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## Recently approved antibacterials for methicillin-resistant Staphylococcus aureus (MRSA) and other Gram-positive pathogens: the shock of the new

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1 Recently approved antibacterials for MRSA and other gram-positive pathogens: The shock of  
2 the new

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20

21 Highlights

22

23 ● Tedezolid, Dalbavancin, Ceftaroline, Ceftriaxone and Oritavancin are new agents

24 ● All 5 drugs are broadly effective against Gram positive bacteria

25 ● They will likely have important roles in therapy of multidrug-resistant infections

26 ● Not yet approved for treatment of most invasive infections

27 ● Monitoring for unanticipated adverse effects and resistance will be essential

28

29 **Abstract**

30 A number of novel antimicrobial drugs with activity against Gram positive bacterial

31 pathogens have been licensed in the past four years. These drugs have the potential to enrich

32 the group of intravenous drugs already available that are in common use against methicillin

33 resistant *Staphylococcus aureus*, vancomycin resistant *Enterococcus*, and other antibiotic

34 resistant Gram positive pathogens. The advantages and disadvantages of these drugs are not

35 yet fully realized. Here we review the five most promising newly approved compounds:

36 ceftaroline, ceftriaxone, oritavancin, dalbavancin and tedizolid. The advantages of their

37 dosing regimens, their mechanisms of action, adverse effect profiles, evidence for their

38 clinical usefulness, and the unique characteristics that distinguish them from one another and

39 from older drugs are reviewed.

40

41 **Keywords**

42 *Staphylococcus aureus*

43 Tedizolid

44 Dalbavancin

45 Ceftriaxone

46 Oritavancin

47

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## 48 1.1 Introduction

49 With the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the  
50 health care setting initially in the United Kingdom in 1960, and then in the community  
51 beginning in the 1990s [1], the limitations of vancomycin or teicoplanin as a primary therapy  
52 for severe and life-threatening MRSA infections have raised concern [2, 3]. MRSA, which is  
53 constitutively resistant to conventional  $\beta$ -lactam antibiotics, including penicillins and  
54 cephalosporins, has variable susceptibility to other classes of older antimicrobial agents, such  
55 as trimethoprim, sulfonamides, rifampicin, sodium fusidate, tetracyclines, and lincosamides  
56 [4]. Therefore, for severe or life-threatening infections, particularly when empiric therapy is  
57 needed, it is essential that patients receive a reliable alternative to these older agents.

58 The oxazolidinone linezolid [5, 6], the cell-wall active lipopeptide daptomycin [7],  
59 and the minocycline derivative tigecycline [8] have now been in widespread use for longer  
60 than a decade. They have served as alternative agents to the “standard” broad-spectrum IV  
61 therapies directed toward antibiotic resistant Gram positive pathogens, vancomycin and  
62 teicoplanin. The place of these drugs in the therapy of MRSA and vancomycin-resistant  
63 *Enterococcus* (VRE) infections has become established in practice although their roles can  
64 still be debated. The initial enthusiasm for tigecycline was diminished after it received a  
65 black-box warning from the U.S. Food and Drug Administration (FDA) in September 2013  
66 for an increased risk of death relative to comparator drugs noted in pooled data from 13 phase  
67 3 and 4 trials (<http://www.fda.gov/drugs/drugsafety/ucm369580.htm>). However, tigecycline  
68 may still play a role in combination therapy in multidrug-resistant Gram negative infections.

69 The value of combination therapy for *S. aureus*, including a possible advantage of  
70 glycopeptides with  $\beta$ -lactams, remains uncertain, and is the subject of a large multicenter,  
71 randomized, controlled trial (RCT) in patients with *S. aureus* bacteraemia [9]. The results of

72 this study, as well as further data from observational studies using daptomycin and linezolid  
73 for invasive infections, are eagerly anticipated.

