Risk of Sepsis Death Soars With Antibiotic Delays

BY JANE SALODOF MACNEIL
Contributing Writer

PHOENIX, ARIZ. — Risk of death from sepsis increases by 6%-10% with every hour that passes from the onset of septic shock until the start of effective antimicrobial therapy, according to a review of more than 2,600 consecutive cases at 15 intensive care units in five U.S. and Canadian cities.

"You already have a substantially increased risk of death if you get antibiotics by the second hour after onset of hypotension compared with the first hour—and that odds ratio continues to climb out to 36 hours," principal investigator Anand Kumar, M.D., said at a meeting sponsored by the Society of Critical Care Medicine.

But relatively few patients received appropriate antibiotics within 2 hours.

Dr. Kumar, head of the emergency department at the University of Manitoba in Winnipeg, reported that at every hospital studied, "Only half of septic shock patients received an antibiotic within 6 hours of onset of recurrent or persistent hypotension."

Early administration of appropriate antibiotics is crucial because it eliminates the source of sepsis, according to Dr. Kumar. "You can keep the patients alive for days, but if you don't eliminate the source in the first couple of hours, they are not going to make it."

All told, 44% of 2,731 septic shock patients reviewed by Dr. Kumar and his colleagues survived to hospital discharge. Removing patients who were moribund at presentation (those who required intubation or cardiopulmonary resuscitation in the field) reduced the population to 2,675 patients, but barely nudged the survival rate up to 48%.

The population had slightly more men than women and an average age of 62.5 years.

Nosocomial infections accounted for 42% of cases. Malignancy was the most common comorbidity (20%), followed by chemotherapy and elective surgery, each about 15%. The average Acute Physiology and Chronic Health Evaluation II score was 25.9.

'Simple administrative changes can reduce time to antibiotics by 2 hours. ... that's a translation to a 15% absolute improvement in mortality.'

Dr. Kumar said emergency departments were about an hour faster than other areas of the hospital in delivering antibiotics, but still too slow. The median emergency department time to treat was 4.5-5 hours, he said.

The investigation started with animal studies. In those experiments, mortality was held to 10% if the animals were given an antibiotic within a 12-hour window before the onset of hypotension, according to Dr. Kumar. The mortality became 80% if the antibiotic was started 15 hours afterward, and 100% at 24 hours.

In the human retrospective study reported at the meeting, 89% of patients who received an appropriate antibiotic within the first half hour survived, he said. By the second hour, the survival rate dropped to 84%, and it continued to drop at a rate of 7.5% every hour thereafter.

Subset analyses by numerous factors mostly produced *P* values of .0001 without changing the risk, according to Dr. Kumar. Patients who were obviously sicker at presentation received antibiotics faster, improving their odds of surviving, he said.

Only about 50 patients, all in the United States, had methicillin-resistant *Staphylococcus aureus*, which was not seen in Winnipeg, according to Dr. Kumar.

He noted that the investigators focused on time to effective antibiotics. If the first choice is not effective, the effects of any initial delay can be all the more overwhelming, he said.

Dr. Kumar called for hospitals to use medical response teams with algorithm protocols for patients in septic shock. He reported that his hospital has instituted the following changes in response to the study:

- ▶ Staff can start intravenous antibiotics in hypotensive sepsis patients without waiting for approval.
- ▶ Nurses have been told that the first dose of any new antibiotic is an automatic stat order.
- ▶ No sepsis patient is transferred to an intensive care unit without receiving an antibiotic before leaving the emergency department.

Many physicians do not realize that an antibiotic order may wait for hours if it is not marked "stat," according to Dr. Kumar. If the patient is transferred to an ICU, more hours might pass before the antibiotic is delivered with scheduled medications, he warned.

"These simple administrative changes can reduce time to antibiotics by 2 hours," he said. "And, if these data hold, that's a translation to a 15% absolute improvement in mortality." ■

Xigris May Not Be Appropriate For Less Critically Ill Patients

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

Drotrecogin alfa, a biologic agent used to treat adults with severe sepsis who are at high risk of death, may not be appropriate for patients with single organ dysfunction and recent surgery, and should only be administered after careful consideration of the potential risks and benefits, according to a new warning by Eli Lilly & Co., which manufactures the drug.

Lilly added the warning to the prescribing information after two studies indicated a small but clinically important increase in the rate of all-cause mortality among these patients treated with the agent, compared with those who received placebo. Physicians and other health care providers received a letter in February alerting them to the new warning.

