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Microbial Translocation and HIV Infection

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Vice Chair, Department of Medicine, Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center

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

Synopsis: *Patients infected with both HIV-1 and HIV-2 underwent measurement of plasma lipopolysaccharide (LPS). LPS was elevated in patients with AIDS vs. earlier-stage infection. LPS levels were correlated inversely with CD4+ lymphocyte count and positively correlated with plasma HIV RNA levels in both HIV-1- and HIV-2-infected patients.*

Source: Nowroozalizadeh S, et al. Microbial translocation correlates with the severity of both HIV-1 and HIV-2 infections. *J Infect Dis*. 2010; 201:1150-1154.

Twenty-one patients with HIV-1/AIDS, seven patients with HIV-2/AIDS, 43 patients with HIV-1 chronic infection, and 66 patients with HIV-2 chronic infection in Guinea-Bissau were studied along with 66 HIV-negative policemen. LPS was measured by limulus amebocyte lysate assay, and IL-12 and IFN-alpha were measured in whole blood following mitogen and toll-like receptor (TLR) stimulation. Elevated microbial translocation (as assessed by LPS levels) was correlated with the presence of AIDS, lower CD4+ lymphocyte count, and higher viral load, but was independent of type of HIV infection (HIV-1 vs. HIV-2). In addition, defective mitogen and innate immune responsiveness was correlated with LPS level.

COMMENTARY

Over the last several years, increasing recognition has been given to the role of microbial translocation in HIV pathogenesis in both adults and children.[1,2] Studies in non-human primates have shown that very early in the course of

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experimental SIV infection, a dramatic depletion of CD4+ lymphocytes from gut-associated lymphoid tissue (GALT) occurs, and that this correlates with increased microbial translocation. Studies in HIV-1 infected humans reveal similar CD4+ depletion from GALT and increased microbial translocation as well. There is increasing evidence that much of the "pro-inflammatory" state associated with HIV infection may be related to this phenomenon and may contribute to acceleration of atherosclerosis and more rapid progression of liver disease associated with chronic hepatitis B and C virus infections. While nonspecific immune activation is commonly seen in HIV infection, hyporesponsiveness to specific pathogens is also characteristic.

This study is important since it demonstrates a significant correlation between disease stage and microbial translocation, as assessed by LPS levels. While HIV-2 infection is generally associated with slower disease progression than HIV-1 infection, this study also shows that when controlled for clinical disease state and CD4+ count that microbial translocation is similar in HIV-1- and HIV-2-infected patients. The data suggest that earlier institution of antiretroviral therapy (ARV) might be beneficial, although small studies presented to date have not conclusively demonstrated that ARVs are very effective in reversing GALT CD4+ depletion and in reducing microbial translocation. At any rate, the data presented in this study are interesting and worthy of larger follow-up studies that include correlation of LPS levels with specific HIV disease manifestations. ■

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Pharmacokinetic, Pharmacodynamic, and Clinical Efficacy of Continuous or Extended Infusion Regimens of Piperacillin/Tazobactam

SPECIAL FEATURE

By Jessica C. Song, MA, PharmD
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Jessica C. Song reports no financial relationships relevant to this field of study.

PIPERACILLIN/TAZOBACTAM (P/T) OFFERS ONE OF THE BROADEST antimicrobial spectrums, and is equipped with an effective mechanism to maintain its potency in the presence of beta-lactamases. The potent and broad spectrum activity of P/T makes it a viable option for empirical treatment of mixed infections, multidrug-resistant pathogens, and beta-lactamase-producing organisms.[1-4] With such a wide spectrum of activity, and potential for many uses, overuse of this agent may account for a sizeable percentage of hospitals' antimicrobial expenditures.[4]

Time-dependent antimicrobial agents, including ß-lactam/ß-lactamase inhibitor antibiotics such as P/T, rely on the length of time that concentrations are maintained above the pathogen's minimal inhibitory concentration (MIC) to maximize bacterial eradication.[5-11] For time-dependent drugs such as P/T, the percentage of time that drug levels exceed the MIC ($\%_{T > MIC}$) required to yield a bactericidal effect can vary to some extent, depending on the pathogen. Adequate drug exposure for *Staphylococcus aureus* and *Streptococcus pneumoniae*/Enterobacteriaceae usually is achieved with $\%_{T > MIC}$ of at least 40%-50% and 60%-70% of the dosing interval, respectively.[12,13]

Recent years have witnessed the development of both prolonged- and continuous-infusion P/T regimens in an at-

tempt to maximize efficacy against challenging pathogens such as *Pseudomonas aeruginosa*, while minimizing acquisition costs associated with P/T.[5-11] At present, limited published data exist on the pharmacokinetics/pharmacodynamics and clinical efficacy of prolonged- and continuous-infusion P/T regimens in critically ill patients. The purpose of this review will be to discuss the pharmacokinetic and pharmacodynamic properties of extended- and continuous-infusion P/T regimens in critically ill patients. In addition, a summary of recently published clinical studies of extended- and continuous-infusion P/T regimens used in critically ill patients will be highlighted in this article.

PHARMACOKINETICS/ PHARMACODYNAMICS

Attainment of target concentrations of P/T in critically ill, septic patients poses a challenge to clinicians, given the pathophysiological changes seen in this population. Critically ill patients have been shown to display increased volume of distribution and clearance of P/T, which places patients at risk for low plasma concentrations.[5] Roberts et al conducted a pharmacokinetic/ pharmacodynamic study of 16 critically ill patients (*see Table 1*) with known or suspected sepsis.[5] Eight patients received continuous infusion P/T (12/1.5 g daily), and eight patients received intermittent bolus P/T, given as 4.5 grams infused every 6 to 8 hours. Monte Carlo simulations were performed using three continuous infusion regimens, four intermittent administration regimens, and two extended infusion regimens.

P/T volume of distribution was approximately 2.5- to nearly four-fold higher in critically ill patients compared with other studies in healthy volunteers. In addition, P/T clearance reported in this study was considerably higher compared with other studies in healthy volunteers. Roberts et al proposed that the disease process led to increased cardiac output and consequent increased renal clearance. The probability of target attainment (PTA) of $f_{T > MIC}$ (free concentration maintained above the MIC for 50% of the dosing interval) ranged from a low of 40% with P/T infused intermittently as 4 g (as piperacillin) every eight hours up to 74% with P/T infused intermittently as 3 g every four hours. Extended-infusions of P/T 4 g every 6 to 8 hours yielded PTAs of 69% to 81%. Continuous infusion of P/T (8/1–16/2 g) yielded PTAs of 89% to 93%.

