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# Infectious Disease [ALERT]

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

## ABSTRACT & COMMENTARY

# Respiratory infections drive inappropriate antibiotic use in ambulatory pediatrics

***By Hal B. Jenson, MD, FAAP***
*Dean, School of Medicine, Western Michigan University School of Medicine,Kalamazoo, MI.*

**Dr. Jenson reports no financial relationships relevant to this field of study.**

SOURCE: Hersh AL, et al. Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics* 2011;128:1053-1061.

A representative analysis of national oral antibiotic prescribing in ambulatory pediatrics was conducted using the National Ambulatory and the National Hospital Ambulatory Medical Care Surveys during 2006—2008 among patients younger than 18 years of age.These surveys, administered by the National Center for Health Statistics, provide geographic sampling data for patient visits to physician practices, hospital outpatient departments, and emergency departments. Visits were categorized based on the primary diagnosis as: respiratory conditions; skin/cutaneous/mucosal conditions; urinary tract infections; gastrointestinal infections; miscellaneous infections; and other conditions.

For respiratory conditions, 3 subcategories were: acute respiratory tract infections for which antibiotics are typically indicated (e.g., otitis media, sinusitis, pharyngitis, pneumonia); acute respiratory tract infections for which antibiotics are not indicated (e.g., nasopharyngitis, bronchitis, viral pneumonia, influenza); and other respiratory conditions for which antibiotics are not definitely indicated (e.g., asthma, allergy, chronic sinusitis, chronic bronchitis). Antibiotics categorized as broad spectrum included antipseudomonal penicillins, β—lactam/β—lactamase inhibitor combinations, second— to fourth—generation cephalosporins, macrolides, quinolones, clindamycin, and carbapenems. Use of topical

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antibiotics was excluded from the study.

There were 10,273 patient visits that were sampled that included prescribing antibiotics. Between 2006—2008, antibiotics were prescribed in an estimated 49 million visits annually (95% CI: 43-55 million), representing 21% of all pediatric ambulatory encounters. Among classes of antibiotics, broad-spectrum antibiotics were prescribed in 50% of the visits for which antibiotics were prescribed, an average of 24.6 million visits annually (95% CI: 21.2—28.1 million). The most commonly prescribed individual antibiotics were for narrow-spectrum penicillins (38%) followed by macrolides (20%).

Among diagnoses, respiratory conditions accounted for 72.3% of visits for which antibiotics were prescribed and included 48.9% of all prescriptions that were for acute respiratory tract infections for which antibiotics are indicated; 13.1% for acute respiratory tract infections for which antibiotics are not indicated; and 10.3% for other respiratory conditions for which antibiotics are not definitely indicated. Thus, 23.4% of antibiotic prescriptions were for respiratory conditions for which antibiotics were not appropriate.

Overall, antibiotics were prescribed for 48.4% of visits for which a respiratory condition was the primary diagnosis. Of the 29.9 million annual visits for acute respiratory conditions for which antibiotics are indicated, 71.7% were prescribed an antibiotic. The next most common diagnostic categories for which antibiotics were prescribed were urinary tract infections (59.3% of 1.4 million annual visits) and skin/cutaneous/mucosal conditions (18.6% of 28.2 million annual visits). Subanalyses showed that relative to other antibiotics, broad-spectrum antibiotics were more likely to be prescribed for acute respiratory infections for which antibiotics are not indicated (OR: 1.80; 95% CI: 1.34—2.42), patients younger than 6 years of age (OR: 1.27; 95% CI: 1.04-1.54), visits in the South compared to the West (OR: 1.82; 95% CI: 1.30-2.55), and less likely to be prescribed among children with public or no insurance compared to those with private insurance (OR: 0.79; 95% CI: 0.66—0.94).

## ■ COMMENTARY

Antibiotic prescriptions are given in 21% pediatric ambulatory visits. Respiratory conditions account for the majority of antibiotic prescriptions in children, with the use of broad-spectrum antibiotics accounting for 50% of antibiotic prescribing and highest for conditions such as viral infections and asthma for which antibiotics are not typically indicated. These data show that respiratory conditions for which antibiotics are potentially inappropriate (23.4%) account for >10 million pediatric visits annually, with >6 million visits with prescriptions for broad-spectrum antibiotics. In addition, the results show that prescriptions are given for only 48.4% of acute respiratory infections for which antibiotics are indicated.

While there are significant limitations of such retrospective analyses, these results show there are substantial gaps in the appropriate use of antibiotics in ambulatory pediatrics. The subanalyses give insights into differences of use among younger children and even practice differences based on geographic region and insurance status.

Antibiotic overuse in pediatrics increases the costs of health care, contributes to avoidable adverse events, and promotes the development of antibiotic resistance. Antibiotic stewardship programs, which have been effective in improving antibiotic prescribing patterns in hospital settings, appear needed in ambulatory pediatric settings to reduce overuse of broad-spectrum antibiotics. ■

SPECIAL FEATURE

# Telaprevir, Boceprevir for HCV: High Cost may warrant 'criteria for use' policies

***By Brenda Le; Paul Hsiao, Pharm D, and Jessica C. Song, M.A., Pharm.D.***

*Jessica C. Song, MA, PharmD, Clinical Supervisor of Pharmacy and Therapeutics, Ambulatory Care, and Mental Health at Santa Clara Valley Medical Center, San Jose, CA, is Associate Editor for Infectious Disease Alert. Brenda Le is a Pharmacy Department Volunteer at Santa Clara Valley Medical Center. Paul Hsiao, is a Pharmacist Specialist in the Purchasing Division of the Santa Clara Valley Medical Center Department of Pharmacy.*

**Brenda Le, Paul Hsiao and Jessica C. Song report no financial relationships relevant to this field of study.**

Hepatitis C virus (HCV) associated liver disease has affected an estimated 180 million people worldwide, and it continues to be the most common indication for liver transplantation.[1] Of the 6 major HCV genotypes, HCV genotype 1 is the most common strain responsible for infections in North America, South America, and Europe.[1] Chronic HCV patients have a 15% to 30% chance of progressing to cirrhosis over the ensuing 3 decades. Moreover, cirrhotic HCV patients are at heightened risk for hepatocellular carcinoma, which occurs at a rate of 1% to 3% per year.[1]

An updated clinical practice guideline for chronic HCV infection was recently developed by the American Association for the Study of Liver Diseases (AASLD).[2] Prior to the publication of the 2011 AASLD guideline for chronic HCV infection, the standard of care for genotype 1 patients was the combination of peginterferon alfa-2a or peginterferon alfa-2b and weight-based ribavirin, administered for 48 weeks.[32] In the updated guideline, the working group recommended the addition of boceprevir, a newly FDA approved NS3/4A protease inhibitor, to peginterferon alfa and weight-based ribavirin after a 4-week lead-in treatment phase of peginterferon alfa/ribavirin in treatment-naïve patients. The duration of treatment depends on the patient's HCV-RNA results at treatment weeks 8,12, and 24; boceprevir treatment duration ranges from 24 to 44 weeks.

