Resistant Gram-Negative Infection May Worsen Patient Outcomes

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BETHESDA, MD. — Evidence suggests that multidrug-resistant gram-negative organisms contribute to worse patient outcomes if patients are not severely ill, Arjun Srinivasan, M.D., said at an annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

"When you factor severity of illness, extremely severe illness overrides the impact of multidrug resistance on mortality," Dr. Srinivasan said in an interview.

In some studies of patients with gram-negative infections, multidrug resistance was not associated with significantly higher all-cause mortality. But many outcome studies in this research area have not differentiated between colonized vs. infected patients, or controlled for severity of illness, noted Dr. Srinivasan, a medical epidemiologist in the division of health care quality promotion at the Centers for Disease Control and Prevention in Atlanta.

Dr. Srinivasan and his colleagues conducted an outcome study of 96 patients with multidrug-resistant *Acinetobacter* in 2004. The researchers used validated definitions to separate colonized and infected patients and used Acute Physiology and Chronic Health Evaluation (APACHE) III scores and the Charleston comorbidity index to assess severity of illness. They compared the infected patients with two different control groups, one group of 90 patients with susceptible *Acinetobacter* infections and one group of 89 patients without *Acinetobacter* infections.

The resulting patient characteristics were "exactly what we had expected from the beginning," Dr. Srinivasan said.

Patients who were infected with multidrug-resistant *Acinetobacter* were significantly sicker than were patients in the two control groups. They also had higher APACHE III scores, which indicated that they were more severely ill, and more comorbidities compared with both control groups.

In a univariate analysis, the patients with multidrug-resistant *Acinetobacter* had a significantly higher rate of mortality (27.1%) compared with both the susceptible *Acinetobacter* group (16.7%) and the no *Acinetobacter* group (12.4%). In addition, the mean length of hospital stay was significantly higher in the multidrug resistant group (27 days) compared with the other two groups (20 days and 19 days, respectively).

To assess the independent impact of resistance, the researchers used a multivariate analysis to control for the effect of severity of illness. Patients with multidrug-resistant *Acinetobacter* were twice as likely as were the controls to have a longer-than-average hospital stay and were 2-3 times more likely to have a longer-than-average ICU stay.

But the multivariate model showed no significant difference in mortality among the groups. The findings emphasize that drug resistance cannot overcome the impact of severity on mortality, although resistance was associated with a longer hospital stay.

Assessment of the role of illness severity continues to challenge researchers in outcome studies of drug resistance, Dr. Srinivasan said.

"The nature of the epidemiology of resistant gram-negative pathogens is a dynamic one. It's not steady, and it is going to continue to evolve," Dr. Srinivasan commented. "The resistant pathogens are becoming a bigger and bigger problem, and our therapeutic options simply are not keeping pace."

Five risk factors for infection or colonization with gram-negative organisms have surfaced frequently in studies: severity of illness, prolonged mechanical ventilation, prior antimicrobial exposures, prolonged hospital or ICU stay, and exposure to invasive medical devices.

Klebsiella pneumoniae carbapenemases, or KPCs, are perhaps the next big thing in gram-negative resistance. They cleave carbapenems, effectively conferring moderate to high levels of drug resistance to all drugs in the carbapenem class. ■

Carbapenems Fail to Foil Klebsiella *and* E. coli

BETHESDA, MD. — Patients infected with extended-spectrum β-lactamase–producing organisms did not have significantly lower mortality if treated with a carbapenem antibiotic, compared with untreated patients (25.8% vs. 26.1%), reported Jeremias L. Murillo, M.D., at an annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

The retrospective study included 91 patients. They ranged in age from 13 to 99 years, with a mean age of 66 years; 45 patients were males and 46 were females.

Extended-spectrum β-lactamase (ESBL)–producing organisms are increasingly recognized as health care–associated pathogens, on par with vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA), said Dr. Murillo of the infection control department at the Newark (N.J.) Beth Israel Medical Center.

The objective of this study was to determine whether there were differences in mortality rate and length of hospital stay between patients who were treated with a carbapenem and those who were not, and whether mortality and length of stay differed among patients infected with different organisms, he said.

Escherichia coli, the most common cause of infection, was found in 45 patients, while *Klebsiella pneumoniae* infection occurred in 40 patients, and *Klebsiella oxytoca* was found in 6 patients.

