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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

Antimicrobial Treatment of Acute Otitis Media — It Works!

By Hal B. Jenson, MD, FAAP
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Dr. Jenson reports no financial relationships relevant to this field of study.

Synopsis: *In a placebo-controlled trial with strict criteria for diagnosis of acute otitis media in young children, amoxicillin-clavulanate reduced treatment failure from 44.9% to 18.6% (P<0.001), with an overall reduction in treatment failure of 62%. Amoxicillin-clavulanate was associated with mild diarrhea that did not require discontinuation of study drug in almost half of recipients.*

Source: Tähtinen PA, et al. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med* 2011;364:116-126.

A randomized, double-blind, placebo-controlled trial of the efficacy of oral amoxicillin-clavulanate treatment (40 mg amoxicillin + 5.7 mg clavulanate/kg/day divided into 2 daily doses for 7 days) of acute otitis media was conducted among children 6-35 months of age in Finland. Three diagnostic criteria were required for study eligibility: 1) middle-ear fluid demonstrated by pneumatic otoscopy with at least two tympanic membrane findings of bulging position, decreased or absent mobility, abnormal color or opacity

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not due to scarring, and air-fluid interfaces; 2) distinct erythematous patches or streaks or increased vascularity over full, bulging, or yellow tympanic membrane; and 3) acute symptoms of fever, ear pain, or respiratory tract symptoms. Assessments were performed by experienced otoscopists.

Adherence to the study drug, as assessed by different measures, was 94%-99%, with no significant differences between the two groups. Treatment failure, measured by six independent components, occurred in 30 of the 161 children (18.6%) in the amoxicillin-clavulanate group and 71 of the 158 children (44.9%) in the placebo group ($p < 0.001$). Kaplan-Meier analysis demonstrated a separation between the curves beginning at the first scheduled return visit on study day 3. To avoid treatment failure in one child, 3.8 children (95% CI, 2.7-6.2) would have to be treated with amoxicillin-clavulanate.

Rescue treatment was initiated in 11 of 30 children in the amoxicillin-clavulanate group (36.7%) and in 53 of 71 children in the placebo group (74.6%) who had treatment failure ($p = 0.007$). The need for rescue treatment was reduced by 81% with amoxicillin-clavulanate as compared to placebo. There was not a significant difference in the use of analgesic or antipyretic agents, with a mean duration of use of 3.6 days in the amoxicillin-clavulanate group and 3.4 days in the placebo group. Amoxicillin-clavulanate resulted in significantly improved otoscopic findings at the end of treatment ($p < 0.001$) and time to resolution of fever, poor appetite, decreased activity, and irritability ($p < 0.001$). Parents of children attending daycare missed significantly fewer days in the amoxicillin-clavulanate group (81 days) than in the placebo group (101 days) ($p = 0.005$).

Diarrhea developed in 77 children (47.8%) in the amoxicillin-clavulanate group and 42 children (26.6%) in the placebo group. The diarrhea was non-watery and non-bloody, and did not require discontinuation of the study drug.

■ COMMENTARY

There are innumerable published studies, which span the spectrum of scientific rigor, over the past decades reporting findings of antibiotic treatment of otitis media. This very rigorous study is of interest because of two findings that differ from what is generally believed — a higher rate (44.9%) of treatment failure with placebo and a greater and earlier benefit of antibiotic treatment. Several meta-analyses of antibiotic treatment of otitis media report that the number of children needed to treat to benefit one child is from 7 to 17, compared to the 3.8 in this study. Rescue treatment of children in the amoxicillin-clavulanate group (6.8% overall) was required about as often as in the treatment group of other studies, but required in 33.5% of children in the placebo group, compared to an average of 12% in other studies. These key differences are likely attributable to the scientific rigor of this study in diagnostic criteria and defining treatment failure, and the use of the most appropriate drug and dosage for otitis media.

There is some controversy over the appropriate management of otitis media in young children. In 2004, the American Academy of Pediatrics recommended observation without the use of antibiotics for selected children with acute otitis media. Even in this study, half of children in the placebo group did not have treatment failure, and two-thirds did not need rescue treatment.

The 2004 recommendation was qualified by acknowledging that it "was based on randomized, controlled trials with limitations." This new study is important, and provides a contemporary, rigorous answer to the question of the benefit of initial antibiotic treatment vs. observation for acute otitis media. These results demonstrate a clear benefit of appropriate antibiotic treatment to a degree that is greater than understood previously, including the finding of significant improvement by study day 3. Though some cases of acute otitis media in children will indeed resolve spontaneously, we do not have the diagnostic acumen to identify that subset of cases. Thus, these results indicate that all children with acute otitis media 6 to 35 months of age should be treated with amoxicillin-clavulanate as the initial management. ■

ABSTRACT & COMMENTARY

Novel Deer-associated Parapoxvirus Found in Deer Hunters

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Clinical Professor, Stanford University School of Medicine
Dr. Winslow reports no financial relationships relevant to this field of study.

Synopsis: *In 2009 parapoxvirus infection was diagnosed in two deer hunters in the eastern U.S. who had field-dressed white-tailed deer. Molecular analysis suggested that these infections represented a unique strain.*

Source: Roess AA, et al. Novel deer-associated parapoxvirus infection in deer hunters. *N Engl J Med*. 2010; 363:2621-2627.

Two cases were reported in this paper. The first case was a 52-year-old wildlife biologist who went deer hunting in Virginia in November 2008. He nicked his right index finger while field-dressing a white-tailed deer. The animal appeared healthy, and the patient noted no external lesions on the deer. The cut did not heal, and about 4 weeks after the injury, the wound site enlarged to form a violaceous nodule. The lesion was excised and the patient empirically treated with doxycycline. Pathology revealed a vascular lesion with histopathology consistent with pyogenic granuloma. Cultures for bacterial, mycobacterial, and fungal pathogens were negative. The lesion subsequently recurred at the edge of the excised area and enlarged. The lesion was re-excised and histopathology was suggestive of orf virus. Specimens were sent to the CDC. The second case was a 60-year-old hunter from Connecticut who cut his left index finger while field-dressing a white-tailed deer in November 2008. Seven weeks after the injury, the patient sought care for a non-healing, 1 cm violaceous lesion. Biopsy subsequently revealed intracytoplasmic viral inclusions within keratinocytes, suggestive of a poxvirus infection. Specimen also were sent to the CDC.

