The December 2009 ASA Newsletter

This edition sees the return of the popular “Picture Quiz”, as well as a comprehensive review of Hepatitis C therapy which helps prove that ASA is not a bacteria-centric society! Thanks to all the contributors, and to Doug and Sebastian for helping with the ICAAC Highlights.

As always, we look forward to your submissions in the form of original articles, picture quiz content, conference reviews or general miscellanea.

I hope you have a happy festive season, and look forward to seeing you at Antimicrobials 2010 in Sydney.

David Andresen,
ASA Newsletter Editor
AUSTRALIAN NEW ZEALAND COOPERATIVE ON OUTCOMES IN STAPHYLOCOCCAL SEPSIS (ANZCOSS) STUDY

Staphylococcal sepsis remains a significant healthcare problem worldwide, both in the community and in hospital practice. The literature demonstrates that outcomes are suboptimal for some cases of invasive staphylococcal infection. Factors known to impact on outcomes include resistance, especially methicillin resistance, and toxin production such as TSST-1 and PVL.

To understand the local epidemiology of severe Staphylococcus aureus disease in Australia and New Zealand a cooperative, under the auspices of the Australian Society for Antimicrobials, has been established; the Australian New Zealand Cooperative on Outcomes in Staphylococcal Sepsis (ANZCOSS).

As from the 21st May 2007 19 sites from 6 Australian states/territories and 3 sites from New Zealand commenced contributing data. Participating institutions are submitting, online, basic demographic, risk factor and outcome data on patients with S aureus sepsis seen at their sites on a continuous basis, with the first full review of outcome data occurring after 12 months of data have been entered. To date, more that 5000 cases have been entered. The first complete analysis of data was published in the Medical Journal of Australia in October 2009.

With a crude mortality rate of nearly 20% identified, there is still much to do and learn about this condition. A substudy examining the relationships between vancomycin treatment and outcome is currently being co-ordinated through the Austin Hospital contributors in Melbourne (vssANZCOSS). Work has also commenced with statistician researchers at the Queensland University of Technology on outcomes of hospital-onset bacteraemia.

We are hopeful that many current contributors will see the long term benefits of continuing their contribution, including intervention studies and attempts to improve mortality rates.

ANZCOSS invites all institutions in Australia and New Zealand to participate, or to continue to contribute if they are able.

For further information please contact John Turnidge (john.turnidge@cywhs.sa.gov.au) or the ANZCOSS Data Administrator, Despina Kotsanas (despina.kotsanas@southernhealth.org.au).

ASA 2010 Foundation Members

The ASA Committee wishes to acknowledge the following companies for becoming Foundation (Sustaining) Members of the Society

| PLATINUM | Janssen-Cilag, Novartis |
| SILVER | GlaxoSmithKline |
| BRONZE | AstraZeneca, BD Diagnostics, Thermo Fisher Scientific (Oxoid), bioMérieux Australia, Bayer Schering Pharma, Pfizer Australia, Immuno, Merck Sharp & Dohme Australia |

Foundation Members websites can be located in the Foundation (Sustaining) Members section of the ASA webpage (http://www.asainc.net.au/foundation_membership/members)
On behalf of the Australian Society for Antimicrobials I would like to invite you to the Society's 11th Annual Scientific Meeting “Antimicrobials 2010” to be held at the Sofitel Sydney Wentworth Hotel, Sydney on Thursday 25th - Saturday 27th February 2010.

I am pleased to announce Hajo Grundmann from the Dutch National Institute for Public Health and the Environment in the Netherlands and Michael Yeaman from the Harbor UCLA-Medical Center in the USA will be participating at the meeting. Hajo will be presenting the plenary “What Resistance Surveillance Tells Us” while Michael will be presenting the plenary “Antimicrobial Peptides”. Both speakers will also be participating in the symposium sessions.

The Australian plenary speaker for “Antimicrobials 2010” is Pat Charles from the Austin Hospital. Pat will be presenting the plenary “Community Acquired Pneumonia (CAP) in Hand”.

The programme’s symposia cover many different aspects on antimicrobials and sessions include “VRE”, “New Understandings of Antimicrobial Resistance Mechanisms”, “Mycobacterium tuberculosis”, “Invasive Fungal Infections”, and “Antimicrobial Resistance as a Public Health Issue”. In addition we have two workshops on Saturday afternoon titled “VRE Screening: Practical and Bench Top Tips” and the “Antimicrobial Stewardship - Where are we and Lessons Learnt?” and “The Drugs” Pharmacy Workshops. Three proffered papers and two poster sessions are also planned for the meeting. Once again ASA is offering travel awards to financial members of the Society who are submitting abstracts for the meeting. These awards include return economy airfare, registration and accommodation. In addition the ASA/bioMérieux travel award will be awarded during the meeting to an abstract dealing with the identification of bacterial resistance to antimicrobials in a routine clinical setting.

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 Welcome and Industry Receptions. I am confident that you will find the meeting's programme both scientifically stimulating and informative and we look forward to meeting you in Sydney.

