**PRINCIPAIS *ABSTRACTS* DE ESTUDOS EM INFECTOLOGIA**

**PRODUTOS:**

1. Ecalta® (anidulafungina)
2. Tazocin (piperacilina-tazobactam)
3. Tygacil (tigeciclina)
4. Vfend (voriconazol)
5. Zitromax (azitromicina)
6. Zyvox (linezolida)

**ECALTA® (ANIDULAFUNGINA)**

**ANIDULAFUNGIN VERSUS FLUCONAZOLE FOR INVASIVE CANDIDIASIS**

Annette C. Reboli, et al.

N Engl J Med 2007;356:2472-82.

**BACKGROUND**

Anidulafungin, a new echinocandin, has potent activity against candida species. We compared anidulafungin with fluconazole in a randomized, double-blind, noninferiority

trial of treatment for invasive candidiasis.

**METHODS**

Adults with invasive candidiasis were randomly assigned to receive either intravenous

anidulafungin or intravenous fluconazole. All patients could receive oral fluconazole

after 10 days of intravenous therapy. The primary efficacy analysis assessed the global response (clinical and microbiologic) at the end of intravenous therapy in patients who had a positive baseline culture. Efficacy was also assessed at other time points.

**RESULTS**

Eighty-nine percent of the 245 patients in the primary analysis had candidemia only.

*Candida albicans* was isolated in 62% of the 245 patients. In vitro fluconazole resistance was infrequent. Most of the patients (97%) did not have neutropenia. At the end of intravenous therapy, treatment was successful in 75.6% of patients treated

with anidulafungin, as compared with 60.2% of those treated with fluconazole (difference, 15.4 percentage points; 95% confidence interval [CI], 3.9 to 27.0). The results were similar for other efficacy end points. The statistical analyses failed to show a “center effect”; when data from the site enrolling the largest number of patients were removed, success rates at the end of intravenous therapy were 73.2% in the anidulafungin group and 61.1% in the fluconazole group (difference, 12.1 percentage points; 95% CI, −1.1 to 25.3). The frequency and types of adverse events were similar in the two groups. The rate of death from all causes was 31% in the fluconazole group and 23% in the anidulafungin group (P = 0.13).

**CONCLUSIONS**

Anidulafungin was shown to be noninferior to fluconazole in the treatment of invasive

candidiasis. (ClinicalTrials.gov number, NCT00056368).

**TAZOCIN® (PIPERACILINA/TAZOBACTAM)**

**MORE POTENCY ASSAY RESULTS FOR GENERIC NON-USA LOTS OF PIPERACILLIN/TAZOBACTAM AND INITIAL REPORTS FOR GENERIC MEROPENEM COMPOUNDS MARKETED IN THE USA**

Ronald N. Jones

An ongoing program of international generic antimicrobial potency assays for piperacillin/tazobactam has been summarized here through December 2010, and the initial results for meropenem generic lots from the United States are also presented. Fifteen additional piperacillin/tazobactam generic lots revealed an average of −10% activity (range, +3 to −23%) compared to the branded product (Zosyn®; Wyeth-pfizer), a finding consistent with prior reports (46 lots) of −16%. In contrast, Meropenem branded and Generic products had equivalent assay results (5 generic lots from 2 manufacturers [Hospira and Sandoz]). In conclusion, potencies for generic lots of parenteral broad-spectrum β-lactams can vary widely when directly compared to branded products, requiring documentation by chemical, in vitro activity (potency assays as measured here), and purity testing before considering their addition to a hospital formulary.

**EXPANDED STUDIES OF PIPERACILLIN/TAZOBACTAM FORMULATIONS: VARIATIONS AMONG BRANDED PRODUCT LOTS AND ASSESSMENT OF 46 GENERIC LOTS**

Gary J. Moet

Diagnostic Microbiology and Infectious Disease 65 (2009) 319–322

The experience with analyzing the potency of piperacillin/tazobactam generic formulations by a precise multiorganism in vitro assay was expanded to 46 lots (29 manufacturers, 17 countries). Across all generic lots, the range of activity compared with a reference branded lot (RLOT; Zosyn®; Wyeth Pharmaceuticals, Philadelphia, PA) was +10% to −42% (average, −16%). Eight lots of Zosyn® were also tested with a range of +7 to −19 (average, only −6%), and the reproducibility (13 replicates) of the RLOT assay was confirmed (±3%). This ongoing quality assurance project demonstrated wide activity variations in piperacillin/tazobactam generic lots with a consistent trend toward subpotent performance (−16%) compared with the branded product. Generic substitutions within hospital formularies should consider parameters of in vitro activity, in addition to applied chemical analyses and measures of bioavailability to avoid potential adverse clinical consequences.

