A 36-year-old farmer presented to his primary care physician for evaluation of cough with white sputum, pleuritic chest pain, and chills with rigors (maximum temperature, 38.9°C), all of 1 day’s duration. While traveling to his local clinic, the patient also developed acute bilateral eye pain with redness, swelling, and discharge. His medical history was notable only for a fractured jaw. He had a 24-pack-year history of smoking and had previously used methamphetamine. He was taking no medications or illegal drugs. He was divorced and denied recent sexual activity or travel. The patient’s symptoms prompted his primary care physician to initiate antibiotic therapy.

1. Which one of the following would be the best choice of empirical outpatient antibiotic therapy for this patient?
   a. Azithromycin
   b. Erythromycin
   c. Doxycycline
   d. Amoxicillin-clavulanic acid
   e. Trimethoprim-sulfamethoxazole

Community-acquired pneumonia was diagnosed on the basis of the patient’s productive cough, pleuritic chest pain, and fever. The 2001 American Thoracic Society guidelines¹ for the treatment of pneumonia base therapeutic recommendations on factors such as treatment locale (eg, outpatient, general hospital ward, or intensive care unit), the presence of coexisting cardiopulmonary disease (eg, congestive heart failure or chronic obstructive lung disease), and the presence of “modifying factors” such as risk for drug-resistant pneumococcal or gram-negative bacterial infections. Because this patient had no risk factors, he could be treated with an advanced-generation macrolide such as azithromycin or clarithromycin. Monotherapy with this drug is recommended only for patients with allergies to or intolerance of advanced-generation macrolides. Amoxicillin-clavulanic acid is not advised because it does not cover atypical organisms such as Chlamydia, Mycoplasma, and Legionella. Trimethoprim-sulfamethoxazole may be added if Pneumocystis jiroveci is suspected but should not be used as empirical outpatient monotherapy.

The patient’s primary care physician prescribed azithromycin. The next day, blisters developed on the patient’s mouth and lips, and lesions appeared on his palms and soles. He continued taking the antibiotic but felt worse the following morning. He returned to his primary care physician, who performed a chest x-ray study that showed a left lingual infiltrate. The patient was admitted to a local hospital with the presumptive diagnosis of hand-foot-and-mouth disease (HFMD). His antibiotic treatment was changed to clindamycin and levofloxacin. Since his condition did not improve after 3 days of treatment at his local hospital, the patient was transferred to the general medicine service at our hospital for further evaluation and treatment.

Examination of the patient’s skin revealed atypical target lesions and areas of bulla formation affecting less than 5% of the body surface area. He also had extensive oral and conjunctival lesions. Chest radiography showed a left lung infiltrate, and antibiotic therapy with oral levofloxacin was continued. Blood tests showed no evidence of liver or kidney involvement.

2. Based on the history and physical examination findings, which one of the following is the most likely diagnosis in this patient?
   a. Secondary syphilis
   b. HFMD
   c. Rocky Mountain spotted fever (RMSF)
   d. Stevens-Johnson syndrome (SJS)—toxic epidermal necrolysis (TEN)
   e. Lyme disease

In view of the rash involving the patient’s palms and soles, secondary syphilis, HFMD, and RMSF were considered possible diagnoses. Although secondary syphilis usually produces a maculopapular or papulosquamous rash on the extremities, vesiculobullous lesions occur only in neonatal patients with congenital syphilis. Hand-foot-and-
mouth disease is a systemic infection usually caused by coxsackievirus A16. It is characterized by ulcerative oral lesions, a vesicular exanthem on the distal extremities, and mild constitutional symptoms and occurs most commonly during the warmer months; however, it does not produce target lesions. Rocky Mountain spotted fever is a tick-borne illness caused by *Rickettsia rickettsii* and is the most common rickettsial disease in the United States.\(^2\) It occurs primarily during the warmer months, but confirmed cases have been reported throughout the year.\(^3\) Involvement of the palms and soles, which is often considered diagnostically important, usually occurs relatively late in the disease course (after day 5 in 43% of cases) and does not occur at all in 18% to 64% of cases. Our patient presented in mid winter and had no travel history, making RMSF unlikely.

