A systematic review of antimicrobial susceptibility testing as a tool in clinical trials assessing antimicrobials against infections due to gram-negative pathogens

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ABSTRACT

Background: Antimicrobial susceptibility testing (AST) is the standard of care for treating bacterial infections. In randomized clinical trials of new antimicrobials, AST might not be performed or reported in real time.

Objectives: To determine local, real-time laboratory AST performance, its usage in the trial flow, quality control (QC) of the local testing, central AST performance and the effect of using AST categorization on the trials’ primary outcomes.

Data sources: We systematically searched PubMed, Embase, PsychINFO and Web of Science.

Eligibility criteria: We included registered randomized controlled trials published in journals between January 2015 and December 2019.

Methods: We included trials comparing different antibiotics for the treatment of infections caused predominantly by Gram-negative bacteria.

Methods: Primary outcomes for different trial populations were extracted and differences between trial arms were compared for patients with infections caused by susceptible versus non-susceptible bacteria. Results are described narratively.

Results: Of 32 randomized trials, 25 trials reported that local AST was performed, 1312 reported the local laboratory AST methods, no trial reported QC, but post-hoc referral for AST at a reference laboratory was common. Patients’ outcomes were superior when patients with infections due to susceptible and non-susceptible pathogens were compared post hoc (median difference 14%, interquartile range 8%–24%) in trials allowing this comparison (seven antimicrobials), except for colistin, where 14-day mortality was 9% higher when patients were treated with colistin for colistin-susceptible versus colistin-resistant carbapenem-resistant Acinetobacter baumannii. When excluding patients with pathogens that were non-susceptible to either antimicrobial in the trials, the difference in the primary outcome between the trial arms was reduced in five out of six trials.

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Introduction

Despite the widespread practice of assessing comparator drugs through observational studies, randomized clinical trials are integral to providing high-level evidence to inform clinical practice [1]. As such, two types of randomized clinical trials are typically performed—registration or approval trials for new antibiotics and those that attempt to provide high-level evidence to clinical questions, typically investigator-initiated [2]. In investigator-initiated trials, antibiotic susceptibility testing (AST) is typically performed according to the local clinical routine (e.g. use of automated methods or disc susceptibility for colistin or piperacillin-tazobactam) as most laboratories do not have routine access to reference AST methods [3,4]. In investigator-initiated trials focusing on Gram-negative bacteria, AST results form the basis for inclusion and exclusion of patients and mistakes at this stage may not be rectified by retesting isolates using reference methods. Results may be significantly affected by the AST errors at local laboratories. Furthermore, AST methods vary considerably by region and country and in addition, laboratories may choose to use Clinical Laboratory Scientific Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations and breakpoints when performing and interpreting AST [5,6].

In registration trials, AST of the new antimicrobial might not be performed in real time because of a lack of commercial tests or because the trials are performed before the setting of clinical breakpoints by regulatory bodies such as the CLSI or EUCAST [7]. Patients enrolled in randomized clinical trials should be treated according to best clinical practice. This means that enrolled patients in trials should be treated with antimicrobials to which the Gram-negative pathogen cultured from the patient is ‘susceptible’ on AST. In the case of drug registration trials, susceptibility breakpoints may be based on provisional data. The rate of in vitro susceptibility to the antimicrobials may impact on the primary outcome rate in the trial arms [5,6].

The potential impact of laboratory AST within clinical trials is largely unknown and, to our knowledge, has not been examined to date. The aim of this systematic review is to describe AST performance in clinical trials comparing antibiotics for the treatment of infections caused by Gram-negative bacteria and to determine the impact of resistance to tested antimicrobials on reported trial outcomes. In particular, we sought to determine (a) performance of AST onsite in real-time, the local laboratory AST methods, incorporation of AST into trial protocol and quality control reporting in trials; (b) primary outcome difference for patients treated with a trial antimicrobial classified as susceptible versus non-susceptible; and (c) trial arm comparisons of the primary outcome for different trial populations that include or exclude patients with infections due to isolates that are susceptible and/or non-susceptible to the trial antimicrobials.

