Future MICROBIOLOGY

SPECIAL REPORT

Susceptibility testing and reporting of new antibiotics with a focus on tedizolid: an international working group report

Mark H Wilcox[1], Natalia Dmitrieva[2], Ana Cristina Gales[3], Irina Petukhova[2], Suleiman Al-Obeid[4], Flavia Rossi[5] & Joseph M Blondeau*[,6]

Inappropriate use and overuse of antibiotics are among the most important factors in resistance development, and effective antibiotic stewardship measures are needed to optimize outcomes. Selection of appropriate antimicrobials relies on accurate and timely antimicrobial susceptibility testing. However, the availability of clinical breakpoints and *in vitro* susceptibility testing often lags behind regulatory approval by several years for new antimicrobials. A Working Group of clinical/medical microbiologists from Brazil, Canada, Mexico, Saudi Arabia, Russia and the UK recently examined issues surrounding antimicrobial susceptibility testing for novel antibiotics. While commercially available tests are being developed, potential surrogate antibiotics may be used as marker of susceptibility. Using tedizolid as an example of a new antibiotic, this special report makes recommendations to optimize routine susceptibility reporting.

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KEYWORDS
• antimicrobial susceptibility testing • surrogate antibiotic • tedizolid

Widespread use and misuse of antibiotics have been associated with the selection and spread of antibiotic-resistant strains in both humans and animals. Antimicrobial resistance now poses a significant threat to public health across the world, with alarming increases in the number of infections due to multidrug-resistant pathogens [1]. Consequently, availability of new antimicrobials is now a critical unmet need. In an effort to promote the development of new, more active antibiotics, the WHO recently published its first list of antibiotic-resistant 'priority pathogens' divided into three categories – critical, high and medium. It is hoped that the publication of this list will help guide research toward pathogens that present the greatest risks to public health [2].

While research on antibiotics to combat multidrug-resistant Gram-negative pathogens (e.g., carbapenem-resistant Enterobacteriaceae) is recognized as being a critical need, high priority is also given to Gram-positive bacteria, which remain a major cause of nosocomial infections [2,3]. Methicillin-resistant *Staphylococcus aureus* (MRSA), in particular, is a prevalent threat in many parts of the world, and is often associated with significant morbidity and mortality, particularly in the elderly [4,5]. While vancomycin has been the mainstay of treatment for the management of MRSA infections [6], therapeutic failures have been reported for isolates possessing minimum inhibitory concentrations

[1]Leeds Teaching Hospitals NHS Trust & University of Leeds, Leeds, UK
[2]N.N. Blokhin Cancer Research Centre, Moscow, Russia
[3]Division of Infectious Diseases, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil
[4]Microbiology Department, Security Forces Hospital, Riyadh, Saudi Arabia
[5]Hospital das Clínicas da Faculdade de Medicina, Seção de Microbiologia, Divisão de Laboratório Central LIM03, Universidade de São Paulo, São Paulo, Brazil
[6]Royal University Hospital, Saskatchewan, Canada
*Author for correspondence: Tel.: +1 306 655 6943; Fax: +1 306 655 6947; joseph.blondeau@saskatoonhealthregion.ca

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(MICs) >1.5 μg/ml [7–9]. In addition, a loading dose of vancomycin is recommended and therapeutic drug monitoring required to optimize outcomes, so complicating clinical use [10], particularly in low-resource settings. The high activity of the novel oxazolidinone antibiotic tedizolid against Gram-positive bacteria, including MRSA and vancomycin-resistant enterococci, presents a new treatment option for these challenging pathogens, providing more potent activity than linezolid *in vitro* [11–14]. Although the *optrA* gene in some strains of Enterococci may confer elevated MICs to both tedizolid and linezolid [15–17], this mechanism has not yet been identified in MRSA. Noninferiority of tedizolid phosphate (given for 6 days) versus linezolid (10 days) has been demonstrated in two Phase III studies in patients with acute bacterial skin and skin structure infections [18,19].

Inappropriate use and overuse of antibiotics are among the most important factors in the development of resistance, and effective antibiotic stewardship measures are needed to optimize the use of antimicrobials [20]. This includes use of restrictive reporting, and/or encouraging diverse prescribing to avoid overuse of valuable antibiotics and help control the increase in antimicrobial resistance. Clinicians' ability to select appropriate antimicrobials relies on accurate and timely antimicrobial susceptibility testing (AST), a process designed to predict clinical efficacy [20]. However, performing effective AST is challenging, particularly for newly approved antibiotics, since availability of clinical breakpoints and inclusion on commercial panels and/or access to other *in vitro* susceptibility materials often lag behind regulatory approval by several years [1]. Obtaining sufficient clinical data to enable clinical breakpoints for new agents to be established is also problematic. A Working Group of clinical/medical microbiologists from Brazil, Canada, Mexico, Saudi Arabia, Russia and the UK was convened to examine issues surrounding AST for novel antibiotics. This article summarizes their recommendations for optimal routine reporting of susceptibility to new antibiotics, using the novel oxazolidinone antibiotic tedizolid as an exemplar.