Graeme Nimmo
President ASA

---

Newsletter Contributions

Submission of articles, material for the Picture Quiz, reviews for the journal club, or letters to the Editor should be sent to:

Dr David Andresen
ASA Newsletter Editor
e-mail: info@asainc.net.au
EMERGING TREATMENT OPTIONS FOR HEPATITIS C VIRUS

Douglas Johnson and Joseph Torresi
Infectious Diseases Department
Austin Hospital - Melbourne

Introduction

Hepatitis C virus (HCV), identified in 1989 [1], is a single stranded RNA virus belonging to the Hepacivirus genus within the Flaviviridae family [2]. HCV is estimated to chronically infect 3% of the world’s population. Of those exposed to HCV the majority (50-85%) become chronically infected and evolve to chronic hepatitis. Chronic infection is characterised by a prolonged asymptomatic phase. Complications of chronic HCV include severe fibrosis and cirrhosis, hepatic failure and hepatocellular carcinoma. Cirrhosis of the liver occurs in 10-30% of patients with chronic HCV infection within 25 years. Hepatocellular carcinoma occurs in 30% of patients with cirrhosis and 5-10% of chronically infected HCV patients overall [3-6].

Six major genotypes of HCV have been defined and more than 100 subtypes described [7]. The most common genotypes of Australia, Europe and the United States are 1a and 1b followed by genotypes 2 and 3 [5]. The 6 genotypes differ from each other by 31-33% at the nucleotide level compared with 20-25% of nucleotides for the different subtypes [8]. The importance of defining the genotype a patient is infected with is highlighted by the wide differential response rates to treatment observed with genotypes 1 and 4 compared to 2 and 3 [9-11].

The treatment of Hepatitis C virus (HCV) infection is a rapidly evolving field. The current standard of care therapy, a combination of peg interferon and ribavirin, achieves a sustained virological response (SVR) in 40%-50% of patients with genotype 1 HCV infection. Specifically Targeted Antiviral Therapies for HCV (STAT-Cs) are in the later stages of clinical development and hold promise as effective adjuncts to the standard of care producing significantly better treatment outcomes. The earliest developed and most effective STAT-Cs to date include direct inhibitors of the HCV nonstructural 3 protease, as well as nucleoside and non-nucleoside inhibitors of the NS5B RNA-dependent RNA polymerase.

STAT-Cs demonstrate potent antiviral activity and their use, in combination with pegylated interferon and ribavirin, significantly improves the rate of sustained virological response (SVR) for HCV Genotype 1 infections when compared with pegylated interferon and ribavirin alone. However, monotherapy with STAT-Cs results in a rapid virological breakthrough and as with HIV treatment, combination therapy is necessary in order to achieve an SVR [12].

The current standard of care treatment for chronic HCV is pegylated interferon alfa-2b or alfa-2a in combination with ribavirin. Recently published data for patients with HCV genotype 1, demonstrated no significant difference in the rates of SVR and tolerability between the two pegylated interferon–ribavirin regimens [13]. The duration and success rate of current treatment for HCV infection is highly genotype dependent. Genotype 1 is typically associated with poor response rates compared with genotypes 2 and 3 (40%-50% versus 70%-80% SVR) and require longer treatment periods (one year versus six months) [11]. Current therapies are toxic, complex, and expensive, and only partially effective [11].

There has been considerable effort to develop alternative, more effective therapeutic agents. Development of these agents has been possible following the discovery of the crystal structures of the HCV NS3 protease and the NS5B polymerase proteins. The recent development of the HCV cell culture system [14] has further enhanced the characterisation of STAT-C molecules. The most developed of the STAT-C drugs are inhibitors of the HCV NS3/4a serine protease and the NS5b RNA-dependent RNA polymerase [15, 16]. We will discuss the STAT-C drugs and other emerging agents for HCV treatment.

Protease inhibitors - NS3/4A protease inhibitors

The non-structural (NS) proteins of HCV, NS2 to NS5B are integral to polyprotein processing and viral replication. NS3/4a protease is necessary for viral replication and is also a key negative regulator of intracellular Interferon pathways, thereby promoting HCV persistence [15]. Not surprisingly the NS3 protein has been extensively scrutinised as an antiviral target. Several STAT-C molecules have been developed to target the NS3 protein but to date only two have progressed to phase II/III clinical trials - Telaprevir and Boceprevir.

Telaprevir

Telaprevir is a reversible potent peptidomimetic inhibitor of the NS3/NS4a protease. In a Phase I monotherapy study Telaprevir demonstrated potent antiviral activity against HCV Genotype 1 but viral breakthrough was noted in the second week of treatment [17].