74 Since 2013, a number of newer antimicrobial agents were approved by North  
75 American and European regulatory agencies for the treatment of MRSA and other multidrug-  
76 resistant Gram positive pathogens. The place of these agents in the therapeutic  
77 armamentarium in a rapidly changing epidemiologic MRSA and VRE infection landscape,  
78 which varies from continent to continent, is not yet determined. These drugs were generally  
79 approved for the treatment of complicated soft tissue infections alone, or less commonly also  
80 for pneumonia. Therefore, their efficacy and safety in the therapy of unapproved, invasive  
81 infections, such as bacteraemia, osteomyelitis, and endocarditis, where they may have a more  
82 important niche to fill, has not been demonstrated. Each drug has certain advantages  
83 compared with older drugs. Here we review these advantages, but also the adverse effects,  
84 the mechanisms, the limited evidence for their clinical usefulness, and the unique  
85 characteristics of the most promising five drugs among those recently approved. They may  
86 play a role in the therapy of MRSA and VRE infections, among other multidrug resistant  
87 Gram positive pathogens, in the coming years.

## 89 **2.1 Tedizolid (Sivextro)**

90 This new oxazolidinone has a licence for short course (6 days) treatment, both  
91 intravenous (IV) and oral, to manage acute bacterial skin and skin structure infections  
92 (ABSSSI). Possible advantages over linezolid include less monoamine oxidase (MAO)  
93 inhibition and serotonergic interactions, less myelosuppression, less neuropathy [10, 11], less  
94 development of spontaneous resistance, less susceptibility to the cfr mobile resistance

95 mechanism and cidal activity of intracellular bacteria. Possible disadvantages are a high price and  
96 limited experience with prolonged dosing schedules.

97 As with linezolid, tedizolid acts by binding to 23S ribosomal RNA of the 50S subunit,  
98 suppressing protein synthesis. It is administered as a microbiologically inactive prodrug  
99 improving absorption (91%) [12], which is rapidly converted in the body into active  
100 tedizolid. Its hydroxymethyl group is masked from MAO by this prodrug formulation. As an  
101 inherently more active molecule than linezolid with improved ribosomal binding (due to  
102 novel C and D rings), it can be administered in lower doses and possibly in shorter courses  
103 which should have ecological benefits and select less for resistance, a point suggested by in  
104 vitro studies [13, 14]. A 12 h half-life allows for once a day dosing. Susceptibility to linezolid  
105 in *S. aureus* is likely a reliable proxy for tedizolid susceptibility [15]. Although susceptible to  
106 ribosomal mutations, tedizolid is not, as yet, inactivated by cfr methyl transferase which  
107 inactivates linezolid [16-18]. Its concentrations in macrophages seems to lead to intracellular  
108 killing of staphylococci which offers potential for preventing infection relapse due to small  
109 colony variants. Spectrum of activity includes most Gram positive bacteria, including  
110 anaerobes, streptococci, staphylococci (coagulase positive and negative) and enterococci.  
111 Activity against MRSA equates to that against methicillin-susceptible *S. aureus* (MSSA).

112 There is rapid tissue distribution, no dosage adjustment in renal or liver failure,  
113 protein binding of 70-90%, >80% elimination via the liver and no metabolic drug  
114 interactions. The registration studies, ESTABLISH 1 and 2 showed significantly less  
115 gastrointestinal adverse events and less platelet suppression than linezolid [10, 11].

116 Tedizolid was approved by the U.S. FDA in June 2014 for ABSSSIs and by the  
117 European Medicine Agency (EMA), and Canada in March 2015 and should allow for earlier  
118 hospital discharge of patients and perhaps an entirely community-based treatment schedule

119 for severe ABSSSI. Experience will tell whether it lives up to its promises, particularly of  
120 less resistance selection, less toxicity and less drug interaction. If so, then it may be useful for  
121 long term treatment of bone, joint and central nervous system infection, which are often  
122 related to foreign bodies, including prostheses, and even as a short term alternative to  
123 linezolid where toxicity or drug interaction precludes the latter's use. Recent data confirm  
124 lack of bone marrow suppression after 3 weeks of the licensed 200-mg dose [19]. Trials in  
125 pneumonia are underway.