Overview of testing methodology

In recent years, few new Gram-positive directed antibiotics have become available, with only dalbavancin hydrochloride, oritavancin and tedizolid phosphate being approved over the past 5 years [21–26]. In order to select the optimal therapy for their patients, clinicians must be aware of changes in resistance patterns and the effectiveness of the antibiotics used to treat particular organisms over time. For this reason, a number of global antimicrobial surveillance programs, including STAR (Surveillance of Tedizolid Activity and Resistance; tedizolid), SOAR (Survey of Antibiotic Resistance; amoxicillin/clavulanic acid, cefuroxime, cefaclor, azithromycin and ofloxacin), ZAAPS (Zyvox® Annual Appraisal of Potency and Spectrum; linezolid) and TEST (Tigecycline Evaluation Surveillance Trial; tigecycline), have been initiated [27–31].

Susceptibility testing can be either automated (e.g., Vitek2, Microscan and Phoenix), or manual (e.g., disk diffusion [as recommended by the European Committee on Antimicrobial Susceptibility Testing – EUCAST – or Clinical and Laboratory Standards Institute – CLSI], broth microdilution or gradient testing [e.g., E-test®]). Each system has advantages and limitations, with some providing quality control ranges [1,32–35]. Working Group members report that the majority of laboratories in their countries use automated testing systems routinely for susceptibility testing, most of which provide MICs. Manual testing is frequently used to confirm automated AST results and/or MICs; E-test® and disk diffusion are the preferred methods, with the latter being the more favored choice in cost-conscious environments. Of note, in routine susceptibility testing, vancomycin MICs may not reflect accurately the actual MICs and their confirmation by E-test® has recently been recommended to minimize the risk of treatment failure [36]. Determination of MICs is important for certain strains not identified by an automated system or disk diffusion (e.g., vancomycin-intermediate *S. aureus* [VISA]). Failure with empiric vancomycin treatment in a Saudi 69-year-old male patient, for example, prompted physicians to obtain more accurate susceptibility data on the pathogen isolated from blood. This led to the discovery of the first heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA), a threatening signal to the effectiveness of empiric vancomycin treatment in hospitalized patients with severe infections [37].

Effective performance of AST by clinical microbiology laboratories is essential in order to determine susceptibility to the chosen empirical antimicrobial agents, and to detect the emergence of resistance [38]. Use of susceptibility

Table 1. Antibiotics used as surrogate agents in clinical practice.

Surrogate agent	Pathogen	Antibiotic(s) for which susceptibility is reported	Ref.
Ampicillin	Enterococci	Amoxicillin-clavulanic acid, ampicillin-sulbactam, piperacillin, piperacillin-tazobactam	[45]
Cefepime	*H. influenzae*	Ceftaroline	[46]
Cefoxitin	Staphylococci	Oxacillin	[45]
		Cephalosporins†	[47]
Ceftazidime	*H. influenzae*	Ceftaroline	[46]
Ceftriaxone	*S. pneumoniae*	Ceftaroline	[46]
	H. influenzae	Ceftaroline	[46]
Cephalothin	Enterobacteriaceae	Cefapirin, cephradine, cefaclor, cefadroxil, cefpodoxime, cephalexin and loracarbef	[45,48]
Ertapenem	Enterobacteriaceae *Haemophilus* spp. *S. pneumoniae*	Doripenem	[49]
Erythromycin	Streptococci	Azithromycin, clarithromycin and dirithromycin	[45]
Imipenem	*S. aureus*	Ceftaroline	[46]
	P. aeruginosa	Doripenem	[50]
Levofloxacin	*S. pneumoniae*	Fluoroquinolones	[51]
Linezolid	Staphylococci Enterococci Streptococci *Streptococcus anginosus* group	Tedizolid	[42]
	Staphylococci Streptococci		[47]
Meropenem	*S. aureus*	Ceftaroline	[46]
	P. aeruginosa	Doripenem	[50]
Nalidixic acid	*H. influenzae* *M. catarrhalis*	Ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin	[47]
Norfloxacin	Staphylococci Streptococci	Ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin	[47]
Oxacillin	*S. aureus*	Cefazolin, ceftriaxone, ceftaroline and nafcillin	[52]
Penicillin	Enterococci	Ampicillin, amoxicillin, amoxicillin-clavulanic acid, ampicillin-sulbactam, piperacillin, piperacillin-tazobactam	[45]
Teicoplanin	Staphylococci Streptococci	Dalbavancin	[53]
Tetracycline	*Vibrio cholerae*	Doxycycline‡	[45]
	Staphylococci Streptococci *H. influenzae* *M. catarrhalis* *N. gonorrhoeae*	Doxycycline and minocycline	[47]
Vancomycin	Staphylococci Streptococci	Dalbavancin	[53,54]
	Staphylococci Streptococci	Dalbavancin and oritavancin	[47]
	Staphylococci Streptococci Enterococci	Oritavancin	[55]

†Not cefixime, ceftazidime, ceftibuten and ceftolozane-tazobactam.
‡Disk diffusion should not be used for doxycycline due to poor correlation with minimum inhibitory concentration results.

breakpoints (e.g., those provided by the CLSI and EUCAST) is important, both for consistent reporting of antimicrobial susceptibility and for consistency and comparability of international surveillance schemes [39]. EUCAST and CLSI also advocate use of epidemiological cut-off

values as one of several tools in the process of establishing clinical breakpoints; determination of such cut-off values may promote more susceptibility testing and allow MIC values to be put into context [40]. While most laboratories follow either CLSI or EUCAST breakpoints for susceptibility testing, some may use both if a pathogen is not included in the guidelines they normally follow. When there is no available information on appropriate clinical breakpoints for certain bacteria, physicians may rely on their best judgment with regard to MIC findings and experience in eradicating those pathogens, and/or on consultation with clinical/medical microbiologists or infectious disease specialists.