Telaprevir is synergistic with pegylated interferon and ribavirin and when used in combination the rate of telaprevir resistance is reduced. Two phase II trials studying the combination of telaprevir with pegylated interferon and ribavirin (PROVE I and PROVE II) have demonstrated safety and efficacy in treatment naive patients with chronic genotype 1 hepatitis C infection. The control group in both trials received the standard therapy of pegylated interferon and ribavirin for 48 weeks. In both PROVE I and II standard therapy yielded SVR rates of 41% and 46%, respectively. In comparison, telaprevir given for 12 weeks together with pegylated interferon and ribavirin given for 24 weeks yielded response rates of 61% and 69% in PROVE I and II respectively. Rash, anaemia and discontinuation of medications were higher in patients receiving telaprevir [18, 19].

The PROVE 3 study is a phase III trial aimed at investigating patients who had failed previous treatment with standard therapy with pegylated interferon and ribavirin (either non responders or relapse). Treatment with telaprevir, pegylated interferon and ribavirin achieved SVR rates of 51% compared with 14% for those treated with 48 weeks of pegylated interferon and...
ribovirin [20]. Phase III studies ADVANCE (treatment naive) and REALIZE (failed previous treatment) are currently also underway.

**Boceprevir**
Boceprevir is the second peptidomimetic protease inhibitor currently in Phase III clinical trials. Like telaprevir, treatment with boceprevir alone is associated with the rapid selection of drug resistance [15]. However, in a Phase II trial (SPRINT) the combination of boceprevir with pegylated interferon and ribavirin resulted in a significant improvement in the SVR rate from 38% in the standard therapy arms to 75% in the boceprevir/pegylated interferon plus ribavirin arm. This study also included a 4 week lead in with pegylated interferon and ribavirin before commencing boceprevir to determine if this strategy could minimise the development of drug resistance [21]. Anaemia and discontinuation of treatment were more common in the boceprevir arms. In both telaprevir and boceprevir studies ribavirin reduced the relapse rate and will be an important part of treatment strategies.

A number of other protease inhibitors are currently in phase I/II clinical development and are discussed in detail by Thompson and Webster [15, 16].

**NS5b RNA-dependent RNA polymerase inhibitors**
NS5b RNA-dependent RNA polymerase is a key enzyme involved in HCV replication. Polymerase inhibitors include nucleoside analogs and non-nucleoside inhibitors (NNIs). Toxicity (severe neutropenia) has limited the development of R1626, a promising polymerase inhibitor. Inform-1, a Phase I trial combining a nucleoside polymerase inhibitor (R7128) and protease inhibitor (R7227/ITMN-191) demonstrated potent antiviral activity in patients with genotype 1 HCV [22]. Other polymerase inhibitors are also in phase 1 and 2 trials and demonstrate impressive antiviral activity. The NS5A protein is another target and NS5A inhibitors are entering phase 2 trials [15].

**Treatments targeting host encoded proteins**
Cyclosporin A inhibits the cellular protein cyclophilin B that binds NS5B to augment HCV replication. A synthetic form of cyclosporin, Debio-025, is a less immunosuppressive cyclophilin inhibitor. A dose finding phase 2 study for 29 days demonstrated that Debio-025 in combination with pegylated interferon reduced the HCV RNA titre by 4.75 log compared with 2.5 log for pegylated interferon [23].

**Drug Resistance**
Of note naturally occurring resistant mutations to HCV protease and polymerase inhibitors in treatment naive patients have been identified. Kunzten's group analysed 507 treatment naive HCV genotype 1 infected patients and identified mutations to various directly acting antiviral inhibitors occurred at a rate of 0.3 - 2.8% of the population. At present their impact on treatment outcomes is unknown [24]. Gaudieri's group have also identified viral resistance mutations that are likely to have implications for optimising therapy for chronic HCV [25].

**Derivatives of current treatments**
Modifications of current forms of interferon's are in clinical trials. The most advanced of these is Albuferon, a form of interferon alpha-2b genetically fused to albumin (Human Genome Sciences). The advantage of albuferon compared with peg interferon is the lower dosing frequency (every two weeks rather than every week). Two phase III trials comparing albuferon and peg interferon (both with ribavirin) demonstrated non-inferiority with respect to SVR for genotypes 1, 2 and 3. The relatively modest increase in convenience of albuferon dosing compared to peg interferon must be weighed against the somewhat higher rates of adverse events, particularly cough [26, 27].

Ribavirin is part of the standard therapy for HCV in combination with pegylated interferon and is the critical component of treatment that prevents relapse after completion of therapy. The most significant dose-limiting side effect of ribavirin is haemolytic anaemia. Taribavirin is a liver targeting prodrug of ribavirin that causes less anaemia. However an initial Phase III study with pegylated interferon demonstrated Taribavirin was inferior when compared to ribavirin (SVR rates 38% compared with 52% for ribavirin) [28]. Post-hoc analysis suggested that the taribavirin dosing may have been inadequate. Thus a Phase 2b study was commenced with weight based taribavirin dosing of 20, 25 and 30mg kg/day compared with weight based ribavirin. Interim week 24 results demonstrate similar virological response with lower rates of anaemia [29].

