Infectious Diseases
RESEARCH REVIEW™

Making Education Easy

Issue 23 – 2020

In this issue:

Abbreviations used in this issue
CV = cardiovascular
HR = hazard ratio
OR = odds ratio
UTI = urinary tract infection

Welcome to issue 23 of Infectious Diseases Research Review.

The first study in this issue sought to determine the utility of follow-up blood cultures for predicting mortality risk in patients with gram-negative bacteraemia. Researchers from Australia developed and validated PEN-FAST, a penicillin allergy clinical decision rule that accurately identified low-risk penicillin allergies without formal allergy testing. We have also reported on a low-intensity, multifaceted intervention for improving antibiotic prescribing in nursing home patients with uncomplicated cystitis. This issue concludes with research reporting that while the degree of pyuria during the preoperative period predicts antimicrobial exposure, it is not associated with improved postoperative outcomes.

We hope you find these and the other selected papers interesting, and we look forward to receiving any feedback you may have.

Kind regards,

Dr Tim Blackmore
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Positive follow-up blood cultures identify high mortality risk among patients with gram-negative bacteraemia

Authors: Maskarinec SA et al.

Summary: The use of blood cultures obtained between 24 hours and 7 days after an initial positive culture for identifying mortality risk in 1702 adult inpatients with gram-negative bacteraemia was evaluated in this prospective observational study conducted between 2002 and 2015. Among patients who underwent follow-up blood cultures (n=1164), the positivity rate was 20%. Acquisition of follow-up blood cultures was associated with lower all-cause in-hospital mortality (20% vs. 15%; adjusted HR 0.629 [95% CI 0.511, 0.772]) and attributable in-hospital mortality (15% vs. 8%; 0.628 [0.480, 0.820]); the respective rates of these outcomes were also increased for positive versus negative follow-up blood cultures (21% vs. 11%; 2.099 [1.567, 2.811] and 12% vs. 7%; 1.800 [1.245, 2.603]). A calibration analysis revealed that patients at high risk of positive follow-up blood cultures could be identified by a scoring system.

Comment: This interesting article is based on the Duke bacteraemia database and includes Vance Fowler as one of the authors; he is the doyen of follow-up blood cultures in staphylococcal bacteraemia. The reduced mortality in those with negative follow-up blood culture is to be expected, but I was disappointed that the paper did not specifically look at removable or drainable foci of infection. The urinary tract appeared to be the major source of infection, but there was no comment made about how many bacteraemias were related to urinary catheters. The graph showing an association with bacterial species is particularly illuminating, and put *Serratia* above *Pseudomonas* in the persistent bacteraemia league. This is in keeping with my experience. The scoring system that they developed is slightly useful, but it seems to have been developed as a way of minimising costs of follow-up blood cultures. I would imagine other common sense-based approaches would work just as well. A similar paper was also published from Italy, which included source control as a protective factor, so together the value of follow-up blood cultures for gram-negative bacteraemia is now well established.

Reference: Clin Microbiol Infect 2020;26:904–10
Abstract

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Association between treatment duration and mortality or relapse in adult patients with *Staphylococcus* aureus bacteraemia

Authors: Abbas M et al.

Summary: The impact of therapy duration (≤14 vs. >14 days) on mortality and relapse was reported for a retrospective cohort of 94 patients with methicillin-resistant *Staphylococcus aureus* bacteraemia and 305 with complicated *S. aureus* bacteraemia in this research. The 90-day mortality rate was 27.0%, with a median time to death of 17 days after the onset of *S. aureus* bacteraemia, and the median therapy duration was 20 days. A significant relationship was seen between therapy duration >14 days and reduced mortality in patients with complicated *S. aureus* bacteraemia (adjusted HR 0.32 [95% CI 0.16, 0.64]), but not in patients with uncomplicated *S. aureus* bacteraemia (0.85 [0.41, 1.78]). The relapse rate was 3.4%, with no association between therapy duration and relapse in a univariate analysis (HR 1.01 [95% CI 0.97, 1.06]).

Comment: This paper caught my eye as part of my current obsession with early oral step-down therapy for *S. aureus* bacteraemia. The current critical issue when deciding if short-course therapy is advisable appears to be whether the bacteraemia is complicated or not. In this paper, complications included endocarditis, implanted prosthetic material, bacteraemia of >2 days or fever for >3 days. The Americans seem to think that uncomplicated bacteraemia is rare, but the Swiss found that almost half of their cases met the uncomplicated definition. It seems that there are multiple cognitive, and perhaps financial, reasons for the Americans to give prolonged intravenous therapy. It was interesting that in this study, staphylococcal pneumonia emerged as a strong risk factor for failure.

