Infectious Diseases
RESEARCH REVIEW™

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Issue 26 – 2021

In this issue:

Abbreviations used in this issue
AMS = antimicrobial stewardship
ESBL = extended-spectrum β-lactamase
MRSA/MSSA = methicillin-resistant/susceptible *Staphylococcus aureus*
MSM = men who have sex with men
OR = odds ratio
RAT = rapid antigen test
RPR = rapid plasma reagin
STI = sexually transmitted infection
TB = tuberculosis

Welcome to issue 26 of Infectious Diseases Research Review.

This issue has ended up with quite a focus on AMS (antimicrobial stewardship). AMS has a lot of dogma associated with it, and antibiotic guidelines usually have stewardship as a major driving principle. As a pragmatist, and someone who has been in hospital getting intravenous treatment, I have become a lot more interested in the convenience of treatment, particularly in regard to once-a-day or multiple dosing. We are in the process of dropping cefuroxime in favour of ceftriaxone in the Wellington region, but concerns are raised that this is more likely to lead to resistance. Well, one paper in this review shows that cefuroxime and metronidazole have profound effects on gram-negative bacteraemia, so perhaps we should not be too sad to replace cefuroxime. Let's start this review with two articles on syphilis. The first has grabbed a lot of attention with editorials and literature reviews.

We appreciate all the comments and feedback we have received from you – please keep them coming.

Kind regards,

Dr Tim Blackmore
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Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France

Authors: Bettuzzi T et al.

Summary: Outcomes for 42 patients who had received ceftriaxone for neurosyphilis at one of eight tertiary care centres in France were compared with those of 166 similar patients who had been treated with benzylpenicillin in this retrospective study; 93.3% of the patients were men. Compared with benzylpenicillin recipients, greater proportions of ceftriaxone recipients achieved clinical and complete responses (98% vs. 76% and 52% vs. 33%, respectively), but only the difference for clinical response remained significant after propensity score weighting (respective ORs 1.22 [95% CI 1.12, 1.33] and 1.08 [0.94, 1.24]). Ceftriaxone recipients also had significantly shorter hospital stays, but there was no significant between-group difference for 6-month serological response rate (88% vs. 82%). There were no major adverse events reported.

Comment: This large retrospective study from France now provides fairly robust data supporting the use of ceftriaxone for 14 days to treat neurosyphilis. Ceftriaxone has always seemed equivalent, it just that there were so few data in comparison with benzyl or procaine penicillin. We now have more defendable choices, and many would prefer a daily antibiotic push rather than having an infuser with all its inconveniences and expense. There may be some who will continue to recommend penicillin on AMS grounds, but I won't be one of them.

Reference: Lancet Infect Dis 2021;21:1441–7

Abstract

Treponema pallidum detection in lesion and non-lesion sites in men who have sex with men with early syphilis

Authors: Towns JM et al.

Summary: MSM with primary (n=54), secondary (n=93) or early latent (n=53) syphilis were prospectively tested for *Treponema pallidum* shedding from potentially asymptomatic sites and the stage of infection at which shedding was most frequent in this cross-sectional study. PCR detected *T. pallidum* DNA in 24% of the men in oral rinses and/or oral lesion swabs, 24 of whom had no oral lesions; it was more frequent in those with secondary syphilis versus other stages (44% vs. 7% [p<0.0001]) and those with RPR (rapid plasma reagin) titres of ≥1/64 versus lower titres (32% vs. 13% [p=0.0026]). *T. pallidum* was also detected in 23.0% of anal and/or lesion swabs (evaluable n=196; ten with no anal lesions), 6.1% of urine samples (evaluable n=198) and 12.0% of semen samples (evaluable n=50). In the secondary syphilis group, 74% had *T. pallidum* detected at any site, and 26% had detection at ≥2 sites; the corresponding proportions for the primary syphilis group were 91% and 20%, and for the early latent syphilis group, they were 8% and 0%.