Another promising treatment is nitazoxanide currently used for treatment of intestinal parasites. Studies in Egypt using nitazoxanide in combination with pegylated interferon and ribavirin have demonstrated improved SVR rates compared with standard therapy for genotype 4 HCV (79% vs. 50%) [30]. Studies for genotype 1 (Stealth C-2 and Stealth C-3) are ongoing in the USA.

Other novel interferon based therapies, therapeutic vaccines strategies, immune based strategies including monoclonal antibodies and drugs targeting lipid metabolism are in earlier stages of development. These are discussed in more detail by Thompson and Webster [15, 16].

**Conclusion**
Chronic HCV is a blood borne disease of major global significance. The current standard of care treatment, pegylated interferon and ribavirin achieves SVR rates of only 40-50% in patients with genotype 1 HCV infection. There has been considerable progress in the development of more effective agents. The STAT-Cs are the most promising in particular telaprevir and boceprevir (inhibitors of the HCV NS3/4a serine protease).

Early trials have highlighted the danger of monotherapy and treatment-limiting toxicities. Drug resistance will be a major issue in the development of treatment regimes that include STAT Cs. Long-term clinical implications of the development of resistance remain unknown and requires careful follow-up.

In the near future, it seems likely protease (and possibly polymerase inhibitors) will be licensed in combination with pegylated interferon and ribavirin. These regimes will improve SVR rates and shorten treatment duration in both treatment naive and relapsed patients infected with HCV genotype 1.
EMERGING TREATMENT OPTIONS FOR HEPATITIS C VIRUS (Cont)

References


WHAT'S NEW WITH THE CDS

**Professor Sydney Bell**

*The Antibiotic Reference Laboratory, Department of Microbiology*

*Prince of Wales Hospital, South Eastern Area Laboratory Services, Randwick NSW*

**Publication of the Fifth Edition of the CDS Manual**

The Fifth Edition of the CDS Manual was launched at the CDS Workshop in Perth this year. There have been multiple additions and modifications made to the Manual and these are listed on the CDS Website under “changes” in the on-line edition of the Manual at http://web.med.unsw.edu.au/cdstest/

In addition, many sections of the Manual have been reformatted to make it more reader friendly and this has largely been the work of Greg Fisher. A hard copy of the Manual is available to CDS registrants from the CDS laboratory (address on website) and as usual it is priceless.

**Addition of a further 8 WHO Reference Strains of Neisseria gonorrhoeae**

At the request of A/Prof. John Tapsall of the Neisseria Reference Laboratory, a further 8 WHO Reference Strains of Neisseria gonorrhoeae have been added to the section on Quality Assurance (3.1) in the on-line version of the Manual. A reference to the publication by Unemo, M., et al (2009) also is included at the end of the QA section. This publication explains the need for and uses of these reference strains.

WHAT'S NEW AT CLSI

*Professor John Turnidge will submit a report on “What’s New at CLSI” for the next edition of the Newsletter*

ASA SUBSCRIPTIONS

Payment of ASA Subscription renewals can be performed on-line in the Members’ Area of the website

(http://www.asainc.net.au/members)

Alternatively, subscription renewal forms can be downloaded from the Members’ Area

(http://www.asainc.net.au/members)

and:

- Faxed: 08 9450 8853
- Emailed: info@asainc.net.au
- Posted: Australian Society for Antimicrobials
  PO Box 8266
  Angelo Street
  South Perth
  Western Australia 6151

ASA Application Membership Forms can be downloaded from the ASA website

(http://www.asainc.net.au/membership)

WHAT'S NEW ON THE ASA WEBSITE

http://www.asainc.net.au

**Antimicrobials 2010:** PDFs of the proposed programme and the Registration and call for Abstract Flyers can be downloaded from the ASA website (http://www.asainc.net.au/meeting)

**Non-ASA Meetings:** Information on non ASA Meetings can be placed on the ASA website. Please send information on meetings to info@asainc.net.au

**Antimicrobials Surveillance Programmes:**

- AGAR
- Western Australian MRSA Epidemiology Report
Doug Johnson was the ASA AstraZeneca ICAAC Travel Award winner and presented his studies of genetically modified Hepatitis C virus like particles as a preventative vaccine strategy. He would like to thank ASA and AstraZeneca for the opportunity to attend the meeting.

Overview
Almost 10,000 delegates attended the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy held in San Francisco, USA (September 12-15). The conference highlighted advances in basic and clinical sciences, infection control, pharmacokinetics/pharmacodynamics (PK/PD), and clinical medicine. The vast program catered for clinicians, microbiologists, researchers, scientists, pharmacists, infection control practitioners and trainees. The biggest challenge was deciding which session to attend with so much packed into 4 days. There was something for everyone with over 1600 accepted abstracts, 116 poster sessions, 62 didactic symposia, 30 meet the expert sessions, 26 slide sessions, and 9 state of the art mini lectures.

Pre meeting workshops covering pharmacokinetics/pharmacodynamics, antibiotic stewardship, organ transplantation, antibiotic resistance, immunisations, pharmacotherapy and HIV were available on September 11th. The HIV workshop I attended emphasised the importance of non-AIDS associated morbidities including cancers, neurocognitive dysfunction, cardiovascular disease, renal and liver disease and osteoporosis in the era of highly active antiretroviral therapy.