126

### 127 **3.1 Oritavancin**

128 Oritavancin is a vancomycin-derived semisynthetic lipoglycopeptide antibiotic with  
129 several mechanisms of action. The unique feature, along with dalbavancin, is an extended  
130 plasma half-life, resulting in single-dose treatment regimens. It may provide a new challenge  
131 to established practice, in the first instance for outpatient management of ABSSSIs [20, 21].

132 Two similarly conducted phase III randomized controlled trials (RCTs), SOLO I and  
133 II, of single dose IV oritavancin, 1200 mg infused over 3 h in adult ABSSSI patients,  
134 demonstrated non-inferiority when compared with 7-10 days of vancomycin therapy [22, 23].  
135 This was unaffected by patient body mass index. Response rates were equivalent for MSSA  
136 and MRSA.

137 Oritavancin displays concentration-dependent bactericidal activity, with a  $C_{max}$  of  
138 ~28.5 mg/L, extensive tissue distribution, ~90% protein binding with slow elimination and  
139 half-life >250 h, without dose adjustment requirements for renal or moderate hepatic  
140 impairment. It achieves high intracellular concentrations and is active against small colony  
141 variants and bacteria in stationary phase [20, 21]. Intermittent dosing with oritavancin could



142 potentially be an ideal addition for treatment of osteomyelitis or biofilm-related infection, but  
143 efficacy data for these conditions are lacking. Indeed osteomyelitis was an exclusion criterion  
144 in registration trials (and though already likely pre-existing in these patients), was noted as an  
145 adverse event in 0.3% [23].

146 Oritavancin has activity against *Staphylococcus aureus*, invasive  $\beta$ -haemolytic  
147 streptococci (Group A, B, C and G), *S. anginosus*, *S. pneumoniae*, *Enterococcus faecalis* and  
148 *E. faecium*. It moreover has extended activity against MRSA (*mecA* and *mecC*), hVISA, and  
149 *vanA*-, *vanB*- and *vanC*-encoded resistance [24], with activity (MICs  $\leq 0.12$   $\mu\text{g/mL}$ ) against  
150 daptomycin non-susceptible VRE (daptomycin MIC  $>4$   $\mu\text{g/mL}$ ) [24].

151 In the SOLO II study, 73% of infections were due to *S. aureus*, but only 25% had a  
152 white blood cell count  $> 12,000$  cells/uL and only 10/340 were bacteraemic [23]. By  
153 inference, these were not severely ill patients, and conceivably many such patients could also  
154 be treated with drainage and oral antibiotic therapy [25]. As the RCTs may not have included  
155 patients with more severe infections, prospective clinical trial efficacy data will be valuable.  
156 ABSSSIs are currently the only approved clinical indication for oritavancin, and clinical use  
157 will therefore be focused on *S. aureus*, more specifically MRSA infection. The role for  
158 oritavancin in the management of infections by other resistant Gram positive organisms, and  
159 infections at other anatomic sites, is undetermined.

160 There are numerous potential benefits by the elimination of multidose and multiday  
161 regimens. These include reduced complications of cannulation, such as catheter-associated  
162 bacteraemia; reduced hospitalisation and health care resource utilisation; no requirement for  
163 ongoing drug concentration monitoring or dose adjustment; and a decrease in non-  
164 compliance.

165           However, along with these advantages comes a challenge for antimicrobial  
166 stewardship; many of these challenges will also be true for dalbavancin as noted below.  
167 There is no de-escalation. Use as empiric therapy may result in commitment to a drug that  
168 diagnostic tests may subsequently confirm as unnecessary or inappropriate, while prescribing  
169 delays would diminish some of its inherent advantages. Absence of a functioning outpatient  
170 treatment service may limit the utility of this agent. There are well-evaluated pre-existing oral  
171 antibiotics available for the majority of non-invasive *S. aureus* infections, including MRSA  
172 infections, (e.g., clindamycin and trimethoprim-sulfamethoxazole), and which can, moreover,  
173 hasten an intravenous-to-oral switch. The high acquisition cost, estimated at 2900 U.S.  
174 dollars [26] may be a disincentive.