**TYGACIL® (TIGECICLINA)**

**THE EFFICACY AND SAFETY OF TIGECYCLINE FOR THE TREATMENT OF COMPLICATED INTRA-ABDOMINAL INFECTIONS: ANALYSIS OF POOLED CLINICAL TRIAL DATA**

Timothy Babinchak et al.

Clinical Infectious Diseases 2005; 41:S354–67

This pooled analysis includes 2 phase 3, double-blind trials designed to evaluate the safety and efficacy of tigecycline, versus that of imipenem-cilastatin, in 1642 adults with complicated intra-abdominal infections. Patients were randomized to receive either tigecycline (initial dose of 100 mg, followed by 50 mg intravenously every 12 h) or imipenem-cilastatin (500/500 mg intravenously every 6 h) for 5–14 days. The primary end point was the clinical response at the test-of-cure visit (12–42 days after therapy) in the co-primary end point microbiologically evaluable and microbiological modified intent-to-treat populations. For the microbiologically evaluable group, clinical cure rates were 86.1% (441/512) for tigecycline, versus 86.2% (442/513) for imipenem-cilastatin (95% confidence interval for the difference, \_4.5% to 4.4%; *P* ! .0001 for noninferiority). Clinical cure rates in the microbiological modified intent-to-treat population were 80.2% (506/631) for tigecycline, versus 81.5% (514/631) for imipenem-cilastatin (95% confidence interval for the difference, \_5.8% to 3.2%; *P* ! .0001 for noninferiority). Nausea (24.4% tigecycline, 19.0% imipenem-cilastatin [*P*p.01]), vomiting (19.2% tigecycline, 14.3% imipenem-cilastatin [*P*p.008]), and diarrhea (13.8% tigecycline, 13.2% imipenemcilastatin [*P*p.719]) were the most frequently reported adverse events. This pooled analysis demonstrates that tigecycline was efficacious and well tolerated in the treatment of patients with complicated intra-abdominal infections.

**THE EFFICACY AND SAFETY OF TIGECYCLINE IN THE TREATMENT OF SKIN AND SKIN-STRUCTURE INFECTIONS: RESULTS OF 2 DOUBLE-BLIND PHASE 3 COMPARISONSTUDIES WITH VANCOMYCIN-AZTREONAM**

E. J. Ellis-Grosse, et al.

Clinical Infectious Diseases 2005; 41:S341–53

Two phase 3, double-blind studies in hospitalized adults with complicated skin and skin-structure infections (cSSSI) determined the safety and efficacy of tigecycline versus that of vancomycin-aztreonam. Patients received tigecycline (100 mg, followed by 50 mg intravenously twice daily) or vancomycin (1 g intravenously twice daily) plus aztreonam (2 g intravenously twice daily) for up to 14 days. Populations were as follows: 1116 patients (566 treated with tigecycline, and 550 treated with vancomycin-aztreonam) constituted the modified intent-to-treat (mITT) population, 1057 patients (538 treated with tigecycline, and 519 treated with vancomycinaztreonam) constituted the clinical mITT (c-mITT) population, and 833 patients (422 treated with tigecycline,

and 411 treated with vancomycin-aztreonam) constituted the clinically evaluable population. Clinical responses to tigecycline and vancomycin-aztreonam at test-of-cure were similar: c-mITT, 79.7% (95% confidence interval [CI], 76.1%–83.1%) versus 81.9% (95% CI, 78.3%–85.1%) (*P*p.4183); and clinically evaluable, 86.5% (95% CI, 82.9%–89.6%) versus 88.6% (95% CI, 85.1%–91.5%) (*P*p.4233). Adverse events were similar, with increased nausea and vomiting in the tigecycline group and increased rash and elevated hepatic aminotransferase levels in the vancomycin-aztreonam group. Tigecycline monotherapy is as safe and efficacious as the vancomycin- aztreonam combination in treating patients with cSSSI.