Other highlights of my ICAAC experience were the HIV, hepatitis, virology and vaccine sessions. Sessions on travel medicine (Plasmodium Knowlesi causing human disease), infectious complications of transplant medicine and transplant tourism, refugee health guidelines (www.asid.net.au), and the countless sessions on multiresistant gram positives, negatives and tuberculosis were very interesting and informative. DJ

ID fellows Session
The meeting commenced with the interactive fellows session covering Staph Aureus, Clostridium difficile and PK/PD. Take home messages were updates on the treatment of Staph Aureus and the new vancomycin guidelines published by IDSA (available from http://www.idsociety.org/Content.aspx?id=9088 ) and the ubiquitous Clostridium difficile 027 strain present in 40 states of the USA. Diagnosis of Clostridium difficile 027 is hampered by the poor sensitivity of ELISA tests (approx 70%) with little improvement in sensitivity with repeat ELISA. Cure rates are lower (85%) compared with the non epidemic strain (96%). DJ

Keynote Speakers
The opening keynote session featured Françoise Barre-Sinoussi (Inst. Pasteur Paris) and King Holmes, (University of Washington, Seattle). Françoise Barre-Sinoussi discussed the pathogenesis of HIV and opportunities for vaccine design. King Holmes spoke of the present and future challenges of global public health. Many global health challenges are well recognised (malaria, TB and HIV). However poorly resourced laboratories in the developing world are the “Achilles heel” of global health. Both lectures were inspiring with their breadth and vision as well as providing hope. According to Holmes the NIH wants the US “to be a doctor to the world rather than a soldier to the world.”

The other major lectures were given by Barry Bloom (Harvard School of Public Health, Boston) and Nick White (University of Oxford and Mahidol University Thailand). Barry Bloom spoke on the Unfinished Business of Infectious Diseases. Currently the majority of funding for global health goes towards treatment of infections. However this is likely to change with chronic diseases as the new emerging epidemic. The majority of deaths worldwide are non infectious (Cardiovascular disease, Cancer, Psychiatric and Trauma) and funding is likely to shift to reflect this change. With the prospect of reduced funding for infectious diseases coordinated approaches in implementing programs and biomedical research to tackle the problems of HIV, malaria and TB will be required.

Professor Nick White was the recipient of the Sanofi Aventis ICAAC award and lecture. Nick’s lecture covered the history of malaria, efforts to control transmission, the recently discovered plasmodium knowlesi, treatment advances with artemisinin based combinations, the emergence of artemisinin drug resistance in Western Cambodia and efforts to roll back malaria.

Of note Anton Peleg an ASA member received the ICAAC young investigator award. Anton trained at Monash Medical School and the Alfred Hospital in Melbourne before his current role at the Massachusettes General Hospital, Beth Israel Deaconess Medical Centre and Harvard Medical School. Anton was recognised for his research on multiresistant Gram negative bacteria, specifically Acinetobacter. DJ
**HIGHLIGHTS FROM THE 49TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY - ICAAC (Cont)**

**Latent TB: an update on detection and treatment.**

The diagnosis of latent TB infection (LTBI) still depends on tuberculin skin testing (TST) and/or interferon gamma release assays (IGRA). Development of a new skin test with more specific antigens (ESAT-6 and CFP-10) is underway. The utility of each test is influenced by several differing factors. TST positivity is influenced by previous BCG use. However, the BCG affect is not absolute and is influenced by administration timing, with minimal lasting effect from a single infant dose. One of the benefits of TST over IGRA is the strong data that results are predictive of the subsequent risk of developing TB. An online model that quantifies this risk using the size of TST reaction, previous BCG status, country of birth and clinical factors can be found at www.meakins.mcgill.ca/respepi/homeE.htm.

In contrast, IGRA are not affected by BCG status, but their sensitivity appears to vary with TB prevalence and immune status. The lower sensitivities of IGRA in high prevalence countries and immunocompromised patients is more marked with QuantiFERON®-TB Gold (Cellestis, Melbourne, Vic) than T-SPOT.TB (Oxford Immunotec, Oxford, UK) (pooled sensitivity 77% vs 92% respectively in a meta-analysis). There have been no major changes in the management of LTBI, with 6 months of INH still the most used regime.  

**SVH**

**Literature Review**


**DJ**

**Update on agents with Gram-positive activity**

These wide-ranging therapy update sessions chaired by Lindsay Grayson has been very well-received. They are particularly useful for the busy clinician who does not have time to review the primary literature in great detail. In this session on Gram-positive chemotherapy, Robert Moellering (Harvard Medical School, Boston) began by discussing the state of play regarding Vancomycin. The PK/PD target of a vancomycin AUC/MIC ratio in excess of >400 is only achievable for isolates with a vancomycin MIC of 1 when vancomycin trough levels approach 20 mg/L, and are simply not attainable for isolates with an MIC of 2. Moellering therefore recommended formal vancomycin MIC testing for serious infections, but noted that the E-test (the most accessible MIC testing method for many laboratories) had been observed to read slightly higher (more resistant) than reference methods. There is a theoretical argument for an initial vancomycin loading dose (say 25-30 mg/Kg) in serious infections, but no clinical data to support this manoeuvre.

