Nosocomial *C. difficile* Common in Pneumonia

BY BRUCE JANCIN

FROM THE ANNUAL EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

VIENNA — The three major guideline-recommended, empiric antibiotic strategies for community-acquired pneumonia are associated with similar rates of nosocomial acquisition of *Clostridium difficile*, according to a prospective, observational study.

The nosocomial *C. difficile* acquisition rates documented in the Dutch study—11.2% overall and 7.2% for the more worrisome toxigenic strains—are far from inconsequential. In the United States, with an estimated 1 million hospital admissions annually for community-acquired pneumonia (CAP), the toxigenic-strain acquisition rate extrapolates to 72,000 new carriers of toxigenic *C. difficile* per year, Dr. Anke H. Bruns pointed out at the annual European Congress of Clinical Microbiology and Infectious Diseases.

"This is a large contributor to the spread of *C. difficile*," observed Dr. Bruns of University Medical Center Utrecht, the Netherlands.

She reported on 107 Dutch patients hospitalized with severe CAP, for which 41% were treated with moxifloxacin, 44% with beta-lactam monotherapy, and the rest with beta-lactam/macrolide combination therapy. Participants were followed for 30 days, with stool samples collected on admission, 5 days later, 3 days after completion of antibiotic therapy, and on day 30.

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Most patients were asymptomatic, constituting a reservoir for the spread of disease, says Dr. Anke H. Bruns.

Infectious Diseases Society of America guidelines recommend either of two antibiotic regimens as first-line treatment for CAP patients on general medical wards who are thought not to have *Legionella* pneumonia: monotherapy with a respiratory fluoroquinolone or combination therapy of beta-lactam and macrolide. Dutch guidelines recommend monotherapy with either a fluoroquinolone or beta-lactam or therapy combining a beta-lactam with either a macrolide or fluoroquinolone.

Regarding those regimens as equally effective for CAP, Dr. Bruns and her coworkers sought to learn whether the regimens are also equal in associated risks of acquiring *C. difficile* colonization. That proved to be so.

Another key finding was that the prevalence of *C. difficile* carriage at admission was 9.4%, as determined from stool cultures. "Most patients were asymptomatic, and therefore they constitute an important reservoir for the spread of disease, especially because skin contamination was also involved in several cases," she said.

In a multivariate analysis, the parameters strongly associated with *C. difficile* carriage were the use of intravenous antibiotics for more than 7 days (associated with a 3.9-fold risk), hospitalization within the previous 3 months (4.1-fold risk), and tube feeding (4.4-fold risk).

The study has several major clinical implications, Dr. Bruns noted. One stems from the finding that no one antimicrobial proved to be associated with increased risk for emergence of *C. difficile*. That argues against banning any specific agent, such as fluoroquinolones or cephalosporins, for the treatment of CAP, as has been advocated.

Instead, said Dr. Bruns, it makes more sense to implement strategies aimed at reducing overall antibiotic use in CAP patients, such as shorter treatment courses or an earlier switch from intravenous to oral agents. That approach has great potential, given that treatment of respiratory tract infections accounts for two-thirds of all antibiotic use worldwide, she continued.

The other take away point is that patients hospitalized for treatment of CAP have a roughly 1-in-10 baseline prevalence of *C. difficile* carriage. Routine screening of CAP patients and institution of appropriate hygiene measures are worth considering, said Dr. Bruns, who disclosed having no financial conflicts regarding the study. ■

Promising New Drugs on Horizon for Pandemic Influenza

BY BRUCE JANCIN

EXPERT ANALYSIS FROM A CONFERENCE ON PEDIATRIC INFECTIOUS DISEASES

VAIL, COLO. — Much-needed help in treating pandemic 2009 H1N1 influenza may be on the way in the form of two promising investigational drugs that could become commercially available within the next several flu seasons.

Favipiravir and laninamivir are in phase III clinical trials abroad, where to date both appear to be performing very well, Dr. Adriana Weinberg said at the annual conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

Favipiravir is an oral RNA polymerase inhibitor effective against both influenza A and B as well as other RNA viruses. It is in phase III testing in Japan. Importantly, it has no cross-resistance with the neuraminidase inhibitors or adamantanes.

