BREAK POINT

2014 - ISSUE 11

FROM THE NEWSLETTER EDITOR'S DESK

Welcome to the December edition of Breakpoint. Following "In the news", a short guide to the use of antibiotics to treat antimicrobial-resistant Gram positive organisms follows, provided by Vid Menon and Sebastian Van Hal from the Royal Prince Alfred Hospital in Sydney, as a follow up of all things Gram positive since the October issue of Breakpoint. Significant notices and a conference calendar follow. Feedback and suggestions are warmly welcome regarding the overall "look" of the newsletter and for improving its content and scope. The newsletter wishes all its readers a happy and safe holiday season.

Sharon Chen

ASA Breakpoint Editor,

On behalf of the ASA committee

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IN THE NEWS

Antibiotic decontamination of the digestive tract in the ICU and antimicrobial resistance - still no definitive answer?

The use of prophylactic antibiotics to decontaminate the oropharyngeal and/or digestive tracts of critically ill patients to reduce risk of infection is not widely used because of concern that this promotes antimicrobial resistance. A recent large multicenter cluster-randomized trial in intensive care units in the Netherlands compared resistance rates with selective oropharyngeal decontamination (SOD; antibiotics applied to the oropharynx only) and selective digestive decontamination (SDD; antibiotics applied to the oropharynx and through a nasogastric tube plus a different intravenous antibiotic). Rates of rectal colonization with highly resistant bacteria were overall lower with SDD than SOD, but colonization with aminoglycoside-resistant gram-negative bacilli increased more over time with SDD than SOD. Given the very low baseline rate of antimicrobial resistance in the Netherlands and the absence of a "control" group that received no prophylaxis, these findings do not sufficiently allay concerns about long-term antimicrobial resistance with antibiotic use for decontamination of the gastrointestinal tract.

Reference: Oostdijk EA, Kesecioglu J, Schultz MJ, Visser CE, de Jonge E, van Essen EH, Bernards AT, Purmer I, Brimicombe R, Bergmans D, van Tiel F, Bosch FH, Mascini E, van Griethuysen A, Bindels A, Jansz A, van Steveninck FA, van der Zwet WC, Fijen JW, Thijsen S, de Jong R, Oudbier J, Raben A, van der Vorm E, Koeman M, Rothbarth P, Rijkeboer A, Gruteke P, Hart-Sweet H, Peerbooms P, Winsser LJ, van Elsacker-Niele AM, Demmendaal K, Brandenburg A, de Smet AM, Bonten MJ. Effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in ICUs: a randomized clinical trial. JAMA. 2014;312(14):1429.

IN THE NEWS (CONT'D)

Infection associated with contaminated endoscopes with NDMs and CREs ! - A cautionary tale

In January 2014, the Centers for Disease Control and Prevention (CDC) reported that since January 2013, 69 cases of New Delhi metallo-beta-lactamase (NDM)-producing carbapenem-resistant Enterobacteriaceae (CRE) had been identified in the USA, 44 of which were from northeastern Illinois. Further investigation identified 39 cases from one hospital. The source of infection was traced to the elevator channel of a single duodenoscope (endoscopes used for endoscopic retrograde cholangiopancreatography. No lapses in the cleaning protocol were identified. Complex design of the elevator mechanism makes it more difficult to clean than other parts of endoscopes. **After changing duodenoscope reprocessing from high-level disinfection to gas sterilization with ethylene oxide**, no new cases were identified. .

Reference: Epstein L, Hunter JC, Arwady MA, Tsai V, Stein L, Gribogiannis M, Frias M, Guh AY, Laufer AS, Black S, Pacilli M, Moulton-Meissner H, Rasheed JK, Avillan JJ, Kitchel B, Limbago BM, MacCannell D, Lonsway D, Noble-Wang J, Conway J, Conover C, Vernon M, Kallen AJ. New Delhi metallo-β-lactamase-producing carbapenem-resistant Escherichia coli associated with exposure to duodenoscopes. JAMA. 2014 Oct;312(14):1447-55.

ANTIMICROBIALS 2015 MEETING REGISTRATION WEBSITE OPEN

26 - 28 February 2015 , Brisbane Exhibition and Convention Centre. **www.antimicrobials2015.com**

On behalf of the Australian Society for Antimicrobials I would like to invite you to the Society's 16th Annual Scientific Meeting "Antimicrobials 2015" to be held at the Brisbane Exhibition and Convention Centre, Brisbane, on Thursday 26th - Saturday 28nd February 2015.

