Consider Kawasaki Disease in Shock Patients

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VAIL, COLO. — Patients with severe Kawasaki disease can present in shock—and that's something not widely appreciated in emergency departments and ICUs.

This was the thrust of two recent studies of severe Kawasaki disease conducted in Denver and San Diego. In both studies, patients with Kawasaki disease who were ill enough to be admitted to the ICU were less likely to have an admitting diagnosis of Kawasaki disease than were less severely ill patients admitted to the wards, Dr. Marsha Anderson said at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

Severe Kawasaki disease presenting with shock was often mistaken for septic or toxic shock. As a result, ICU patients with Kawasaki disease were treated with intravenous immunoglobulin (IVIG)—the first-line therapy—a median of 2 days later than were Kawasaki disease patients on the general wards.

"I think we have to consider Kawasaki disease in our differential diagnosis in patients who present in shock," said Dr. Anderson of the University of Colorado, Denver.

In the Denver study, for which she was a coauthor, patients with severe Kawasaki disease as defined by ICU admission constituted 3.3% of a consecutive series of 423 Kawasaki disease patients (Pediatrics 2008;122:e786-90).

In San Diego, severe Kawasaki disease was defined as systolic hypotension unresponsive to fluids, with resultant ICU admission. Severely affected patients accounted for 7% of 187 consecutive Kawasaki disease patients (Pediatrics 2009;123:e783-9).

In both studies, patients with severe disease were significantly more likely to be female and have low platelet counts and high levels of C-reactive protein and band counts.

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In San Diego, patients with severe Kawasaki disease had significantly lower hemoglobin levels than did less-ill patients; however, in Denver this wasn't the case. On the other hand, in Denver (but not San Diego) severely affected patients had lower serum albumin levels than did those on the wards.

In both studies, patients with severe Kawasaki disease were more likely to have IVIG resistance and to require a second dose of IVIG or a second-line therapy. This was the case for 64% of ICU patients in Denver, compared with 5% on the wards. Similarly, 46% of severely affected patients in San Diego were IVIG resistant, as were 18% of those on the wards.

Coronary artery abnormalities, mitral regurgitation, and left ventricular systolic dysfunction were significantly more common in patients with severe Kawasaki disease than in controls in the San Diego study. In Denver, there was a strong trend for more coronary artery abnormalities in the ICU patients, but it didn't quite achieve statistical significance. ■

Genetic Findings May Point to Dx Test for Kawasaki Disease

VAIL, COLO. — By far the greatest need in Kawasaki disease is for a diagnostic laboratory test, and recent developments suggest that gene expression testing may be the answer.

"I don't think we're going to have a diagnostic test tomorrow, but with refinement I'm hopeful that gene expression profiling might be the basis of a diagnostic test," Dr. Marsha Anderson said at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

Patients who meet the original Kawasaki disease case definition are just the tip of the iceberg. That was acknowledged 5 years ago in the revised American Heart Association Kawasaki disease guidelines, which highlighted the diagnosis and treatment of what has come to be termed incomplete Kawasaki disease (Circulation 2004;110:2747-71).

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Patients with incomplete Kawasaki disease—that is, with fewer than four of the standard criteria—are at increased risk of coronary artery complications, just like patients who meet the original diagnostic criteria, and they too respond to intravenous immunoglobulin. But the lack of a diagnostic test results in delays in diagnosis and treatment, which can have critical long-term impact.

"I suspect that once we get a diagnostic test, we're going to quadruple the number of patients. We're going to have patients we never dreamed had Kawasaki disease who turn out to have very mild forms of it," said Dr. Anderson, a pediatric infectious disease specialist at the University of Colorado, Denver.

Strong evidence suggesting that genetic predisposition plays a role in the development of Kawasaki disease comes from Japan, where the disease incidence is 10- to 15-fold higher than in white populations. Japanese studies indicate that within 1 year after a first case occurs in a family, the incidence of Kawasaki disease in a sibling is 2.1%. And Kawasaki disease is twice as common in children whose parents had the disease.