Materials and methods

We performed this systematic review in line with PRISMA guidelines. We included randomized controlled trials comparing different oral or intravenous antibiotics for the treatment of infections caused predominantly by Gram-negative bacteria. This included syndrome-based trials of urinary tract infections, intra-abdominal infections and hospital-acquired or ventilator-associated pneumonia; and pathogen-directed trials of Gram-negative bacteria. We limited inclusion to trials published between 2015 and December 2019 to examine contemporary trial and AST methodology. We included both industry-sponsored registration trials and investigator-initiated trials. We excluded trials without comparator antimicrobial treatment arms, pilot and phase 1 trials, and trials where the primary objective was safety or dosing; and trials that were not registered in a trial database before commencing the enrolment of patients, because we needed to assess the full trial methodology from its registry. Randomized controlled trials involving *Helicobacter pylori* were excluded because these trials included comparator arms involving multiple antimicrobial and non-antimicrobial pharmacological combinations. We also documented but excluded trials where AST was not performed or reported either by the local participating laboratories or a post-hoc reference laboratory.

A search of PubMed, Embase, PsyhCINFO and Web of Science was performed using a search strategy including the MeSH terms: ‘intra-abdominal infection’ or ‘bloodstream infection’ or ‘urinary tract infection’ or ‘nosocomial pneumonia’ or ‘hospital associated pneumonia’. Additional filters restricted studies to randomized clinical trials in humans. We excluded trials reported in abstract format as we did not expect full reporting of AST methods in them. In addition, we screened the reference list of included studies and sought additional information on trials published during the defined period from infectious diseases physicians and clinical microbiologists involved in clinical trials. Further details of the search strategy can be found in the Supplementary material (Appendix S1).

Title, abstract, full-text reviews and reference checking were performed by AH and EB, who applied eligibility criteria. Trial publications, supplementary material and clinical trial protocols were reviewed to extract data by AH and cross checked by EB. We extracted the local laboratory AST methods, whether results were reported in real time and whether the trial design incorporated the results of local laboratory AST in patients’ management within the trial. Where the trial used post-hoc reference AST testing, we extracted the reported method and results. We extracted data on the trials’ primary outcomes, as defined in the trial and the comparative effect for the primary outcome. Trial antimicrobials with a ≥5% difference in cultured pathogen susceptibility rates were considered significant. We calculated the primary outcome rate when the isolate cultured from the patient was categorized as susceptible or non-susceptible to the antimicrobial with which they were treated based on EUCAST or CLSI criteria. It is important to note that although the technical method for determining MICs is the same for EUCAST and CLSI, the criteria for interpreting results as susceptible, intermediate (or susceptible, increased exposure) and resistant may not be.

As this systematic review includes significant heterogeneity in the compared antibiotics and primary outcome assessed, we did
not perform a meta-analysis for the effect of resistance in the trial. Within each trial, we sought to estimate the effect of resistance to the study antibiotics on the primary outcome and the difference between arms in the primary outcome. We calculated the absolute difference between trial arms for the primary outcomes, including 95% CI, for each trial sub-population (definitions provided in the Supplementary material, Table S1). The overall impact of AST in trials is shown by comparing the primary outcome difference in trial arm A versus trial arm B for all patients where a pathogen was isolated regardless of susceptibility, compared with patients with pathogens susceptible to both trial antimicrobials only. This was performed by comparing the susceptible microbiologically Modified Intention-to-Treat (mMITT) population with the mMITT population and comparing the Microbiologically Evaluable (ME) population with the extended Microbiologically Evaluable (eME) population.

Results

Thirty-two randomized clinical trials were included in this systematic review from 479 studies identified in the search (Fig. 1), summarized in the Supplementary material (Tables S2 to S4). Eleven trials (nine investigator-initiated and two registration trials) that did not report AST procedure or results locally or centrally were excluded. The included studies comprised 30 multicentre trials and two single-centre trials, with 23 trials performed as new antimicrobial registration trials and nine performed as investigator-initiated trials. The trials included 39 to 1049 enrolled patients (median 424, interquartile range 178–565). Of the registration trials, 13 trials reported that local AST was performed for the purpose of the trial, with six of these trials reporting the AST method used by the local laboratory. One study (RESTORE-IMI) used custom-made Sensititre™ panels (Thermo Fisher Scientific, Waltham, MA, USA) standardized across participating local laboratories that were supplied by the study sponsor. No study reported quality control data for any local laboratory AST sites. In comparison, eight investigator-initiated trials reported use of local AST and only one trial did not report the AST method used at participating local laboratories.

