Linezolid versus Vancomycin for MRSA Nosocomial Pneumonia (ZEPHyR Study)

Pneumonia is the second most common hospital-associated infection in the United States, and its risk increases in patients receiving mechanical ventilation. Methicillin-resistant *Staphylococcus aureus* (MRSA) may cause as many as 10% to 40% of cases of health-care associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP). Previous, prospective, randomized, double-blind trials have found that linezolid was statistically noninferior to fixed-dose vancomycin (1 gram twice daily) for the treatment of nosocomial pneumonia. Post hoc analysis of these studies found that survival and clinical cure were significantly improved in the MRSA pneumonia subgroup when treated with linezolid, compared with vancomycin. However, the reason for these differences could have been attributed to failure to optimize vancomycin dosing. Current guidelines recommend an initial vancomycin dose based on body weight and subsequent doses adjusted based on trough serum levels.

This phase IV, randomized, double-blind, comparator-controlled study was done to assess the efficacy, safety, and tolerability of fixed-dose linezolid compared with dose-optimized vancomycin for the treatment of proven MRSA nosocomial pneumonia. Patients with radiographically documented HAP or HCAP and signs and symptoms were eligible for inclusion in the study. Patients were required to have a baseline respiratory or sputum specimen positive for MRSA. Patients were randomized to receive either intravenous linezolid 600 mg every 12 hours or vancomycin 15 mg/kg every 12 hours for 7 to 14 consecutive days. A pharmacist monitored and adjusted the vancomycin doses according to local protocols, based on trough levels and renal impairment. Patients were clinically assessed at baseline, on day three, and every three days during treatment. Clinical outcomes were assessed within five days of the end-of-treatment (EOT) and at the end of study (EOS). EOS was defined as 7 to 30 days after the end of treatment. Microbiological responses were determined at EOT and EOS, based on culture results from the original site of infection. The primary end point of the study was clinical outcome at EOS in evaluable per-protocol (PP) patients. There were additional prespecified secondary end points.

There were 448 patients who comprised the modified intention-to-treat (mITT) population. Of these, 348 comprised the PP population. In the PP patients, infection was diagnosed by tracheal aspirate (43.4%), bronchoalveolar lavage (31.3%), or sputum specimen (16.7%). Slightly more vancomycin-treated patients received mechanical ventilation at baseline (73.9% vs. 66.9%, respectively), and had MRSA bacteremia (10.8% vs. 5.2%). In the PP population, 57.6% of linezolid-treated patients were clinically cured at EOS, compared with 46.6% of vancomycin-treated patients, [P=0.042]. Linezolid also showed clinical efficacy superior to vancomycin at EOT and in the mITT patients at both time points. At EOT, 81.9% of linezolid-treated and 60.6% of vancomycin-treated PP patients had microbiologic success. Twenty patients had serious adverse events judged to be related to study drug, 7 in the linezolid group and 13 in the vancomycin group. Investigator-reported renal failure was twice as common in the vancomycin arm, 3.7% vs. 7.3%, respectively. All-cause 60 day mortality in the mITT population was 28.1% in the linezolid arm and 26.3% in the vancomycin arm.

In this direct, prospective comparison, clinical response at EOS in the PP population was significantly better with linezolid than with vancomycin for the treatment of nosocomial pneumonia due to MRSA. There were no statistically significant differences in mortality or adverse events.


Accessed at: http://cid.oxfordjournals.org/content/early/2012/01/12/cid.cir895.abstract