175           Prior experience indicates that antibiotic resistance follows an antimicrobial's  
176 introduction into the clinical arena. Although lipoglycopeptide resistance has not been  
177 reported, trailing oritavancin and dalbavancin levels may encourage the development of  
178 resistance. It will also be important to recognise patients with glycopeptide allergies.  
179 Fortunately, hypersensitivity is uncommon for vancomycin and the range of adverse events  
180 were minor for both drugs after 60-day follow-up [22, 23]. Nonetheless, occurrence of severe  
181 hypersensitivity in long half-life drugs could deliver a difficult management scenario.  
182 Oritavancin, similar to dalbavancin (described below) is an innovative development which  
183 may anticipate a new paradigm in therapeutics but will require careful outpatient appraisal to  
184 avoid misplaced use.

185

#### 186 **4.1 Dalbavancin**

187           Dalbavancin is a semisynthetic lipoglycopeptide derived from a teicoplanin-like  
188 natural antibiotic produced by *Nonomuria spp.* Its structure has been altered to enhance

189 activity against *S. aureus*, and to extend its half-life [27]. The minimum inhibitory  
190 concentration (MIC) breakpoint was defined as 0.0125 mg/L by the FDA, with MIC<sub>50</sub> and  
191 MIC<sub>90</sub> of 0.06 mg/L for MSSA as well as MRSA. Dalbavancin interacts with terminal D-  
192 alanyl-D-alanine residues of peptidoglycan precursors, and inhibits both transpeptidase and  
193 transglycosylase [28]. Dalbavancin is 95% protein-bound, with an elimination half-life of 346  
194 h (14.5 days). After a single 1000-mg infusion, the serum level peaks at >200 mg/L and is  
195 still >20 mg/L at day 7. Dose adjustment is recommended in patients with creatinine  
196 clearance <30 mL/min. Dalbavancin does not interact with the P450 metabolic pathway [29].

197 Most randomized trials evaluated the dosage of 1000 mg on day 1 followed by 500  
198 mg on day 8. One phase II trial found that dalbavancin was at least as effective as  
199 vancomycin for uncomplicated, catheter-related bloodstream infections due to Gram positive  
200 bacteria [30]. Two phase III studies, DISCOVER 1 and DISCOVER 2, demonstrated that  
201 dalbavancin was non-inferior to comparators (vancomycin/linezolid) in ABSSSI, with a  
202 79.7% success rate with dalbavancin (n=659) vs. 79.8% with comparators (95% confidence  
203 interval difference, -4.5 to 4.2%) [31].

204 Strengths of dalbavancin include activity against more than 99% of clinical MRSA  
205 isolates, including VISA (4-8 times more active than vancomycin *in vitro*); convenient  
206 dosage due to an extended half-life with an FDA-approved regimen of 1000 mg on day 1  
207 followed by 500 mg on day 8; the potential for a single 1500 mg dose also shown to be  
208 effective for ABSSSI [32]; concentrations similar to plasma levels in numerous tissues,  
209 including bones (above staphylococcal MIC<sub>90</sub> 14 days after a single 1000-mg infusion [33]);  
210 and a satisfactory safety profile with no nephrotoxicity [34].

211 Despite the potential advantages that the long half-life afford this drug, there are also  
212 weaknesses that must be noted. Many of the weakness are the same as for oritavancin, noted

213 above. The susceptibility of *S. aureus* is reduced in isolates with reduced susceptibility to  
214 vancomycin; some limitations in efficacy have been suggested in experimental animal studies  
215 (e.g., it was not bactericidal in the rabbit model of endocarditis [35], and it was unable to  
216 eradicate adherent MRSA in a foreign-body infection model in guinea pigs [36]); clinical  
217 data in humans remain largely limited to non-inferiority trials in patients with ABSSSI; high  
218 cost; and the extended terminal half-life may be detrimental in case of a severe adverse event.  
219 The drug is not cleared by haemodialysis, making it difficult to reverse in such cases.

220 Dalbavancin is FDA-approved only to treat ABSSSI due to Gram positive bacteria.  
221 However, both dalbavancin and oritavancin have great promise, pending the accumulation of  
222 additional data, to treat invasive infections that now require long-term intravenous therapy  
223 with other drugs, such as vancomycin or daptomycin. These might include MRSA  
224 bloodstream infections (including catheter-related infections), bone and joint infections  
225 (including prosthetic joints), and endocarditis.