Table 1 summarizes key findings of other pharmacokinetic/pharmacodynamic studies of continuous-infusion and extended-infusion P/T. Briefly, Patel et al conducted a pharmacodynamic study[6] of P/T extended-infusion and intermittent infusion regimens in 105 hospitalized patients, three of whom displayed creatinine clearances below 40 mL/min. The FDA recommends lowering P/T doses from 4.5 g given every six hours to 3.375 g infused every six hours in patients with creatinine clearances of 20-40 mL/min. A Monte Carlo simulation determined PTAs (50% $f_{T > MIC}$) of intermittent-infusion and extended-infusion P/T regimens in patients with varying degrees of renal impairment. Of note, all P/T regimens yielded suboptimal PTAs at an MIC of 32 mg/L in patients with creatinine clearances ranging from 20 mL/min to 100 mL/min. Based on the PTAs observed in the few patients with creatinine clearances between 20 to 40 mL/min, Patel et al recommended a dose of intermittent P/T 3.375 g infused every six hours or P/T 3.375 g infused over four hours every 12 hours in patients with creatinine clearances at or below 20 mL/min.

Roberts et al measured subcutaneous tissue piperacillin concentrations (used microdialysis technique) in 13 ventilator-associated pneumonia patients who either received P/T 4.5 g infused every 6 to 8 hours or P/T (12/1.5 g) as a continuous infusion on a daily basis.[7] The intermittent-infusion group received 235 mg/kg of piperacillin during the first 30 hours, whereas the continuous-infusion group received 164 mg/kg ($p = 0.06$). Patients who received intermittent-infusion P/T were significantly older ($p = 0.04$) than patients who received continuous-infusion P/T. Median tissue concentrations did not differ significantly between the two groups on days one and two of therapy.

Boselli et al determined alveolar concentrations of P/T in 40 ventilator-associated pneumonia (VAP) patients with normal/mild renal impairment (n = 20) or moderate-advanced renal impairment (n = 20). Patients in each group underwent randomization to receive P/T 12/1.5 g or 16/2 g daily as a continuous infusion, following a loading dose of P/T (4/0.5 g). Nine of the 20 patients with normal/mild renal impairment had infections caused by *Pseudomonas aeruginosa* (MICs, 1-4 mg/L). Sixty percent of the patients receiving the lower P/T dose yielded epithelial lining fluid concentrations of piperacillin below 16 mg/L; median epithelial lining fluid concentration/serum concentration ratios for piperacillin were 0.43 and 0.46, respectively, for higher and lower doses of P/T. None of the patients with moderate/advanced renal impairment yielded epithelial lining fluid concentrations of piperacillin below 16 mg/L. Roberts et al cautioned against using the lower dose of P/T (12/1.5 g) as a continuous infusion in VAP patients with normal renal function, since this regimen may not yield sufficiently high epithelial lining fluid concentrations of piperacillin in order to exceed the susceptibility breakpoint (16 mg/L) for both Enterobacteriaceae and nonfermentative gram-negative bacteria.

STUDIES OF CRITICALLY ILL PATIENTS

Table 2 summarizes key points from three recently published clinical studies of continuous-infusion and extended-infusion P/T regimens in critically ill patients. Unfortunately, with the exception of one small study (n = 40), none of the published studies were prospective, randomized, and controlled studies. Lorente et al conducted a historical

Table 1: Pharmacokinetics/Pharmacodynamics of Continuous Infusion/Extended Infusion Piperacillin/Tazobactam in Critically Ill Patients . . . continued on next page

Study Outcomes	Inclusion Criteria	Dosing Regimens	Patient Population	Results	Comments
Roberts (2010) 1. Probability of target attainment (PTA) of 50% time for which the free concentration of piperacillin/ tazobactam (P/T) is maintained above minimum inhibitory concentration (MIC) during a dosing interval 2. Clearance (Cl), volume of distribution (V_d), maximum concentration (C_{max}), and minimum concentration (C_{min})	Known or suspected sepsis; normal renal function (plasma creatinine < 120 µmol/L).	Intermittent bolus (IB): 4.5 g IV Q 6-8 h; continuous infusion (CI): day 1, 4.5 g loading dose followed by 8/1g P/T (in 500 mL normal saline); day 2 CI: 12/1.5 g P/T in 500 mL normal saline (given over 24 h) **Other Regimens Evaluated for PTA** P/T 3.375 g IV Q4h; P/T 3.375 g IV Q6h; P/T extended infusion 4.5 g IV Q6-8 h; P/T CI 16/2 g/d.	Sixteen critically ill patients (half assigned to each group); median ages, 41 y IB, 20 y CI; day 1 APACHE II[a] scores 24 IB, 20, CI; all patients ventilated.	**PTA:** cumulative fraction of response (CFR) for P/T 3.375 g IV Q6g, 74%; P/T 3.375 g IV Q4h, 49%; P/T 4.5g IV Q8h, 40%; P/T 4.5g IV Q6h, 53%: P/T extended infusion (EI, over 3h for Q6 h and 4h for Q8h) 4.5g IV Q8h, 69%; P/T EI 4.5g IV Q6h, 81%; P/T CI 8/1g/d, 89%; P/T CI 12/1.5g/d, 92%; P/T CI, 16/2g/d, 93% **Pharmacokinetics:** Cl 17.1 L/h (95% CI, 14.4-20.6); V_d: 25.0 L (95% CI, 19.2-34.4) ; C_{max} 266.6 mg/L (208.2-292.3) for IB and 144 mg/L (118-224) for CI; day 1 C_{min} 7.2 mg/L (3.2-12.5) for IB and 7.1 mg/L (3.8-26.4) for CI; day 2 C_{min} 6.2 (2.7-10.7) mg/L for IB and 21.2 mg/L (15.9-30.6) for CI.	1. Cl of P/T in critically ill patients 52%-112% higher vs. healthy volunteers; 25% higher in critically ill vs. patients with intra-abdominal infections. 2. V_d of P/T in critically ill patients 2.5-3.4-fold higher vs. healthy volunteers and 12% higher vs. intra-abdominal infection patients. 3. Likelihood of attaining 50% $f_{T > MIC}$[b] improved with EI and CI P/T regimens.

cohort study of 74 VAP patients during a five-year time period.[9] Comparators included P/T (4.5 g given every six hours) and P/T administered as a continuous infusion (4.5 g infused over 6 hours every six hours). Compared with intermittent infusion-treated patients, continuous infusion-treated patients showed significantly higher cure rates when infected with gram-negative bacteria with higher MICs (8-16 mg/L). Continuous-infusion P/T showed similar efficacy as intermittent-infusion P/T with regard to mortality rate, length of ICU stay, and duration of mechanical ventilation.