Drotrecogin alfa (Xigris) is indicated only for adult patients with severe sepsis who are at high risk of death. The subset of patients with single organ dysfunction and recent surgery, "may not be at high risk of death, and therefore may not be indicated for Xigris," the warning states.

The warning was based on a preliminary analysis of the Administration of Drotrecogin Alfa [Activated] Early Stage Severe Sepsis (ADDRESS) randomized, placebo-controlled trial and a reanalysis of Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS), the drug's phase III registration trial. In the PROWESS trial of almost 1,700 patients, only 98 had single organ dysfunction and recent surgery (within 30 days of therapy). Among the 49 treated patients, 10 died within 28 days of treatment and 14 were hospitalized; among the placebo-treated patients, 8 died within 28 days and 8 were hospitalized.

The ADDRESS trial studied the drug's effect in patients who were less critically ill (Acute Physiology and Chronic Health Evaluation [APACHE] II score less than 25, or single sepsis-induced organ failure at any APACHE II score). Among 323 treated patients, 67 died within 28 days and 76 were hospitalized; among the placebo-treated patients, 44 died within 28 days and 62 were hospitalized.

"The important thing to note is that this is a preliminary finding," said Carole Puls, spokesperson for Lilly. "We issued the warning because we felt these patients may not be at high risk for death and so the drug is not indicated for them."

During Food and Drug Administration approval hearings for drotrecogin alfa, members of the Anti-Infective Drugs Advisory Committee noted that the drug was less effective in reducing mortality in patients with less severe sepsis, who had a better prognosis.

The main safety concern during the hearings was serious bleeding events, which the company said appeared to be associated with vessel trauma or severe coagulopathy and were consistent with the product's antithrombotic and profibrinolytic effects. Serious bleeding adverse events occurred in 3.5% of those on drotrecogin alfa, compared with 2% of those on placebo. Of the serious bleeding events among those on drotrecogin alfa, most occurred during or immediately after the patients received the infusion. Bleeding sites were gastrointestinal, intraabdominal, intrathoracic, retroperitoneal, intracranial, genitourinary, and skin/soft tissue. ■

Study Supports Early Use Of Xigris in Sepsis Patients

BY DOUG BRUNK
San Diego Bureau

SEATTLE — When it comes to initiating therapy with drotrecogin alfa in patients with severe sepsis, the earlier the better.

That's the key message from a large study of patients who received drotrecogin alfa (Xigris) at 139 hospitals in the United States between November 2001 and June 2003, Frank Ernst, Pharm. D., reported at the annual meeting of the American College of Chest Physicians.

Drotrecogin alfa (activated) is recombinant human activated protein C; it mimics endogenous protein C, which inhibits coagulation and inflammation when activated.

Waiting 2 or more days to initiate the drug predicted hospital mortality, whereas earlier initiation predicted lower hospital costs and shorter lengths of stay among survivors, reported Mr. Ernst, a pharmacist at Eli Lilly and Co., Indianapolis.

In a study funded by Lilly, Mr. Ernst and his associates studied database records of 1,179 patients who received drotrecogin alfa during their hospital stay following evident severe sepsis, defined as concurrent antibiotic use plus ventilator and/or vasopressor use. The records were obtained from a large national database of hospital discharge records maintained by Solucient, a health information technology company.

Of the 1,179 patients, 509 received drotrecogin alfa on the same day that they had evident severe sepsis (same-day patients), 354 received the drug the day after they had evident severe sepsis (next-day patients), and 323 received the drug 2 days or more after they had evident severe sepsis (day 2-plus patients).

At ICU admission, day 2-plus patients had fewer organ dysfunctions than did patients in the other two groups. But between ICU admission and initiation of drotrecogin alfa, organ dysfunctions increased significantly more among day 2-plus patients than did next-day and same-day patients.

Hospital mortality was predicted by ventilator use (odds ratio [OR] 5.1), vasopressor use (OR 2.6), and initiation of drotrecogin alfa on day-2 plus (OR 1.7).

Among survivors, 7% shorter length of stay and 10% lower adjusted post–drotrecogin alfa administration costs were predicted by same-day or next-day initiation.

Limitations of the study were its retrospective design and the fact that the database used contained limited clinical information, Mr. Ernst noted. ■