226 How dalbavancin compares with oritavancin with the accumulation of clinical  
227 experience may demonstrate important differences in efficacy or adverse reactions. Thus  
228 careful monitoring of their strengths and weaknesses will be essential to the establishment of  
229 their respective roles in empiric and definitive therapeutic regimens. Both of the novel long-  
230 acting drugs may enable a remarkable shift in the approach to treating multidrug-resistant  
231 Gram positive invasive infections in the outpatient setting. As for oritavancin, this is likely to  
232 decrease noncompliance, decrease the overall costs compared with more frequently dosed  
233 drugs, obviate the need for the monitoring of drug levels, make possible earlier discharge  
234 from hospitals, and prevent the complications associated with indwelling outpatient  
235 intravenous catheters.

236

## 237 5.1 Novel Cephalosporins (Ceftaroline and Ceftobiprole)

238 Ceftaroline and ceftobiprole are the only  $\beta$ -lactams with the property of additional  
239 coverage against both hospital- and community-acquired MRSA with activity extending to *S.*  
240 *aureus* with reduced susceptibility to vancomycin [37, 38]. Both antibiotics have similar  
241 broad-spectrum activity, retaining bactericidal activity against not only Gram positive but  
242 also Gram negative organisms. Being  $\beta$ -lactams, they have a relatively mild side effect  
243 profile, similar to other cephalosporins.

244 Like all other  $\beta$ -lactam antibiotics, they are bactericidal, binding to penicillin-binding  
245 proteins (PBPs) of susceptible organisms to interfere with cell wall synthesis. In contrast to  
246 traditional  $\beta$ -lactam agents, they have high binding affinity for PBP-2a, which gives them  
247 unique bactericidal activity against nearly all strains of methicillin-resistant staphylococci.  
248 They also show increased binding affinity for PBP-2x, a PBP modification seen in  $\beta$ -lactam  
249 resistant *Streptococcus pneumoniae* [37]. The efficacy and safety of ceftaroline was assessed  
250 in two large phase III RCTs for community-acquired pneumonia (CAP) (FOCUS 1 & 2  
251 studies) and ABSSSIs (CANVAS 1 & 2 studies) [39, 40]. For both indications, ceftaroline  
252 was observed to be non-inferior to the comparator agents (ceftriaxone for CAP and  
253 vancomycin plus aztreonam for ABSSSIs) at both a standard test of cure assessment time (8–  
254 15 days after discontinuation of study drug) and an early assessment time point (day 3 or 4 of  
255 study). Early response [39] may facilitate decisions to de-escalate antibiotic treatment to a  
256 narrower-spectrum agent, switch from IV to oral therapy and discharge of a patient based on  
257 clinical improvement. The adverse effect profile of ceftaroline in the registration trials was  
258 comparable to other cephalosporins.

259 The recommended standard dose of ceftaroline in adult patients with adequate renal  
260 function is 600 mg IV 12 hourly infused over 60 minutes. In patients with impaired renal  
261 function, the dose is reduced. There may be a case for increasing the dose frequency in

262 pneumonia and bacteraemia. A recent trial has shown that an 8 hourly dosing regimen does  
263 not confer any benefit over a 12-h regimen in patients with sepsis [41]. For the two approved  
264 indications, the duration of ceftaroline therapy is 5–14 days for ABSSSIs and 5–7 days for  
265 CAP.

266 Ceftaroline is likely to be combined with the  $\beta$ -lactamase Avibactam which will  
267 extend the spectrum of activity to include Enterobacteriaceae that express extended spectrum  
268  $\beta$ -lactamases, including AmpC  $\beta$ -lactamases [42].