Most laboratories in the Working Group members' countries report an isolate's susceptibility to be 'susceptible', 'resistant' or 'intermediate' according to either CLSI or EUCAST criteria. The 'intermediate' category has been used in a number of various ways, for example as a buffer to prevent very major and major errors, to be used alongside the 'resistant' category to indicate results that are 'nonsusceptible' and to indicate pathogen or drug combinations where an increased drug exposure may be necessary for optimal results [40]. However, antibiotic decision-making is usually based on 'susceptible' or 'resistant' categories, since treatment choices for 'intermediate' susceptibility are not clear-cut. 'Intermediate' should be interpreted as 'nonsusceptible' and physicians should thus choose an alternative antibiotic to which the pathogen is susceptible. Nevertheless, reporting susceptibility as 'intermediate' can be useful in some cases, for example if two antibiotics are used synergistically (e.g., meropenem and colistin) or to optimize the antimicrobial dosage regimen [41].

Selection of antibiotics for routine susceptibility testing depends primarily on the type of AST method, particularly if an automated panel is used. All antibiotics included on the panel are routinely tested, although not all of those tested may be reported; reports are usually issued only for first-line antibiotics. Until the cause of an infection is known, initial therapy is generally empiric and guided by clinical presentation [20]. Clinical/medical microbiologists and infectious disease specialists have an important role in advising physicians on the most appropriate antibiotics to use, although decision-making can also involve infectious disease specialists and clinical pharmacologists. The number and selection of antimicrobials tested is dependent on the organism isolated, infection site, the institution's formulary, physician requests and the automated panel or other testing methodology used [38]. Notably, the choice of antibiotics to be tested via automated methods can be limited, including for new antibiotics that have yet to be adopted by automated systems. While inclusion of an antibiotic on the hospital formulary is a key factor in selection for susceptibility testing, availability on the automated panel, supply of the manual testing equipment (disks or gradient strips) and requests from physicians are also important.

The inclusion of new antibiotics on commercial, automated test panels is often delayed for a considerable time after approval [38,42]. However, agents from the same class with similar activities can be used as surrogate markers (i.e., class representatives) to predict susceptibility of clinical isolates to new agents and/or to those not included in routine testing. Clinical laboratories have used surrogate testing successfully for decades (see **Table 1**). Reliability of a surrogate marker is typically analyzed by testing the categorical agreement between the susceptibility results for the two agents, defining errors as very major (i.e., false-susceptibility), major (i.e., false-resistance) or minor (i.e., the result for one agent was intermediate while the other agent was susceptible, nonsusceptible or resistant) [43]. However, it should be noted that the chance of a very major error is extremely low when the occurrence of resistant isolates is rare or absent. Furthermore, in rare cases, susceptibility to a surrogate antibiotic might not reveal resistance to the agent in question, for example a recently recognized, uncommon variant of *fexA* conferring resistance to florfenicol, but not to chloramphenicol [44]. Such reports highlight the need to review the utility of surrogate susceptibility testing as new data emerge.

Testing of new antibiotics: a focus on tedizolid

An alternative approach to susceptibility testing is needed for new antibiotics as their inclusion on commercial AST panels is often delayed for several years after approval, which complicates testing and reporting [1]. Despite inclusion on hospital formulary, the use of new antibiotics may be restricted for some months, which limits the opportunity for physicians to gain clinical experience. This may be difficult to explain to physicians if the antibiotic is already included in

clinical practice guidelines. Consequently, clinical/medical microbiologists have a responsibility to provide clinically relevant information to physicians and explain why it is or is not appropriate to use an antibiotic. Additional barriers to susceptibility testing of new antibiotics include: problems with the availability and regular supply of materials required for manual testing; not being included on the hospital formulary; lack of breakpoints for certain pathogens; and the increased workload and costs associated with supplementary testing. Working Group members report that novel antibiotics will most likely be routinely tested once they become available on an automated panel(s). Until then, susceptibility testing for new agents is performed manually, but often undertaken only upon physician request. In the short term, surrogate agents (that are included on automated panels) can be used to predict pathogen susceptibility to new antibiotics [1].

