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## INSIDE



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*Infectious Disease Alert's* Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth and does research for Merck.
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# Dissemination of Metallo-β-Lactamase Gene blaIMP-4 Among Gram-Negative Pathogens in a Clinical Setting

ABSTRACT & COMMENTARY

***By Robert Muder, MD***

*Hospital Epidemiologist, Pittsburgh VA Medical Center*

*Dr. Muder does research for Aventis and Pharmacia.*

***Synopsis:*** *Investigators reported finding the presence of a metallo-β-lactamase gene mediating resistance to multiple β-lactam antibiotics, including carbapenems, among multiple species of Gram-negative pathogens isolated from a single hospital in Australia. Epidemiologic and molecular evidence suggested horizontal transmission of a mobile genetic element.*

**Source:** Peleg AY, et al. Dissemination of Metallo-β-Lactamase Gene blaIMP-4 Among Gram-Negative Pathogens in a Clinical Setting in Australia. *Clin Infect Dis*. 2005;41:1549-1556.

METALLO-β-LACTAMASE (MBL) ENZYMES MEDIATE RESISTANCE TO multiple β-lactam antibiotics, including carbapenems. Carbapenems are often the agents of last resort against multiply resistant Gram-negative pathogens, as agents of this class of antibiotics are resistant to the action of AmpC and extended-spectrum β-lactamases. Acquisition of MBL genes by common nosocomial pathogens could seriously limit available treatment options.

Utilizing the fact that MBL's require zinc ions for hydrolytic activity, Peleg and colleagues used differential susceptibility to imipenem in the presence of EDTA to detect the MBL phenotype. They then tested nosocomial Gram-negative isolates positive on phenotypic testing for the presence of 2 MBL genetic determinants, *blaIMP* and *blaVIM*.

Over a 7-month period, they tested 2100 unique clinical isolates for resistance to multiple b-lactam antibiotics and identified 204. Of these, 20 isolates from 16 patients had the MBL phenotype according to the study definition. Nineteen of these isolates carried the same MBL gene,

*blaIMP-4*. These isolates included 10 Serratia marcescens, 4 Klebsiella *pneumoniae*, 3 *Pseudomonas aeruginosa*, 1 *Escherichia coli*, and 1 *Enterobacter cloacae*. All of the isolates were resistant to cephalosporins and b-lactam/b-lactamase inhibitor combinations. Susceptibility to carbapenems as determined by automated broth icro-dilution (Vitek) was variable, with MICs of 2 to >8 ug/mL. Most isolates were susceptible to aztreonam. All isolates were hospital acquired, and 14 of the 16 patients could be linked in space and time to the ICU. Seventy-five percent of patients had received a carbapenem before isolation of an MBL bearing strain, and 75% of the isolates were associated with clinical infection.

## COMMENTARY

MBL's were first described as constitutive enzymes mediating resistance to beta-lactams in relatively uncommon Gram negative pathogens such as *Stenotrophomonas maltophilia*. Unlike the beta-lactamases commonly found in *P. aeruginosa* and Enterobacteriaceae, MBLs hydrolyze carbapenems, as well as cephalosporins and extended-spectrum penicillins. There have been reports of sporadic detection of MBLs in isolates of *P. aeruginosa* and Enterobacteriaceae, but these enzymes do not appear to be widely disseminated among these common nosocomial pathogens.

The work by Peleg and colleagues is notable in that an outbreak of MBL-carrying organisms occurred in a single hospital. Even more notable, the outbreak appeared to involve transmission of a mobile genetic element among multiple species, and among different strains of the same species. The evidence for this is compelling. Fourteen of the 16 patients could be epidemiologically linked and the identical MBL gene, *blaIMP-4*, was detected in 19 of the 20 MBL isolates. In addition, the same class I integron, IntI1, was found in all 19 by PCR.

These findings have disturbing implications for the spread of carbapenem resistance. This MBL gene appears to be readily transferable among species of nosocomial Gram-negative pathogens. Further, it is not reliably detected by standard microbroth dilution techniques. Widespread dissemination of strains carrying these genes may dramatically limit treatment options for nosocomial Gram-negative infections. ■

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**Questions & Comments**

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# Immunogenicity and Safety of the New MMRV Vaccine

ABSTRACTS & COMMENTARY

***By Hal B. Jenson, MD, FACP***
*Chair, Department of Pediatrics, Director, Center for Pediatric Research, Eastern Virginia Medical School and Children's Hospital of the King's Daughters*
*Dr. Jenson is on the speaker's bureau for Merck.*

***Synopsis:*** *In these 2 studies, the quadrivalent measles, mumps, rubella, and varicella (MMRV) vaccine, with increased potency of varicella compared to the current monovalent varicella vaccine, provides a varicella response rate of 81% and 91% after 1 dose, and 99% and 100% after 2 doses. One dose of MMRV is immunologically comparable to separate administration of measles-mumps-rubella and varicella vaccines in healthy children 12-23 months of age.*

**Sources:** Shinefield H, et al. Evaluation of a Quadrivalent Measles, Mumps, Rubella and Varicella Vaccine in Healthy Children. *Pediatr Infect Dis J*. 2005;24:665-669; Shinefield H, et al. Dose-Response Study of a Quadrivalent Measles, Mumps, Rubella and Varicella Vaccine in Healthy Children. *Pediatr Infec Dis J*. 2005;24:670-675.

THE QUADRIVALENT MEASLES, MUMPS, RUBELLA, AND varicella (MMRV) vaccine was studied in 480 healthy children 12-23 months of age who were randomized 2:1 to receive either MMRV (4.81 $\log_{10}$ PFU of varicella) and placebo (323 children) or the current measles-mumps-rubella (MMR-II) and varicella (Varivax) vaccines (157 children). Injections were given concomitantly at separate sites. Children receiving MMRV and placebo received a

second dose of MMRV 90 days later. Immunogenicity at 6 weeks showed that the response rates to all vaccine components were > 90% in both groups. Geometric mean titers (GMT) to measles (1.4 fold increase, 95% CI, 1.2-1.7 fold increase) and mumps (1.4 fold increase, 95% CI, 1.1-1.7 fold increase) were significantly higher after 1 dose of MMRV than after administration of MMR and varicella vaccines. The second dose of MMRV resulted in increased GMT for all components, with the greatest increase for varicella (588.1 gpELISA units/mL after 2 doses vs 13.0 gpELISA units/mL after 1 dose).

Vaccinations were well-tolerated. Measles-like rash and fever during the 5-12 days after MMRV (rash, 5.9%; fever, 27.7%) were significantly more frequent than after MMR and varicella vaccines (rash, 1.9%; fever, 18.7%).