Electron microscopy examination of sections of material prepared from both patients revealed ovoid virions 113-130 nm X 250-258 nm in the two patients. Histopathology revealed dilated vascular spaces lined with swollen endothelial cells and scattered lymphohistiocytic inflammatory-cell infiltrates. Immunohistochemical staining revealed intracellular viral antigens. "Pan-pox" universal PCR and parapoxvirus-specific real-time PCR confirmed the presence of parapoxvirus infection in both patients. Phylogenetic analysis of the amplified sequences from the viruses obtained from the two patients showed that the infectious agents were closely related and cluster with pseudocowpox viruses.

■ COMMENTARY

These two case reports describe infection due to molecularly confirmed novel parapoxviruses. Parapoxviruses cause infections in ruminants (sheep, goats, and cattle), and are common worldwide. A proliferative dermatitis develops in the mouth, teats, and skin of infected animals, and can cause fatal infection in young animals. Previously recognized zoonotic infections due to parapoxviruses include orf and milker's nodule, and result from close contact with infected animals. These infections are an occupational risk for farmers and animal health care workers. These two cases reported in this paper emphasize the importance of taking a careful exposure history and being persistent in the approach to diagnosis of non-healing cutaneous infections. The identification of this previously unrecognized parapoxvirus is a testament to the power of modern molecular diagnostic methods. Since specific antiviral agents to treat parapoxviruses are not available, surgical debridement probably plays a role in treatment.

Due to reforestation in the East Coast of the United States and loss of natural predators, the population of white-tailed deer has increased dramatically over the past 100 years, and humans are now living in closer proximity to deer than at any time in the past. We are certain to see more of this infection in the years to come. ■

SPECIAL FEATURE

Pharmacokinetics, Pharmacodynamics, Clinical Efficacy, and Stability of Continuous or Extended Infusion Regimens of Carbapenems

By Andy Chan, PharmD Candidate, and Jessica C. Song, MA, PharmD

Andy Chan is PharmD Candidate, University of the Pacific,
and Jessica C. Song is PharmD, University of the Pacific

Both Andy Chan and Jessica C. Song report no financial relationships relevant to this field of study.

In intensive-care units, death attributable to infections caused by multidrug-resistant bacteria, especially *Pseudomonas aeruginosa* and *Acinetobacter baumannii* species, is a common occurrence.[1] Given their broad spectrum of activity, carbapenems are frequently prescribed for empirical treatment of hospital-acquired infections.[2] Furthermore, this class of antimicrobial drugs has been shown to be consistently effective against difficult-to-treat pathogens, including extended-spectrum beta-lactamase producing Gram-negative bacilli and Acinetobacter species.[3]

In theory, the clinical efficacy of time-dependent antibiotics, such as carbapenems, could be maximized with increased exposure times that the antimicrobial concentrations remain above the minimum inhibitory concentration (MIC) (T > MIC).[4-5] In-vitro and in-vivo animal studies have suggested that a T > MIC in excess of 40% is required for optimal activity of carbapenems.[6] However, Li et al recently questioned the validity of this pharmacodynamic target.[7] Their study of meropenem-treated patients with lower respiratory tract infections revealed that a 54% T > MIC predicted microbiological success.

Extended- or continuous-infusion dosing schemes have been explored to improve bactericidal exposure β-lactam antibiotics require for bacterial eradication. At present, pharmaceutical manufacturers recommend intermittent administration of carbapenems. However, intermittent administration could potentially lead to high peaks and troughs that fall below the MIC during the dosing interval. In contrast, continuous infusion of carbapenem antibiotics results in constant serum levels above the MIC.[6]

The intent of this review is to discuss the pharmacokinetic and pharmacodynamic properties of continuous- and extended-infusion carbapenems in critically ill patients. In addition, carbapenem stability is addressed due to concerns about decreased potency in extended- and continuous-infusion regimens. A summary of recently published clinical studies of extended- and continuous-infusion carbapenem regimens used in critically ill patients will be highlighted in this article.

Pharmacokinetics/Pharmacodynamics

Critically ill patients pose a significant challenge with regard to antimicrobial dosing, given the wide array of pathophysiological changes that can occur in this population. Increases in volume of distribution (V_d) and clearance of antimicrobials can result in reduced plasma concentrations of drug in critically ill patients with septic shock.[6] Roberts and associates conducted a pharmacokinetic/pharmacodynamic study that enrolled 10 septic, ventilator-dependent patients with normal renal function.[8] Five patients received intermittent bolus (IB) meropenem (MP), and the other patients received continuous infusion (CI) MP. Monte Carlo simulation was performed using three IB, three CI, and three extended-infusion (EI) dosing regimens. *Table 1* summarizes demographic data, inclusion criteria, and doses reported in this study and the other pharmacodynamic/pharmacokinetic studies discussed in this section.

Of note, Roberts et al reported that their patients' V_d (median 22.7 L) and drug clearance (mean 13.6 L/H) were significantly larger compared with healthy volunteers in other studies.[8] The increase in V_d was attributed to the level of sickness severity in septic patients. Also, since the relatively youthful cohort population lacked signs of renal dysfunction, increased clearance levels were seen compared with previous studies in critically ill patients. Overall, continuous infusion maintained a higher trough level than intermittent bolus in both plasma and subcutaneous tissue.

