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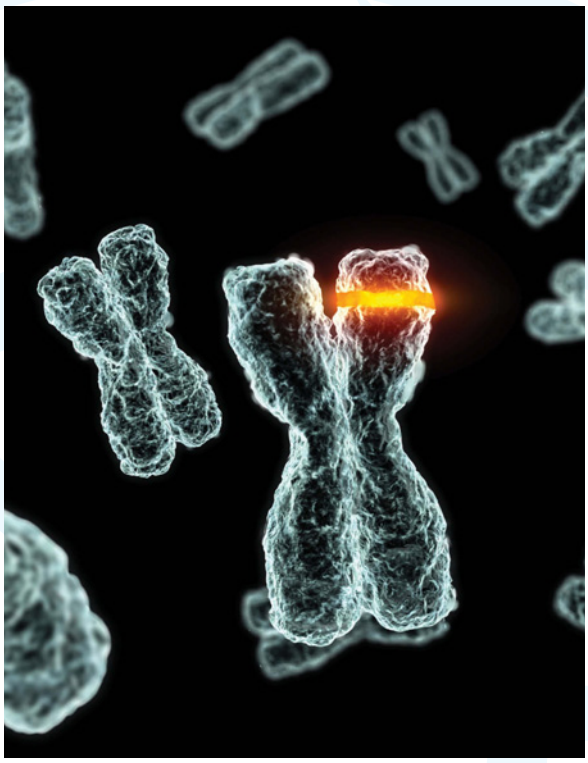
INFECTIOUS DISEASE



OFFICIAL PEER-REVIEWED HIGHLIGHTS FROM THE

51st Interscience Conference on Antimicrobial Agents and Chemotherapy

CHICAAC GO
51st ICAAC ~ SEPT. 17-20, 2011 ~ CHICAGO

September 17 - 20, 2011
Chicago, Illinois, USA

Infectious Disease Genomics: Individual Variability, New Opportunitites

Technological advances now enable comparisons of more than a half a million genetic variants in subjects with disease and population controls. A large number of novel genetic loci involved in susceptibility to common immune-related diseases, such as rheumatoid arthritis and inflammatory bowel disease, have been identified through genome-wide association studies. More recently, this methodology has been successfully applied to identify loci involved in infectious disease susceptibility [Vannberg FO et al. *Immunol Rev* 2011]. See page 4.

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ALSO IN THIS ISSUE

Dear Colleagues,

On behalf of the American Society of Microbiology (ASM), I am pleased to present the official peer-reviewed highlights of ICAAC 2011, held in September in Chicago, Illinois. We chose to partner with *MD Conference Express*® on this special issue because of their unique, peer-reviewed approach to conference highlights reporting.

There is a very real need for a scientifically vetted overview of key findings from major conferences like ICAAC. While in most cases, the science presented at a major conference like ICAAC has not undergone the rigors of peer-review for publication in a scientific journal, the data presented through the trials, posters, and special sessions may provide useful information for practitioners. The careful process used in creating these conference highlights provides reassurance that the content of the presentations is being accurately represented.

In addition to coverage of top clinical trials, other topics selected for this special edition include antibiotic resistance, drug discovery and vaccines. These topics were determined in direct consultation with the scientific leadership of the ASM. All articles were written strictly from primary source data (no press releases, no third-party opinion). The faculty who presented these data live were invited to review and comment on the resulting articles. Finally, an independent board of world experts reviewed the content to ensure accuracy and a balanced perspective.

This is a new approach to conference highlights reports – and one which the ASM felt would of service to its members. I hope you enjoy this special edition of *MD Conference Express* and find it to be useful to your practice.

We welcome your comments on this new initiative and please plan to join us in San Francisco for the ICAAC 2012. You can learn more at www.icaac.org.

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Infectious Disease Genomics: Individual Variability, New Opportunities

Written by Rita Buckley

Technological advances now enable comparisons of more than 500,000 genetic variants in subjects with disease and population controls. A large number of novel genetic loci that are involved in susceptibility to common immune-related diseases, such as rheumatoid arthritis and inflammatory bowel disease, have been identified through genomewide association studies (GWAS). More recently, this methodology has been successfully applied to identify loci that are involved in infectious disease susceptibility [Vannberg FO et al. *Immunol Rev* 2011]. David B. Goldstein, PhD, Duke University School of Medicine, Durham, North Carolina, USA, discussed recent studies, challenges, and next steps in infectious disease genomics.

According to Dr. Goldstein, susceptibility to pathogens is a genetic trait, with heritability as high as the most heritable diseases. He emphasized that, so far as can be discerned, there are differences amongst people in their response to all known pathogens; citing findings from studies on the hepatitis C virus (HCV) as examples.

Chronic infection with HCV affects 170 million people worldwide and is the leading cause of cirrhosis in North America. The recommended treatment involves a 48-week course of peginterferon-alpha-2b (PegIFN-alpha-2b) or alpha 2a (PegIFN-alpha-2a), combined with ribavirin (RBV)—an expensive process that is accompanied by significant adverse effects, (eg, anemia) that prevent some patients from completing treatment [Ge D et al. *Nature* 2009].

Many patients are not cured by treatment, and those with European ancestry have a significantly higher probability than patients of African descent of achieving sustained virological response (SVR) [Ge D et al. *Nature* 2009]. Response rates to pegIFN and RBV are also lower for Latino Americans and for those who are coinfected with HIV [Rodriguez-Torres M et al. *N Engl J Med* 2009]. East Asians, however, have higher SVR rates than patients of European ancestry [Yan KK et al. *World J Gastroenterol* 2008].

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SVR Rates and rs12979860 on Chromosome 19

In a GWAS, Ge et al. [*Nature* 2009] reported that a genetic polymorphism on chromosome 19, rs1297860, was strongly associated with SVR in all patient groups, with the Caucasian population sample showing overwhelming genomewide significance ($p=1.06 \times 10^{-25}$) versus that seen in African-Americans ($p=2.06 \times 10^{-3}$). It is also known that the variants that are associated with SVR also influence natural clearance.

In patients with HCV genotypes 2 or 3 (n=341) who were treated with 12 or 24 weeks of pegIFN/RBV therapy, rs12979860 determined the first phase of viral elimination ($p<0.001$). In patients who were treated for 24 weeks, rs1279860 also predicted the rate of SVR ($p=0.02$), especially in those with high baseline hepatitis C virus ribonucleic acid (HCV RNA levels ($p=0.02$) or aged >45 years ($p=0.01$). Patients who carried the CC genotype had higher baseline HCV RNA levels ($p<0.001$). When treated for 12 weeks, they did not achieve SVR more often than those who were carrying CT or TT genotypes.

The results indicate that IL28B gene testing may identify HCV genotype 2 or 3 patients who could benefit from extended treatment [Lindh M et al. *J Infect Dis* 2011]. IL28B genotyping could also aid in PegIFN/RBV clinical decision-making and may be useful in the selection of candidates for triple therapy with PegIFNB/RBV plus direct-acting antiviral drugs [Marcias J et al. *Curr Opin HIV AIDS* 2011].

In a recent study of HCV, 4 patients who were treated with PegIFN/RBV, 49% achieved an SVR (88% in CC patients vs 37% in CT/TT patients; p<0.0001). CC patients had a rapid virologic response (RVR) more often than CT/TT patients (50% vs 23%; p=0.08), while also showing lower relapse rates (0% vs 36; p=0.0013). In non-RVR patients, SVR ratings were higher in CC than CT/TT patients (75% vs 23%; p=0.001). By logistic regression, the IL28B rs12979860 CC genotype was an independent predictor of SVR, with an odds ratio of 11.1 (95% CI, 3.04 to 40.57; p<0.0001) [De Nicola S et al. *Hepatology* 2011].

Looking for Answers in the Extremes: The CHAVI 014 Hemophilia Study

Translation of the genetic architecture of HCV into therapeutic opportunities has been slow [Thurs M et al. *Semin Liver Dis* 2011]. The specific mechanisms of how IL28B polymorphisms affect HCV suppression remain unknown, and how to incorporate current IL28B data into treatment algorithms with pegIFN and RBV is a matter of ongoing debate. However, new technology (eg, whole-genome sequencing) and searches at the extremes of disease transmission might provide new insights and knowledge.

The Center for HIV/AIDS Vaccine Immunology has been looking at a small cohort of hemophiliacs who had been exposed to HIV but remained uninfected despite receiving factor VIII concentrates that were derived from large pools of blood that was collected from donors, some of whom were infected with HIV.

The study, known as CHAV 014, set out to identify any key genetic determinants that might explain the apparent resistance of these exposed seronegatives (ESNs) to HIV. To date, whole-genome sequencing has failed to find any common genetic variants that are associated with HIV resistance among 393 non-HIV infected cases compared with 823 HIV-infected controls.

With the protective genes unlikely to be common ones, the search for much rarer genetic variants that may explain the ESNs' resistance to HIV infection is underway. In the past 2 years, researchers have identified close to 1000 rare variants of interest that might have contributed to protection against HIV acquisition in certain hemophiliacs.

According to Dr. Goldstein, the job now is to confirm genotypes of variants of interest by other techniques, sequence additional ESN and HIV-positive samples, and deep-sequence interesting genes. He concluded that there are sample and phenotype limitations in the study of infectious disease genomics. At the same time, natural variation offers a tremendous resource for leads into vaccine development and treatment.

Emerging Resistance Among Gram-Negative Pathogens: State of the Challenge

Written by Noelle Lake, MD

In the 1980s, antimicrobial resistance among gram-negative (Gm) pathogens seemed to be under control, with the availability of a growing anti-Gm armamentarium, including oxyimino-cephalosporins, fluoroquinolones, and carbapenems. Multiple treatment options were available in most infections and, while resistance to older antibiotics was common, it was caused by a relatively few stable mechanisms—TEM-1 β-lactamase, for example, accounted for over 90% of ampicillin resistance in *E. coli*. What is more, the residents of India and China—a third of the world's population—had yet to experience large-scale exposure to modern medicine, modern antibiotics, and their consequences.

Much has since changed, and physicians are now facing unprecedented clinical challenges due to the growing proliferation of multidrug-resistant Gm pathogens. David Livermore, PhD, Antibiotic Resistance Monitoring and Reference Laboratory, London, United Kingdom (UK), described current epidemiological, mechanistic, and demographic trends that are related to this worldwide epidemic.

E. coli is a crucially important Gm pathogen, causing 80% of urinary tract infections, and is the most frequent Gm agent of bacteremia. For 20 years, *E. coli* was among the most susceptible Gm bacteria to modern antibiotics, but, over the past decade it has joined *Enterobacter*, *Klebsiella*, and *Pseudomonas*. According to recent data from the European Antimicrobial Resistance Surveillance Network (EARS-net), increasing proportions of *E. coli* bloodstream isolates are nonsusceptible to fluoroquinolones and cephalosporins. In Italy, for example, rates of fluoroquinolone resistance among *E. coli* bloodstream isolates jumped from between 1% and 5% to between 25% and 50% from 2001 to 2009 [http://www.ecdc.europa.eu]. These Southern European resistance rates pale in comparison to those observed in South and East Asia. According to a 2007 survey, *E. coli* isolates from intraabdominal infections in China and India, 50% and 80% respectively, carried extended-spectrum β-lactamases (ESBLs), rendering them resistant to modern oxyimino-generation cephalosporins [Hawser SP et al. *AAC* 2009]. It is striking that resistance to third-generation cephalosporins among *E. coli* in India and China is now more prevalent than ampicillin resistance in *E. coli* in Sweden or Norway—countries that are known for their low antibiotic use and resistance.

The accumulation of resistance to fluoroquinolones and cephalosporins in *E. coli* and related species is clinically important, and is dramatically supported by a 2007 meta-analysis by Schwaber and Carmeli [*JAC* 2007], who found that patients with bacteremia due to ESBL-containing pathogens had increased mortality rates compared with those with non-ESBL strains (pooled RR, 1.85; 95% CI, 1.39 to 2.47; p<0.001). The difference was attributed to delayed effective treatment, with many of the ESBL-producing strains resistant to the physician's choice of empiric therapy. Early use of carbapenems, which are stable to ESBLs, might seem a logical solution to this problem; however, diverse carbapenemases are starting to emerge among Gms [Patel G et al. *Expert Rev Anti Infect Ther* 2011]. These include the VIM and NDM metallo and the KPC and OXA-48 nonmetallo types.

EARS-net data reveal that although most European countries still have very low rates of carbapenem nonsusceptibility (<1% in *Klebsiella* bacteremia isolates across the continent), resistance is widespread in Greece, where rates among *Klebsiella* species reached 40% in 2005 and 50% by 2009. A major shift in carbapenemase type also occurred in Greece. The initial problem was the spread of plasmids that encoded VIM metallo-β-lactamases among *Klebsiella* strains, but this has now been supplanted by the problem of a single *Klebsiella* strain with a nonmetallo 'KPC' carbapenemase that is spreading nationally [http://www.ecdc.europa.eu; Vatopoulos A *Eurosurv* 2008; Giakkoupi P et al. *Eurosurv* 2009]. Outbreaks of *Klebsiella* that produce the KPC carbapenemase were first noted in the United States (US) in 2005, but in addition to dissemination in the US, Israel and Greece, there are now growing clusters elsewhere in Europe, South America, and East Asia [Bratu S et al. *Arch Int Med* 2005; Nordmann P et al. *Lancet ID* 2009].

Pathogens that produce another carbapenemase, OXA-48, are resistant to carbapenems but are susceptible to cephalosporins (unless they also have ESBLs), a pattern that is not always recognized by automated systems and therefore often missed. OXA-48 carbapenemase has spread from Turkey, where it has been recorded since 2000, into North Africa and Europe, while similar enzymes have been recorded in India and South America [Benouda et al. *Ann Trop Med Para* 2010; Moquet et al. *EID* 2011; Cuzon et al. *IJAA* 2010; Cuzon et al. *AAC* 2008; Cuzon et al. *AAC* 2011; Goern et al. *IJAA* 2011; Matar et al. *CMI* 2008; Carrer et al. *AAC* 2010; Carrer et al. *AAC* 2008; Poirel et al. *AAC* 2011; Castanheira et al. *AAC* 2011].

NDM-1 carbapenemase is prevalent in India and Pakistan and has repeatedly been exported to Europe, North

America, and Asia by people who have had contact with medical facilities in the Indian subcontinent [Kumarasamy KK et al. *Lancet ID* 2010]. NDM-1 is often coded by plasmids that can spread readily among bacteria and is commonly produced together with rRNA methylases that confer aminoglycoside resistance. Some Gm pathogens with NDM enzymes have near-complete resistance—susceptible only to colistin, with or without moderate susceptibility to fosfomycin and tigecycline [Kumarasamy KK et al. *Lancet ID* 2010]. The dissemination of NDM-1 in parts of India is striking, with one survey revealing a 5% to 7% prevalence among *Enterobacteriaceae* species in Mumbai [Deshpande P et al. *Clin Infect Dis* 2010].

