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Update in infectious disease treatment

ABSTRACT

Studies published during the past year on the treatment of several infectious diseases provide valuable information that should enable us to treat our patients more effectively. Among those findings:

- Oral vancomycin (Vancocin) is superior to oral metronidazole (Flagyl) for treating patients with severe *Clostridium difficile*-associated disease.
- The risk of death from any cause may be higher with the use of cefepime (Maxipime) than with other beta-lactam antibiotics.
- In patients presenting to primary care physicians with symptoms of acute maxillary sinusitis, antibiotics and topical nasal steroids do not seem to be effective, either alone or in combination.
- For patients with Bell palsy, early treatment with prednisolone improves the chance of complete recovery; antiviral therapy may be indicated for patients with complete facial nerve paralysis.
- In patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplasia, posaconazole (Noxafil) prevented fungal infections more effectively than fluconazole (Diflucan) or itraconazole (Sporanox) and improved overall survival.
- Anidulafungin (Eraxis) was not inferior to fluconazole in the treatment of invasive candidiasis.

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STUDIES PUBLISHED during the past year provide information that could influence how we treat several infectious diseases in daily practice. Here is a brief overview of these "impact" studies.

VANCOMYCIN BEATS METRONIDAZOLE FOR SEVERE *C DIFFICILE* DIARRHEA

ZAR FA, BAKKANAGARI SR, MOORTHI KM, DAVIS MB. A COMPARISON OF VANCOMYCIN AND METRONIDAZOLE FOR THE TREATMENT OF CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA, STRATIFIED BY DISEASE SEVERITY. CLIN INFECT DIS 2007; 45:302–307.

Clostridium difficile is the most common infectious cause of nosocomial diarrhea. Furthermore, a unique and highly virulent strain has emerged.

Which drug should be the treatment of choice: metronidazole (Flagyl) or oral vancomycin (Vancocin)? Over time, some infectious disease practitioners have believed that oral vancomycin is superior to oral metronidazole for the treatment of severe C *difficile*-associated diarrhea. Indeed, in a recently published survey, more than 25% of infectious disease practitioners said they used vancomycin as initial therapy for C *difficile*-associated diarrhea.[1] Until recently, there has been no evidence to support this preference.

Ever since the first description of C *difficile*-associated diarrhea in the late 1970s, only two head-to-head studies have compared the efficacy of metronidazole vs vancomycin for the treatment of this disorder. Both studies were underpowered and neither was blinded. In 1983, Teasley et al[2] treated 101 patients with metronidazole or vancomycin in a nonblinded, nonrandomized study and found no difference in efficacy. In 1996, Wenisch et al,[3] in a prospective, randomized, but nonblinded study in 119 patients, compared vancomycin, metronidazole, fusidic acid, and teicoplanin (Targocid) and also found no significant difference in efficacy.

The study. Zar et al,[4] in a prospective, double-blind trial at a single institution over an 8-year period, randomized 172 patients with C difficile-associated diarrhea to receive either oral metronidazole 250 mg four times a day or oral vancomycin 125 mg four times a day, both for 10 days. (The appropriate dosage of vancomycin has been debated over the years. In 1989, Fekety et al[5] treated patients who had antibiotic-associated C difficile colitis with either 125 or 500 mg of vancomycin, four times a day, and found that the low dosage was as effective as the high dosage.) Both groups also received an oral placebo in addition to the study drug.

In the study of Zar et al, criteria for inclusion were diarrhea (defined as having more than two nonformed stools per 24 hours) and the finding of either toxin A in the stool or pseudomembranes on endoscopic examination. Patients were excluded if they were pregnant, had suspected or proven life-threatening intra-abdominal complications, were allergic to either study drug, had taken one of the study drugs during the last 14 days, or had previously had C *difficile*-associated diarrhea that did not respond to either study drug.

Patients were followed for up to 21 days. The primary end points were cure, treatment failure, or relapse. Cure was defined as the resolution of diarrhea and no C *difficile* toxin A detected on stool assay at days 6 and 10.

Disease severity was classified as either mild or severe based on a point system: patients received a single point each for being older than 60 years, being febrile, having an albumin level of less than 2.5 mg/dL, or having a white blood cell count of more than 15 $\times 10^9$/L. Patients were classified as having severe disease if they had two or more points. They received two points (ie, they were automatically classified as having severe disease) if they had pseudomembranous colitis or if they developed C *difficile* infection that required treatment in an intensive care unit.

Findings. The overall cure rate in patients receiving vancomycin was 97%, compared with 84% for those on metronidazole (P = .006). This difference was attributable to the group of patients with severe disease; no difference in treatment outcome was found in patients with mild disease. The relapse rates did not differ significantly between treatment groups in patients with either mild or severe disease.