**COMMENT:** Previously published noninferiority trials have compared linezolid with vancomycin in HAP and VAP with pooled analyses not showing a significant advantage in clinical cure rates. However, post hoc analyses showed significant advantages in favor of linezolid for both clinical cures and mortality. These analyses have been criticized because of their retrospective nature, and because the dosages of vancomycin were not adjusted to obtain optimal serum trough levels. Also, the minimum inhibitory concentrations (MICs) for MRSA as well as the impact of mixed gram-positive/gram-negative infections were not taken into account. The above study was designed to address some of these deficiencies and showed that clinical and microbiological cures were significantly better for linezolid. Some of the criticisms of the above study include a lack of statistical significance when the combined results are broken down into HAP, VAP, and HCAP, inclusion of mixed gram-negative/gram position pneumonias, and no difference in 60 day mortality rates. In any event, effort must be made to administer linezolid only in clinically and microbiologically well-documented cases of HAP and VAP MRSA infections. The latest guidelines from the Infectious Diseases Society of America put vancomycin and linezolid on equal footing for MRSA pneumonia (Clin Infect Dis Feb. 2012). Linezolid should also be preferred in
those patients with MRSA infections and concomitant renal insufficiency.

**Fidaxomicin versus Vancomycin for C. difficile Infection**

*Clostridium difficile* infection generally occurs after exposure to broad-spectrum antibiotic therapy, but any antibiotic that disrupts normal gut flora can increase the chance of infection. Of particular worry is the hypervirulent, fluoroquinolone-resistant *C. difficile* strain, NAP1/BI/027, which is associated with severe symptoms, high recurrence rates, and substantial mortality. Fidaxomicin (*Fidicid™*) is a poorly absorbed oral antibiotic that is eight-times as potent as vancomycin against *C. difficile*, has restricted activity against most gut bacteria, and a long post-antibiotic effect. A previous phase 3 study done in Canada and the United States showed that fidaxomicin was noninferior to vancomycin for clinical cures in patients with *C. difficile* infection, but was superior for fewer recurrences and sustained responses four weeks after completion of treatment. The aim of this study was to compare the efficacy of fidaxomicin and vancomycin in Europe, as well as in North America.

This was a prospective, double-blind, randomized, non-inferiority trial conducted between April 19, 2007 and December 11, 2009. Patients were eligible if they had *C. difficile* infection, defined by more than three unformed bowel movements (UBM) in the 24 hours before randomization, and either *C. difficile* toxin A or B in stools within 48 hours of randomization. Patients were randomized to receive either oral fidaxomicin 200 mg every 12 hours with intervening placebo given six hours after each fidaxomicin dose or oral vancomycin 125 mg every six hours for 10 days. Patients were assessed at the end-of-treatment and at an end-of-study visit when recurrence had not been reported. The primary study end point was clinical cure, defined as resolution of diarrhea (i.e. three or fewer UBM per day for two consecutive days) for the duration of treatment, and no further need for treatment as of the second day after the last dose of study drug. Patients who had a clinical cure were assessed sequentially for recurrence and then sustained clinical response. Recurrence was defined as the return of more than three UBM in 24 hours, a positive stool toxin test, and the need for retreatment within 30 days of treatment completion. Sustained response was clinical cure without recurrence.

There were 535 patients enrolled in the study, of which 270 received fidaxomicin and 265 received vancomycin. Clinical cure was seen in 91.7% of the per-protocol patients receiving fidaxomicin and 90.6% who received vancomycin, meeting the criterion for non-inferiority. In the modified intention to treat (mITT) patients, clinical cure was achieved in similar proportions of patients receiving fidaxomicin (87.7%) and those receiving vancomycin (86.8%). More mITT patients cured after treatment with vancomycin had recurrence (26.9%) than those treated with fidaxomicin (12.7%), [P=0.0002]. This difference was reflected in a significantly higher rate of sustained clinical response for the fidaxomicin group (76.6%) than for the vancomycin group (63.4%), [P=0.001]. Adverse events of treatment were primarily gastrointestinal symptoms in both groups, such as nausea, vomiting, diarrhea, and abdominal pain.

Fidaxomicin was non-inferior to vancomycin in the initial clinical response in patients with *C. difficile* infection. Patients successfully treated with fidaxomicin were less likely to have a recurrence of disease within four weeks after treatment completion, translating to a superior sustained response for fidaxomicin. These results are similar to those seen in the previously reported phase 3 trial of fidaxomicin versus vancomycin, done solely in North America.

Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomized controlled trial. Lancet 2012 published on-line

http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(11)70374-7/abstract

**Results of Self-Monitoring of Oral Anticoagulation**

Oral anticoagulation with vitamin K antagonists substantially reduces the incidence of thromboembolic events. However, the use of these oral anticoagulants is limited by the requirements to maintain the international normalized ratio (INR) within a narrow range, frequent laboratory testing, and dosage adjustments. Currently, accurate point-of-care devices are available to allow patients to self test at home. Patients can have their test result managed by a health-care provider (self-testing), or they can interpret their INR result and adjust their own dose of anticoagulant (self-management). Previous studies of self-monitored anticoagulant therapy have been limited by methodological problems. To clarify the value of self-monitoring of oral anticoagulation, a meta-analysis of individual patient data was done, which updated previous reviews. The specific aims included estimating the effect of self-monitoring on time to death, first major hemorrhage, and first thromboembolic event. A secondary outcome was time in the therapeutic range.

Embse and Medline searches were performed of randomized trials that compared the effects of self-monitoring (self-testing) or self-management (self-testing and self dosing) of anticoagulation with a control group, whose dosage was managed by personal physicians or anticoagulation services. There were 21 clinical trials with 7598 participants included in the analysis. All the trials were published between 2000 and 2010. The self-management group used the Coaguchek (Roche Diagnostics), Pro time microcoagulation (ITC Nexus Dx), and Coumatrak (Du Pont Pharmaceuticals) for testing. Participants in the self-management group were on average 1.7 years younger than the control group, [P<0.0001]. Over one-third of the participants had a mechanical heart valve insertion and over one-half had atrial fibrillation. A significant reduction in thromboembolic events was seen in the self-monitoring group, hazard ratio (HR) = 0.51, [P=0.01]. At one year, the number needed to treat to prevent one thromboembolic event was 78, and by five years it was 27. There was no significant reduction in major hemorrhagic events, HR = 0.88, [P=0.18], or deaths, HR = 0.82, [P=0.18]. Participants younger than 55 years of age who self-monitored had a striking reduction in thromboembolic events, whereas those in other age groups showed
nonsignificant effects. Patients with a mechanical heart valve who self-monitored had a significant reduction in thromboembolic events \[P=0.001\]. Effects for both atrial fibrillation and other indications were not significant.

This study using individual patient data for assessment of self-monitoring of oral anticoagulation showed a significant reduction in thromboembolic events. However, there was not a significant effect on the rate of major hemorrhage or mortality.


**Intramuscular versus Intravenous Benzodiazepines for Status Epilepticus**

The randomized, controlled Prehospital Treatment of Status Epilepticus trial compared intravenous diazepam, lorazepam, and placebo administered by paramedics to treat patients with prolonged convulsive seizures. The trial showed that both benzodiazepines were an effective prehospital treatment for seizures compared to placebo. The proportion of patients whose seizures were terminated at the time of arrival at the emergency department was 59.1% in the intravenous lorazepam group, 42.6% in the intravenous diazepam group, and 21.1% in the placebo group. Many emergency medical services (EMS) have begun to use intramuscular midazolam rather than an intravenous agent, largely because intramuscular administration is faster and consistently achievable. This is despite the absence of clinical trial data regarding efficacy and safety of intramuscular midazolam. The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) was performed to determine whether intramuscular midazolam is as effective as intravenous lorazepam, with a similar degree of safety, for terminating status epilepticus seizures before arrival at the hospital. RAMPART was a randomized, double-blind phase 3, noninferiority trial.