Multiresistant bacteria carriage rates among healthy individuals is facilitating the spread and repeated introduction into hospitals, and is a critical subject of international interest. Separate studies have shown gastrointestinal tract colonization by ESBL *E. coli* in 13% of job applicants in Saudi Arabia [Kadar et al. *ICHE* 2007] and in nursing home residents in Northern Ireland (40%) and Italy (64%) [Rooney PJ et al. *JAC* 2009; March A et al. *CMI* 2010]. A prospective study in Sweden revealed that one quarter of previously uncolonized individuals became colonized with ESBL *E. coli* during travel, with the highest rates of colonization associated with travel to East Asia (29%) and India (88%) [Tangden T et al. *AAC* 2010]. NDM-carrying bacteria were shown to inhabit the gut of 27% of inpatients and 14% of outpatients in military hospitals in Pakistan [Perry et al. *JAC* 2011].

The molecular basis of proliferating resistance among Gm bacteria is more complex than previously thought. Potent bacterial strains, such as sequence type (ST) 131 *E. coli* serotype 025 [Uchida et al. *IJAA* 2010; Guenther S et al. *JAC* 2010] and ST258 *K. pneumoniae* [Woodford N et al. *FEMS Micro Revs* 2011], play a pivotal role. *E. coli* ST131 commonly hosts plasmids that encode CTX-M-15 ESBL and has been instrumental in their international dissemination, while ST258 *K. pneumoniae* is playing a similar role in the spread of KPC carbapenemases. However, ST131 *E. coli* may also carry other ESBL types, including CTX-M-3 (Belfast) and CTX-M-14 (Far East), or may have no ESBL.

Deeper analysis shows that the plasmids that carry β-lactamase genes are remarkably dynamic and are constantly in flux. The dominant *E. coli* ST131 variant in the UK ('Strain A') typically contains a complex CTX-M-15 plasmid, EK499, which is a fusion between two parent plasmids, one of which (pEK516) resembles, but is not identical to those that commonly host CTX-M-15 internationally [Woodford N et al. *AAC* 2009]. Moreover, although CTX-M-3—prevalent in *E. coli* ST131 from Belfast—differs from CTX-M-15 by only 1 amino acid, the plasmids that encode CTX-M-3 and CTX-M-15 are completely different. In the case of NDM, the encoding gene has transferred swiftly among plasmids that belong to diverse incompatibility groups, though the mechanism of transfer is unclear. Prof. Livermore suggests that this genetic fluidity among bacteria is perhaps "the finest but most disturbing evidence of evolution we shall ever see."

The emergence of carbapenem resistance is beginning to drive the use of nonconventional antibiotics, such as colistin, tigecycline, and fosfomycin, but none of these is ideal, and some resistance is beginning to emerge, even to colistin [Kontopoulou K et al. *JHI* 2010]. In addition, current pipeline agents represent incomplete solutions. Avibactam, a new β-lactamase inhibitor, inhibits KPC but not metallo-β-lactamases, and while CXA-201 (cephalosporin CXA101+tazobactam) evades ESBLs and has very good anti-*Pseudomonas* activity, it lacks activity against carbapenemase producers [Livermore DM et al. *AAC* 2011; Livermore DM. *JAC* 2010].

Aging populations, shifting world economies, and inadequate sanitation add to an already complex problem of emerging resistance. The elderly, who form a growing percentage of the population, are more vulnerable to infections, and economic growth in India and China is greatly increasing access to sophisticated medicine and modern antibiotics, often in settings where infection control and regulation of antibiotic use are weak. These are the perfect conditions to drive the selection of resistance, illustrated by the ESBL rates. In India, the lack of public health infrastructure is a tremendous concern. A recent study by the Health Board of the Delhi Municipal Council found that 18% of tap water samples were contaminated with fecal bacteria and that hundreds of millions lack access to a flush toilet [UN News Center 2010]. Improving sanitation here to prevent the spread of resistant bacteria is as important as it was in the US in the early twentieth-century in preventing the spread of classical infectious diseases.

Development of new anti-Gm antibiotics is urgently needed and hinges on overcoming three challenges. First, discovery of agents that are capable of permeating the Gm cell wall and evading efflux is a key scientific challenge. Second, the regulatory pathway needs to confirm efficacy and safety, but has become too complex and often fails to test antibiotics in the types of patients or settings where they are most likely to be used. The third, and key economic challenge, is the likely return of antibiotic development. Short-term agents for acute infection do not generate the long-term income. These and other challenges must be confronted in order to effectively halt the spread of resistant Gm pathogens.

Procalcitonin-Guided Antibiotic Therapy In Patients with Lower Respiratory Tract Infections

Written by Eric Butterman

To date, evidence regarding the effectiveness of procalcitonin (PCT)-guided antibiotic therapy has been obtained in randomized, controlled trials (RTCs), which may not be representative of routine clinical settings. Werner Albrich, MD, University of Basel, Kantonsspital Aarau, Aarau, Switzerland, presented data from a quality control survey [ISRCTN40854211] that monitored PCT-guided antibiotic therapy and algorithm adherence in simulated "real-life" conditions. The PCT algorithm effectively reduced antibiotic exposure without increasing complications. Regional and cultural differences did not affect outcomes. The integration of the PCT algorithm into daily practice requires ongoing reinforcement and involves a learning process by prescribing physicians [Schuetz P et al. *Eur J Clin Microbiol Infect Dis* 2010].

This was an observational, prospective, multicenter, international survey of consecutive patients with community-acquired lower respiratory tract infections (LRTIs) in emergency departments or physicians' offices in Switzerland (n=10), France (n=3), and the United States (n=1) from September 2009 to February 2011. PCT was measured using a rapid, sensitive immunoassay with a functional assay sensitivity of 0.06–0.09 ug/L (KRYPTOR®, Brahms or (Mini-)Vidas®, BioMérieux). Diagnostic workup, antibiotic choice(s), and management were at the physician's discretion.

The algorithm was based on the level of circulating PCT, which correlates with the likelihood for a bacterial infection, and was as follows:

- <0.1 µg/L - antibiotic therapy strongly discouraged
- 0.1 to 0.25 µg/L - antibiotic therapy discouraged
- 0.26 to 0.5 µg/L- antibiotic therapy recommended
- >0.5 µg/L - antibiotic therapy strongly recommended

The primary endpoint was duration of antibiotic treatment within 30 days (effectiveness). Compliance with the PCT algorithm, adverse medical outcomes (safety), and influence of PCT on antibiotic decision were secondary endpoints. A total of 1810 patients were enrolled (1520 with LRTI and 1425 with 30-day follow-up information). The majority presented with community-acquired pneumonia, followed by acute exacerbations of chronic obstructive pulmonary disease (COPD) and bronchitis.

There was good overall algorithm compliance (68.2%), which was affected by treatment site, country, experience, and diagnosis. Good compliance led to significantly shorter antibiotic duration (-43% or 3.8 fewer antibiotic days; HR, 1.27; 95% CI, 1.13 to 1.43; p<0.0001) but did not increase the risk of complications (adj. OR, 1.40; 95% CI, 0.78 to 2.52; p=0.26; Table 1).

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Table 1. Compliance Does Not Increase Risk for Complications.

	Compliant*	Noncompliant*	p value
In-hospital complications	20.5%	16.6%	0.07
30-day mortality	7.7%	6.0%	0.23
Recurrences	6.4%	7.6%	0.20
Antibiotic side effects	3.8%	6.0%	0.05

*only patients with low PCT value could be in the noncompliant group

Antibiotic duration in the ProReal study was shorter than that seen for standard care but longer than that seen in the PCT intervention group of the ProHosp RCT (Table 2) [Schuetz P et al. *JAMA* 2010].

Table 2. Antibiotic Duration.

	Days of use	p value
ProHosp PCT intervention group	5.0	0.001; 1 vs 2
ProReal study	6.2	<0.001; 2 vs 3
ProHosp control group (standard care)	7.9	

PCT affected the decision to withhold or initiate antibiotics. Its greatest effect in patients with COPD exacerbation or bronchitis was to reduce initial prescription of antibiotic therapy, whereas for patients with pneumonia, it was most effective in shortening antibiotic duration. No significant increases in adverse medical outcome were detected.

Published evidence on PCT-guided antibiotic therapy to date has been obtained in trials in which physicians knew that they were being monitored, possibly resulting in higher adherence to the PCT algorithm. This study mirrors the use of PCT-guided antibiotic therapy in clinical practice, outside of trial conditions. If algorithm adherence is reinforced, antibiotic exposure can be markedly reduced with subsequent reduction of antibiotic-associated side effects and antibiotic resistance.

Combination Therapy with Flucytosine Improves Survival in AIDS-Related Cryptococcal Meningitis

Written by Noelle Lake, MD

The first randomized, controlled trial to show a survival benefit of an antifungal treatment in HIV-infected patients with cryptococcal meningitis was completed this year in Vietnam [ISRCTN 95123928]. Results were presented by Jeremy N. Day, MD, Oxford University Clinical Research Unit, Wellcome Trust Major Overseas Programme Vietnam, in collaboration with colleagues from the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam.

The study compared three induction-phase treatment strategies that are currently recommended by the Infectious Disease Society of America [Perfect JR et al. *Clin Infect Dis* 2010]. Although combination therapy with flucytosine is considered first-line therapy, a mortality benefit over other regimens has not been shown in a randomized, controlled trial. Also, there are distinct disadvantages to flucytosine use—namely expense, toxicity, and poor availability in areas with high cryptococcal disease rates.

Dr. Day and his colleagues were interested in whether combining antifungal therapies in the induction phase of treatment would offer a survival advantage when compared with amphotericin monotherapy, the standard practice in Vietnam.

Enrolled patients presented with a syndrome that was consistent with cryptococcal meningitis and microbiological evidence of *Cryptococcus* in the CSF and/or blood. All patients were >14 years of age and HIV-positive. Patients with prior history of cryptococcal infection or prior antifungal treatment (>3 days) were excluded. Patients were randomly assigned to receive one of three possible induction treatments: amphotericin B 1 mg/kg/day monotherapy for 4 weeks (Arm I, the standard of care in Vietnam); amphotericin B 1 mg/kg/day plus flucytosine 100 mg/kg/day for 2 weeks (Arm II); or amphotericin B 1 mg/kg/day plus fluconazole 400 mg twice daily for 2 weeks (Arm III; Table 1). The coprimary endpoint was mortality at 2 and 10 weeks. Secondary endpoints included survival to 6 months and disability at 70 days and 6 months.

Table 1. Study Design.

Treatment Arm	Week										
	1	2	3	4	5	6	7	8	9	10	26
I	APT B 1 mg/kg/day				FLCZ 400 mg daily						FLCZ 200 mg/day
II	APT B 1 mg/kg/day + FLTS 200 mg/day		FLCZ 400 mg daily								FLCZ 200 mg/day
III	APT B 1 mg/kg/day + FLCZ 200 mg/day		FLCZ 400 mg daily								FLCZ 200 mg/day

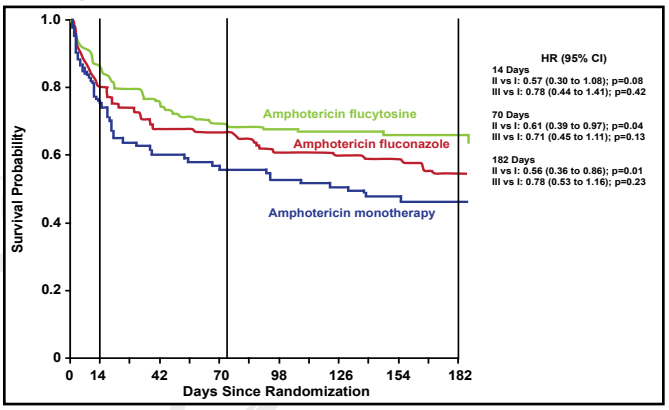
APT=amphotericin; FLCZ=fluconazole; FLTS=flucytosine.
Reproduced with permission from J. Day, MD.

The intent-to-treat (ITT) population comprised 298 patients, predominantly male, with a median age of 28 years. Approximately 30% had some level of impaired consciousness, reflected by a Glasgow coma score of <15. All patients underwent lumbar puncture, which revealed elevated CSF opening pressure (>18 cm/CSF) in over two-thirds of patients and high yeast burdens (median 5.9 log 10 CFU/mL).

Compared with amphotericin monotherapy, the amphotericin+flucytosine combination was associated with a significantly reduced hazard of death by both Day 70 [HR, 0.61; 95% CI, 0.39 to 0.97; p=0.04] and Day 182 [HR, 0.56; 95% CI, 0.36 to 0.89; p=0.01] (Figure 1). Amphotericin B, combined with fluconazole, offered

no survival advantage compared with amphotericin monotherapy. After adjusting for fungal burden and Glasgow coma score at study entry, the hazard of death by 6 months was also significantly higher among amphotericin-fluconazole-treated patients versus those who received amphotericin-flucytosine (adjusted HR for all-cause mortality, 1.81; 95% CI, 1.14 to 2.88; p=0.01). The death rate at 70 days was 30% for patients who were on combination therapy with flucytosine versus 44% for those who were on monotherapy. Rates of adverse events between the two combination regimens were comparable and included anemia, neutropenia, and renal impairment.

Figure 1. Kaplan-Meier Curve of Survival Outcomes Among ITT Population.



Significantly improved survival noted among patients treated with flucytosine-containing combination therapy (Arm II, green line) compared with amphotericin monotherapy (Arm I, blue line) at 70 days and 182 days.
Reproduced with permission from J. Day, MD.

Dr. Day concluded by saying that in light of this research, improving access to amphotericin and flucytosine in regions where cryptococcal disease is prevalent, such as southeast Asia and Africa, has the potential to significantly reduce the global burden of deaths due to this devastating disease.

CXA-201 Effective Against Common ICU Pathogens, Including MDR Gram-Negative Pathogens and *Pseudomonas aeruginosa*

Written by Eric Butterman

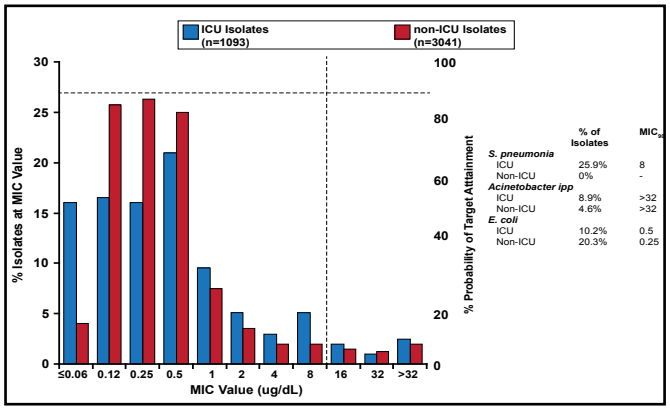
Using a pharmacokinetic/pharmacodynamic (PK/PD) target algorithm, the *in vitro* potency of CXA-201 (CXA101/tazobactam), a novel cephalosporin and β-lactamase inhibitor combination that is being developed to treat serious bacterial infections, was reported to be lower in isolates from the intensive care unit (ICU) compared with non-ICU isolates. This is largely driven by the differences in pathogen incidence in the two environments. Judith Steenbergen, PhD, Cubist Pharmaceuticals, Lexington, Massachusetts, USA, presented data from a study that evaluated the CXA-201 potency for pathogens that were isolated from ICU and non-ICU patients. In addition, the potency of CXA-201 against isolates from different sources of infection was evaluated.

