Severe Acute Respiratory Failure in Healthy Adolescents Exposed to Trimethoprim-Sulfamethoxazole

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Pulmonary toxicity induced by trimethoprim-sulfamethoxazole (TMP-SMX) has been described, although the disease process is poorly understood. We report 5 previously healthy adolescent patients who developed acute respiratory failure while taking TMP-SMX. Four of the 5 adolescents required extracorporeal membrane oxygenation support, and 2 of the teenagers died. All children required a tracheostomy, and all cases were complicated by pneumothoraces and pneumomediastinum. The majority of children were prescribed TMP-SMX for the treatment of acne vulgaris.

CASE SERIES

Trimethoprim-sulfamethoxazole (TMP-SMX) is associated with idiosyncratic adverse drug reactions, including cutaneous reactions and hypersensitivity syndromes. Rarely, TMP-SMX has been implicated in pulmonary reactions, including interstitial lung disease, fibrinous pneumonia, and pneumonitis.[1–4] Diagnosis of these adverse reactions is based on the exclusion of other etiologies, the close timing of drug exposure as related to the reaction, and, in some cases, recurrence of symptoms with the reintroduction of TMP-SMX.

In children, reports of drug-induced pulmonary toxicity resulting in severe acute respiratory distress syndrome (ARDS) are rare. We describe 5 previously health adolescents who presented with acute respiratory failure at different academic centers across the United States, all with a recent exposure to a 2- to 4-week course of TMP-SMX. These patients required invasive respiratory support, with 4 out of 5 patients requiring extracorporeal membrane oxygenation (ECMO) for an extended duration. In each case, an extensive evaluation did not reveal an etiology of the severe and rapid onset of prolonged ARDS in these otherwise healthy adolescents. The TMP-SMX exposure, pulmonary evaluation, and clinical course for each patient is outlined in Table 1.

These patients were identified when the story of patient 5 was published in a national news outlet about a case of ARDS in an otherwise healthy female patient who was hospitalized and ambulating while on ECMO. The first author (J.O.M) had cared for patient 5 and was referenced in the story and subsequently was contacted by 4 additional patients or family members of patients who reported similar clinical events (patients 1–4). Subjects included in this case series provided signed consent, authoring presentation of a case report, and provided all medical records from outside facilities for review by the authors, and the institutional review board reviewed this study and deemed it as nonresearch.

abstract

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Drs Miller and Goldman designed the case series, collected data, conducted the analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Taylor conducted the analyses, drafted the initial manuscript, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CASE REPORT

Patient 1 is a 16-year-old, previously healthy girl with a history of acne vulgaris being treated with TMP-SMX who presented to a primary care clinic with fever, headache, pharyngitis, cough, fatigue, dizziness, and chest pain. After a negative result on the rapid streptococcal antigen test, she was diagnosed with a presumptive viral respiratory tract infection and was discharged from the clinic with supportive care. Two days later, she presented to a local emergency department and subsequently was admitted to the hospital because of tachypnea and hypoxemia. She was hospitalized, and broad-spectrum antibiotics, including ceftriaxone, vancomycin, and azithromycin, were empirically started. Her respiratory status rapidly deteriorated, and she was intubated on hospital day (HD) 2. On HD 6, she was placed on high-frequency oscillating ventilation and received inhaled nitric oxide. Venovenous ECMO was initiated on HD 7 and was quickly changed to venoarterial ECMO because of upper-body hypoxemia. Despite an extensive evaluation, no etiology of her respiratory failure was identified. She required 193 days of ECMO before decannulation. At 1 point, she was listed as status 1A for lung, heart, and kidney transplants, but her multiorgan failure eventually resolved without necessitating an organ transplant.

Patient 2 is a 17-year-old, previously healthy girl with a history of acne vulgaris being treated with TMP-SMX who presented to a primary care clinic with fever, pharyngitis, chest tightness, and tender cervical adenopathy. She was initially diagnosed with a left lower lobe community-acquired pneumonia and was administered a single dose of intramuscular ceftriaxone in the clinic and discharged with azithromycin. The initial evaluation included rapid streptococcal antigen and influenza testing (results for both tests were negative) and a chest radiograph revealing bilateral infiltrates. She returned 2 days later with fever, tachypnea, and hypoxemia and was admitted to the hospital. She required immediate intubation and was transitioned from a conventional ventilator to high-frequency oscillating ventilation. A tracheostomy was performed on HD 25. She was eventually weaned off mechanical ventilation with tracheostomy decannulation at 56 days after hospital admission.

