Sepsis Segue
by David Nash, MD, MBA

I imagine that many of our readers remember HA1A, a.k.a. Centoxin. How tantalizingly close we once came to a seemingly effective therapy for septic shock caused by gram-negative organisms and their deadly endotoxins. Indeed, our research team at Thomas Jefferson University Hospital (TJUH) in Philadelphia, in collaboration with our colleagues at the University Healthsystem Consortium (UHC) in Chicago, worked collaboratively for a year prior to the anticipated release and approval of Centoxin.

We recognized more than a decade ago that the widespread and perhaps indiscriminate use of an extremely expensive and marginally effective therapy for septic shock could have had ruinous economic implications for many hospitals. To the relief of our own hospital CEO, Centoxin of course was not approved by the Food and Drug Administration (FDA), and researchers re-evaluated their approach to the challenge of caring for patients with septic shock and multiple organ dysfunction.

Segue then to the fiscal challenges of a new century in which major teaching hospitals get by on a 1% margin and drug costs are the culprit in an ever-escalating round of insurance company premium hikes. With this fiscal reality in the background, researchers have come to recognize that sepsis is a heterogeneous syndrome and that blocking a single inflammatory mediator was too simplistic an approach. According to a report published last year, “Many of the animal models for sepsis use endotoxin challenges or injections of live or killed gram-negative bacteria to induce sepsis. Many times in humans, sepsis is caused by fungi or gram-positive bacteria. Drugs that are effective against endotoxin or gram-negative bacteria may not have the same effect on other pathogens.”

The report continues: “In sepsis there are multiple clinical, microbiologic, and host derived indicators of prognosis that are difficult to control such as severity of underlying disease, co-morbidities, degree of organ dysfunction, and adequacy of antibiotic therapy. Finally, the clinical definitions of sepsis and septic shock are too broad and non-specific to be used as entry criteria for many clinical trials. These criteria do not distinguish between patients who are in a pro-inflammatory state vs. an anti-inflammatory state.”

Remarkably, Bernard and his colleagues, in a landmark New England Journal of Medicine article describing the so-called PROWESS trial, demonstrated that drotrecogin alfa or recombinant human activated protein C has anti-thrombotic, anti-inflammatory and pro-fibrinolytic properties. Treatment with this human activated protein C, marketed by Eli Lilly as Xigris, significantly reduces mortality in patients with severe sepsis. According to an accompanying editorial, the treatment was effective regardless of age, severity of illness, the number of dysfunctional organs or systems, the site of the infection, and the type of infecting organism. It now looks as though these early reports describe our successful segue to effective therapy for sepsis in the new century. What, then, are the implications of final FDA approval and the widespread utilization of Xigris?

I believe there should be a three-pronged approach to our strategy regarding the deployment and implementation of Xigris nationwide. This three-pronged approach would involve massive educational efforts, coordination of our activities at the regional and local level, and appropriate prescribing restrictions at the point of care. Allow me to describe each of these in turn.

At the group purchasing level, the Premier Purchasing Alliance reports that a sub-study of PROWESS demonstrated that regardless of whether patients received placebo or Xigris, survivors had significantly longer lengths of stay, higher therapeutic intervention scoring system (TISS) scores, and higher costs than non-survivors. Clearly, large organizations such as the UHC, Premier, and others, have an important obligation to educate all of their members about the ongoing research and analyses associated with the early use of Xigris. At a projected charge of $10,000 per one-time intravenous dose, Xigris will rival Centoxin in its budget-busting properties.

At the integrated hospital system level, I believe Xigris requires widespread coordination of pharmacy department efforts to appropriately utilize this new entity. Intrasytem coordination is essential in the sharing of data about the number of sepsis cases, their clinical characteristics, and outcomes with and without the use of Xigris. Integrated systems should have a systemwide approach to Xigris use, emphasizing a judicious and circumspect prescribing behavior on the part of all clinicians. National hospital systems might need to undertake a highly centralized approach to the purchase and implementation of Xigris.

At the individual hospital level, members of the P&T committee have an important obligation to educate, coordinate, and restrict the use of Xigris to key specialists, such as critical care physicians, infectious disease specialists, and others. This will need to be resolved on an individual hospital basis, taking into account the appropriate cultural issues that define each institution.

The Jefferson Health System and TJUH have been well prepared for the final approval of Xigris. Our P&T committee, pharmacy staff members, and our chief medical officer have been tracking these issues and have prepared an algorithm for the appropriate use of Xigris in our system. We also need to commit to an ongoing drug-use evaluation of Xigris to further study solid organ transplant patients, patients with liver failure, and others who have had recent major surgery. These are groups that were excluded from the PROWESS trial.

Education, coordination, and restriction will characterize our segue to effective sepsis therapy in 2002. I would be happy to share our progress with you in the spirit of cooperation that will be necessary as we move forward with this exciting but expensive therapeutic modality. You can reach me at my email address: david.nash@mail.tju.edu.

References