CXA-201 is active against gram-negative pathogens, including *Pseudomonas aeruginosa* and *Enterobacteriaceae*, and select gram-positive organisms. The PK/PD parameter that was used in this study to predict efficacy was the time that was necessary to maintain concentrations of CXA-201 above the minimum inhibitory concentration (MIC) for approximately 40% to 50% of the time between dose administrations (T>MIC).

CXA-201 was tested by broth microdilution against 4134 isolates that were collected in 2008 from both ICU (n=1093) and non-ICU (n=3041) patients. A population PK model that was derived from healthy volunteers and infected patients was used to perform the Monte Carlo simulations (taking into account variability between subjects, residual variability, demographic covariates, and MIC). Target attainment rates were obtained for 1-hour infusion of 1500 mg CXA-201 every 8 hours. For pathogens with an MIC of 8 µg/mL (cutoff target), the target attainment rate was 98.2% for 40% T>MIC.

MIC_{90} was higher for isolates from the ICU (MIC_{90} =8 µg/mL) than non-ICU isolates (MIC_{90} =2 µg/mL). This was largely driven by differences in the percentage of *Streptococcus pneumoniae*, *Acinetobacter spp.*, and *Escherichia coli* isolates in the ICU versus non-ICU patients (Figure 1).

Figure 1. Potency of CXA-201 for ICU and Non-ICU Isolates.



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More than 95% of all isolates had an MIC ≤8 µg/mL (8 µg/mL being the provisional breakpoint), with a

range of 68% (*Acinetobacter spp.*) to 100% (*Haemophilus influenzae*). When CXA-201 potency was analyzed by site of infection, approximately 95% of all isolates had an MIC ≤8 µg/mL, with a range of 94% (blood) to 96.9% (urine).

Whether sorted by site or source, approximately 95% of isolates had an MIC value <8 µg/mL. All pathogens had an MIC_{90} ≤8 µg/mL except *Enterobacter cloacae* (88% inhibited at ≤8 µg/mL) and *Acinetobacter spp.* (68.5% inhibited at ≤8 µg/mL). Thus, CXA-201 is predicted to achieve excellent target attainment of 40% T>MIC against common ICU pathogens and multidrug-resistant gram-negative pathogens, including *P. aeruginosa* (99.3% inhibited at ≤8 µg/mL).

Tigecycline Plus Standard Therapy Is More Effective Than Standard Therapy Alone For Treating Infections in Febrile Neutropenic Cancer Patients

Written by Eric Butterman

Tigecycline, first in a new class of glycylcyclines, in combination with piperacillin/tazobactam, is effective, safe, and well tolerated in high-risk febrile neutropenic oncohematologic patients. Giampaolo Bucaneve, MD, University of Perugia, Perugia, Italy, believes that tigecycline in combination should be considered one of the "first-line" empiric antibiotic therapies (particularly in a specific epidemiological setting (eg, high rate of extended-spectrum β-lactamase-producing gram-negatives and/or methicillin-resistant *Staphylococci*). This combination therapy may aid in reducing the increase and extensive use of carbapenems, which have been associated with an increase in multidrug-resistant bacteria.

This prospective, randomized, multicenter study included 364 cancer patients from 28 Italian oncohematological departments with profound (<500 neutrophils/mmc) chemotherapy-induced neutropenia and fever (>38.5°C once or >38°C on at least two occasions during a period of 12 hours) due to presumed infection. Patients were randomized centrally and stratified according to center and underlying disease (acute leukemia vs lymphoma and solid tumors). Patients received either IV (n=174) piperacillin/tazobactam (4.5 g 3x daily) plus tigecycline (50 mg twice daily) or IV (n=190) piperacillin/tazobactam (4.5 g 3x daily) as monotherapy. All other antibiotic therapy was stopped at randomization.

Successful treatment was defined as resolution of fever (maintained for at least 4 days) or any clinical sign of infection whenever present and eradication of the infecting microorganism whenever isolated, without change in the initial allocated treatment. Failure was defined as one of the following: death from primary infection, persistence of bacteremia beyond the first 24 hours of therapy, breakthrough bacteremia, documented pathogen resistant to assigned antibiotic(s), lack of response that required antibacterial therapy modification, development of shock or acute respiratory distress syndrome or disseminated intravascular coagulation or multiple organ failure, relapse of infection within 7 days of treatment discontinuation, or toxicity requiring treatment discontinuation.

Overall response to therapy was significantly ($p<0.01$) more effective following piperacillin/tazobactam plus tigecycline (72%) compared with monotherapy (47%; Table 1). Piperacillin/tazobactam plus tigecycline treatment success rates were significantly ($p\leq0.01$) greater for microbiologically (with bacteremia) and clinically documented infections compared with monotherapy. Single gram-positive and -negative (*E. coli*) bacteremias and coagulase-negative *Staphylococcus* species were more successfully treated with combination therapy than monotherapy (Table 2).

Table 1. Classification of Febrile Episodes and Response To Therapy.

Type of infection	Piperacillin/ tazobactam + tigecycline*	Piperacillin/ tazobactam*	p value
Total febrile episodes	174	190	
Microbiologically documented infections	54/88 (61%)	27/96 (28%)	<0.01
with bacteremia	52/86 (60%)	26/94 (27%)	<0.01
without bacteremia	2/2 (62%)	1/2 (25%)	0.5
Clinically documented infections	16/19 (84%)	9/19 (47%)	0.01
Unexplained fever	56/67 (83%)	54/75 (72%)	0.07
Total	126/174 (72%)	90/190 (47%)	<0.01

*success/total

Table 2. Agents of Bacteremias and Antibiotic Susceptibility.

Organism	Tigecycline*	Piperacillin/ tazobactam*
Total Gram-positives	80/89 (90%)	23/94 (24%)
Total Gram-negatives	53/66 (80%)	45/71 (63%)
Coagulase-negative *Staphylococcus*	54/58 (93%)	4/62 (6.5%)

Treatment success rates were significantly ($p \leq 0.01$) higher with combination therapy for infections that were associated with skin and soft tissues and for bacteremias of unknown origin. Overall treatment failures were greater for monotherapy. Overall mortality rates, deaths due to bacteremia, and treatment-related adverse events were similar between the two arms.

Tigecycline in combination with piperacillin/tazobactam, compared with the standard regimen of piperacillin/tazobactam, is more effective overall in bacteremias and clinically documented infections as well.

Interventions Aimed at Reducing MRSA BSIs Led to Decreased Rates of Nosocomial MSSA BSIs: Ten-Year Data from a UK Center

Written by Eric Butterman

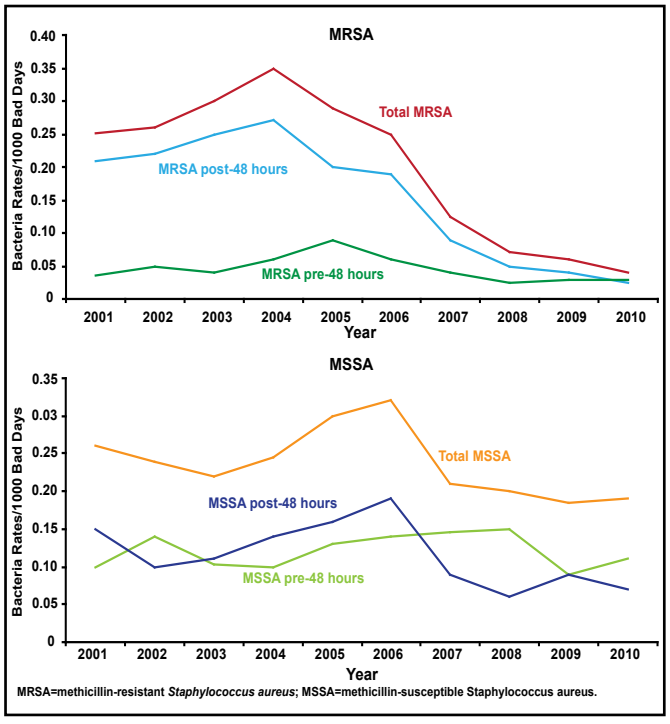
Addenbrooke's Hospital in Cambridge, United Kingdom, once known for having high rates of *Staphylococcus aureus* bloodstream infections (BSIs), has been able to significantly reduce rates of methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) BSIs using a number of infection control interventions under the lead of Infection Control Doctor Nick Brown, MD. Staff physician Theodore Gouliouris, MD, presented data from a study that showed a decline in MRSA and MSSA BSI rates that was driven by reductions in nosocomial infections.

The purpose of the study was to analyze trends of MSSA and MRSA BSIs according to onset (community vs hospital) and assess the impact of infection control interventions. The interventions were initiated over several years and included: starting a hand hygiene campaign (November 2004), establishing a vascular access team (January 2006), improving line care bundles (June 2006), screening all emergency (April 2007) and elective (January 2009) admissions for MRSA carriage, and routinely decolonizing all MRSA-positive patients (entire study period). This was a retrospective study in a tertiary referral university hospital setting with 1200 beds and 70,000 in-patient admissions per year. All *S. aureus* bacteremia (SAB) episodes from January 2001 to December 2010 at Addenbrooke's Hospital were included. The number of episodes was converted to rates per 1000 bed days, which allowed comparison with other hospitals. Only the first episode of SAB per patient during the study period was analyzed. Patients were categorized according to onset: community onset (<48 hours from hospital admission) and nosocomial onset (≥48 hours from hospital admission).

There were 1607 SAB episodes following deduplication; 861 (53.6%) MSSA, of which 437 (50.8%) were community onset and 424 (49.2%) were nosocomial onset, and 746 (46.4%) MRSA, of which 163 (21.8%) were community onset and 583 (78.2%) were nosocomial onset.

MRSA rates started to decline in 2004, driven more by a reduction in nosocomial infections, with the largest decrease (53%) occurring during the 2006 to 2007 period. MSSA rates started to decline in 2006, driven again by reductions in nosocomial infections, with the largest decrease (59%) occurring during 2006–2007. Community-acquired infections remained stable over the same period (Figure 1). Hand washing affected MRSA transiently but not MSSA rates, while having a vascular access team and performing line care bundle had a large impact on decreases for both MRSA and MSSA. Extended MRSA screening may have contributed to the larger decline in MRSA infections. Potential confounders (hospital 1000 bed-day activity and number of blood cultures processed) did not influence results.

Figure 1. Community Acquired Infection Rates.



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The results of this study are limited by the fact that it was a retrospective, noncomparative study. There was also a lack of data regarding the MSSA molecular epidemiology in the hospital, the proportion of community-onset bacteremias that were health care-associated, and the proportion of nosocomial bacteremias that were line-related.

Dr. Gouliouris concluded from the study that local rates of nosocomial MSSA BSIs have declined since 2006, though not as markedly as those for MRSA. The establishment of a vascular access team and the implementation of line care bundles appear to have had the most impact toward reducing both nosocomial MRSA and MSSA BSIs. MRSA screening and decolonization likely accounted for the greater reductions that were achieved in MRSA BSIs compared with MSSA. Finally, MSSA-targeted interventions may be needed to achieve reductions that are comparable with those for MRSA BSIs.

Is the Effectiveness of Acellular Pertussis Vaccine in Pre-Adolescents Insufficient?

Written by Noelle Lake, MD

A retrospective, single-center chart review of the 2010 *Bordetella pertussis* outbreak in California found that a time interval greater than 3 year since vaccination with acellular pertussis (aP) correlated with increased risk for acquiring the disease. Research assistant Maxwell Witt, Kaiser Permanente Medical Center, San Rafael, California, USA, reported that children between 8 and 12 years had higher attack rates and reduced vaccine effectiveness compared with children aged 2 to 7 and 13 to 18 years, possibly a reflection of greater time since their last aP dose.

Since the replacement of whole-cell pertussis vaccine with the better-tolerated aP version in 2002, questions regarding its efficacy and durability have lingered [Zhang L et al. *Cochrane Database Syst Rev* 2011]. Researchers at San Rafael Kaiser Permanente (KP) Medical Center, led by David Witt, MD, saw the California outbreak as an opportunity to observe aP vaccine performance by age, time since last vaccine, and vaccine status.

Between March and October 2010, patients who presented to the San Rafael KP pediatrics department with a severe cough for greater than 1 week and a positive PCR for *B. pertussis* were considered infected and included in the review. Electronic medical records were examined for demographic information and vaccine status.

In all, 132 patients <18 years were included. Vaccination status among children aged ≤12 years at presentation revealed that 85% were fully vaccinated, 7% was under vaccinated, and 8% was unvaccinated (never vaccinated). *B. pertussis* attack rates were shown to be highest among 8- to 12-year olds, compared with 2- to 7- and 13- to 18-year olds (p=0.002, one sample t-test; Table 1). Among children <12 years, a trend toward lower attack rates among fully immunized children versus under- or never-immunized children was observed, but the difference was not statistically significant. In contrast, children aged 13 to 18 years who were not fully immunized had significantly higher attack rates compared with other age groups (p=0.009). No patients in the cohort were hospitalized or died from their illness.

Vaccine effectiveness, a metric of the field performance of the vaccine, was calculated by comparing attack rates between under- and never-immunized versus fully immunized patient groups (of note, *effectiveness* should not be confused with *efficacy,* which reflects performance in a prospective placebo-controlled trial). The effectiveness of aP varied by age group: 41% (95% CI, 21% to 54%) and 79% (95% CI, 73% to 84%) within the 2- to 7- and 13- to 18-year olds, respectively, possibly reflecting more recent immunization, but only 24% (95% CI, 0% to 40%) in the 8- to 12- year old age group.

Table 1. Peak Attack Rates Observed Among 8- to 12-Year Olds.

Age Group	Attack Rate in Vaccinated Persons*	Attack Rate in Under and Unvaccinated Persons*	p value
2-7	359	606	0.57
8-12	2453	3211	0.43
13-18	452	2189	0.009
2-18	1011	2073	0.01

The authors concluded that aP is highly effective within 3 years of administration after which its protection may diminish. Should larger studies confirm these findings, additional scheduled dosing or targeted vaccine programs during outbreaks may be proposed. One attendee, however, challenged the relevance of the findings including the use of the phrase "vaccine failure," arguing that strict case definitions had not been used. In Dr. Witt's opinion, *B. pertussis* carriage in the face of a viral illness had not been ruled out and therefore, these results cannot be used to question the efficacy of the vaccine.

TMC435 Effective in the Treatment of HCV Genotype 1 Infection

Written by Eric Butterman

Michael W Fried, MD, University of North Carolina, Chapel Hill, North Carolina, USA, presented the results of the PILLAR [TMC435-C205; NCT00882908 and ASPIRE [TMC435-C206; NCT00980330] trials. Both studies demonstrated that TMC435 (an oral inhibitor of the hepatitis C virus [HCV] NS3/4A protease) administered once-daily with pegylated interferon alpha-2a (PegIFNa-2a) and ribavirin (RBV) is safe, has potent antiviral activity, and shortens total treatment by 24 weeks compared with PegIFNa-2a/RBV alone.