The quadrivalent MMRV vaccine was also studied in 1559 healthy children from 11-23 months of age. Children were randomized 1:1:1:1 to receive MMRV with low potency varicella (3.48 $\log_{10}$ PFU), MMRV with middle potency varicella (3.97 $\log_{10}$ PFU), MMRV with high potency varicella (4.25 $\log_{10}$ PFU), or separate injections of MMR vaccine and varicella vaccine, as a control group. Children receiving MMRV were administered a second dose of MMRV at 90 days. The subgroups were comparable with respect to age (overall mean of 12.9 months), race (including 66% Caucasian and 15% African American), and gender (54% male and 46% female).

Response rates to varicella after 1 dose of the 3 combination vaccine lots were 64% (low potency), 81% (middle potency), and 87% (high potency), and geometric mean titers (GMT) were 5.7, 10.5, and 11.9, respectively, compared to a response rate of 93% and GMT of 16.5 for the control group. Hypothesis testing of similarity demonstrated that 2 injections of MMRV (low, middle, and high dose) and 1 injection of MMRV (high dose) were comparable to separate MMR and varicella vaccinations, in terms of response rate. (> 5 gpELISA units/mL, a value that has been shown to correlate with protection). The GMT responses after 2 injections of MMRV (low, middle, and high dose) and 1 injection of MMRV (middle and high doses) were similar to separate MMR and varicella vaccinations. Response rates for measles, mumps, and rubella were comparable (98.2% to 100%) after 1 dose for all groups, including the control group. The GMT for measles was higher for MMRV (middle and high doses) compared to the control group (1.2 fold increase, 95% CI, 1.1-1.4 for each).

Vaccinations were well-tolerated. The incidence of injection site reactions was comparable for the 3 combination vaccines after 1 or 2 doses (30% and 22% for low potency, 27% and 22% for middle potency, and 27% and 20% for low potency) compared to that of the control group (28% at the MMR site and 30% at the varicella site). During the first 42 days after the first vaccination, as reported by the parents, the incidence of fever (31%, 34%, and 39%) and duration of fever (1.6, 1.5, and 1.9 days) were comparable to the control group (36% and 1.6 days, respectively). There was a significantly lower incidence of fever after the second MMRV (23%, 27%, and 28%) compared to the control group. The incidence of rash was comparable to the incidence of rash from varicella vaccine alone. Only one adverse event, a febrile seizure 8 days after MMRV with middle potency, was assessed to be vaccine-related.

## COMMENTARY

Earlier studies demonstrated that combining varicella vaccine with MMR vaccine results in lower antibody response rates and GMTs for varicella and higher GMTs for measles, with no appreciable differences for mumps and rubella. These results suggest that, when combined in a single vaccine, the measles component interferes with the varicella component. It has been shown previously that acceptable varicella GMTs are achievable using MMRV containing a higher varicella potency (4.81 $\log_{10}$PFU) than that used in the monovalent varicella vaccine. These new studies show that a single vaccination with MMRV with ~4.25 $\log_{10}$PFU of varicella induces comparable immunity to separate injections with MMR-II and varicella vaccines. Furthermore, a second injection of all 3 MMRV formulations yielded response rates and GMTs comparable to the control group for all vaccine components. A second MMRV dose resulted in significant increases both of varicella response (≥ 5 gpELISA units/mL) seroconversion among the small number of subjects who had not responded to the first MMRV dose, and in varicella GMT.

The Food and Drug Administration (FDA) recently approved the combined MMRV produced by Merck & Co., Inc. and marketed as ProQuad®. This vaccine is licensed for children 12 months to 12 years of age. This formulation contains "a minimum of 3.99 $\log_{10}$ PFU," at product expiry comparable to the middle potency vaccine used in the current study. The results of combined studies reported in the product circular indicate that the overall response rates among 5446 children 12 to 23 months of age were 97.4% for measles, 95.8%-98.8% for mumps , 98.5% for rubella, and 91.2% for varicella. Response rates after a second dose were 98-99% for the 4 antigens with 2-fold increases in GMT for measles, mumps, and rubella and a 41-fold increase in GMT for varicella.

Both the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics are reviewing these data and are expected to announce soon guidelines for the recommended use of MMRV in the childhood immunization schedule. The results of this study, as well as the 10-year efficacy study of 1 vs 2 doses of the monovalent varicella vaccine, indicate that 2 doses of this

MMRV vaccine may be the optimal immunogenic strategy for routine childhood immunization. This fits well with the current recommendation for 2 doses of MMR vaccine. It is likely that the first dose of MMRV vaccine will be recommended to be given at 12-15 months, the same as the current recommendation for the first dose of MMR vaccine, with a second dose at least 3 months later in selected circumstances. Because of the concern for interference, if MMR and varicella vaccine are not administered at the same time, at least 30 days should elapse between a dose of measles-containing vaccine and varicella vaccine. ■

# Cumitech Blood Cultures

***By J. Peter Donnelly, PhD***

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*Dr. Donnelly is a consultant for Ortho Biotech, and does research for Janssen, Merck, Novartis, Numico, Pharmacia, and Pfizer.*

**Source:** Baron EJ, et al. Cumitech 1C, Blood Cultures. Coordinating ed., E.J. Baron. ASM Press, 2005.Washington, D.C.

THE AMERICAN SOCIETY FOR MICROBIOLOGY PERIODICALly publishes updates, called *Cumitechs*, to their recommendations regarding specific areas of clinical microbiology. The following is a brief summary, written primarily from a clinician's point of view, of their recent monograph on blood cultures. The recommendations, with the exception of the recommended volume of blood draws, apply to both children and adults.

## Purpose

The taking of blood cultures is standard practice in the diagnosis of infection in patients ill enough to be admitted to hospital for suspected sepsis. As such, they are usually the most productive of samples, as they allow detection of a variety of microorganisms. This *Cumitech* is written in such a way as to help the clinician and the laboratory get the most of such cultures.

## Definition of a Blood Culture

It may seem incredible but there are several different notions of what constitutes a blood culture. The definition used in this monograph helps clarify this. A blood culture is defined as a volume of blood from a single phlebotomy obtained under aseptic conditions that is inoculated into one or more bottles or vials usually containing broth culture medium. In effect, this means that even if a sample of blood is distributed into several sets of blood cultures, they should be none-the-less considered as a single blood culture. Why is this important? Simply that many laboratories try to assess the significance of a positive blood culture by the number of sets or bottles that yield growth. This is not only fallacious but is also misleading. This definition holds true even when a set contains an aerobic culture and an anaerobic culture as is usually the case.

## Sensitivity and Specificity of Blood Cultures

The most important factor that determines the sensitivity of a blood culture is the volume of blood obtained. Hence, the recommended volume of blood for investigating adults is 20-30 mL divided into 2 bottles, typically an anaerobic and an aerobic bottle. However, 2 aerobic bottles may be beneficial in cases in which bacteremia due to anaerobes is unlikely. The clinical status of patients should be the primary guide to the timing of blood cultures—there is no evidence that particular (or any) intervals between sampling is beneficial, and there should be a second, third, or fourth blood culture obtained right after one another if circumstances dictate with 2-4 blood cultures being necessary for optimal detection of bacteremia and fungemia. A laboratory policy mandating a second blood culture (if only one has been ordered) as a reflexive test is warranted to ensure compliance. The table on the next page shows that this generally amounts to 4% or less of the total blood volume.

