BREAK POINT

2015 - ISSUE 13

FROM THE NEWSLETTER EDITOR'S DESK

This issue of "Breakpoint" brings reports from the ASA 2015 meeting and ASA-supported research. It begins with a report on Annual Meeting from the three ASA travel award recipients, Jason Kwong, Josh Ramsay and Samuel Abraham. David Paterson then provides an update of the work supported by an ASA research grant (2014), entitled "Randomised controlled trial of meropenem vs. piperacillin-tazobactam for definitive treatment of bloodstream infections due to ceftriaxone non-susceptible *Escherichia coli* and *Klebsiella spp.*". The committee looks forward to updates from this year's ECCMID conference in Copenhagen. As always suggestions towards improving the Newsletter are very welcome.

Sharon Chen
ASA Breakpoint Editor

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IN THE NEWS

FDA approval of isavuconazole for invasive aspergillosis and mucormycosis (March 2015)

A long time in the wings, **Isavuconazole** was approved by the US Food and Drug Administration in March 2015 for the treatment of invasive aspergillosis and mucormycosis (1). It is formulated as the pro-drug, isavuconazonium sulfate, and is available as an IV as well as an oral formulation (2). For patients with invasive aspergillosis who do not tolerate the first-line antifungal agent, voriconazole, either a lipid formulation of amphotericin B or now, isavuconazole, may be used in place of voriconazole. For patients with mucormycosis, isavuconazole can be used as an alternative to posaconazole for step-down therapy or salvage therapy in patients who do not tolerate posaconazole.

IN THE NEWS CONT'D

Already, a number of Australian Hospitals have reported their clinical experience on use of this drug. We look forward to hearing more on their collective experience.

1. FDA news release. FDA approves new antifungal drug Cresemba. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm437106.htm (Accessed on April 7, 2015).

2. CRESEMBA (isavuconazonium sulfate). Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207500Orig1s000lbl.pdf (Accessed on April 7, 2015).

REFLECTIONS FROM ANTIMICROBIALS 2015: *ANTIMICROBIAL RESISTANCE – TIME TO PUSH THE AGENDA*

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A key recurring theme, antimicrobial resistance was again a major focus of discussion at Antimicrobials 2015. Addressing this, Professor Jan Kluytmans from Erasmus Medical Centre in The Netherlands delivered three talks. He first described the issues regarding antimicrobial use in animals, which despite being frequently used for non-therapeutic purposes, is not always reported. The Netherlands was used as an example, highlighting the paradox of having one of the lowest rates of antibiotic use in humans among European countries, but being one of the highest users of antibiotics in livestock. High antimicrobial use in animals, often at subtherapeutic doses for growth promotion, creates the potential for emergence of resistant organisms in livestock, before being transferred to humans. This has already been seen with livestock-associated CC398 methicillin-resistant *Staphylococcus aureus* (LA-MRSA), which emerged in pig farmers, but is now disseminated in Europe causing community-associated MRSA infections.[1] In Denmark, LA-MRSA now accounts for 43% of MRSA bacteraemia, and 20% of the pork products sold in supermarkets was found to have MRSA – a sobering thought for those who travelled to Copenhagen for ECCMID.

News on the Gram-negative side was even more concerning. Extended-spectrum beta-lactamase (ESBL) producing organisms were isolated from 80% of retail chicken products in The Netherlands.[2] A Swiss-based study found ESBLs in 100% of supermarket chicken samples, while a recent Australian study found ESBLs in 95% of retail chicken and pork products sampled.[3,4] Other studies

REFLECTIONS FROM ANTIMICROBIALS 2015: *ANTIMICROBIAL RESISTANCE – TIME TO PUSH THE AGENDA* CONT'D

sampling vegetables, soil, and water sources have also found a plethora of ESBLs. Although genetic comparisons of ESBL-producing *E. coli* in poultry and humans have indicated that the strains differ, the ESBL-carrying plasmids were highly related.[5] Thus, in contrast to the LA-MRSA story, the link between antimicrobial use in animals and the appearance of ESBLs in human clinical isolates may be through plasmid and other horizontal gene transfer.

Once these resistance genes appear in humans, it seems to be increasingly difficult to remove them. In his other presentations, Prof Kluytmans conveyed the difficulties of tracking and stopping outbreaks of resistant Gram-negative *Enterobacteriaceae*, including a description of the previously reported KPC-producing *Klebsiella pneumoniae* outbreak at the National Institutes of Health (NIH) Clinical Center.[6,7] Having found a number of additional cases after implementing enhanced infection control procedures, it was realised that tracking transmission events using epidemiologic data was more complex than anticipated, with an exponentially increasing number of possible transmission pathways. As a result, the outbreak was finally concluded by using a "kitchen-sink" approach – employing a number of interventions that were not necessarily evidence-based, but were reasonable and common sense. The message from this outbreak was to hit early, and hit hard.