For treatment-experienced patients (prior-relapse, partial-responder), the FDA label4 and the updated AASLD guideline[2] recommends the addition of boceprevir to peginterferon alfa and weight-based ribavirin, following a 4-week lead in treatment period, with triple drug therapy lasting from 32 to 44 weeks. Cirrhotic patients require 44 weeks of triple therapy, following 4 weeks of dual therapy with peginterferon alfa and ribavirin. Treatment cessation of all three drugs should be considered if the patient's HCV RNA level exceeds 100 IU/mL at week 12 or week 24.[2]

The 2011 AASLD guideline also recommends the use of another FDA-approved NS3/4A protease inhibitor, telaprevir, for use in genotype 1 HCV patients (treatment naïve and experienced).[2] Unlike boceprevir-treated patients, patients placed on telaprevir do not require a 4-week lead in period. Telaprevir should be used in combination with peginterferon alfa and ribavirin for 12 weeks in both treatment naïve and treatment experienced patients. Of note, telaprevir can be considered for use in prior null responders to a course of dual therapy with peginterferon alfa and weight-based ribavirin.[2] Upon completion of 12 weeks of triple drug therapy, dual therapy with peginterferon alfa and weight-based ribavirin needs to be continued for an additional 12 to 36 weeks, depending on HCV-RNA levels at weeks 4 and/or 12, cirrhosis status, along with prior treatment history.[2,5] Patients who display HCV RNA levels in excess of 1000 IU/mL at treatment weeks 4 or 12 should consider discontinuing all three drugs.[2] With the inclusion of the new protease inhibitors in evidence-based treatment guidelines, formulary decision makers have many factors to consider in developing a strategy for ensuring cost-effective management of genotype 1 HCV patients. Increased drug costs, adherence, adverse effects, and appropriate utilization management are critical issues faced by institutions considering the addition of protease inhibitors to formularies. This article will review cost considerations associated with adding boceprevir or telaprevir to peginterferon alfa/ weight-based ribavirin regimens for genotype 1 HCV patients.

## FORMULATIONS, ADVERSE EFFECTS, ACQUISITION COSTS

Boceprevir is marketed in the U.S. as a 200 mg capsule, priced at $9.06/capsule, and telaprevir is available as a 375 mg tablet, priced at $75.07/ tablet.[4,5] The pill burden of boceprevir might prove burdensome for some chronic hepatitis C patients,

since patients will require 12 capsules a day to meet the recommended dose of 800 mg every 7 to 9 hours.[4] Patients receiving telaprevir will face a lower pill burden, since the dosing regimen of 750 mg every 7-9 hours would require the ingestion of six tablets per day.[5] A 24-week treatment course of boceprevir would cost $18,264.96 and longer treatment courses of 32 weeks to 44 weeks would increase the cost to $24,353.28 and $33,485.76, respectively. A 12-week treatment course of telaprevir would cost $37,835.28.

At Santa Clara Valley Medical Center (San Jose, CA), an estimated 30 to 60 patients will require the addition of boceprevir or telaprevir to peginterferon alfa and weight-based ribavirin in 2012. The estimated cost impact will range from $1,135,058 to $2,270,117 for the addition of telaprevir to the standard dual therapy regimen of peginterferon alfa and weight-based ribavirin. The projected financial impact of adding boceprevir to peginterferon alfa and weight-based ribavirin will depend on treatment duration. The costs of treating 30 to 60 patients with boceprevir for 24 weeks, 32 weeks, and 44 weeks will range from $547,948.80 to $1,095,897.60; $779,304.96 to $1,558,609.92; and $1,473,373.44 to $2,946,746.88, respectively.

Additional costs will be incurred in the management of anemia that may result from the use of boceprevir or telaprevir. Anemia occurred in 43% to 49% of boceprevir-treated patients in Phase III trials, compared with 20% to 29% of patients who received dual therapy regimens consisting of peginterferon alfa and weight-based ribavirin.[6,7] In the SPRINT-2 trial, patients qualified for the use of once weekly subcutaneous injections of erythropoietin 40,000 units if their serum hemoglobin levels dropped to a level of 10 g/dL or lower.[6] Forty-three percent of boceprevir-treated patients required erythropoietin therapy, with mean durations of 94 weeks and 156 weeks in response-guided subjects and fixed-duration subjects, respectively. Nearly 1 in 4 dual therapy (peginterferon alfa and weight-based ribavirin) patients required erythropoietin, with a mean duration of 121 weeks. The cost of once weekly erythropoietin 40,000 units at Santa Clara Valley Medical Center approaches $394. Assuming a percentage increase of 20% for anemia rates in boceprevir-treated patients versus peginterferon-ribavirin-treated patients, the additional cost of using erythropoietin in 6 to 12 patients (20% of 30 to 60 patients) would range from $222,216 to $444,432 (treatment duration of 94 weeks). Study investigators of the REALIZE and ADVANCE studies did not use erythropoietin for the management of anemia in study patients, but reduced ribavirin doses if warranted.[8,9] Anemia occurred in 37% to 39% of telaprevir-treated patients and in 19% to 22% of placebo-treated patients.