Roberts et al also used the Monte Carlo simulation model to determine probability of target attainment (PTAs) (40% *f*T>MIC) and cumulative fraction of response (CFR) with IB, CI, and EI regimens.[8] All three simulated dosing regimens achieved 100% pharmacodynamic targets against most Gram-negative bacteria. Higher doses (3 grams to 6 grams) were required to achieve *f*T>MIC > 40% with EI and CI regimens in less susceptible organisms such as *Pseudomonas aeruginosa* (MIC_{90} 8 mg/L) and Acinetobacter species (MIC_{90} 16 mg/L).

In patients with renal failure who require continuous renal replacement therapy, ineffective antimicrobial therapy occurs more frequently than toxicity due to excessively high doses of drug.[4] In a prospective, randomized, crossover design, Langgartner and associates studied pharmacokinetic properties of CIMP and IBMP in six critically ill patients receiving continuous haemodiafiltration.[4] Median %T>MICs for CIMP at 4mg/L (100%) and 8 mg/L (100%) surpassed %T>MICs seen for IBMP (45.9%-67.9%). Meropenem maintained its potency in the infusion solution at room temperature (25^0C) for 12 hours, with a 7% loss in concentration at the end of the dosing interval.

Sakka and associates assessed the free-drug concentrations exceeding the MIC (*f*T>MIC) value of imipenem in a prospective, randomized, controlled study that included 20 critically ill patients with nosocomial pneumonia.[2] Due to stability concerns, the study investigators reconstituted imipenem 250 mg every three hours for patients who underwent continuous infusion. Despite the achievement of *fT*>MICs of 100% in all patients, three patients died, two from the CI treatment group, and one from the IB treatment group. Logistic-regression analysis revealed that a SOFA (sepsis-related organ failure assessment) score of 8 predicted survival outcome ($p = 0.012$). The pharmacokinetic analysis revealed a mean clearance of imipenem/cilastatin of 12.3 L/h and a V_d (central compartment) of 12.2 L, similar to that observed in healthy volunteers. However, increases in both parameters were noted in younger patients (≤ 46 years) and in patients with higher body surface areas (BSA ≥ 1.84 m^2), suggesting the need for higher doses of imipenem/cilastatin for those patients.

Thalhammer et al analyzed pharmacokinetic properties of meropenem in 15 intensive-care unit patients with suspected or proven community- or hospital-acquired infections.[5] This prospective, randomized, crossover study used a CIMP regimen that delivered a 50% lower dose of MP than the intermittent administration (IA) regimen. CIMP yielded a mean steady-state serum concentration of 11.9 mg/L, whereas IAMP treatment resulted in a mean trough serum concentration of 8.5 mg/L. Steady state and trough serum concentrations of MP seen with CI and IA, respectively, exceeded the MICs of most Gram-positive and Gram-negative pathogens recovered in the ICU. No adverse effects were noted in any patients during the study period. The study investigators highlighted the potential cost savings associated with CIMP, given that half of the dose required by IAMP maintained bactericidal serum concentrations of MP.

Studies of Critically Ill Patients

Two recent clinical studies have assessed clinical cure rates associated with the use of extended- and continuous-infusion MP regimens.[1,9] To date, there is limited published data on the clinical efficacy of other carbapenems administered through continuous- or extended-infusion. Wang et al conducted a prospective cohort study that included 30 patients with hospital-acquired pneumonia caused by multidrug resistant *Acinetobacter baumannii*.[1] *Table 2* summarizes demographic data, inclusion/exclusion criteria, doses reported in this study, as well as the second study discussed in this section. The two treatment groups (extended infusion and intermittent infusion) showed similar clinical efficacy with regard to treatment duration, relapse ratio, and successful bacterial eradication. However, extended-infusion MP lowered total antibiotic cost by 34% ($p < 0.01$), thereby highlighting the potential cost savings that may occur when replacing intermittent therapy with prolonged-infusion therapy.

A retrospective cohort study conducted by Lorente and colleagues featured 89 patients with ventilator-associated pneumonia (VAP) primarily caused by *Pseudomonas aeruginosa*, *Escherichia coli*, *Serratia marcescens*, and Enterobacter species.[9] Outcome measures included: 1) overall clinical cure rates in VAP patients (given CIMP or intermittent infusion (II) MP), 2) clinical cure rates observed in patients with VAP caused by *Pseudomonas aeruginosa*, and 3) clinical cure rates observed in patients infected with pathogens with MIC_{90} ≥ 0.50 mg/L. CIMP-treated patients showed improved clinical cure rates compared with IIMP-treated patients (90.5% vs. 59.6%; OR 6.4, 95% CI, 2.0-21.1, $p < 0.001$). In addition, CIMP therapy resulted in superior cure rates compared with IIMP (84.6% vs. 40%; OR 8.2, 95% CI 1.3-51.3, $p = 0.02$) in the

Table 1: Pharmacokinetic/Pharmacodynamics of Continuous Infusion/Extended Infusion Carbapenems in Critically Ill patients