Several methods are currently available to test tedizolid susceptibility, including the use of linezolid as a surrogate antibiotic. Linezolid susceptibility is considered a highly reliable surrogate for tedizolid susceptibility; a high categorical agreement has been reported between the susceptibility of tedizolid and linezolid; and the very major error rates were low (≤0.2%) for all organisms tested [42]. Based on these findings, EUCAST recommends that isolates susceptible to linezolid can be reported as susceptible to tedizolid [47]. For isolates intermediate/resistant to linezolid, an MIC test must be performed to confirm susceptibility or resistance to tedizolid. Most laboratories in Working Group members' countries would add to the AST report a 'tedizolid susceptible' result based on a surrogate 'linezolid-susceptible' actual testing result, but would not report a 'tedizolid-resistance' result without knowledge of the results of actual tedizolid susceptibility testing. AST results are typically discussed with the treating physician before reporting so as not to delay clinical decision-making. The CLSI recommends that tedizolid and linezolid are included in the Group B optional primary test and reported selectively [45]. Additional methods available for tedizolid susceptibility testing include MIC test strips (Liofilchem s.r.l., Roseto, Italy) and a broth microdilution device (Sensititre™, Thermo Fisher Scientific Inc., OH, USA) developed primarily for research purposes [56]. Use of 20 μg disk diffusion has been approved by the CLSI for measurement of tedizolid susceptibility as a quality control measure [45]. To obtain susceptibility results in microbiology laboratories, currently a more practicable 2 μg disk diffusion method is under development, in addition to automated susceptibility testing panels. It should be noted that methodological testing issues have been observed with tedizolid and linezolid which suggest that 80% inhibition MIC end point criterion should be employed for testing both agents [57].

Tedizolid has demonstrated more potent activity *in vitro* than linezolid against Gram-positive bacteria, including MRSA and vancomycin-resistant enterococci, as well as noninferiority in patients with skin and skin structure infections [11–14,18–19]. Of note, tedizolid retains *in vitro* activity against *S. aureus* and other Gram-positive bacterial strains that harbor the *cfr*-gene encoded methylase enzyme [58,59]. This methylase enzyme confers resistance against five structurally different antibiotic classes (e.g., clindamycin in the lincosamide class, chloramphenicol in the phenicol class, and linezolid, but not tedizolid, in the oxazolidinone class) [58]. The encoded enzyme methylates the A2053 nucleotide in the peptidyltransferase center of the 23S ribosomal RNA, which is a very highly conserved site, and this methylation prevents binding of antibiotics to peptidyl-transferase center [60]. Importantly, chromosomal mutations in Domain V of rRNA or ribosomal L3 protein identified to date were demonstrated to confer resistance to both linezolid and tedizolid, stressing the need to test tedizolid susceptibility [59,61]. The Working Group stresses the importance of providing tedizolid susceptibility results in order to guide clinicians in selecting the most effective agent for their patients, and to provide an alternative option in cases of resistance development. They recommend the adoption of EUCAST guidelines on use of linezolid as a surrogate to predict tedizolid susceptibility [47], in order to enable routine inclusion of tedizolid in AST reports by microbiology laboratories. The Working Group also advocates having tedizolid MIC test strips in place in laboratories so that it is possible to perform tedizolid susceptibility testing, particularly when nonsusceptibility to linezolid is detected. Furthermore, they highlight the importance of a surveillance program for monitoring resistance and appropriate antibiotic use of all new antibiotics.