Peter Wilson (University College London) reviewed the published and unpublished data regarding Teicoplanin, a glycopeptide which was never FDA-approved in the United States but is used extensively elsewhere in the world. There has traditionally been caution in the use of teicoplanin for endocarditis, since no trials of its used for this indication were ever published, but Professor Wilson claimed that endocarditis studies were performed during the licensure process and showed encouraging results. In meta-analysis teicoplanin seems as efficacious as vancomycin and less nephrotoxic. About 10% of patients who develop a non “red-man” rash on vancomycin will also react when challenged with teicoplanin. Some coagulase negative staphylococci, in particular S. haemolyticicus, have elevated teicoplanin MIC’s and vancomycin may be preferred for such strains. A trough of less than 20 mg/L has been associated with increased rates of treatment failure in serious infections, and 6 mg/Kg daily is usually required to achieve this. Burns patients in particular may require higher doses, and some even need regular BD dosing.

David Snydman (Tufts University School of Medicine, Boston) reviewed the newer Gram-positive agents Linezolid and Daptomycin with an emphasis on the development of resistance to these compounds. Linezolid is the first member of the oxazolidinone class of protein synthesis blockers to reach clinical use. The main resistance mutations occur in the central loop of the 50s ribosomal subunit multicyclic gene, although resistance due to ribosomal methylation has occasionally been described as well. Elevated linezolid MIC’s in coagulase negative staphylococci have been described in units with high linezolid usage. The combination of linezolid and rifampicin seems to have been moderately successful in a salvage study of prosthetic joint infections. Daptomycin is a...
cyclic lipopeptide which has calcium-dependent bactericidal activity by inducing cell membrane dysfunction. Resistance occurs commonly during therapy, especially if there is a refractory focus of sepsis, and is related to membrane and cell wall changes. Interesting as daptomycin MIC’s increase, those to anti-staphylococcal beta-lactams fall, so combination therapy with daptomycin and beta-lactams has been proposed as a theoretically appealing solution to the problem of treatment-emergent resistance. DA

Laboratory and Clinical aspects of Nocardia Infections

With molecular typing the taxonomy of Nocardia continues to develop with over 80 “species” associated with clinical infection identified. The difficulties with phenotypic testing were highlighted. Non-selective agars (i.e blood agar) should still always accompany the use of selective agars (e.g. BCYE) as the latter may inhibit several species. Plates should ideally be incubated at 35 and 30°C for 2 weeks. Modified AFB stains are dependent on the type of media used and the age of the culture and can be negative in some isolates. Given all these difficulties molecular methods are now considered the diagnostic modality of choice. Targets used include the secA1 gene, 16s rRNA and 65hsp. The American reference laboratory uses the single copy secA1 gene as it has superior ability to discriminate between species, and less intra-species genetic variation when sequencing ≤500bp.

Broth microdilution is still considered the gold standard for susceptibility testing. Bactrim remains the treatment of choice, with combination therapy recommended in patients with disseminated or CNS disease. Although linezolid (proposed MIC breakpoint ≤4) is the most active agent against Nocardia spp., toxicity may preclude longterm use. Linezolid 600 mg once daily is anecdotally effective and may have lower toxicity than the BD regimen, making it a possible alternative in the sulfa-allergic patient. SVH

Update on agents with Gram-negative activity

Karen Bush (Indiana University) discussed the development of “neoglycosides” - novel aminoglycosides resistant to common inactivating enzymes. As for traditional aminoglycosides, Cmax/MIC or AUC/MIC are the best predictors of efficacy. One promising agent is ACHN-490, currently in Phase I safety/PK studies. It appears to be very active against amikacin-resistant staphylococci and coliforms, but shows elevated MIC’s against Acinetobacter spp and pseudomonads probably due to a combination of impermeability and efflux.

Yehuda Carmeli (Tel Aviv Medical Centre, Israel) reviewed the current status of tigecycline. This agent is active in vitro against most coliforms (excluding Proteus, Providencia and Morganella), Stenotrophomonas, and Acinetobacter spp. Resistance (in Pseudomonas and the aforementioned coliform genera) is principally due to efflux. Acquired resistance in Klebsiella, E.coli and Enterobacter has been described due to upregulation of MDR efflux pumps. This drug has several feature which might mitigate against its use in sepsis – it is bacteriostatic and extensively protein bound with a high volume of distribution and low serum levels. The AUC/MIC ratio appears to be the best determinant of efficacy. FDA approval for Tigecycline has been for the indications of skin and soft tissue infection and intra-abdominal infection. It failed to meet noninferiority criteria compared with imipenem for hospital acquired and ventilator-associated pneumonia. Its main remaining interest is for multi-drug resistant coliforms (looks good in vitro, but limited clinical experience) and Acinetobacter baumanni (reasonable outcomes in case series, but most had combination therapy with tigecycline and a second agent).