Author (Year)	Design/ Study Outcomes	Inclusion Criteria	Dosing Regimens	Patient Population	Results	Comments
Roberts (2009)[8]	Prospective, randomized **Outcomes** 1.To determine differences in plasma and subcutaneous tissue concentration–time profiles of meropenem (MP) administered by intermittent bolus dosing (IB) or continuous infusion (CI) to critically ill patients with sepsis and normal renal function. 2. Utilization of population pharmacokinetic modeling and Monte Carlo simulations to assess the cumulative fraction of response (CFR) against Gram-negative pathogens	Known or suspected sepsis of a critically ill patient; normal renal function[a]	IB MP (n = 5): 1.5 g first dose (infused over 5 min.), then 1 g q8h (infused over 3 min.) CI MP (n = 5): loading dose 500 mg (infused over 3 min.), followed by 1 g q8h (administered as three separate doses of 1,000 mg over 8 h in 250 mL of 0.9% sodium chloride)	Ten critically ill ventilated patients with sepsis IB: mean age, 55 years; mean day 1 cSOFA score 3; mean CrCl, 106 mL/min. CI: mean age, 57 years; mean day 1 SOFA score, 5; mean CrCl, 93 mL/min.	**PTA (Probability of Target Attainment) for P. aeruginosa:** CFR for CI: MP 1,500 mg/day, 43.8%; MP 3,000 mg/d, 100%; MP 6,000 mg/d, 100%. CFR for extended infusion (infused over 4 h): 500 mg q8h, 50%; 1,000mg q8h, 68.8%; 2,000 mg q8h, 96.9. CFR for IB: 500 mg q8h, 12.5%; 1,000 mg q8h, 40.6%; 2,000 mg q8h, 68.8%. **Pharmacokinetics** Median Vd, 22.7 L; mean CL, 13.6 L/h; Subcutaneous Tissue Day 1 and 2 Cmin (mg/L): 0 for IBMP; 4 for CIMP (p = 0.02-0.03) . Plasma Day 1 and 2 C_{min} (mg/L): 0 for IBMP; 7-8 for CIMP (p = 0.01-0.02).	Meropenem is stable for at least 8 h at 22°C, thus three 1,000 mg infusions given. Continuous infusion MP resulted in significantly higher Cmin in subcutaneous tissue and plasma compared with intermittent bolus MP. Meropenem Vd and clearance were shown to be higher in this cohort of septic patients, compared with values reported in healthy volunteer studies. Higher doses of CIMP (3 g or 6g) suggested by authors for *P. aeruginosa* (MIC90 8 mg/L) and Acinetobacter spp. (MIC90 16 mg/L)
Langgarter (2007)[4]	Prospective, randomized, crossover outcomes to test whether CI of MP achieves effective drug concentrations comparable to IB in patients treated by continuous hemodiafiltration.	1. Suspected infection requiring antibiotic therapy 2. Suspected pathogen susceptible to MP 3. > 18 years 4. I.V. antibiotic treatment of infection anticipated to be necessary for more than 4 days 5. Renal failure requiring CRRT	Patients received MP as 0.5 g IV loading dose followed by 2 g CI over 24 h divided into two 1 g fractions or 1 g IB over 15-20 min given every 12 h. IB or CI were continued for 48 hours then patients were crossed over to the other treatment for another 48 hours.	Investigators enrolled 11 patients, but 5 were excluded. Mean age, 53.6 years; pneumonia (n = 1), pneumonia and sepsis (n = 2), acute pancreatitis (n = 1), and sepsis (n = 2)	**Pharmacokinetics:** CI median: %(T)> 8mg/L, 100%; CL: 4.40 L/h; C_{max} 20 mg/L; C_{min} 15.7 mg/L IB median: %(T) > 8mg/L, 45.9; CL: 4.32 L/h; C_{max} 62.8 mg/L; C_{min} 8.2 mg/L; t1/2 5.3 h	Meropenem showed stability in the infusion solution at 25 °C for 12 h, with a loss of concentration of 7%. %T>MIC of CIMP patients surpassed %T>MIC of IBMP patients.

Table 1: Continued from previous page

Author (Year)	Design/ Study Outcomes	Inclusion Criteria	Dosing Regimens	Patient Population	Results	Comments
Sakka (2007)[2]	Prospective, randomized, crossover, controlled. **Outcomes** To study PTA of *f*T≥MIC of 20%, 30%, and 40% for imipenem/cilastatin (I/C) concentrations	ICU-acquired pneumonia[b] (length of time of endotracheal intubation and mechanical ventilation > 3 days); normal renal function	CI (n = 10): 7g/7g IC infused over 76 h (83.3/83.3 mg/h started 4h post loading dose of 1g/1g), then received 1 g/1 g I/C q8h Intermittent infusion (II) (n = 10): 1g/1g I/C (infused over 40 min) TID for 3 days	Patients were randomized to either II or CI II: mean age, 59 years; mean APACHE II score, 28; CrCl (mL/min), 128; mean ICU length of stay, 12d; mean SOFAc score, 6 CI: mean age, 62 years; mean APACHE II score, 26; CrCl (mL/min), 122; mean ICU-length of stay, 14 d; mean SOFA, 7	**PTA:** *f*T≥MIC of 20%, 30%, 40% for all recovered pathogens was 100% (n = 20) **Pharmacokinetics**[a] CL 12.3 ± 4.2 L/h; $V_{central\ compartment}$: 12.2 L ± 9.9 L	Antibiotic pretreatment was given in the II and CI groups Covariates of age, weight, height, and body surface area explained 88.8% of the variance in imipenem clearance SOFA score of 8 predicted survival using logistic regression where this was entered as a dichotomous variable (p = 0.012)
Thalhammer (1999)[5]	Prospective, randomized, crossover **Outcomes** 1. To determine the differences in pharmacokinetic parameters of CIMP and intermittent administration (IA) MP 2.To determine therapeutic concentrations with 3 g CIMP over 24 h 3.Side effects of IAMP regimen	Predicted duration of treatment required to be at least 4 days & any two of the following: elevated C-reactive protein > 10 mg/dL; ≥ one positive blood culture (Gram-negative or Gram-positive bacteria) or two positive blood cultures showing coagulase-negative staphylococci; clinical signs of infection; respiratory tract infection (new infiltrate on chest X-ray); positive urine culture	All patients received 2g IV loading dose of MP followed by 3 g CI (over 48 hours) or IA 2 g MP IV q8h for 2 days. After 2 days patients were switched to alternative MP regimen.	Fifteen patients in the intensive care unit: mean age, 55.3 years; hospitalized with pneumonia (n = 7), sepsis (n = 3), systemic inflammatory distress syndrome (n = 5); mean CrCl, 83.7 mL/min; white blood cell count, 16.5 G/L; C-reactive protein level, 19.8	**Pharmacokinetics**[a] IA mean values: AUC mg/L x h, 193.8; Cl_{tot} L/h, 9.4 ± 1.2; C_{max} mg/L, 110.1; C_{min} mg/L 8.5; Vss L, 26.6 ± 3.2; $t_{1/2}$ 2.4 h; k_{el}, 0.32 h^{-1} CI mean values: AUC mg/Lx h, 117.5; Cl_{tot} L/h, 7.7 ± 1.4; Vss L, 25.9 ± 5.7; C_{ss} mg/L 11.9 Only AUC and Cltot achieved $p \leq 0.01$	2 g MP was diluted in 100 mL of isotonic saline solution, 1 g MP was reconstituted according to the manufacturer's guidelines and then diluted with 50 mL of isotonic saline solution. No adverse effects were observed during study period. CIMP yielded cost savings, given that half of the amount required by IAMP maintained bactericidal serum levels of MP. Note: wide confidence intervals and retrospective study design.