The mortality rates for patients infected with these three organisms were 20.0%, 22.5%, and 16.6%, respectively.

Patients infected with *Klebsiella pneumoniae* spent significantly more time in the hospital, compared with the overall average length of stay for infected patients (75 days vs. 54 days).

Eight of 31 patients (25.8%) who received a carbapenem and 11 of 42 patients (26.1%) who did not receive a carbapenem died.

Acute Physiology and Chronic Health Evaluation (APACHE) II scores proved to be an accurate predictor of mortality; patients who died had significantly worse APACHE II scores at the time of positive culture, compared with patients who survived.

"This review was prompted by two observations. The first was the introduction of ESBL-producing organisms into our institution—a 600-bed inner-city tertiary care center—in 2002, and the second observation is the fact that there were some patients infected with ESBL-producing organisms who did fairly well in the absence of carbapenem treatment," Dr. Murillo explained. ■

Nalidixic Acid Resistance Rises In *Salmonella enteritidis* Isolates

BETHESDA, MD. — The percentage of nalidixic acid–resistant *Salmonella enteritidis* isolates increased significantly, from 1% to 5%, between 1996 and 2003, Felicita Medalla, M.D., said at an annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

Participating state health departments have submitted *Salmonella* isolates to the National Antimicrobial Resistance Monitoring System (NARMS) since 1996. Between 1996 and 2003, 2,349 *Salmonella enteritidis* isolates were tested, and 64 (3%) were resistant to the antimicrobial agent nalidixic acid, noted Dr. Medalla, a member of the NARMS working group at the Centers for Disease Control and Prevention in Atlanta.

Salmonella enteritidis was the second most common serotype reported in laboratory-confirmed cases in 2003, Dr. Medalla reported.

Most *Salmonella* infections stem from the consumption of eggs, chicken, and egg-containing foods. The illness causes symptoms similar to gastroenteritis and usually does not require treatment. However, when treatment is needed, resistance is a concern. Quinolones have been the mainstay treatment, and nalidixic acid resistance in *Salmonella* has been associated with decreased susceptibility to quinolones such as ciprofloxacin in previous studies. Overall, 88% of the nalidixic acid–resistant *S. enteritidis* isolates from the 1996-2003 NARMS data sets showed decreased susceptibility to ciprofloxacin.

Resistance to nalidixic acid in any non-typhi *Salmonella* increased significantly during the study, from 5 of 1,326 isolates in 1996 (0.4%) to 47 of 1,873 isolates in 2003 (3%).

Whether the nalidixic acid–resistant *Salmonella* infections were acquired internationally or domestically remains to be studied, Dr. Medalla said, but clinical monitoring of resistance is important, given the public health implications. ■

Vancomycin-Resistant Enterococci Are at Large Outside Hospital Setting, With Numbers Rising

BETHESDA, MD. — The presence of vancomycin-resistant enterococci in 29 (1.4%) of 2,061 stool samples collected from healthy volunteers suggests that VRE is at large outside of the hospital setting, Amie May reported at the annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

In an ongoing study, Ms. May and her colleagues at the Centers for Disease Control and Prevention's National Center for Infectious Diseases collected 10-20 stool specimens each month between 2000 and 2002 from healthy volunteers or outpatients with diarrhea who had no hospital contact within 6 months of their sampling.

The samples came from sites in five states: Georgia, Maryland, Michigan, Minnesota, and Oregon. Two isolates were found in Maryland, 23 were found in Michigan, and 4 were found in Minnesota.

The number of samples containing VRE increased each year: 7 were found in 2000, 9 were found in 2001, and 13 were found in 2002. A total of 28 samples were *Enterococcus faecium*, while only 1 was *E. faecalis*. Fourteen (48%) of the 29 samples had minimum inhibitory concentrations greater than 256 mcg/mL.

Overall, 12 (50%) of 24 of the VRE samples had high levels of gentamicin resistance, 3 (12%) of 25 were resistant to quinupristin (Synercid), 13 (54%) of 24 were resistant to tetracycline, and 20 (83%) of 24 were resistant to penicillin.

The finding that both *E. faecium* and *E. faecalis* samples were resistant to quinupristin was of particular concern, since it is one of the few available options for treating VRE, Ms. May noted. ■