Cause for appropriate action and re-action

The time to think about how to manage these scenarios is now. ESBL and carbapenemase outbreaks have already been reported on our shores. In Victoria, a number of KPC-2 producing *K. pneumoniae* were isolated from patients in multiple different healthcare institutions across the state between 2012-2014. Most of these belonged to the well-recognised ST258 clade implicated in the majority of KPC outbreaks worldwide. Based on whole genome sequencing, the local isolates were genetically similar, and appeared to be different from international ST258 *K. pneumoniae* previously isolated and sequenced. As a result, an epidemiologic investigation is currently underway. However, while we have experience in investigating foodborne outbreaks, such as the *Salmonella* that plighted the concurrent School Principals' Conference, and single institution outbreaks, tackling a large multi-facility outbreak of highly-resistant pathogens is a relatively new challenge.

Can expertise be drawn from previous outbreaks of resistant organisms? Possibly, though it is not always applicable. For example, despite what we might imagine, environmental sampling of nursing homes involved in an ESBL ST131 *E. coli* outbreak in The Netherlands found very few ESBLs,[8] in contrast with the environmental reservoirs that were implicated in the NIH KPC outbreak. Although food and water sources have been found to contain ESBLs and some carbapenemases (eg. NDM-1), KPC have not typically been derived from these sources. One factor common to both ESBLs and carbapenemases is that prolonged human colonisation is likely to be a major reason for propagation of these outbreaks. Based on modelling of the ST131 nursing home outbreak, a reduction in the colonisation (>12 months) was predicted to have the greatest impact in controlling the outbreak.

REFLECTIONS FROM ANTIMICROBIALS 2015: *ANTIMICROBIAL RESISTANCE – TIME TO PUSH THE AGENDA* CONT'D

More alarming though, is the possibility of undetected colonisation. Prof Kluytmans reported a case that tested negative on eight occasions screening for KPC following attempted decolonisation with faecal microbiota transplantation, an interesting concept in itself. However, despite negative screening tests, the patient died from KPC sepsis 17 months after the last positive test.

These messages are important. The NIH Clinical Center took over 12 months, with an expansive array of resources, to end their KPC outbreak involving 18 patients – the Victorian outbreak has already surpassed 50 patients. To ensure that we are equipped for managing the spread of increasingly resistant clinical pathogens, a coordinated approach is required. Control of antimicrobial use in Australian livestock is important, though with globalisation and ready access to imported products, this may simply be locking the door when the windows are open. Early detection of outbreaks is critical to rapid control and minimising spread. For this, local surveillance systems to monitor resistance threats must be established. The antimicrobial resistance agenda needs to be pushed with state and federal health departments, engaging the community and the media. As demonstrated in Israel, while national interventions are painstaking, they may be required in this era of growing antimicrobial resistance.

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REFLECTIONS FROM ANTIMICROBIALS 2015: *ANTIMICROBIAL RESISTANCE – TIME TO PUSH THE AGENDA* CONT'D

6. Snitkin ES, Zelazny AM, Thomas PJ, *et al.* Tracking a hospital outbreak of carbapenem-resistant *Klebsiella pneumoniae* with whole-genome sequencing. Sci Transl Med, 2012; 4(148): 148ra116.

7. Palmore TN and Henderson DK. Managing Transmission of carbapenem-resistant *Enterobacteriaceae* in healthcare settings: a view from the trenches. Clin Infect Dis, 2013: 57(11): 1593-1599.

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ANTIMICROBIAL 2015 REPORT

Sam Abraham[1] and Josh Ramsay[2]
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This year the ASA compiled a very attractive programme with a range of international and local speakers in the areas of antimicrobial stewardship, resistance and susceptibility testing. The conference was scientifically stimulating and informative and the calibre of the research presented was of the highest standard. The conference had a number of different sessions that included key note lectures, symposiums, proffered sessions and posters. All sessions were well received by the attendees demonstrated by large turn-out to the sessions. The ASA conference also provided a fantastic networking opportunity by having the Howard Florey and Industry receptions and providing lunch, morning and afternoon tea breaks.

