it is imperative to recognize that PVL-secreting MRSA is a highly virulent strain of MRSA that results in significant morbidity and mortality. Early and appropriate empirical therapy should be initiated in an attempt to thwart the fatal process that may ensue. Unfortunately, the risk factors for the presence of this pathogenic organism have yet to be determined. Therefore, starting empirical treatment with broad-spectrum antimicrobials and de-escalating the therapy after the pathogen is identified and susceptibility profiles are available are justified when there is a suspicion of Staphylococcus aureus carrying the PVL genes.

Acknowledgments


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References


Reply to Wargo and Eiland

Sir—in their letter [1], Wargo and Eiland review the published literature on community-acquired pneumonia caused by \textit{Staphylococcus aureus} strains that carry the genes for Panton-Valentine leukocidin (PVL) [2–5]. On the basis of the observed mortality rate of 70% (14 of 20 patients) among previously healthy adults, despite the receipt of “appropriate” antibiotic therapy, the authors rightly conclude that PVL-producing \textit{S. aureus} is a highly virulent pathogen.

We agree with Wargo and Eiland [1] that these grim outcomes should encourage efforts to rapidly identify patients infected with highly virulent staphylococci to administer therapy in a timely fashion. Fortunately, most community-onset methicillin-resistant \textit{S. aureus} (CO-MRSA) isolates are susceptible to many antibiotics, including vancomycin, linezolid, clindamycin, trimethoprim-sulfamethoxazole, and tetracyclines. Unfortunately, as illustrated by Wargo and Eiland [1], too few data exist to make specific therapeutic recommendations. In fact, the poor outcomes raise the possibility that even appropriate antibiotics have a limited capacity to alter the outcome of severe infections. Improved outcomes may require alternative approaches with the use of adjunctive agents, as in the case of immunoglobulin for toxic shock syndrome or activated protein C for septic shock. Indeed, commercial immunoglobulin preparations containing anti-PVL antibody can neutralize the cytopathic effects of PVL in vitro [6]. Antibiotics that inhibit protein synthesis (i.e., by shutting off toxin production) might be uniquely advantageous, as with clindamycin for streptococcal necrotizing fasciitis. If such alternative treatment methods are proven to be effective, the rapid identification of PVL-producing strains, as described elsewhere [7], may be helpful.

Wargo and Eiland [1] raise the issue about whether routine testing for PVL would be likely to influence treatment decisions. In this regard, it should be pointed out that PVL production is not a specific attribute of CO-MRSA. In fact, of the 25 cases tallied by the authors, only 8 involved methicillin-resistant isolates. Thus, if one took the presence of PVL production to indicate CO-MRSA infection, one might refrain from using a penicillinase-resistant penicillin that would otherwise be a drug of choice. It also remains to be shown conclusively that PVL is the primary pathogenic factor in necrotizing pneumonia. Other virulence factors could be involved that are not always associated with PVL production.

In any event, the best clinical outcomes will likely require the rapid identification of infected patients and the prompt initiation of treatment, well before the results of susceptibility testing or assays for PVL are available. For this reason, we believe that clinicians need to be aware of the distinctive clinical features described in infections caused by PVL-producing strains.
and to consider MRSA as an etiologic agent in patients with influenza or an influenza-like prodrug, necrotizing pneumonia, leukopenia, respiratory failure, and/or shock who present with severe community-acquired pneumonia.

Fortunately, most infections caused by CO-MRSA involve skin and soft tissues and respond well to drainage. However, the cases of necrotizing pneumonia reviewed by Wargo and Eiland [1] represent another manifestation that is highly lethal among previously healthy children and adults, despite receipt of conventional antibiotic treatment based on in vitro susceptibility. There is still much to be done to improve management of this form of infection.

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How Infrequent Are Opportunistic Diseases and Immune Reconstitution Syndromes among HIV-Infected Individuals Who Have Favorable CD4+ Cell Count Responses to Antiretroviral Therapy?

Sir—In a recent article in the journal, Kolotar et al. [1] reported long-term follow-up data for 612 HIV-infected patients who responded to HAART who were observed for a median duration of 184 weeks. They observed a remarkably low number of opportunistic diseases and/or complications that occurred at any time and that occurred irrespective of whether CD4+ cell counts were maintained. They noted that 33 AIDS-defining illnesses occurred, representing 1.75 events per 100 person-years of follow-up. However, the study design was such that a large proportion of the immune reconstitution syndromes (IRSs) were probably not captured. Eligibility criteria for enrollment included a previous baseline CD4+ cell count of <50 cells/mm3 and a HAART-induced increase in the CD4+ cell count to >100 cells/mm3. Furthermore, patients with prior Mycobacterium avium complex (MAC)–positive cultures of specimens obtained from normally sterile body sites were excluded. At study entry, subjects had received HAART for a median duration of 43 weeks. The median CD4+ cell count at enrollment was 226 cells/mm3, at which point 63% of patients had an HIV RNA level of <500 copies/mL.

The focus of the study was only AIDS-defining events that occurred after enrollment. The median interval from the time that HAART was initiated to the development of IRS events has generally been <6 months for each of the many opportunistic infections, including MAC infection, tuberculosis, cytomegalovirus (CMV) infection, cryptococcosis, Pneumocystis jiroveci (formerly “carinii”) infection, herpes zoster, and progressive multifocal leukoencephalopathy [2]. Only occasional cases of IRS have been reported to develop >6 months from the time of initiation of HAART with respect to MAC infection [3, 4]. M. tuberculosis infection [2], CMV infection [5], and cryptococcosis [6]. As a result, the majority of the IRS events in this patient population would likely have already occurred before study entry and were excluded from the analysis. The clinical recognition of IRS events was also relatively low during the first few years that HAART became available, and such occurrences may not have been well documented in the medical record during or prior to the study period, which ended in April 1999.

Although incomplete, the frequencies of IRS complications among patients who initiated HAART and who have baseline CD4+ lymphopenia have been estimated for MAC infection and herpes zoster to be 3.5% and 7%–8%, respectively [4, 7]. Among the HIV-positive population with severe CD4+ lymphopenia (CD4+ cell count <50 cells/mm3) at my institution, there would have been an expected 20 cases of MAC-related IRS (3.5% of 612 patients) [4]; however, in the study by Kolotar et al. [1], only 4 cases (0.7%) of MAC infection were documented, at least 2 (50%) of which had presentations consistent with MAC-related IRS osteomyelitis. Bone or joint involvement [3, 4] appears both to occur late and to be rare (4%),