## Acquisition and Initial Handling of Routine Blood Cultures

For skin antisepsis, chlorhexidine products and tincture of iodine appear to be equivalent, and both are superior to povidone-iodine. Ideally, blood should be drawn by percutaneous venipuncture. As this is not always possible, blood can be obtained for culture from vascular access devices, but should always be paired with another sample obtained by venipuncture. After blood is drawn, it should be put into sufficient liquid medium to achieve a 5- to 10-fold dilution to neutralize naturally occurring inhibitory substances (eg, phagocytes, as well as antimicrobial agents). Despite many investigations, there is no commercially available system or culture medium that has been shown to be best suited for the detection of all potential blood pathogens. However, there are supplements which have been shown to improve yield. For instance, the use of antibiotic-binding resins or activated charcoal may improve the yield of microorganisms in patients receiving antibiotics, but at the price of an increased rate of contamination.

In the laboratory:

• with the use of automated continuous monitoring systems, 5 days of incubation is adequate, including when infection with organisms such as Brucella or the HACEK group are suspected.

• the results of Gram stains of positive blood cultures should be reported to the clinician in some detail (Gram stains from positive blood cultures containing activated charcoal may be difficult to interpret).

**Table 1**

**Blood Volume and Blood Cultures**

| Weight (kg) | Total blood volume (mL) | Volume of blood for culture 1 (mL) | Volume of blood for culture 2 (mL) | Total Volume for blood culture (mL) | % of total blood volume |
|---|---|---|---|---|---|
| .1 | 50-99 | 2 | - | 2 | 2-4 |
| 1.1-2 | 100-200 | 2 | 2 | 4 | 2-4 |
| 2.1-12.7 | 200-800 | 4 | 2 | 6 | .8-3 |
| 12.8-36.3 | 800-2200 | 10 | 10 | 20 | 0.9-2.5 |
| > 36.3 | 2200-5000 | 20-30 | 20-30 | 40-60 | 1.2-1.8 |

Adapted from *Cumite !C Blood Cultures IV*

For instance:

Gram-positive cocci

- use "resembling pneumococci, enterococci, or group B streptococci" if in pairs or short chains.
- use "resembling other beta-hemolytic streptococci and viridans streptococci" if in long chains.
- use "resembling staphylococci" if in irregular clusters.

Gram-positive bacilli

- use "resembling *Bacillus* species" if boxcar shape and recovered from aerobic.
- use "resembling *Clostridium* species" if boxcar shape and recovered from anaerobic cultures only gram negative rods.
- to deal with the threat of bioterrorism all small gram-variable coccobacilli should be handled as if they were bioterrorism agents until proven otherwise.

## Detection of Rare and/or Fastidious Organisms

Some organisms (eg, *Cryptococcus neoformans*, *Legionella* spp., some *Helicobacter* spp., moulds, and dimorphic fungi) may not be sufficiently metabolically active to trigger detection in a growth detection system or may not produce visible growth. If cultures are negative, but bacteremia or fungemia is still suspected, alternative methods should be considered to improve the chance of recovery of mycobacteria, fungi, and rare or fastidious microorganisms:

- The acridine orange stain may allow visualization of organisms that do not counterstain well, such as *Mycoplasma*, *Brucella*, and *Francisella*.
- Cryptococcus can be detected by routine subculture at the end of the routine blood incubation period; antigen testing is effective.
- *Malassezia furfur* requires the addition of olive oil (filtered extra virgin) as a thin film on the agar plate used for subculture.
- *Fusarium*, *Histoplasma* require special approaches (eg, use of lysis-centrifugation cultures).
- *Bartonella*—Use lysis centrifugation with pro longed incubation.
- *Brucella*—"With sufficient volume of blood, it is reasonable to expect almost all Brucella to be detected within the standard 5-day protocol."
- *Legionella* survive but do not multiply in blood culture broth media. Use lysis centrifugation with subculture to BYCE agar.
- *Mycoplasma* (questionable importance)—Add gelatin to neutralize SPS, arginine to promote growth, sub to special medium.
- *Leptospira*—First 2 weeks of illness use 2 drops blood inoculated directly into 10 mL semisolid oleic acid albumin medium at the bedside.
- *Mycobacteria*—A variety of commercial systems are effective in recovering mycobacteria from blood.
- Molecular methods—Except for some viruses (eg, HIV, CMV, HBV, EBV), these are not ready for prime time.

## Detection of Bacteremia Related to Intravascular Devices

If the clinical setting dictates catheter removal (eg, shock, local purulence), the catheter should be removed and sent for semiquantitative or quantitative culture together with 2 blood samples should be obtained by separate venipuncture for aerobic culture only. However, there are many circumstances where immediate removal of the catheter is not warranted. In this case, an attempt should be made to determine whether the catheter is the source of the bacteremia in one of 2 ways:

1. Perform quantitative cultures on blood obtained from both the vascular access device and a peripheral vein; the presence of a central to peripheral ratio > 4:1 is indicative of CRI.
2. Determine the difference in time to positivity (the time from the initiation of culture incubation to a positive signal in automated systems) between catheter blood and peripheral blood: CRI diagnosed if the difference is > 2 hours, with peripheral blood requiring the longer incubation.

When blood is only available from the central venous catheter, CRI infection can be diagnosed if the culture yields > 100 CFU bacteria/mL or > 25 CFU yeasts/mL.

## Laboratory Quality Improvement Measures of Interest

The following should be monitored to indicate the quality of blood cultures:

• Contamination rates (compared to national rate of 2% to 3%), with separate audits for individual patient care units, phlebotomists (individuals and groups). Monitor cultures obtained percutaneously and from central vascular devices separately.

• Volume of blood obtained per culture (can be monitored by weighing bottles: 1mL blood • 1g).

• Number and proportion of single blood cultures (best performing hospitals had only 3.4% solitary blood cultures).

• Whether too many blood cultures are being performed (flag patients with > 80 ml total blood drawn for culture).

• Proportion of blood cultures that are positive; if positivity is < 5% or > 15%, investigate whether physician ordering is appropriate.

• Number of blood cultures per 1000 patient days; recommended range is 103-188.

• Correlation between smear result and culture result.

• Time interval from time of detection of a positive culture to notification of individual clinically responsible for the patient.

• If direct susceptibility testing is performed, the results should be compared to those obtained by testing the isolated organism.