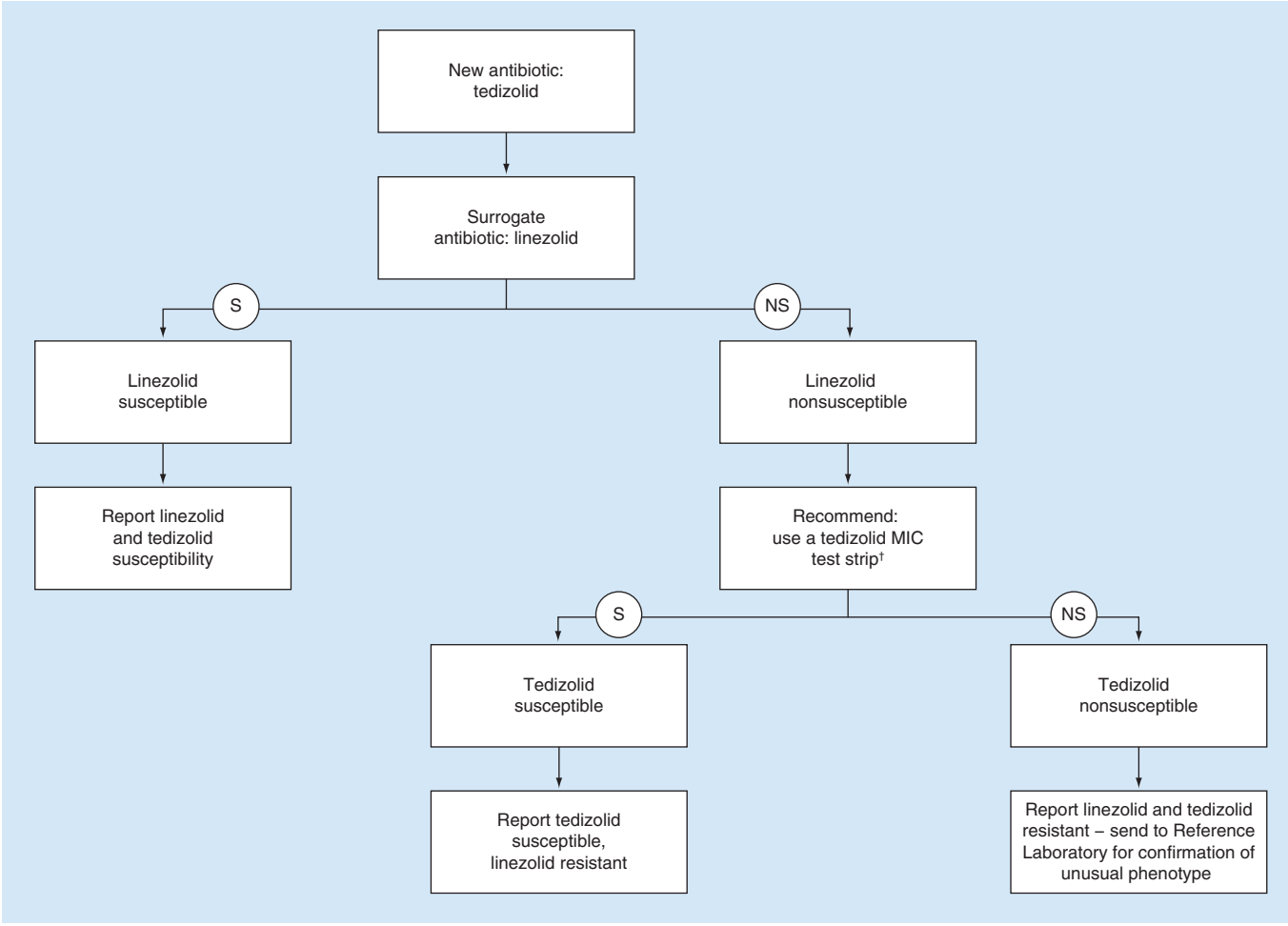

Figure 1. Recommended approach for routine reporting of susceptibility of new antibiotics, for example, tedizolid.
†Use of broth microdilution is also applicable.
As recommended by published evidence/according to susceptibility testing guidance [42,47].
NS: Nonsusceptible; S: Susceptible.

Conclusion & recommendations

The Working Group has highlighted the difficulty in acquiring sufficient clinical data to enable clinical breakpoints for new antibiotics to be established and the time taken (possibly up to 5 years) for such agents to be included in automated testing panels, which are often used for routine susceptibility testing. Policy makers should aim to minimize delays in the adoption of new breakpoints for antibiotics against emerging pathogens, particularly when containment of spread is vital; delays should be reduced to less than 1.5 years whenever possible [62]. However, to guide clinicians on appropriate treatment, it is critical that the susceptibility of new antibiotics is reported. Using tedizolid as an example, if it is not possible to determine susceptibility, data may be extrapolated by using linezolid as a surrogate, allowing subsequent appropriate use of tedizolid. In situations identified by a clinical/medical microbiologist (e.g., linezolid nonsusceptible strains of Gram-positive bacteria) an appropriate manual test for tedizolid will be necessary **(Figure 1)**. Susceptibility testing and routine reporting of selected new antibiotics can be desirable to ensure that clinicians make the appropriate choices for the management of infection, and that development of resistance is closely monitored as new agents become available.

Future perspective

At present, there is a considerable time lag between approval of new antibiotics, availability of clinical breakpoints and inclusion on

commercial AST panels. It is hoped that closer coordination in the coming years between those involved in drug development and AST panels and regulatory authorities will shorten this delay, enabling routine testing of new agents at the time of approval. In the meantime, to ensure appropriate antibiotic choice, it is essential that laboratories use the available tools to enable them to report susceptibility of new antibiotics.

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EXECUTIVE SUMMARY

Background

- A Working Group of clinical/medical microbiologists from Brazil, Canada, Mexico, Saudi Arabia, Russia and the UK has made recommendations for optimal routine testing and reporting of susceptibility to new antibiotics, using the novel oxazolidinone antibiotic tedizolid as an example.

Overview of testing methodology

- Most laboratories use automated testing systems (e.g., Vitek2, Microscan and Phoenix) routinely for susceptibility testing, with manual testing (e.g., EUCAST or CLSI disk diffusion, broth microdilution or gradient testing [e.g., E-test®]) used to confirm the results and minimum inhibitory concentrations (MICs).
- The inclusion of new antibiotics on commercial, automated test panels and/or the availability of susceptibility testing materials, are often delayed for a considerable time after approval; however, agents from the same class with similar activities can be used as surrogate markers to predict susceptibility of clinical isolates to new agents and/or to those not included in routine testing.

Testing of new antibiotics: a focus on tedizolid

- Several methods are currently available to test tedizolid susceptibility: use of linezolid as a surrogate antibiotic, MIC test strips (Liofilchem s.r.l.) and a broth microdilution device (Sensititre™, Thermo Fisher Scientific Inc.).
- Adoption of EUCAST guidelines on use of linezolid as a surrogate to predict tedizolid susceptibility is recommended in order to enable routine inclusion of tedizolid in antimicrobial susceptibility testing reports; having tedizolid MIC test strips in place in laboratories is also advocated so that tedizolid susceptibility testing can be performed when nonsusceptibility to linezolid is detected.