Patient 3 is a 13-year-old, previously healthy girl with a history of acne vulgaris being treated with TMP-SMX who presented with headache, pharyngitis, and fever. Results of rapid streptococcal antigen and influenza testing were negative, and she was discharged from the clinic with symptomatic care. She returned 5 days later to the emergency department with respiratory distress, hypoxia, chest pain, cough, and persistent pharyngitis. The initial chest computed tomography (CT) scan revealed interstitial lung disease with pneumomediastinum and bilateral pneumothoraces. She was intubated on HD 6 and was taken to the operating room for a bronchoscopy and lung biopsy. Her condition worsened, and she was placed on venovenous ECMO support on HD 7. Because of her failure to recover, she underwent a bilateral lung and heart transplant on ECMO day 114. She initially survived the transplant but later died because of solid-organ transplant complications.

Patient 4 is an 18-year-old, previously healthy man with a history of acne vulgaris being treated with TMP-SMX who presented to a primary care clinic with pharyngitis, cough, fevers, nausea, vomiting, and dizziness. Results of a rapid streptococcal antigen test and monospot test were negative. He was discharged from the clinic with symptomatic care guidance for a presumptive viral infection. He returned the following day to the emergency department with new-onset dyspnea and hypoxemia. He developed respiratory failure and required intubation with mechanical ventilatory support within the first 48 hours of admission. He was extubated for a brief period of time; however, he developed pneumomediastinum with bilateral pneumothoraces and subsequently required reintubation on HD 23. On HD 24, he was placed on venovenous ECMO. He was evaluated for a lung transplant; however, he clinically improved and was weaned off ECMO on HD day 53.

Patient 5 is a 15-year-old girl who was prescribed TMP-SMX for a urinary tract infection before admission. On day 10 of TMP-SMX treatment, she developed malaise, cough, chest pain, dyspnea, and fever. She was hospitalized, and an initial chest CT scan obtained to rule out a pulmonary embolus identified bilateral ground-glass opacities and interstitial pulmonary thickening consistent with interstitial lung disease. She was intubated on HD 4 and was trialed on inhaled nitric oxide. She required venovenous ECMO cannulation on HD 8. On HD 178, a tracheostomy was performed, and she was decannulated from ECMO on HD 198 after 190 days of support. Her course was complicated by pneumomediastinum and multiple pneumothoraces. Because of her persistent requirement of high ventilatory support and because of hypoxia after decannulation, she was being considered for a lung transplant. She died from complications of the disease process prior to transplantation.

DISCUSSION

We reviewed 5 cases of previously healthy adolescents who were receiving TMP-SMX when they

TABLE 1 Characteristics of Adolescent Patients With Severe Respiratory Failure and Recent TMP-SMX Exposure

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, y	16	17	13	18	15
Sex	Female	Female	Female	Male	Female
Days of TMP-SMX exposure at point of ARDS presentation	24	17	25	23	10
Other medications at time of presentation	Topical miconazole	Topical clindamycin, lutera oral contraceptive	Topical tazarotene, topical clindamycin, topical benzoyl peroxide	Topical adapalene, topical benzoyl peroxide, topical dapsone	Viane oral contraceptive, ondansetron, cetirizine
Chest radiograph findings early in clinical course	Markedly diffuse and patchy alveolar pulmonary opacities	Bilateral airspace disease, small bilateral pleural effusions	Extensive bilateral pulmonary infiltrates, small bilateral pneumothoraces, pneumomediastinum	Right lower lobe and right middle lobe parenchymal densities suggesting consolidation or pneumonia	Hazy bilateral perihilar opacities, bilateral pleural effusions, pneumomediastinum and soft tissue gas
Bronchoscopy results	Not performed	Present: neutrophils, lymphocytes, macrophages; not present: monocytes, eosinophils	Present: neutrophils, lymphocytes, macrophages, monocytes, eosinophils	Present: neutrophils, macrophages, eosinophils; not present: lymphocytes, monocytes	Present: neutrophils, lymphocytes, macrophages; not present: monocytes, eosinophils
Lung biopsy pathology	Not performed	Not performed	Diffuse alveolar damage, acute and organizing with increased eosinophils consistent with acute eosinophilic pneumonia	Not performed	Diffuse alveolar damage, acute and organizing with increased eosinophils consistent with acute eosinophilic pneumonia
Additional complications	Tracheostomy, pleural effusion pneumothorax, pneumomediastinum, renal failure	Tracheostomy, pleural effusion, pneumothorax, pneumomediastinum, pulmonary emboli	Tracheostomy, pleural effusion, pneumothorax, pneumomediastinum	Tracheostomy, pleural effusion, pneumothorax, pneumomediastinum, internal jugular thrombosis	Tracheostomy, pleural effusion, pneumothorax, pneumomediastinum, bilateral pulmonary emboli
Immunosuppressive therapy	Mycophenolate mofetil	Steroids	Steroids, hydroxychloroquine	Steroids	Steroids, azathioprine, rituximab, cyclophosphamide, plasma exchange
ECMO duration, d	193	N/A	114	29	190
Organ transplant	Lung, heart, and kidney transplants considered; not performed	Transplant not considered	Lung and heart transplant performed	Lung transplant considered; not performed	Lung transplant considered; not performed
Disposition	Survived	Survived	Died	Survived	Died