Lodise et al performed a retrospective cohort study of 194 patients who had cultures positive for Pseudomonas aeruginosa (~ 50% from respiratory tract).[10] Outcome measures included 14-day mortality and hospital length of stay. Patients either received P/T 3.375 g infused every four hours or P/T 3.375 infused over four hours every eight hours. The study investigators conducted a classification- and regression-tree analysis and found that patients with APACHE II scores of 17 and higher showed significantly lower 14-day mortality rates, along with significantly shorter median length of stay with extended-infusion P/T compared with intermittent-infused P/T.

In a prospective, randomized, controlled trial of 40 septic patients presenting with systemic inflammatory response syndrome,[11] the clinical efficacy of piperacillin-intermittent (not combined with tazobactam; 3 g every six hours) infusion and piperacillin-continuous infusion (8 g daily) was assessed. Clinical outcome measures included reduction in APACHE II score, time to defervescence, normalization of white blood cell count, and mortality rate. Continous infusion-treated patients trended toward a shorter time to defervescence compared with intermittent infusion-treated patients ($p = 0.08$). Patients receiving continuous-infusion piperacillin exhibited significantly greater reductions in APACHE II scores compared with intermittent-infusion-treated patients ($p < 0.05$) on days two through four of piperacillin therapy. Continuous infusion-treated patients did not demonstrate superior mortality rates or shorter times to normalize white blood cell count compared with intermittent infusion-treated patients.

CONCLUSION

Over the past decade, novel dosing strategies for P/T, such as prolonged and continuous infusion, have been con-

Table 1: Pharmacokinetics/Pharmacodynamics of Continuous Infusion/Extended Infusion Piperacillin/Tazobactam in Critically Ill Patients . . . continued on next page

Study Outcomes	Inclusion Criteria	Dosing Regimens	Patient Population	Results	Comments
Patel (2010) To determine PTA of 50% $f_{T > MIC}$ for patients with varying degrees of renal impairment who received traditional (IB) vs. extended infusion (EI) P/T.	Provision of plasma samples from hospitalized patients receiving P/T.	**IB P/T:** If CrCl[c] > 40 mL/min, 4.5 g IV Q6 h; if CrCl 20-40 mL/min, 3.375 g IV Q6h; infusion, 0.5h **EI P/T:** If CrCl > 40 mL/min, 3.375 g IV Q8h (infused 4h); if CrCl 20-40 mL/min, 3.375 g IV Q12h (infused 4 h)	93 hospitalized patients received IB P/T, and 12 hospitalized patients received EI P/T; mean age 53.2 y, 63% male, mean weight 71.3kg, mean CrCl, 91.6 mL/min **(only 3 patients had CrCl < 40 mL/min)**	**Probabilities of achieving 50% $f_{T>MIC}$ with IB P/T:** **4.5 g IV Q6 h (CrCl 100 mL/min)**: 0.93 for MIC (mg/L) 1; 0.88 for MIC 2; 0.81 for MIC 4; 0.67 for MIC 8; 0.46 for MIC 16; **3.375g IV Q6h (CrCl 40 mL/min)**: 0.99 for MIC 1; 0.98 for MIC 2; 0.95 for MIC 4; 0.90 for MIC 8; 0.77 for MIC 16; **3.375g IV Q6h (CrCl 20 mL/min)**: 0.99 for MIC 1; 0.99 for MIC 2; 0.98 for MIC 4; 0.95 for MIC 8; 0.88 for MIC 16 **Probabilities of achieving 50% $f_{T>MIC}$ with EI P/T:** **3.375 g IV (4h) Q8 h (CrCl 100 mL/min)**: 0.99 for MIC (mg/L) 1; 0.99 for MIC 2; 0.99 for MIC 4; 0.97 for MIC 8; 0.73 for MIC 16; **3.375g IV Q12h (CrCl 40 mL/min):** 0.98 for MIC 1; 0.96 for MIC 2; 0.90 for MIC 4; 0.79 for MIC 8; 0.52 for MIC 16; **3.375g IV Q12h (CrCl 20 mL/min**): 0.99 for MIC 1; 0.98 for MIC 2; 0.96 for MIC 4; 0.90 for MIC 8; 0.74 for MIC 16	1. This analysis included a small number of patients with CrCl < 40 mL/min 2. Consider using P/T 3.375 g IV Q6h for patients with CrCl ≤ 20 mL/min and extended infusion P/T 3.375 g IV Q12h for patients with CrCl ≤ 20 mL/min 3. Avoid using P/T (both bolus and extended infusion) if MIC ≥ 32mg/L
Roberts (2010) To determine plasma and tissue concentrations achieved with IB P/T and CI P/T in ventilator-associated pneumonia (VAP) patients	Critically ill patients with known or suspected sepsis with plasma creatinine < 120 µmol/L	**Traditional (IB) P/T:** 4.5 g IV Q6-8 h **CI P/T : day 1**, 4.5g P/T loading dose, then 8/1g P/T over 24h (*p* = 333 mg/h) ; **day 2**, 12/1.5 g P/T over 24h (*p* = 500 mg/h).	13 VAP patients; seven randomized to IB and six to CI group. Patients in CI group significantly younger (*p* = 0.04); day 1 APACHE II scores of 24.0 for IB and 17.5 for CI group (*p* = 0.17).	**Tissue Concentrations:** day 1, 2.4 mg/L in CI and 2.2 mg/L in IB (*p* = 0.48); day 2, 5.2 mg/L in CI and 0.8 mg/L in IB (*p* = 0.45). **Plasma Concentrations:** day 1, 8.9 mg/L in IB and 4.9 mg/L in CI (*p* = 0.078); day 2, 16.6 mg/L in CI and 4.9 mg/L in IB (*p* = 0.007).	1. Small number of patients. 2. Patients with impaired renal function excluded. 3. Comparable degree of tissue penetration seen with 25% lower dose used in CI vs. bolus dosing.