**VFEND® (VORICONAZOL)**

**VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY**

**OF INVASIVE ASPERGILLOSIS**

Raoul Herbrecht et al.

N Engl J Med 2002;347:408-15

**Background**

Voriconazole is a broad-spectrum triazole that is active against aspergillus species. We conducted a randomized trial to compare voriconazole with amphotericin B for primary therapy of invasive aspergillosis.

**Methods**

In this randomized, unblinded trial, patients received either intravenous voriconazole (two doses of 6 mg per kilogram of body weight on day 1, then 4 mg per kilogram twice daily for at least seven

days) followed by 200 mg orally twice daily or intravenous amphotericin B deoxycholate (1 to 1.5 mg per kilogram per day). Other licensed antifungal treatments were allowed if the initial therapy failed or if the patient had an intolerance to the first drug used. A complete or partial response was considered to be a successful outcome.

**Results**

A total of 144 patients in the voriconazole group and 133 patients in the amphotericin B group with definite or probable aspergillosis received at least one dose of treatment. In most of the patients, the underlying condition was allogeneic hematopoietic-cell transplantation, acute leukemia, or other hematologic diseases. At week 12, there were successful outcomes in 52.8 percent of the patients in the voriconazole group (complete responses in 20.8 percent and partial responses in 31.9 percent) and 31.6 percent of those in the amphotericin B group (complete responses in 16.5 percent and partial responses in 15.0 percent; absolute difference, 21.2 percentage points; 95 percent confidence interval, 10.4 to 32.9). The survival rate at 12 weeks was 70.8 percent in the voriconazole group and 57.9 percent in the amphotericin B group (hazard ratio, 0.59; 95 percent confidence interval, 0.40 to 0.88). Voriconazole-treated patients had significantly fewer severe drug-related adverse events, but transient visual disturbances were common with voriconazole (occurring in 44.8 percent of patients).

**Conclusions**

In patients with invasive aspergillosis, initial therapy with voriconazole led to better responses and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with amphotericin B.

**ZITROMAX® (AZITROMICINA)**

**IS AZITHROMYCIN THE FIRST-CHOICE MACROLIDE FOR TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA?**

F. Sanchez et al.

Clinical Infectious Diseases 2003; 36:1239–45

Combination treatment with a b-lactam plus a macrolide may improve the outcome for elderly patients with community-acquired pneumonia (CAP). The prognoses and mortality rates for elderly patients with CAP who receive ceftriaxone combined with a 3-day course of azithromycin or a 10-day course of clarithromycin were compared in an open-label, prospective study. Of 896 assessable patients, 220 received clarithromycin and 383 received azithromycin. There were no significant differences between groups with regard to the severity score defined by the Pneumonia Patient Outcomes Research Team (PORT) study group; the incidence of bacteremia was also not significantly different. However, for patients treated with azithromycin, the length of hospital stay was shorter (mean\_SD, 7.4\_5vs.9.4\_7 days; P ! .01) and the mortality rate was lower (3.6% vs. 7.2%; P ! .05), compared with those treated with clarithromycin. There might be a difference in the outcome for patients with CAP depending on the macrolide used. A shorter treatment course with azithromycin may

result in better compliance with therapy.

**ANTIBIOTICS FOR BACTEREMIC PNEUMONIA. IMPROVED OUTCOMES WITH MACROLIDES BUT NOT FLUOROQUINOLONES.**

Mark L. Metersky, et al.

CHEST 2007; 131:466–473.

Background: The questions of whether the use of antibiotics that are active against atypical organisms is beneficial in the treatment of community-acquired pneumonia and of the potential mechanisms of any beneficial effects remain unresolved. Proposed mechanisms include activity against atypical organisms vs the immunomodulatory effects of these antibiotics. The study of outcomes of a large cohort of patients with bacteremic pneumonia provides a unique opportunity to address these questions by excluding patients with primary atypical infection.

Methods: We reviewed data from the charts of 2,209 Medicare patients who were admitted to hospitals across the United States from either home or a nursing facility with bacteremic pneumonia between 1998 and 2001. Patients were stratified according to the type of antibiotic treatment. Multivariate modeling was performed to assess the relationship between the class of antibiotic used and several outcome variables.

