

Atypical Severe Shock-like Reactions in Adolescents After Trimethoprim-Sulfamethoxazole Therapy

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Severe drug hypersensitivity reactions to antibiotics are rare but trimethoprim-sulfamethoxazole (TMP-SMX) is uniquely associated with numerous and varied manifestations including a reaction resembling septic shock, first observed in human immunodeficiency virus (HIV)/AIDS patients. Over the past 25 years about 20 cases have been reported and an association with the virus and related immune system dysregulation was assumed. However, recent reports in adults have recognized similar shock-like reactions in non-HIV infected individuals. Here we review severe TMP-SMX hypersensitivity reactions and within the context of these known reactions, describe three non-HIV infected adolescent patients with shock-like reactions to TMP-SMX observed in one institution over 1.5 years.

Key words. adolescents; drug allergy; hypersensitivity reactions; shock; trimethoprim-sulfamethoxazole.

Trimethoprim-sulfamethoxazole (TMP-SMX) is associated with a wide range of adverse drug reactions, of which a small proportion are severe drug hypersensitivity reactions (DHRs). TMP-SMX commonly causes mild reactions such as fever, rash, neutropenia, and gastrointestinal discomfort [1–3]. More severe DHRs include drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS)/toxic epidermal necrosis (TEN), and anaphylaxis [2, 4–7]. Unique TMP-SMX DHRs have been observed such as aseptic meningitis, severe acute respiratory distress syndrome (ARDS), and shock-like reactions [8–11].

In the late 1980s, a hypersensitivity reaction to TMP-SMX resembling shock was described in the human immunodeficiency virus (HIV)/AIDS population. The phenomenon was characterized by a priming drug exposure followed by reaction to a second exposure weeks to months later. Patients presented with high fevers, hypotension, and pulmonary infiltrates with rapid resolution of symptoms after discontinuation of TMP-SMX [11–20]. Pediatric HIV presentations of this phenomenon shared similar symptoms to adults but without pulmonary infiltrates [12]. The mechanism of this hypersensitivity reaction is unknown, though data suggest it is a distinct entity from anaphylaxis, DRESS, and SJS/TEN [13, 14, 17].

Three adults without HIV infection and TMP-SMX shock-like hypersensitivity reactions were reported in the literature recently, with presentations similar to those described in HIV populations: high fevers, hypotension, and rapid resolution with drug discontinuation [21, 22]. This phenomenon in patients without HIV suggests that HIV and associated immune dysregulation are not required to experience the reaction. However, 2 of the patients were of advanced age (85 years) and the third had systemic lupus erythematosus (SLE), both associated with decreased immune system function or dysfunction. We present 3 adolescents without HIV infection with shock-like hypersensitivity reactions to TMP-SMX.

CASE REPORTS

The 3 cases described below were observed at Seattle Children's Hospital during October 2016–December 2017.

Case 1

A 15-year-old boy presented to the emergency department with high fever ($\geq 40^{\circ}\text{C}$), vomiting, and hypotension (blood pressure [BP]: 75/25) in the setting of presumed recurrent methicillin-resistant *Staphylococcus aureus* (MRSA) perianal cellulitis. He was unresponsive to fluid resuscitation and was admitted to the pediatric intensive care unit (PICU) on vasopressors. Vancomycin, piperacillin-tazobactam, and clindamycin were administered with concern for septic shock due to MRSA. He recovered rapidly in the PICU with discontinuation of vasopressors within 12 hours and clinical recovery by 24 hours. Blood cultures were negative. See Table 1 for pertinent laboratory test results observed at the time of initial presentation. Two weeks prior, he completed 7 days of TMP-SMX for a perianal dermatitis with a positive MRSA culture. Two days prior to this presentation, he was prescribed a second course of TMP-SMX

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Table 1. Laboratory Results in 3 Adolescents Presenting with a Shock-like Reaction to Trimethoprim-Sulfamethoxazole

Chemistry and CBC	Patient 1	Patient 2	Patient 3	Inflammatory and Infectious Testing	Patient 1	Patient 2	Patient 3
Lactic acid, mmol/L	1.9	3.2	1.3	CRP, mg/dL	<0.8	<0.8	<0.8
Creatinine, mg/dL	0.9	0.6	0.6	ESR, mm/h	NA	18	NA
BUN, mg/dL	10	21	14	Blood culture Gram stain	NO	NO	NO
ALT, U/L	29	271	144	Blood culture	NG × 4 ^a	NG × 4 ^a	NG × 9 ^a
WBC count, cells/μL	9600	2300	4900	Yeast blood culture	NG × 4 ^a	NG × 4 ^a	NG × 9 ^a
ANC, cells/μL	6240	897	2421	Respiratory pathogen panel ^b	Negative	Negative	Negative
Lymphocyte count, cells/μL	672	1081	2278	...	...	...	...
Eosinophil count, cells/μL	96	0	0	...	...	...	...
Polymorphonuclear cells	77%	45%	44%	...	...	...	...
Bands	12%	6%	5%	...	...	...	...
Lymphocytes	7%	47%	47%	...	...	...	...
Platelet count, K/μL	201	270	236	...	...	...	...

