YELLOW FEVER VACCINE-ASSOCIATED VISCEROTROPIC DISEASE (YEL-AVD) AND CORTICOSTEROID THERAPY: ELEVEN UNITED STATES CASES, 1996–2004

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Abstract. During 1996 through 2004, 29 cases of yellow fever vaccine-associated viscerotropic disease (YEL-AVD) have been reported worldwide; 17 were fatal. Stress-dose corticosteroid (SDS) therapy has recently been found to improve survival among patients with septic shock but benefit for the treatment of YEL-AVD patients in septic shock is unknown. We retrospectively reviewed medical records of 11 U.S. YEL-AVD cases reported to the Vaccine Adverse Event Reporting System (VAERS) from 1996 through 2004. Four of 11 case-patients received SDS; 3 of these 4 (75%) survived. Seven patients did not receive SDS and 2 (29%) survived. Altered mental status was documented on admission for 5 of the 11 patients; 4 of these 5 did not receive SDS and died, whereas one received SDS and survived. The use of stress-dose steroids might be a factor that influenced the survival of these YEL-AVD patients and should be further evaluated in the management of both YEL-AVD and wild-type yellow fever septic shock.

INTRODUCTION

Yellow fever is a viral hemorrhagic febrile illness caused by a flavivirus and transmitted by mosquitoes. It is endemic in tropical South America and sub-Saharan Africa; the World Health Organization (WHO) estimates that 200,000 cases occur annually, but only a small percentage of these cases are identified due to underreporting.1 Most cases occur in sub-Saharan Africa and during epidemics the incidence of infection can be as high as 20%.2 Clinical presentation ranges from a mild febrile illness to a serious infection leading to hepatic and renal failure, myocardial injury, hemorrhage, and shock with a case fatality rate of 20–30%.3,4 Prevention with a live attenuated vaccine, first developed in 1936, has been considered highly effective and safe.5

The yellow fever live virus vaccine is prepared from the 17D yellow fever virus strain, grown in chick embryos. Within 30 days of vaccination, over 90% of individuals develop neutralizing antibodies to yellow fever.5,6 Immunity is long lasting, possibly lifelong.7 The Advisory Committee on Immunization Practices (ACIP) currently recommends revaccination every 10 years in persons 9 months of age and older traveling to or living in endemic areas.8 Since 1996 through 2004, 29 cases of yellow fever vaccine-associated viscerotropic disease (YEL-AVD) (previously called multiple organ system failure) have been reported to the Centers for Disease Control and Prevention (CDC) after yellow fever vaccination worldwide (CDC unpublished data). The pathogenesis of YEL-AVD is unknown but older age and thymic dysfunction may be risks factors for the development of this adverse event.9,10 Eleven of these cases occurred in the United States and were reported to the Vaccine Adverse Event Reporting System (VAERS), a federally mandated national passive surveillance system established in 1990 that receives reports of adverse events after immunization with U.S.-licensed vaccines.11 Six of the 11 cases have previously been reported in detail in the literature.12,13

Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) is clinically indistinguishable from wild-type yellow fever illness. Most YEL-AVD reports describe patients with fever and multiple organ system failure, and often death (17 deaths/29 cases worldwide). This clinical presentation is frequently identified and managed as septic shock. Since 2002 there has been evidence to support the use of stress-dose steroid (SDS) treatment (200–300 mg/day) in the management of septic shock.14 In 2003 the Surviving Sepsis Campaign Management Guidelines Committee (a committee of critical care and infectious disease experts representing 11 international organizations) recommended the use of SDS for the treatment of septic shock to reverse shock and increase survival.15 This committee also strongly discouraged the use of high-dose steroids (> 300 mg/day) in the management of septic shock since this has been shown to decrease survival.16 We describe the use of corticosteroids in the management of the 11 YEL-AVD reported U.S. cases and their clinical outcomes.

METHODS

Medical records were obtained for all 11 U.S. YEL-AVD cases reported to VAERS from 1996 through 2004. We retrospectively reviewed medical records and determined the dates of vaccination, onset of adverse event (onset of illness following vaccination), and hospital admission. We searched the medical records for the use of steroids in the treatment of the case-patient and, if administered, we recorded the initiation date, dosage, and duration. We also abstracted clinical and laboratory data and the clinical outcome. We describe the relationship between clinical findings, clinical outcome, and steroid administration.