Results: The initial use of any antibiotic active against atypical organisms was independently associated with a decreased risk of 30-day mortality (odds ratio [OR], 0.76; 95% confidence interval [CI], 0.59 to 0.98; p \_ 0.03) and hospital admission within 30 days of discharge (OR, 0.67; 95% CI, 0.51 to 0.89; p \_ 0.02). Further analysis revealed that the benefits of atypical treatment were associated with the use of macrolides, but not the use of fluoroquinolones or tetracyclines, with macrolides conferring lower risks of in-hospital mortality (OR, 0.59; 95% CI, 0.40 to 0.88; p \_ 0.01), 30-day mortality (OR, 0.61; 95% CI, 0.43 to 0.87; p \_ 0.007), and hospital readmission within 30 days of discharge (OR, 0.59; 95% CI, 0.42 to 0.85; p \_ 0.004).

Conclusions: Initial antibiotic treatment including a macrolide agent is associated with improved outcomes in Medicare patients hospitalized with bacteremic pneumonia. These results have implications regarding the mechanism by which the use of a macrolide for treatment of pneumonia is associated with improved outcomes.

**ANTI-INFLAMMATORY EFFECTS OF MACROLIDES—AN UNDERAPPRECIATED BENEFIT IN THE TREATMENT OF COMMUNITY-ACQUIRED RESPIRATORY TRACT INFECTIONS AND CHRONIC INFLAMMATORY PULMONARY CONDITIONS?**

G. W. Amsden

Journal of Antimicrobial Chemotherapy (2005) 55, 10–21

Background: It has been recognized for more than 20 years that the macrolides have immunomodulatory effects that are beneficial for those suffering from chronic pulmonary inflammatory syndromes, such as diffuse panbronchiolitis, cystic fibrosis, asthma and bronchiectasis. The macrolides have consistently been associated with decreased length of stay and mortality when used alone or in combination with b-lactam antibiotics. This effect can be demonstrated against combinations consisting of b-lactams and other antibiotics active against ‘atypical chest pathogens’ when treating communityacquired pneumonia (CAP) in hospitalized patients. As such, it appears that the macrolides’ effects in CAP patients are more than just antibacterial in nature. Aims of this review: This review aims: to give the reader information on the background areas described, as well as related areas; to review the CAP benefits with macrolides and how they may be related to the immunomodulatory properties they demonstrate, albeit in a shorter period of time than previously demonstrated with chronic pulmonary disorders; to use ex vivo data to support these extrapolations. Literature search: A literature search using Medline was conducted from 1966 onwards, searching for articles with relevant key words such as macrolide, diffuse panbronchiolitis, community-acquired pneumonia, biofilm, immunomodulation, cystic fibrosis, erythromycin, clarithromycin, roxithromycin and azithromycin, bronchiectasis and asthma. When appropriate, additional references were found from the bibliographies of identified papers of interest. Any relevant scientific conference proceedings or medical texts were checked when necessary. Conclusions: (1) Research into macrolide immunomodulation for chronic pulmonary disorders demonstrates consistent positive effects, although of types other than seen with diffuse panbronchiolitis. These effects, together with their inhibitory activity on biofilms, have the potential to make them a useful option. (2) The benefits for CAP are consistent, and higher when a macrolide is given with another atypical agent than if the other atypical agent is given alone, suggesting a non-antibacterial benefit. (3) Recent research of the immunomodulatory properties of azithromycin imply that azithromycin may have a previously unknown short-term biphasic effect on inflammation modulation: enhancement of host defence mechanisms shortly after initial administration followed by curtailment of local infection/inflammation in the following period. (4) Additional in vivo research is needed prior to developing any firm conclusions.

**ZYVOX® (LINEZOLIDA)**

**LINEZOLID IN METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS NOSOCOMIAL PNEUMONIA: A RANDOMIZED, CONTROLLED STUDY**

Richard G. Wunderink et al

Clinical Infectious Diseases 2012;54(5):621–9

Background. Post hoc analyses of clinical trial data suggested that linezolid may be more effective than vancomycin for treatment of methicillin-resistant Staphylococcus aureus (MRSA) nosocomial pneumonia. This study prospectively assessed efficacy and safety of linezolid, compared with a dose-optimized vancomycin regimen, for treatment of MRSA nosocomial pneumonia.