## CONCLUSIONS

The addition of telaprevir or boceprevir to the combination of peginterferon alfa and weight-based ribavirin will bring substantial new pharmacy costs to the management of chronic genotype 1 HCV patients. Institutions will likely resort to utilizing "criteria for use" policies that will ensure that appropriate patients will receive these vital, but expensive medications.[10] Coverage criteria should consider the following factors:
(1) exclusion criteria (with special emphasis on checking for non-adherence to prior medications),
(2) inclusion criteria,
(3) limiting prescriptions to a 28-day supply,
(4) treatment duration,
(5) recommended monitoring,
(6) use in specific populations,
(7) drug interactions,
(8) patient education.
County institutions with Medication Assistance Programs may minimize the costs associated with stocking such expensive medications by maintaining a non-formulary status for the drugs. Following approval of non-formulary drug requests, the necessary paperwork required for medication assistance will be submitted by prescribers and patients prior to the dispensing of boceprevir or telaprevir. Despite the great advancement in hepatitis C treatment, the significant pill burden, adverse effect profile, and exorbitant cost of protease inhibitors will necessitate the implementation of appropriate utilization management strategies by institution decision makers. ■

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# Severe Sepsis and Septic Shock in 2012: What Have We Learned?

*By David J. Pierson, MD, Editor*

*Dr. Pierson is Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle.*

**This article originally appeared in the December 2011 issue of Critical Care Alert. At that time it was peer reviewed by William Thompson, MD Associate Professor of Medicine, University of Washington, Seattle. Dr. Pierson reports no financial relationships relevant to this field of study.**

When I was a medicine resident 40 years ago just as the first ICUs were being introduced, treatment for life-threatening bacterial infections consisted of antibiotics, control or removal of the primary source, intravenous fluids, and vasopressors. The intervening decades have brought unimaginable technical advances in critical care, as well as the ability to cure some conditions that were once uniformly fatal and to greatly extend survival in many incurable but now-treatable diseases. Since I trained, we have refined our concepts and clinical classification of sepsis, with gradations of severity from SIRS (the systemic inflammatory response syndrome), to sepsis, to severe sepsis, to septic shock. In North America, the last two of these sepsis categories develop in some 750,000 patients each year, and one-third of them die. What progress have we made in their treatment? I will briefly consider several aspects of this question, a number of which are discussed in more detail by Suffredini and Munford in a recent review.[1]

## THE RISE AND FALL OF XIGRIS

On, October 25, 2011, Eli Lilly and Company announced a worldwide voluntary market withdrawal of Xigris (drotrecogin alfa [activated])[2,3] bringing to a close a decade of contention and controversy since that drug was first introduced in critical care. The Xigris story illustrates several aspects of the challenges facing attempts to improve care for patients with severe sepsis and septic shock.

Drotrecogin alfa (activated), also known as activated protein C (APC), represents an attempt to target an aspect of the sepsis process itself rather than the causative microorganism. It is a recombinant anticoagulant protein intended to inhibit the widespread thrombosis that occurs in sepsis, and thus to ameliorate at the tissue level the multiple organ dysfunctions that lead to morbidity and mortality in this condition. The initial clinical trial of APC in severe sepsis and septic shock (the PROWESS trial)[4] was stopped early because an interim data analysis showed a 6.1% decrease in 28-day mortality among patients who received the new agent, and it was promptly approved by the Food and Drug Administration (FDA) for use in patients with sepsis and APACHE II scores > 25, indicating a high risk of death.

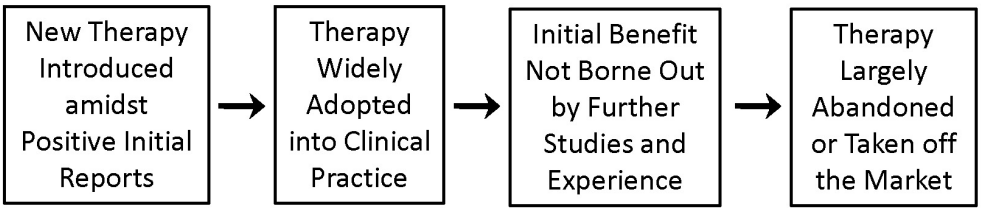
From the beginning, APC was controversial, not only with respect to its clinical effectiveness and adverse effects (primarily hemorrhage, sometimes fatal) but also because of its manufacturer's marketing and alleged role in the promulgation of worldwide practice guidelines and clinical bundles for sepsis management. Studies subsequent to the PROWESS trial were generally unable to confirm its positive results. A trial of APC in patients with severe sepsis who were less severely ill (with APACHE II scores < 25) was stopped early because of futility,[5] as was a trial in pediatric patients.[6] A clinical trial of APC vs placebo in acute lung injury and the acute respiratory distress syndrome in patients who did not have severe sepsis and APACHE II scores > 25 also showed no survival benefit.[7]

Because of growing concern about the efficacy of APC, even in its original high-risk patient population, in 2007 the European Medicines Agency asked Eli Lilly to essentially repeat the original PROWESS study.[8] The results of this second trial (PROWESS-SHOCK)[9] have recently been made public. Data from the company, subsequently submitted to the FDA, showed a 28-day, all-cause mortality rate of 26.4% (223/846) in APC-treated patients as compared to 24.2% (202/834) in the placebo group (relative risk, 1.09; 95% confidence interval, 0.92-1.28), with a non-significant *P* value of 0.31.[3] Because of this, and in keeping with the findings of a recent Cochrane Review that recommended APC not be used because of lack of evidence of efficacy and substantial risk for adverse effects,[10] the company withdrew the drug from the market worldwide.

## EFFECTIVENESS OF OTHER NEW AGENTS FOR SEPSIS

Numerous other new agents have been studied in treating patients with severe sepsis and septic shock.[1] Because multi-organ dysfunction is both a primary manifestation of severe sepsis and a main determinant of overall patient outcome, much investigation has focused on interfering with

**Figure. Natural History of Many Breakthroughs in Critical Care**




Chronological history of many new therapies and other putative innovations in critical care, as exemplified for sepsis management by APC. This sequence may also turn out to apply to several other currently recommended approaches to managing severe sepsis and septic shock. The timing may vary, although APC's 10-year life is in keeping with those of many new drugs and non-pharmaceutical interventions in critical care.

systemic inflammation and its mediators. After an initial positive report of the use of anti-endotoxin serum in sepsis, subsequent trials of anti-endotoxin monoclonal antibodies showed no benefit. Studies of polyclonal immunoglobulin, also aimed at neutralizing endotoxin and preventing its adverse effects, have been disappointing. Clinical trials of agents targeting individual pro-inflammatory mediators, such as tumor necrosis factor, platelet-activating factor, bradykinin, and others, have been negative despite favorable preliminary reports.

