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Trimethoprim-sulfamethoxazole—induced aseptic meningitis—not just another sulfa allergy

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ABSTRACT

Objective: To review the literature on trimethoprim-sulfamethoxazole (TMP-SMX)—induced aseptic meningitis (TSIAM) and discuss the features, possible mechanisms, evaluation, and treatment options relevant for the allergist.

Data Sources: A MEDLINE search was performed using the terms *aseptic meningitis*, *trimethoprim-sulfamethoxazole*, *trimethoprim*, and *sulfamethoxazole*.

Study Selections:: Cases were included that fit the case definition of headache, neck pain, or change in mental status with elevated cerebrospinal fluid white blood cell count or protein attributable to TMP-SMX or either medication alone.

Results: Forty-one patient cases were reviewed. There was a predominance of female patients and patients with autoimmune disease reported. Fever, headache, neck pain, and altered mental status were the most common findings reported in TSIAM reactions. Severe reactions ranged from hypotension to seizure and unconsciousness or coma. Typical cerebrospinal fluid findings included elevated white blood cell count with neutrophil predominance, elevated protein, and normal glucose. Symptoms quickly remitted with withdrawal of TMP-SMX, typically over 48 to 72 hours. Full recovery was typically experienced, although permanent paraplegia was reported in 1 case. The mechanism of reaction is unknown, although an IgE-mediated reaction is unlikely. Many patients experienced multiple TSIAM reactions before the diagnosis was made. Diagnosis can be confirmed with drug challenge or graded test dosing when necessary. Patients with TSIAM subsequently reacted to TMP and SMX alone and therefore should be advised to avoid these 2 classes of medication after diagnosis.

Conclusion: TMP-SMX is the most common antibiotic to cause drug-induced aseptic meningitis. By being aware of this reaction, allergists are well poised to diagnose TSIAM and prevent future reoccurrences for the patient.

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Introduction

Drug-induced aseptic meningitis is a rare manifestation of drug-induced hypersensitivity of the central nervous system. It is well reported to several classes of medication, most notably nonsteroidal anti-inflammatory drugs, immunomodulating agents, and antibiotics. Of the antibiotics, trimethoprim (TMP) plus sulfamethoxazole (SMX) is most commonly implicated.¹ TMP-SMX—induced aseptic meningitis (TSIAM) is a diagnostic challenge for the clinician because patients are often started on the antibiotic out of concern for infection and the progression of aseptic

meningitis symptoms are difficult to distinguish from true infectious meningitis. Symptoms can quickly progress over a few hours from fever and headache to confusion, coma, and even respiratory failure if the medication is not stopped. TSIAM has been reported in the medical literature of multiple medical specialties, but to the authors' knowledge, it has not been reported or reviewed in the allergy literature. Allergists may be asked to evaluate a patient for TMP-SMX allergy and should consider this syndrome in their evaluation. In this article, the authors review the literature on TSIAM and discuss the features, possible mechanisms, and diagnostic tests that could be helpful for the allergist in diagnosing and managing this condition.

Methods

A literature search was conducted using the MEDLINE database. Search terms of *aseptic meningitis*, *trimethoprim-sulfamethoxazole*, *trimethoprim*, and *sulfamethoxazole* were used and limited to