[a]Normal renal function defined as: plasma creatinine concentration < 120 mol/L

[b]Pneumonia classified as the presence of infiltrates in the chest X-ray and microbiology tests positive for bacteria in tracheal or bronchial secretions

[c]SOFA: sepsis-related organ failure assessment

Table 2: Clinical Efficacy of Continuous/Extended Infusion Carbapenem in Critically Ill Patients

Author (Year)	Study Design/ Primary Outcomes	Inclusion Criteria	Exclusion Criteria	Patient Population	Dosing Regimens	Results
Wang (2008)	Prospective cohort **Outcomes:** 1. Clinical Cure and Bacterial Response: Using Clinical and Pulmonary Infection Score and Ministry of Public Health diagnosis 2. Relapse rate 3. Days of treatment 4. Meropenem (MP) cost	Patients with HAP[a] due to cultured multidrug-resistant[b] *A. baumannii*	N/A	Conventional Bolus (CB) MP (n = 15): Mean age 39.7 years; Sex(M:F) 9:6; APACHEII[c] mean score, 17.33 Extended Infusion (EI) MP (n = 15): Mean age 44.3 years; Sex (M:F) 10:5; APACHEII mean score, 20.33 MIC_{90} for *A. baumannii*: 2 mg/L	CB MP: 1 g IV Q8h (infused over 1 hour) EI MP: 500 mg Q6h (infused over 3 hours)	**Clinical Cure for CB vs. EI:** Successful cure rate on day 3, 40% vs. 33% ($p > 0.05$); day 5, 87% vs. 93% ($p > 0.05$); day 7, 100% vs. 100% ($p > 0.05$) **Cost:** CB vs. EI ($): 1038.38 vs. 684.05, $p < 0.01$ **Mean days of treatment:** 5.27 for CB vs. 4.80 for EI ($p > 0.05$) **%T>MIC:** EI, 75%; CB, 54% (*p* value not reported)
Lorente (2006)	Retrospective cohort study **Outcomes** To assess the clinical efficacy of continuous vs. intermittent infusion of meropenem for the treatment of ventilator-associated pneumonia (VAP) caused by Gram-negative bacilli.	Patients with VAP[c] due to Gram-negative bacteria who were administered MP from July 2002 to June 2005.	≤ 18 years; pregnancy; lactation; β-lactam allergy; VAP caused by MP-resistant microorganism; AIDS; neutropenia (WBC < 1x $10^3/mm^3$); solid or hematologic tumor; CrCl < 60 mL/min	Continuous Infusion (CI) (n = 42): mean age 57.25 year; APACHE II[c] score on ICU admission, 15.3; common causative organisms for VAP: *P. aeruginosa* (30.9%), *E. coli* (16.7%); *Serratia marcescens* (14.3%); Enterobacter spp (11.9%); *K. pneumonia* (9.5%); H. influenzae (7.1%) Intermittent Infusion (II) (n = 47): mean age 56.5 years; APACHE II score on ICU admission, 15.2; common causative organisms for VAP: *P. aeruginosa* (31.9%), *E. coli* (17.0%); *Serratia marcescens* (14.9%); Enterobacter spp (12.8%); *K. pneumonia* (8.5%); *H. influenzae* (6.4%)	II: MP 1 g q6h (infused over 30 min.) CI: MP loading dose 1 g over 30 min, then 1 g q6h (infused over 6 hours)	Cure rates: in all VAP patients, CI (90.5%) vs. II (59.6%), OR 6.4 (95% CI, 2.0-21.1, $p < 0.001$) VAP due to Pseudomonas, CI (84.6%) vs. II (40%), OR 8.2 (95% CI, 1.3-51.3, $p = 0.02$) MIC > 0.50 mg/L, CI (80.9%) vs. II (29.4%), OR 7.8 (95% CI, 2.3-46.1, $p = 0.003$) Note: wide confidence intervals and retrospective study design.

[a]HAP = Hospital-acquired pneumonia

[b]Multidrug-resistance defined by: susceptible to no more than one class of antimicrobial agents, excluding colistin, but susceptible to carbapenems (meropenem)

[c]APACHE, Acute Physiology and Chronic Health Evaluation

[d]VAP = ventilator-associated pneumonia as defined by the following: chest radiography showing new or progressive infiltrate; new onset of purulent sputum or alteration in sputum character; body temperature < 35.5^0C or > 38^0C; white blood cell count > 10,000 cells/mm^3 or < 4,000 cells/mm^3; tracheal aspirate > 10^6 colony-forming units/mL or isolation of the same microorganism in respiratory secretions and blood.

treatment of VAP caused by *Pseudomonas aeruginosa* and when the MIC of the organism was 0.5 µg/mL or greater (80.9% vs. 29.4%; OR 7.8, 95% CI 2.3-46.1, $p = 0.003$).