Examination of multiple such studies suggests that failure to demonstrate overall survival benefits may be due in part to divergent effects of at least some of these agents in different patients.[1] For example, because the studied therapies have their own risks, positive effects on survival in the most severely ill patients may be masked by worse outcomes due to adverse effects in patients with milder illness. This remains speculative, although it is a point in favor of careful stratification of illness severity and other factors potentially related to outcome in such trials.

## OTHER ASPECTS OF SEPSIS MANAGEMENT

The use of high-dose corticosteroids in patients with severe sepsis and septic shock goes back five decades, but analysis of the numerous clinical trials conducted into the late 1980s showed that this actually worsened survival, and it was abandoned. By the turn of the century, though, there had been an upsurge of interest in the use of steroids in lower, "replacement" doses, for longer courses than had been given earlier, which was associated in multiple relatively small studies with both decreased vasopressor use and improved survival. The administration of low-dose corticosteroids is a feature in many current guidelines, although the clinical benefit of this and how steroids should best be used remain to be established definitively.

Because of associations of infection and other adverse outcomes with hyperglycemia in critically ill patients, its avoidance has emerged during the last decade as an important topic in sepsis management. An initial study showed improved survival in ICU patients with intensive insulin therapy and careful control of serum glucose levels, and so-called "tight glucose control" was both widely embraced in clinical practice and incorporated into practice guidelines. However, subsequent studies in other patient populations and practice settings have demonstrated increased hypoglycemia-related complications and less clear outcome benefits. Again, although the control of glucose levels continues to be included in many current guidelines for managing sepsis and other critical illness, it is doubtful that we have heard the final word in this area.

A facet of sepsis management that has profoundly influenced both clinical practice guidelines and institutional policies is what has come to be known as early goal-directed therapy (EGDT). This is a package of assessments and interventions aimed at identifying the presence of sepsis, assessing its severity in terms of adequacy of tissue perfusion, and initiating therapy as quickly as possible — within 6 hours in all cases. Although the EGDT approach is only 10 years old, and essentially based on the results of one single-center clinical trial,[11] current evidence and clinical consensus support the concept that this may be the most important innovation in recent decades for improving outcomes in severe sepsis and septic shock.

## WHAT HAVE WE LEARNED?

Progress in the management of sepsis, like that in mechanical ventilation for severe respiratory failure and in numerous other aspects of critical care, proceeds in identifiable cycles. One such cycle, particularly when potential innovations have commercial implications, is illustrated in the Figure above.

A new therapy or approach, typically with a sound pathophysiologic rationale, is introduced on the basis of initial reports of benefit. In the case of pharmaceutical agents like APC, this requires preliminary clinical studies to meet FDA requirements, although with novel ventilator approaches and new medical devices much less preliminary investigation is usually carried out. Because of promotion by advocates and/or corporate marketing efforts, the new therapy becomes well known and is put into wide clinical use, perhaps even finding its way into institutional protocols and guidelines issued by professional groups. It is typically only after this point that more extensive studies are undertaken. These further studies, frequently larger and better controlled for bias and confounding than the initial reports, typically demonstrate that the new therapy or approach is less effective than initially hoped — or no better than previous therapies, or even worse. There are many examples of this in critical care.

The construct shown in the Figure is a gross oversimplification of the challenges to innovation in the complex environment of the ICU, and it is not meant as a condemnation of the system. For clinicians confronted by high-mortality illnesses and imperfect therapies, motivation to embrace new interventions with the potential for better patient outcomes is to be expected and hard to criticize. And the fact is that most of what we do in the ICU — including the management of severe sepsis and septic shock — rests on a foundation that is much less than completely solid.

Prompt initiation of antibiotic therapy, after appropriate cultures are obtained, has stood the test of time as perhaps the most important aspect of sepsis management. There seems little doubt that antibiotic therapy should be tailored to the patient and the clinical context, including:

- The patient's underlying health and immune status
- Whether the infection is community- or health care-associated
- Recent antibiotic treatment
- Local organism prevalence and antibiotic resistance patterns
- Available specific microbiological data, such as Gram stain findings and previous culture results

Antibiotic therapy, source control, supplemental oxygen, protection of the airway, and mechanical ventilation if needed remain clear requirements for managing severe sepsis and septic shock. Beyond these, however, the clinician faces many uncertainties. A few of the latter are the following:

- Assessment and monitoring of the adequacy of tissue perfusion — physical exam vs serum lactate vs central venous oxygen saturation vs gastric tonometry
- Intravenous fluids — how much; what kind
- Vasopressors — which one(s); optimal usage
- Inotropes — whether to use; if so, which one(s)
- Red blood cell transfusion — when; how much
- Serum glucose — desirable ranges; how to control most effectively and safely
- Corticosteroids — whether to use, how to assess, which one, how much, and how long
- Procalcitonin and other potential indicators of inflammation and response — clinical value; whether and how to use

Severe sepsis and septic shock are among the most common and vexing challenges confronting the intensivist. Although critical care now deals with different types of patients and takes place in a far different environment than was the case four decades ago, many of the most important aspects of managing these conditions have not changed very much. Sepsis remains one of the most active and important areas of critical care research, and help with the controversies and unknowns described above is to be hoped for — and expected — in the future. ■

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# The Globalization of Antibiotic Resistance — India and Cambodia

***By Ellen Jo Baron, PhD, D(ABMM),***

*Professor of Pathology and Medicine, Stanford University; Medical School Director, Clinical Microbiology Laboratory, Stanford University School of Medicine, is Associate Editor for Infectious Disease Alert.*

**Conflict of interest: Ellen Jo Baron is a co-founder and Secretary-Treasurer of Diagnostic Microbiology Development Program, a non-profit corporation that builds laboratory capacity in the resource-poor world. (More information at www.dmdp.org)**

During November, 2011, I attended separate meetings dedicated to exploring the incidence of antimicrobial resistance in two areas of the developing world, India and Cambodia. The first, sponsored jointly by the American Society for Microbiology (ASM), the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), and the Indian Association of Medical Microbiologists (IAMM), was named the "International Workshop on Antimicrobial Resistance" and was held at the Haffkine Institute in Mumbai, India. Organized by Prof. Lance Peterson (ASM representative), Prof. Abhay Chowdhary (Director of Haffkine Institute), Prof. V. Ravi (President of the IAMM), and Prof. Guiseppe Cornaglia (President of ESCMID), the workshop brought together around 250 participants, principally from India, to discuss various aspects of antimicrobial resistance over a 2.5 day program.