I am pleased to announce Sara Cosgrove, Johns Hopkins University School of Medicine, USA; Jan Kluytmans, Erasmus Medical University, The Netherlands; Sally Roberts, Auckland City Hospital, New Zealand; and Gunnar Kahlmeter, Central Hospital, Sweden will be participating at the meeting. Sara will be presenting the plenary "Multiple Prongs of Stewardship: Less is More – Debunking Stewardship Myths", while Jan and Sally will be presenting "Resistance Links to Animals" and "Improving Care: Infection Prevention and Patient Safety" respectively. In addition to presenting the plenary "EUCAST and Beyond", Gunnar with Erika Matusckek will be presenting two EUCAST workshops on susceptibility testing.

The 2015 Howard Florey Oration will be delivered by Benjamin Howden from Melbourne University, Victoria. Ben will be presenting the talk "Vancomycin and *Staphylococcus aureus* – A Complex Relationship"

The programme's symposia cover many different aspects on antimicrobials and sessions include "Alternative Perspectives on Antimicrobial Use", "Carbapenemases", "What to Report and How to Treat", "Enterococci" and "SMART Platforms". In addition we have two pharmacy symposia on Saturday afternoon titled "The Bugs and Treatment" and "Antimicrobial Stewardship". Six proffered papers and two poster sessions are also planned for the meeting.

To promote discussion and interaction between delegates and the invited speakers the meeting's registration includes lunches, morning and afternoon teas and admission to the Howard Florey Reception and the Industry Reception. I am confident that you will find the meeting's programme both scientifically stimulating and informative and we look forward to meeting you in Brisbane.

Important Dates
Abstract Submission Deadline: Friday 12th December 2014
Early Bird Registration Deadline: Friday 2nd January 2015

Thomas Gottlieb
President ASA

THERAPEUTIC OPTIONS FOR RESISTANT GRAM POSITIVE ORGANISMS

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Methicillin Resistant *Staphylococcus aureus*

Vancomycin remains the current gold standard for treatment of serious MRSA (methicillin resistant *Staphylococcus aureus*). A vancomycin pharmacodynamic target of Area under the curve/Minimum Inhibitory concentration (AUC/MIC] of ≥ 400 is recommended by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America (IDSA) and the Society of Infectious Diseases Pharmacists in 2009. [1,2] Nevertheless, multiple controversies still exist re the dosing and pharmacodynamic targets required for optimal outcomes. These are partly explained by the variability observed with MIC testing [3] and the observed inter-patient variability between and within methods available to calculate vancomycin AUC.[4] Despite an AUC/MIC target, dosing and monitoring is still directed towards attaining a serum trough level between 15 and 20 mg/L. This recommendation is partly due to pragmatic considerations of therapeutic drug monitoring but carries with it other potential difficulties. These include vancomycin overexposure and possible nephrotoxicity [5] or underexposure and poor outcomes.[6] It is possible therefore that future recommendations will be refined and that individualised dosing towards AUC/MIC targets will be considered optimal therapy especially in specific groups (e.g. the critically ill patient in intensive care).

Other anti-MRSA drugs including daptomycin (at a recommended dose of 6mg/kg), currently, the only drug that has randomised clinical trial data comparing it to vancomycin in serious MRSA infections including blood stream infections (BSIs) and right-sided infective endocarditis.[7,8] Nevertheless, current IDSA guidelines considers Daptomycin as a viable option in native valve left sided endocarditis.[1] With the emergence of resistance in the original trial linked to its registration, greater doses (between 8-10mg/kg/day), without any increased adverse side effects, are now being used to reduce this risk.[1,9] Daptomycin's role following vancomycin as salvage therapy is unclear as daptomycin cross resistance has been observed with reduced vancomycin susceptible *S. aureus* isolates *in vitro* and *in vivo*. The potential mechanism for this cross resistance is that changes in the cell wall associated with glycopeptide resistance (i.e increased cell wall thickness) also impairs daptomycin diffusion through the cell wall to the cell membrane, its site of action. Subsequent cohort studies, using the higher doses, have not been able to detect these reported increased failure rates.[10] In addition, in the setting of high vancomycin MIC infections (a possible marker for reduced vancomycin susceptibility), two retrospective cohort studies have observed improved outcomes when converting to daptomycin compared to continuing vancomycin in MRSA infections. Although these data would confirm the use of higher doses and use in salvage settings, they are unable to definitively determine daptomycins' role as first-line therapy for high vancomycin MIC infections.[11,12]