N/A, not applicable.

developed acute severe ARDS requiring prolonged hospitalization and cardiopulmonary support. In all cases, patients were transferred to academic medical facilities, and pediatric pulmonologists and infectious diseases specialists performed extensive evaluations. Blood testing for possible rheumatologic and/or immunologic triggers was obtained in all patients, and in 4 of 5 patients, rheumatology and/or immunology was consulted, all with negative results. The Naranjo causality assessment tool for adverse drug reactions[5] was completed on review, and all cases scored as probable for implicating TMP-SMX on the basis of timing of TMP-SMX exposure as related to the event, lack of alternative explanation despite extensive evaluations, and previous reports of TMP-SMX pulmonary toxicity. A rechallenge was not performed in any patient to confirm the reaction because of severity of presenting symptoms. Immunosuppressive therapy was prescribed in all cases. Mortality occurred in 2 cases and morbidity was significant in all cases (Table 1).

Clinical symptoms and radiologic pulmonary findings reported in drug-induced lung disease can be variable and nonspecific. Acute onset of respiratory symptoms and chest radiography revealing bilateral pulmonary infiltrates have been described with TMP-SMX–associated pulmonary toxicity.[1–4,6] TMP-SMX reactions may involve the lung parenchyma, pleura, airways, mediastinum, and/or pulmonary vasculature.[7] CT scan findings in our cases revealed diffuse abnormalities of the lung parenchyma with predominant ground-glass appearance (Fig 1). All cases reported here were complicated by pneumomediastinum and pneumothoraces; however, this complication is not reported in previous TMP-SMX–induced lung disease case series.[1–4,6]

In drug-induced pulmonary toxicity, eosinophils are often reported on bronchoalveolar lavage samples.[8] A bronchoscopy was performed in 4 of our patients during their illness; however, eosinophils were only reported in 2 patients: patients 3 and 4. The lack of eosinophils could be due to the fact that a bronchoscopy was performed at various times during each clinical course (HD 2–56). A single report of a lung biopsy in an adult patient confirmed acute fibrinous and organizing pneumonia and increased eosinophils suggestive of a drug reaction.[2] A lung biopsy was performed in patient 3 and patient 5, and eosinophils were present in both patients. Interestingly, peripheral eosinophilia was noted in all patients at varying times during the clinical courses, although not at initial presentation, with a maximum absolute eosinophil count ranging from 1200 to 3200 μL.

TMP-SMX–induced lung disease has been described; however, the available literature is composed of case reports and 1 case series in which all patients were adults and most patients had underlying rheumatologic disease.[1–4,6] None of these existing reports describe severe and prolonged ARDS in previously healthy adolescents. In the 1 available case series found, 10 adults who did not have discernable respiratory symptoms were described, and diagnosis was made via a chest CT scan.[4] In 1 case report, intubation for a third exposure to TMP-SMX was described[6]; however, no other reports conveyed need for invasive respiratory support. All of the cases reported here required tracheotomy for prolonged mechanical ventilation needs. After extensive review, there are no current known reports of TMP-SMX exposure in association with severe ARDS requiring prolonged hospitalization and intensive care management or requiring ECMO support.[1–4,6]

Cessation of TMP-SMX alone or in combination with steroid therapy has been associated with resolution of symptoms, and reappearance of symptoms has been associated with reintroduction of the drug.[1–3] In the cases presented in this report, discontinuation of TMP-SMX did not result in rapid clinical improvement. In fact, 4 of 5 patients required ECMO support and were considered or listed for an organ transplant. There does not seem to be discernable differences between the 2 patients with comparably shorter times in the ICU and the 3 patients requiring longer ECMO and ICU times. There is no obvious association with selection of immunosuppressive therapy and outcome, nor are there obvious clues on initial presentation or treatment strategies that separate the more and less severe cases. Although these data suggest a possible alternative pathophysiology or a more severe disease compared with data from previous reports, the spectrum of disease observed in these cases is variable, and further understanding of the pathophysiology is needed.