One key topic was susceptibility methods, including the use of new molecular tools and a comparison between laboratory practice guidelines established by the Clinical Laboratory Standards Institute (CLSI; used throughout the U.S. and in those resource-poor laboratories in the rest of the world fortunate enough to have support from an outside non-governmental organization) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST; used in Europe and in many parts of the developing world). Since the CLSI changed many of the breakpoints used to determine resistance to cephalosporins and carbapenem antibiotics, the two guidelines are very similar with regard to methods and interpretive criteria. Also presented were talks on the epidemiology of resistance among viruses, parasites and fungi, in addition to the major focus on bacteria.

Of interest to infectious diseases practitioners in the U.S. was the prevalence of drug resistance among gram-negative bacteria, particularly given the numbers of American workers who travel back and forth between India and the U.S. and the rise in medical tourism to India, as these travelers are potentially capable of bringing a dangerously drug-resistant bacterium back with them to a hospital or clinic in the U.S. A recent publication from Sweden highlighted this problem, showing that 7 of 8 tourists returning from India were colonized with an extended spectrum beta-lactamase producing organism that they had acquired overseas. One of the most recently recognized such hitchhikers is the New Delhi type 1 metallo-beta-lactamase (NDM-1), now an emerging pathogen in the United States. According to Dr. Ashok Rattan, Chairman of Laboratory Medicine at Medanta Medicity Medical School Gurgaon, near New Delhi, one of the presenters, use of antibiotics has increased dramatically in India in recent years. Dr. Rattan previously published that between 2005 and 2009, the units of antibiotics sold increased by about 40%. Increased sales of cephalosporins were particularly striking, with sales (in units sold) increasing by 60% over the 5-year period.[2] In 2010, one survey from a hospital in Mumbai showed that NDM-1 was carried by 92% of carbapenem resistant *Enterobacteriaceae*, including *Klebsiella*, *Enterobacter* species, and *E. coli*.[1] This is not the only resistance mechanism in Enterobacteriaceae from India, as another survey revealed The organisms were collected from two different sites, Chennai (formerly Madras) in the southeast with 4% carbapenem-resistant isolates from >3500 *Enterobacteriaceae* tested and Haryana in the north central area near New Delhi with 24% carbapenem-resistant organisms (all *K. pneumoniae*) from among only 198 tested.

Reasons for this alarming situation include broad availability of antibiotics, many obtained over-the-counter without prescriptions and many of low quality or suffering from inadequate storage conditions leading to loss of potency and thus enhancing the chance that patients' isolates will develop resistance. Additional reasons are inadequate dosing when antibiotics are taken, poor infection control processes in many hospitals, and somewhat surprisingly, the lack of adequate public hygiene and inadequate water treatment facilities. Yes, bacteria producing

NDM-1 were found in drinking water and water sources in the community in New Delhi.9 (9) But another reason for the rapid spread of these resistant organisms is the lack of ability of local laboratories to isolate the organisms and perform adequate antimicrobial susceptibility tests.

Unfortunately, methods for testing the organisms are changing, with no one method considered optimal except for molecular methods, which are beyond the capabilities and resources of those laboratories most likely to encounter the organisms.[5,7] When countries do not have surveillance information on the extent of resistant organisms in their patients and the environment, there is very little incentive to develop national policies on antibiotic utilization, including limiting distribution to accredited providers.

This is clearly a major problem in Cambodia, where the first National Workshop on the Containment of Antibiotic Resistance was held in Phnom Penh November 16-18. The conference was initiated by scientists from the Institute of Tropical Medicine, Antwerp, Belgium, which supports the laboratory at the Sihanouk Hospital Center of Hope, and workers from Mahidol Oxford Tropical Medicine Research Unit, who support microbiology at Angkor Hospital for Children in Siem Reap (home of the Angkor Wat). Conveners and supporters also included the Cambodian Ministry of Health, World Health Organization, Fondation Merieux, University Research Company (URC) Cambodia, and numerous other NGO's including my own Diagnostic Microbiology Development Program, which supports laboratories in Battambang, Kampong Cham, Takeo, and Phnom Penh.

One reason that this conference could be achieved is the growing ability of at least some local laboratories in Cambodia to perform reliable microbiology testing, albeit so far limited and only with the help of volunteers from abroad. The increasing expertise of local microbiologists is a hopeful sign for the future, where previously there were minimal resources available for patients who were not in the upper political or economic (actually they occur together) echelons.

Although MRSA had not penetrated Cambodia in any serious way 3 years ago, with only 3.5% of children colonized, as determined from a large scale surveillance conducted in Siem Reap in 2008 and reported last year, this has changed dramatically, at least at some centers who presented data at the workshop.[6] Representatives from the Sihanouk Hospital, located in the capital city Phnom Penh, presented data from 500 blood culture isolates recovered from adult patients since 2007. The results revealed 22% of S. aureus isolates were MRSA.This high rate of MRSA was not limited to Phnom Penh. Pharmacist Nhem Somary from Kampong Cham (located 124 km northeast of Phnom Penh and also on the Mekong River), presented her data showing 45% MRSA among staphylococcal isolates from all sites. The laboratory in the hospital in Takeo, a town 77 km south of Phnom Penh, found that 22% of *S. aureus w*ere MRSA.

