

Abstracts of current literature on epidemiology, diagnosis, and treatment

Series Editor: Jihad Slim, MD

ANTITHROMBIN III IN THE TREATMENT OF SEPSIS

A randomized, double-blind, placebo-controlled, multicenter phase 3 clinical trial was conducted, from March 1997 through January 2000, to determine if high-dose antithrombin III would provide a survival advantage to patients with severe sepsis and septic shock. Adult patients (N = 2314) were randomized into 2 equal groups of 1157 to receive either 30,000 IU of intravenous antithrombin III (with a loading dose of 6000 IU [administered over 30 minutes], followed by a continuous IV infusion of 6000 IU per day for 4 days) or an equivalent volume of placebo solution (1% of human albumin). The antithrombin III was administered within 6 hours of the onset of illness. The main outcome measure was all-cause mortality 28 days after initiation of study medication. Mortality at 28 days in the antithrombin III group was 38.9% vs 38.7% in the placebo group. In patients receiving antithrombin III and concomitant heparin, a significantly increased bleeding incidence was observed (23.8% for the antithrombin III group vs 13.5% for the placebo group). The researchers concluded that high-dose antithrombin III therapy had no effect on 28-day all-cause mortality in adult patients with severe sepsis and septic shock when administered within 6 hours after onset. They further concluded that high-dose antithrombin III was associated with an increased risk of hemorrhage when administered with heparin.

Warren BL, Eid A, Singer P, et al. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001;286:1869-78.

PNEUMOCOCCAL MACROLIDE RESISTANCE

A study was conducted to examine trends of macrolide resistance among isolates of invasive *Streptococcus pneumoniae* in the United States, trends in macrolide use (1993 to 1999), the prevalence of strains with M and MLS_B phenotypes, factors associated with macrolide resistance, and minimum inhibitory concentrations (MICs) of macrolide-resistant isolates. The researchers analyzed 15,481 invasive isolates collected from 1995 to 1999 by the Centers for Disease Control and Prevention's Active Bacterial Core surveillance system in 8 states. Isolates that were erythromycin resistant and clindamycin susceptible were classified as M phenotype, and those that were both erythromycin resistant and clindamycin resistant were classified as MLS_B phenotype. Macrolide resistance increased from 10.6% in 1995 to 20.4% in 1999; increases were significant in all but 1 of the states. From 1993 to 1999, the number of macrolide prescriptions increased 13%. The proportion of M phenotype isolates increased from 7.4% in 1995 to 16.5% in 1999, whereas the proportion of MLS_B phenotype isolates remained stable (3.4% in 1995; 3.7% in 1999). The median erythromycin MIC of M phenotype isolates increased from 4 µg/mL to 8 µg/mL. In 1999,

M phenotype strains were more often from children younger than 5 years than from persons 5 years of age or older (25.2% vs 12.6%) and from whites than from blacks (19.3% vs 11.2%). The researchers concluded that pneumococcal resistance has become common and that most resistant strains have MICs in the range for which treatment failures have been reported.

Hyde TB, Gay K, Stephens DS, et al. Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. *JAMA* 2001;286:1857-62.

PREVALENCE OF ADVERSE EVENTS ASSOCIATED WITH POTENT ANTIRETROVIRAL TREATMENT

A 4-week cross-sectional, observational study of 1160 patients with HIV-1 infection who were receiving potent antiretroviral treatment was conducted to investigate potential associations between clinical and laboratory abnormalities and different antiretroviral treatment regimens and between such abnormalities and specific drugs by using multiple logistic regression. Sixty percent of the patients were receiving single-protease inhibitor (PI) antiretroviral treatment (containing 1 PI and no nonnucleoside reverse transcriptase inhibitors), 15% PI-sparing antiretroviral treatment (containing no PIs and 1 nonnucleoside reverse transcriptase inhibitor, or triple nucleoside analogue reverse transcriptase inhibitors including abacavir), 15% dual-PI antiretroviral treatment (containing 2 PIs and no nonnucleoside reverse transcriptase inhibitors), and 10% 3-class antiretroviral treatment (containing nucleoside analogue reverse transcriptase, PI, and nonnucleoside reverse transcriptase inhibitors). Forty-seven percent (545 of 1160) of the patients had clinical and 27% (194 of 712) had laboratory adverse events probably or definitely attributable to the antiretroviral treatment. Single-PI antiretroviral and PI-sparing antiretroviral treatments were associated with a comparable prevalence of adverse events. Compared with single-PI antiretroviral treatment, use of dual-PI antiretroviral treatment and 3-class antiretroviral treatment was associated with a higher prevalence of adverse events. Compound-specific associations were identified for zidovudine, lamivudine, stavudine, didanosine, abacavir, ritonavir, saquinavir, indinavir, nelfinavir, efavirenz, and nevirapine. The researchers concluded that in their study, there was a high prevalence of toxic effects caused by antiretroviral treatment for HIV-1 infection.

Fellay J, Boubaker K, Ledergerber B, et al. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV cohort study. *Lancet* 2001;358:1322-7.

Dr. Slim is an Assistant Professor of Medicine, Seton Hall University, South Orange, NJ, and Infectious Disease Specialist, St. Michael's Medical Center, Newark, NJ. Abstracts written by Lamont Williams, Hospital Physician.