This summary highlights the aspects of blood cultures that we feel most important for getting the best results out of this important diagnostic tool. The booklet can be ordered online from www. asm.org but it is a pity that there is, as yet, no electronic version available for ready access to the widest possible community. Given the drive towards cost-effective diagnostics, we recommend that every laboratory and infectious diseases department at least have a copy and encourage their staff to read and digest its contents. ■

# The Changing (Uglier) Face of CDAD

ABSTRACT & COMMENTARY

***By Stan Deresinski, MD, FACP***

***Synopsis:*** Clostridium difficile-*associated disease (CDAD) is increasing in incidence and severity, and is appearing in patients even in the absence of recent hospitalization or antimicrobial use.*

**Source:** CDC. Severe *Clostridium difficile*-Associated Disease in Populations Previously at Low Risk—Four States, 2005. *MMWR Morb Mortal Wkly Rep*. 2005;54:1201-1205.

CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA (CDAD) IS most often nosocomially acquired, and usually affects older, sicker patients. The incidence of hospital discharges with a diagnosis of CDAD in the United States increased by 26% between 2000 and 2001.[1] At the same time, some evidence suggests that, in some areas, CDAD has become more severe and more recalcitrant to treatment. In a demonstration of the apparently increasing and expanding danger of CDAD, the CDC has now reported on the occurrence of severe CDAD in individuals not normally considered at risk.

Their investigation was initially precipitated by the report of cases of severe CDAD in otherwise healthy patients with minimal or no exposure to health care facilities. One of these was a 31-year-old woman who presented during the 14th week of pregnancy with a 3-week history of intermittent diarrhea due to *C. difficile*, which had significantly worsened in the last 3 days. She had received trimethoprim-sulfamethoxazole for treatment of a urinary tract infection approximately 3 months previously. She relapsed after each of 2 courses of therapy and, despite a subtotal colectomy, died. A second patient, a previously healthy 10-year-old girl, who had received no antimicrobials in the preceding year, developed CDAD with 14 liquid stools per day. She responded to intravenous fluids and metronidazole.

A request for voluntary reports from several states resulted in the identification of 10 peripartum (within 4 weeks before or after delivery) and 23 community-acquired cases from 4 states. In 4 cases, there had been apparent transmission from close contacts. Three (9%) of the 23 patients had received 3 or fewer doses of antibiotics. There had been no antimicrobial exposure in 8 (24%), and 3 of the 8 without antibiotic exposure were close contacts of index cases.

### ■ COMMENTARY

This experience has emerged at the same time that significant outbreaks of severe healthcare-associated CDAD have occurred in North America and Europe. An epidemic in Montreal and southern Quebec, beginning in 2002, resulted in 14,000 reported cases between 2003 and 2004, with incidence rates 5 times greater than the historical average.[2] At the same time, at a University hospital in Quebec, the 30-day crude mortality of patients with CDAD increased from 4.7% to 13.8%. A comparable experience in Sweden has been reported.[3] And, outbreaks have occurred in recent years in multiple states of the United States. Some evidence indicates that at least some of these outbreaks, as well as the frequently associated increased severity of disease, may be the result of the emergence of hypervirulent strains of *C. difficile*.

The damage to colonic mucosa in patients with CDAD is the result of the production of exotoxins. Genes encoding toxins A (*tcdA*) and B (*tcdB*) are located within *PaLoc*, a 19.6 kb pathogenicity locus carried on the chromosome of pathogenic strains of *C. difficile*. These toxins are coregulated by 2 genes, *tcdC* and *tcdD*. The latter, *tcdD*, is a positive regulator, while the former, *tcdC*, is strongly expressed

during logarithmic growth of the organism, resulting in transcriptional suppression of the genes encoding these toxins. Transcription of the toxin genes is, in contrast, increased during stationary growth. Both toxins A and B translocate to the cytosol and inactivate small GTP-binding proteins, such as Rho, resulting in disruption of the actin cytoskeleton and cell death.[4] Some strains also encode a binary toxin, similar to the iota toxin of *Clostridium perfringens*, whose pathogenic role remains unproven. One component of this toxin is important for binding to the cell membrane and intracellular translocation while the other causes cell death by disruption of actin filament assembly.

Several typing systems are generally used in the examination of strains of *C. difficile*. These include ribotype determination by restriction endonuclease analysis and pulsed-field gel electrophoresis. In addition, toxinotype is determined by determination of polymorphisms in *PaLoc*. Some of the recent outbreaks of severe CDAD have been associated with the emergence of a strain designated ribotype 027, toxinotype III. An additional feature common to strains implicated in some of the outbreaks has been the presence of an 18-bp deletion, the negative regulator, *tcdC*, probably accounting for the increased toxin production by these strains.

Patients affected during the epidemic in the province of Quebec, had an attributable mortality of 6.9%. Factors identified as risks for CDAD, some cases of which were community acquired, were prior receipt of fluoroquinolones (82% of isolates were fluoroquinolone resistant) or cephalosporins.[5] In addition to toxins A and B, 84% of isolates bore the genes for the binary toxin, as well as deletions in *tcdC*. Peak in vitro toxin A and toxin B production by this dominant strain was 16- and 23-fold higher than that of historic strains, presumably as a consequence of the deletions in *tcdC*.[2]

The predominant strain among isolates from recent outbreaks in 6 US states were of the same ribotype as the predominant Canadian strain, and belonged to toxinotype III.[6] They also contained genes encoding binary toxin and had 18-bp deletions in *tcdC*. Organisms with these characteristics were resistant to gatifloxacin and moxifloxacin, and most were resistant to clindamycin.

Thus, the evidence of emergence of a dominant strain as a cause of severe CDAD, often in epidemic fashion, continues to accumulate. Complicating matters for the clinician is the fact that CDAD may becoming increasingly recalcitrant to treatment, especially with metronidazole. This is occurring despite the fact that detection of in vitro resistance to metronidazole has been quite rare. This may, also, however, be changing. In Montreal, while only 6% of pre-epidemic *C. difficile* isolates had an MIC > 1 mcg/mL, 38% of epidemic isolates ($P < 0.001$) had an MIC > 1 mcg/mL.[7] In addition, investigators in Spain recently reported a 1.1% prevalence of homogenously expressed metronidazole resistance. However, 32% expressed heterogeneous resistance as defined by the presence of colonies within the zone of inhibition in an E-test.[8]

All of these reports clearly demonstrate the need for implementation of proactively aggressive interventions aimed at preventing CDAD. While many of the following recommendations apply to inpatient settings, the increasing risk of severe community-acquired CDAD in patients without known risk factors (including no antibiotic exposure) must also be taken into account.

## Recommendations

- Monitor for changes in incidence and severity of CDAD.
- Upon identification of a case, discontinue antibiotics, if possible, and treat with orally administered metronidazole or, in severe cases, vancomycin.[9]
- Prevent transmission by strictly enforced contact precautions, barrier nursing where appropriate, prohibition of use of shared patient bathrooms, enhanced environmental cleaning with sporicidal agents (eg, dilute bleach), and hand washing with soap and water (not alcohol).
- Contact precautions should consist of: use of a single room or of cohorting (although variable antibiotic resistance and virulence would argue against this); use of gloves and gowns on entering the patient's room; and exclusive use (or cleaning between patients) of blood pressure cuffs, stethoscopes, and other patient care equipment.
- Institutional implementation of effective antibiotic stewardship, with elimination of unnecessary antibiotics use, especially of implicated agents.
- Reduction of unnecessary use of proton pump inhibitors (identified in other studies as a risk factor for CDAD).