Comment: This study from Melbourne is fascinating in that it demonstrates the frequency of treponemal detection from oral and anal samples in primary and secondary syphilis, whereas the rash itself was not a significant source of bacterial DNA. I was particularly interested in the observation that the RPR was a predictor of putative infectivity, with a level of 1:64 selected for statistical analysis. It is unfortunate that they did not provide further details of the spread of RPRs and infectivity because it relates to infectious syphilis notification. At present 'infectious syphilis' is notified by clinicians in NZ rather than by direct laboratory notification, but overseas a titre of 1:8 or greater is used as a surrogate for infectious syphilis. At some time very soon, NZ will have to settle on a trigger for direct laboratory notification, so we may need to contact the authors of this paper to help select a pragmatic RPR titre.

Reference: Lancet Infect Dis 2021;21:1324–31

Abstract


MSD Rahway Research Team, 1980s[1]

Colonization with fluoroquinolone-resistant Enterobacterales decreases the effectiveness of fluoroquinolone prophylaxis in hematopoietic cell transplant recipients

Authors: Satlin MJ et al.

Summary: These researchers reported on the prevalence of colonisation with fluoroquinolone-resistant Enterobacterales in 234 patients admitted for haematopoietic cell transplantation with the risk of gram-negative bloodstream infection compared with those who were colonised and those who were not; all patients received prophylaxis with levofloxacin during neutropenia. Fluoroquinolone-resistant Enterobacterales colonisation was detected in 23% of the patients prior to transplantation (25% allogeneic, 21% autologous), and was significantly associated with recent antibacterial use (p=0.048). Of the colonising fluoroquinolone-resistant Enterobacterales isolates, 91% were *Escherichia coli* and 29% produced ESBLs. Compared with patients not colonised with fluoroquinolone-resistant Enterobacterales, a significantly greater proportion of those who were developed a gram-negative bloodstream infection despite levofloxacin prophylaxis (31% vs. 1.1% [p<0.001]). Among the 17 gram-negative bloodstream infections in fluoroquinolone-resistant Enterobacterales-colonised patients, 88% were caused by isolates that were genetically identical to the colonising strain.

Comment: Continuing the AMS line, this study from New York should make the haematologists take notice and reconsider routine fluoroquinolone prophylaxis. There appears to be a general selection effect that not only leads to increased fluoroquinolone-resistant bacteraemia, but to increased gram-negative bacteraemia in general. As commented on previously, we abandoned ciprofloxacin prophylaxis for transrectal prostate biopsies because of the number of breakthrough sepsis episodes. This study provides good data showing the risk of fluoroquinolone prophylaxis, particularly if colonised with fluoroquinolone-resistant organisms. Their baseline rate of 23% is very high compared with what I imagine our rates would be, but I would imagine that at least 10% of our patients, particularly of Asian ethnicity, should have fluoroquinolone prophylaxis carefully reconsidered.

Reference: Clin Infect Dis 2021;73:1257–65
Abstract

Quantifying the rates of late reactivation tuberculosis

Authors: Dale KD et al.

Summary: This systematic review of 110 studies reporting on TB reactivation rates occurring >2 years after infection divided them into the following four methodological groups: 1) 14 studies that reported late reactivation rates from conversion; 2) 11 studies reporting late reactivation rates in latent TB cohorts from exposure; 3) 86 studies in latent TB cohorts with unknown exposure history; and 4) seven ecological studies. Since treatment of TB with antibiotics began, only 11 studies have documented late reactivation rates in infected, untreated cohorts from conversion or exposure; six of these studies have a duration of ≥4 years but none have a duration >10 years. These studies found that TB rates declined over time to ≤200 cases per 100,000 person-years by the fifth year, possibly with further declines after 5 years; interpretation was limited by decreasing or unspecified cohort sizes. TB rates were generally lower in the group 3 studies compared with those in groups 1 and 2, and rates had declined to <100 per 100,000 person-years beyond 10 years postscreening. Interpretation of all studies was limited by risk or reinfection and the impact of age was unclear.