Investigators at Stanford (Calif.) University are pursuing the genetic connection using DNA microarray technology to examine patterns of gene expression in whole blood from patients with acute and convalescent Kawasaki disease. They demonstrated that patients with Kawasaki disease had increased expression of clusters of genes that are associated with platelet and neutrophil activation, including genes coding for cell adhesion, innate immunity, and B-cell activation, whereas interferon-gamma was turned off.

They also reported that gene clusters that were turned on in Kawasaki disease were turned off in adenovirus infection, and vice versa. When blinded evaluators were asked to use a set of 38 gene transcripts to categorize 23 Kawasaki disease patients and 8 with adenovirus infections, they got the diagnosis right in 21 of 23 Kawasaki disease patients and in 7 of 8 with adenovirus (J. Infect. Dis. 2009;200:657-66). This is the most promising lead to date in the effort to develop a diagnostic test for Kawasaki disease, in Dr. Anderson's view. ■

Anti-TNF-Alpha Shows Promise in Treatment of Kawasaki Disease

VAIL, COLO. — The next frontier in Kawasaki disease therapy will involve determining the role of anti–tumor necrosis factor–alpha therapy.

There are sound theoretical reasons why an anti-TNF agent such as infliximab should be beneficial in patients with Kawasaki disease. Anecdotal reports have suggested that this is indeed the case when infliximab is given to patients with persistent fever after a first dose of intravenous immunoglobulin (IVIG).

Moreover, results of the first major randomized trial of infliximab vs. a second dose of IVIG in patients with persistent or recrudescent fever after an initial dose of IVIG showed infliximab to be safe, well tolerated, and effective. However, the trend for better outcomes with infliximab fell far short of significance in the 24-patient trial, which was powered as a safety study, Dr. Marsha Anderson said at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

"We'll need another study to say definitively if one treatment is better than the other," noted Dr. Anderson of the University of Colorado at Denver.

In the meantime, infliximab is gaining traction as an off-label alternative to a second dose of IVIG at centers of expertise in managing Kawasaki disease.

At the Children's Hospital, Denver, for example, a purified protein derivative (PPD) skin test or tuberculin skin test is now routinely started as soon as a child with possible Kawasaki disease comes through the door. That's because a negative PPD is one of the prerequisites for infliximab. Because the PPD takes a couple of days to produce results, starting the test as soon as possible means that the results should come in around the time it will be apparent if a first infusion of IVIG at 2 g/kg isn't working, making it possible to give infliximab without delay. While awaiting the PPD results, the clinician can check off the other prerequisites to infliximab therapy, including a chest x-ray, assessment of immune status, and possible recent tuberculosis exposure, she explained.

More than a decade ago, a multicenter U.S. study showed that 13% of patients with Kawasaki disease fail to respond to a single infusion of IVIG, and half of these nonresponders are resistant to a second dose. So alternative second-line agents are definitely needed.

In the first-ever randomized trial, 24 Kawasaki disease patients with persistent or recrudescent fever 2-7 days after initial treatment with IVIG at 2 g/kg, plus aspirin, were assigned to second-line therapy with either a second dose of IVIG or infliximab at 5 mg/kg given intravenously over 2 hours at six participating U.S. centers.

Eleven of 12 infliximab-treated patients became afebrile, as did 8 of 12 IVIG-treated patients. Per protocol, patients with persistent fever after a second dose of IVIG were given infliximab, resulting in two of the four becoming afebrile; the two nonresponders to third-line infliximab were placed on corticosteroids and became afebrile (J. Pediatr. 2008;153:833-8).

All told, only 3 of 16 patients (19%) who received infliximab as second- or third-line therapy after not responding to first-line IVIG required additional therapy, compared with 4 of 13 (31%) who received IVIG as second- or third-line therapy.

The initial randomized trial was kept small because of safety concerns. Infliximab is known to increase the risk of serious infections, including tuberculosis and opportunistic infections. It also has adverse effects in patients with moderate to severe heart failure. But infliximab proved safe and well tolerated in the randomized trial. ■