Stevens-Johnson syndrome and TEN are considered part of the same disease spectrum. In the Severe Cutaneous Adverse Reactions (SCAR) study, investigators reviewed several hundred photographs of historical cases and agreed that it was possible to identify 2 distinct clinical groups.\(^4\) The first group was characterized by acrally distributed target lesions typical enough to fit the original description of erythema multiforme major.\(^5\) The second group comprised patients with both SJS and TEN with widespread skin lesions consisting of blisters arising on erythematous or purpuric macules.\(^6\) This new classification implied that SJS and TEN were variants of the same disorder, distinguishable only by the percentage of skin involved with blisters (ie, <10% in SJS, 10%-29% in SJS-TEN overlap, and ≥30% in TEN). The vast majority of patients with SJS-TEN have target and blistering skin lesions, mucosal involvement, and conjunctivitis. Lyme disease is also associated with target lesions, but they usually appear singly in the region of the tick bite. Moreover, Lyme disease is unlikely to occur in winter, nor is it typically associated with pneumonia.

The patient was diagnosed as having SJS based on his history and characteristic findings of conjunctivitis, mucosal involvement, and skin lesions covering less than 5% of his body surface area. While hospitalized, the patient reported gradual improvement in his overall symptoms. Subsequently, serologic testing was positive for acute infection (IgM) with *Mycoplasma pneumoniae*.

### 3. Which one of the following is the most likely risk factor for the development of SJS in this patient?

- **a. Medication exposure**
- **b. Long-term tobacco use**
- **c. Infection with *M pneumoniae***
- **d. Human immunodeficiency virus (HIV) infection**
- **e. Idiopathic**

Several medications have been implicated in the etiology of SJS, most commonly antiepileptics (phenobarbital, phenytoin, carbamazepine, and valproate), sulfonamides, certain nonsteroidal anti-inflammatory drugs (oxicams and butazone derivatives), and allopurinol. A number of other medications have also been implicated.\(^7\) The SCAR study found that 64% of patients with SJS had been exposed to some type of medication and that 48% had been exposed to highly suspected drugs (oxicams, allopurinol, phenobarbital, phenytoin, sulfonamides, and chlormezanone).\(^4\) Our patient had not been exposed to any medications, and his symptoms clearly antedated the initiation of antibiotic therapy. Long-term tobacco use has not been implicated in the etiology of SJS. *M pneumoniae* was identified as the likely cause of the patient’s SJS, and treatment with levofloxacin, which covers *M pneumoniae*, was continued. Patients with HIV have a high risk of developing TEN,\(^8\) and several mechanisms have been proposed to explain this association. However, our patient had no HIV risk factors. A likely etiology (*M pneumoniae*) was identified in our patient, ruling out an idiopathic diagnosis.

### 4. Which one of the following would be the most important next step in managing this patient?

- **a. Supportive treatment including intravenous fluids and appropriate wound and ophthalmological care and discontinuation of any drugs suspected to be associated with the disorder**
- **b. Broaden the spectrum of the antibiotic coverage**
- **c. Systemic corticosteroids**
- **d. Intravenous immunoglobulin (IVIG)**
- **e. Cyclophosphamide**

After diagnosing SJS-TEN, the most important step is to identify and withdraw any precipitating agents. Indeed, patient mortality has been shown to decrease when “culprit” medications (especially those with short half-lives) are discontinued early.\(^3\) However, our patient was taking no medications before the onset of his symptoms. Some investigators have advised that patients with severe SJS-TEN be admitted to an intensive care unit or burn center,\(^10\) although patients can often be managed in standard hospital settings. Supportive treatment with intravenous fluids and appropriate skin and eye care is the cornerstone of therapy. Because broad-spectrum antibiotics are not recommended, our patient continued to receive levofloxacin monotherapy for the *M pneumoniae* infection. Various studies have investigated the treatment of SJS with systemic corticosteroids, IVIG, and cyclophosphamide.\(^11-13\) However, these studies were limited by small sample sizes, uncontrolled study designs, and confounding due to multiple concomitant treatments. Hence, no expert consensus exists regarding these treatments.\(^14\)
Our patient was treated with IVIG (500 mg/kg per day) for 4 days. He received daily skin care consisting of 0.1% triamcinolone cream for the skin lesions and scrotal care consisting of topical 1% hydrocortisone twice daily and Sweitzer’s solution (1:64 dilution) applied as wet, warm compresses to prevent secondary bacterial infection. Daily eye care was provided with erythromycin ointment in both eyes every 2 hours to prevent bacterial infection, prednisone eyedrops 4 times daily to decrease inflammation, and symblepharon rings to minimize symblepharon formation.