And not surprisingly, multi-drug resistant gram negative bacteria are rampant in Cambodia, which is the 37th poorest country in the world according to some measurements, with an annual per capita income of around US $2100. Half of the bloodstream E. coli isolated at the Sihanouk Hospital laboratory were ESBL positive and multi-drug resistant; 70% of Salmonella typhi (the most common blood culture organism) demonstrated decreased susceptibility to fluoroquinolones and were multi-drug resistant.
These numbers were echoed by scientists from the United States Naval Army Medical Research Unit (NAMRU-2) who conducted targeted surveillance of *S. typhi* in Cambodia. Their well-controlled results revealed multi-drug resistance in 56% of all strains tested. The Kantha Botha pediatric hospitals (located in several major cities of Cambodia) reported on a recent increase in *Salmonella cholerasuis* bloodstream infections, primarily in children <2 years old. They also showed dramatic decreases in susceptibilities to amoxicillin-clavulanate, ofloxacin, and ceftriaxone in *E. coli* urinary tract isolates since 2003.

At Kampong Cham, although Pseudomonas aeruginosa isolates were quite susceptible to most antibiotics (only piperacillin and ceftazidime showed resistance, and then only <5%), more than half of the Klebsiella species showed resistance to all cephalosporins and the E. coli isolates were pan-resistant to all major antibiotics tested except imipenem. The Institute Pasteur, which receives reference cultures for testing from a number of clinics and other facilities throughout the country, so the data are gathered from a convenience sample rather than epidemiologically conducted surveillance, reported 20% MRSA, 30% ESBL in *E. coli*, 18% carbapenem resistance among *Acinetobacter* species, and a worrisome 3.5% resistance to cefixime among *Neisseria gonorrhoeae*.

Although there is a clear need based on the data and many presenters requested government action, a national policy on antimicrobial stewardship was not put forth by the Ministry of Health officials at the workshop. Instead, they have decided to focus on improving infection control

efforts where they felt they had sufficient resources to make some progress. In a country where antibiotics of varying reliability are available universally to anyone with the money to pay for them, the situation of drug resistance is likely to become even worse in the future. Thus the name of the conference "…Containment of Antibiotic Resistance…" would seem to be more wishful than prescient, at least for the near future.

Physicians in the industrialized world need to realize the potential for the presence of multi-drug resistant organisms (MDRO's) in patients with compatible travel history, and institute appropriate infection control and treatment algorithms.10 (10) Microbiology laboratories also need to be notified so that they will perform all available tests necessary to detect MDRO's in samples sent from these types of patients. Given that there is a growing movement in the developed world to perform surveillance cultures on patients at risk for carriage of MDRO's, surely travelers returning from the developing world should be added to that category. ■

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## ABSTRACT & COMMENTARY

# Absence of pathogens in intestinal tissue of patients with necrotizing enterocolitis


***By Dean L. Winslow, MD, FACP, FIDSA,***

*Chief, Division of AIDS Medicine, Santa Clara Valley, Medical Center; Clinical Professor, Stanford University School of Medicine, is Associate Editor for Infectious Disease Alert.*

**Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostic.**



**SYNOPSIS:** 28 surgical specimens from patients with necrotizing enterocolitis (NEC) were examined using multiplex real-time polymerase chain reaction (RT-PCR) to detect gastrointestinal pathogens. Infectious enteritis pathogens were not detected in any specimens.



SOURCE: Ullrich T, et al. Absence of gastrointestinal pathogens in ileum tissue resected for necrotizing enterocolitis. *Ped Infect Dis J* 2012; epub ahead of print.


Fresh ileum tissue specimens from infants with NEC or non-NEC diagnoses were provided by the Pathology departments at the children's hospitals at Vanderbilt and at University of Illinois. Standard methods of nucleic acid extraction were employed. Multiplex RT-PCR was used to detect 15 bacterial and viral pathogens (including Salmonella, Shigella, Campylobacter, *C. difficile* toxin A/B, ETEC, *E.coli* O157, STEC E. coli, V.cholerae, Yersinia, Giardia, *Entamoeba histolytica*, Cryptosporidium, Adenovirus 40/41, Rotavirus, and Norovirus). 23 ileum samples from 22 cases of NEC, 14 samples from non-NEC controls, 1 tissue sample from a child with confirmed Giardia enteritis, and one stool specimen from a child with Norovirus infection were examined. Median gestational age of

NEC patients was 28.2 weeks and all samples were collected between 2007 and 2011. All of the NEC and non-NEC tissue specimens were negative for gastrointestinal pathogens included in the multiplex assay. The two positive controls were strongly positive for Giardia and Norovirus respectively.

**■ COMMENTARY:**
NEC is a severe and poorly understood complication of prematurity characterized by a generally irreversible inflammatory process leading to bowel necrosis. It occurs in 7% of infants less than 1,500 grams at birth and is associated with significant morbidity and mortality with most patients requiring surgical resection of variable amounts of small bowel. Anecdotal reports and small case series have suggested etiological roles for a variety of gastrointestinal pathogens including *C. difficile*, C. perfringens, E. coli, adenovirus and other enteric viruses. Formula feeding has also been implicated by association in many case series.

This study, which utilized a sensitive and specific multiplex RT-PCR technique, is an important advance in our understanding of this disease, and may reduce the use of unnecessary and potential harmful antibiotics in the NICU, which are often given empirically for treatment of NEC. While the multiplex PCR method used in this study ruled out the presence of the specific pathogens examined, it may still be of use to repeat this study using broad-spectrum 16S rDNA PCR primers to look for potentially unidentified potential pathogens. However, the present study along with the lack of histopathological evidence of bacterial pathogens in resected specimens suggests that infectious agents are not generally causal in NEC. ■

Infectious Disease [ALERT]

# Updates

By Carol A. Kemper, MD, FACP

## XDR gone TOTALLY Resistant?

Source: ProMED-mail alert January 13, 2012; promedmail.org

Following reports of the discovery of a strain of totally-drug resistant *M. tuberculosis* (TDR-TB) infecting 4 individuals in a Mumbai Hospital this month, another hospital in Bangalore may have identified two additional patients infected with an equally resistant strain of MTb. And the scary news is that one of the two patients seems to have gone AWOL and has not been seen for 2 weeks. Totally-drug resistant strains of MTb do not respond to any recognized antimycobacterial agent.