TMP-SMX is a widely prescribed antibiotic that is typically well tolerated; however, it has been implicated in rare, yet severe, adverse drug reactions, including cutaneous reactions (ie, Stevens-Johnson syndrome and toxic epidermal necrolysis), blood dyscrasias, and liver injury. To date, a single mechanistic explanation for these reactions has not been uncovered, although the assumption that drug metabolism resulting in the formation of reactive intermediate species that can bind toproteins may play an important role in these idiosyncratic reactions.[9,10] Further investigation of the pathophysiology of idiosyncratic drug-induced pulmonary toxicity is warranted because immunologic markers and/or genetic polymorphisms of drug-metabolizing

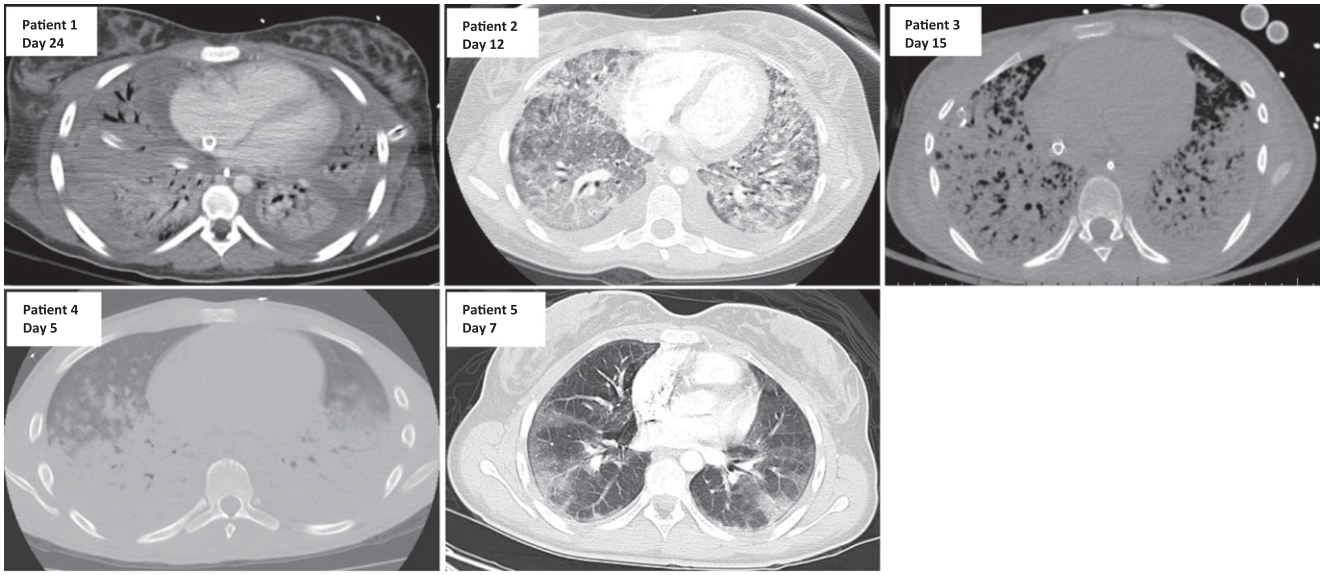

FIGURE 1

Chest CT imaging from 5 adolescent patients with severe respiratory failure and recent TMP-SMX exposure. CT images are from the 5 patients and include the denoted day of illness on which the image was obtained. Although the images are heterogeneous as related to timing and imaging modalities, all patients had diffuse ground-glass opacities and pulmonary infiltrates.

enzymes may serve as predictors of risk.[7,11] These genetic or immunologic polymorphisms may partially explain why only a small number of patients receiving TMP-SMX have these life-threatening reactions and may also be able to assist in identification of those at risk for these reactions before drug exposure.

Although there is no available clinical test to confirm causality between TMP-SMX and ARDS in these adolescents, the extensive negative workup, paired with recent TMP-SMX exposure and similarity among these cases, raises the possibility that the observed ARDS was TMP-SMX triggered. The findings from this case series is a reminder that the benefits must be weighed against the known and unknown risks of any medication, and those physicians caring for patients presenting with severe acute respiratory failure of unclear etiology must obtain a detailed drug-exposure history. Identification of rare adverse drug reactions is dependent on clinical recognition of an unusual or unexpected pattern of events that is consistent with a biologically plausible explanation.[12] Further work is needed to investigate potential rare occurrences of severe adverse drug reactions that may go unrecognized or unreported.

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ABBREVIATIONS

ARDS: acute respiratory distress syndrome
CT: computed tomography
ECMO: extracorporeal membrane oxygenation
HD: hospital day
TMP-SMX: trimethoprim-sulfamethoxazole

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