Conclusion & recommendations

- It can take up to 5 years for new antibiotics to be included in automated testing panels yet it is critical that the susceptibility of these agents is reported.
- If it is not possible to determine susceptibility, data may be extrapolated by using a surrogate, for example, linezolid susceptibility as a reliable surrogate for tedizolid.
- Susceptibility testing and routine reporting of selected new antibiotics is desirable to ensure that clinicians make the appropriate choices for the management of infection.

conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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References

Papers of special note have been highlighted as:
•• of considerable interest

1 Humphries R, Hindler J. Emerging resistance, new antimicrobial agents…but no tests! The challenge of antimicrobial susceptibility testing in the current US regulatory landscape. *Clin. Infect. Dis.* 63, 83–88 (2016).

2 World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. February 27, 2017. www.who.int/medicines/publications/

•• **This first list of antibiotic-resistant 'priority pathogens' published by WHO will help guide research toward pathogens that present the greatest risks to public health.**

3 Liu C, Bayer A, Cosgrove SE *et al.* Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin. Infect. Dis.* 52, e18–e55 (2011).

4 Rollnik JD. Outcome of MRSA carriers in neurological early rehabilitation. *BMC Neurol.* 14, 34 (2014).

5 Schmid H, Romanos A, Schiffl H, Lederer S. Persistent nasal methicillin-resistant *Staphylococcus aureus* carriage in hemodialysis outpatients: a predictor of worse outcome. *BMC Nephrol.* 14, 93 (2013).

6 Appelbaum PC. Reduced glycopeptide susceptibility in methicillin-resistant *Staphylococcus aureus* (MRSA). *Int. J. Antimicrob. Agents* 30(5), 398–408 (2007).

7 Rybak MJ, Lomaestro BM, Rotschafer JC *et al.* Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin. Infect. Dis.* 49, 325–327 (2009).

8 Choi EY, Huh JW, Lim CM *et al.* Relationship between the MIC of vancomycin and clinical outcome in patients with MRSA nosocomial pneumonia. *Intensive Care Med.* 37, 639–647 (2011).

9 Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. *Clin. Infect. Dis.* 52, 975–981 (2011).

10 Ye ZK, Tang HL, Zhai SD. Benefits of therapeutic drug monitoring of vancomycin: a systematic review and meta-analysis. *PLoS ONE* 8(10), e77169 (2013).

11 Chen KH, Huang YT, Liao CH, Sheng WH, Hsueh PR. *In vitro* activities of tedizolid and linezolid against gram-positive cocci associated with acute bacterial skin and skin structure infections and pneumonia. *Antimicrob. Agents Chemother.* 59(10), 6262–6265 (2015).

12 Flanagan S, Bartizal K, Minassian SL, Fang E, Prokocimer P. *In vitro*, *in vivo*, and clinical studies of tedizolid to assess the potential for peripheral or central monoamine oxidase interactions. *Antimicrob. Agents Chemother.* 57(7), 3060–3066 (2013).

13 Prokocimer P, Bien P, DeAnda C, Pillar CM, Bartizal K. *In vitro* activity and microbiological efficacy of tedizolid (TR-700) against Gram-positive clinical isolates from a Phase II study of oral tedizolid phosphate (TR-701) in patients with complicated skin and skin structure infections. *Antimicrob. Agents Chemother.* 56(9), 4608–4613 (2012).

14 Shaw KJ, Poppe S, Schaadt R *et al. In vitro* activity of TR-700, the antibacterial moiety of the prodrug TR-701, against linezolid-resistant strains. *Antimicrob. Agents Chemother.* 52(12), 4442–4447 (2008).

15 Wang Y, Lv Y, Cai J *et al.* A novel gene, *optrA*, that confers transferable resistance to oxazolidinones and phenicols and its presence in *Enterococcus faecalis* and *Enterococcus faecium* of human and animal origin. *J. Antimicrob. Chemother.* 70(8), 2182–2190 (2015).

16 Gawryszewska I, Żabicka D, Hryniewicz W, Sadowy E. Linezolid-resistant enterococci in Polish hospitals: species, clonality and determinants of linezolid resistance. *Eur. J. Clin. Microbiol. Infect Dis.* 36(7), 1279–1286 (2017).

17 Pfaller MA, Mendes RE, Streit JM, Hogan PA, Flamm RK. Five-year summary of *in vitro* activity and resistance mechanisms of linezolid against clinically important Gram-positive cocci in the United States from the LEADER Surveillance Program. *Antimicrob. Agents Chemother.* 61(7), e00609–e00617 (2017).

18 Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. *JAMA* 309(6), 559–569 (2013).

19 Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, Phase 3, non-inferiority trial. *Lancet Infect Dis.* 14(8), 696–705 (2014).

20 Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. *Mayo Clin. Proc.* 86, 156–167 (2011).