Table 1: Pharmacokinetics/Pharmacodynamics of Continuous Infusion/Extended Infusion Piperacillin/Tazobactam in Critically Ill Patients

Study Outcomes	Inclusion Criteria	Dosing Regimens	Patient Population	Results	Comments
Boselli (2008) To determine epithelial lining fluid (ELF) concentrations of lower and higher dose CI P/T in VAP patients with normal or impaired renal function	Critically ill patients on mechanical ventilation with suspected VAP (developing five or more days after start of mechanical ventilation)	**CI P/T Regimens** P/T 4/0.5 g loading dose followed by 12/1.5 g or 16/2 g over 24 h (diluted in 48 mL sterile water, infused at rate of 2 mL/h).	Forty patients (20 normal renal function, 20 renally impaired): age, 56-59 years for no/mild renal failure and 65-68 for moderate/advanced renal failure; SAPS II scores[d]: 33-41 for no/mild renal failure and 60-63 for moderate/advanced renal failure; CrCl of 34 ml/min in moderate/ advanced renal failure.	**Steady State ELF Concentration** **No/Mild Renal Failure Patients with Identified Pathogens (20):** 60% had ELF levels of piperacillin < 16 mg/L with P/T 12/1.5 g and 40% had ELF levels of piperacillin < 16 mg/L with P/T 16/2 g; median ELF/serum ratios were 0.43-0.46 for piperacillin. **Moderate/Advanced Renal Failure Patients with Identified Pathogens** None of the 20 patients receiving P/T 12/1.5g or 16/2 g had ELF levels of piperacillin < 16mg/L; median ELF/serum ratios were 0.39-0.49 for piperacillin.	1. Authors suggested target serum concentration of piperacillin of 35-40 mg/L to provide alveolar concentrations of P/T necessary to eradicate Enterobacteriaceae and non-fermentative gram-negative bacteria in VAP patients. 2. P/T CI 12/1.5 g too low for VAP patients with normal renal function?

[a]APACHE, Acute Physiology and Chronic Health Evaluation

[b]$f_{T>MIC}$: time for which the free (unbound) concentration is maintained above the minimum inhibitory concentration (MIC) during a dosing interval

[c]CrCl = creatinine clearance

[d]SAPS II, Simplified Acute Physiology Score

sidered over traditional intermittent infusion in an attempt to optimize efficacy against challenging pathogens. Pharmacokinetic/ pharmacodynamic studies have primarily utilized doses of continuous infusion P/T ranging from 12/1.5 g to 16/2 g in critically ill patients. Clinical studies assessing the efficacy of continuous-infusion regimens have used daily doses of piperacillin ranging from 8g/day up to 16 g/day. In contrast, studies of extended-infusion P/T have used lower daily doses of P/T (9/1.125 g), which could result in substantial cost savings, given the high acquisition cost of P/T.

At Santa Clara Valley Medical Center (San Jose, CA), the acquisition costs of P/T 4.5 g IV Piggyback and P/T 3.375 g vial are $19.70 and $14.40, respectively (per Pharmacy Purchasing, Feb. 9, 2010). Typical daily doses of P/T in critically ill patients range from 4.5 g infused every six hours to 4.5 g infused every eight hours. Reducing the daily dose of P/T from 12/1.5 g-16/2 g to 9/1.125 g (given as extended infusion) would result in a 27%-45% dose reduction for each patient. Since the estimated annual P/T expenditure (2009) approached $800,000, switching from intermittent infusion of P/T to extended infusion of P/T could potentially lower annual expenditures by $216,000 to $360,000.

Numerous pharmacodynamic studies have established the efficacy of continuous-infusion and extended-infusion P/T regimens in attaining 50% T > MIC. However, randomized clinical studies with larger patient populations are warranted to further substantiate the benefits of extended infusion of piperacillin-tazobactam. ■

Table 2: Clinical Efficacy of Continuous/Extended Infusion Piperacillin/Tazobactam in Critically Ill Patients . . . continued on the next page

Study Design/ Primary Outcomes	Inclusion Criteria	Exclusion Criteria	Patient Population	Dosing Regimens	Results
Lorente (2009) Historical cohort study **Outcomes** 1. Clinical Cure: complete resolution of all clinical signs and symptoms of pneumonia. 2. Mortality rate 3. Length of ICU stay 4. Duration of mechanical ventilation	Patients with VAP[a] due to gram-negative bacteria who were administered P/T (Piperacillin/ Tazobactam) from June 2002 to December 2007.	Age < 18 y; pregnancy or lactation; allergy to ß-lactam antibiotics; VAP due to gram (-) bacteria resistant to P/T; acquired immune deficiency syndrome (AIDS); neutropenia (< 1000 cells/mm^3); solid or hematological tumor; CrCl < 60mL/ min	**Continuous Infusion (CI) P/T (n = 37)**: mean age 63.2 y; APACHE II[b] score on ICU admission, 16.1; common causative organisms for VAP: *P. aeruginosa* (29.7%), *E. coli* (13.5%); Enterobacter spp (10.8%); *Serratia marcescens* (10.8%); *H. influenzae* (10.8%) **Intermittent Infusion (II) P/T (n = 37):** mean age 61.8 y; APACHE II score on ICU admission, 16.2; common causative organisms for VAP: *P. aeruginosa* (28.3%), *E. coli* (17.4%); Enterobacter spp (10.9%); *Serratia marcescens* (10.9%); *H. influenzae* (8.7%)	II P/T: 4.5 g IV Q6h (infused over 30 minutes) CI P/T: P/T loading dose of 4/0.5 g infused over 30 minutes, followed by 4/0.5 g infused over 6 hours IV Q 6h (each P/T dose diluted in 100 mL normal saline).	**Clinical Cure for CI P/T vs. II P/T:** MIC (mg/L) 4, 18/20 (90%) vs. 19/25 (76%), $p = 0.20$; MIC 8, 8/9 (88.9%) vs. 6/15 (40%), $p = 0.02$; MIC 16, 7/8 (87.5%) vs. 1/6 (16.7%), $p = 0.02$. **Other Outcomes:** no difference between two different dosing regimens with regard to mortality rate, length of ICU stay, and duration of mechanical ventilation.
Lodise (2007) Retrospective, cohort study **Outcomes** 1. 14-day mortality after *P. aeruginosa* culture collection 2. Hospital length of stay (LOS) after collection of *P. aeruginosa* positive culture sample up to discharge or death	Patients with cultures positive for *P. aeruginosa*: age ≥ 18 y; absolute neutrophil count ≥ 1000 cells/mm; P/T given within 1st 72 h of onset of *P. aeruginosa* infection; receipt of P/T ≥ 48 h; culture results meeting the Centers for Disease Control and Prevention's criteria for infection	Receipt of > 1d II of P/T prior to converting to extended infusion (EI); receipt of concomitant ß-lactam antibiotic with activity against *P. aeruginosa* ≤ 5 d of starting P/T; *P. aeruginosa* isolate with intermediate activity against P/T or resistant; requiring dialysis; solid-organ or bone marrow transplant; cystic fibrosis	**EI P/T (n = 102):** age 62.8 y; use of mechanical ventilator at culture sample collection, 54.9%; mean APACHE II score at onset of infection, 15.3; concomitant use of aminoglycoside, 22.8%; primary source of culture sample: respiratory tract (53.9%); urinary tract (20.6%); skin or soft tissue (10.8%) **II P/T (n = 92):** age 63.9 y; use of mechanical ventilator at culture sample collection, 56.5%; mean APACHE II score at onset of infection, 16.2; concomitant use of aminoglycoside, 25.5%; primary source of culture sample: respiratory tract (52.2%); urinary tract (13%; skin or soft tissue (25%, $p = 0.009$ vs. EI P/T	II P/T 3.375 g IV (infused over 30 minutes) Q4 h EI P/T 3.375 g (infused over 4 hours) IV Q8 h	**Overall 14-day mortality** EI P/T vs. II P/T: 8.8% and 15.2% ($p = 0.17$) Overall median LOS 18 d for EI P/T vs. 22.5 d for II P/T ($p = 0.09$) **Classification and Regression Tree Analysis** Patients with APACHE II score ≥ 17 showed lower 14-day mortality rates when receiving EI P/T vs. II P/T ($p = 0.04$) and shorter median LOS ($p = 0.02$).