Comments. The study was limited in that it was done at a single center and was done before the current highly virulent strain emerged. Whether these data can be extrapolated to today's epidemic is unclear. Moreover, the investigators did not test for antimicrobial susceptibility (although metronidazole resistance is still uncommon). Finally, the development of colonization with vancomycin-resistant enterococci, one of the reasons that oral vancomycin is often not recommended, was not assessed.

Despite the study's limitations, it shows that for severely ill patients with C *difficile*-associated diarrhea, oral vancomycin should be the treatment of choice.

IS CEFEPIME SAFE?

YAHAV D, PAUL M, FRASER A, SARID N, LEIBOVICI L. EFFICACY AND SAFETY OF CEFEPIME: A SYSTEMATIC REVIEW AND META-ANALYSIS. LANCET INFECT DIS 2007; 7:338–348.

Cefepime (Maxipime) is a broad-spectrum, fourth-generation cephalosporin. It is widely used for its approved indications: pneumonia; bacteremia; urinary tract, abdominal, skin, and soft-tissue infections; and febrile neutropenia.

Whether vancomycin is best for our epidemic of *C difficile*-associated disease is unclear

In 2006, Paul et al[6] reviewed 33 controlled trials of empiric cefepime monotherapy for febrile neutropenia and found a higher death rate with cefepime than with other beta-lactam antibiotics. That preliminary study spawned the following more comprehensive review by the same group.

The study. Yahav et al[7] performed a meta-analysis of randomized trials that compared cefepime with another beta-lactam antibiotic alone or combined with a non-beta-lactam drug given in both treatment groups. Two reviewers independently identified studies from a number of databases and extracted data.

The primary end point was the rate of death from all causes at 30 days. Secondary end points were clinical failure (defined as unresolved infection, treatment modification, or death from infection), failure to eradicate the causative pathogens, superinfection with different bacterial, fungal, or viral organisms, and adverse events.

More than 8,000 patients were involved in 57 trials: 20 trials evaluated therapy for neu-

tropenic fever, 18 for pneumonia, 5 for urogenital infections, 2 for meningitis, and 10 for mixed infections.

Comparison drugs for febrile neutropenia were ceftazidime (Ceptaz, Fortaz, Tazicef); imipenem-cilastatin (Primaxin) or meropenem (Merrem); piperacillin-tazobactam (Zosyn); and ceftriaxone (Rocephin). Aminoglycosides were added to both treatment groups in six trials and vancomycin was added in one trial.

For pneumonia, comparison drugs were ceftazidime, ceftriaxone, cefotaxime (Claforan), and cefoperazone-sulbactam.

Adequate allocation concealment and allocation-sequence generation were described in 30 studies. Scores for baseline patient risk factors did not differ significantly between study populations.

Findings. The death rate from all causes was higher in patients taking cefepime than with other beta-lactam antibiotics (risk ratio [RR] 1.26, 95% confidence interval [CI] 1.08–1.49, $P = .005$). The rate was lower with each of the alternative antibiotics, but the difference was statistically significant only for cefepime vs piperacillin-tazobactam (RR 2.14, 95% CI 1.17–3.89, $P = .05$).

The rate of death from all causes was higher for cefepime in all types of infections (except urinary tract infection, in which no deaths occurred in any of the treatment arms), although the difference was statistically significant only for febrile neutropenia (RR 1.42, 95% CI 1.09–1.84, $P = .009$). No differences were found in secondary outcomes, either by disease or by drug used.

Comments. This meta-analysis supports previous findings that more patients die when cefepime is used. The mechanism, however, is unclear. The authors call for reconsideration of the use of cefepime for febrile neutropenia, community-acquired pneumonia, and healthcare associated pneumonia. In November 2007, the US Food and Drug Administration (FDA) launched an investigation into the risk of cefepime but has not yet made recommendations. Practitioners should be aware of these data when considering antimicrobial options for treatment in these settings. Knowledge of local antimicrobial susceptibility data of key pathogens is essential in determining optimal empiric and pathogen-specific therapy.

Amoxicillin plus budesonide: no better than placebo for acute maxillary sinusitis

AN ANTIBIOTIC AND A NASAL STEROID ARE INEFFECTIVE IN ACUTE SINUSITIS

WILLIAMSON IG, RUMSBY K, BENGE S, ET AL. ANTIBIOTICS AND TOPICAL NASAL STEROID FOR TREATMENT OF ACUTE MAXILLARY SINUSITIS: A RANDOMIZED CONTROLLED TRIAL. JAMA 2007; 298:2487–2496.

