Clinical Digest

INTENSIVE CARE

Treat Sepsis Right the First Time

Patients with sepsis have a better chance of survival when they're given the correct antimicrobial drugs to begin with, say a team of Swiss researchers who conducted a study of 904 patients in 108 North American and European hospitals.

Previous studies have shown that between 3% and 19% of patients with sepsis are treated inadequately. These researchers say that though the evidence of a statistical association between inappropriate antimicrobial treatment and death doesn't prove causality, their analyses suggest that other factors (comorbid conditions, severity of illness, and baseline organ dysfunction) can't account solely for the increased risk.

The researchers considered treatment to be inappropriate if the patient didn't receive at least one antimicrobial agent to which the causative microorganisms were susceptible within 24 hours of severe sepsis diagnosis. Of the 904 patients, 211 (23%) received inappropriate initial antimicrobial therapy, either because the agent was inactive against at least one of the infecting pathogens (77%) or because an adequate drug was not given quickly enough (23%). Over the course of the 28-day study, 250 patients (28%) died: 168 (24%) of 693 adequately treated patients and 82 (39%) of 211 inadequately treated patients. After adjusting for other confounding factors (such as baseline organ dysfunction and characteristics of infection), the researchers found inappropriate initial antimicrobial therapy was associated independently with increased mortality, regardless of the hospital or geographic location.

The researchers offer another notable finding: The database of patients came from a double-blind, placebo-controlled, phase III study of the immunomodulator lenercept. Among the lenercept patients, 80 (24%) of 335 adequately treated patients died, compared with 45 (40%) of 113 inadequately treated patients. After excluding patients with microbiologically documented severe sepsis who had received inadequate antimicrobial treatment, the researchers say, lenercept wasn't associated with a survival benefit.

Source: *Am J Med.* 2003;115: 529–535.

ONCOLOGY

Psoriasis: The Lymphoma Link

Psoriasis is a disease of immune activation. For this reason, some clinicians have speculated that patients with psoriasis may be at an increased risk for lymphoproliferative malignancies. And after conducting a retrospective cohort study to test this theory, researchers from the University of Pennsylvania, Philadelphia found that among patients over age 65 who have psoriasis, the rate of lymphoma is nearly three times that of those who don't have psoriasis.

Because lymphoma is a relatively rare form of cancer, a very large study group was needed to detect incidence differences between groups. Also, most of the previous research has been performed using hospitalized patients. For this study, the researchers analyzed information from a random sample (10% of the patients 65 years or older) of the United Kingdom's General Practice Research Database, which contains more than eight million ambulatory patients and more than 35 million person-years of follow-up. Of the 107,921 patients who comprised the sample, 2.52% had psoriasis. Patients 65 years or older who had psoriasis developed an additional 122 lymphomas per 100,000 patients annually. No significant difference was noted in the frequency of psoriasis based on sex.

The researchers say the immunosuppressive drugs and immunomodulating drugs used to treat psoriasis may be independent risk factors for lymphoproliferative malignancies. Or, it may be that psoriasis itself is a substantial risk factor.

An important limitation of the study is that it included patients with different degrees of psoriasis, and the researchers were unable to assess the effect

of psoriasis severity or of treatment on the rate of lymphoma. Only a small number of subjects, however, had been treated with medications (such as methotrexate) that are associated with an elevated lymphoma risk.

Source: *Arch Dermatol*. 2003; 139:1425–1429.

EMERGENCY MEDICINE

Pediatric Fasting in the ED

When children are rushed to the emergency department (ED), there's little time to think about whether, what, or when they've eaten. Under such circumstances, consensus-based guidelines for preprocedural fasting, recommended by the American Academy of Pediatrics and the American Society of Anesthesiologists, may be followed less often than not.

But researchers from the Children's Hospital Boston and Harvard Medical School, Boston, MA and the St. Louis University School of Medicine, St. Louis, MO say that this may not be a great cause for concern. They conducted an 11-month prospective case series study of 1,014 primarily pediatric, ED patients who required procedural sedation and analgesia. The 905 patients who had documentable dietary histories were included for analysis. Of those, 509 (56%) didn't meet fasting guidelines.

The researchers observed 77 adverse events (including arterial oxygen saturation below 90% and airway complications) in 68 (6.7%) of the original cohort. Preprocedural fasting didn't have a significant effect on the rate of adverse events, which occurred in 32 of 396 patients who met fasting guideline requirements, 35 of 509 who didn't, and one for whom a dietary history was unavailable. Furthermore, there was no significant difference in median fasting duration between patients who experienced adverse events and those who didn't. All adverse events were treated successfully.

This study provides further evidence, the researchers conclude, that procedural sedation and analgesia is generally safe, with few adverse events and no serious complications. In fact, the researchers cite earlier studies that suggest there might be a downside to preprocedural fasting: It was more difficult to sedate younger children and infants who were hungry.