Comment: This paper is a very difficult read, but appears to be the most complete analysis of risk of TB reactivation published so far. There are many graphs and tables, and much discussion on the different methods of follow-up, chances of reinfection, and tuberculin skin test cutoffs. The bottom line seems to be that the chances of late reactivation have been overemphasised, with the 10% rate being commonly but selectively quoted. The authors' estimate is that there is approximately 1 in 500 chance of reactivation more than 5 years after exposure. This will make me rethink my approach to latent TB to some extent, particularly for people who came to NZ more than 5 years ago. I think this paper can still be used to justify recommending treatment to those with strong interferon responses who likely were infected in the previous 5 years or are known converters.

Reference: Lancet Infect Dis 2021;21:e303–17
Abstract

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Doxycycline versus azithromycin for the treatment of rectal chlamydia in men who have sex with men

Authors: Dombrowski JC et al.

Summary: MSM with rectal *Chlamydia trachomatis* infection were randomised to receive doxycycline 100mg twice daily for 7 days (n=88) or a single dose of azithromycin 1g (n=89) in this trial. Compared with single-dose azithromycin, the doxycycline regimen resulted in a greater incidence of microbiological cure in both the intent-to-treat and complete case populations (91% vs. 71% and 100% vs. 74%, respectively [p<0.001 for both]).

Comment: This study has the advantage of being randomised and prospective, and reinforces the push away from azithromycin as being less effective for treatment of STIs. AMS principles have been learnt the hard way for treating STIs, with the increasing macrolide resistance of *Mycoplasma genitalium* and much lower success rates with rectal chlamydia. Convenience often comes at a cost. Many STI treatment guidelines have already moved back to doxycycline, which fortunately remains a remarkably effective antibiotic for most indications.

Reference: Clin Infect Dis 2021;73:824–31
Abstract

The impact of the Auckland cellulitis pathway on length of hospital stay, mortality readmission rate, and antibiotic stewardship

Authors: Ritchie SR et al.

Summary: This paper from NZ reported on the development and implementation of a pathway for guiding management of adults with cellulitis according to Dundee severity class. Outcomes were compared between a baseline cohort of patients admitted to Auckland City Hospital between July 2014 and July 2015 and an intervention cohort of patients admitted between June 2017 and June 2018. Compared with the baseline cohort, the intervention cohort had a shorter median length of hospital stay (0.7 vs. 1.8 days [p<0.001]) and a lower 30-day mortality rate (0.7% vs. 1.8% [p=0.02]), but an increased 30-day cellulitis readmission rate (11% vs. 6% [p<0.001]). Adherence to the hospital's cellulitis antibiotic guideline improved significantly from 38% to 48% and was an independent predictor of reduced length of stay.

Comment: It is always good to find a NZ study in a major impact journal. This paper will add to the literature favouring oral over prolonged intravenous treatment. I would question the dose of flucloxacillin used; a 500mg four times per day regimen is less likely to be adhered to than a three times per day regimen, and I would be concerned that it would result in underdosing in many adults. Also, the pathway does not seem to be changed for MRSA carriers, which would be not insignificant in Māori and Pasifika. The great results they got suggest to me that most of the cellulitis they treated was in fact caused by β-haemolytic streptococci (or got better despite rather than because of antibiotic therapy).

Reference: Clin Infect Dis 2021;73:859–65
Abstract

The effect of prophylaxis with ertapenem versus cefuroxime/metronidazole on intestinal carriage of carbapenem-resistant or third-generation-cephalosporin-resistant Enterobacterales after colorectal surgery

Authors: Hoffman T et al., on behalf of Resistance in Gram-Negative Organisms: Studying Intervention Strategies (R-GNOSIS) WP4 Study Group