In the United States and Europe 1% to 2% of all primary care office visits are for acute sinusitis. Studies indicate that 67% to nearly 100% of patients with symptoms of sinusitis receive an antibiotic for it, even though the evidence of efficacy is weak and guidelines do not support this practice. Cochrane reviews[8,9] have suggested that topical corticosteroids, penicillin, and amoxicillin have marginal benefit in acute sinusitis, but the studies on which the analyses were based were flawed.

The Berg and Carenfelt criteria were developed to help diagnose bacterial sinusitis.[10] At the time they were developed, computed tomography was not routinely done to search for sinusitis, so plain film diagnosis was compared with clinical criteria. The Berg and Carenfelt criteria include three symptoms and one sign: a history of purulent unilateral nasal discharge, unilateral facial pain, or bilateral purulent discharge and pus in the nares on inspection. The presence of two criteria has reasonable sensitivity (81%), specificity (89%), and positive predictive value (86%) for detecting acute bacterial or maxillary sinusitis in the office setting.

The study. Williamson et al[11] conducted a double-blind, randomized, placebo-controlled trial of antibiotic and topical nasal steroid use in patients with suspected acute maxillary sinusitis. The trial included 240 patients who were seen in 58 family practices over 4 years in the United Kingdom and who had acute nonrecurrent sinusitis based on Berg and Carenfelt criteria. Patients were at least 16 years old; the average age was 44. Three-quarters were women. Few had fever, and 70% met only two Berg and Carenfelt criteria; the remaining 30% met three or all four criteria. Patients were excluded who had at least two sinusitis attacks per year, underlying nasal pathology, significant comorbidities, or a history of penicillin allergy, or if they had been treated with antibiotics or steroids during the past month.

Patients were randomized to receive one of four treatments:

- Amoxicillin 500 mg three times a day for

7 days plus budesonide (Rhinocort) 200 µg in each nostril once a day for 10 days
- Placebo amoxicillin plus real budesonide
- Amoxicillin plus placebo budesonide
- Placebo amoxicillin plus placebo budesonide.

The groups were well matched. Outcomes were based on a questionnaire and a patient diary that assessed the duration and severity of 11 symptoms.

Findings. No difference was found between the treatment groups in overall outcome, in the proportion of those with symptoms at 10 days, or in daily symptom severity. The secondary analysis suggested that nasal steroids were marginally more effective in patients with less severe symptoms.

The authors concluded that neither an antibiotic nor a nasal steroid, alone or in combination, is effective for acute maxillary sinusitis in the primary care setting, and they recommended against their routine use.

Comments. This study had limitations. Some cases of viral disease may have been included: no objective reference standard (ie, computed tomography of the sinuses or sinus aspiration) was used, and although the Berg and Carenfelt criteria have been validated in secondary care settings, they have not been validated in primary care settings. In addition, fever was absent in most patients, and mild symptoms were poorly defined. Moreover, recruitment of patients was slow, raising questions of bias and generalizability. The study also did not address patients with comorbidities.

Nevertheless, the study shows that outpatients with symptoms of sinusitis without fever or significant comorbidities should not be treated with oral antibiotics or nasal steroids. Otherwise, antibiotic therapy may still be appropriate in certain patients at high risk and in those with fever.

PREDNISOLONE IS BENEFICIAL IN ACUTE BELL PALSY, ACYCLOVIR IS NOT

SULLIVAN FM, SWAN IR, DONNAN PT, ET AL. EARLY TREATMENT WITH PREDNISOLONE OR ACYCLOVIR IN BELL PALSY. N ENGL J MED 2007; 357:1598–1607.

Bell palsy accounts for about two-thirds of cases of acute unilateral facial nerve palsy in the United States. Virologic studies from patients undergoing surgery for facial nerve decompression have suggested a possible association with herpes simplex virus. Other causes of acute unilateral facial nerve palsy include Lyme disease, sarcoidosis, Sjögren syndrome, trauma, carotid tumors, and diabetes. Bell palsy occurs most often during middle age, peaking between ages 30 and 45. As many as 30% of patients are left with significant neurologic residua. Corticosteroids and antiviral medications are commonly used to treat Bell palsy, but evidence for their efficacy is weak.

The study. Sullivan et al[12] conducted a double-blind, placebo-controlled, randomized trial over 2 years in Scotland with 551 patients, age 16 years or older, recruited within 72 hours of the onset of symptoms. Patients who were pregnant or breastfeeding or who had uncontrolled diabetes, peptic ulcer disease, suppurative otitis, zoster, multiple sclerosis, sarcoidosis, or systemic infection were excluded. They were randomized to treatment for 10 days with either acyclovir (Zovirax) 400 mg five times daily or prednisolone 25 mg twice daily, both agents, or placebo.