David Hooper (Harvard Medical School, Boston) reviewed the literature on combination therapy versus monotherapy for Gram-negative infections. In general there are few data supporting an advantage to combination therapy, apart from an improved initial spectrum of coverage. A recent retrospective observational study (AL-Hasan MN et al, Antimicrobial Agents and Chemotherapy 2009; 53: 1386-94) suggested that less severely ill patients in whom a quinolone was added to a beta-lactam “backbone” in bacteraemia had reduced mortality, even after statistical adjustment for propensity to receive combination therapy. The recipients of dual therapy had a nonsignificantly higher C. difficile rate. A recent multicentre RCT (Heyland DK et al. Critical Care Medicine 2008; 36: 737-44) compared meropenem to meropenem + ciprofloxacin in ventilator-
associated pneumonia, with known pseudomonas colonisation as an exclusion criterion. Clinical outcomes were not improved by combination therapy, but a subgroup analysis suggested better microbiological eradication of “difficult” organisms (Pseudomonas, Acinetobacter and MDR-GNB) when ciprofloxacin was added. He concluded that while it seems intuitive to consider combination therapy if the “backbone agent” is of marginal or borderline activity, there are few firm data to support this practice. DA

Non-TB Mycobacteria
Treatmente of pulmonary Mycobacterium avium complex (MAC) continues to be difficult, and the best culture conversion, radiographic and symptomatic improvement rates in immuno-competent patients are approximately 63%, 77% and 53% respectively. Relapse occurs in 60% of “cured” patients. However, it remains unclear whether this represents a re-infection or a relapse as typing studies have not been done. Cure rates drop substantially and mortality increases (34%) with the emergence of clarithromycin resistance. Drivers of resistance include the use of macrolides as an “anti-inflammatory” agent in long term respiratory patients (cystic fibrosis and lung transplantation). It was thus recommended that MAC surveillance cultures be performed in these patients as a means to initial combination therapy or cease the macrolide. Treatment of patients with macrolide-resistant MAC remains difficult, with some evidence that an injectable agent (aminoglycoside for 6 months) is associated with better outcomes. New agents are being considered include mefloquine (which has excellent antimycobacterial activity) and TMC-207 (a novel agent of the diarylquinoline class - undergoing clinical trials at present). However, prognosis remains poor, and surgery should be considered as adjunctive treatment in patients who are failing to respond. The National Jewish Medical and Research Centre presented their data showing that in the appropriately selected patients surgery has a low mortality rate (4%), high success rate (67-100%) and low relapse rate (<1%). SVH

Antifungal susceptibility testing for moulds
Barbara Alexander (Duke University medical Centre, North Carolina) presented the current status of anti-mould susceptibility testing in the USA. The CLSI 2nd edition M-38 standard was approved in April 2008, and is very similar to EUCAST method. It utilises broth microdilution with RPMI-1640 broth at pH 7.0, and modifications for dermatophytes are required. Correlation with alternative methods is limited at present. Also lacking at present are breakpoints and clinical correlation – there was comment from the floor that clinical outcome data do not really support any particular breakpoint, probably because of the dominance of host factors over “bug factors” in the outcome of invasive mould infections. DA

Voriconazole prophylaxis in Bone Marrow Transplantation?
The use of voriconazole as antifungal prophylaxis in bone marrow transplantation is not uncommon, but there are few good data to support this practice. An RCT by Wingard et al (ASH Annual Meeting Abstracts 2007: Abstract 163) which has never been published in full despite oral presentation in 2007, showed no advantage of voriconazole over fluconazole in allogeneic BMT recipients. There was therefore great anticipation of a late-breaker presentation by DI Marks (University Hospital Bristol) of preliminary results from a multicentre RCT of anti-mould prophylaxis in BMT. The IMPROVIT study was a Pfizer-sponsored European multicentre RCT wherein 489 haematogenous stem cell transplant recipients over 12 years were randomised to either itraconazole suspension or voriconazole prophylaxis against invasive fungal infections (IFI). The study drug was given orally after a single intravenous loading dose, and continued for at least 100 days and longer if the ongoing risk for invasive fungal infection remained high. The primary endpoint was a composite of tolerability and IFI-free survival. This composite outcome showed a significant advantage to voriconazole, entirely attributable to its better tolerability. There was no significant difference in survival or IFI rates. The side-effect profiles differed markedly, with much higher rates of vomiting, nausea and diarrhoea in the itraconazole arm, and much more visual and hepatic side-effects in the voriconazole arm.