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# Updated Guidelines for Antiretroviral Therapy—2005

ABSTRACT AND COMMENTARY

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

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***Synopsis:*** *The US Department of Health and Human Services (DHHS) periodically updates their guidelines for antiretroviral therapy. The latest iteration of these guidelines was published in October 2005. While continuing to emphasize triple drug antiretroviral regimens, a number of changes were made. These changes included since the previous DHHS Guidelines (published April 7, 2005) are summarized below.*

**Source:** Panel on Clinical Practices for Treatment of HIV Infection, Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. October 6, 2005; www.AIDSinfo.nih.gov

WHAT NOT TO USE AS INITIAL THERAPY: THE PANEL recommends that a regimen containing ddI+tenofovir+NNRTI not be used as an initial regimen, due to reports of early virologic failure and rapid emergence of resistance mutations with this regimen, as well as a poor incremental CD4 response and, possibly, enhanced nucleoside-related toxicity due to a pharmacologic interaction between ddI and tenofovir. Also, while ritonavir-boosted tipranavir has been shown to be an important advance in treatment of patients who have developed virologic failure on other regimens, the panel does not recommend its use in treatment-naïve patients due to lack of clinical trial data in this setting.

Management of treatment experienced patients: This section of the Guidelines has been updated to redefine the goal of antiretroviral therapy in the management of treatment-experienced patients with virologic failure and reviews the role of more potent ritonavir-boosted protease inhibitors such as tipranavir with or without enfuvirtide. Table 23 clearly restates that the goal of antiretroviral therapy remains suppression of HIV viremia, but also now states that attempts to preserve some degree of immune response by using antiretroviral drugs which by resistance testing only partial virologic suppression is anticipated, may be appropriate.

The following additional tables have been updated:

• Table 7 (Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data)-Outcome data with once daily abacavir/lamivudine and lopinavir/ritonavir have been added.

• Table 12 (Characteristics of Protease Inhibitors) was updated to include description of tipranavir and the option of once daily dosing of lopinavir/ritonavir in treatment naïve patients.

• Tables 16-21b (all pertain to toxicities) was updated with information about tipranavir including the black box warning relating to reports of clinical hepatitis and hepatic decompensation, and the recommendation to use this drug with caution in patients co-infected with hepatitis B or hepatitis C.

• Tables 23-25 (all pertain to management of virologic failure) have been updated and emphasize the importance of resistance testing in selecting a salvage regimen and, as expected, recommend regimens containing lopinavir/ritonavir, tipranavir/ritonavir as well as enfuvirtide. Structured treatment interruptions are discouraged as a management strategy.

• Table 26 (Suggested Minimum Target Trough Concentrations for Persons with Wild-type HIV-1) is updated with a suggested Cmin for atazanavir given as 150 ng/mL.

• Tables 28 and 29 (both pertain to use of antiretroviral agents in pregnant patients) update the USPHS perinatal antiretroviral guidelines and make reference to the use of tipranavir. (Animal teratogenicity studies have been essentially negative but since there has been little clinical experience or clinical trials of this agent in pregnancy, the guidelines conclude,". . . data are insufficient to recommend use during pregnancy.")

• Table 30 (Antiretroviral Agent Available Through Expanded Access Program) has been updated to include enrollment information for the Tibotec HIV protease inhibitor, TMC-114. This agent, like tipranavir, has shown good activity in clinical trials studying patients infected with PI-resistant HIV.

These updated guidelines have, as expected, grown quite voluminous (approximately 115 pages including appendices) as the number of available antiretroviral agents has increased over the last 18 years, and our experience in managing patients and using these agents has matured. The document is, over all, well referenced. These consensus guidelines present practical approaches to this important field of clinical practice. ■

# Dysregulation of Bacterial Proteolytic Machinery

ABSTRACT & COMMENTARY

***By Joseph F. John, Jr., MD***

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***Synopsis:*** *Antibiotics useful against human bacterial infections have classically been derived from higher bacteria and fungi. In that tradition, a new class of antibiotics called acyldepsipeptides, have been isolated (then patented) from* Streptococcus hawaiiensis. *A group predominantly of German scientists from industry and academia have now published the mechanism of action for a group of these acyldepsipeptides (ADEP).*

**Source:** Brotz-Oestehelt H, et al. Dysregulation of Bacterial Proteolytic Machinery By a New Class of Antibiotics. *Nat Med*. 2005;11:1082-1087.

ADEP 1-6 HAVE A COMPLEX RING STRUCTURE. ADEP-1 is the primary natural product ("factor A"). ADEP-1 has congeners that have been optimized for antibacterial activity, with the addition of 2 fluorides, to produce a difluoronated phenylalanine side chain. ADEP-2 has MICs for *Streptococcus pneumoniae* of 0.05 ug/mL, for *Streptococcus pyogenes* (Group A streptococcus) of 0.05 ug/mL, *Enterococcus faecalis* of < 0.01 ug/mL, for *E. faecium* of 0.02 ug/mL, and for *Staphylococcus aureus* (MRSA) of 0.4 ug/mL. ADEP-4 has an MIC for *S. aureus* of 0.05 ug/mL. ADEP-3, which is the R epimer of ADEP-2, has MICs for all these bacterial species of > 100 ug/mL.

In lethal *S. aureus* sepsis, 80% of mice were protected with 12.5 mg/kg dosing. Lower doses (1 mg/kg) were protective for *E. faecalis* sepsis. In *S. pneumoniae* sepsis in rats, ADEP performed better than linezolid.

ADEPs act through a complex. likely novel, mechanism. Labeling of precursor DNA, RNA, protein, and fatty acid showed that metabolism of these components was unhindered by ADEP. Microscopic examination of bacteria, immediately after exposure to ADEP, showed distinct filamentous forms, reaching a length of 200 uM, suggesting interruption of routine cell division through a secondary pathway.

Through a set of experiments using a genomic library of *E. coli* derivatives, some of which had become resistant to ADEP, Brotz-Ostehelt and colleagues found that a caseinolytic protease, designated by the gene ClpP, is necessary for the bactericidal activity of ADEP. Further experiments showed that ClpP specifically interacts with ADEP, independently of ATPases traditionally needed for ClpP to function.

So, what is it about the ClpP-ADEP product that is lethal to bacteria?