Source: *Ann Emerg Med*. 2003;42:636–646.

DIABETES CARE

Balancing Glucose Control and Mental Health

As a determinant of free fatty acids in the blood, insulin resistance is believed to be a key factor in tryptophan metabolism and brain serotonin concentrations. In fact, a previous, large cohort study of nearly 15,000 individuals found that insulin sensitivity is associated with an elevated risk of suicide and depression. And now, a cross-sectional analysis of 4,286 randomly selected women aged 60 to 79 supports these findings. The researchers, from the University of Bristol, Bristol, United Kingdom, found the prevalence of depression dropped as insulin resistance increased.

Three indicators of depression—current use of antidepressant medication, self-report of ever having received a diagnosis of depression, and a mood questionnaire—produced consistent findings, which according to the researchers support an inverse association between insulin resistance and depression. Still, they don't believe their results should discourage appropriate interventions to prevent and treat insulin resistance. Rather, they say their findings point to a need for assessing individuals being treated for insulin resistance for depressive symptoms too, since these can be disabling and interfere with treatment adherence as well as overall quality of life.

Source: *BMJ*. 2003;327: 1383–1384.

INTENSIVE CARE

Is Noninvasive Ventilation Worth the Effort?

For patients experiencing acute exacerbations of chronic obstructive pulmonary disease (COPD) or severe cardiogenic pulmonary edema (CPE), non-

invasive ventilation (NIV) can not only reduce the need for endotracheal intubation and invasive mechanical ventilation, but also can reduce complication and mortality rates.

Such were the conclusions reached by a team of French researchers who analyzed patient data during an eight-year span in the medical intensive care unit (ICU) of Hôpital Henri Mondor in Créteil, France. The results of their retrospective, observational cohort study attributed a marked reduction in mortality and nosocomial infections to improved delivery of NIV.

Over the eight years, there was no change in the therapeutic management of COPD or CPE other than the introduction of NIV and continuous educational efforts directed at its administration. Rates of pneumonia acquired in the ICU dropped from 20% in 1994 to 8% in 2001, and the crude ICU mortality rate decreased from 21% to 7%. The risk of death was three times lower in patients with COPD or CPE who had received NIV.

Early reports on NIV described the technique as time consuming for staff. Its effective implementation requires health care professionals to take annual training sessions, and recommendations have to be distributed and explained. Specifically, staff has to learn to interact with a nonsedated dyspneic patient, manage the patient-ventilator interface, monitor and manage air leaks, and monitor parameters reflecting the efficacy of the treatment. Although the researchers concede that there's a learning curve for the practice of NIV, they feel the results make it well worth the effort.

Source: *JAMA*. 2003;290: 2985–2991.

WOMEN'S HEALTH

New Management Strategies for HPV

Testing for human papillomavirus (HPV) is a more sensitive—but less specific—method of screening for high-grade cervical cancer when compared with cytology. But if HPV testing is to be used as the primary screening tool, those HPV-positive women with negative or borderline cytology shouldn't be referred immediately for a colposcopy, but instead scheduled for repeat testing, say researchers from the HPV in Addition to Routine Testing (HART) study in the United Kingdom.

Their multicenter screening study included 11,085 women, aged 30 to 60, who had either borderline cytology or a positive test for high risk HPV and negative cytology. They randomly assigned each to either: (1) immediate colposcopy, or (2) surveillance by repeat HPV testing with cytology at six and 12 months and colposcopy at 12 months (or at six months if the cytology result showed mild dyskaryosis or worse).

The researchers found that HPV testing was more sensitive than borderline or worse cytology (97.1% versus 76.6%) but less specific for detecting high-grade cervical intraepithelial neoplasia (CIN2+). HPV testing had a predictive value of 128%, which was similar to that for a borderline or worse smear. Higher levels of HPV were more likely to be associated with CIN2+.

Of 825 women in the minimal abnormality group, surveillance at 12 months was as effective as immediate colposcopy. Of the women positive for HPV at baseline who were assigned to surveillance, 45% of those with negative cytology and 35% of those with borderline cytology were HPV negative at six to 12 months. Cervical cancer wasn't found in those women, nor in the women with an initial negative HPV test with borderline or mild cytology.

The researchers suggest that HPV testing could be used for primary screening in women over age 30, with cytology used to triage HPV-positive women. Any normal or borderline cytology (found in about 6% of the women who were screened) could be managed by repeat testing after 12 months. HPV testing also might help reduce the referral rate (and associated costs) for women with mild dyskaryosis, say the researchers, by immediately referring for colposcopy only those women who tested positive for high risk types of HPV. ●

Source: *Lancet*. 2003;362: 1871–1876.