The two trials were international, randomized, double-blind studies that enrolled men and women, aged 18 to 70 years who were chronically infected with HCV genotype 1 (plasma HCV RNA >100,000 IU/mL at screening). In the PILLAR trial, patients were HCV treatment-naïve and received TMC435 for 12 or 24 weeks with PegIFNa-2a/RBV. In the ASPIRE trial, patients were HCV treatment-experienced, although naïve to direct-acting antivirals. The participants were stratified by prior virological response (relapsers, partial responders, null responders). TMC435 with PegIFNa-2a/RBV was administered for 12, 24, or 48 weeks.

The primary efficacy endpoint, which was the same in both studies, was the proportion of patients with undetectable HCV RNA (<25 IU/mL) 24 weeks after the planned end of treatment. Secondary objectives included an evaluation of the safety and tolerability of TMC435 plus PegIFNa-2a/RBV compared with PegIFNa-2a/RBV/placebo over the trial period. Virologic response rates and 95% confidence intervals were calculated using a logistic regression model, including baseline HCV RNA and the stratification factors as covariates. The results of planned interim 24-week efficacy and safety analyses, including the proportion of patients with undetectable HCV RNA (<25 IU/mL) at Weeks 4, 12, and 24, from both studies were reported.

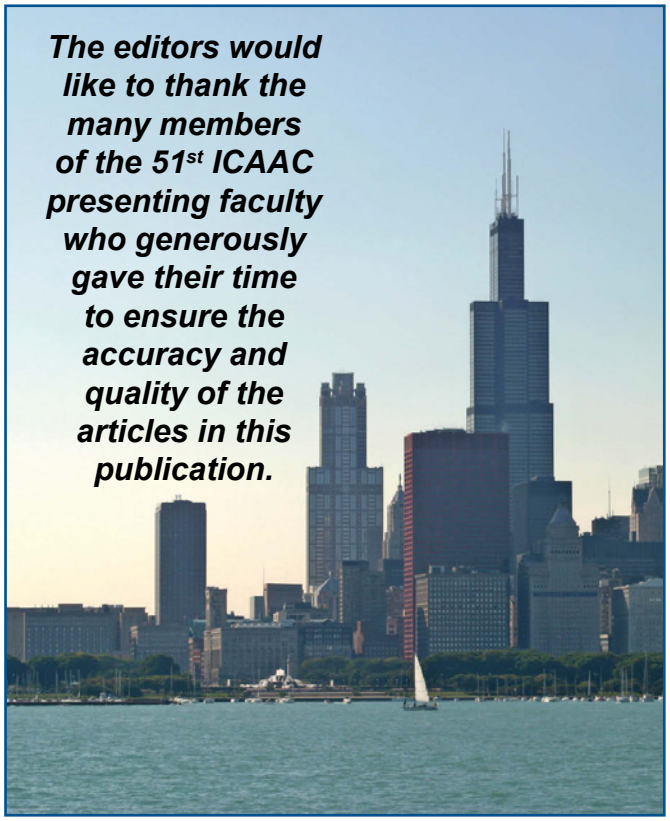
In the PILLAR trial, 68 to 79% of patients who were treated with TMC435 achieved a rapid virologic response (HCV RNA <25 IU/mL) compared with 5% in the control arm at Week 4.

At Week 12, rapid virologic response was 91% to 97% for the TMC435 arms compared with 58% in the control arm, and at Week 24, rapid virologic response was 94% to 97% for the TMC435 arms compared with 82% in the control arm. In the TMC435 arms, 79% to 86% of subjects were eligible to stop treatment by Week 24.

In the ASPIRE trial, at Weeks 4, 12, and 24, significantly higher virologic response rates were observed following active treatment compared with placebo plus PegIFNa-2a/RBV. In null and partial responders, higher virologic response rates were observed in the TMC435 150-mg dose arms, compared with 100-mg dose arms, at early time points.

The distribution of the IL28B genotype (TT, CC, and CT) was similar across treatment groups with the higher responses rates for the CC genotype in the placebo arms. In the TMC435 groups, higher-than placebo responses were observed in the TT, CC, and CT categories, with no major differences between IL28B genotypes.

Given in combination with PegIFNa-2a/RBV, the safety and tolerability profile of TMC435 was generally similar to those of the placebo control. In treatment-naïve and treatment-experienced patients, TMC435, administered once-daily with PegIFNa-2a/RBV, has potent antiviral activity, rapidly achieving undetectable HCV RNA levels in the majority of patients.



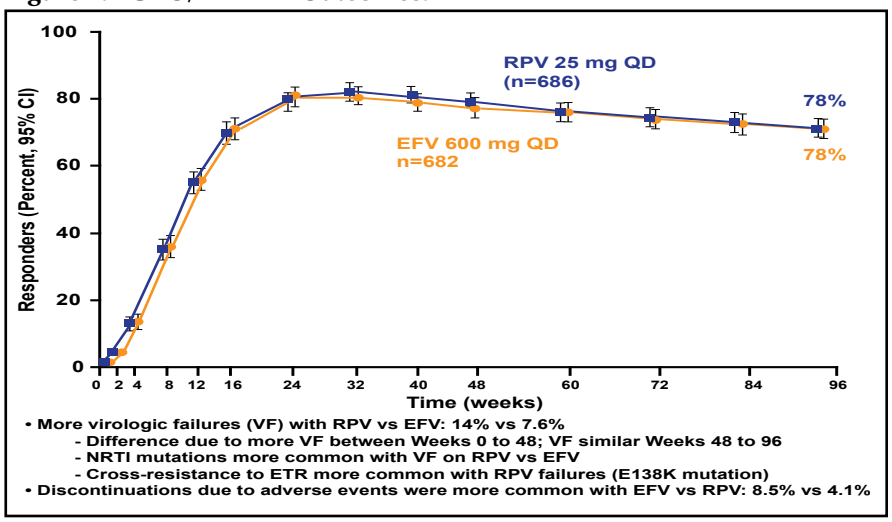
Fighting HIV – New Antiretroviral Agents and Novel Regimens

Written by Rita Buckley

Improvements in antiretroviral therapy (ART) have made the treatment of HIV infection more potent and better tolerated. While current treatment regimens still have limitations, they are more effective, more convenient, and less toxic than those that were used in the early ART era. Joel E. Gallant, MD, MPH, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, discussed studies that have shown the effectiveness of new and potential ART therapies, including single-tablet regimens, coformulations, nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens, CCR5 antagonists as initial therapy, and new entry inhibitors.

ECHO [NCT00540449] and THRIVE [NCT00543725], two randomized Phase 3 trials, showed that the recently approved non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV) has sustained efficacy that is noninferior to efavirenz (EFV) in ART-naïve adults who are infected with HIV-1 [Cohen CJ et al. *Lancet* 2011; Molina JM et al. *Lancet* 2011]. There were fewer discontinuations that were due to adverse events and fewer treatment-limiting side effects (especially neurological and dermatological) in the RPV arm but more virological failure and resistance compared with the EFV arm, most notably in participants with baseline viral loads >100,000 copies/mL (Figure 1). RPV has been approved both as a single agent and in a coformulation with tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). It is taken once daily with a meal and is contraindicated in patients who are taking proton pump inhibitors.

Figure 1. ECHO/THRIVE Outcomes.



Reproduced with permission from The *Lancet*. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Molina JM et al. July 16, 2011;378(9787)238-246.

In the MERIT study [NCT00098293], maraviroc (MVC) BID was not noninferior to EFV at <50 copies/mL in the primary analysis in ART-naïve patients with CCR5-tropic virus. However, 15% of patients in the original MERIT trial had dual/mixed-tropic virus, using the more sensitive tropism assay. After exclusion of data from those patients, the MVC arm met noninferiority criteria compared with EFV [Cooper DA et al. *J Infect Dis* 2010] (Figure 2). QD administration of MVC is also being studied. In a post hoc analysis from the original MOTIVATE trials, which initially included a QD MVC arm, virological suppression

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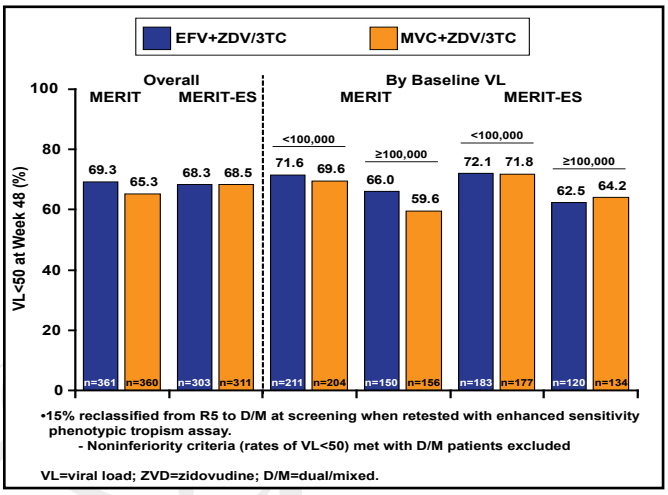
was comparable in patients who were treated with MVC QD and BID. MVC has been approved for initial therapy. Potential advantages include its excellent tolerability, its high barrier to resistance, and the fact that treatment-naïve patients are more likely to have CCR5-tropic virus than treatment-experienced patients. The main disadvantage is the need for baseline tropism testing.

Figure 2. Virological and Immunological Outcomes.



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A variety of "nucleoside-sparing regimens" have been studied in clinical trials, though none to date has demonstrated sufficient efficacy and/or tolerability to make it a standard-of-care regimen. Examples that have been studied to date include combinations of a boosted protease inhibitor plus EFV, raltegravir (RAL), or MVC.

Elvitegravir (EVG) is an investigational integrase inhibitor that requires pharmacological "boosting" by either ritonavir (RT) or cobicistat (COBI), an experimental pharmacokinetic enhancer, or "booster." Phase 2 data suggested that a 'quad' regimen of once-daily EVG/COBI/FTC/tenofovir disoproxil fumarate (TDF) achieves and maintains a high rate of virological suppression with fewer central nervous system and psychiatric adverse effects compared with the current standard-of-care regimen (EFV/FTC/TDF) [Cohen C. *AIDS* 2011], and a similarly designed Phase 3 study apparently shows noninferiority of the "quad" compared with EFV, with similar discontinuation rates due to adverse events in both arms [Gilead press release. August 15, 2011]. A study that compared EVG with raltegravir (RAL) in treatment-experienced patients found that EVG was noninferior to RAL [Molina JM. IAS 2011 Rome]. COBI is also being studied as a booster for protease inhibitors. In a Phase 2 trial, the efficacy of a COBI-boosted atazanavir (ATV)-based regimen was similar to that of a RT-boosted ATV-based regimen [Cohen C. *AIDS* 2011]. Cobicistat is associated with a modest increase in serum creatinine, with a resulting decrease in estimated glomerular filtration rate (GFR), but not measured GFR. This appears to be due to its effect on creatinine transport by the renal tubules rather than to true nephrotoxicity [German P. ICAAC 2011; Lepist EI. ICAAC 2011].

Dolutegravir (DTG) is another promising integrase inhibitor. In the SPRING-1 trial, which was conducted in ART-naïve patients, it was noninferior to EFV with better tolerability [van Lunzen J. IAS 2011 Rome]. There was no selection of integrase mutations in patients who failed, and tolerability was better than with EFV. As with COBI, DTG decreases estimated GFR but not actual GFR, by a mechanism that is similar to that of COBI [Koteff J et al. ICAAC 2011]. DTG may have some activity against RAL- or EVG-resistant virus, especially when dosed twice daily [Eron J. CROI 2011].

GS-7340 is a new tenofovir prodrug that achieves higher intracellular tenofovir levels with lower plasma levels compared with TDF [Markowitz M. CROI 2011]. The hope is that it will be more potent than TDF at smaller doses with less nephrotoxicity.

Lersivirine (LRV) is an investigational NNRTI that had overall efficacy that was similar to that of EFV in a Phase 2 study of treatment-naïve patients [Pozniak A. IAS 2011]. Efficacy was lower in patients with viral loads >100,000 copies/mL. The incidence of grade 3 and 4 adverse events was higher in the EFV arm, although nausea and headache were common with LRV.

There are a number of potential HIV entry inhibitors that can act at various stages of HIV development, such as coreceptor binding, and virus-cell fusion. They include BMS-663068, an oral HIV attachment inhibitor; ibalizumab, an HIV-neutralizing monoclonal antibody; and cenicriviroc, a CCR5 antagonist with anti-CCR2 activity.

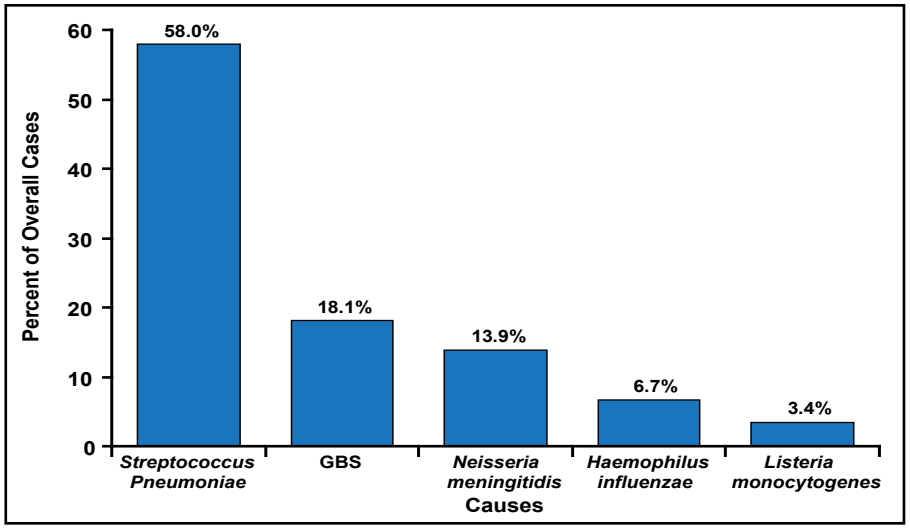
Hot Topics in Vaccines

Written by Eric Butterman

The following is a summary of several presentations which discussed recent publications that covered important advances in vaccinology.

Kathryn M. Edwards, MD, Vanderbilt University, Nashville, Tennessee, USA, opened the session with a discussion of a publication that analyzed bacterial meningitis trends in the United States between 1998 and 2007 [Thigpen MC et al. *N Engl J Med* 2011]. Using data from eight surveillance areas, consisting of approximately 17.4 million persons, the authors identified 3188 cases of meningitis. During the study period, there was a 31% decrease in the incidence of meningitis and an increase in the median age of patients from 30.3 to 41.9 years. There was no change in case fatality rate (15.7% to 14.3%) or in the rate of disease in children aged <2 months. Dr. Edwards noted the marked reduction, by as much as 50% to 60%, in cases among children aged 2 to 10 years, which she attributed to the introduction of the conjugate pneumococcal vaccine in 2000. The study showed a much greater change in children than in adults, which raises a question as to whether herd immunity is going to be good enough to allow children to be immunized, without having adults immunized. In concluding, Dr. Edwards noted that while the rates of meningitis have decreased since 1998, largely due to effective immunization programs among children, the burden of disease is now being borne by adults, for whom new vaccine approaches are needed. In addition, there remains an enormous burden of Group B *Streptococcus* (GBS) disease in children aged <2 months that still needs to be addressed (Figure 1).