In *B. subtilis*, ClpP requires a Clp-ATPase and ATP to degrade proteins like casein. When exposed to ADEP 1 or ADEP 2, ClpP degrades casein without ATPase. Thus, ADEPs turn a docile ClpP into a proteolytic machine. Using modern proteomic chemistry, Brotz-Ostehelt et al also showed that ClpP was markedly upregulated by ADEP. Further induction by ADEPs was shown for a set of molecules called chaperones (genetic names like ClpC, DnaK, GroEL, and Tig). There were additional novel spots on the proteome pattern after ADEP induction, suggesting a very wide set of interactions for ADEP.

## ■ COMMENTARY

Clinicians are increasingly faced with treating resistant bacteria, particularly Gram-positive cocci like staphylococci and enterococci, which are very broadly resistant. Thus, it is crucial that academia and industry continue to work discovering new antibiotics. ADEPs are attractive because they are bactericidal, work through a conserved bacterial mechanism, and have low inhibitory concentrations.

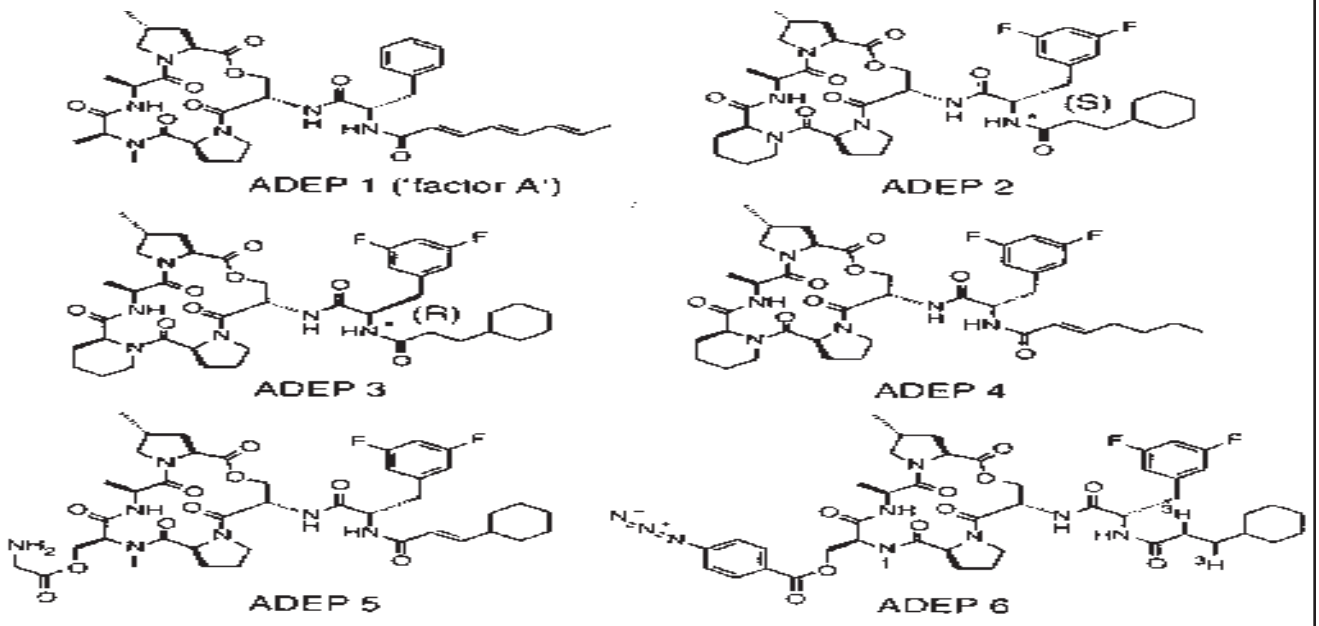
ADEP 1 is also known as "factor A"-the patented product. In the current paper, additional ADEPs 2-6 congeners were derived that showed, in some cases like ADEP 2 and ADEP 4, improved antibacterial activity.

The discovery of highly active ADEPs is encouraging but also daunting in view of the scope and complexity of the work needed to discover and validate new classes of antimicrobials. Modern genomics and proteomics are indispensible for characterizing a gamut of molecules that are altered by the new antimicrobial moieties: for ADEP showing that an intermediate ADEP-bound product triggers a cascade of events leading to cell elongation and death probably through a series of cell regulators that are modified by ClpP-ADEP. The involvement of ADEPs at multiple sites is indeed complex, but the end result is a highly active group of antibacterials.

Resistance is always lurking, however, and it clouds even this novel discovery. ClpP is clearly not indispensable to bacterial cell function since

**Figure 1**

**ADEP Structures**




**Source:** Brotz-Ostehelt H, et al. Dysregulation of Bacterial Proteolytic Machinery By a New Class of Antibiotics. *Nature Medicine*. 2005;11:1082-1087.

ADEP-resistant mutants arise in vitro at frequencies around 106. At this point, it is concerning that such frequencies of resistance may obviate monotherapy with ADEPs, but only further animal work and clinical trials will answer that question. The use of monotherapy for a lethal systemic Gram-positive murine infections in the current report was highly efficacious.

This work was done under the senior mentoring of Hans-Georg Sahl in Bonn and Harald Labischinski, both of whom have contributed immensely to the field of antibiotic development. Peptides have long been known for their antibacterial potential. With this current work, we now are armed with compounds like the ADEPs that work through novel bacterial cellular mechanisms and offer new hope against the rising tide of resistant Gram-positive bacteria and the ever growing scourge of staphylococcal infections. ■



## CME Questions

1. **All of the following are true concerning metallo β-lactamase enzymes *EXCEPT*:**
   a. they may be carried on mobile genetic elements and can be transferred among different bacterial species.
   b. they are typically inhibited by tazobactam.
   c. they are dependent on zinc ions for hydrolytic activity.
   d. they are not reliably detected by automated microbroth dilution testing.

2. **Which has been the primary obstacle to development of a combined measles-mumps-rubella-varicella (MMRV) vaccine?**
   a. High rate of vaccine-associated rashes
   b. High rate of serious adverse events
   c. Interference of the varicella component by the rubella component
   d. Interference of the varicella component by the measles component
   e. Interference of the measles component by the varicella component

3. **Acyldepsipeptides act through which novel mechanism?**
   a. Cell wall inhibition
   b. Proteolytic cleavage of vital protein molecules
   c. DNA cleavage
   d. Ribosomal binding

**Answers:** 1. (b); 2. (d); 3. (b)

## In Future Issues:

**Blood Culture Incubation—How Long Is Long Enough?**

# UPDATES

By Carol A. Kemper, MD, FACP

## Honeymoon Meningitis?

Agouridakis P, et al. "Honey Moon" Meningitis. *Emerg Med J*. 2005;22: 803-804.

THESE AUTHORS REPORT ON THE unique presentation of a 17-year-old previously healthy woman who developed acute onset fever, headache, nausea, and vomiting. Lumbar puncture confirmed a cerebrospinal fluid pleocytosis, and blood and CSF (but not urine) cultures yielded Group B streptococcus (*S. agalactiae*). Further investigation for a possible source found no evidence of intraabdominal abscess, endometritis, or endocarditis. Tests for HIV antibody and serum immune globulins were unremarkable.