Reference: Clin Microbiol Infect 2020;26:626–31
Abstract

Development and validation of a penicillin allergy clinical decision rule

Authors: Trubiano JA et al.

Summary: These researchers developed a penicillin allergy clinical decision rule for point-of-care risk assessment of patient-reported penicillin allergies. A cohort of 622 patients from two Australian tertiary-care sites was used for derivation and internal validation, and external validation was undertaken in a retrospective penicillin allergy-tested cohort of 945 patients. The following features associated with a positive penicillin allergy test result contributed to the development of the PEN-FAST decision rule: penicillin allergy ≤5 years ago (2 points), anaphylaxis/angio-oedema or severe cutaneous adverse reaction (2 points) and treatment required for an allergy episode (1 point). Internal validation revealed minimal mean optimism of 0.003 with an internally validated area under the curve value of 0.805. At a cutoff of <3 points for PEN-FAST, the negative predictive value was 96.3%; external validation findings were similar.

Comment: Hopefully this article will allow us to move ahead with a more streamlined approach to oral challenge for those with reported but dubious penicillin allergies. The PEN-FAST rules and interpretation are very simple and now validated. There has been major reluctance to simplify challenge testing, based on fear of complications, but this paper now allows protocols to move forward so that patients can receive the best antibiotics. This is most important for those requiring surgical prophylaxis, at least in my practice.

Reference: JAMA Intern Med 2020;180:745–52
Abstract

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Inter-technique variability between antimicrobial susceptibility testing methods affects clinical classification of cefuroxime in strains close to breakpoint

Authors: Ballestero-Téllez M et al.

Summary: These researchers evaluated the accuracy of susceptibility methods for testing cefuroxime against 80 *Escherichia coli* strains with a cefuroxime minimum inhibitory concentration value of 16 mg/L obtained by broth microdilution with Vitek 2. Resistance was seen for all strains according to Vitek 2, but 72.5% were categorised as susceptible according to reference standard microdilution. The respective categorical and essential agreement values between Vitek 2 and the reference standard microdilution were 27.5% and 86.3%. Statistically significant differences were seen when the isolates were classified as susceptible or resistant according to EUCAST breakpoints between diffusion methods (disc and gradient) and reference standard microdilution. The respective proportions of results that were false susceptible for BioMérieux and Liofilchem gradient testing and for Oxoid and Bio Rad cefuroxime discs were 24.1%, 13.8%, 22.5% and 17.2%, and the respective proportions that were false resistant were 4.5%, 40.9%, 9.1% and 13.6%.

Comment: We are currently reviewing our antibiotic guidelines and there have been several key discussions. They include removing piperacillin-tazobactam from the formulary and replacing cefuroxime with ceftriaxone. It is self-evident that the laboratory should provide reliable susceptibility results for agents on the formulary, and there have been a lot of problems with piperacillin-tazobactam testing. I have also had my doubts about cefuroxime, so this paper comes along at the right time. It will not be of huge interest to those outside a microbiology lab, but the short summary is that there is little reproducibility around the breakpoint between different methods. These technical issues make it difficult to compare antibiograms and hence whether cefuroxime is suitable for empiric use. We mainly use our susceptibility data to determine our empiric treatment recommendations, and this paper shows that a proportion of results will be poorly reproducible. It may explain why cefuroxime, cephalexin and ceftriaxone test results are sometimes inconsistent; testing issues may be more important than fundamental differences in antibiotic activity.

Reference: Clin Microbiol Infect 2020;26:648E1–3
Abstract

CONGRATULATIONS TO

Ruth Pattillo (a Pharmacist at Total Health Pharmacy), **Lisa Hesp** (a Health Manager at Pegusus Health Charitable Ltd) and **Jenny Carston** (a Health Manager at BOPDHB) who each won a $200 Visa Prezzy Card by taking part in our recent Research Review Annual Subscriber Update.

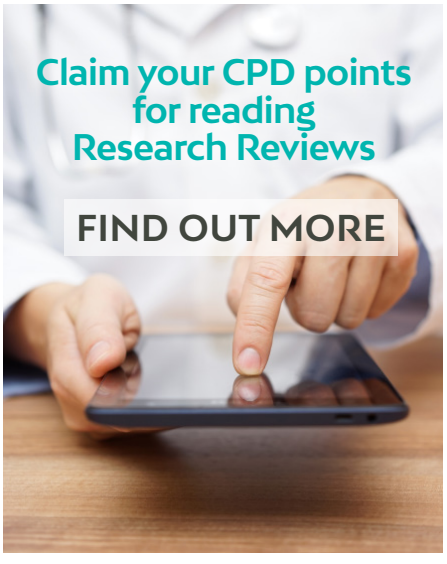
Association of azithromycin use with cardiovascular mortality

Authors: Zaroff JG et al.