Nine registration trials reported incorporation of local AST in the study flow based on the results of local laboratory AST. Four trials reported that local AST results were included as part of the entry criteria for inclusion before enrolment and five trials incorporated AST results for continuation in the trial after enrolment. Two double-blinded randomized trials allowed patients to continue if the isolate was resistant to one of the two trial antimicrobials and the principal investigator assessed the patient as clinically improving [8,9]. Six of nine investigator-initiated trials used local laboratory AST as part of entry criteria before enrolment of patients and one trial incorporated AST as part of trial flow methodology.

One trial comparing gatifloxacin to ceftriaxone for treatment of enteric fever in Nepal was halted early following review by the drug safety monitoring board because of a high prevalence of quinolone-resistant Salmonella serotype Typhi [10]. Post-hoc central testing was performed in 26 trials, though one trial used Etest (BioMérieux, Marcy L’Etoile, France) and 15 reported that the testing was performed according to reference methods. Of the 32 included trials, 19 reported susceptibility rates for one or both trial antimicrobials according to reference AST. Susceptibility rates for isolates cultured from patients in syndrome-specific registration trials with ≥5% difference between trial arms in susceptibility rates to the trial antimicrobials were reported for...
that cultured a pathogen were excluded from final analysis because of discordant results for imipenem, imipenem/relebactam and/or colistin between the local laboratory and reference laboratory [14,15]. Similarly, 13% and 9.9% of patients were excluded from

ZEUS (fosfomycin versus piperacillin/tazobactam; 100% versus 90%) [8,11–13]. In the RESTORE-IMI study, 24% of randomized patients that cultured a pathogen were excluded from final analysis because of discordant results for imipenem, imipenem/relebactam and/or colistin between the local laboratory and reference laboratory [14,15]. Similarly, 13% and 9.9% of patients were excluded from

The review has demonstrated significant variability in performance of the AST procedures in local trial sites, inconsistent incorporation of AST results into the trial workflow, and, most seriously, a lack of quality control procedure or reporting. Among trials performed for registration of new antibiotics to treat Gram-negative bacteria, seven did not address local laboratory bacterial susceptibilities in the protocol or final report and nine out of 23 did not consider local (real-time) susceptibility testing. There is a significant effect difference in the primary outcome between patients

Table 1
Outcome differences between patients with infections treated with antimicrobials to which the pathogen is categorized susceptible versus resistant

Trial Antimicrobial and indication Outcome measured Clinical breakpoint reported for susceptibility in trial Outcome when pathogen susceptible Outcome when pathogen non-susceptible

<table>
<thead>
<tr>
<th>Trial</th>
<th>Antimicrobial and indication</th>
<th>Outcome measured</th>
<th>Clinical breakpoint reported for susceptibility in trial</th>
<th>Outcome when pathogen susceptible</th>
<th>Outcome when pathogen non-susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPECT-UTI [11]</td>
<td>Ceftolozane/tazobactam versus levofloxacin; 97% versus 71%, ASPECT-NP [9]</td>
<td>Composite cure (clinical cure and microbial eradication)</td>
<td>CLSI breakpoints: Enterobacterales ( \leq ) 0.5 mg/L; Pseudomonas aeruginosa ( \leq 1 ) mg/L</td>
<td>210/259 (81.1%)</td>
<td>44/112 (39.3%)</td>
</tr>
<tr>
<td>ASPECT NP [9]</td>
<td>Meropenem for nosocomial pneumonia</td>
<td>28-day mortality</td>
<td>CLSI breakpoints: Enterobacterales ( \leq 1 ) mg/L; P. aeruginosa ( \leq 2 ) mg/L</td>
<td>55/209 (26.3%)</td>
<td>7/24 (29%)</td>
</tr>
<tr>
<td>ASPECT NP [9]</td>
<td>Ceftolozane/tazobactam for nosocomial pneumonia</td>
<td>28-day mortality</td>
<td>Enterobacterales ( \leq 4 ) mg/L; P. aeruginosa ( \leq 8 ) mg/L</td>
<td>36/216 (16.7%)</td>
<td>16/49 (33%)</td>
</tr>
<tr>
<td>TANGO 1 [8]</td>
<td>Piperacillin/tazobactam for complicated urinary tract infections due to Enterobacterales</td>
<td>Composite cure (clinical cure and microbial eradication)</td>
<td>CLSI breakpoint: ( \leq 16 ) mg/L</td>
<td>94/124 (75%)</td>
<td>17/30 (56.7%)</td>
</tr>
<tr>
<td>ZEUS [13]</td>
<td>Piperacillin/tazobactam for complicated urinary tract infections</td>
<td>Composite cure (clinical cure and microbial eradication)</td>
<td>CLSI breakpoint: ( \leq 16 ) mg/L</td>
<td>85/150 (56.7%)</td>
<td>8/17 (47.1%)</td>
</tr>
<tr>
<td>AIDA [3,20]</td>
<td>Colistin + meropenem for infections due to carbapenem-resistant Acinetobacter baumannii</td>
<td>14-day mortality</td>
<td>EUCAST colistin breakpoint: ( \leq 2 ) mg/L</td>
<td>57/178 (32%)</td>
<td>13/30 (43.3%)</td>
</tr>
<tr>
<td>AIDA [3,20]</td>
<td>Colistin monotherapy for infections due to carbapenem-resistant A. baumannii</td>
<td>14-day mortality</td>
<td>EUCAST breakpoint: ( \leq 2 ) mg/L</td>
<td>57/169 (33.7%)</td>
<td>7/29 (24.1%)</td>
</tr>
<tr>
<td>MERINO [4,21]</td>
<td>Piperacillin/tazobactam for bloodstream infections due to ceftriaxone resistant Escherichia coli and Klebsiella spp.</td>
<td>30-day mortality</td>
<td>EUCAST/CLSI breakpoints: ( \leq 16 ) mg/L</td>
<td>13/147 (8.8%)</td>
<td>5/10 (50%)</td>
</tr>
</tbody>
</table>