The primary outcome was recovery of facial function based on the House-Brackmann grading system. Digital photographs of patients at 3 and 9 months of treatment were evaluated independently by three experts who were unaware of study group assignment or stage of assessment. These included a neurologist, an otorhinolaryngologist, and a plastic surgeon. The secondary outcomes were quality of life, facial appearance, and pain, as assessed by the patients.

Antibiotics may be used for acute sinusitis with fever or if other diseases are present

Findings. At 3 months, 83% of the prednisolone recipients had no facial asymmetry, increasing to 94% at 9 months. In comparison, the numbers were 64% and 82% in those who did not receive prednisolone, and these differences were statistically significant. Acyclovir was found to be of no benefit at either 3 or 9 months.

The authors concluded that early treatment of Bell palsy with prednisolone improves the chance of complete recovery, and that acyclovir alone or in combination with steroids confers no benefit.

Comments. At about the same time that this study was published, Hato et al[13] evaluated valacyclovir (Valtrex) plus prednisolone vs placebo plus prednisolone and found that patients with severe Bell palsy (defined

as complete facial nerve paralysis) benefited from antiviral therapy.

Corticosteroids are indicated for acute Bell palsy. In patients with complete facial nerve paralysis, valacyclovir should be considered.

POSACONAZOLE AS PROPHYLAXIS IN FEBRILE NEUTROPENIA

CORNELY OA, MAERTENS J, WINSTON DJ, ET AL. POSACONAZOLE VS. FLUCONAZOLE OR ITRACONAZOLE PROPHYLAXIS IN PATIENTS WITH NEUTROPENIA. N ENGL J MED 2007; 356:348–359.

Use of cefepime in febrile neutropenia and pneumonia should be reconsidered

For many years, amphotericin B was the only drug available for antifungal prophylaxis and therapy. Then, in the early 1990s, a number of studies suggested that the triazoles, notably fluconazole (Diflucan), were effective in a variety of clinical settings for both prophylaxis and therapy of serious fungal infections. In 1992 and 1995, two studies found that fluconazole prophylaxis was as effective as amphotericin B in preventing fungal infections in patients undergoing hematopoietic stem cell transplantation.[14,15] Based on these studies, clinical practice changed, not only for patients undergoing hematopoietic stem cell transplantation, but also for empiric antifungal prophylaxis in patients receiving myeloablative chemotherapy to treat hematologic malignancies.

Fluconazole is not active against invasive molds, and newer drugs—itraconazole (Sporanox), voriconazole (Vfend), and most recently posaconazole (Noxafil)—were developed with expanded clinical activity. Studies in the 1990s found that itraconazole and voriconazole performed better than fluconazole but did not provide complete prophylaxis.

The study. Cornely et al[16] compared posaconazole with fluconazole or itraconazole in 602 patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplasia. Although patients were randomized to either the posaconazole group or the fluconazole-or-itraconazole group, investigators could choose either fluconazole or itraconazole for patients randomized to that group. Most patients in the latter group (240 of 298) received fluconazole.

Patients were at least 13 years old, were able to take oral medications, had newly diagnosed disease or were having a first relapse, and had or were anticipated to have neutropenia for at least 7 days. The study excluded patients with invasive fungal infection within 30 days, significant liver or kidney dysfunction, an abnormal QT interval corrected for heart rate, an Eastern Cooperative Oncology Group performance status score of more than 2 (in bed more than half of the day), or allergy or a contraindication to azoles.

The trial treatment was started with each cycle of chemotherapy and was continued until recovery from neutropenia and complete remission, until invasive fungal infection developed, or for up to 12 weeks, whichever came first.

The primary end point was the incidence of proven or probable invasive fungal infection during the treatment phase. Secondary end points included death from any cause and time to death.

Findings. Posaconazole recipients fared significantly better than patients in the other treatment group with respect to the incidence of proven or probable invasive fungal infection, invasive aspergillosis, probability of death, death at 100 days, and death secondary to fungal infection. Treatment-related severe adverse events were a bit more common with posaconazole.

The authors suggest that posaconazole prophylaxis may have a place in prophylaxis in patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplasia.

Comments. It is not surprising that posaconazole performed better, because the standard treatment arm contained an agent (fluconazole) that did not cover *Aspergillus*, the most frequently identified source of invasive fungal infection during the treatment phase of the study.