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

Study Design/ Primary Outcomes	Inclusion Criteria	Exclusion Criteria	Patient Population	Dosing Regimens	Results
Rafati (2006) Prospective, randomized, controlled trial **Outcomes** 1. APACHE II score 2. Defervescence 3. WBC normalization 4. Mortality 5. $\%_{T > MIC}$	All septic patients presenting with systemic inflammatory response syndrome (SIRS)[c] due to suspected or documented infection.	Age < 18 years; allergy or hypersensitivity to ß-lactam antibiotics; dialysis or CrCl < 40 mL/min.	**CI Piperacillin (n = 20):** mean age 50.1 y; mean baseline APACHE II score, 16.4; common infection sites: respiratory tract (45%), intra-abdominal (20%), urinary tract (20%) **II Piperacillin (n=20):** mean age 48 y; mean baseline APACHE II score, 14.2; common infection sites: respiratory tract (45%), intra-abdominal (20%), urinary tract (15%)	Piperacillin (not combined with tazobactam) given as 2 g IV loading dose, followed by daily CI of 8g over 24 h Piperacillin 3g IV Q 6 h (infused 0.5 h)	**APACHE II Score** Days 2-4: significantly greater reductions in APACHE II score seen in CI vs. II groups ($p < 0.05$) **Defervescence** Times to normalize temperature: 1.7 ± 0.7 d for CI vs. 2.4 ± 1.5d for II ($p = 0.08$). **Other Clinical Outcomes** No difference between CI vs. II in normalizing WBC or improving mortality rates. **$\%_{T > MIC}$** 1. Ten pathogens from eight CI patients and six pathogens from four II patients 2. MIC of 16: $\%_{T > MIC}$ of 100% with CI and 62% with II 3. MIC of 32: $\%_{T > MIC}$ of 65% with CI and 39% with II

[q]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°C or > 38°C; white blood cell count > 10,000 cells/mm^3 or < 4000 cells/mm^3; tracheal aspirate > 106 colony-forming units/mL or isolation of the same microorganism in respiratory secretions and blood.

[b]APACHE, Acute Physiology and Chronic Health Evaluation

[c]SIRS definition: presentation of two or more of the following criteria: temperature > 38°C or < 36°C; heart rate exceeding 90 beats/minute; respiratory rate > 20 breaths/minute or P_{CO2} < 32 mmHg; WBC (white blood cell) count < 4000 cells/mm^3 or > 12,000 cells/mm^3; or band (immature) cells > 10%

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Tetracycline and T-cell Activation

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, IDSA

Synopsis: *In cell culture, minocycline demonstrated a dose-dependent decrease in single-cycle HIV infection and decreased viral RNA expression. Minocycline also decreased reactivation from latency and modulated activation marker expression and cytokine secretion of CD4+ T-cells in response to activation.*

Source: Szeto GL, et al. Minocycline attenuates HIV infection and reactivation by suppressing cellular activation in human CD4+ T cells. *J Infect Dis*. 2010;201:1132-1140.

CD4+ T CELLS WERE OBTAINED FROM HIV-NEGATIVE DONORS and HIV-positive patients receiving HAART with suppressed viremia. Using a single-cycle replication system and an X4 pseudovirus used to infect cells, minocycline, at concentrations from 0-50 ug/mL, demonstrated a dose-dependent reduction in the percentage of infected cells. T cells pretreated with minocycline, infected with HIV NL4-3, followed by activation with anti-CD3/CD28, yielded unchanged intracellular HIV DNA, but minocycline significantly reduced HIV RNA expression. In a cell-culture model of HIV latency, minocycline reduced the frequency of reactivation events by approximately 20%. In CD4+ T cells from HIV-infected patients with suppressed viremia on HAART pretreated with minocycline, reduced activation in response to anti-CD3/CD28 was observed as assessed by HIV gag RNA expression, although some degree of cytotoxicity was observed in vitro in the presence of the highest concentrations of minocycline. Dose-related suppression of expression of various cell-surface activation markers by minocycline was also demonstrated.