The lectures from the plenary speakers along with the Howard Florey Oration were the highlights of the conference. The plenary by Prof. Sarah Cosgrove from Johns Hopkins University School of Medicine, USA highlighted the multiple Prongs of Stewardship: Less is More – Debunking Stewardship Myths. It was great to hear her experience in this area in multiple sessions during the conference. Prof. Jan Kluytman covered the area of resistance links to animals, hospital transmission of carbapenamase resistance and the success of ST131 treatment in health care settings. Prof. Kluytman's talks were of importance to ASA members from both human and animal areas. Prof. Sally Roberts talked about Infection Prevention and Patient Safety.

ANTIMICROBIAL 2015 REPORT CONT'D

It was entertaining to listen to Prof. Gunnar Kahlmeter, Central Hospital, Sweden about the making and global uptake of EUCAST. The EUCAST workshop on susceptibility testing presented by Prof. Kahlmeter, Ms Erika Matusckek and Prof. John Turnidge was well received and it provided a platform for the microbiologist to ask specific questions regarding susceptibility testing. This session also highlighted the need for the standardization of antimicrobial susceptibility testing in Australia.

Professor Gunnar Kahlmeter's talk focused on:

1. The history and evolution of antimicrobial susceptibility testing and standardization.
2. MIC wild type distribution and how epidemiological cut off values (ECOFFs) and clinical breakpoints are identified:
    a. Clinical Breakpoints are an MIC concentration defined by man to predict clinical success and failure. This is used for obtaining basis for empiric therapy. Clinical breakpoints are determined by dose and mode of administration, clinical targets, target organism, MIC distribution, resistance mechanism, pharmacokinetics and dynamics and clinical outcome. The clinical breakpoints are set by medicine agencies and breakpoint committees.
    b. The ECOFF is the highest MIC of isolates devoid of phenotypically expressed resistance. It is used as a tool to determine clinical breakpoints, to understand and predict resistance development, surveillance of antimicrobial resistance and screen for organisms with exceptional resistance mechanism. ECOFFS are determined by plotting the distribution of MIC and identifying the wild type MIC.
3. Success of EUCAST:
    a. Uniting European susceptibility testing committees under one umbrella and developing common European breakpoints.
    b. Determining clinical breakpoints, ECOFFS, development and standardisation of antimicrobial susceptibility testing in Europe and act as an expert committee for a number of different governmental and regulatory bodies.

EUCAST is now the primary susceptibility testing standard across Europe and is now branching out into Asia and Australia.

The Howard Florey Oration by Prof. Ben Howden from the University of Melbourne was titled "Vancomycin and *Staphylococcus aureus* – A Complex Relationship". Prof. Howden's lecture highlighted his valuable contribution in the area of MRSA, VISA and hVISA evolution. Some of the key points from his talk were:

ANTIMICROBIAL 2015 REPORT CONT'D

1. S. *aureus* evolved intermediate vancomycin resistance by acquiring mutations in the important WalKR regulator[1, 2]
2. Discovery of The RpoB H Y Rifampicin Resistance Mutation are linked to resistance and persistence in MRSA clones[3]
3. Highly susecssfull hospital-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) clone ST239 isolated from 1980-2010 in Australia belong to two distinct clades. The first clade was predominant from 1980s till 2007 while the second clade that emerged in 2001 is now the most prominent clade in Australia. Comparative genome sequencing analysis revelaved that the recent clade (clade 2) was introduced into Australia from Asia and has perpetuated the epidemic in Australia in recent years[4].

Plenary speaker Prof. Jan Kluytmans presented a fascinating account of the epidemiology and animal-human transfer of livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) in the Netherlands. Historically the Dutch have encountered a relatively low level of hospital-associated MRSA, but have until recently had high use of antimicrobials in an agricultural setting. The Netherlands was one of the highest users of antimicrobials for growth promotion in food-producing animals in Europe until strategies were implemented to reduce and eventually ban the use of antibiotics for growth promotion in 2006. The LA-MRSA clonal complex 398 (CC398), which is thought to have a limited reservoir in humans, caused 38% percent of human infections in the Netherlands in 2010. Pigs are a significant reservoir of CC398 and Kluytman & colleagues revealed 44% of veterinarians carried CC398 compared to only 4% of the general population. There was seemingly little evidence of human-human transfer of this clonal complex, based on typing methodologies available at the time. More recent work using whole-genome mapping has shown that human-human transfer of CC398 is indeed occurring in households shared with CC398-carrying veterinarians. LA-MRSA strains isolated from individual veterinarians exhibited considerable genotypic diversity, but in contrast very low diversity was observed for strains isolated within individual households. Analyses indicated that veterinarians may be persistently colonised with unique CC398 clones and may act as reservoirs for within-household human-human transmission of these clones.[5,6]

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ASA RESEARCH GRANT PROGRESS REPORT 2013-2014

David L. Paterson
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MERINO – (pilot) Randomised controlled trial of meropenem vs. piperacillin-tazobactam for definitive treatment of bloodstream infections due to ceftriaxone non-susceptible *Escherichia Coli* and Klebsiella spp.