Figure 1. Proportion of the 1670 Cases of Bacterial Meningitis Reported in 2003 to 2007 Caused by Each Pathogen, According to Age Group.



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Dr. Edwards also discussed an animal study that provided a new method of identifying protective antigens of *Staphylococcus aureus* [Kim HK et al. *FASEB J* 2011]. Staphylococcal sepsis and skin and soft tissue infections are major problems. Antibiotic resistance is increasing, there are no vaccines to prevent staphylococcal infections, and staphylococcal infection does not confer immunity from repeat infection. This study hoped to address

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two questions: 1) whether a live, attenuated vaccine for *S. aureus* could be developed; 2) whether this information could be used to contribute to our understanding of the pathogenesis of staphylococcal infections.

An early step in this study was the development of a renal abscess model, in which mice were injected with various strains of *Staph*. Those strains that did not produce an abscess were then injected into another cohort of mice that were treated with antibiotics on Day 19, rechallenged with virulent *Staph* at Day 26, and sacrificed on Day 30, after which their kidneys were assessed for bacterial load and the presence of abscesses. "There were three interesting findings," said Dr. Edwards. "Mice that were not vaccinated had lots of bacteria and abscesses when they were rechallenged with wild-type *Staph*. After vaccination and then rechallenge with wild-type *Staph*, there was no change in the load of the *Staph* nor in the number of abscesses; however, inoculation with srtA variants (and, to a lesser extent, saeR variants) led to a diminution in the number of organisms and in the number of abscesses, indicating that it confers some protection against rechallenge with virulent *Staph*."

In the next step, the animals were immunized using the isolated antigens that were identified in the prior step (Combo 1: ClFA, fibronectin-binding protein, SdrD; or Combo 2: ClfA, fibronectin-binding protein, SdrD, and SpA) or a mock injection and then rechallenged with virulent *Staph*. When the bacteria in the renal tissues were counted at Day 4, animals that received the mock injection had about 4.5 logs; for Combo 1, it was 2.5 logs, and for Combo 2, there were about 1.5 logs. At Day 18, there was a further diminution in colony-forming units in Combo 1. Essentially no organisms were seen with Combo 2. In the final step, the animals were given active immunization with Combo 1 or 2 and then given lethal doses of *Staph*. Four days postchallenge, all animals that received mock injections had died; 30% of the remaining animals survived to Day 18, with the survival rate of Combo 2 being significantly better than with Combo 1, suggesting that these antigens should be further studied. Dr. Edwards concluded by stating that the attenuated *Staph* strains induced protection and that combinations of *Staph* antigens resulted in nearly complete protection against lethal challenge in mice.

Jacek Mrucowicz, MD, Polish Institute for Evidence Based Medicine, Krakow, Poland, presented data from a Canadian study of the AS03-adjuvanted pandemic H1N1 vaccine [Skowronski DM et al. *Br Med J* 2011]. The study group comprised 209 confirmed flu patients from over 500 community-based clinics. Participants were mostly (>80%) children and adults aged <50 years who received a single vaccination using the AS03 vaccine at least 14 days prior to their flu diagnosis. Data were collected during two periods: November 8 to December 5, 2009 (primary) and November 1 to December 31 2009 (secondary). The investigators concluded that the AS03-adjuvanted vaccine that was used was highly effective (adjusted vaccine effectiveness 93% [95% CI, 69% to 98%]) in preventing medically attended, laboratory-confirmed pandemic H1N1 illness. Similar positive results for the 2009–2010 pandemic and seasonal influenza vaccines were seen in the European I-MOVE trial [Valenciano M et al. *PLOS Med* 2011]. Prof. Mrucowicz concluded by saying that although both studies found the adjuvanted H1N1 flu vaccines to be effective, as with all observational trials, there remains room for uncertainty.

Carol J. Baker, MD, Baylor College of Medicine, Houston, Texas, USA, discussed the results of a study from the United Kingdom that assessed the kinetics of immune responses to nasal challenge with meningococcal polysaccharide 1 year after serogroup glycoconjugate vaccination [Wing JB et al. *Clin Infect Dis* 2011]. The study objective was to measure the persistence of antibodies to serogroup C *N. meningitidis* 1 year postimmunization with meningitis C conjugate vaccine (CV) and to investigate the kinetics of systemic and mucosal immune responses to intranasal challenge with meningococcal group C polysaccharide vaccine (PV). The study enrolled 116 vaccine-naïve young adults (median age 23 years) who received meningococcal C CV. Eighty-nine participants (77%) consented to have meningococcal C PV inoculated into each nostril at 1 year. All subjects had protective (≥8) serum bactericidal antibody titers (SBA) 28 days after the initial CV vaccination. One patient failed to respond to immunization when a 1:128 titer was used for response. After 12 months, 12.3% had SBA titers <8 (20.2% using a titer of 1:128). In the 12% to 20% of healthy adults who failed to retain protective serum bactericidal antibody (SBA) titers 1 year after meningitis C CV, immunological memory was unable to create a protective systemic or mucosal bactericidal antibodies until 7 days postchallenge. It is possible that the speed of this response is too slow to protect from natural meningococcal infection.

In the United States, we have had an adolescent vaccine program with a quadravalent conjugate vaccine ($MenACWY_D$) for several years. Protective SBA titers in 50% of the adolescents who received the vaccine have fallen to nonprotective levels 5 years after vaccination. The data that were presented by Wing et al. support the recent ACIP recommendation for a booster dose of $MenACWY_D$ vaccine at age 16 years for individuals who were first vaccinated before the age of 15 years. The booster should provide protection through age 20 years, when the incidence of invasive meningococcal disease falls.

Preventing Resistance – The Role of Optimized Dosing

Written by Rita Buckley

Resistance in the Gut

The rapid emergence of antibiotic resistance is a major public health concern [Zhang L et al. *Appl Environ Microbiol* 2011]. Johan W. Mouton, MD, Nijmegen Institute for Infection, Inflammation & Immunity, Nijmegen, The Netherlands, discussed five questions of resistant bacteria in the gut:

- Their possible presence without antibiotic exposure
- Whether there is selection of resistant gut bacteria during antimicrobial exposure
- Whether there is selection of resistance during systemic treatment for other infections
- Whether it is possible to avoid or minimize selection
- How optimization of treatment relates to selection of resistance in the gut

Data suggest that early development of antibiotic resistance in human gut microbiota is independent of an infant's exposure to antibiotics but is likely to be affected by exposure to maternal and environmental microbes during and after delivery. The population of food-borne antibiotic-resistant bacteria is also significantly amplified within the host, even in the absence of antibiotic-selective pressure [Zhang L et al. *Appl Environ Microbiol* 2011].

Prof. Mouton cited a study in which 2 of 20 children with no known antibiotic exposure, living in a very remote Senegalese village, were fecal carriers of a multiresistant *Escherichia coli* clone that produced CTX-M-15 [Ruppe E et al. *Antimicrob Agents Chemother* 2009], strongly suggesting that the pC15-1a multidrug-resistant region can persist in the intestinal flora in the absence of significant selective pressure, at least that we know of.

Based on a report by de Smet et al. [*Lancet Infect Dis* 2011], Prof. Mouton justified the widespread use of selective digestive tract decontamination in intensive care units with low levels of antibiotic resistance. Prof. Mouton presented an extensive analysis of an experimental study that looked at the effects and duration of antimicrobial treatment for pneumonia in selecting resistant microorganisms in the gut [Goessens WH et al. *JAC* 2007]. This showed that the more frequent the dosing regimen, the higher the propensity for selecting resistant bacteria. Emergence of resistance is dependent on dose (inverse U shape), duration of therapy, and dosing regimen. For the first three questions that were posed, Prof. Mouton answered "yes;" "perhaps" to the fourth; and "not good" to the fifth.

Resistance in a Dynamic Model

Didier Guillemot, MD, Institut Pasteur/Univ. Versailles Saint Quentin/Inserm, Paris, France, discussed the impact of antibiotic dose on resistance selection in the community. His findings were based on a dynamic model of *Streptococcus pneumoniae*. His presentation covered β-lactam doses and pneumococci susceptibility, accounting for β-lactam doses.

From a public health point of view, antibiotics do more to increase the clearance of susceptible bacteria than the acquisition of a new mechanism or resistant strain. Prof. Guillemot noted that much is known about the relation between *S. pneumoniae*, antibiotics, and resistance, but not at the population level.

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The mathematical model that he discussed assessed the influence of modifying doses of β-lactam at the population level to estimate the impact on resistance levels and prevalence in colonized individuals. Questions that were considered using this model included the effects of prescription frequency, prescribed dose, and whether defined daily dose (DDD) is a good indicator to predict the evolution of β-lactam resistance to *S. pneumoniae*. Simulations over a 50-year period of fixed- and variable-dose exposure showed a bimodal distribution and that the prevalence of resistance increases with the frequency of exposure. Both findings were consistent with prior epidemiological studies.

Dosing outcomes indicated that higher doses may reduce the prevalence of resistance and increase the minimum inhibitory concentration (MIC) of resistant strains. The model also showed that DDD is not an accurate indicator for predicting pneumococcal resistance to β-lacams. "Don't use DDD to anticipate the future of *S. pneumoniae* dissemination or to analyze the relationship between antibiotic use and *S. pneumoniae* resistance," he said.

Which Matters More – Antibiotic Dose or the Bacterium?

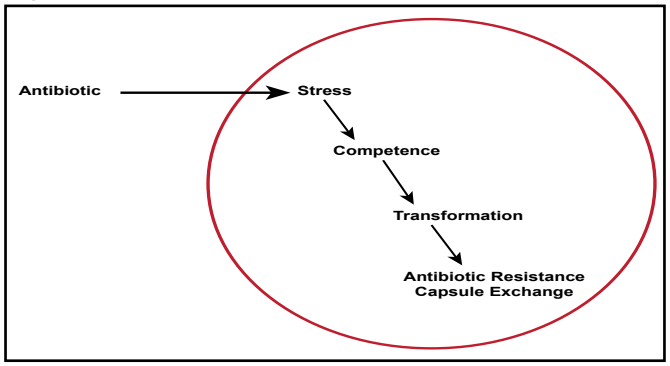
Patrice Courvalin, MD, Institut Pasteur, Paris, France, discussed the relative importance of antibiotic dose or changes in the bacterial genome in causing antibiotic resistance. Bacteria respond to many changes in their environment by sensing small molecules; yet, competence for genetic transformation is transient. In several bacterial species, it depends on achieving a specialized cellular state [Harvarstein LS et al. *Proc Natl Acad Sci* 1995].

Harvarstein et al. [*Proc Natl Acad Sci* 1995] found that competence-stimulating peptide induced competence in pneumococcal cultures in a dose-response fashion to the synthetic peptide, with the highest yield (about 5% of cells transformed) observed at doses of 30 to 1000 ng/mL and a monotonic dose response in the intervening region.

Resistance in *Acinetobacter spp.*, particularly *Acinetobacter baumannii*, provides another example. *A. baumannii* possesses two intrinsic β-lactamase genes, in addition to weak permeability and efflux systems. Together, they confer a natural reduced susceptibility to antibiotics. Numerous acquired mechanisms of resistance and genetic elements, such as resistance islands, have also been identified [Poirel L et al. *IUBMB Life* 2011].

Based on these and other findings, Prof. Courvalin concluded that antibiotics promote evolution of resistance (Figure 1).

Figure 1. Antibiotics Promote Evolution of Resistance.



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PK-PD and Resistance

William A. Craig, MD, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA, discussed the use of pharmacodynamics/pharmacokinetics (PD/PK) to establish the target that is required to prevent an increase in resistant populations; to identify which PK/PD indices (C_{max}, AUC/MIC, T>MIC) or other characteristics best prevent the emergence of resistance; and to determine the magnitude of the PK/PD indices or other characteristics that is required to prevent the development of resistance.

With regard to the mutant prevention concentration (MPC) that stops mutant selection at 10^{10} organisms, he reported that MPC is usually 2- to 16-fold higher than MIC, with selection of resistance higher if drug concentrations persist in the zone between the two concentrations [Blondeau JM et al. *Antimicrob Agents Chemother* 2001]. He also pointed out the inverted U-shaped distribution of resistance emergence versus dose intensity [Tam VH et al. *Antimicrob Agents Chemother* 2007].

Dr. Craig discussed aminoglycide dosing to minimize resistance for *Enterobacteriaceae* and *Staphyloccocus aureus* (Cmax/MIC >6 [once-daily dosing]) and the need for a Cmax/MIC of 30 with twice-daily dosing of gentamicin to prevent emergence of resistance with *P. aeruginosa* [Tam VH et al. *Antimicrob Agents Chemother* 2008].

In addition, he covered PK/PD indices that are associated with *in vitro* enhancement or suppression of fluoroquinolone resistance, including AUC_{24}/MIC, AUC_{24}/MPC, and Cmax/MIC, and how doxycycline, combined with moxifloxacin, can reduce emergence of resistant *S. aureus* [Allen GP, Deshpande LM. *Int J Antimicrob Agents* 2010]. Dr. Craig concluded that there is a need for more *in vivo* studies on optimal dosing and combination therapy to effectively prevent resistance.

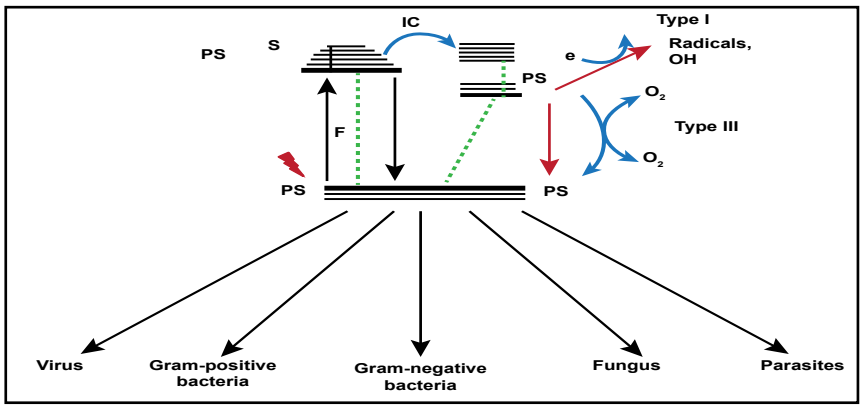
MD CONFERENCE EXPRESS

The Next Wave of Antimicrobial Approaches and Agents

Written by Noelle Lake, MD

A novel approach to treat drug-resistant microorganisms is antimicrobial photodynamic therapy (PDT), which is under investigation in animal models in the lab of Michael R. Hamblin, PhD, Wellman Center for Photomedicine, Massachusetts General Hospital Boston, Massachusetts, USA. PDT involves applying light from a laser, light-emitting diode, or other light source to an infected area that has been sprayed with a pathogen-penetrating photosensitizing agent. The combination of photosensitizer and light results in the generation of cytotoxic reactive oxygen species, which kills bacteria or fungi instantly (Figure 1). "There has never been a single pathogen discovered that is resistant to photodynamic therapy," Dr. Hamblin said.