COMMENTARY

This study reports a series of in vitro studies which demonstrate that minocycline suppresses HIV replication in CD4+ T cells, decreases response of CD4+ T cells to costimulation, blunts secretion of cytokines, and alters surface marker expression. In this paper, the authors speculate that the immunomodulatory and anti-HIV effects of minocycline might be useful clinically. I am skeptical about this since the concentrations of minocycline needed to see such clinically useful dramatic effects are close to the levels that would likely be toxic in vivo. (One weakness of the cell-culture experiments is that the authors used the very insensitive trypan blue-dye exclusion assay to assess cytoxicity instead of more sensitive studies that use tetrazolium dyes to assess cellular oxidative function.)

Despite the likelihood that the findings of this study may not have clinical application, I still found the results to be very interesting. Over the last 20 years or so, the immunomodulatory and anti-inflammatory effects of several protein-synthesis-inhibiting antibiotics have received increasing attention. For example, antibiotics such as clindamycin and linezolid have been shown to reduce toxin production by both staphylococci and streptococci, and are of benefit in animal models and in human toxic-shock syndrome. Similarly, macrolides, such as azithromycin, have been shown to have beneficial anti-inflammatory effects (independent of antimicrobial activity) in pneumonia when combined with either cell wall-active antibiotics or fluoroquinolones. Similarly, tetracyclines have been demonstrated to have anti-inflammatory activities and can even have some activity in non-infectious diseases such as rheumatoid arthritis. In HIV infection, where viral transcription is, to a large extent, driven by pro-inflammatory cytokines and CD4+ T cell activation, adjunctive therapy with other immunomodulatory

agents more specific than tetracyclines, may still have a role some day in the treatment of HIV-infected patients. ■

CME Questions

33. Which of the following is correct with regard to the antibacterial effect of piperacillin/tazobactam?

A. It is concentration-dependent.

B. It is time-independent.

C. It is time-dependent.

D. It is neither concentration- nor time-dependent.

34. Which is correct regarding the administration of piperacillin/tazobactam?

A. Continuous infusion has been shown to result in lower drug-acquisition costs than is administraton by extended infusions.

B. Both continuous infusion and extended infusion are more likely to achieve pharmacodynamic targets in the treatment of Gram-negative bacillary infections than is standard intermittent infusion.

C. Standard intermittent infusion has been demonstrated to be associated with improved clinical outcomes in treatment of Gram-negative bacillary infections relative to continuous or extended infusions.

35. Which of the following is correct regarding the volume of distribution of intravenously administered piperacilli/tazobactam?

A. It is significantly smaller in critically ill patients than in healthy volunteers.

B. It does not differ between critically ill patients and healthy volunteers.

C. It is irrelevant to the likely success of therapy with this antibiotic formulation.

D. It is significantly greater in critically ill patients than it is in healthy volunteers.

Answers: 33. (c); 34. (b); 53. (d)

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. ■

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In Future Issues:

Anthrax in Injection Drug Users

UPDATES

By Carol Kemper, MD, FACP

Household Transmission of Influenza

Source: Ng S, et al. Effects of Oseltamivir treatment on duration of clinical illness and viral shedding and household transmission of Influenza virus. *Clin Infect Dis*. 2010;50:707-714.

These authors assessed the benefits of antiviral therapy of the index flu patient on reduced viral shedding and prevention of secondary household cases who did not receive chemoprophylaxis. They followed 384 patients with influenza during the 2007 and 2008 flu seasons (65% of whom had influenza A) and tracked 331 household contacts for up to 7-10 days using RT-PCR and viral culture of nose and throat specimens every 2-3 days. None of the household contacts received antiviral prophylaxis.

As anticipated, index cases who received oseltamivir within 24 hours of symptom onset had a statistically significant reduction in the duration of symptoms. However, while there was some reduction in the duration of viral shedding in these patients, the results were not statistically significant. The mean duration of viral shedding was six days (up to a maximum of 12 days). For patients receiving oseltamivir within 48 hours, the reductions in viral shedding were minimal (acceleration factor, 0.76 and 0.99 for 2007 and 2008, respectively, compared with index cases who did not receive antivirals). In such settings, shedding of virus has been well documented, and shedding of antiviral-resistant virus on therapy even been demonstrated.

The overall secondary attack rate in household contacts was 8.1%. Based on the initiation of oseltamivir within < 24 hrs., 24-48 hrs., or > 48 hrs of the index case, the secondary attack rate in their respective household members varied from 4.7% (95% CI, 1%-13%), 6.0 (CI 95%, 2.5%-12%), to 7% (95% CI, 1.5%-19%), compared with 8.7% (95% CI, 6.8-11.6%) in contacts of index cases who did not receive antiviral treatment ($p < .01$ for trend). The unadjusted protective effect of treatment of the index case began within 24 hours or > 24 hours of symptom onset was 46% and 31%, respectively. While the risk of secondary infection was lower if the household contact had been previously vaccinated, it was also lower if the index case was older or the household member was older. Household contact of index patients < 18 years of age had the highest risk of secondary infection. Thus, there appeared to be a modest reduction in infectivity of index cases who received oseltamivir, especially if they received prompt antiviral therapy.

Reintroduction of TB Meds following Hepatotoxicity

Source: Sharma SK, et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. *Clin Infect Dis*. 2010;50:833-839.

Drug-related hepatotoxicity during treatment for tuberculosis is a common barrier to initiation of antimycobacterial. While most hepatotoxicity results in minimal to no gastrointestinal complaints, some patients experience significant nausea, anorexia, vomiting, or abdominal pain. While there are several proposed methods for reintroducing TB therapy in these patients, there is no consensus as to how to proceed. Our local public health department strongly discourages the stepwise reintroduction of medications based on concerns about the potentiation of resistance, although this approach has been recommended by both the American Thoracic Society and the British Thoracic Society.

These investigators selected 237 consecutive patients with clinical and laboratory evidence of hepatotoxicity occurring during antimycobacterial treatment, and prospectively evaluated the risk of recurrent hepatotoxicity upon reintroduction of TB therapy over a three-month period. Hepatotoxicity was defined as ≥ 3 times the upper limit of normal transaminases on three consecutive occasions, $\geq$ 5 times the ULN transaminase on one occasion, or any elevation in transaminase associated with nausea, vomiting, anorexia, and jaundice. Patients were screened for other contributing causes of hepatotoxicity, such as hepatitis, HIV, and alcohol use; based on this, 58 patients were excluded from the analysis and four patients died.