Please cite this article as: Henderson A et al., A systematic review of antimicrobial susceptibility testing as a tool in clinical trials assessing antimicrobials against infections due to gram-negative pathogens, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2021.03.019
with pathogens susceptible and non-susceptible to the trial antimicrobial they receive. As a result, the overall effect of excluding patients treated with an antimicrobial to which the pathogen is not susceptible 
\textit{in vitro} by reference post-hoc AST was a reduced difference in the primary outcome rate between the trial arms for most trials that allowed a comparison. Although AST in clinical trials is ethically important for the individual management of patients enrolled in clinical trials, this study demonstrates that AST consideration in the analysis is also essential in relation to the integrity of reporting trial results.

In this systematic review, 19 out of 32 studies were syndrome-specific registration trials for which enrolment into the trial occurs before results of AST. Therefore, differences in the \textit{in vitro} susceptibility rates of the antimicrobial agents in these trials usually reflect the overall differences in \textit{in vitro} susceptibility rates for the agents in the real-world population for which the antimicrobials are used. As only one trial used the reference broth microdilution method in local laboratories, trials that incorporated AST results into the inclusion or exclusion protocol of the trial relied on the accuracy of local laboratory AST methods. At a later stage, commercial devices may be identified as having significant problems leading to major errors—a situation where isolates resistant to a trial antimicrobial are incorrectly categorized as susceptible by the local AST device or method [24–27]. In cases where issues with commercial AST devices are identified by standards-setting bodies such as EUCAST, laboratories that continue to use these devices are at increased risk of reporting false susceptibility to one or both of the trial antimicrobials [28,29]. However, as standards-setting bodies are unable to monitor all commercial AST devices, local laboratories must perform and report on quality control of AST following recommendations issued by international standards-setting organizations in addition to manufacturers [35].
Table 2
Difference in trial arm comparison primary outcome rate based on subpopulations including and excluding patients with infections due to non-susceptible pathogens

