving the abdominal wall, perineum and genital tract. Both animal and human bite infections with their specific and unusual pathogens can also be effectively treated with moxifloxacin. The characteristics of fluoroquinolones in general may explain their demonstrated efficacy in the treatment of ABSSSIs. These include a broad spectrum of activity, rapid bactericidal action and adequate tissue concentrations at skin and deep tissue sites. Specifically, moxifloxacin has broad-spectrum activity *in vitro* against all common pathogens implicated in both uncomplicated and complicated SSTIs [85]. However, many strains of MRSA are fluoroquinolone-resistant and class cross-resistance means that moxifloxacin is not active against the majority of MRSA strains. Moxifloxacin has excellent pharmacokinetics and tissue penetration, can be delivered via both intravenous and oral routes allowing a seamless intravenous/oral switch and is particularly suitable as monotherapy for infections that are likely to be polymicrobial. The RELIEF study [86,87] demonstrated its efficacy compared with piperacillin/tazobactam intravenously and comoxiclav orally in a wide range of serious ABSSSIs including deep-seated abscess, diabetic foot infection [87,88], infected ischaemic ulcers and surgical-site infections.

Moxifloxacin has good activity against Gram-positive organisms, such as *S. aureus* and streptococci with the MIC_{90}s for methicillin-susceptible *S. aureus* ranging from 0.25 to 1.0 mg/l [84,85]. Although some strains of community-acquired-MRSA are sensitive to fluoroquinolones, many strains are resistant. Moxifloxacin may, therefore, be a treatment option for infection caused by susceptible strains of MRSA, which may be more common in community-acquired infections [7,84], but the unpredictability of fluoroquinolone activity against MRSA means that the use of fluoroquinolones should be reserved for definitive treatment once antibiotic sensitivities are known. The RELIEF study demonstrated efficacy of moxifloxacin in cSSI caused by strains of MRSA, even though MIC_{90} was 2 mg/l [86–89].

Moxifloxacin is also active against Enterobacteriaceae and anaerobes (e.g. *Peptostreptococcus* spp., *Clostridium perfringens*, *Clostridium* spp. and *Bacteroides fragilis*), but has relatively poor activity against *Pseudomonas* spp. [90,91]. Moxifloxacin also has good in-vitro activity against other pathogens isolated from patients with either animal or human bite infections (e.g. *Pasteurella multocida*, coagulase-negative *Staphylococcus* spp., *Prevotella* spp., *Fusobacterium* spp. and *Eikenella corrodens*), and the causes of more exotic ABSSSIs, such as *Bacillus anthracis*, *Yersinia pestis*, *Vibrio* spp. and *Francisella tularensis* [7,8].

Currently, a number of fluoroquinolones, including delafloxacin (RX3341), finafloxacin (BAY35-3377), nadifloxacin (WCK771), JNJ-Q2 and ACH-702, are being investigated for their potential use in treating MRSA infections.

CEPHALOSPORINS

Ceftaroline is the only ß-lactam with the unique property of additional coverage against both hospital and community-acquired MRSA with activity extending to *S. aureus* with reduced susceptibility to vancomycin [92▪▪,93]. It is a broad-spectrum cephalosporin and so retains bactericidal activity against not only Gram-positive but also Gram-negative organisms. Being a ß-lactam, it has a relatively mild side-effect profile, similar to other cephalosporins, and in clinical trials it has been shown to lead to a more rapid clinical response [94,95]. Ceftaroline has been considered by the IDSA as the first of the hoped-for '10 × '20' drugs. (The '10 × '20 Initiative' launched by IDSA in 2010 calls for development and regulatory approval of 10 novel, efficacious and well tolerated systemically administered antibiotics by 2020).

Like all other ß-lactam antibiotics, it exerts its bactericidal effect by binding to penicillin-binding proteins (PBPs) of susceptible organisms to interfere with cell wall synthesis. In contrast to traditional ß-lactam agents, ceftaroline has high binding

affinity for PBP-2a, which gives it unique bactericidal activity against all strains of MRSA. It also shows increased binding affinity for PBP-2x, a PBP modification seen in ß-lactam-resistant *Streptococcus pneumoniae* [91,96].

The efficacy and safety of ceftaroline were assessed in two large phase III programmes of randomized, double-blind, clinical trials for community acquired pneumonia (CAP) (FOCUS 1 and 2 studies) and ABSSSIs (CANVAS 1 and 2 studies) [94,95]. For both indications, therapy with ceftaroline was observed to be noninferior to the comparator agents (ceftriaxone for CAP and vancomycin plus aztreonam for ABSSSIs) at both a standard test of cure assessment time (8–15 days after discontinuation of study drug) and an early assessment time point (day 3 or 4 of study). Early response [95] may facilitate decisions to de-escalate antibiotic treatment to a narrower-spectrum agent, switch from intravenous to oral therapy and discharge of a patient based on clinical improvement. The adverse effect profile of ceftaroline is generally categorized as mild and comparable with other cephalosporins.

The recommended standard dose in adult patients with adequate renal function is 600 mg intravenously 12 hourly infused over 60 min. In patients with impaired renal function, the dose of ceftaroline is reduced. There may be a case for increasing the dose frequency in pneumonia and bacteraemia. Trials are currently in progress to assess the effect of 8-h dosing regime in ABSSSI bacteraemia and paediatric infection. The aim of this is to determine the clinical efficacy of ceftaroline in infections caused by strains of *S. aureus* with ceftaroline MIC's of 2 mg/l. This is being investigated in postmarketing trials. For the two approved indications, the duration of ceftaroline therapy is 5–14 days for ABSSSIs and 5–7 days for CAP.

Other cephalosporins are being developed for ABSSSI. Ceftobiprole has a similar spectrum to ceftaroline, and excludes activity against MDR Gram negatives and *Pseudomonas aeruginosa*. Ceftaroline is likely to be combined with the β-lactamase inhibitor avibactam which will extend the spectrum of activity to include Enterobacteriacae which express extended-spectrum β-lactamases. Ceftolozane/tazobactam is currently in phase III trials for the treatment of complicated urinary tract infections, cIAIs, and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, but not specifically for ABSSSIs. It is a combination of a novel cephalosporin and a well established β-lactamase inhibitor with in-vitro activity against *P. aeruginosa,* including drug-resistant strains, and other common Gram-negative pathogens, including most extended-spectrum β-lactamase-producing Enterobacteriaceae.

OTHER AGENTS

Other promising agents for ABSSSI, such as dalbavancin with its exceptionally long half-life, ceftabiprole with broad-spectrum activity including MRSA, and iclaprim, a trimethoprim derivative, have all met with major obstacles in the licensing process. They may be important therapeutic options if these barriers can be overcome.

CONCLUSION

ABSSSIs represent a very varied group of clinical conditions. Of primary clinical and epidemiological interest are those infections caused by *S. aureus,* whose predominant causative strains appear to be becoming more resistant and more pathogenic. This convergence of antimicrobial resistance and pathogenicity requires vigilant epidemiology and creativity in the development of therapeutic options. The number of new agents with activity against MDR Gram-positive bacteria is encouraging, but the challenge for the future is in ensuring these agents maintain efficacy and in the development of agents that are also active against MDR Gram-negative organisms. Good antimicrobial stewardship, good infection prevention and the discovery of new antibiotics are all required.

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Conflicts of interest

M.D. has received honoraria for lectures from Pfizer, Bayer, AstraZeneca, Jansen-Cilag, Cubist.

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