269 Ceftobiprole has a similar spectrum to ceftaroline, and excludes clinical activity  
270 against extended-spectrum  $\beta$ -lactamase-producing Gram negatives and *Pseudomonas*  
271 *aeruginosa*. Ceftobiprole has received national licenses for the treatment of adult patients  
272 with CAP and hospital-acquired pneumonia, excluding ventilator-associated pneumonia, in  
273 most European countries and Canada, but not yet in the U.S. Ceftobiprole medocaril, the  
274 prodrug of ceftobiprole, is converted by plasma esterases to ceftobiprole in <30 minutes.  
275 Peak serum concentrations of ceftobiprole observed at the end of a single 30-minute infusion  
276 were 35.5  $\mu\text{g/mL}$  for a 500-mg dose and 59.6  $\mu\text{g/mL}$  for a 750-mg dose. Protein binding is  
277 16%, and its serum half-life is approximately 3.5 h. Ceftobiprole is renally excreted, and  
278 systemic clearance correlates with creatinine clearance; therefore, dosage adjustment is  
279 required in patients with renal dysfunction [38].

280 Currently, only limited clinical trial data are published for ceftobiprole [43, 44]. A  
281 phase III RCT compared ceftobiprole 500 mg every 8 h with vancomycin 1 g every 12 h plus  
282 ceftazidime 1 g every 8 h in patients with complicated skin and skin structure infections. Of  
283 the 828 subjects, 31% had diabetic foot infections, 30% had abscesses, and 22% had wounds.  
284 No difference in clinical cure was reported in the clinically evaluable, intent-to-treat and  
285 microbiologically evaluable populations with cure rates of 90.5%, 81.9%, and 90.8%,

286 respectively, in the ceftobiprole-treated patients and 90.2%, 80.8%, and 90.5%, respectively,  
287 in the vancomycin plus ceftazidime-treated group [43].

288 The clinical role for these novel cephalosporins has been debated [45]. As  $\beta$ -lactam  
289 antibiotics, the class is tried and tested. They have activity against all methicillin-resistant  
290 staphylococci, and have all the advantages of a  $\beta$ -lactam: familiarity of use over many  
291 decades, good tolerability and low rate of adverse effects. They also have activity against  
292 penicillin-resistant pneumococci and so have a role for treating CAP where such organisms  
293 are prevalent. Their antistaphylococcal activity extends to heteroresistant, vancomycin-  
294 intermediate, vancomycin-resistant and daptomycin-nonsusceptible isolates of both  
295 coagulase-positive and -negative species. They may have roles in the treatment of complex  
296 infections such as endocarditis, osteomyelitis and prosthetic device infections. Resistance to  
297 ceftaroline, related to alterations in PBP2a, has been identified in MRSA; several studies  
298 have suggested that resistance is especially common in ST239 MRSA, a healthcare-  
299 associated strain type that predominates in many countries of the world [46, 47]. A  
300 mechanism of resistance to ceftaroline independent of PBP-2a sequence, linked to a mutation  
301 in PBP4, has also been detected [48].

302 The two broad-spectrum cephalosporins may also have a role in the empirical  
303 treatment of patients with comorbidities who may be infected with MRSA. In these patients it  
304 is reassuring to have the possibility of using a broad spectrum  $\beta$ -lactam with activity against  
305 MRSA, as in complex skin and soft tissue infection and surgical or traumatic wound  
306 infections. The registration trials showed that there may be an early response in  
307 defervescence of fever and reduction in inflammation with ceftaroline [39]. As for other  $\beta$ -  
308 lactams, the pharmacokinetics are favourable, with good serum and cerebrospinal fluid levels,  
309 suggesting that these agents are suitable for treating bacteraemia and suspected meningitis

310 alone or in combination. Ceftaroline has also been used in combination with daptomycin as a  
311 potent and effective treatment for complex MRSA sepsis [49].

312

### 313 **6.1 Conclusion**

314 These novel agents may take on important roles in the therapy of multidrug-resistant,  
315 invasive infections, particularly those caused by MRSA and VRE. The lack of approved  
316 indications for treatment of invasive infections, however, may slow the introduction of the  
317 novel agents for severe disease. In addition, the emergence of resistance in MRSA and VRE  
318 to each of these new drugs must be monitored, as resistance has emerged to all previously  
319 introduced antistaphylococcal drugs [4]. Resistance has already been identified in MRSA to  
320 each of the described drugs, but now remains relatively rare. Future trials for additional  
321 indications and monitoring for unanticipated adverse effects will be essential to establish the  
322 optimal roles for these newly approved drugs, particularly in regions with a low incidence of  
323 MRSA infection.