Abnormal values are italicized.

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; BUN, blood urea nitrogen; CBC, complete blood count; CRP, C-reactive protein; NA, not applicable; NG, no growth after 72 hours (blood) and 7 days (yeast); NO, no organism seen; WBC, white blood cell.

^aNumber of blood cultures per patient.

^bRespiratory pathogen panel includes influenza A and B, adenovirus, parainfluenza virus, human metapneumovirus, respiratory syncytial virus, rhinovirus/enterovirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Bordetella pertussis*.

due to worsening of the perianal dermatitis. He developed the above-described symptoms 4 hours after taking the first dose of TMP-SMX. As he recovered rapidly from presumed early septic shock secondary to MRSA, he was restarted on oral TMP-SMX. He again developed fever and hypotension (BP: 91/44) requiring vasopressor support 4 hours after the first dose. He recovered rapidly with supportive care and was discharged home the next day without antibiotics.

Case 2

A 16-year-old girl with SLE presented to the emergency department with sudden onset of high fever ($\geq 40^{\circ}\text{C}$), hypotension (BP: 56/30), vomiting, and malaise. Unresponsive to fluid boluses, she was started on vasopressors, stress dose steroids, ceftriaxone and vancomycin, and was admitted to the PICU. She responded rapidly with vasopressors discontinued after 8 hours, and all symptoms resolved by 24 hours. At presentation, laboratory and infectious testing was unremarkable (Table 1). One month prior, she had received high-dose steroids, mycophenolate mofetil, and rituximab during a hospitalization for an SLE flare. TMP-SMX prophylaxis (ppx) for *Pneumocystis jirovecii* pneumonia was initiated at discharge. She took her first doses of TMP-SMX on consecutive days and experienced fevers, nausea, and dizziness, diagnosed as a viral illness. Symptoms resolved until the day of presentation when she took her next dose of TMP-SMX. Four hours later, she developed the symptoms described above. She was diagnosed with culture-negative sepsis with rapid recovery. TMP-SMX ppx was restarted 1 week later and she again developed fevers and hypotension (BP: 86/35) requiring vasopressors and PICU admission. Her symptoms resolved within 24 hours and her ppx was changed to pentamidine.

Case 3

An 18-year-old woman with relapsed acute myeloid leukemia presented with sudden onset of fever and hypotension during a central line flush. She was admitted to the PICU with high fever ($\geq 40^{\circ}\text{C}$) and hypotension (BP: 74/50) requiring multiple vasopressors. She was started on ceftazidime, gentamicin, and vancomycin with concern for septic shock secondary to an infected central line. She slowly improved but required pressor support for 3–4 days. All infectious studies were negative on testing at presentation of initial and recurrent shock-like episodes (Table 1). On the subsequent Monday, she experienced fever and hypotension (BP: 47/26) again requiring vasopressor support. The suspected diagnosis continued to be an infected line. Repeat cultures and infectious testing were negative. The line was removed and symptoms resolved in 3–4 days. When her symptoms recurred the next Monday, the workup was expanded to examine her extensive list of medications and to evaluate for cardiac and endocrine abnormalities (BP: 81/35). No abnormalities were identified except for mild adrenal insufficiency. She was given stress dose steroids, after which she recovered more rapidly. When symptoms again recurred after the fourth weekly dose of TMP-SMX, the association with the antibiotic was recognized (BP: 80/41). She received 1 dose of TMP-SMX but not the second, and her symptoms rapidly resolved. Pentamidine was started for ppx, and she has had no further episodes. Just prior to the current presentation, she had been started on TMP-SMX ppx while completing inpatient treatment for an *Enterococcus faecalis* line infection and had 2 days of unexplained fevers that resolved without any other symptoms. At the next dose 1 week later, she decompensated in clinic with the presentation described above. The 4 episodes

of shock all presented 3–5 hours after her Monday dose of TMP-SMX.

DISCUSSION

Laboratory values and infectious studies for the 3 cases presented here are similar to those reported in other cases of TMP-SMX shock-like reactions. Neither our cases nor those identified in the literature had consistent findings of eosinophilia, neutrophilia, or lymphopenia. Different from the other shock-like reactions, our cases had a normal C-reactive protein (CRP) on presentation. However, all 3 developed an elevated

CRP with repeat episodes. Notably, no infectious cause was identified for any of the reported cases [11–22].