Summary: The risks of CV and sudden cardiac death following outpatient receipt of azithromycin versus amoxicillin were explored in a retrospective cohort study of 1,736,976 azithromycin exposures and 6,087,705 amoxicillin exposures prescribed to 2,929,008 unique patients from two large, diverse, community-based integrated care delivery systems. Azithromycin was associated with significantly increased risks of CV-related death (HR 1.82 [95% CI 1.23, 2.67]), non-CV-related death (2.17 [1.44, 3.26]) and death from any cause (2.00 [1.51, 2.63]), but not sudden cardiac death (1.59 [0.90, 2.81]) within 5 days of exposure; no increased risks were seen during days 6–10 after exposure. Patients from the top CV risk decile had similar outcomes.

Comment: This is a very large observational study that adds to several others that have shown increased CV mortality with azithromycin use. It appears to be a short-lived effect. The study population receiving azithromycin did appear to have more CV morbidity, which must reflect the perceived indications for the drug, i.e. most needed in the sickest people. Despite the excess mortality translating to small absolute numbers, this is one of the articles to quote when trying to dissuade clinicians from prescribing azithromycin as a general respiratory tonic.

Reference: JAMA Netw Open 2020;3:e208199
Abstract



Clinical and economic impact of implementing OVIVA criteria on patients with bone and joint infections in outpatient parenteral antimicrobial therapy

Authors: Marks M et al.

Summary: These authors found that 79.7% of 133 outpatients requiring parenteral antimicrobial therapy at their centre would be eligible for oral antibiotics according to criteria from the OVIVA study, which demonstrated noninferiority for managing bone and joint infections with oral antibiotics. This would have saved a median of 19.5 intravenous antibiotic days and GBP1234 per patient.

Comment: I found it a bit hard to work out how much of this study was theoretical and how much was a study of what they actually did. The financial savings realised in this study are probably an underestimate because nursing costs do not appear to have been included. They also did not appear to use infusion pumps, etc. Most importantly, this study did not address patient quality of life issues and satisfaction with therapy. It was not made clear whether outpatient parenteral antimicrobial therapy was delivered in centres or at the patient home, and the social disruption from receiving outpatient parenteral antimicrobial therapy should not be underestimated. Nevertheless, this article provides some rough indication of the potential cost saving for their service – I doubt whether the real numbers would be similar in NZ. The main issue is that it will take time and studies like this to convince all infectious diseases physicians that oral treatment is as good, if not better, than prolonged intravenous treatment.

Reference: Clin Infect Dis 2020;71:207–10
Abstract

A multifaceted antimicrobial stewardship program for the treatment of uncomplicated cystitis in nursing home residents

Authors: Nace DA et al.

Summary: In this randomised trial, 12 nursing homes were assigned to a quality improvement intervention targeted at antimicrobial use for unlikely cystitis among noncatheterised residents (512,408 resident-days), and 13 were assigned to usual care (443,912 resident-days); the intervention consisted of a 1-hour introductory webinar, pocket-sized educational cards, system change tools and educational clinical vignettes addressing the diagnosis and treatment of suspected uncomplicated cystitis, and the staff received monthly web-based coaching calls. Compared with the usual care facilities, those assigned to the intervention reported fewer unlikely cystitis cases treated with antibiotics (adjusted incident rate ratio, 0.73 [95% CI 0.59, 0.91]), lower *Clostridioides difficile* infection rates (0.35 [0.19, 0.64]) and less antibiotic use for any type of UTI (0.83 [0.70, 0.99]), with no increase in all-cause hospitalisations (0.95 [0.75, 1.19]) or all-cause mortality (0.92 [0.73, 1.16]).

Comment: I think this is a very important study, as it describes a well-developed and effective programme for dealing with UTIs, particularly uncomplicated cystitis, in rest-home residents. It would be interesting to have more detail on the educational material provided to staff, and there are some excellent references in the article. It is hard to know how much effort is worth it to produce some modest benefits, because this sort of project is a big undertaking. Another useful recent article was published in J Clin Microbiol, which provides some of the laboratory perspectives. It must be time for some national co-ordination on such an important issue.