RESULTS

Of the 11 case-patients we reviewed, 4 received stress-dose steroids (SDS), 4 received high-dose steroids (> 300 mg/day),
1 received low-dose steroids (< 200 mg/day), and 2 received no steroids during the course of illness. Three (75%) of the 4 case-patients who received SDS survived. Only 2 (29%) of the 7 case-patients who did not receive SDS survived (Figure 1); 1 received high-dose steroids and the other received no steroids. All of the case-patients who were treated with SDS were vaccinated after 2002 (Figure 2).

The time interval from date of vaccination (DOV = day 0) to onset of adverse event (mean = 4, median = 4.5) and the time interval from DOV to initiation of steroids (mean = 9, median = 8.5) were similar for those receiving SDS and not receiving SDS (Table 1). Past medical and surgical histories were also similar for those receiving SDS and not receiving SDS. The mean ages were 54 and 62 years, respectively. Both groups had one case-patient with a history of thymic disease (see Table 1).

All case-patients had hepatic and renal injury; the case-patients not receiving SDS had much higher mean and median peak aspartate aminotransaminase (AST) levels than those case-patients who received SDS (mean = 44.5, median = 28.9 units/L in multiples of the normal [i.e., the mean is 44.5 times higher than the upper limit of normal] and mean = 8.1, median = 8.5 units/L in multiples of normal, respectively). However, the median AST on admission was lower among those who were not treated with SDS (2.2 units/L in multiples of normal) compared with the median AST for those who received SDS (3.6 units/L in multiples of normal).

We found that steroids of any dose were started among 6 case-patients after the admission serum samples for AST were obtained; 3 of these case-patients received SDS. It was not possible to determine whether the serum samples were obtained immediately upon admission and prior to the initiation of SDS for the other 3 case-patients who received steroids. It was also not possible to discern the timing of serum collection resulting in peak AST levels in relationship to the initiation of steroid treatment. Peak serum creatinine levels were only slightly higher among those not receiving SDS (mean 5.7 mg/dL versus 4.3 mg/dL). We found documentation that all but one case-patient experienced hypotension requiring pressors; information about treatment with pressors in this case-patient’s medical record was not available, but this case-patient was intubated and had a temperature of 105°F (case-patient #8, see Table 1). All but 2 case-patients were intubated (these 2 case-patients received SDS and both survived), all had thrombocytopenia, and all but 1 experienced a peak temperature of > 103°F. The peak temperature of 1 case-patient was unknown; this case-patient received high-dose steroids and survived.

Altered mental status was documented on admission for 4 of the 7 (57%) case-patients who did not receive SDS and only 1 of the 4 (25%) who received SDS. The case-patient with mental status changes who received SDS survived, whereas the 4 case-patients with mental status changes who did not receive SDS all died. In contrast, an initial diagnosis of sepsis or septic shock was given to 3 of the 4 (75%) case-patients receiving SDS, but only 2 (30%) of those who did not receive SDS (see Table 1).

**DISCUSSION**

Our review of 11 case-patients having YEL-AVD accompanied by shock has led us to question whether SDS treatment might be beneficial in the management of these cases. This is in accordance with the recently published recommendation to treat septic shock with SDS rather than high-dose steroids.

Sepsis is defined as a clinical syndrome characterized by the presence of both infection and a systemic inflammatory response, which would include at least 2 of the following clinical features: body temperature > 100.4°F or < 96.8°F, increased heart rate (> 90 beats/min), hyperventilation (respiratory rate > 20 breaths/min or Pa CO₂ < 32 mm of Hg), and white blood cell count > 12,000 cells/mm³, < 4000 cells/mm³, or > 10% immature (band) forms. Septic shock is characterized by persistent arterial hypotension in a patient with sepsis. Patients presenting to an emergency room with fever, hypotension, multiorgan system dysfunction, and hematologic diagnosis are usually diagnosed as, and treated for, septic shock. An etiology may not always be determined. Two to four percent of septic shock cases are the result of viral infections and in up to 50% of patients with septic shock, no microbial etiology is found. Clinically and pathophysiologically, patients with YEL-AVD can present in septic shock; 10 of the 11 cases we investigated received pressor therapy for hypotension (meeting the criteria for shock) and 5 were given an admitting diagnosis of septic shock.