Methods. This was a prospective, double-blind, controlled, multicenter trial involving hospitalized adult patients with hospital-acquired or healthcare–associated MRSA pneumonia. Patients were randomized to receive intravenous linezolid (600 mg every 12 hours) or vancomycin (15 mg/kg every 12 hours) for 7–14 days. Vancomycin dose was adjusted on the basis of trough levels. The primary end point was clinical outcome at end of study (EOS) in evaluable per-protocol (PP) patients. Prespecified secondary end points included response in the modified intentto-treat (mITT) population at end of treatment (EOT) and EOS and microbiologic response in the PP and Mitt populations at EOT and EOS. Survival and safety were also evaluated.

Results. Of 1184 patients treated, 448 (linezolid, n 5 224; vancomycin, n 5 224) were included in the mITT and 348 (linezolid, n5172; vancomycin, n5176) in the PP population. In the PP population, 95 (57.6%) of 165 linezolid-treated patients and 81 (46.6%) of 174 vancomycin-treated patients achieved clinical success at EOS (95% confidence interval for difference, 0.5%–21.6%; P 5 .042). All-cause 60-day mortality was similar (linezolid, 15.7%; vancomycin, 17.0%), as was incidence of adverse events. Nephrotoxicity occurred more frequently with vancomycin (18.2%; linezolid, 8.4%).

Conclusions. For the treatment of MRSA nosocomial pneumonia, clinical response at EOS in the PP population was significantly higher with linezolid than with vancomycin, although 60-day mortality was similar.

**EFFICACY AND SAFETY OF LINEZOLID VERSUS VANCOMYCIN FOR THE TREATMENT OF COMPLICATED SKIN AND SOFT-TISSUE INFECTIONS PROVEN TO BE CAUSED BY METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS***

Kamal M.F. Itani et al

The American Journal of Surgery (2010) 199, 804–816

**BACKGROUND:** This open-label study compared oral or intravenous linezolid with intravenous vancomycin for treatment of complicated skin and soft-tissue infections (cSSTIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

**METHODS:** Patients with proven MRSA cSSTI were randomized to receive linezolid or vancomycin. Clinical and microbiologic outcomes, duration of antimicrobial therapy, length of hospital stay, and safety were assessed.

**RESULTS:** In the per-protocol population, the rate of clinical success was similar in linezolid- and vancomycin-treated patients (*P* \_ .249). The rate of success was significantly higher in linezolid-treated patients in the modified intent-to-treat population (*P* \_ .048). The microbiologic success rate was higher for linezolid at the end of treatment (*P* \_ .001) and was similar at the end of the study (*P* \_.127). Patients receiving linezolid had a significantly shorter length of stay and duration of intravenous therapy than patients receiving vancomycin. Both agents were well tolerated. Adverse events were similar to each drug’s established safety profile.

**CONCLUSIONS:** Linezolid is an effective alternative to vancomycin for the treatment of cSSTI caused by MRSA.

**LINEZOLID AND VANCOMYCIN IN TREATMENT OF LOWER-EXTREMITY COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS CAUSED BY METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS IN PATIENTS WITH AND WITHOUT VASCULAR DISEASE**

Therese M. Duane et al.

Surgical Infections 2012; 13 (3): 147-153.

Background: We evaluated drug efficacy and safety among patients with and without vascular disease who were treated with linezolid or vancomycin for a lower-extremity complicated skin and skin structure infection (cSSSI) caused by methicillin-resistant Staphylococcus aureus (MRSA).

Methods: We pooled data from two randomized clinical trials evaluating the efficacy and safety of linezolid 600mg intravenously (IV) or orally every 12 h and vancomycin 15mg/kg or 1 g IV every 12 h for the treatment of cSSSI caused by culture-proved MRSA.

Results: There were 477 patients for analysis. Among patients with vascular disease (linezolid n = 139, vancomycin n = 135), the clinical success rate was 80.4% and 66.7% (p = 0.02) for patients treated with linezolid and vancomycin, respectively. Among patients without vascular disease (linezolid n = 91, vancomycin n = 112), the

clinical success rate was 94.5% and 89.4%, respectively (p = 0.24). Linezolid-treated patients had fewer IV catheter-site complications and less kidney impairment but more frequent thrombocytopenia than those who received vancomycin, regardless of the presence or absence of vascular disease.

Conclusion: Linezolid is an effective treatment for patients with and without vascular disease who have a lowerextremity cSSSI caused by MRSA. The safety data were consistent with the known safety profiles of linezolid and vancomycin given for this indication.