Laninamivir is a neuraminidase inhibitor administered only by inhalation. However, the drug has an extremely long half-life such that a single inhalation constitutes an entire course of treatment. Laninamivir is effective against oseltamivir-resistant isolates. It is in phase III trials in Australia, where it is establishing a very favorable safety profile, according to Dr. Weinberg, professor of medicine, pediatrics, and pathology of the University of Colorado, Denver, and medical director of the clinical virology laboratory at University of Colorado Hospital.

Current treatment options for pandemic H1N1 flu are quite limited, so these two new drugs are badly needed, she added.

More than 90% of H1N1 isolates from the 2009 pandemic were resistant to adamantanes. So basically all that physicians had available early on were the oral neuraminidase inhibitor oseltamivir (Tamiflu) and the inhalation-only formulation of zanamivir (Relenza), another neuraminidase inhibitor.

These were supplemented during the pandemic by intravenous peramivir, a drug that was in phase III trials but was decreed available for use in critically ill patients as a result of an Emergency Use Authorization. The Emergency Use Authorization was terminated in June 2010. Peramivir has a resistance profile and efficacy similar to oseltamivir. Thus, its sole advantage is that it can be given intravenously. The recommended dosing is 6 mg/kg in neonates, 8 mg/kg for infants aged 31-90 days, 10 mg/kg for 91- to 180-day-olds, 12 mg/kg for children aged 181 days through 5 years, 10 mg/kg for 6- to 17-year-olds, and 600 mg for patients aged 18 years and older. The infusion is given over 30-60 minutes.

Laninamivir is in phase III trials and is showing a favorable safety profile against oseltamivir resistance.

DR. WEINBERG

Intravenous zanamivir became available on a compassionate-use basis during the pandemic. Unlike peramivir, it is effective against oseltamivir-resistant isolates.

Ribavirin is commercially available for indications other than influenza. However, it does have in vitro activity against influenza, and although it's not a very good anti-influenza drug by itself, it may have a future in combination therapy for severe pandemic H1N1 disease.

Combo therapy with neuraminidase inhibitors, ribavirin, adamantanes, and interferon was widely used for avian influenza A(H5N1), but due to the lack of controls it's hard to draw any conclusions as to whether this resulted in enhanced efficacy. In animal models, two drugs for pandemic H1N1 disease are more effective than one, regardless of the drugs tested, provided the virus is susceptible to both drugs. Results thus far are conflicting when the virus is resistant, according to Dr. Weinberg.

Oseltamivir performed well last season against pandemic H1N1. When started within 2 days following symptom onset, it reduced mortality by 50%. It also reduced the duration of symptoms. There is some evidence that if the drug is given within the first 3 days, it reduces duration of viral shedding, which is 14 days without treatment compared with 7 days for seasonal influenza. Oseltamivir did a good job of limiting disease transmission during outbreaks in nursing homes and other closed communities.

Under an Emergency Use Authorization issued during last year's pandemic, oseltamivir became available for the treatment of patients of all ages with H1N1 flu. Recent interim data from a National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group trial suggest the best dose in infants is 3-mg/kg per dose twice daily. In premature babies, the optimal dose appears to be 1-mg/kg per dose twice daily (J. Infect. Dis. 2010;202:563-6).

In the middle of last year's pandemic, the World Health Organization recommended that the standard 75-mg b.i.d adult and adolescent dose of oseltamivir could be doubled in severe cases of H1N1 disease, an announcement Dr. Weinberg dismissed as "weirdness that made little sense" since the pharmacokinetics of the drug are linear up to 500 mg/dose.

Her advice: Consider quadrupling the standard dose in severe cases.

Prophylactic administration of oseltamivir is a common inducer of resistance in immunocompetent patients, which is why the WHO recommends not using the drug for prophylaxis. Resistance also develops quickly in lung transplant recipients.

There was concern that oseltamivir resistance would spread widely through communities, but that didn't prove to be the case. All documented cases have occurred in patients on oseltamivir or in close contacts of patients treated with the drug, according to Dr. Weinberg.

Dr. Weinberg disclosed serving as a consultant to MedImmune, Astellas, GlaxoSmithKline, and Merck. ■