5. Which one of the following statements regarding this patient’s condition is false?
   a. Sepsis is a major cause of death
   b. Corneal ulcers may lead to blindness
   c. Patients with impaired immunity are at increased risk
   d. TEN is associated with a higher mortality than SJS
   e. The pathogenesis of this syndrome is well understood

Sepsis is a major cause of death in patients with SJS, with skin flora predominating during the first few days and gram-negative strains appearing later. Severe eye involvement is a typical feature of SJS. Purulent conjunctivitis leads to swelling, crusting, and ulceration with pain and photophobia. Conjunctival erosions with subsequent revascularization, fibrous adhesions, and corneal ulceration and blindness are common complications. Eye care is essential, and early and ongoing ophthalmological assessment is recommended. Ocular cicatricial pemphigoid is associated with SJS and has been reported as late as 31 years after the initial diagnosis of SJS. As discussed previously, patients with impaired immunity (eg, HIV infection) are at high risk of developing SJS and TEN. Overall, TEN is associated with a higher mortality than SJS. In the SCAR study, mortality was 3% in patients with SJS and 39% in patients with TEN. Finally, the pathogenesis of SJS is poorly understood.

After 5 days in the hospital, the patient’s skin lesions and energy level improved substantially, and his mucosal lesions nearly resolved. He was discharged home to complete a 10-day course of oral levofloxacin.

REFERENCES

DISCUSSION
The incidence of SJS is about 1 to 3 cases per million persons each year.16-18 Both TEN and SJS are characterized histologically by pronounced keratinocyte apoptosis in the epidermis with dermoepidermal separation resulting in bulla formation. The pathophysiology of SJS-TEN is unknown. Possible explanations focus on immune mechanisms and impaired drug metabolism. At the molecular level, Fas is activated through the Fas ligand FasL, thereby activating caspases and causing apoptosis. Indeed, the Fas-FasL interaction has been proposed as a target for blocking antibodies such as IVIG, which may explain IVIG’s role in the treatment of SJS.

M pneumoniae is the most common infectious cause of SJS. In a 1978 report from the United Kingdom, 19 (3.2%) of 596 patients with M pneumoniae infection had skin eruptions, and 7 (1.2%) were diagnosed as having SJS.

Until the early 1980s, patients with SJS were commonly treated with systemic corticosteroids. Currently, however, the role of systemic corticosteroids in the treatment of SJS is controversial because no randomized trials support this or any other treatment modality. Several studies have investigated the use of IVIG to treat SJS. One retrospective analysis reported a 100% survival rate and complete skin healing in 12 patients with SJS after an average of 8.3 days of treatment with IVIG. However, no expert consensus exists regarding the use of IVIG for SJS. Regarding monotherapy with cyclophosphamide, we identified one study involving 8 consecutive patients with SJS-TEN, all of whom improved with treatment. Nevertheless, most studies have included patients treated with both cyclophosphamide and corticosteroids, making it impossible to attribute any treatment benefit to cyclophosphamide alone.

In summary, the immune system’s central role in SJS is being reconsidered, and additional clinical trials involving IVIG, cyclosporine, and cyclophosphamide may be seen in the future.
RESIDENTS’ CLINIC


25. Communicable Disease Surveillance Centre (Public Health Laboratory Service) and Communicable Disease (Scotland) Unit. *Mycoplasma pneumoniae*. BMJ. 1978;1:726.

Correct answers: 1. a, 2. d, 3. c, 4. a, 5. e