The young woman admitted to having had vaginal intercourse for the first time only 2 days before the onset of symptoms. Vaginal cultures yielded a Group B streptococcus with a similar susceptibility profile to the blood and CSF isolates, suggesting the vaginal flora may have been the source for her bacteremia and meningeal seeding. (No comment was made regarding the type of sexual activity or whether there was any trauma). The organism was resistant to ceftriaxone. The patient fully recovered with 15 days of vancomycin therapy.

Group B strep rarely causes meningitis in otherwise healthy nonpregnant adults. In a review of 50 patients with Group B strep meningitis, 20% had endometritis, 8% had endocarditis, and 6% had urinary tract infection; 60% had no identifiable source. ■

## Sharing HCV With Your Best Friend

Daniel AR, Sheha T. Transmission of Hepatitis C Through Swapping Body Jewelry. *Pediatrics*. 2005;116:1264-1265.

THIS AUTHOR REPORTS THE UNIQUE presentation of a previously healthy 17-year-old with newly diagnosed HCV infection. The patient was a regular blood donor, along with her mother, and tested negative for HCV antibody on several prior occasions. At the age of 17, with the permission of her mother who accompanied her to a reputable salon, she got a single umbilical piercing. Six months later, she again tested negative for HCV. However, 16 months following her body piercing, blood tests revealed evidence of HCV antibody, with confirmation of an uncommon genotype (genotype 3c), found in only 3-5% of those with HCV infection.

The young woman denied any high risk activities. She had a single sexual partner who tested negative for HCV. It turns out that many young teenagers and college-aged women commonly swap body jewelry. The young woman had frequently swapped her umbilical ring for a friend's jewelry. Unfortunately, the friend had several risk factors for HCV infection (including the use of intranasal cocaine, sharing straws, and multiple sexual partners) and tested positive for HCV genotype 3a. This case report suggests that transmission of HCV (and presumably other blood born pathogens, such as HIV and HBV) can occur when swapping body jewelry. While some umbilical, nipple, and eyebrow rings are semi-permanent and can not be easily removed, young people with removal rings should be counseled to avoid sharing. n

## The Hazards of Adult Sex Filming

CDC. HIV Transmission in the Adult Film Industry—Los Angeles, California. *MMWR Morb Mortal Wkly Rep*. 2005; 54:923-926.

THIS ARTICLE IS A SURPRISE TO read for no other reason than that the Division of Occupational Health and Safety (Cal/OSHA) now monitors the adult film industry as part of its responsibilities under the California Department of Industrial Relations (no pun intended). The adult film industry encompasses about 200 production companies in Los Angeles County with an estimated 1200 actors and actresses who engage in sex acts for the camera. As can be imagined, many of these individuals engage in high risk sexual activity with multiple partners for prolonged periods of time, without the use of condoms or other protection. The Adult Industry Medical Health Care Foundation, a private not-for-profit organization, located in Los Angeles, has provided HIV and STD testing for adult film workers since 1998. The service is entirely voluntary, and many of the actors/actresses pay for the screening tests out of pocket, although the practice is encouraged by their production companies and the test results are generally shared among employees and employers.

In April 2004, the Los Angeles County Department of Health Ser-

vices requested Cal/OSHA assistance in the investigation of 4 newly diagnosed cases of HIV infection in heterosexual adult film industry workers. The index case was a 40-year-old male who tested HIV negative on 2/12/04 and 3/17/04, but tested positive on 4/9/04 (using the Amplicor™ HIV-1 Detection Kit, Roche Diagnostics). Between the 2 negative tests, he traveled to Brazil, where he participated in a number of unprotected sexual acts during movie production. He also developed flu symptoms while working in Brazil. Upon returning to LA, he continued to work, engaging in sex with 13 different female partners. During this period, the index case denied any sex partners outside of work (an interesting twist on the usual desire to avoid taking your work home).

Three of the 13 women, each of whom had tested HIV negative within the previous 30 days, subsequently tested HIV-positive, for an attack rate of 23%. All 3 had engaged in sexual acts with an increased risk of mucosal tears, 2 on the same day and within 7 days of his final negative test. One of the women had just arrived in Los Angeles and was barely 20 years old, and had just started working in the adult film industry weeks earlier. Specimens from the index case and 2 of the women were available for HIV DNA sequencing of regions of the gag and env genes, which convincingly demonstrated that the index patient was the source of infection for at least 2 of the women. Following identification of these cases, 25 first-generation sex partners and 36 second-generation sex partners received counseling and HIV testing; none have thus far tested HIV-positive.

Clearly the index case, who tested negative only a week before contact with 2 of the women, was able to transmit virus before the PCR test was able to detect it. Although the PCR test is highly sensitive, it is not as specific, and is not approved for diagnostic testing. The lesson learned from this case is that individuals engaging in frequent high risk sexual activity, who may have been depending on a potential sex partner's negative test result, should be aware of the small risk that recent infection may escape detection, at least for a few days. The eclipse period between exposure and a positive PCR plasma test is estimated to average 10-15 days (but may be longer in some), and the window period, which is the time to a positive antibody test, may be an additional 10-15 days.

Cal/OSHA responded to this event by issuing citations to 2 production companies for failing to provide prompt reporting of a serious work-related injury, by failing to provide a written policy for occupational injury and illness prevention to workers, and by failing to adhere to Cal/OSHA Bloodborne Pathogens Standards. Apparently, if the adult film production companies encouraged testing and were aware of the results, then they should also be responsible for appraising employees of the risks, and encourage barrier protection to prevent exposure to hazardous or infectious substances, just like another California employer. The film industry is appealing the ruling. Somehow the State electing to fine the adult film industry at this juncture, just as they are making attempts to encourage screening for HIV and STDs and reduce exposure risks, seems a bit like a double-bind. ■

## Raw Camel Liver Plague

Bin Saeed AA. Plague From Eating Raw Camel Liver. *Emerg Infect Dis*. 2005;11:1456-1457.

Four residents of Goriat, in a desert area of Saudi Arabia, were admitted with fever and severe pharyngitis and tonsillitis. Three had dysphagia and tender submandibular lymphadenitis. The initial presumptive diagnosis was diphtheria. Two died, one with hemorrhagic manifestations. Blood cultures were positive for *Yersinia pestis*.

Investigators found that members of 11 families, comprising 106 individuals, had shared the meat of a camel that had been butchered. The camel had been ill. The man who had slaughtered the camel (not one of the 4 cases above) subsequently developed plague with cellulites of his arm (which he had cut) and axillary buboes. Six individuals ate the raw liver of the camel and 4 developed plague pharyngitis. None who ate only cooked meat or liver were affected (except for the butcher). *Y. pestis* was isolated from leftover camel meat, from nearby jirds, small desert rodents related to gerbils, and from fleas combed from the jirds.