Figure 1. Mechanisms of Action of Antimicrobial Photodynamic Therapy.



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PDT is safe for human tissue, because the photosensitizing agents penetrate bacteria quickly and take longer to affect eukaryotic cells. It is inexpensive and versatile and involves minimal training for staff and patients. Dr. Hamblin cites a further advantage in treating infections, such as traumatic infections and burns, since systemic antibiotics have trouble reaching damaged tissue. PDT has a broad therapeutic range, including viruses and parasites, and can reach pathogens in biofilms. In addition, Dr. Hamblin projects that PDT may be useful in the treatment of otitis media, necrotizing fasciitis, bacterial cystitis, gastric *H. pylori*, sinusitis, or any infection where dye and light can be infused.

Two interesting areas of PDT research are: (1) the pursuit of ideal photosensitizing agents, such as bacteriochlorins and porphycenes, and (2) assessing the effects of PDT in animal models of infection with bioluminescent organisms. Decreasing bioluminescence (correlating with decreased colony-forming units) and improved survival have been seen with burns in mouse models [Dai et al. *Virulence* 2001], soft tissue [Gad et al. *Photochem Photobiol Sci* 2004], and sepsis across a range of pathogens, including MRSA [Dai et al. *Lasers in Surg and Med* 2010], *E. coli, Pseudomonas, Acinetobacter* [Dai et al. *Antimicrob Agents Chemother* 2009], *S. aureus* [Gad et al. *Photochem Photobiol Sci* 2004], and *Candida* [Dai et al. *Antimicrob Agents Chemother* 2011]. PDT may also stimulate wound healing.

Scott F. Singleton, PhD, University of North Carolina, Chapel Hill, North Carolina, USA, is leading a team of researchers in the development of novel antibacterial adjunct agents that inhibit bacterial enzymes that are involved in DNA repair. Their current focus is a RecA inhibitor to combine with and potentiate the effect of DNA-damaging antibiotics. RecA protein of *Escherichia coli* and other anabolic enzymes are upregulated by intracellular stress that is induced by antibiotic treatment and enable bacteria to survive [Kohanski

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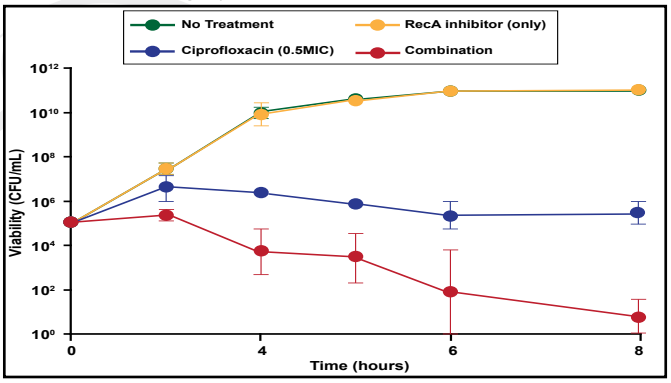
MA et al. *Nature Rev Microbiol* 2010]. Furthermore, bacteria that are deficient in ReA show increased susceptibility to fluouroquinolones, aminoglycosides, trimethoprim, some β-lactams, and other agents [Thi TD et al. *J Antimicrob Chemother* 2011; Lui et al. *Antimicrob Agents Chemother* 2010].

Lead candidate compound BRITE-345133, discovered by a collaborative effort between Dr. Singleton's lab and Dr. Li-An Yeh's lab at North Carolina Central University, is an allosteric inhibitor of RecA's ATPase activity. BRITE-345133 has been shown to potentiate *E. coli* killing by ciprofloxacin (Figure 2), which translates into a dose-dependent reduction in ciprofloxacin MIC. An added benefit of RecA inhibition and improved bacterial killing is suppression of resistance emergence. New RecA inhibitors with improved physiochemical and activity spectra are under development.

Figure 2. RecA Inhibitor BRITE-345133 Augments Bacterial Killing by Ciprofloxacin *in vitro*.



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Terry Roemer, PhD, Merck Infectious Disease Research, Kenilworth, New Jersey, USA, presented his work on chemical genetic interaction networks that are aimed at uncovering targets for resensitization of methicillin-resistant *S. aureus* (MRSA) to β-lactam antibiotics. Plasmid-based antisense interference is a technique that impairs transcription and translation of a targeted protein and has the potential to restore the susceptibility of MRSA to β-lactam antibiotics. A wide array of genes that are involved in β-lactam tolerance processes, including early- and late-stage peptidoglycan synthesis, cell division, and cell wall biogenesis, are potential antisense targets in MRSA [Lee et al. *Chem Biol*. In press 2011]. Dr. Roemer shared data regarding the development of small-molecule inhibitors to resistance targets that have been identified on genetic potentiation maps, including PC190723, a novel antistaphylococcal agent that targets a component of cell division initiation, FtsZ [Haydon DS et al. *Science* 2008].

David Shlaes, MD, Anti-Infectives Consulting, Stonington, Connecticut, USA, offered hope in the battle against microbial resistance in the form of new β-lactamase inhibitor combinations, focusing on tazobactam, clavulanic, and a newer class of agents—avibactam (formerly called NXL-104) and MK-7655.

Pipeline agents to watch include CXA-201, a 2-to-1 combination of a new cephalosporin (CXA-101) and tazobactam. CXA-201 demonstrates good activity against strains of *P. aeruginosa* with diverse resistance mechanisms [Cabot G et al. ICAAC 2010] but is less active against other gram-negative pathogens, particularly those that produce extended-spectrum β-lactamases (ESBLs) [Sader HS et al. *Antimicrob Agents Chemother* 2011].

A 4-to-1 combination of ceftazidime and avibactam is in development for use in complicated intraabdominal abscess (IAI) and urinary tract infections (UTIs) and is expected to enter Phase 3 by early 2012. This compound shows strong activity against *E. coli, Klebsiella* species, and *Enterobacter* species, including ESBL-producing strains [Sader HS et al. ICAAC 2010]. The addition of avibactam also improves ceftazidime's activity against *Pseudomonas* strains with various resistance mechanisms [Eurofins Medinet Study #5006-08]. In a prospective trial for the treatment of UTI, similar efficacy was demonstrated for ceftazidime/avibactam compared with imipenem, and a greater proportion of ceftazidime-resistant *E. coli* responded favorably to ceftazidime/avibactam compared with imipenem (86% and 80%, respectively) [Vazquez JA et al. ECCMID 2011].

Other combinations of interest include a 1-to-1 combination of ceftaroline and avibactam that is in Phase 2 for complicated UTI and a triple combination of imipenem, cilastatin, and MK7655 that is in Phase 1. Dr. Shlaes concluded by emphasizing that he hopes drugmakers will heed the call to develop a compound, such as aztreonam (or other monobactam base agents) and avibactam (or MK7655), which should retain activity against gram-negative pathogens that bear NDM-1 or other metallo-β-lactamases.

According to Joyce Sutcliffe, PhD, Tetraphase Pharmaceuticals, Watertown, Massachusetts, USA, *Streptomyces* that grew on stored grain supplied ancient cultures with naturally occurring tetracycline. The 1940s and 1950s saw the development of legacy and semisynthetic tetracyclines with great oral bioavailability, and now, a technique, called total synthesis, in which the right- and left-hand segments are designed in total and then connected together, has made possible the development of new classes of tetracyclines, including 8-aminomethyl, penta/polycyclic, and 7,9 disubstituted analogs. Dr. Sutcliffe presented information on several promising agents that are in development, including orally active compounds that are effective against multidrug-resistant gram-positive and gram-negative pathogens.

PTK0796 is a new C-9-aminomethyl minocycline analog that has shown efficacy against *S. aureus, E. faecalis*, and *E. coli* in mouse models of infection [McKenney D et al. ICAAC 2003]. It is under development for intravenous and oral use in humans. PTK0796 is in Phase 2/3 development for skin and skin structure infections, with plans to study it in community-acquired pneumonia.

The 8-aminomethyl tetracycline class demonstrates activity that is comparable with tigecycline against key gram-negative pathogens, including ESBL-producing strains. From this class, TP-2758 has broad-spectrum activity, including excellent coverage of MRSA and gram-negatives, excluding *Pseudomonas*, and has entered Phase 1 clinical trials as an oral formulation. Other notable pipeline tetracyclines include TP-834, a pentacycline that is in development against MRSA community-acquired pneumonia, and TP-434, a 7,9 disubstituted analog with broad spectrum activity against aerobes, anaerobes, gram-positives, and gram-negatives except *Pseudomonas*. TP-434 is currently in Phase 2 for treating complicated IAI.

Stuart Johnson, MD, Loyola University Medical Center, Maywood, Illinois, USA, discussed a new option in the treatment of *Clostridium difficile* infections (CDIs). Approved in May 2011, fidaxomicin, a narrow-spectrum, nonabsorbed bactericidal RNA polymerase inhibitor that is effective against *C. difficile*, is the first FDA-approved agent for use in the treatment of CDI in 25 years, making it one of two approved CDI therapies, along with vancomycin. Vancomycin use is complicated by a greater-than-20% recurrence rate for CDI and has the potential to select for vancomycin-resistant strains in the gut [Kelly and LaMont. *N Engl J Med* 2008].

In two large, multicenter, double-blinded, randomized Phase 3 trials, fidaxomicin (200 mg BID) was shown to be noninferior to vancomycin (125 mg 4x/day) for clinical cure—88% versus 86%, respectively—in the modified intent-to-treat population. Notably, fidaxomicin treatment was associated with reduced rates of CDI recurrence compared with vancomycin (15% vs 25%; p=0.005) in the first trial [Louie TJ et al. *New Engl J Med* 2011]. Adverse events were similar between the two drugs, and results were similar in the second study.

The mechanism by which fidaxomicin prevents recurrence may be related to suppression of *Enterobacteria* overgrowth in the gut [Tannock GW et al. *Microbiol* 2010].

In a separate analysis of the combined Phase 3 trials of fidaxomicin- and vancomycin-treated patients, the use of concomitant antibiotics with CDI treatment was a risk factor for prolonged duration of diarrhea [Mullane KM et al. *Clin Infect Dis* 2011]. This is consistent with what is known about risk factors for CDI, including antibiotic use and alterations of gastrointestinal microbiota. The adverse effect of concomitant antibiotic use on cure and recurrence rates was significantly ($p<0.05$) more prominent among vancomycin-treated patients. Vancomycin and fidaxomicin performed similarly against infections with epidemic strain BI/NAP1/027 [Patrella L. et al. ICAAC 2011].

Looking to the future, Dr. Johnson suggested that CDI prevention strategies include immunotherapy and more effective probiotics.

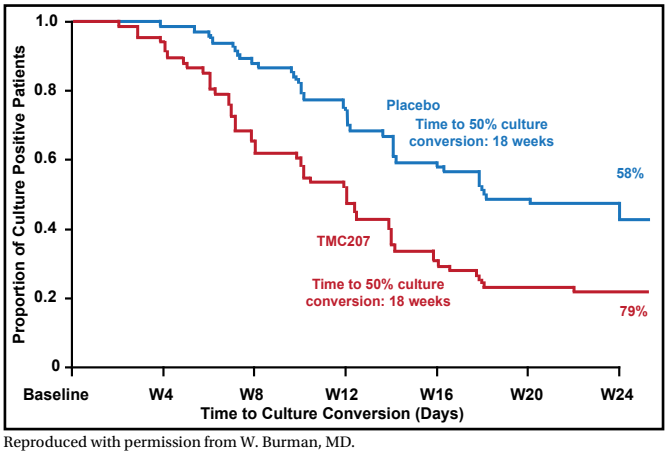
With tremendous increases in the incidence of tuberculosis (TB) infection due to the HIV epidemic and the emergence of multidrug-resistant TB (MDR-TB), antituberculosis drug development has resurfaced as a major priority. Citing 2010 World Health Organization data, William Burman, MD, University of Colorado, Denver, Colorado, USA, said that a 55% increase globally in new MDR-TB cases has occurred in the past decade, with 440,000 new cases occurring each year, most of which remain undiagnosed.

Treatment of MDR-TB takes 18 to 24 months, is very expensive, and has high rates of side effects. Therefore, there is a critical need for new agents for MDR-TB.

The most advanced pipeline agent in this area is TMC207 (bedaquiline). Bedaquiline is an ATPase synthetase inhibitor with good activity against MDR-TB and has the advantage of having no activity against bacterial pathogens.

Since it interacts with rifampin, bedaquiline was evaluated as an add-on agent to optimized background therapy (excluding rifampin) in a prospective trial among patients with MDR-TB. Treatment substantially reduced (by 50%) time to sputum culture conversion (Figure 3) and was well tolerated [McNeeley DF et al. IUATLD 2010]. A FDA application is planned for 2012 for accelerated approval as an MDR treatment.

Figure 3. Time to Sputum Culture Conversion Among Patients with MDR-TB Treated with Optimized Background Therapy plus Placebo or TMC207.



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The Conundrum of MDR-TB and Combination Therapy

Written by Rita Buckley

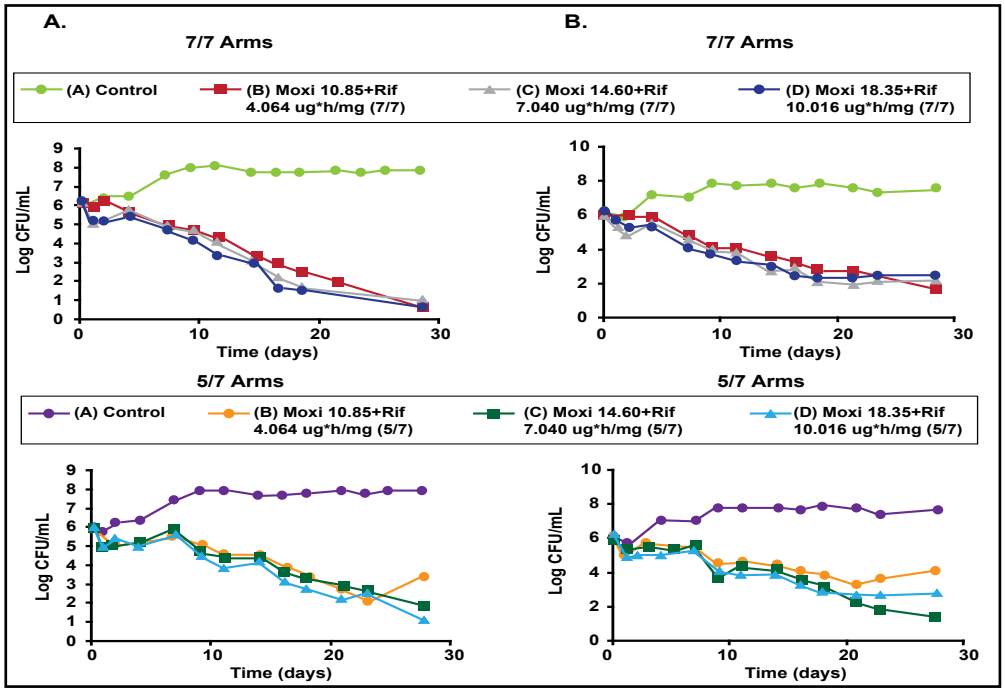
Cases of multidrug-resistant tuberculosis (MDR-TB), defined as TB that is resistant to isoniazid (INH) and rifampin (RMP) and extremely (or extensively) drug-resistant TB [ie, TB that is not only resistant to INH/RMP, but also to quinolone and capreomycin (cyclic peptide) or an aminoglycoside (amikacin or kanamycin)], are increasing. MDR complicates therapy and results in lower success rates and higher mortality, especially in HIV coinfected patients. George L. Drusano, MD, University of Florida, Gainesville, Florida, USA, discussed the conundrum of MDR-TB and combination therapy and ways to address it.