Stability

Earlier studies have shown that carbapenems lack the stability shown by other antimicrobial agents, such as ceftazidime or piperacillin, in concentrated solutions stored under warmer incubation conditions.[10] Berthoin et al examined the influence of time and concentration on degradation rates of MP and doripenem solutions at lower and higher temperatures (25^0C, 37^0C).[10] MP concentrations in excess of 4 g/100 mL reached the degradation threshold of 10% in 12 hours at 25^0C. The 10% degradation threshold occurred at 6 hours for MP 4 g/100 mL stored at 37^0C and for MP 6 g/100 mL stored at 25^0C. In contrast, doripenem 1 g/100 mL (maximal approved concentration, 0.5 g/100 mL) maintained its potency for 12 hours at 37^0C and for 24 hours at 25^0C. The study investigators recommended limiting the concentration of MP to 4 g/100 mL and maintaining temperatures at or below 25^0C.

Conclusion

Over the past decade, novel dosing strategies for β-lactams, such as prolonged and continuous infusion, have been considered over traditional intermittent infusion in an attempt to optimize efficacy against challenging pathogens. Pharmacokinetic/pharmacodynamic studies of meropenem, the best-studied carbapenem, have primarily utilized loading doses ranging from 0.5 g to 2 grams and doses of continuous-infusion meropenem ranging from 2 g to 3 g/24 hours in critically ill patients. Clinical studies assessing the efficacy of continuous-infusion/extended-infusion regimens have used daily doses of meropenem ranging from 2 g/day up to 4 g/day.

Numerous pharmacodynamic studies have established the efficacy of continuous-infusion meropenem regimens in attaining 40% T>MIC. However, randomized clinical studies with larger patient populations are warranted to further substantiate the benefits of continuous infusion of meropenem.

Package inserts for meropenem, imipenem/cilastatin, ertapenem, and doripenem recommend usage within 4, 4, 6, and 12 hours, respectively, at room temperature.[11-14] Based on the standards set forth by U.S. pharmaceutical companies, continuous infusion of carbapenems cannot be performed without the possibility of excessive drug degradation. However, investigators of studies that used continuous- or extended-infusion meropenem regimens argued in favor of the maintenance of drug potency at room temperature despite prolonged use.

Meropenem is traditionally given as a 1 g intravenous dose administered every 8 hours. However, doses as low as 2 g infused over 24 hours (extended- or continuous-infusion) have been studied in pharmacodynamic/pharmacokinetic and clinical studies. Given that continuous- or extended-infusion meropenem regimens potentially require lower doses than conventional intermittent dosing regimens, additional pharmacoeconomic studies are warranted to further elucidate the benefits of prolonged-infusion carbapenem regimens. ■

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CME Questions

19. **Which of the following is correct with regard to antibiotic therapy of acute otitis media in children 6-35 months of age?**

a. Amoxicillin-clavulanate use was associated with diarrhea in 67% of patients.
b. Amoxicillin-clavulanate use was associated with a reduced risk of treatment failure relative to placebo administration that was first apparent after 6 days of therapy.
c. Amoxicillin-clavulanate therapy was associated with reduced overall treatment failure relative to placebo administration, but there was no difference in the rate of resolution of otoscopic abnormaities.
d. Treatment with amoxicillin-clavulanate relative to placebo was associated with a "number needed to treat" to avoid treatment failure was 3.8.

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

a. The antibacterial activity of carbapenems is time-dependent, rather than concentration dependent.
b. Doripenem is more stable in solution than meropenem.
c. The volume of distribution (Vd) of meropenem is reduced in septic patients compared to healthy vounteers.
d. High pathogen MIC is associated with an increasd likelihood of pharmacodynamic target attainment with meropenem administration.

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

a. Lorente et al found that administration of meropenem by continuous infusion was associated with improved clinical cure rates compared to its intermittent administration.

B. The concentration of carbapenems in serum must be above the MIC of the infecting organism for > 80% of the dosing interval to assure an optimal antibacterial effect in vivo.

C. The concentration of carbapenems in serum must be above the MIC of the infecting organism for > 62% of the dosing interval to assure an optimal antibacterial effect in vivo.

D. Meropenem maintains 100% of its original antibacterial activity in solution over the 24 hour period used for continuous infusion.

Answers: 19. (d); 20. (b); 21. (b)

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]

Neutrophil Band Count

UPDATES

By Carol Kemper, MD, FACP

Do I Smell a Rat — Smelling TB?

Source: Poling A, et al. Using giant African pouched rats to detect tuberculosis in human sputum samples: 2009 findings. *Am J Trop Med Hyg*. 2010;83:1308-1310.

As reported here in 2003, the World Bank began funding a project to train giant pouched Gambian rats to sniff out tuberculosis (TB) in sputum specimens in sub-Saharan Africa. Rats have been successfully trained to target landmines, and using a similar training/reward technique, pilot data suggested that rats could be trained to detect TB in respiratory specimens. Compared to a trained technician (~ 95% accuracy), preliminary data in 2003 suggested the rats were able to detect TB in 92% of smear-positive cases and 77% of culture-positive cases, with a 2% false-positive rate.

The rats have since gotten better. While trained technicians were able to identify AFB in 13.3% of 10,523 respiratory specimens by light microscopy, the rats were able to detect an additional 600 cases. When multiple rats were allowed to pause for 5 seconds over each specimen, the specificity improved to 89%. All it takes is training — and bananas. Compared to a trained technician, who can process about 20 specimens in a day, the rats are much more efficient — but they don't do any clean up.

Safer-sex Intervention for HIV-discordant Couples

Source: El_Bassel N, et al. National Institute of Mental Health Multisite Eban HIV/STD prevention intervention for African-American HIV serodiscordant couples. *Arch Intern Med*. 2010;170:1594-1601.