Of interest, the possibility of plague as the cause of the pharyngitis was first considered by a local preventive medicine specialist who had seen similar cases in years before. It is also of interest that almost one-half of domestic plague-infected cats in New Mexico, who presumably acquired the disease by eating infected prey, had submandibular lymphadenitis.

This episode contains 2 lessons. First—plague may result from ingestion of meat or viscera removed from infected animals. Second—do not eat raw liver removed from the carcasses of sick camels. ■

# PHARMACOLOGY WATCH

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


## FDA Recommends Approval of Muraglitazar, But May Need To Reconsider

In September of 2005, an FDA advisory committee recommended approval of muraglitazar for the treatment of type 2 diabetes. However new review of the data presented to the FDA challenges the safety of the drug, and suggests that compared with placebo or standard treatment, muraglitazar is associated with excess mortality.

The drug is a peroxisome proliferator-activated receptor (PPAR) that has both alpha receptor activity (similar to fenofibrate and gemfibrozil) and gamma receptor activity (similar to pioglitazone and rosiglitazone). Muraglitazar has been widely anticipated because of its dual effect of improving lipid profiles and increasing insulin sensitivity in patients with type 2 diabetes.

In the new study, researchers from the Cleveland clinic reviewed the data submitted to the FDA from phase 2 and 3 clinical trials. The combined studies included 3725 patients who were randomized to receive differing doses of muraglitazar, pioglitazone, or placebo in combination with metformin or glyburide in trials ranging from 24 to 104 weeks. The primary end points were death, nonfatal MI, or nonfatal stroke and a more comprehensive composite outcome, which included those 3 outcomes plus incidence of CHF or TIA. The primary outcome (death, MI, or stroke) occurred in 35 of 2374 (1.47%) of muraglitazar treated patients and in 9 of 1351 (0.67%) of patients in the combined placebo and pioglitazone treatment groups (RR 2.23; 95% CI, 1.07-4.66; *P*. = .03). The more comprehensive outcome occurred in 2.11% of muraglitazar treated patients and 0.81% of control patients (RR, 2.62; 95%CI, 1.36-5.05; *P* = .004). Incidence of CHF was 0.55% muraglitazar and 0.07% controls (*P* = .053).

The authors conclude that compared with placebo or pioglitazone, muraglitazar was associated with increased risk of death, major adverse cardiovascular events, and CHF. They also recommend the FDA not approve the drug until safety can be documented (Nissen SE, et al. Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes Mellitus. *JAMA*. 2005;294: 2581-2586).

In a related, provocative editorial, James Brophy MD from McGill University suggests tactics that pharmaceutical companies use to "foster an allusion of safety" when presenting data as part of a FDA application including selecting study populations unlikely to have adverse outcomes, conducting under powered studies that are unable to detect meaningful safety differences, reporting individual rather than composite safety outcomes, and others. He poses the question "which safety message will the FDA buy?" (Brophy JM. Selling Safety—Lessons From Muraglitazar. *JAMA*. 2005;294:2633-2635).


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) 262-5416. E-mail: leslie.hamlin@thomson.com.

## Which Antipsychotics Are More Dangerous?

Newer atypical antipsychotic drugs have been associated with higher death rates in elderly patients. Now, a new study shows that conventional antipsychotics are at least as dangerous as the newer drugs. In a retrospective cohort study, nearly 23,000 patients age 65 and older who had received conventional or atypical antipsychotic medications between 1994 and 2003 were studied. Conventional antipsychotic medications were associated with a significantly higher adjusted death rate then atypical antipsychotic medications for all time intervals studied up to 180 days (relative risk 1.37; 95% CI, 1.27-1.49). The relative risk was also higher for less than 40 days (RR, 1.56), 40-79 days (RR, 1.37), and 80-180 days (RR, 1.27). The greatest risks were for death occurring within the first few weeks after initiation of medication especially higher doses of conventional antipsychotics drugs.

The authors conclude that conventional antipsychotic medications are least as likely as atypical agents to increase the risk of death among elderly patients, and that conventional drugs should not be used to replace atypical agents if they were discontinued because of recent FDA warnings (Wang PS, et al. Risk of Death in Elderly Users of Conventional Vs. Atypical Antipsychotic Medications. *N Engl J Med*. 2005;353:2335-2341).

## Should CPOE Undergo Evaluation?

Physicians who use computerized physician order entry (CPOE) systems often report that it is not a panacea for saving time and preventing medication errors. A new study raises concerns about an increase in adverse outcomes associated with CPOE. Researchers from Children's Hospital of Pittsburgh reviewed demographic, clinical, and mortality data before and after implementation of a commercially sold CPOE. Mortality rates were significant higher after implementation (75 deaths among 1942 children, 3.86% after implementation vs 39 of 1394, 2.80% prior to implementation, odds ratio: 3.28; 95% CI; 1.94-5.55). The authors suggest that while CPOE may hold great promise, "Institutions should continue to evaluate mortality effects, in addition to medication air rates. . ." They also suggest that CPOE should undergo rigorous review and evaluation, similar to drugs, to assess safety prior to implementation (Han YY, et al. Unexpected Increased Mortality After Implementation of a Commercially Sold Computerized Physician Order Entry System. *Pediatrics*. 2005;116:1506-1512).

## New Treatment for Tennis Elbow

Botulinum toxin may be effective for treating tennis elbow, according to new study. Sixty patients with lateral epicondylitis were randomized to injections of 6 units of botulinum toxin type A or normal saline placebo injections. Subjective pain was significantly reduced in the botulinum group at 4 weeks (visual analog scale 25.3 mm botulinum vs 50.5 mm placebo [$P < 0.001$]) and was sustained at 12 weeks. Grip strength was not statistically different between the 2 groups, although mild paresis of the fingers occurred in 4 patients in the botulinum group at 4 weeks, but none of the patients in the placebo group. In only one patient did the symptoms persist until week 12. More patients in the botulinum group experience weak finger extension at 4 weeks as well (10 patients botulinum vs 6 patients placebo).

The authors conclude that botulinum toxin may be effective in treating pain over 3-month periods in patients with lateral epicondylitis, but the injections may be assisted with digit paresis and weakness of finger extension (Wong SM, et al. Treatment of Lateral Epicondylitis with Botulinum Toxin: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann Int Med*. 2005;143: 793-797).

## FDA Actions

Moxifloxacin (Avelox-Bayer) has been approved for the treatment of complicated intra-abdominal infections including polymicrobial infections. The approval was based on a study which showed that intravenous or oral moxifloxacin was as effective as IV therapies such as piperacillin/tazobactam (Zosyn) followed by oral amoxicillin/clavulanic acid (Augmentin). In a separate study, moxifloxacin was found to be equivalent to ceftriaxone plus metronidazole followed by oral amoxicillin/clavulanic acid for treating complicated intraabdominal infections. Moxifloxacin is also approved for treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, and skin and skin structure infections caused by susceptible organisms. ■