The study population included children with a body weight of 13 kg or more, and adults requiring treatment with benzodiazepines for status epilepticus in a prehospital setting. Subjects were required to be having convulsive seizures at the time of treatment by paramedics, and reported to have been continuously convulsing for longer than five minutes. Upon arrival on the scene, paramedics assessed the patient according to local protocol. Each subject was treated with either 10 mg of intramuscular midazolam followed by intravenous placebo or intramuscular placebo followed by 4 mg of intravenous lorazepam. All subjects were treated with an intramuscular injection first, followed by an intravenous injection. The primary study outcome was termination of seizures before arrival at the emergency department without the need for paramedics to provide rescue medication. The termination of seizures on arrival was determined by the emergency department physician.

Seizures were absent without rescue therapy on arrival at the emergency department in 329 (73.4%) of subjects receiving intramuscular midazolam, and in 282 (63.4%) of subjects receiving lorazepam \[P<0.001\] for noninferiority, \(P < 0.001\) for superiority.

Among subjects in the intravenous group who did not reach the primary outcome, 31 never received the intravenous study medication because of failure to obtain intravenous access. The two treatment groups were similar with respect to the need for endotracheal intubation and recurrence of seizures. Among those patients whose seizures ceased before arrival at the emergency department, the median time to active treatment was 1.2 minutes in the intramuscular midazolam group and 4.8 minutes in the intravenous lorazepam group. Adverse events were similar between the two groups.

Intramuscular midazolam is noninferior to intravenous lorazepam in stopping seizures before arrival in the emergency department in patients with status epilepticus.


**Dose Escalation Study of Caspofungin**

Invasive aspergillosis remains an important cause of infectious death in immunocompromised patients, particularly those with hematological malignancies. High dose liposomal amphotericin (i.e. 10 mg/kg /day for the first two weeks of treatment) did not yield better outcomes than a standard dose of 3 mg/kg/day, but resulted in a higher rate of adverse renal events. Dose escalation of voriconazole is not attempted due to its nonlinear pharmacokinetics and narrow therapeutic window. Caspofungin (Cancidas™) is generally well tolerated in patients and exhibits favorable pharmacokinetic properties. Preclinical and limited clinical data support the concept of dose-dependent antifungal efficacy of caspofungin. Healthy volunteers have demonstrated drug safety when given doses of up to 210 mg/day. The objective of this phase 2 study was to evaluate the maximum tolerated dose of caspofungin, ranging from 70 mg to 200 mg a day, in patients with invasive aspergillosis.

Patients were eligible if they were 18 years of age or older, had an immunocompromising condition associated with invasive fungal disease, and evidence of proven or probable invasive aspergillosis. Caspofungin was administered once daily as an intravenous infusion over 120 minutes at doses of 70 mg, 100 mg, 150 mg, or 200 mg. In the absence of dose-limiting toxicity, treatment was continued until at least a partial response to treatment was achieved, or a switch to sequential oral antifungal regimen was considered feasible. The maximum duration of treatment with caspofungin was limited to 28 days. Responses to treatment and survival were assessed at the end of therapy, at 4 weeks, and 12 weeks post-end-of-treatment. Complete response was defined as the resolution of all attributable symptoms, signs and radiographic abnormalities, and a partial response was defined as a clinically meaningful improvement of attributable symptoms, signs, and radiographic abnormalities (\(\geq 50\%\) decrease), if present at enrollment. The primary end points of the study were the safety and tolerability of caspofungin.

From September 2006 until July 2009, a total of 46 patients with proven or probably invasive aspergillosis were enrolled in the study.
Baseline characteristics of the 46 enrolled patients were comparable between the cohorts. Of the 46 patients, 12 were female, 27 had acute leukemia, and 31 were neutropenic. The median duration of study drug treatment was 24.5 days. There was no clear relationship between the caspofungin dose and the incidence of adverse events. Only two events with a probable relationship to the study drug were reported. In the 100 mg group, one patient had grade one loss of appetite, and one patient in the 200 mg group had a grade three elevation of γ-glutamyl transferase. A total of 42 serious adverse events occurred in 26 patients, but none were related to the study treatment. Dose-normalized trough concentrations revealed dose linearity of caspofungin across the investigated dosage range. A population pharmacokinetic analysis showed that a linear two-compartment pharmacokinetic model, with weight as a covariate on clearance and sex as a covariate on central volume of distribution, best fit the group data. Favorable responses at the end-of-treatment (EOT), 4 weeks follow-up, and 12 weeks follow-up, (defined as complete and partial responses) were observed in 57%, 57%, and 52% of patients respectively. Concerning the dosage groups, favorable outcomes in the 70 mg, 100 mg, 150 mg, and 200 mg groups at EOT were observed in 4 (44%), 3 (36%), 6 (67%) and 12 (60%) of patients, respectively. The median observation time (ending with the completion of follow-up or patient death) was 109 days. Thirteen of the 46 patients (28.3%) died during treatment or the 12-week follow-up period.