Several studies have observed a survival advantage with linezolid over vancomycin in the treatment of MRSA BSI, [13] however these are limited by their study design, sample sizes and lack of vancomycin treatment details making it difficult to draw any firm conclusions.

Clinical studies are also currently lacking in the use of ceftaroline in the treatment of MRSA BSI and endocardtis, however case series and animal studies have shown comparable efficacy to alternative agents when treating MSSA, MRSA, VISA and hVISA with ceftaroline.[14] Given that we know that MSSA BSI infections do better when treated with beta lactams compared to glycopeptides[15], it is speculated that similar results will be seen with ceftaroline, which shows promise as a safe and effective treatment option.

Televancin is an attractive option given its long half life and potential for outpatient treatment with once daily dosing, however randomised controlled data is only available for non BSI infections, and there is concern re increased rates of nephrotoxicity compared with vancomycin, as well as QT prolongation.[16,17]

In the treatment of MRSA complicated skin and skin structure infections (cSSSIs), daptomycin, linezolid, ceftaroline and telavancin have all been shown to be equally effective to vancomycin [18,19] and thus the choice of agent is dependent on the side effect profile and patient setting.

In the treatment of nosocomial MRSA pneumonia, both linezolid and telavancin have been shown to be non-inferior to vancomycin.[17,19] Linezolid was shown to have improved microbiological and clinical cure rates compared with vancomycin, but with no mortality benefit in a randomised controlled trial by Wunderink et al.[20,21] Debate still exists, however, whether these studies in the absence of a mortality benefit provide sufficient evidence to recommend linezolid above vancomycin in treating of

THERAPEUTIC OPTIONS FOR RESISTANT GRAM POSITIVE ORGANISMS (CONT'D)

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MRSA pneumonia.

Much debate also surrounds the role of teicoplanin in the treatment of complicated MRSA infections. This is partly due to the failures observed with what is now considered suboptimal dosing. Recent meta-analysis would suggest comparable outcomes[22], however, difficulties with monitoring and cost issues restrict its use. In vivo studies investigating the efficacy of Quinupristin-dalfopristin are limited and the agent's side effect profile makes it a less desirable option in the treatment of MRSA. Tigecycline has comparable efficacy to Vancomycin in the treatment of MRSA cSSTIs[23] but showed increased mortality in the treatment of HAP and subsequently received the FDA black box warning. [24]

Although combination treatments, including vancomycin plus rifampicin[25], daptomycin puls rifampicin[26] and beta lactams combined with daptomycin or vancomycin[27,28] have showed promise, robust clinical data is lacking and thus these treatments cannot be endorsed and are limited to settings where there are no alternatives.

Vancomycin resistant Enterococcus

For the treatment of VRE BSI, prospective data is lacking and recommendations are based on *in vitro* activity and cohort studies. Quinupristin-dalfopristin is limited by its side effect profile and need for a central line. As such the first line agents include daptomycin and linezolid. However, no randomised controlled or prospective data comparing these two agents exists. Furthermore, resistance to both these agents has been described and may occur even in treatment naïve patients.[29,30]Although two recent meta-analyses suggest improved outcomes with linezolid over daptomycin this may reflect suboptimal daptomycin dosing rather than linezolid superiority.[31,32] Tigecycline although active against VRE has been shown to be inferior in eradication rates compared with linezolid. [33]

Teicoplanin has no activity against *vanA* VRE but does have some activity against *vanB* VRE. However, mutations can occur in sensor region resulting in teicoplanin resistance. This may occur during therapy and as such debate exists as to the utility and appropriateness of teicoplanin in the treatment of *vanB* VRE.[34] Televancin, similarly, has in vitro activity against *vanB* VRE with similar MICs to vancomycin susceptible isolates.[35,36] Similar, to other agents no clinical data is available to assist in defining televancins role in therapy. Tigecycline has been shown to have significantly lower eradiation rates compared with linezolid in the treatment of VRE infections.[33]

Combination therapy for VRE infections is based on case reports and cannot currently be endorsed.