Treatment was not reintroduced until normalization of liver function test results. The median time to normalization of liver test results was 18 days (range, 14 to 28 days), and the median time to reintroduction of medications was 23 days (range, 14 to 44 days).

Patients were randomly assigned to one of three retreatment strategies: the simultaneous reintroduction of all three meds (isoniazid, rifampin and pyrazinamide) at maximal dosages at day one; the stepwise reintroduction of medications at full dosages with rifampin at day one, INH at day eight, and PZA at day 15 (similar to the ATS recommendations); and the stepwise reintroduction of medications with dose-escalation beginning with INH 100 mg/day at day

one, increasing to full dose by day four, then rifampin 150 mg/day at day eight, increasing to full dose by day 11, and finally PZA at 500 mg/day at day 15, increasing to maximal dose by day 18 (according to the BTS guidelines).

Nineteen (10.9%) patients had recurrent treatment-related hepatotoxicity. The frequency of recurrent hepatotoxicity was similar (13.8% vs. 10.2% vs. 8.6%), (p = .69), respectively, for each of the three groups outlined above. In addition, the peak bilirubin and transaminase values were similar between the three groups. The median number of days to recurrent of hepatotoxicity was similar (14 for group 1 vs. 21 days for the other two groups, with a maximum of 35 days). No deaths were observed. The only risk factor associated with recurrent hepatoxicity was lower pretreatment albumin levels.

These data support the simultaneous reintroduction of full-dose TB medications in patients who have experienced hepatoxicity. The severity of the initial hepatotoxicity did not appear to predict the risk of recurrent hepatotoxicity, nor the severity of symptoms if recurrent hepatotoxicity occurred.

Chronic Fatigue Patients Banned from Blood Donation

Sources: Lombardi VC, et al. Detection of an infectious retrovirus, XMVR, in blood cells of patients with chronic fatigue syndrome. *Science*. 2009;326:585-589; Erlwein O, et al. Failure to detect the novel retroviral XMVR in chronic fatigue syndrome. *PLoS ONE*. 2009;5:e8519.

The debate regarding the potential infectious cause for chronic fatigue syndrome (CFS) became more intense during the past year, with a report published in *Science* in October 2009, suggesting a link between CFS and a murine retrovirus called xenotrophic murine leukemia virus-related virus (XMRV). Lombardi et al at the National Cancer Institute and the Cleveland Clinic identified XMRV gag sequences by nested polymerase chain reaction (PCR) in 68 (67%) of 101 samples from patients with CFS, compared with only eight (3.7%) of 218 peripheral blood mononuclear cells from healthy controls. XMRV *gag* and *env* sequences were detected in seven of 11 CFS patients and one of 11 controls. Although only fragments of virus were detected by molecular means, and it was not clear whether viable or infectious XMRV was present in these patients, additional work suggested that patient-derived XMRV was able to infect culture cell lines.

While attracting lots of attention, a causative link between XMRV and CFS has not been established. And there has been criticism levied at this report based on the limited description of the CFS patients, who were not randomly selected, and how the controls were defined. Furthermore, two other studies from the United Kingdom and the Netherlands were unable to reproduce these findings. Erlwein et al examined PBMCs from 186 patients with CFS in the United Kingdom, none of whom had evidence of XMRV.

Nonetheless, the Canadian Blood Service has decided to ban blood donations from patients with CFS. Although I cannot imagine that too many patients with CFS actually pony up their blood products, the Canadians have decided to take a cautious approach until further information is available. The U.S. Blood Service is in the process of evaluating the data, as well. One wonders, with the availability of molecular techniques for identifying viral particles, how many of us don't have fragments of something drifting through our systems, or minimally detectable upregulation of various latent viruses simply during periods of stress? How safe is safe enough for utilization of this important resource?

Chilblains: A Medical Mystery?

Sources: Prakash, et al. Idiopathic Chilblains. 2009; 122:1152-5; Bohman KD, et al. Perniosis (chilblains) masquerading as CA-MRSA: A case report. *Cases J*. 2009;2:6500; Noaimi AA and Fadheel BM. Treatment of perniosis with oral pentoxifylline in comparison with oral prednisolone plus topical clobetasol ointment in Iraqi patients. *Saudi Med J*. 2008;29:1762-1764.

I was recently requested to evaluate an elderly Pakistani male with recurrent lower extremity ulcerations and bullae with intermittent and progressive violaceous blisters and ulcers at the ends of his toes, mostly on the pads but also at the base of the nail bed. The lesions on the shins would occur every several weeks, mostly in the winter and spring months. He also had onychomycosis involving several toes and, at first, was thought to maybe have an "ID" reaction, but he failed to respond to a four-month course of terbinafine. An extensive workup, including biopsies and cultures, blood and stool examination for parasites and evaluation for auto-immune etiology or vasculitis was unrevealing. He had no evidence of hepatitis B, C, or E, and cryoglobulins were negative. Skin biopsy of a bullous lesion showed supepidermal blisters with mild perivascular inflammation and eosinophils.

The working diagnosis? Chilblains — also called perniosis. I remember my grandmother in Minnesota talking about chilblains, which is an old term for the vasospastic effect of cold exposure on the hands and feet. The lesions are characterized by blisters, ulcers, or even pustules are often accompanied by inflammation, burning, or itching. They resemble a vasculitic or thromboembolic lesion, but there is no evidence for either on biopsy. Interestingly, once it occurs, it apparently can continue for months after cold exposure has been removed. The treatment is conservative, although it's important to rule out a vasculitis or cryoglobulinemia, and includes avoiding cold or damp weather, and keeping the extremity warm. Calcium channel blockers, such as nifedipine, have been effective in many patients, and one Saudi study suggested that pentoxifylline may be beneficial. ■

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.*

Atypical Fractures and Bisphosphonate Therapy

In this issue: Fractures and bisphosphonate therapy, warfarin anticoagulation and influenza vaccine and cotrimoxazole, antiplatelet therapy with clopidogrel and aspirin, FDA Actions.