These 3 pediatric cases expand the epidemiology of those at risk for shock-like hypersensitivity reactions to TMP-SMX and further support these reactions as different from other DHRs. Figure 1 compares our cases to the other patient populations with shock-like reactions as well as to anaphylaxis, DRESS, and SJS/TEN. The reactions in the cases described above most resemble the shock-like DHRs previously identified in HIV and non-HIV-infected adults [11–14, 16–22]. The defining characteristics of anaphylaxis, DRESS, and SJS/TEN such as eosinophilia, mucosal involvement, liver/kidney injury,

Panel A	Number of Doses	Time to Onset	Time to Resolution
Case #1	Prior exposure 14 days later, 1 dose	4 hours	Within 12–24 hours
Case #2	Prior exposure ppx* 3rd dose	4 hours	Within 24–48 hours
Case #3	Prior exposure ppx* 3rd dose	4 hours	48–72 hours
HIV Cases	Prior exposure weeks to months	0–12 hours	Majority 24–48 hours; a few up to 1 week
Non-HIV Adult Cases	Prior exposure weeks to months	0–5 hours	Within 24–72 hours
Aseptic Meningitis	No prior exposure, at first dose	0 hours–11 days	Within 48–72 hours
ARDS	After 10–25 days of contiguous therapy	Days to weeks	Weeks to months
Anaphylaxis	1st dose primes 2nd dose = reaction	Usually 0–1 hour, up to 6 hours	24–48 hours
DRESS	After 10–60 days of therapy	Weeks	Weeks
SJS/TEN	After 10–60 days of therapy	Days to weeks	Weeks

Panel B	Fever	Hypotension	Rash	Hives	Mucosal Involvement	Angioedema	Eosinophils	Liver Injury	Renal Injury	Lung Injury	CNS Symptoms
Case #1											
Case #2											
Case #3											
HIV Cases											
Non-HIV Adult Cases											
Aseptic Meningitis											
ARDS											
Anaphylaxis											
DRESS											
SJS/TEN											

Figure 1. Comparisons of characteristics of drug hypersensitivity reactions (DHRs) to trimethoprim-sulfamethoxazole. *A*, Time to and resolution of symptoms for DHRs. *B*, Key characteristics of DHRs. Solid blocks denote symptoms shared by the majority of cases. Half-shaded blocks denote less common findings. Case data collected from the following references: for human immunodeficiency virus (HIV) and pediatric adult cases [11–22]; for adult non-HIV cases [21, 22]; for aseptic meningitis and acute respiratory distress syndrome cases [8–11]. *Prophylaxis for *Pneumocystis jiroveci* pneumonia was a once-daily dose for 2 contiguous days per week. Abbreviations: ARDS, acute respiratory distress syndrome; CNS, central nervous system; DRESS, drug rash with eosinophilia and systemic symptoms; HIV, human immunodeficiency virus; ppx, prophylaxis for *Pneumocystis jiroveci* pneumonia; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrosis.

hives, and angioedema were not present in our patients [2]. Furthermore, the timing of the shock-like hypersensitivity reaction is not consistent with DRESS or SJS/TEN as both of these diagnoses present after prolonged exposure and do not resolve rapidly with drug cessation. Aseptic meningitis is an uncommon TMP-SMX hypersensitivity reaction that shares some characteristics with the shock-like reaction including rapid resolution with drug discontinuation. Rarely, aseptic meningitis cases have also had hypotension or altered mental status, but the lack of other shared characteristics suggests that these are more likely separate entities [8]. Last, the recently identified TMP-SMX-related ARDS cases appear distinct. ARDS patients have not had systemic shock-like symptoms and have had prolonged pulmonary reaction/damage even after drug discontinuation [10].

While no specific immune dysregulation has been consistently associated with shock-like hypersensitivity cases, the majority have had some underlying immune system dysfunction, particularly HIV [3, 13]. Conversely, TMP-SMX hypersensitivity presenting with aseptic meningitis has occurred with and without underlying immune dysfunction [8]. While the organ systems affected in aseptic meningitis and shock-like hypersensitivity suggest a different mechanism of drug reaction, they share similarities in timing of onset and resolution of symptoms, suggesting shared immunologic pathways.

The shock-like reaction to TMP-SMX identifies most with the hapten model of drug reactions. Haptens are drug or drug metabolites that bind to patient proteins or cells, creating a new “antigen” the immune system recognizes as foreign and to which it develops a response. This response is heterogeneous, involving any or all parts of the immune system including antibodies, cytokines, and lymphocytes [23]. Anaphylaxis falls within this same category, but the clinical phenotype is different and patients tested at the time of shock-like episodes showed no immediate mast cell/immunoglobulin E response to TMP-SMX [13, 17]. A possible mechanism involves a T-cell-mediated immune response against a new antigen, resulting in inflammatory cytokine release causing shock-like reactions [23]. However, there is a paucity of functional studies and the exact mechanism of the TMP-SMX shock-like hypersensitivity reaction is unknown.

TMP-SMX adverse drug reactions are numerous, with highly variable clinical presentations. Here we expand the patient population at risk for shock-like DHRs to include non-HIV-infected adolescents. The reported cases in the literature are few in number, but with striking clinical similarity to septic shock, it is possible that shock-like hypersensitivity to TMP-SMX is underrecognized and therefore underreported. In patients presenting with symptoms of shock and currently receiving TMP-SMX for treatment or ppx, it is important to include a DHR on the differential diagnosis. TMP-SMX shock-like drug hypersensitivity remains a diagnosis of exclusion

but should be considered in the patient with a negative infectious workup and rapid recovery after discontinuation of TMP-SMX.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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