Drugs in Development

Several drugs are in development, including ceftobiprole, active against MRSA and *E faecalis* but with limited activity against *E faecium*.[37] Oritavancin and dalbavancin are glycopeptides with long half-lifes enabling once weekly dosing. Oritavancin has in vitro activity against MRSA, VISA and VRSA as well as VRE (*vanA* and *vanB).* In the treatment of cSSSIs ortivancin has demonstrated non-inferiority to vanomcyin in a phase III trial. Dalbavancin has similar in vitro activity against MRSA and VRE (*vanB* only) and has shown promising results for catheter related blood stream infections and SSTIs. [38] Tedizolid is a new oxazolidinone prodrug that inhibits protein synthesis and has broad activity even against linezolid resistant bacteria, with less myelosuppression than linezolid.[39]

Conclusion

Vancomycin despite multiple difficulties concerning its use remains the recommended first line therapy in MRSA BSI. Nevertheless, alternative agents include daptomycin, linezolid and ceftaroline. The role of telavancin, and tigeyclince in treatment is restricted to specific settings. Of concern, is the emergence of resistance to all these alternative agents with reduced susceptibility to linezolid daptomycin, vancomycin, ceftaroline between 0.1 and 2%.[40]

The optimal treatment of VRE BSI is unclear due to the lack of prospective studies. Linezolid and daptomycin remain first line therapy for VRE infections.

In conclusion, decisions about the optimal agent in any given setting should be based on the available data, expert opinion, guidelines (if they exist), and considering the strengths and weaknesses of each agent.

THERAPEUTIC OPTIONS FOR RESISTANT GRAM POSITIVE ORGANISMS (CONT'D)

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2015 - 2016 MEETING CALENDAR

2015

Microbiome Forum Asia
19-20 January, Kuala Lumpur, Malaysia
Website: www.globalengage.co.uk

Update on Implant-associated Infections
12-14 February, Budapest, Hungary
Website: www.escmid.org/

ASA 16th ANNUAL MEETNG
February 26-28, Brisbane, Queensland
Website: www.asainc.net.au

Pathology Update 2015
Feb 27 – Mar 1, Melbourne, Victoria
Website: www.rcpa.edu.au

New Perspectives in Infection Control
12-14 March, Kayseri, Turkey
Website: www.escmid.org/

ASID annual meeting
Mar 18-21, Auckland, New Zealand
Website: www.asid.net.au

The 2015 TB Summit
March 24-26, London, UK
Website: https://www.regonline.co.uk/

7th international Congress of the Asia Pacific Society for Infection Control
26-29 March 2015, Taipei, Taiwan
website: www.apsic2015.org

25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2015)
25 - 28 April 2015, Copenhagen, Denmark
Website: http://escmid.org/dates_events/

19th Congress of the International Society for Human and Animal Mycology
4-8 May 2015, Melbourne, Australia
Website: www.isham2015.com.au

115th Annual General Meeting, American Society for Microbiology
May 30 – June 5, New Orleans, USA
Website: http://www.asm.org

International Conference in Prevention and Infection Control
16-19 June, Geneva, Switzerland
Website: http://www.icpic2015.com

Australian Society for Microbiology Annual Meeting
12 -15 July, Canberra, ACT
Website: www.theasm.org.au

***Clostridium difficile*: Practical Aspects of Diagnosis and Comparative Genomics**
2-4 Sept, Maribor, Slovenia
Website: www.escmid.org/

55th ICAAC/ISC Meeting
18-21 Sept, San Diego, USA
Website: http://www.asm.org

ID week 2015
7-11 Oct, San Diego, CA
Website: www.idweekinternationa.com/

2016

26th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2015)
9-12 April 2016, Instanbul, Turkey
Website: http://escmid.org/dates_events/

16th Asia Pacific Conference on Clinical Microbiology and Infection (APCCMI)
30 Nov- 3 Dec, Melbourne, Australia
Website: http://www.asainc.net.au

In 2016, the ASM general meeting and ICAAC will be co-located in Boston, June 2016. No organisational details available as on Oct 3 2014.