Bisphosphonates and atypical fractures

Atypical fractures of the femur have been linked with bisphosphonate therapy in several recent news stories. A recent industry-sponsored study looks to quell these concerns. Secondary analysis from three large randomized bisphosphonate trials with more than 14,000 women showed that among 284 hip or femur fractures recorded, a total of 12 fractures in 10 patients were classified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient years. As compared with placebo, the relative hazard ratio for the three trials did not meet statistical significance, although confidence intervals were wide. The authors conclude that the occurrence of fracture of the subtrochanteric or diaphyseal femur was very rare even among women who had been treated with bisphosphonates for as long as 10 years (*N Engl J Med*; published on-line March 24, 2010). An accompanying editorial published on-line at the same time by Elizabeth Shane, MD, Columbia University, acknowledges that despite excellent safety profiles, bisphosphonates have been associated with "atypical" fractures of the femur that occur with minimal or no trauma, generally affecting the proximal third of the femoral shaft. Most of these fractures have occurred in women on long-term alendronate therapy, occasionally taken together with other antiresorptive drugs, corticosteroids, or proton pump inhibitors. Shane points out that while these fractures represent concern, they are uncommon and actually occur more frequently in patients who are not on bisphosphonates. The results of this study "provide assurance that subtrochanteric fractures are extremely rare" and many more hip fractures are "prevented by bisphosphonates than are potentially caused by the drugs." Treatment with bisphosphonates up to 10 years is more effective than shorter-term treatment in preventing new vertebral fractures and nonvertebral fractures, but she also suggests that patients should be considered for "drug holidays with careful observation" if they have been on long-term therapy.

Warfarin, flu vaccine, and cotrimoxazole

Anticoagulation with warfarin requires careful monitoring. Concomitant use of medications may result in changes in the international normalized ratio (INR), which may increase the risk of bleeding or decrease the effectiveness of therapy. Two studies in the April 12 issue of *Archives of Internal Medicine* clarify the risk of two commonly used medications, influenza vaccine and the antibiotic trimethoprim-sulfamethoxazole. Patients on warfarin have been told that they need careful monitoring after the influenza vaccine, although the effect is not clear. Some guidelines have suggested that flu shots prolonged INRs, while others suggest the vaccine reverses the anticoagulation effect.

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) 262-5468; E-mail: paula.cousins@ahcmedia.com.

In this study, 104 patients on a stable warfarin regimen were randomized to receive influenza vaccine and subsequent placebo administration or vice versa. All patients were tested for coagulation variables and followed for clinical events. The influenza vaccine had no effect on anticoagulation compared to placebo. There were no fatal or major bleeding events. The authors conclude that the influenza vaccine has no significant effect on INR values or warfarin weekly doses in patients on chronic warfarin therapy and that close monitoring of INR values after influenza vaccine is not required (*Arch Intern Med* 2010;170:609-616).

Conversely trimethoprim-sulfamethoxazole (cotrimoxazole) may significantly prolong INRs with adverse clinical outcomes. In the population-based, nested case-controlled study using health care databases in Canada, residents 66 years or older who were treated with long-term warfarin were evaluated for upper gastrointestinal (GI) tract hemorrhage. Of the more than 134,000 patients on warfarin, 2151 patients were hospitalized for upper GI hemorrhage. Recent use of cotrimoxazole was almost four times more common in those hospitalized (adjusted odds ratio, 3.84; 95% CI, 2.33-6.33). The odds ratio for treatment with ciprofloxacin also was higher (1.94), but no significant association was observed with amoxicillin, ampicillin, nitrofurantoin, or norfloxacin. The authors conclude that among older patients receiving warfarin, cotrimoxazole is associated with a significantly higher risk of upper GI tract hemorrhage. Ciprofloxacin was also associated with risk and whenever possible clinicians should prescribe alternate antibiotics in patients receiving warfarin (*Arch Intern Med* 2010;170:617-621).

Clopidogrel and aspirin

What is the optimal duration of dual antiplatelet therapy with clopidogrel and aspirin in patients with drug-eluting stents? In previous studies, early discontinuation of dual antiplatelet therapy has been identified as a risk factor for late stent thrombosis. A new study seeks to determine whether dual antiplatelet therapy for more than 1 year is of value. In a study that merged data from two concurrent randomized, clinical trials, 2701 patients who had received drug-eluding stents and had been free of major adverse cardiac events, cerebrovascular events, or major bleeding for a period of at least 12 months were randomized to receive clopidogrel plus aspirin or aspirin alone. The primary endpoint was a composite of myocardial infarction (MI) or death from cardiac causes. The cumulative risk of the primary outcome at 2 years was 1.8% with dual antiplatelet therapy as compared with 1.2% with aspirin monotherapy (hazard ratio, 1.65; 95% confidence interval, 0.80-3.36; $P = 0.17$). The individual risks of MI, stroke, stent thrombosis, need for repeat revascularization, major bleeding, and death did not differ significantly between the two groups. However, there was a trend toward higher risk for these outcomes in the dual therapy group ($P = 0.051$ for MI, stroke, or death from any cause; $P = 0.06$ for MI, stroke, or death from cardiac cause). The authors conclude that use of dual antiplatelet therapy for longer than 12 months is not more effective than aspirin alone in patients who have received drug-eluding stents (*N Engl J Med* 2010; 362:1374-1382).

FDA Actions

Rifaximin, Salix Pharmaceutical's minimally absorbed (nonsystemic) oral antibiotic has been approved to reduce the risk of recurrent hepatic encephalopathy in patients with advanced liver disease. Rifaximin was previously approved to treat traveler's diarrhea. The drug, which is taken orally twice a day, appears to reduce ammonia levels by reducing gut flora. It is marketed as Xifaxan®.

The FDA has approved Pancreaze, a new pancreatic enzyme product for patients who do not produce enough pancreatic enzymes (due to cystic fibrosis, chronic pancreatitis, pancreatic surgery, etc.). Pancreaze is the third approved pancreatic enzyme product on the market after Abbott's Creon® and Eurand's Zenpep®. The approval coincides with the FDA's deadline to cease marketing unapproved pancreatic enzyme products that have been available for many years. In October 2007, the FDA announced a deadline of April 28, 2010, after which time unapproved products would no longer be available.

The FDA has approved the first generic version of the popular antihypertensive losartan (Cozaar®) as well as the combination of losartan and hydrochlorothiazide (Hyzaar®). This represents the first generic angiotensin receptor blocker on the market, a development that has been anxiously awaited by consumers. Losartan carries a boxed warning against using the drug during pregnancy. Generic losartan is available in 25 mg, 50 mg, and 100 mg strengths, while losartan/hydrochlorothiazide is available in 50 mg/12.5 mg, 100 mg/12.5 mg, and 100 mg/25 mg strengths.