21 US FDA. Dalvance: FDA News Release (2014). www.fda.gov/NewsEvents/Newsroom/

22 US FDA. Orbactiv: FDA News Release (2014). www.fda.gov/NewsEvents/Newsroom/

23 US FDA. Sivextro: FDA News Release (2014). www.fda.gov/NewsEvents/Newsroom/

24 European Medicines Agency. Xydalba (2015). www.ema.europa.eu/ema/index.jsp?curl

25 European Medicines Agency. Orbactiv (2015). www.ema.europa.eu/ema/ind

26 European Medicines Agency. Sivextro (2015). www.ema.europa.eu/ema/index

27 Sahm DF, Deane J, Bien PA *et al.* Results of the surveillance of tedizolid activity and resistance program: *in vitro* susceptibility of gram-positive pathogens collected in 2011 and 2012 from the United States and Europe. *Diagn. Microbiol. Infect. Dis.* 81(2), 112–118 (2015).

28 Van PH, Binh PT, Minh NH, Morrissey I, Torumkuney D. Results from the Survey of

Antibiotic Resistance (SOAR) 2009–11 in Vietnam. *J. Antimicrob. Chemother.* 71(Suppl. 1), i93–i102 (2016).

29 Mendes RE, Hogan PA, Streit JM, Jones RN, Flamm RK. Zyvox® Annual Appraisal of Potency and Spectrum (ZAAPS) program: report of linezolid activity over 9 years (2004–12). *J. Antimicrob. Chemother.* 69, 1582–1528 (2014).

30 Sader HS, Castanheira M, Farrell DJ, Flamm RK, Mendes RE, Jones RN. Tigecycline antimicrobial activity tested against clinical bacteria from Latin American medical centres: results from SENTRY Antimicrobial Surveillance Program (2011–2014). *Int. J. Antimicrob. Agents* 48, 144–150 (2016).

31 Giammanco A, Calà C, Fasciana T, Dowzicky MJ. Global assessment of the activity of tigecycline against multidrug-resistant Gram-negative pathogens between 2004 and 2014 as part of the Tigecycline Evaluation and Surveillance Trial. *mSphere* 2(1), e00310–e00316 (2017).

32 Matuschek E, Brown DF, Kahlmeter G. Development of the EUCAST disk diffusion antimicrobial susceptibility testing method and its implementation in routine microbiology laboratories. *Clin. Microbiol. Infect.* 20, O255–O266 (2014).

33 Cantón R, Livermore DM, Morosini MI, Díaz-Regañón J, Rossolini GM, PREMIUM Study Group. Etest® versus broth microdilution for ceftaroline MIC determination with *Staphylococcus aureus*: results from PREMIUM, a European multicentre study. *J. Antimicrob. Chemother.* 72(2), 431–436 (2017).

34 Steward CD, Stocker SA, Swenson JM *et al.* Comparison of agar dilution, disk diffusion, MicroScan, and Vitek antimicrobial susceptibility testing methods to broth microdilution for detection of fluoroquinolone-resistant isolates of the family Enterobacteriaceae. *J. Clin. Microbiol.* 37, 544–547 (1999).

35 Karatuna O. *Quality Assurance In Antimicrobial Susceptibility Testing, Latest Research Into Quality Control*. Akyar I (Ed.). InTech (2012).

36 Van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. *Clin. Infect. Dis.* 54, 755–771 (2012).

37 Al-Obeid S, Haddad Q, Cherkaoui A, Schrenzel J, Francois P. First detection of an invasive *Staphylococcus aureus* strain (D958) with reduced susceptibility to glycopeptides in Saudi Arabia. *J. Clin. Microbiol.* 48(6), 2199–2204 (2010).

38 Jorgensen J, Ferraro M. Antimicrobial susceptibility testing: a review of general principles and contemporary practices. *Clin. Infect. Dis.* 49, 1749–1755 (2009).

39 Brown D, Canton R, Dubreuil L *et al.* Widespread implementation of EUCAST breakpoints for antibacterial susceptibility testing in Europe. *Euro Surveill.* 20, pii:21008 (2015).

40 Silley P. Susceptibility testing methods, resistance and breakpoints: what do these terms really mean? *Rev. Sci. Tech.* 31(1), 33–41 (2012).

41 Daoud Z, Mansour N, Masri K. Synergistic combination of carbapenems and colistin against *P. aeruginosa* and *A. baumannii*. *Open J. Med. Microbiol.* 3, 253–258 (2013).

42 Zurenko G, Bien P, Bensaci M, Patel HN, Thorne G. Use of linezolid susceptibility test results as a surrogate for the susceptibility of Gram-positive pathogens to tedizolid, a novel oxazolidinone. *Ann. Clin. Microbiol. Antimicrob.* 13, 46 (2014).

•• **The high categorical agreement between MIC values for tedizolid and linezolid, and low very major error rates reported in this article for all organism groups tested support the use of linezolid as a reliable surrogate for tedizolid susceptibility testing.**

43 Clinical and Laboratory Standards Institute (CLSI). Development of *In vitro* Susceptibility Testing Criteria and Quality Control Parameters; Approved Guideline. (document M23–A3, 3rd Edition). CLSI, Wayne, PA (2008).

44 Gómez-Sanz E, Kadlec K, Feßler AT, Zarazaga M, Torres C, Schwarz S. A novel fexA variant from a canine *Staphylococcus pseudintermedius* isolate that does not confer florfenicol resistance. *Antimicrob. Agents Chemother.* 57(11), 5763–5766 (2013).