Approximately half of the patients with septic shock display deficiencies in adrenal function, and evidence indicates...
that SDS are of benefit in the management of septic shock. A 2004 meta-analysis of 14 randomized controlled trials revealed that while short doses of high-dose glucocorticoids actually decrease survival in septic shock, physiologic stress-doses equivalent to 200–300 mg of hydrocortisone daily for 5–7 days reduced mortality and promoted earlier shock reversal. Current (2004) guidelines developed by the Surviving Sepsis Campaign Management Guidelines Committee recommend the administration of stress-dose steroids for 7 days in patients with septic shock.  

Corticosteroids have not been evaluated in treatment of yellow fever, and our review is the first description of their use for the management of YEL-AVD. Results of the first studies evaluating SDS treatment of septic shock became available after 2002 at which time we might expect changes in the management of septic shock; our findings of the use of SDS are consistent with the timing of these studies and the subsequent recommendations published in 2004. All 4 cases who received yellow fever vaccine and developed YEL-AVD after 2002 were treated with SDS (see Fig. 2). The timing of initiation of steroid treatment, of any dose, after vaccination did not appear to affect the clinical outcomes of the case-patients overall. All but one of the case-patients who were started on steroids were given the initial dose about 8–9 days after vaccination, regardless of the dates of hospitalization or onset of the adverse event. This finding suggests that the dose, rather than the timing of steroid therapy, may be more important in survival.

Although 75% (3/4) of the case-patients who received SDS survived and only 29% (2/7) of those who did not receive SDS survived, our numbers are still too small to determine if SDS therapy contributed to a better outcome. Several other factors may have been responsible for the greater percentage of survivors among the case-patients who received SDS. Advanced age (∋ 60 years) appears to be a risk factor for developing YEL-AVD and the case-patients who did not receive SDS had a greater mean age, possibly contributing to fewer survivors. Four (57%) of those not receiving SDS were admitted with signs of altered mental status, which usually occurs in the late stages of illness. The peak median AST levels were also many times higher among the case-patients not receiving SDS (although on admission the median AST levels were actually lower), another possible indicator of illness severity among this group. Furthermore, we found that 3 of the 4 case-patients who received SDS were given an admitting diagnosis of sepsis and had slightly higher median AST levels upon hospital admission, which may have triggered more aggressive management and support, including the adoption of current recommendations for steroid dosing in septic shock. We also found that those who received SDS were among the more recent cases (all occurred after 2001). In more recent years it is possible that the overall management of intensive care patients has improved resulting in a decrease in mortality of all patients with septic shock. With these limitations we can not determine if the case-patients who did not receive SDS simply had a more fulminant illness and therefore less chance of survival, and/or whether the management of those receiving SDS was more rigorous, improving their survival.

Thymic dysfunction also appears to be a risk factor for developing YEL-AVD, and it is interesting to note that we found 1 case-patient in each group (those receiving SDS and
all others) had a history of thymic dysfunction; the case-patient who received SDS survived, whereas the other case-patient received low-dose steroids (< 200–300 mg/day) and did not survive.

We obtained our data from a retrospective review of medical records, and at times the data was difficult to interpret; we could not always determine baseline health and accurate past medical history. Furthermore, reports of an adverse event after yellow fever vaccination were captured through a passive surveillance system (VAERS), which is known to be limited by underreporting; there may have been cases that were not reported but were diagnosed and treated as septic shock and possibly given steroid treatment. Nevertheless, we believe that our report supports the need for further study of the use of SDS in the management of YEL-AVD. Future YEL-AVD surveillance with standardized, “real time” data collection should include data regarding steroid treatment.

Our review of these 11 cases of YEL-AVD and the use of SDS may also stimulate studies that have broader public health implications. Since YEL-AVD and wild-type yellow fever illnesses have the same clinical findings it might be worthwhile to evaluate the impact of using SDS among patients with wild-type yellow fever. The worldwide burden of wild-type yellow fever illness is great. From 1990 through 1999 over 13,000 cases of yellow fever with over 3,500 deaths were reported from Africa and South America; however, WHO estimates the annual incidence to be 200,000 and an increase in the number of cases has been observed over the past two decades. The use of SDS in the management of septic shock as a result of wild-type yellow fever illness should be evaluated.

This small case series of patients suggests that a change in the management of YEL-AVD has occurred over time, as demonstrated by our finding of increased usage of stress-dose steroids since 2002. Although we cannot fully determine all of the factors that may have influenced the survival of these patients, we believe our data points out that the benefit of SDS should be further evaluated in the management of both YEL-AVD and wild-type yellow fever septic shock.

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