Reference: JAMA Intern Med 2020;180:944–51
Abstract

Fluoroquinolone use for uncomplicated urinary tract infections in women

Authors: Daneman N et al., for the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators

Summary: These researchers sought to determine if non-fluoroquinolone alternatives are as effective as fluoroquinolones for treating UTIs in a retrospective population-based cohort of 1,585,997 women who received antibiotic treatments in Canada for 2,857,243 episodes of uncomplicated UTIs. Five of the six Canadian provinces reported a decline in fluoroquinolone use for UTIs over the 2005–2015 study period; fluoroquinolones accounted for 22.3–48.5% of treatments overall. Data pooled from all provinces revealed that fluoroquinolone use was associated with reductions in return outpatient visits (OR 0.89 [95% CI 0.87, 0.92]), emergency department visits (0.74 [0.61, 0.89]), hospitalisations (0.83 [0.77, 0.88]) and repeat antibiotic dispensations (0.77 [0.75, 0.80]) within 30 days.

Comment: This is the study we might want to try and find fault with, because it shows something that we would rather not believe! The Canadians have shown with an observational study that quinolones outperform other antibiotics for UTIs, despite their resistance rates being higher than NZ. The number needed to treat to prevent the need for second-line antibiotics was only 25. The authors suggest that the quinolone superiority they found may have been due to a longer course of treatment than that used in previous comparisons. I, for one, am not ready yet to make quinolones first-line, and the fact that this is an observational rather than controlled prospective study allows me to remain sceptical… I think. Regardless, this is a paper worth reading.

Reference: Clin Microbiol Infect 2020;26:613–8
Abstract

Chlorhexidine bathing to prevent central line-associated bloodstream infections in hematology units

Authors: Tien K-L et al.

Summary: Outcomes were compared between hospitalised adults receiving cytotoxic chemotherapy for haematological malignancies who accepted an offer of chlorhexidine bathing (n=485) and those who received usual care after declining chlorhexidine bathing (n=408) in this prospective research. Compared with the usual care group, the chlorhexidine group had a lower crude incidence rate of gram-positive cocci-related, skin flora-related or central line-associated bloodstream infections (primary outcome; 3.4 vs. 8.4 per 1000 patient-days; adjusted HR 0.4 [p<0.001]), but no significant difference for the crude incidence rate of the negative control outcome of gut-origin bacteraemia (4.5 vs. 3.2 per 1000 patient-days; 1.1 [p=0.781]). Chlorhexidine bathing was well tolerated.

Comment: This is a great paper – pragmatically designed and well written. The take-home message is that chlorhexidine washes or wipes reduce gram-positive bacteraemia and are associated with a significant reduction in adverse events. It also includes two approaches to chlorhexidine: body washes and wipes. It is not the perfect study because patients were not randomised, but this is well covered in the discussion. It is definitely a paper to discuss with haematology-oncology.

Reference: Clin Infect Dis 2020;71:556–63
Abstract

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Independent commentary by Dr Tim Blackmore

Dr Blackmore is based in Wellington where he works as a microbiologist and infectious diseases physician. He provides specialist support to Wellington, and Hutt hospitals. He trained in New Zealand and South Australia where he completed fellowships with the RCPA and RACP, and completed a PhD thesis.

He has a busy clinical and laboratory practice, including infection prevention and control and is on a Ministry of Health advisory committee for vaccines and publishes the occasional paper.

How testing drives treatment in asymptomatic patients: level of pyuria directly predicts probability of antimicrobial prescribing

Authors: Gupta K et al.

Summary: The relationship between pyuria and antimicrobial initiation during the perioperative period was explored, with harms versus benefits of treatment also investigated, for a retrospective cohort of 41,373 patients who had a urinalysis performed during a 30-day preoperative period; patients with positive urine cultures were excluded. Patients with pyuria (n=3617) were more likely to receive antimicrobials than those without pyuria (24.5% vs. 5.1%). There was a linear association between degree of pyuria and the likelihood of receiving antimicrobials, with antimicrobial receipt rates of 14.7%, 24.0% and 37.4% for low, moderate and high degrees of pyuria, respectively. A significant association was seen between preoperative pyuria and postoperative *C. difficile* infection (adjusted OR 1.7 [95% CI 1.2, 2.4]), with a higher risk in antimicrobial recipients (2.4 [1.7, 3.4]). Pyuria was also associated with more UTIs following orthopaedic and vascular procedures; this association was not mitigated by antimicrobial therapy. There was no association between pyuria and surgical-site infections.

Comment: This is another excellent recent article from Clin Infect Dis, again about UTI diagnosis and treatment. The preoperative groups studied were patients who would not get urine samples sent normally in my hospital, but the principle of 'more white cells equals more antibiotics' would probably hold true in other patients. For this reason, we removed urine dipsticks from the wards because no amount of laboratory diagnostic stewardship will help when point-of-care testing is available. This research group has a great track record in the area of appropriate UTI diagnosis, and I recommend this paper for some excellent graphs and a great discussion.

Reference: Clin Infect Dis 2020;71:614–21
Abstract