Summary: These researchers sought to determine the impact of ertapenem prophylaxis on postoperative colonisation with carbapenem-resistant Enterobacterales and third-generation cephalosporin-resistant Enterobacterales in participants from a quality improvement prophylaxis study in carriers of ESBL-producing Enterobacterales undergoing colorectal surgery. There were 56 ESBL-producing Enterobacterales carriers who received cefuroxime/metronidazole prophylaxis (group 1), 66 ESBL-producing Enterobacterales carriers who received ertapenem (group 2) and 103 noncarriers of ESBL-producing Enterobacterales who received cefuroxime/metronidazole (group 3). Postoperative carriage of carbapenem-resistant Enterobacterales was detected in one participant from group 1 compared with eight from group 2 (1% vs. 14.3%; difference, –12.8% [95% CI –22.4, –3.1]). Comparisons of preoperative ESBL-producing Enterobacterales and postoperative carbapenem-resistant Enterobacterales isolates in seven of the nine participants revealed five had identical pre- and postoperative clones. Postoperative third-generation-cephalosporin-resistant Enterobacterales carriage was detected in a lower proportion of group 2 participants compared with group 1 (56.1% vs. 82.1%; difference –20.7% [95% CI –37.3, –4.1]).

Comment: I like this article partly because it references a paper I was involved with! When investigating and publishing on the use of ertapenem prophylaxis for prostate biopsy, we came across a lot of bias on the basis of AMS, and even urologists were claiming to be agents of AMS, despite recommending the use of ciprofloxacin as prophylaxis! Our study was limited by the rarity of ESBL and carbapenem-resistant Enterobacterales, but this study from Israel does not have that limitation. The finding that ertapenem is less likely to be associated with the emergence of resistance than cefuroxime should provoke a more open consideration of which antibiotics are 'good' for AMS. Effective prophylaxis reduces antibiotic exposure, and more work like this is required to reach scientific opinions regarding AMS; antibiotics of last resort may actually be the antibiotics of first resort. It's getting time for us to conduct country-wide trials so that we use the most appropriate surgical prophylaxis for our human and bacterial populations in NZ.

Reference: Clin Microbiol Infect 2021;27:1481–7
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.

Safety and tolerability of fluoroquinolones in patients with staphylococcal periprosthetic joint infections

Authors: Vollmer NJ et al.

Summary: Fluoroquinolone-associated adverse events leading to unplanned drug discontinuations were reported for 156 adults treated for staphylococcal periprosthetic joint infections with debridement, antibiotics and implant retention. Compared with patients who did not receive fluoroquinolone regimens, those who did had a higher rate of unplanned drug discontinuations overall (35.6% vs. 3%), including in both the total hip and total knee arthroplasty subgroups (27.5% vs. 4.2% [p=0.021] and 42% vs. 2.4% [p<0.001], respectively); fluoroquinolone recipients also had a significantly higher rate of nonsevere adverse events (43.3% vs. 6.1% [p<0.001]), but not severe adverse events. Adverse events associated with fluroquinolone use included tendinopathy, myalgia, arthralgia and nausea.

Comment: This is quite a large case series review, but may be limited in its applicability because almost all patients received levofloxacin rather than ciprofloxacin. A high dose was used, consistent with pharmacokinetic/pharmacodynamic considerations, but this dose is relatively poorly tolerated. I have had many patients complain whenever I have tried to use the Zimmerli protocol of 900mg of rifampicin and 1500mg of ciprofloxacin per day, and this anecdote appears to be reinforced by this paper. I am not quite sure what we can do about this other than not to use them in combination and to stick with our local policy of using a β-lactam with one of those two other drugs according to the infecting organism. We certainly need to counsel our patients that joint preservation comes at a cost of drug side effects and we should be alert to them.

Reference: Clin Infect Dis 2021;73:850–6
Abstract

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Comparable outcomes of short-course and prolonged-course therapy in selected cases of methicillin-susceptible *Staphylococcus aureus* bacteremia

Authors: Thorlacius-Ussing L et al.