Researchers in four American cities (Los Angeles, Philadelphia, Atlanta, and New York) participated in a multistate HIV- and STD-prevention trial in African-American HIV-discordant heterosexual couples (> 18 years of age). A total of 535 couples who reported unprotected sex within the prior three months were randomized to a safer-sex intervention based on the "Eban" system or to a health-promotion (HP) group. The Eban system is based on an African concept of fencing off a safe space for loved ones and family as a form of protecting the family unit. Couples in this group participated in eight weekly 2-hour sessions with play acting, problem solving, communication, and negotiation. Using a blocked randomization algorithm, different couples received Eban intervention as a single couple, in groups of couples, or in same-sex groups. In contrast, the HP group received individual health counseling.

The primary outcome was the number of condom-protected acts of intercourse over the next 12-month period. Secondary outcomes included the cumulative incidence of STDs and HIV seroconversion.

The woman was the positive partner in 60% of the couples (varying from 57% to 64% between sites). Attendance at the Eban sessions was remarkably good — the average attendance was 91%, with 86% of the couples attending all eight sessions. In comparison, 76% of the couples participated in all of the HP sessions.

Following the Eban sessions, the number of couples who consistently used condoms 100% of the time increased from 11% at baseline to 42% within the immediate post-intervention period. The effect was remarkably sustained, with approximately 36% of couples maintaining 100% compliance at 6 and 12 months. In the HP group, 100% consistent condom use increased from 14% at baseline to 27% immediately post-intervention, and also remained fairly stable at 6 and 12 months. The number of unprotected sex acts in "inconsistent" users also was significantly reduced in both intervention groups, although the reduction was similar between groups. The cumulative incidence of STDs did not significantly differ between groups over the 12-month period.

HIV seroconversion occurred in two persons in the Eban group and three persons in the HP group, giving an overall annual seroconversion rate for HIV-discordant

couples in studies was 935 per 100,000. When compared to the general annual HIV seroconversion rate in the African-American community in the United States (about 84 per 100,000), the risk of HIV transmission within discordant couples, as demonstrated in this study, is still alarmingly high — despite whatever the intervention.

Transfusion-associated HIV

Source: CDC. HIV transmission through transfusion — Missouri and Colorado, 2008. *MMWR*. 2010;59: 1335-1339.

Estimates of the risk of HIV transmission from blood products in the United States are approximately 1 in 1.5 million. This translates into approximately 11 potential HIV+ donors and 20 contaminated blood products. Despite these risks, this report details the only case of documented transfusion-associated HIV transmission reported to the CDC since 2002.

A 40-year-old male who reported no risk factors for HIV infection, and was a regular blood donor (for no remuneration), donated blood in June and November 2008. His specimens in June tested HIV negative by EIA and by nucleic acid testing of mini-pooled plasma specimens, but the November donation tested positive. As per the Missouri Department of Health's protocol, the donation from June was re-examined and potential recipients of that donation identified.

Blood products from the donor went to two individuals, including an older man who died within two days of cardiac surgery; there were no specimens or tissues available to examine whether HIV could have been transmitted. The second patient had chronic renal failure on hemodialysis for several years, and received a single unit of fresh frozen plasma during kidney transplant surgery. He had last tested HIV negative three years earlier. By the time the recipient was identified, he had a negative HIV EIA, a plasma RNA viral load of 7,240, and a CD4 count of 48 cell/mm^3. He was pre-emptively started on antiretroviral therapy and, by April, his EIA was positive and his CD4 had improved. Sequencing of the donor and recipient HIV DNA demonstrated > 99% similarity.

The (former) blood donor was married but admitted to casual and anonymous sex (both male and female), generally when intoxicated.

While the blood donation system for infectious screening is obviously effective, the weakest link is the failure of individuals, such as this man, to honorably acknowledge their own risky behaviors and refrain from putting others at risk. But if you are practiced in deception (and willingly place your wife and sexual partners at risk), how can we expect the safety of a stranger to matter?

Is There a Safer Stud?

Source: MedPage Today, January 10, 2011.

Investigators examined the risk of periodontal infection and longer-term consequences of tongue piercings in a randomly selected group of people (ages 16 to 26 years of age) who were getting their first tongue piercing. As reported in the *Journal of Adolescent Health* (Kapferer I, et al. Tongue piercing: The effect of material on microbiological findings. *J Adolesc Health*. 2011; e-pub), colony counts of 80 different bacteria were examined by DNA hyberidization methods in the oral cavities, tongues, and on the studs of 85 patients within two weeks of tongue piercing. The studs were either made of stainless steel, titanium, polytetrafluoroethylene, or polypropylene.

Concentrations of bacteria were significantly greater on the tongue, and especially in the stud tract in patients with tongue piercings. Unlike the usual gingival bacterial flora found in the oral cavity, 18 other types of bacteria were found at significantly higher colony counts on the tongues, and eight bacteria were more commonly found on the studs. Colony counts were significantly higher on the stainless steel studs than on other products, suggesting that bacteria could more effectively create biofilms with stainless steel studs.

Late complications of tongue piercing included recession of the tongue from around the stud in 29%, and in 5% had chipped teeth. No one developed gingivitis. Based on this data, tongue-piercers should consider the safety of different tongue studs. ■

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.*

Statin Use in Patients with Abnormal Liver Function

In this issue: Statins and liver function; dosing timing for thyroxine; rivaroxaban for VTE, DVT, and stroke; echinacea and the common cold; and FDA actions.