324

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326 **Funding:** This research did not receive any specific grant from funding agencies in the  
327 public, commercial, or not-for-profit sectors.

328 **Competing Interests:** MZD has no potential conflicts of interest to report. MD has served on  
329 advisory boards or received honoraria for lectures from Pfizer, Bayer, MSD, AstraZeneca,  
330 Cubist and The Medicines Company. TG reports that within the past 3 years serving on  
331 advisory boards for MSD, Pfizer and Astra-Zeneca. PT has received support from Astra-  
332 Zenica, Basilea, The Medicines Company, and MSD, for consultancies or travel to meetings  
333 and accommodation. IMG reports receiving consultancy and/or lecture fees from  
334 AstraZeneca, Basilea, Bayer, Clinigen, Cubist, MSD, Novartis, Pfizer and The Medicines



335 Company. In his capacity as President of the International Society of Chemotherapy, IMG  
336 frequently requests meeting support from a wide range of diagnostic and pharmaceutical  
337 companies, including many of those involved in the manufacture of diagnostics and  
338 antibacterials for MRSA.

339 **Ethical Approval:** Ethical approval was not required for this study.

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	Tedizolid	Oritavancin	Dalbavancin	Ceftaroline	Ceftobiprole
<b>Drug class</b>	Oxazolidinone	Lipoglycopeptide		Cephalosporin	
<b>Spectrum</b>	Most Gram positive bacteria, including anaerobes, streptococci, staphylococci and enterococci	Most Gram positive bacteria, including VRE ; small colony-variants of <i>S. aureus</i> , <i>mecC+</i> MRSA; VRSA (oritavancin); and some VISA/hVISA		Most Gram positive bacteria, including methicillin-resistant staphylococci <i>Enterobacteriaceae</i> (although not those with ESBL or ampC)	
<b>Pharmacokinetics</b>	Bio-availability, 91% Half life, 12 h Extensive tissue distribution Protein binding 80%	Half life > 250 h Extensive tissue distribution Protein binding 90%	Half life 350 h Extensive tissue distribution Protein binding 95%	Half life 2 h Good tissue distribution Protein binding 20% Time/MIC	Half life 3.5 h Good tissue distribution Protein binding 16% Time/MIC
<b>Dosage</b>	200 mg daily, IV or PO	1200 mg IV, only one dose	1000 mg IV day 1, 500 mg IV day 8	600 mg IV 2 times per day	500 mg IV 3 times per day
<b>Approved for</b>	ABSSSI	ABSSSI		ABSSSI and community-acquired pneumonia	
<b>Weaknesses</b>	Bacteriostatic Cost	Only IV Cost		Only IV Cost	Only IV Cost
<b>Strengths</b>	Oral drug Tissue diffusion No dose adjustment for renal failure Safety profile better	Bactericidal Long half life Convenient dosing Safety profile Reduce duration of inpatient stay		Bactericidal Safety profile Some Gram negative coverage	Bactericidal Safety profile Some Gram negative coverage

	than linezolid Active against <i>cfr+</i> <i>S. aureus</i>			
<b>Comments</b>	May be useful for CNS and osteo-articular infections	May be useful for osteo-articular, bloodstream, and foreign body-related infections	May be useful for bloodstream infections, including endocarditis Ceftaroline under development as a combination with avibactam	

ABSSSI, Acute bacterial skin and skin structure infections; CNS, central nervous system ; ESBL, Extended spectrum  $\beta$ -lactams; h, hours; IV, intravenous ; PO, orally; VISA/hVISA, (heteroresistant) vancomycin-intermediate *S. aureus*; VRE, vancomycin-resistant enterococci; VRSA, vancomycin-resistant *S. aureus*.

**Table 1.** Characteristics of newer drugs included in this review

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