Background: No randomised controlled trials (RCTs) have yet been performed comparing different treatment options for AmpC or ESBL-producing *Enterobacteriaceae*. During the last 10 years we have seen an exponentially increasing rate of carbapenem resistance worldwide, including Australia and New Zealand. We urgently need data from well-designed RCTs to guide clinicians in the treatment of antibiotic resistant Gram-negative infections. We face a situation where a commonly used antibiotic for these infections (meropenem) may be driving carbapenem resistance. For this reason, we are seeking to compare a carbapenem-sparing regimen with a carbapenem for the treatment of these infections. Formal evaluation of safety and efficacy of generic antibiotics in the treatment of infection is of immense clinical and public health importance, and no formal trial has yet been conducted to address these issues. The international collaboration between teams of clinician researchers, some of whom are leaders in their field, makes it highly likely that the outcomes of this trial will have a significant impact on clinical practice.

Aims: To compare the 30-day mortality post bloodstream infection of piperacillin/tazobactam and meropenem, and to evaluate the temporal and clinical microbiologic factors towards successful resolution of infection and/or risk of relapse and superinfection.

Study sites and recruitment: Currently we have eight clinical sites actively recruiting participants: Royal Brisbane and Women's Hospital (QLD), Princess Alexandra (QLD), Brisbane Private Hospital, St. Andrew's War Memorial Hospital (QLD), Monash Heath (VIC), The North Shore Hospital (NZ), Tan Tock Seng Hospital (Singapore) and National University Hospital (Singapore). There are six additional clinical sites currently undertaking the ethical approval process towards joining the trial this year. As of July 23rd, 2014 we have successfully recruited 25 participants out of our aimed pilot sample size of 100. Once recruitment has reached 50, a mid-point safety analysis by a pre-selected DSMB panel will be performed.

Clinical data and specimen collection: Detailed screening forms are collected on all potential participants, along with detailed CRFs being performed on those successfully recruited. Clinical data collected includes participant demographics, risk factors and acquisition relating to identified infection, antimicrobial usage, daily monitoring parameters, comorbidities, microbiologic susceptibility

ASA RESEARCH GRANT PROGRESS REPORT 2013-2014 CONT'D

of all identified organisms during the study period and discharge/in hospital mortality. A platform in the web-based electronic database REDCap has been designed specifically for the MERINO trial and is currently being utilised for data collection by all active sites. The trial has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613000532707) and the NIH Clinical Trials.gov (NCT02176122).

Research plan for remainder of 2014: Our goal is to collect and analyse the pilot data acquired up until the end of 2014, which will then be utilized for submission of a NHMRC project grant application to conduct an adequately powered RCT. Manuscript submission of the MERINO protocol is being finalized with submission aimed for July/August 2014. We also aim to perform detailed phenotypic and molecular analysis of the cultured isolates, including the application of whole genome sequencing, to characterise established or novel resistance genes, virulence factors and phylogenetic relationships. Such data will also be useful to determine the influence of these genetic factors on patient outcomes in the trial.

Thank you on behalf of the entire MERINO trial research team for the ASA's financial award towards the initiation and continuation of the MERINO trial.

David L. Paterson

2015 - 2016 MEETING CALENDAR

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

International Conference on the evolution and transfer of Antibiotic Resistance
24 - 26 June, Amsterdam, The Netherlands
Website: www.evostar.eu

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

ESCMID-SHEA Training Course in Hospital Epidemiology
20 - 24 July, Cairns, Australia
Website: www.escmid.org/

9th International Conference on Emerging Infectious Diseases
24 - 26 Aug, Atlanta, USA
Website: www.iceid.org/

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

STI and AIDS World Congress 2015-02-06
14 - 16 Sept, Brisbane, Australia
Website: www.worldsti2015.com/

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

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

9th International Transplant Infectious Diseases Conference
13 - 15 Oct, Cancun, Mexico
Website: www.tts.org/

2016

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

New ASM Microbe 2016 (Inaugural combined ASM general meeting with ICAAC)
16 - 20 June 2016, Boston, MA
Website: www.asm.org/microbe2016

21st International AIDS Conference
17 - 20 July, Durban, SA
Website: www.aids2016.org/

10th International Transplant Infectious Diseases Conference
Aug 17 - 19, Hong Kong, China
Website: www.tts.org/

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.