45 Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing (document M100-S26) (2016).

•• **Susceptibility breakpoints for antimicrobial susceptibility testing.**

46 Jones RN, Flamm RK, Sader HS, Stilwell MG. Interim susceptibility testing for ceftaroline, a new MRSA-active cephalosporin: selecting potent surrogate β-lactam markers to predict ceftaroline activity against clinically indicated species. *Diagn. Microbiol. Infect. Dis.* 75(1), 89–93 (2013).

47 European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 6.0 (2016). www.eucast.org.

•• **Susceptibility breakpoints for antimicrobial susceptibility testing.**

48 Turnidge JD, Subcommittee on Antimicrobial Susceptibility Testing of the Clinical and Laboratory Standards Institute. Cefazolin and enterobacteriaceae: rationale for revised susceptibility testing breakpoints. *Clin. Infect. Dis.* 52(7), 917–924 (2011).

49 Jones RN, Sader HS, Fritsche TR, Janechek MJ. Selection of a surrogate beta-lactam testing agent for initial susceptibility testing of doripenem, a new carbapenem. *Diagn. Microbiol. Infect. Dis.* 59(4), 467–472 (2007).

50 Hagihara M, Kuti JL, Nicolau DP. Predicting doripenem susceptibility based on meropenem and imipenem interpretation for *Pseudomonas aeruginosa*. *Diagn. Microbiol. Infect. Dis.* 72(3), 258–262 (2012)

51 Sader HS, Koeth LM, Poupard JA, Jones RN. Interpretive categorical accuracy of fluoroquinolone reference broth microdilution MIC results when testing *Streptococcus pneumoniae*: selection of a surrogate testing agent. *Diagn. Microbiol. Infect. Dis.* 62, 460–463 (2008).

52 Kang N, Housman ST, Nicolau DP. Assessing the surrogate susceptibility of oxacillin and cefoxitin for commonly utilized parenteral agents against methicillin-susceptible *Staphylococcus aureus*: focus on ceftriaxone discordance between predictive susceptibility and *in vivo* exposures. *Pathogens* 4(3), 599–605 (2015).

53 Jones RN, Sader HS, Fritsche TR, Hogan PA, Sheehan DJ. Selection of a surrogate agent (vancomycin or teicoplanin) for initial susceptibility testing of dalbavancin: results from an international antimicrobial surveillance program. *J. Clin. Microbiol.* 44, 2622–2625 (2006).

54 Dunne MW, Sahm D, Puttagunta S. Use of vancomycin as a surrogate for dalbavancin *in vitro* susceptibility testing: results from the DISCOVER studies. *Ann. Clin. Microbiol. Antimicrob.* 14, 19 (2015).

55 Jones RN, Moeck G, Arhin FF, Dudley MN, Rhomberg PR, Mendes RE. Results from oritavancin resistance surveillance programs (2011 to 2014): clarification for using vancomycin as a surrogate to infer oritavancin susceptibility. *Antimicrob. Agents Chemother.* 60(5), 3174–3177 (2016).

56 Jones RN, Holliday NM, Rhomberg PR. Validation of a commercial dry-form broth microdilution device (Sensititre) for testing tedizolid, a new oxazolidinone. *J. Clin. Microbiol.* 53(2), 657–659 (2015).

57 Pfaller MA, Flamm RK, Jones RN, Farrell DJ, Mendes RE. Activities of tedizolid and linezolid determined by the reference broth microdilution method against 3,032 Gram-positive bacterial isolates collected in Asia-Pacific, Eastern Europe, and Latin American countries in 2014. *Antimicrob. Agents Chemother.* 60(9), 5393–5399 (2016).

58 Long KS, Poehlsgaard J, Kehrenberg C, Schwarz S, Vester B. The Cfr rRNA methyltransferase confers resistance to Phenicols, Lincosamides, Oxazolidinones, Pleuromutilins, and Streptogramin A antibiotics. *Antimicrob. Agents Chemother.* 50(7), 2500–2505 (2006).

59 Locke JB, Finn J, Hilgers M *et al.* Structure-activity relationships of diverse oxazolidinones for linezolid-resistant *Staphylococcus aureus* strains possessing the *cfr* methyltransferase gene or ribosomal mutations. *Antimicrob. Agents Chemother.* 54(12), 5337–5343 (2010).

60 Stefani S, Bongiorno D, Mongelli G, Campanile F. Linezolid resistance in Staphylococci. *Pharmaceuticals* 3, 1988–2006 (2010).

61 Zhanel GG, Love R, Adam H *et al.* Tedizolid: a novel oxazolidinone with potent activity against multidrug-resistant Gram-positive pathogens. *Drugs* 75(3), 253–270 (2015).

62 Bartsch SM, Huang SS, Wong KF *et al.* Impact of delays between Clinical and Laboratory Standards Institute and Food and Drug Administration revisions of interpretive criteria for carbapenem-resistant enterobacteriaceae. *J. Clin. Microbiol.* 54(11), 2757–2762 (2016).