<table>
<thead>
<tr>
<th>Trial</th>
<th>Antimicrobials, indication and primary outcome</th>
<th>Clinical breakpoint reported for susceptibility in trial</th>
<th>Primary outcome difference in trial arm (absolute difference between arms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients with culture-positive infections due to susceptible pathogens</td>
</tr>
<tr>
<td>ASPECT NP [9]</td>
<td>Ceftriaxone/tazobactam vs meropenem for nosocomial pneumonia 28-day mortality</td>
<td>Ceftriaxone/tazobactam: Enterobacteriales ≤4 mg/L; Pseudomonas aeruginosa ≤8 mg/L</td>
<td>mMITT: −5% (−12% to 2%)</td>
</tr>
<tr>
<td>ASPECT cUTI [11]</td>
<td>Ceftriaxone/tazobactam vs levofloxacin for complicated urinary tract infections</td>
<td>Ceftriaxone/tazobactam: ≤8 mg/L; Levofloxacin: ≤2 mg/L</td>
<td>mMITT: −8% (−14% to −2%)</td>
</tr>
<tr>
<td>REPROVE [22]</td>
<td>Ceftriaxone/avibactam vs meropenem for nosocomial pneumonia</td>
<td>Ceftriaxone/avibactam: ≤8 mg/L; Meropenem: Enterobacteriales ≤1 mg/L; P. aeruginosa ≤2 mg/L</td>
<td>eME: 2% (−8% to 13%)</td>
</tr>
<tr>
<td>RECLAIM 3 [23]</td>
<td>Ceftriaxone/avibactam vs meropenem for complicated intra-abdominal infections</td>
<td>Ceftriaxone/avibactam: ≤8 mg/L; Meropenem: Enterobacteriales ≤1 mg/L; P. aeruginosa ≤2 mg/L</td>
<td>eME: 2% (−4% to 9%)</td>
</tr>
<tr>
<td>RESTORE [14,15]</td>
<td>Imipenem/relebactam vs colistin</td>
<td>Imipenem/relebactam: ≤1 mg/L; Colistin: ≤2 mg/L</td>
<td>mMITT: 2% (−23% to 35%)</td>
</tr>
<tr>
<td>MERINO [4,21]</td>
<td>Piperacillin/tazobactam vs meropenem for ceftriaxone non-susceptible Escherichia coli and Klebsiella spp. 30-day mortality</td>
<td>Piperacillin-tazobactam: ≤16 mg/L; Meropenem: ≤2 mg/L</td>
<td>mMITT: 7% (2%–13%)</td>
</tr>
</tbody>
</table>

Abbreviations: eME, Extended Microbiologically Evaluable population; ME, Microbiologically Evaluable population; mMITT, microbiologically Modified Intention to Treat population.

Although RESTORE IMI attempted to improve local laboratory AST accuracy by supplying Sensititre™ plates produced by ThermoFisher, 10 out of 41 (24%) of enrolled patients were excluded from the analysis due to AST categorical errors when compared with the post-hoc broth microdilution testing [15]. MIC are variable regardless of method used. Reading broth microdilution plates requires training and skill and when target isolates have MICs that challenge the clinical breakpoint of the antimicrobials, high categorical error rates are not unexpected, even if essential agreement is close to 100% [defined as within 1 dilution of the reference method MIC] [28]. Reflecting this issue, six out of ten isolates from excluded patients from RESTORE IMI had a difference of one dilution for colistin and imipenem/relebactam between reference and commercial method [36].

On the basis of this review, we suggest that future trials of Gram-negative antimicrobials should incorporate the following approaches to AST reporting. In syndrome-specific registration trials, attention should be given to comparator antimicrobial agents based on in vitro susceptibility rates for the real-world population in which the agents are to be used. Before embarking on trials where the results of AST will severely affect actions and outcome, AST training exercises should be performed and AST performance should be assessed. Where new antimicrobials are being assessed and do not have established breakpoints by CLSI or EUCAST, either organization should be asked to provide provisional breakpoints based on pharmacokinetic/pharmacodynamic cut-offs and wild-type MIC distributions of target species. Protocols that do not provide for withdrawal of the patient from the trial once resistance has been demonstrated in the local laboratory to the trial antimicrobial that the patient is given, even if clinically improving or remaining stable, may not reflect best practice. Reporting on AST methods used and publishing quality control results from individual laboratory sites should be considered essential in all clinical trials. Lack of space is no longer an excuse when journals will allow the online publication of supplementary material. Importantly, in this review, no trials published quality control results relating to local laboratory AST. The AST errors identified in relation to specific commercial devices affecting individual trial participants, or the overall trial outcome, should be notified to the relevant diagnostic company as well as to EUCAST and CLSI to allow investigation and notification if appropriate.

As a result of our recommendations, it is likely that a higher rate of patient withdrawals will occur based on AST results demonstrating resistance to the trial antimicrobial after enrolment has occurred. Therefore, trials will need to ensure that the calculated sample size will allow for a sub-group analysis based on enrolled patients with infections due to pathogens that are susceptible to the trial antimicrobial they are treated with. As local laboratory AST errors may also lead to some patients with infections due to resistant pathogens being included in the intention-to-treat population, we recommend that the primary analysis is performed for all enrolled patients, thereby reflecting the current efficacy of the trial antimicrobials in a real world application, and for enrolled patients with infections due to susceptible pathogens only, thereby reflecting the true effect difference for the trial antimicrobials in patients who are given directed therapy. This is particularly important for trials where AST errors related to commercial devices are identified, as these errors may be corrected by using alternative AST devices and should inform laboratories on the importance of AST accuracy.

