

Sepsis Death Risk Soars With Antibiotic Delays

Relatively few patients received necessary antibiotics in a timely manner in either EDs or hospital ICUs.

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.

Relatively few patients received appropriate antibiotics within 2 hours, however.

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," he said.

All told, 43.8% 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 44.7%.

The population had slightly more men than women and an average age of 62.5 years. Nearly half the patients, 43%, came from emergency departments. Another 28% had been in medical wards, and 18% on surgical floors.

Nosocomial infections accounted for 42% of cases. Malignancy was the most common comorbidity (20%), followed by chemotherapy and elective surgery, each

Of patients treated within the first half-hour, 89% survived. By the second hour, survival dropped to 84%, and fell at a rate of 7.5% every hour thereafter.

about 15%. The average Acute Physiology and Chronic Health Evaluation II score was 25.9.

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.

The investigation started with animal studies. 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 was 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 Unit-

ed 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 his hospital 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 ICU without receiving an antibiotic before leaving the emergency department.

Many emergency 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." ■

Aggressive Treatment Can Improve Outcomes in Sepsis

BY DIANA MAHONEY
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STOWE, VT. — Aggressive therapy upon presentation can improve the mortality and morbidity associated with septic shock, according to Stephen Leffler, M.D.

Early appropriate antibiotics, rapid fluid resuscitation, and timely use of vasopressors can improve outcome substantially, Dr. Leffler said in a presentation on sepsis management at an emergency medicine update sponsored by the University of Vermont. Options for the most critical patients also include blood transfusions, intubation/paralysis, activated protein C, and corticosteroids.

Standard emergency department therapy for patients presenting in septic shock typically includes hemodynamic support and appropriate antibiotics, with more targeted aggressive therapy being delayed until the patient is transferred to the intensive care unit, said Dr. Leffler of the university. Recent evidence suggests that holding off on the most aggressive therapy may result in early tissue hypoxia and irreversible tissue damage, while implementing standard ICU management techniques in the ED increases the likelihood of interrupting the destructive cascade.

An investigation of early goal-directed therapy (EGT) at Henry Ford Hospital in Detroit showed that using central venous oxygen saturation (ScvO₂) and pressure, measured continuously by central venous cannulation, to balance systemic oxygen delivery and consumption during the first 6 hours after presentation can significantly reduce mortality in patients with septic shock.

In the 2002 study, 236 emergency department patients with septic shock were randomized to receive either usual care or the EGT protocol. All of the patients received arterial and venous catheters. The patients in the control group were transferred to the ICU and treated according to clinician discretion. The patients who were randomized to EGT received a central line for measurement of ScvO₂ and were managed in the emergency depart-

ment for 6 hours before being transported to the ICU.

The EGT protocol included providing a 500-mL bolus of fluid every 30 minutes as needed to maintain central venous pressure between 8 and 12 mm Hg, administering vasopressors in the presence of mean arterial pressures less than 65 mm Hg, and giving blood transfusions to keep hematocrit levels greater than 30% if ScvO₂ was below 70%. After transfusion, if ScvO₂ persisted at less than 70%, the patients received dobutamine and in some cases were intubated and paralyzed to decrease oxygen consumption.

Patients in the intervention group had a 30% hospital mortality, compared with 46% for those receiving standard therapy. "The EGT group also had improved lactate, pH, and ScvO₂ levels," Dr. Leffler said.

"There are some important take-home messages in these findings, even if we're not going to get central venous oxygen saturation in every patient," Dr. Leffler said. For example, patients in the EGT group received 5 L of fluid in the first 6 hours of treatment—1.5 L more than the standard therapy group. "This tells us that we are probably underhydrating these patients, and that we should be more aggressive with fluids. The standard 1,500 cc is not going to be enough," he said.

Additionally, the blood transfusion rate was 64% for EGT patients, compared with 18% for the control group. The message in this, Dr. Leffler said, "is to go ahead and type and cross if the patient's [hematocrit] goes below 30%. A couple of units of blood might help."

There was no difference in the rates of intubation and vasopressor use between the two groups.

While studies of similar management strategies implemented in the ICU have failed to show similar outcome improvements, "I think the critical element is the timing," Dr. Leffler said. "The intervention in the emergency department was probably initiated earlier, before irreversible end-organ dysfunction."

Specific subsets of patients in septic shock may also

benefit from treatment with activated protein C or corticosteroids, Dr. Leffler said. "There is some evidence that treatment with [recombinant] activated protein C can reduce mortality in septic shock, but this benefit appears only in the sickest patients," specifically those with respiratory and hemodynamic failure, who are at increased risk of death from sepsis, Dr. Leffler said.

To be effective, the drug must be administered within 24 hours of sepsis-induced failure, and it should not be considered for patients with coagulopathy because of the increased bleeding risk, he said.

The drug's high cost also is a caveat, Dr. Leffler said. "At \$7,250 per dose, [activated protein C] is not yet used routinely and won't be until more evidence shows it to be far better than other options," he contended.

Corticosteroids also have a role in sepsis management, but not the high-dose, short-course, broadly administered regimens of the 1970s that proved ineffective in later trials, he said.

Recent studies have shown that more than half of all septic patients could have a relative adrenal insufficiency that may be implicated in worse outcomes. In a study of patients with relative adrenal insufficiency—identified by a corticotrophin stimulation test on admission—those treated with steroids had lower 28-day mortality than did those randomized to receive placebo in addition to standard therapy.

"This tells us that steroids may have a place in the treatment of critically ill patients in septic shock, and that maybe we want to do stim tests more often to determine who might benefit from steroid therapy," he said.

The bottom line, according to Dr. Leffler, is that there is a huge cost associated with sepsis, in terms of dollars and lives. "We can do more for these patients in the emergency department than getting antibiotics on board," he said. "If we improve their hemodynamics—through fluids, vasopressors, and possibly steroids—we can improve their chances." ■