In an editorial accompanying the article, De Pauw and Donnelly[17] pointed out that whether posaconazole prophylaxis would be appropriate in a given case depends upon how likely infection is with *Aspergillus*. An institution with very few *Aspergillus* infections would have a much higher number needed to treat with posaconazole to prevent one case of aspergillosis than in this study, in which the number needed to treat was 16. Thus, knowledge of local epidemiology and incidence of invasive mold infections should guide selection of the optimal antifungal agent for prophylaxis in patients undergoing myeloablative chemotherapy for acute myelogenous leukemia or myelodysplasia.

ANIDULAFUNGIN VS FLUCONAZOLE FOR INVASIVE CANDIDIASIS

REBOLI AC, ROTSTEIN C, PAPPAS PG, ET AL; ANIDULAFUNGIN STUDY GROUP. ANIDULAFUNGIN VERSUS FLUCONAZOLE FOR INVASIVE CANDIDIASIS. N ENGL J MED 2007; 356:2472–2482.

In 2002, caspofungin (Cancidas) was the first of a new class of drugs, the echinocandins, to be approved by the FDA. The echinocandins have been shown to be as effective as amphotericin B for the treatment of invasive candidiasis, but how they compare with azoles is an ongoing debate. Currently approved treatments for candidiasis, an important cause of disease and death in hospitalized patients, include fluconazole, voriconazole, caspofungin, and amphotericin B. Anidulafungin is the newest echinocandin and has been shown in a phase 2 study to be effective against invasive candidiasis.

The study. Reboli et al[18] performed a randomized, double-blind, noninferiority trial comparing anidulafungin and fluconazole to treat candidemia and other forms of candidiasis. The trial was conducted in multiple centers over 15 months and involved 245 patients at least 16 years old who had a single blood culture or culture from a normally sterile site that was positive for *Candida* species, and who also had one or more of the following: fever, hypothermia, hypotension, local signs and symptoms, or radiographic findings of candidiasis. Patients were excluded if they had had more than 48 hours of systemic therapy with either of these agents or another antifungal drug, if they had had prophylaxis with an azole for more than 7 of the previous 30 days, or if they had refractory candidal infection, elevated liver function test results, *Candida krusei* infection, meningitis, endocarditis, or osteomyelitis. Removal of central venous catheters was recommended for all patients with candidemia.

Patients were initially stratified by severity of illness based on the Acute Physiology and Chronic Health Evaluation (APACHE II) score (≤ 20 or > 20, with higher scores indicating more severe disease) and the presence or absence of neutropenia at enrollment. They were then randomly assigned to receive either intravenous anidulafungin (200 mg on day 1 and then 100 mg daily) or intravenous fluconazole (800 mg on day 1 and then 400 mg daily, with the dose adjusted according to creatinine clearance) for at least 14 days after a negative blood culture and improved clinical state and for up to 42 days in total. After 10 days of intravenous therapy, all patients could receive oral fluconazole 400 mg daily at the investigators' discretion if clinical improvement criteria were met.

The primary end point was global response at the end of intravenous therapy, defined as clinical and microbiologic improvement. A number of secondary end points were also studied. Response failure was defined as no significant clinical improvement, death due to candidiasis, persistent or recurrent candidiasis or a new *Candida* infection, or an indeterminate response (eg, loss to follow-up or death not attributed to candidiasis).

Of the 245 patients in the primary analysis, 89% had candidemia alone, and nearly two-thirds of those cases were caused by *Candida albicans*. Only 3% of patients had neutropenia at baseline. Fluconazole resistance was monitored and was rare.

Findings. Intravenous therapy was successful in 76% of patients receiving anidulafungin and in 60% of fluconazole recipients, a difference of 15.4 percentage points (95% CI 3.9–27.0). Results were similar for other efficacy end points. The rate of death from all causes was 31% in the fluconazole group and 23% in the anidulafungin group (P = .13). The frequency and types of adverse events were similar in the two groups. The authors concluded that anidulafungin was not inferior to fluconazole in the treatment of invasive candidiasis.

Comments. Does this study prove that anidulafungin is the treatment of choice for invasive candidiasis? Although the study noted trends in favor of anidulafungin, the differences did not achieve statistical significance for superiority. In addition, the study included so few patients with neutropenia that the results are not applicable to those patients. Finally, anidulafungin is several times more expensive than fluconazole.

Fluconazole has stood the test of time and is probably still the treatment of choice in patients who have suspected or proven candidemia or invasive candidiasis, unless they have already been treated with azoles or are critically ill. In those settings, echinocandins may be the preferred treatment. ■

Use of posaconazole as prophylaxis depends on how common *Aspergillus* is

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