Statins and liver function

Most physicians are hesitant to use statins in patients with abnormal liver function tests (ALT or AST less than three times the upper limit of normal). A new study suggests that not only are statins safe and effective, they may improve liver abnormalities in patients with fatty liver. In a study recently published in the *Lancet*, 437 patients enrolled in the Greek Atorvastatin and Coronary Heart Disease Evaluation study population were noted to have moderately abnormal liver tests at baseline, which were possibly associated with non-alcoholic fatty liver disease. Of that group, 227 were treated with a statin (atorvastatin) and 210 were not. Patients treated with a statin had substantial improvement in liver tests ($P < 0.0001$), whereas the group not treated with a statin had further increases in liver enzyme concentrations. Cardiovascular events occurred in 10% of atorvastatin-treated patients vs 30% of the non-statin group (60% relative risk reduction; $P > 0.0001$). This was a greater improvement in benefit than seen in patients with normal liver function tests. Fewer than 1% of the participants who received a statin had to discontinue statin treatment because of transaminase concentrations more than three times the upper limit of normal. The authors concluded that "statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in patients with mild to moderately abnormal liver tests that are potentially attributable to nonalcoholic fatty liver disease" (*Lancet* 2010;376:1916-1922). ■

Dosing timing for thyroxine

When is the best time to take thyroxine? Patients are generally told to take it on an empty stomach in the morning and wait at least 30 minutes before eating. A new study suggests that taking thyroxine at bedtime might be a better option. Over 6 months, 105 patients were randomized to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Taking levothyroxine at bedtime lowered thyrotropin levels and increased free thyroxine and total triiodothyronine levels (the primary outcome). Treatment did not change secondary outcomes including quality of life. The authors concluded that taking levothyroxine at bedtime is a good alternative to morning intake (*Arch Intern Med* 2010;170:1996-2003). This would likely benefit patients who find it difficult to wait 30 minutes to eat after taking their thyroxine each morning. ■

Rivaroxaban: an oral, factor Xa inhibitor

Rivaroxaban is an oral, direct factor Xa inhibitor that is approved in several countries for the prevention of venous thromboembolism (VTE) after orthopedic surgery. It is currently being evaluated by the FDA for this indication. Based on the findings of the EINSTEIN study, it appears the drug is also effective for the treatment of acute deep vein thrombosis (DVT). EINSTEIN consists of three randomized trials of rivaroxaban, one for the treatment of acute DVT, one for treatment of acute pulmo-

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nary embolism, and one for continued, long-term treatment in patients who have received treatment for acute DVT or pulmonary emboli. The results of the first and third wings of the study were recently reported in the *New England Journal of Medicine*.

In the DVT treatment arm, 3449 patients with acute DVT were randomized to rivaroxaban (50 mg twice daily for 3 weeks, followed by 20 mg once daily) or subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months. In the continued treatment wing of the study, patients were randomized in a double-blind fashion to rivaroxaban 20 mg once daily or placebo for additional 6 or 12 months after completion of 6-12 months of treatment for VTE. The primary outcome for both studies was recurrent DVT. For the treatment of acute DVT, rivaroxaban was non-inferior to enoxaparin-vitamin K antagonist (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.44-1.04; $P < 0.001$). In the continued treatment study, rivaroxaban had superior efficacy compared to placebo (8 events [1.3%] vs 42 events [7.1%] with placebo; HR 0.18; 95% CI, 0.09-0.39; $P < 0.001$). There were four patients in the rivaroxaban group with non-fatal major bleeding vs none in the placebo group. The EINSTEIN authors concluded that "Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation" (*N Engl J Med* 2010;363:2499-2510).

Rivaroxaban is also being evaluated for the prevention of stroke in patients with nonvalvular atrial fibrillation based on the ROCKET AF study, which was presented at the American Heart Association meetings in November 2010. If approved, it will join the recently approved direct thrombin inhibitor dabigatran (Pradaxa®) for this indication. Both drugs have the advantage over warfarin of not requiring ongoing lab monitoring. ■

Echinacea and the common cold

The National Center for Complementary and Alternative Medicine (NCCAM), a division of NIH, has been in existence for nearly 20 years, much of the time under the intense scrutiny of the mainstream medical community. Despite NCCAM's attempts to verify the effectiveness of alternative healing practices, most if not all rigorously studied modalities have been shown to be ineffective. The benefit of another alternative staple, echinacea, is questioned with the publication of a NCCAM-sponsored study testing the benefit of the herbal remedy for treating the common cold. More than 700 patients in Wisconsin with new-onset common cold were assigned to one of four groups: no pills, placebo pills (blinded), echinacea pills (blinded), or echinacea pills (unblinded). The primary outcome was severity of the cold by self reporting with secondary outcomes of interleukin-8 levels and neutrophil counts from nasal washes. The comparison of the two blinded groups showed a trend toward benefit for the echinacea group (an average decrease in duration of cold of 7-10 hours out of 1 week; $P = 0.089$), but no difference in mean illness duration. There were no differences in the secondary outcomes. The authors concluded that the differences in illness duration and severity were not statistically significant with echinacea compared to placebo (*Ann Intern Med* 2010;153:769-777). ■

FDA Actions

The FDA is removing the breast cancer indication for bevacizumab (Avastin-Genentech). The somewhat unusual move was made after an FDA advisory panel suggested last summer that the drug did not provide a survival benefit for patients with breast cancer and at the same time caused serious side effects. The drug is still approved for treating cancer of the brain, colon, kidney, and lung.

The **FDA advisory panel is recommending approval for the first new diet pill in a decade. Orexigen Therapeutics' Contrave® is a combination of the antidepressant bupropion and the opioid antagonist naltrexone.** The drug was recommended for approval by a vote of 13-7, with some committee members voicing concern about potential side effects of the drug and recommending close post-marketing follow-up and studies to assess the risk of major cardiac events. The recommendation to approve the drug was based on studies that show an average weight loss 4.2% greater than placebo.

The **FDA has approved denosumab for the prevention of skeletal related events (fracture and bone pain) in patients with bone metastases from solid tumors.** The drug, which is given as a once monthly injection, was approved after a 6-month priority review. Denosumab is a monoclonal antibody to RANKL, a protein essential for the formation, function, and survival of osteoclasts. Denosumab in a lower-dose formulation was recently approved for the treatment of osteoporosis under the trade name Prolia™. Amgen Inc. will market the drug for this new indication under the trade name Xgeva™. It is expected to compete strongly with Novartis Pharmaceutical's zoledronic acid (Zometa®), which is approved for the same indication. ■