According to Dr. Drusano, combination therapy generally suppresses resistance (Table 1). [Drusano GL et al. *mBio* 2010]. However, when drugs have vastly different half-lives (eg, rifampin and moxifloxacin) and one induces error-prone replication (as with moxifloxacin), resistance can develop with drug holidays (Figure 1) [Drusano GL et al. *mBio* 2011]. "If we wish to shorten therapy," he said, "we have to suppress resistance, pay attention to schedule, and find combinations that are not only antagonistic but, hopefully, synergistic."

Table 1. Resistance Suppression: Log-Phase.

Regimen	AUC/MIC Ratio of Free:		Resistance Suppression
	Rifampin	Moxifloxacin	
600 mg rifampin QD	168.2		Failure
800 mg moxifloxacin QD		177.2	Failure
100 mg rifampin QD + 100 mg moxifloxacin QD	24.2	21.5	Success

Figure 1. Resistance Emergence in Drug Holidays.



Moxi=moxifloxacin; Rif=rifampin.
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For the first time in decades, new TB drugs are available. Dr. Drusano stressed the importance of not risking the emergence of resistance to these agents and questioned the use of a study design in which these drugs are being evaluated against MDR-TB in an optimized background. Lack of knowledge of the detailed susceptibility pattern of the isolate prior to initiation of therapy increases the risk of creating resistant mutants. The question then becomes how to test the drugs in clinical trials.

He suggested starting by examining INH, to which the bug must be resistant, to be called MDR-TB. INH kills rapidly, with multilog decline at standard drug exposures with low minimal inhibitory concentration (MIC) values. Doses as large as 1200 mg cannot completely counter-select resistance amplification as monotherapy. Area under the curve/MIC is the pharmacodynamic-linked variable for cell kill. Because of the fast/slow acetylator divide, different populations will respond somewhat differently to INH. Specifically, fast acetylators will obtain suboptimal results at MIC values >0.25 mg/L. Therefore, noted Dr. Drusano, "wouldn't it be nice to know the MIC distributions in different areas of the world?" Unfortunately, such a database does not exist. In the absence of that information, Dr. Drusano noted that he would test the new drugs in standard patients to learn how to optimize them in combination and to suppress resistance. He stressed the risk of generating and spreading a number of resistant isolates if new drugs are used to treat MDR- and extremely drug-resistent-TB patients as single drugs.

"Combination therapy is the key for successful treatment of TB," he said. He stressed the need to learn to use new agents alone and, more importantly, in combination to optimally kill organisms and suppress resistance. He also suggested a dialog with regulatory officials to get these issues out on the table.

The United States Food and Drug Administration's (FDA) Critical Path Initiative is already transforming the way FDA-regulated products are developed, evaluated, and manufactured. One way is by publishing articles on models and approaches for anti-TB drug testing. "The Global Alliance is taking similar actions," said Dr. Drusano.

New Drugs on the Horizon to Treat MDR Pathogens

Written by Eric Butterman

Aminoglycosides are a well-known class of drugs with proven efficacy; however, they are being used less frequently because of resistance, nephrotoxicity, and ototoxicity. George Zhanel, PhD, University of Manitoba, Winnipeg, Manitoba, Canada, discussed plazomicin (formerly ACHN-490), a new aminoglycoside that is used to treat gram-negative infections, which was evaluated against gentamicin, tobramycin, and amikacin. Dr. Zhanel believes plazomicin is a next-generation aminoglycoside that retains its activity against multidrug-resistant gram-negative and gram-positive bacterial strains that express all clinically relevant aminoglycoside-modifying enzymes. It is not active against organisms that harbor rRNA methyltransferases. Plazomicin is synergistic with daptomycin and ceftobiprole against a variety of MRSA phenotypes and with a variety of β-lactams (eg, cefepime, doripenem, imipenem, and piperacillin-tazobactam) and against *P. aeruginosa* (*in vitro*). At 15 mg/kg IV, plazomicin has a C_{max} of 113 µg/mL, an AUC_{0-24} of 239 h·µg/mL, $t_{1/2}$ of 3.0 hr, and V_{ss} of 0.24 L/kg. Animal and human studies have not reported nephrotoxicity or ototoxicity [Zhanel G et al. *Expert Rev Anti Infect Ther* 2011. Submitted; Zhanel G et al. IDSA 2011]. Plazomicin is currently being investigated in a Phase 2 study to treat complicated urinary tract infections and acute pyelonephritis [NCT01096849].

Prabhavathi Fernandes, PhD, Cempra Pharmaceuticals, Chapel Hill, North Carolina, USA, presented information on macrolides and ketolides with improved antibacterial properties. Dr. Fernandes discussed several investigational programs: a novel series of azetidinyl ketolides that mitigate hepatotoxicity by minimizing hepatic turnover and time-dependent inactivation of CYP3A isoforms in the liver [Magee TV et al. *J Med Chem* 2009]; cethromycin, a ketolide antibiotic that has shown potent activity (similar to telithromycin) against macrolide-resistant bacterial strains but failed to obtain United States Food and Drug Administration approval for community-acquired bacterial pneumonia (CABP) and is now being pursued in superiority trials in simple drug-resistant respiratory infections; and modithromycin, a bridged bicyclic macrolide that is also similar in potency to telithromycin that is active against pneumococcal strains with *erm* and *mef* resistance but has a relatively high (8 µg/mL) MIC_{90} for *H. influenzae* and a very long half-life. Dr. Fernandes concluded her presentation with solithromycin (CEM-101), an oral (Phase 2) and intravenous (Phase 1) fluoroketolide that is being evaluated for the treatment of CABP that has shown activity against *S. pneumoniae,* CA-MRSA, *Enterococci,* and *M. avium* and in animal models of malaria. MICs are similar to azithromycin for gram-negatives, but on average, solithromycin is 8 to 16 times more active for the gram-positive organisms and is active against azithromycin-resistant strains. Solithromycin has 67% oral bioavailability, as compared with 38% for azithromycin; is well distributed into tissues

and cells; has a plasma half-life of approximately 7 hours; shows no significant effect against nACH receptors; and has been shown to be safe and well tolerated in Phase 1 studies [Still JG et al. *Antimicrob Agents Chemother* 2011]. In the recently completed Phase 2 trials, it has shown noninferiority to levofloxacin, with favorable safety and tolerability. Plans are underway for a Phase 3 oral trial and Phase 2 intravenous-oral trial in CABP in 2012.

Kelly Aubart, PhD, GlaxoSmithKline, Collegeville, Pennsylvania, USA, discussed GSK1322322, a novel peptide deformylase inhibitor that is in development for hospitalized CABP, acute bacterial skin, and skin structure infections. The new agent has good activity against gram-positive pathogens, including those that infect the skin and soft tissue, as well as the respiratory tract. It is potent *in vivo* and *in vitro* against a range of pathogens, including MRSA. GSK1322322 was safe and well tolerated in Phase 1 studies. A Phase 2 study in skin and soft tissue infections has recently been completed [NCT01209078].

A Critical Precaution – Immunizations in Reproductive Health

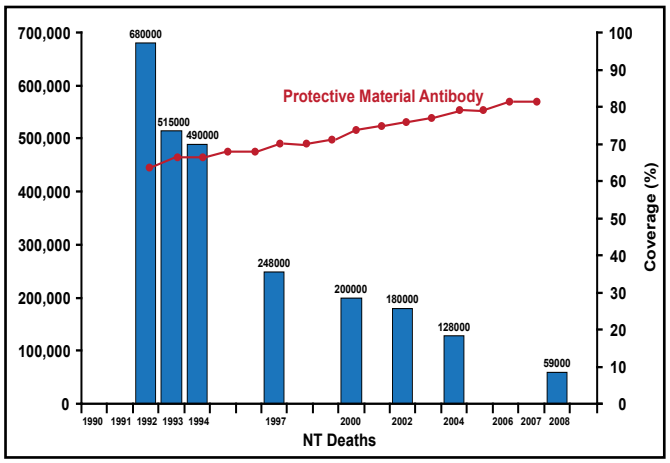
Written by Rita Buckley

Vaccination is one of the most efficient and cost-effective ways to prevent maternal and neonatal morbidity and mortality. For women in their reproductive years, it serves two roles—primary prevention of disease and protection for infants. Linda O. Eckert, MD, University of Washington School of Medicine, Seattle, Washington, USA, discussed vaccines and their recommended use in reproductive-age women.

In the late 1980s, tetanus caused approximately 800,000 neonatal and 30,000 maternal deaths per year. Since the launch of a renewed global maternal-neonatal tetanus elimination program in 2000, there has been a 92% reduction in neonatal tetanus deaths between 1992 and 1998 (Figure 1).

Pertussis cases in the United States (US) jumped from under 10,000 in 2000 to over 25,000 in 2003 [*MMWR* 2004 53:19]. Adults, including grandparent caretakers, were the suspected source of 56% of infant pertussis cases [Bisgard K et al. *Pediatr Infect Dis J* 2004]. The tetanus, diphtheria, pertussis (Tdap) vaccine is now licensed for use in adults aged 65 years and older and is also recommended, rather than tetanus, diphtheria (Td), for use in pregnant women, for those who are health care or child care providers, and in cases of high community incidence or wound prophylaxis [*MMWR* 2011;60(41):1424-1426].

Figure 1. Outcomes From a Global Campaign to Eliminate Neonatal Tetanus.



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The United States Advisory Committee on Immunization Practices (ACIP) currently recommends that women who will be pregnant during the influenza season receive inactivated influenza vaccine to reduce excess maternal mortality during influenza pandemics, offset physiological changes during pregnancy that may increase the morbidity of influenza infections, and reduce the risk of cardiopulmonary hospitalizations during the influenza season.

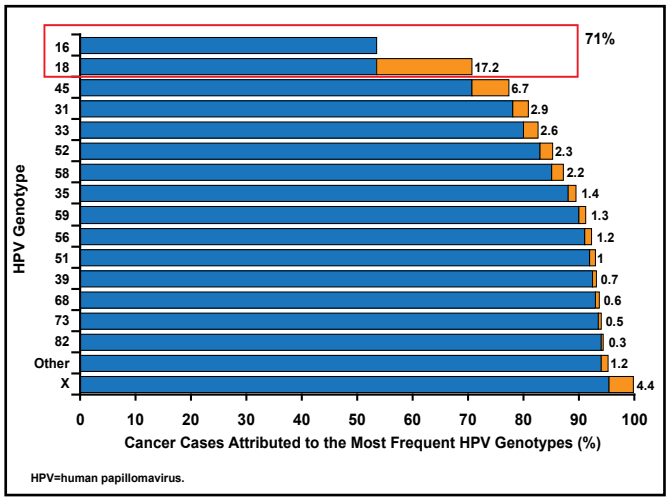
Influenza vaccine that is given to pregnant women is 91.5% effective in preventing hospitalization of their infants for influenza in the first 6 months of life [Benowitz I et al. *Clin Infect Dis* 2010].

Rubella continues to be a significant disease burden. The goal of rubella vaccination is to prevent congenital rubella syndrome (CRS). According to Dr. Eckert, The Americas 2003–2008 campaign to eliminate CRS led to the vaccination of 250,000,000 adolescents and adults in 32 countries and reduced CRS cases by 98%—from 135,947 cases in 1998 to 2998 cases in 2006 [Castillo-Solórzano C et al. *JAMA* 2009].

In the US, 10 women die of cervical cancer every day. However, worldwide, it is the second most common cause of cancer mortality, accounting for 240,000 deaths per year. Most victims are relatively young and poor women, often with dependent children. At least 15 types of human papillomavirus (HPV) have been associated with cervical cancer. Current vaccines confer type-specific immunity to HPV types 16 and 18, which account for 71% of cases of cervical cancer (Figure 2). In contrast, a vaccine that contains the seven most common HPV types would prevent about 87% of cervical cancers [Munoz N et al. *Int J Cancer* 2004]. ACIP recommendations for females aged 9 to 26 years call for immunization with quadrivalent or bivalent vaccine. The former protects against types 6, 11, 16, and 18,

and in Phase 3 trials (n=17,622), it had 100% (95% CI, 75 to 100) efficacy [FUTURE II Study Group. *J Infect Dis* 2007]. The latter protects against types 16 and 18. In a Phase 3 trial (n=16,126), it had 92.9% efficacy (95% CI, 80 to 99) [Paavonen J et al. *Lancet* 2009].

Figure 2. HPV Genotypes in Cervical Cancer.



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Why Can't Microbes Just Get Along?

Written by Noelle Lake, MD

Deborah Hogan, PhD, Department of Microbiology and Immunology, Dartmouth Medical School, Hanover, New Hampshire, USA, has been hard at work exploring the love-hate relationship between two important pulmonary pathogens that are common among patients with cystic fibrosis (CF). She shared the institution's discoveries and discussed the clinical relevance of microbe-microbe interactions in the State-of-the-Art lecture, "*Pseudomonas* and *Candida*: Friends or Foes?"

Today, increasing numbers of patients are experiencing multispecies infections, often bacterial-fungus infections, due to greater use of medical devices, transplantation, and other interventions that allow patients to live longer with chronic diseases. Understanding the interplay between co-infecting organisms and how they affect their hosts may lead to refinements in patient management.

In the environment, *Pseudomonads* have a rather fickle relationship to fungi—sometimes synergistic, as with the colonization and protection of the chanterelle mushroom, and sometimes antagonistic. Dr. Hogan's laboratory is attempting to untangle a similarly convoluted relationship between *Pseudomonas aeruginosa*, a gram-negative bacterium that is common in soil and hospitals, and *Candida albicans*, a ubiquitous fungus that is capable of causing invasive disease. *P. aeruginosa* readily attaches to filamentous *C. albicans*, creating a biofilm, and together they infect catheters, ventilator tubing, and other devices, as well as eyes, wounds, burns, and the lungs of CF patients. Coinfection can negatively affect patients. A 2010 prospective study in *P. aeruginosa*-infected CF patients demonstrated a correlation between the advent of *C. albicans* colonization and an increase in exacerbations [Chotirmall et al. *Chest* 2010].