Comment: This study showed a low 1.9% incidence of IFI, reflecting the fact that “all comers” were included rather than only BMT patients identified as being at high fungal risk. The main conclusion is that discontinuation rates were higher for itraconazole, principally due to GIT side-effects. Practically, once can conclude that in a low-risk BMT population an attempt at itraconazole prophylaxis is reasonable, with an alternative azole reserved for those who are intolerant. In a higher risk population (such as BMT recipients with moderate-severe GVHD) posaconazole remains the prophylactic agent for which there is the best efficacy data. Fluconazole remains the only prophylactic antifungal that has been associated with better post-BMT survival than its comparator in an RCT. DA

ASA Newsletter, December 2009
MEETING CALENDAR

National Foundation for Infectious Diseases (NFID) Annual Conference on Antimicrobial Resistance
1 – 3 February, 2010
Bethesda, MD, USA
website: http://www.nfid.org/

European Society for Paediatric Infectious Diseases (ESPID) 28th Annual Meeting
4 – 8 May, 2010
Nice, France
website: http://www.kenes.com/espid

ESCMID Conference on Invasive Fungal Infections
18 – 19 February, 2010
Rome, Italy
website: http://www.escmid.org/

Viruses in May
7 – 9 May, 2010
Katoomba, NSW
website: http://www.virusesinmay.com/

Antimicrobials 2010: ASA 11th Annual Scientific Meeting
25 – 27 February, 2010
 Sofitel Sydney Wentworth Hotel
website: www.antimicrobials2010.com

American Society for Microbiology 110th General Meeting
23 – 27 May, 2010
San Diego, USA
website: www.asm.org

14th International Congress on Infectious Diseases
9 -12 March, 2010
Miami, FL, USA
website: http://www.isid.org/14th_icid/index.shtml

ASID Annual Scientific Meeting
26 – 29 May, 2010
Darwin Convention Centre, NT

12th International Symposium on Febrile Neutropenia
12 -13 March, 2010
Luxembourg
website: www.imedex.com/appweb/announcements/a135-01.asp

Virology Masterclass
20 June – 2 July, 2010
University of Adelaide, South Australia

Society for Healthcare Epidemiology of America (SHEA), Decennial Scientific Meeting
18 – 21 March, 2010
Atlanta, Georgia, USA
website: http://www.shea-online.org

ESCMID-SHEA-ASID Comprehensive Course in Hospital Epidemiology
21 – 25 June, 2010
Port Douglas, QLD

20th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
10 – 13 April, 2010
Vienna, Austria
website: http://www.escmid.org

16th Symposium on Infections in the Immunocompromised Host
27 – 30 June, 2010
Budapest, Hungary
website: http://www.ichs.org/budapest.htm

International Forum on Quality and Safety in Health Care
20 – 23 April, 2010
Nice, France
website: http://internationalforum.bmj.com/
Australian Society for Microbiology 2010 – Bridging Diverse Cultures
4 – 8 July, 2010
Sydney, NSW

Viral Hepatitis – 7th Australasian Conference
6 – 8 September, 2010
Melbourne, VIC

International Symposium on Staphylococci and Staphylococcal Infections (ISSSI)
6 – 9 September, 2010
Bath, UK
website: http://www.isssi2010.com/

50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)
12 – 15 September, 2010
Boston, Massachusetts
website: http://www.icaac.org/

Australian Infection Control Association Conference (AICA)
4 - 6 October, 2010
Perth, WA

Australasian Sexual Health Conference 2010
18 – 20 October, 2010
Sydney, NSW

Infectious Diseases Society of America (IDSA) 48th Annual Meeting
21 - 24 October, 2010
Vancouver, Canada
website: http://www.idsociety.org

Society for Hospital Pharmacists of Australia (SHPA) National Conference – Medicines Management 2010
11 -14 November, 2010
Melbourne, Victoria
website: http://www.shpa.org.au

6th World Melioidosis Congress
30 November – 3 December, 2010
Melbourne, Victoria

12th Western Pacific Congress on Chemotherapy and Infectious Diseases
2 - 5 December, 2010
Singapore
website: http://www.wpschemo.org/

Society for Healthcare Epidemiology of America (SHEA), 21st Annual Scientific Meeting
1 – 4 April, 2011
Dallas, Texas
website: http://www.shea-online.org

21st European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
7 - 10 May, 2011
Milan, Italy
website: http://www.eccmid.org

7th European Congress on Tropical Medicine and International Health
October 2011
Barcelona, Spain
website: http://www.festmihbarcelona2011.org/

22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
31 March – 3 April, 2012
London, UK
website: http://www.eccmid.org
This edition’s quiz continues the Gram-positive theme:

A specimen was obtained from a young woman with a symptomatic UTI. Urine culture revealed pure growth of a coagulase-negative staphylococcus with the following susceptibility results.

1. Which organism and beta-lactam resistance mechanism is demonstrated?

2. How would you report susceptibilities on this isolate?

Please email your responses to Dr David Andresen at info@asainc.net.au. Answers will be published in the next issue and correct responses will be acknowledged.

Picture Quiz submitted by Dr. Paul Ingram, Diane Hume and Barbara Henderson,
PathWest Laboratory, Nedlands, WA