Time from Illness Onset to Death, 1918 Influenza and Pneumococcal Pneumonia

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To the Editor: Brundage and Shanks (1) have studied time to death from the onset of influenza symptoms during the 1918 pandemic in military and civilian populations and found a median time to death of 7–11 days. They argue that these data support the idea that the deaths may be predominantly due to bacterial superinfection after the acute phase of influenza. We observed a similar 10-day median time to death among soldiers dying of influenza in 1918 (2), a finding consistent with the time to death for a bacterial superinfection, specifically pneumococcal bacteremic pneumonia (3).

The major bacterial pathogen associated with influenza-related pneumonia in 1918 was *Streptococcus pneumoniae* (1,3). Neither antimicrobial drugs nor serum therapy was available for treatment in 1918. To further analyze the time course of death from influenza in relation to that of pneumococcal pneumonia in 1918, we examined data collected by Tilghman and Finland (4) from the pre–antimicrobial drug era of the 1920s and 1930s. The Figure shows the distribution of time from onset of illness to death due to influenza-related pneumonia in 1918 compared with time to death due to untreated pneumococcal pneumonia in the 1920s and 1930s. The Figure indicates a close concordance of the times to death. Similar times to death do not prove the specific bacterial etiology of the 1918 deaths. However, pneumococcal bacteremia was associated with most of the pneumonia deaths reported by Tilghman and Finland (4), and most 1918 influenza-related deaths were due to bacterial pneumonia (5). Also, up to 50% of patients dying from pneumonia in 1918 had pneumococcal bacteremia (3). These similar times to death provide additional evidence that the influenza-related pneumonia deaths during the 1918 influenza pandemic were largely due to the pneumococcus.
Unusual Manifestation of Toscana Virus Infection, Spain

To the Editor: Toscana virus (TOSV) causes acute meningitis and meningoencephalitis in Mediterranean countries (1). In Spain, neurologic TOSV infection has been reported since 1988. All cases have been self-limited aseptic meningitis (2). Since 2003, we have routinely investigated TOSV in cerebrospinal fluid (CSF) specimens from patients with suspected viral meningitis and encephalitis by using cell culture and reverse transcription–PCR (RT-PCR) (3,4). Also, as part of a regional project (05/305, Consejería de Salud, Junta de Andalucía, Spain), we investigated TOSV in mild nonneurologic syndromes by detection of immunoglobulin (Ig) M against TOSV by using enzyme immunoassay (Diece Diagnostica S. S.p.A., Siena, Italy). From May through September of 2006 and 2007, a total of 358 serum samples were randomly selected from patients for whom microbiologic determinations had been requested to investigate febrile illnesses.

As a result of these virologic and serologic surveys, we detected 7 cases of TOSV infection. Mild aseptic meningitis developed in 4 patients; in 3 patients, the infection had an atypical manifestation, as described below.

Patient 1, a 45-year-old man, was referred to the Hospital Universitario Virgen de las Nieves in September 2004 with confusion and a temperature of 39°C. He had had a splenectomy 20 years before, and in 2002, he had received a kidney transplant after renal failure resulting from meningococcal sepsis. On admission, the patient was receiving chronic immunosuppressive treatment. Ten days after admission, he had tonic-clonic seizures. Aphasia and paresis developed after an ictus of the left hemisphere, and his level of consciousness decreased rapidly. Treatment with corticosteroids was initiated because vasculitis was suspected. The patient responded to treatment, and 2 months after admission, he was discharged. Four months later, he still had impaired speech and paresis. Lymphocytic pleocytosis, a normal glucose level, and elevated protein levels were observed in CSF samples taken during the 2-month period of hospitalization. Bacterial and fungal cultures, as well as results of PCR for enterovirus, herpes simplex virus (HSV), and varicella-zoster virus (VZV), were negative in CSF specimens taken at admission and 1 month later. TOSV was detected by cell culture and nested RT-PCR in both samples (3). Anti-TOSV IgG was not detected in serum samples obtained on days 1 and 10; 5 months later, a borderline result was obtained. Anti-TOSV IgM was not detected on day 1 but was detected on day 10; 5 months later, anti-TOSV IgM was detected. Sequence analysis of amplified fragments from L and S segments (GenBank accession nos. FJ356705 and FJ356706, respectively) indicated 95%–98% homology with sequences from Spanish TOSV strains (3) and 84% homology with Italian reference strain ISS Phl.3.

Patient 2, a 54-year-old man, was admitted to a regional hospital in Granada Province in November 2007. He was confused and agitated, and he reported having fever and headache 2 days before. On admission, he was receiving treatment with corticosteroids for Crohn disease. Analysis of the CSF specimen showed lymphocytic pleocytosis, a normal glucose level, and increased protein levels. Results of PCR for HSV, VZV, and enterovirus were negative. TOSV was detected in the CSF sample by cell culture and real-time RT-PCR (4). The patient was treated with antimicrobial drugs and acyclovir. He recovered and was discharged 3 weeks after admission. One month later, he returned with paresis and aphasia, secondary to an ischemic...