This dose escalation study evaluated caspofungin as a first-line treatment of invasive aspergillosis in adults, and demonstrated acceptable safety and tolerance of daily doses up to 200 mg daily over extended periods of time. Dose-limiting toxicity was not observed.


Population-Based Study of Patients Receiving Clopidogrel and a Proton Pump Inhibitor

Clopidogrel is the mainstay drug for prevention of vascular events in patients with coronary artery disease of ischemic stroke. It is a prodrug that requires activation by cytochrome P450 enzymes, primarily 2C19 and 3A4, to its active form. Several proton pump inhibitors (PPIs) are also metabolized by this enzyme system and there is debate on the significance of this potential drug-drug interaction. This population-based study examined the clinical outcomes of the clopidogrel-PPI interaction in patients receiving coronary artery stents.

The study used the medical databases of Western Denmark, which has 3 million inhabitants. The Danish National Health Service provides universal tax-supported health care and provides accurate and unambiguous linkage of all patients on an individual level. All patients receiving percutaneous coronary interventions (PCIs) between January 2002 and June 2005 were identified. The Danish Nationwide Prescription Database was used to identify patients who received prescriptions for clopidogrel or PPIs, and who had undergone PCI. All five available PPIs were available during this time period. The main outcome was the occurrence of major adverse cardiac events (MACE) occurring within 12 months of the patient’s PCI. MACE was defined as the first occurrence of myocardial infarction, ischemic stroke, stent thrombosis, target lesion revascularization, or cardiac death.

There were 13,001 patients who underwent PCI with a median age of 64 years, with 28% of them women. During follow-up, 91% of patients filled at least one prescription for clopidogrel and 2742 (21%) filled at least one prescription for a PPI. Of all the patients, 155 experienced a MACE. The rates for MACE per 1000 person-years were 154 for concomitant clopidogrel and PPI use, 104 for clopidogrel without PPI use, 267 for PPI without clopidogrel use, and 263 for no use of either drug. There appeared to be no substantial difference from the overall results in subgroups based on age, gender, PCI indication, or the presence or absence of diabetes. Patients with longer-term PPI use had a 25% increased rate of MACE compared to PPI non-users, independent of whether or not they were using clopidogrel.

In this population-based study in patients undergoing PCI, clopidogrel use was associated with a markedly reduced rate of MACE within 12 months after coronary stent implantation, independent of PPI use. The use of a PPI individually, or as a class, did not modify the protective effect of clopidogrel substantially. However, PPI use was associated with an increased risk of MACE itself, particularly among long-term users. This study supports the hypothesis that patients receiving a PPI represent a generally sicker patient population and a higher incidence of MACE should be expected.


About Amerinet

As a leading national healthcare solutions organization, Amerinet collaborates with acute and non-acute care providers to create and deliver unique solutions through performance improvement resources, guidance and ongoing support. With better product standardization and utilization, new financial tools beyond contracting and alliances that help lower costs, raise revenue and champion quality, Amerinet enriches healthcare delivery for its members and the communities they serve.

To learn more about how Amerinet can help you successfully navigate the future of healthcare reform, visit www.amerinet-gpo.com.

Amerinet, Inc.
2060 Craigshire Road, St. Louis, MO 63146
P 877-711-5600
www.amerinet-gpo.com