There are several limitations to this systematic review. Data were extracted from trial publications, protocols and
supplementary material, without access to the full trial protocols; this was conceived on the basis that data presented in this systematic review were designed to reflect what is available in the public domain. However, an individual patient data systematic review could have better appraised the primary trial and other important outcome differences between treatment arms in relation to including or excluding patients with infections due to non-susceptible pathogens. In EUCAST 2019 and onwards definitions, there are two susceptible AST categories, S and I, and one resistant, R, whereas CLSI has the categories ‘susceptible’, ‘susceptible dose dependent’, ‘intermediate’, ‘resistant’ and ‘non-susceptible’ [5,6].

We encourage future trials to incorporate consistent pre-specified population definitions according to Table 1 in this systematic review in order to standardize the impact of AST in trials involving antimicrobial agents active against Gram-negative pathogens. Although this systematic review focused on antimicrobials primarily active against Gram-negative pathogens, it is likely that the impact of AST is similar for infections involving Gram-positive pathogens.

In addition, the dosing of comparator agents may also play a significant role in the efficacy of trial antimicrobials. The ASPECT-NP study showed an increased efficacy for cefotaxime/tazobactam compared with meropenem for the susceptible mITT population compared with the mMITT population [9]. In this trial, patients with nosocomial pneumonia were randomized to either cefotaxime/tazobactam (3 g three times per day) or to the comparator meropenem (1 g three times per day), both given over a 1-hour infusion period [9]. The 28-day mortality difference for meropenem in the ASPECT-NP study due to susceptible versus resistant strains was only 3% (26% versus 29%) but was 16% (17% versus 33%) for cefotaxime/tazobactam. Potentially reflecting the importance of higher dosing of meropenem for VAP, the MAGIC BULLET study [37] be noted that isolates were not tested by a reference AST method in the MAGIC BULLET study [37].

Conclusion

This systematic review highlights an important area of clinical trials of antimicrobial agents against Gram-negative pathogens. In particular, triallists and companies that are designing and performing clinical trials should be aware of the potential impact of AST on clinical trial results. Matching the antimicrobial choice in trials to the in vitro susceptibility pattern is part of routine clinical practice and should be considered critical to enrolment and progression of patients in all trials. Similarly, ongoing participation for patients in clinical trials should be dependent on local AST results. To this effect, quality control and reporting of the method/devices used should be considered mandatory, as should the reporting of local AST trial results comparative to reference testing in all trial publications. As we attempt to expand our knowledge of optimal therapy for multidrug-resistant and extremely drug-resistant pathogens, clinical trials will play a significant role in defining future patient therapy. The relationship between in vitro AST and clinical outcome for patients with infections due to Gram-negative pathogens should not be forgotten when planning and reporting future trials.

Author contributions

AH and EB performed the search, data extraction and validation. AH, EB and MDC analysed the data. PNAH, DP, JRB, MP, JDT and GK supervised the study. AH wrote the original draft. All authors contributed to the conception and design of the study and to review and editing of the manuscript.

Transparency declaration

AH reports personal fees from Sandoz outside the submitted work; PNAH reports grants from Shionogi and MSD, grants and personal fees from Sandoz and personal fees from Pfizer outside the submitted work; JDT reports personal fees from EUCAST, an entity of the European Society for Microbiology and Infectious Diseases, outside the submitted work; DP reports grants from National Health and Medical Research Council, non-financial support from Ecolab Pty Ltd and Whiteley Corporation and non-financial support from Kimberly-Clark Professional during the conduct of the study; personal fees from Merck, Shionogi, Achaogen, AstraZeneca, Leo Pharmaceuticals, Bayer, GlazosSmithKline, Cubist, Venetox and Accelerate, grants from Shionogi and Merck (MSD) and personal fees from Pfizer outside the submitted work. All other authors have no conflicts of interest to declare.

Funding

No external funding was received for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.03.019.

References


Please cite this article as: Henderson A et al., A systematic review of antimicrobial susceptibility testing as a tool in clinical trials assessing antimicrobials against infections due to gram-negative pathogens, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2021.03.019