The two patients were being cared for at the Rajiv Ghandi Institute for Chest Disease (RGICD) in Bangalore, a public hospital that provides care for patients with active MTb, including those with resistant MTb. The patients are a 29-year old woman and a 56-year old man, and were initially receiving treatment for MDR-TB. After failing to respond to 8 months of initial therapy, their sputum culture results indicated the development of XDR-TB (eXtremely drug resistant version of the organism, which means they had developed resistance to at least 3 classes of antimycobacterial drugs). Both have now been treated for approximately 2.5 years, and both show evidence of ongoing treatment failure. Conflicting reports from the RGICD suggest that sputum cultures from both are now consistent with a totally-drug resistant strain, although specialized microbiologic susceptibility testing has not yet been performed.

Even worse, the RGICD failed to notify authorities regarding their findings and that the patient, who remains infectious, was missing. Sounds like India needs to tighten up their public health policies. ■

## Aspergillosis in the ICU patient

Source: Hsu JL, et al. Diagnosing invasive fungal disease in critically ill patients. *Critical Rev Micro* 2011; 37(4):277-312.

Twice in the past year, I've been asked to evaluate the clinical significance of a positive sputum or endotracheal specimen for *Aspergillus spp*. in a critically ill non-immunocompromised cardiac surgery patient in the ICU. Both patients grew scant amounts of *Aspergillus fumigatus* from two or more respiratory specimens in the absence of any recognized malignancy or immunosuppression. Neither was a candidate for endobronchoscopic lung biopsy at the time of consultation, which may have been helpful in determining the presence of invasive disease. Both had underlying COPD; one had been treated with a single dose of methylprednisolone; and the other (from China) had a positive gamma-interferon TB blood test, and evidence of old healed MTb on chest radiographs. How significant was this information?

This helpful review by Hsu and colleagues examines the host and risk factors, and clinical and radiographic findings in patients with invasive fungal disease (IFD) in the ICU setting. Because diagnostic techniques are often inadequate at confirming IFD in critically ill patients in the absence of histopathologic data demonstrating invasive disease, the diagnosis can be problematic. Available serologic studies provide poor test performance, a high frequency of false-positives, and delayed results.

An awareness of risk factors and host factors is important. Beyond the usual overt immunosuppression, risk factors include corticosteroids, indwelling central venous catheters, the use of prolonged antibiotics and total parenteral nutrition, breakdown of mucosal surfaces, and renal failure. Certain groups of non-immunocompromised patients are also at increased risk for fungal infection, including patients with a history of COPD, bronchiectasis, previous pulmonary tuberculosis, and cirrhosis. Among 89 ICU

patients without malignancy diagnosed with invasive aspergillosis, 42% had COPD and 7% had cirrhosis. Another study found that, among 65 COPD patients diagnosed with invasive aspergillosis, the mean forced expiratory volume was 39% of predicted (consistent with severe disease), the mean corticosteroid use was 24 mg per day, and the mortality was 91%.

The authors advocate a "diagnosis centered approach" including prompt CT scanning and bronchoalveolar lavage (including BAL-b-D-glucan testing), and the use of CT-guided percutaneous lung biopsy in non-mechanically ventilated patients whenever possible. As many specimens as possible should be submitted to the lab for respiratory culture, blood fungal culture, and non-culture techniques, such as galactomannin and b-D-glucan [This should b as in "Beta" symbol.] testing of blood; Cryptococcal antigen of blood is relatively easy and reliable.

Radiographically, fungal lung infection may present differently in non-immunosuppressed patients compared with those with immunosuppression. For example, in one survey of critically ill patients without malignancy diagnosed with invasive aspergillosis, only 17% exhibited the "classic" halo sign; other radiographic findings such as bronchpenumonia, atelectasis and pleural effusion were more common. In another survey, only 6% of COPD patients without malignancy with invasive aspergillosis exhibited a halo sign. More commonly such patients with IFA may exhibit bronchopneumonia, centrilobular nodularity, a "tree-in-bud" pattern, peribronchial changes, or ground glass attenuation. The typically angioinvasive disease, with macronodules > 1 cm are not as likely to occur, as the disease typically begins with a respiratory portal of entry. ■

## CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

## CME QUESTIONS

**1. Which of the following is correct?**

A. Telaprevir is recommended as mono therapy for chronic hepatitis C virus infection.
B. Neither boceprevir nor telaprevir is associated with the development of anemia in patients receiving treatment for chronic hepatitis C virus infection.
C. A lead-in period of treatment with pegylated interferon alpha and ribavirin is recommended prior to the addition of boceprevir in the treatment of patients with chronic hepatitis C virus infection.
D. A lead-in period of treatment with pegylated interferon alpha and ribavirin is recommended prior to the addition of telaprevir in the treatment of patients with chronic hepatitis C virus infection.

**2. Which of the following should be considered in choosing an initial antibiotic regimen for a patient with severe sepsis or septic shock?**

A. The patient's underlying immune status
B. Whether the infection is community-acquired or health care-associated
C. Local microbial antibiotic resistance patterns
D. Results of Gram stain and/or recent cultures
E. All of the above

**3. Which of the following was found to be associated with necrotizing enterocolitis in infants?**

A. *Clostridium difficile*
B. Adenovirus
C. Enteropathogenic *E. coli*
D. None of the above.

## CME OBJECTIVES

**Upon completion of this educational activity, participants should be able to:**

- discuss the diagnosis and treatment of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.

## [IN FUTURE ISSUES]

Methicillin-Resistant S. aureus Meningitis in Adults: A Multicenter Study of 86 Cases.

Immunologic Response to Oral Polio Vaccine in HIV-infected and Uninfected Zimbabwean Children.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

# New, Shorter Treatment Regimen for Tuberculosis

***In this issue:*** New treatment for TB; safety of dabigatran; quality of antidepressants; systolic hypertension treatment; and FDA actions.