Summary: This analysis of data from three retrospective cohorts (total n=1005) compared the clinical outcomes for short-course (6–10 days) versus prolonged-course (11–16 days) antibiotic therapy for low-risk MSSA bacteraemia. Across the cohorts, the median short-course durations were 8–9 days and the median prolonged course durations were 13–14 days. There was no significant difference between short-course versus prolonged-course antibiotics for 90-day mortality for any of the three cohorts analysed separately (ORs 0.85–1.24) or pooled (OR 1.05 [95% CI 0.71, 1.51]), nor was the risk of relapse significantly different.

Comment: The evidence supporting shorter courses of antibiotics gets stronger and stronger. This study is large and used fancy statistical methods that I do not fully understand. Most importantly though, it brings 'short course' down to 8 days and 'long course' to 14 days… heresy for Americans, but this study was conducted in Denmark. Of potential concern is the observation that the mortality of 27% was high for uncomplicated MSSA bacteraemia, and is discussed in an accompanying editorial by Steve Tong. I remain of the opinion that how long a person is treated for is less important than ensuring that the patient can easily get attention if their infection is not responding or relapsing. The most frustrating thing about this paper is that it does not clearly break down the balance of intravenous versus oral antibiotics. Intuitively, the risk-benefit ratio is much better for oral than intravenous therapy, so it would not be a surprise if short-course intravenous therapy looked as good as long-course intravenous/mixed intravenous and oral. I remain comfortable with 2 weeks total, with early oral switch for uncomplicated MSSA bacteraemia, but maybe we will get to 10 days soon.

Reference: Clin Infect Dis 2021;73:866–72
Abstract

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Performance evaluation of serial SARS-CoV-2 rapid antigen testing during a nursing home outbreak

Authors: McKay SL et al., CDC Infection Prevention and Control Team and the CDC COVID-19 Surge Laboratory Group

Summary: The performance of a RAT (rapid antigen test) for SARS-CoV-2 (BinaxNOW) in a nursing home during an outbreak was prospectively evaluated in this research. Three facility-wide rounds of testing of 532 paired respiratory specimens collected from 234 staff and residents were compared with virus culture and real-time reverse transcription PCR results. The percentage of positive agreement between the RATs and virus cultures was 95%, but between RAT and PCR it was 69% and the percentage of negative agreement was 98%. When only first positive test results from each participant were analysed, the respective percentages of positive agreement between RAT and PCR for symptomatic (n=45) and asymptomatic (n=343) individuals were 82% and 52%. Compared with PCR and virus culture, RAT performed well in early infection (86% and 95%, respectively) but less well in late infection (51% and no recovered virus, respectively).

Comment: I have not generally included COVID papers in Infectious Diseases Research Review, but have made an exception for this paper and correspondence. There has been a lot of media airplay around RATs and saliva testing. NZ has been slow to introduce RAT, mainly because the elimination strategy makes people nervous about missing cases. This study from the CDC provides further evidence that RATs perform well early in the illness of symptomatic people, particularly compared with viral culture. Furthermore, serial testing found cases missed on single tests. This is consistent with another article using much the same methodology, but testing university students. My (over)simplified summary is that RATs and point-of-care nucleic acid tests compare well with culture and reverse transcription PCR at a Ct of 30 or less from nasopharyngeal swab sampling, and these are likely to be the infectious cases. Also of relevance is a letter in Lancet Infect Dis that relates to a study comparing different sample types for PCR, which also has been a subject of much discussion. Essentially the conclusion of the authors was that a combined nasal and throat swab performs about as well as a nasopharyngeal swab. This is a useful finding, because many RATs use a combined swab, and it will be less confusing if the same sample type is acceptable whether using a RAT or PCR test. Taken together, as COVID increases in NZ, the use of RAT will increase, which will be necessary to maintain diagnostic testing with a reasonable turnaround time. The laboratories are gearing up, but staff fatigue, instrument failure and increasing test volumes mean that we will need to use combinations of laboratory, point-of-care tests and self-tests. RATs are now established as reasonably reliably for detecting infectious people quickly, but lab tests will be needed to exclude false-positives.

Reference: Ann Intern Med 2021;174:945–51
Abstract