On a cellular level, this seeming kinship between *P. aeruginosa* and *C. albicans* is actually highly contentious, as it is subject to a kind of interspecies molecular warfare and continual adaptation in the effort to survive. Dr. Hogan highlighted various facets of the relationship, both friendly and antagonistic. *P. aeruginosa* is able to kill filamentous *C. albicans* hyphae by secreting a group of toxic small molecules, called phenazines [Peleg et al. *Nat Rev Microbiol* 2010]. Candida fights back by secreting farnesol, which, in some instances, dismantles *P. aeruginosa*'s phenazine production [Hornby et al. *Appl Environ Microbiol* 2001] but, in other instances increases it by bumping up downstream production [Cugini et al. *Microbiol* 2010]. Farnesol also promotes the conversion of filamentous fungal elements to the more stable yeast morphology, resistant to *P. aeruginosa* attachment and killing [Westwater et al. *Eukaryot Cell* 2005; Deveau et al. *Eukaryot Cell* 2010]. Over time, a chronic co-infection milieu may select for a more synergistically inclined *P. aeruginosa* variant that demonstrates reduced antifungal capacity (due to defective quorum sensing and phenazine production) but improved growth. However, *P. aeruginosa* is also armed with a novel, highly toxic 5-methylphenazine, possibly specifically intended for its *C. albicans* foe, as it is not generally produced by solitary *Pseudomonas* species.

Importantly, microbe-microbe interactions may also impact a host's ability to clear the infection. Recent data show that the presence of *P. aeruginosa* may suppress host immune response to *C. albicans*. In a recent study, single-pathogen infection models with *P. aeruginosa* and *C. albicans* produced the expected immune responses in total cell count and cell differential, with *P. aeruginosa* causing a strong neutrophilic response and *C. albicans* inducing more of a macrophage and eosinophilic response. However, when the two organisms were combined, the immune response more closely resembled that of *P. aeruginosa*, as if *C. albicans* was not present [Allard and Whittaker. *Med Mycol* 2010]. This suggests that coinfection may allow organisms, such as *C. albicans*, to evade immune recognition and set up persistent infections in patients.

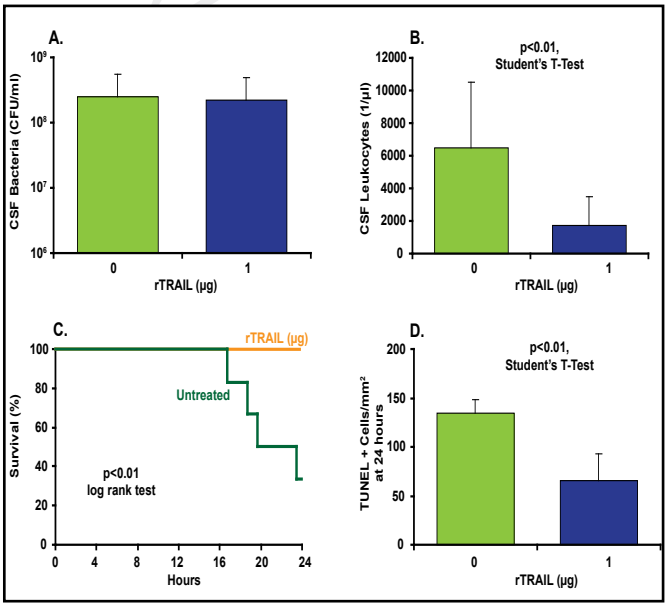
The Role of Adjunctive Steroids in the Treatment of Bacterial Meningitis

Written by Noelle Lake, MD

Steroids have an important place in the treatment of bacterial meningitis (BM), according to W. Michael Scheld, MD, University of Virginia, Charlottesville, Virginia, USA. Dr. Scheld was unable to attend this year's ICAAC, but graciously agreed to share highlights from that talk for the benefit of *MD Conference Express* readers.

The rationale for employing anti-inflammatory medication in the treatment of BM is based upon the observation that hyperactive central nervous system (CNS) immune responses underlie brain swelling and neuronal loss and likely contribute to morbidity and mortality. In animals, steroids have been shown to reduce CNS inflammation, intracranial pressure, and neuronal loss. In addition, new investigational anti-inflammatory agents, such as recombinant tumor necrosis factor-related apoptosis-inducing ligand (rTRAIL), significantly decrease cerebrospinal fluid leukocytes and apoptosis in mouse models of pneumococcal meningitis and significantly improve survival (Figure 1) [Hoffmann O et al. *J Clin Invest* 2007].

Figure 1. Effects of Treatment with rTRAIL in Meningitis Induced By Live *pneumococci* in Mice.



(A) At 24 hours after infection, CSF bacterial load in untreated and rTRAIL-treated wild-type mice did not differ. (B) CSF leukocyte concentration was significantly lower in rTRAIL-treated mice than in controls. **p<0.01, Student's t-test. (C) Mortality was higher in untreated versus rTRAIL-treated mice. **p<0.01, log rank test. (D) Apoptosis was reduced by treatment with rTRAIL. **p<0.01, Student's t-test.

After review of the clinical literature over the past decade, Dr. Scheld believes that intravenous dexamethasone for the first 2 to 4 days in the treatment of community-acquired BM is indicatedin all ages in developed nations. De Gans et al. demonstrated an overall reduced risk for unfavorable outcomes and mortality in adults (RR=0.59; 95% CI, 0.37 to 0.94; p=0.03; and RR=0.48; 95% CI, 0.24 to 0.96; p=0.04, respectively) with dexamethasone [*New Engl J Med* 2002]. Data from the Netherlands reveal that national implementation of adjunctive dexamethasone in patients with *S. pneumoniae* BM has significantly reduced unfavorable outcomes, hearing loss, and mortality [Brouwer MC et al. *Neurology* 2010].

In contrast, steroids are not recommended where resources are limited and in populations with high HIV-positivity rates. A Vietnamese study showed a benefit to dexamethasone use only among patients with a proven microbiological diagnosis of BM but not among those with a probable diagnosis [Nguyen TH et al. *New Engl J Med* 2007]. A study in Malawi among patients with high rates of HIV infection showed no benefit to using steroids in the treatment of BM [Scarborough M et al. *New Engl J Med* 2007]. Further, a 2010 meta-analysis that examined the issue showed that benefits of reduced hearing loss and neurologic sequelae, but not overall mortality among patients with BM who were treated with adjunctive steroids were observed in developed nations only [Brouwer MC et al. *Cochrane Rev* 2010].

Other potential strategies for improving BM outcomes include selection of highly bactericidal, non lytic antibacterials such as rifampin, which has been shown to reduce β-lactam-induced cytotoxicity in animals [Spreer A et al. *Crit Care Med* 2009], and daptomycin plus ceftriaxone, which has been associated with reduced neuronal injury and hearing loss [Grandgirad et al. ECCMID 2009]. In addition, prompt initiation of antibacterial therapy has been shown to reduce mortality [Proulx N et al. *Q J Med* 2005; Auburtin M et al. *Crit Care Med* 2006] and remains a central tenant of proper treatment.

Human and Animal Viruses Share "One World" and Emerging Zoonotic Infections Continue to Threaten

Written by Noelle Lake, MD

While infectious diseases are no longer a major cause of mortality in developed countries, new viral infections continue to emerge due to our globalizing and changing

world, as well as improved detection methods. In the 2011 ICAAC lecture, Albert Osterhaus, PhD, Erasmus Medical Center, Rotterdam, The Netherlands, made the point that, "the human species is just another animal species that really belongs to an ecosystem." Public health, animal health, the food supply, world economies, and biodiversity all depend on anticipating and controlling new viral outbreaks [Kuiken T et al. *Science* 2005].

Contributing factors for viral crossover from animals include animal contact, human behaviors, urbanization, air travel, wars, poverty, medical practices, and viral adaptation. The ongoing AIDS pandemic is a powerful example of the devastation that can arise from the passage of animal viral strains to humans, as HIV-1 and HIV-2 originated in chimpanzees sooty mangabeys, respectively.

Prof. Osterhaus cautioned that vaccine success comes with potential risks. The eradication of smallpox is perhaps the twentieth century's major medical achievement, but now we are seeing a rise in other Orthopoxviruses in humans, including cowpox and monkeypox, which is fatal in up to 5% of cases [Stittelaar K et al. *Nature* 2006; Pelkonen PM et al. *Emerg Infect Dis* 2003]. Notably, this year marks the second successful global eradication of a mammalian virus, Rinderpest, a morbillivirus viral disease in cattle that is closely related to measles. Other morbilliviruses, however, continue to cause deadly outbreaks among animals year after year, such that even as strides are made toward the global eradication of measles, the possibility of emergence of a human morbillivirus from the animal world is strong and discontinuation of measles vaccine may not be recommended, even if measles is eradicated.

Prof. Osterhaus emphasized that the discovery of new viruses requires a team approach that utilizes clinicians, pathologists, epidemiologists, and laboratory evaluation with both classical virological and novel molecular techniques. The discovery of the severe acute respiratory syndrome (SARS) coronavirus involved identifying a new clinical syndrome, culturing and sequencing the SARS virus, creating an animal model of disease, and then testing antivirals in infected animals. Epidemiologists traced the mammalian source to a similar virus in carnivores in live animal markets in Hong Kong and China, which likely received the virus from bats. Since bats constitute 60% of all mammals on the globe, the virus can be spread quite easily.

Another virus that required fast, coordinated action was West Nile virus (WNV) which was introduced in the United States (US) in 1999, likely via air transport of infected mosquitoes, and spread rapidly across the US via mosquitoes as vectors and birds as intermediate hosts. The first serodetection of WNV in Europe was in 1958 in Albania. With recent cases and virus isolation on several European borders, Prof. Osterhaus and his team are following WNV closely.

Other potentially threatening emerging viruses include human metapneumovirus (hMPV), chikungunya virus, Hendra and Nipah viruses, and avian flu. hMPV crossed the species barrier from birds over 200 years ago and is currently responsible for 10% of the severe respiratory infections in young children. Chikungunya causes a severe flu-like illness and has the potential to spread widely within southeastern US, which shares the same mosquito vector with the northern Italian town where it emerged in 2007. Transmitted from fruit bats, outbreaks of Hendra virus in horses in Australia and the related Nipah virus in pigs in Malaysia caused hundreds of deaths among farmers and handlers in the late 1990s and continues to cause disease throughout Bangladesh [Luby SP et al. *Emerg Infect Dis* 2009].

Avian flu represents a crossover from birds (or sometimes pigs) to humans, and has only occurred in sporadic, isolated cases to date (Table 1). Although avian flu is highly pathogenic and frequently fatal, a pandemic would require that the virus develop better human-to-human transmissibility. Unfortunately, mutant H5N1 strains that have been created in the laboratory have been shown to be transmissible between ferrets, an indication that human-to-human spread could evolve [Munster VJ et al. *Science* 2009].

Prof. Osterhaus concluded by urging international coordination around outbreaks, collaboration between public and private sectors, and use of all available technology for effective control of emerging infections.

Table 1. Recent Zoonotic Transmissions.

Subtype	Country	Year	No. Cases	No. Deaths
H7N7	United Kingdom	1996	1	0
H5N1	Hong Kong	1997	18	6
H9N2	Southeast Asia	1999	>2	0
H5N1	Hong Kong	2003	2?	1
H7N7	Netherlands	2003	89	1
H7N2	USA	2003	1	0
H7N3	Canada	2004	2	0
H5N1	Southeast Asia/ Middle East/Europe/ West Africa	2003-11	>550	>320*

*=CFR~60%

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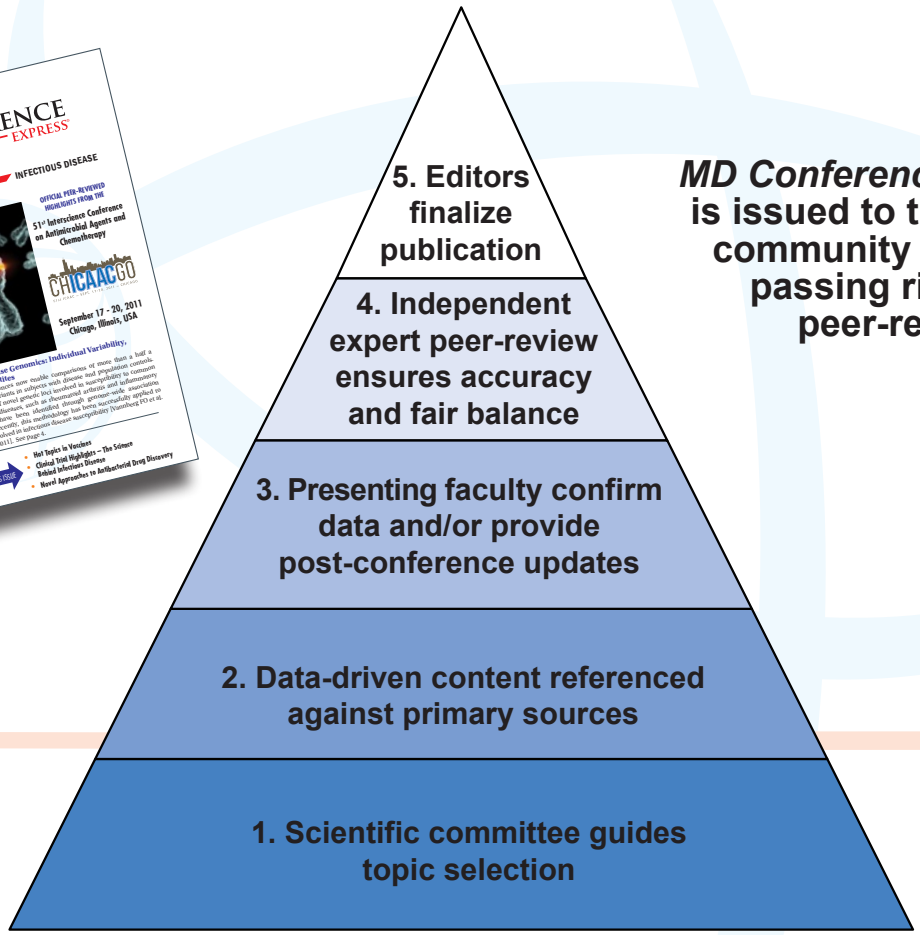

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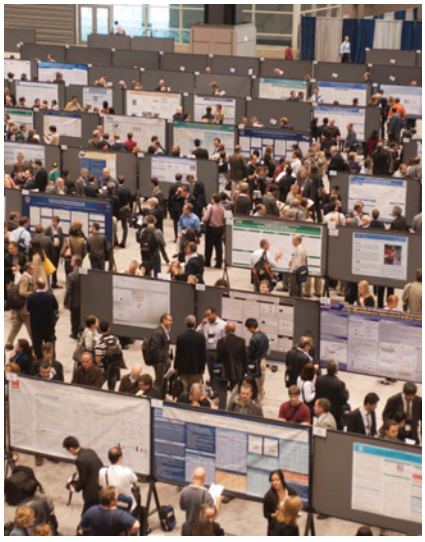

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