## Short course treatment for latent TB

Three months of two drugs administered once weekly is as effective as 9 months of daily isoniazid (INH) for the treatment of latent tuberculosis infection (LTBI), according to a new study. An international team of researchers randomized nearly 8000 patients with latent tuberculosis (TB) to 3 months of directly observed once-weekly therapy with rifapentine 900 mg plus INH 900 mg or 9 months of self-administered daily INH 300 mg. The primary endpoint was confirmed TB after 33 months of follow-up. In the modified intention-to-treat analysis, TB developed in 0.19% of the once-weekly combination group and in 0.43% of the INH only group. Rates of completion were much higher with the short course, once-weekly regimen (82.1% in the combination-therapy group and 69.0% in the INH only group, $P < 0.001$). Rates of hepatotoxicity were higher in the INH only group. The authors conclude that use of rifapentine plus INH given once a week for 3 months is as effective as 9 months of INH in preventing tuberculosis and has a higher treatment-completion rate (*N Engl J Med* 2011;365:2155-2166). Based on this study and others, the CDC has issued a new recommendation on the use of short-course combination therapy for latent TB infection. The recommendation states, "The new regimen is recommended as an equal alternative to the 9-month INH regimen for otherwise healthy patients ≥ 12 years who have LTBI and factors that are predictive of TB developing (e.g., recent exposure to contagious TB)." It also recommends that the new regimen may be considered for other categories of patients when it offers advantages. Daily INH continues to be the preferred regimen for children between the ages of 2 and 11 (*MMWR Morb Mortal Wkly Rep* 2011;60:1650-1653). ■

## Bleeding concerns with dabigatran

Dabigatran (Pradaxa), Boehringer Ingelheim's blockbuster anticoagulant, is the subject of a December 7, 2011, Drug Safety Communication by the FDA regarding serious bleeding events. The FDA is evaluating postmarketing reports of serious bleeding events that may lead to serious or even fatal outcomes. Experts are working to determine whether the reports of bleeding associated with the drug are occurring more commonly than would be expected based on observations from large clinical trials. The drug was approved in October 2010 to reduce the risk of stroke in patients with non-valvular atrial fibrillation. More than a million prescriptions have been filled by nearly 400,000 patients since approval. ■

## All antidepressants are created equal

When it comes to choosing an antidepressant, all modern drugs are roughly equivalent, according to a new study in the *Annals of Internal Medicine*. Researchers performed a large meta-analysis of 234 studies that looked at the treatment of major depressive disorder (MDD) with second-generation anti-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

depressants. There were no differences among the drugs with regard to efficacy or effectiveness for the treatment of acute, continuation, and maintenance phases of MDD. There were also no significant differences when accompanying symptoms were taken into account or other factors such as age, sex, ethnicity, or comorbid conditions. There were differences among the drugs with regard to onset of action, adverse effects, and some quality-of-life issues. There was also a significant difference in cost and dosing convenience. Drugs considered in the study were bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine. The authors suggest that familiarity with the broad spectrum of antidepressants is prudent given the difficulty of predicting which medication will be effective and tolerated by any given patient (*Ann Intern Med* 2011;155:772-785). ■

## Benefits of treating systolic hypertension

Older adults with isolated systolic hypertension gained about 5 months of life when treated with chlorthalidone-based stepped care 2 decades after completion of the Systolic Hypertension in the Elderly Program (SHEP) trial. SHEP, conducted between 1985 and 1990, was a clinical trial of patients aged 60 years or older (mean age 72) with isolated systolic hypertension who were randomized to chlorthalidone-based antihypertensive therapy or placebo. Over a mean follow-up of 4.5 years, chlorthalidone-based therapy resulted in prevention of approximately 1 of 2 admissions for heart failure, 1 out of 3 fatal or nonfatal strokes, and 1 of 4 coronary heart disease events, but there was no effect on all-cause mortality or cardiovascular death. At the end of the trial, all participants were advised to receive active therapy. The new study reviewed cardiovascular death and all-cause mortality in SHEP trial participants 22 years after the study ended. Life expectancy gain between the active treatment group and placebo group was 105 days (95% confidence interval [CI], -39 to 242; $P = 0.07$) for all-cause mortality and 158 days (95% CI, 36-287; $P = 0.009$) for cardiovascular death. Each month of active treatment was associated with approximately 1 day extension in life expectancy. The authors conclude that treatment of isolated systolic hypertension with chlorthalidone stepped-care therapy for 4.5 years was associated with longer life expectancy at 22 years of follow-up (*JAMA* 2011;306:2588-2593). This study may help convince older patients with systolic hypertension that compliance with diuretic-based hypertensive therapy is worth the effort as it will prolong their lives. ■

## Aliskiren and ACEIs/ARBs don't mix

Aliskiren (Tekturna), Novartis' direct renin inhibitor, should not be combined with an ACE inhibitor or angiotensin receptor blocker (ARB) to treat hypertension, according to the manufacturer. Novartis recently terminated the ALTITUDE trial when it was found that patients with type 2 diabetes or impaired renal function who were given the combination of aliskiren with an ACEI or ARB had a higher incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension. More information can be found at www.novartis.com/newsroom/media-releases/en/2011/1572562.shtml. ■

## FDA actions

**The FDA approved generic atorvastatin (Lipitor) on November 30, 2011.** Ranbaxy Laboratories will make the first generic in 10, 20, 40, and 80 mg strengths. Atorvastatin as Lipitor was first marketed in 1997 and became the best-selling prescription medication in history with sales of more than $125 billion. It has dominated the statin market in recent years, representing nearly a quarter of Pfizer's annual revenue, and the giant pharmaceutical company aggressively defended their patent against multiple challenges. Ranbaxy has 180 days of exclusivity on generic atorvastatin after which time multiple manufacturers are expected to seek approval for their generic version of the drug.

**The FDA has approved Prevnar 13 for adults age 50 and older to prevent pneumonia and invasive disease caused by *Streptococcus pneumoniae*.** The vaccine was previously approved for children up to 5 years of age. The approval was based on head-to-head studies with Pneumovax 23 which is already approved for use in adults. According to the FDA, "for the 12 common serotypes, Prevnar 13-induced antibody levels were either comparable to or higher than the levels induced by Pneumovax 23." Prevnar 13 is manufactured by Wyeth Pharmaceuticals.

**Dronedarone (Multaq) should not be prescribed to patients with permanent atrial fibrillation (AF), based on results from the PALLAS trial which showed that the drug doubles the risk for cardiovascular death, stroke, and heart failure in such patients.** The FDA is requiring revised labeling for the antiarrhythmic drug and has issued a Drug Safety Communication after a safety review was completed. If dronedarone is to be prescribed, the FDA recommends ECGs every 3 months and immediately stopping the drug if the patient is found to be in AF. The drug is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of non-permanent AF (paroxysmal or persistent AF). Dronedarone is manufactured by Sanofi-Aventis. ■