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Table 1
Cases reviewed

Patient number	Age (y)	Sex	Comorbid condition	Medicine	Previous exposure	Medical indication	Symptoms	Episodes, n	Time of symptom onset (first→last)	Time to resolution	Reference
1	30	F		TS	no	UTI	f, HA, np, n/v	1	3 h	48 h	2
2	28	F		TS	yes—no symptoms	UTI	f, HA, np	2	within hours→shortly afterward	48 h	3
3	57	F	RA	TS	NS	UTI	f, HA, co, stupor, np, ci, ARF	4	1 d→2 h	promptly	4
4	25	F		TS	NS	ST	f, HA, np, meningismus	2	shortly afterward→4 h	24 h	4
5	54	F		TS	no	UTI	f, HA, np, n/v, p, my, progressive weakness, drowsy	1	3 d	72 h	4
6	19	F		TS	NS	UTI	f, HA, lethargy, np, n/v	1	24 h	48 h	5
7	38	F		TS	no	UTI	f, HA, np, n/v	3	7 d	24 h	6
8	6	M		TS	no	OM	f, HA, np, n/v	2	“several hours after first dose”→2 h	NS	7
9	52	F		TS	NS	sinus, UTI	co, rigors, my, ci	5	shortly afterward		8
10	24	F	Crohn disease, spina bifida (repaired)	TS	NS		f, HA, np, n/v, p	3	hours after first dose→30 min	48 h	9
11	46	F	SLE	TS	NS	UTI	f, HA, co, np	1	30 min	1 d	10
12	62	F	arthritis	TS	NS	UTI	co, combative, slurred speech, generalized T/C seizure	2	few hours	2–3 d	11
13	15	M	T1DM	TS	no	URI	f, HA, np, meningismus, n/v, p	2	few hours→15 min	48 h	12
14	26	M	HIV (CD4 count 15), chronic hepatitis C	TS	yes—vague intolerance	PCP PNA	f, co, generalized T/C seizure, required intubation	1	6→8 h	36 h	13
15	43	M	HIV (CD4 count 117), CMV hepatitis	TS	yes—vague intolerance	PCP proph	f, HA, p, my, hypotension (68/48 mmHg), ARF	1	3 d	1 d	13
16	16	M	HIV (CD4 count <15)	TS	no	PCP proph	f, HA, np, p, ci, my, hypotension, diffuse erythematous macular rash, mucosal inflammation	2	2 wk→2 h	24–48 h	14
17	34	M	HIV (CD4 count 14), IVDU	TS	yes—LOC, recovered quickly, no medical eval	PCP proph	f, sudden-onset coma (no seizure)	1	1 h	3 d	15
18	90	F	temporal arteritis	TS	yes—same symptoms 1 y previously, resolved after medicine was stopped	UTI	f, obtunded, n/v, abdominal pain, guarding	1	12 h	3 d	16
19	52	M	migraines	TS	yes—1 wk previously—HA resolved after medicine was stopped	folliculitis	f, HA, np, p, back pain	1	1 h	24 h	17
20	45	F	SLE	TS	yes—8 mo previously—HA, weakness after 2 d of TS	UTI	f, HA, lethargic, np, n/v, my, abdominal pain, facial flushing, faint maculopapular rash, weakness, unable to walk	2	24 h→1 h	2 d	18
21	41	M	HIV, PCP PNA	TS	yes—flushing	PCP PNA	f, HA, flushing, diffuse erythroderma and b/l hearing loss	1	within several hours of first dose	72 h	19
21	41	M		T	yes—case above	PCP proph	f, HA, n/v, somnolent, disoriented, flushing, global aphasia, diffuse weakness, hyperreflexia	1	4 h	48 h	19
22	45	M	SLE, ESRD (s/p renal transplantation)	TS	yes—same symptoms 2 y previously—diagnosed with cx negative meningitis	PCP proph	f, HA, np, n/v, confusion	2	same day→30 min	2–3 d	20
23	46	M	HIV	TS	yes—same sxs 2 wk previously—diagnosed with aseptic meningitis	PCP proph	f, HA, co, np, nuchal rigidity, positive Brudzinski sign	2	1 h→30 min	6 d	21
24	25	M		TS	NS	flulike symptoms	f, HA, coma, severe hypertonia requiring paralysis	1	<12 h	3 d	22
25	18	F	AML s/p chemotherapy	TS	NS	PCP proph	HA	1	3 mo	1 d	23

26	15	M		TS	NS	UTI	f, HA, np, n/v, my, acute paraparesis and urinary retention, then 3 d later paraplegic with D8 sensory level, nystagmus, ophthalmoplegia and b/l facial palsies—required intubation	2	3 d → 1 d	gradual improvement—paraparesis did not resolve	24
27	71	M		TS	yes—same but milder symptoms—no medical treatment	UTI proph	f, HA, nuchal rigidity, co, my	2	12 h → 5 h	48 h	24
28	61	F	SS, Diabetes	TS	NS	UTI	f, HA, lethargic, np, n/v, back pain, generalized T/C seizure, coma	4	11 d → few hours	72 h	25
28	61			T	yes—case above	UTI	f, co, lethargy	1	3 h	“rapidly improved”	25
29	70	F		TS	yes—nausea	UTI	f, n, co, lethargy	1	within hours	NS	26
29	70			T	yes—case above	UTI	f, HA, n/v, lethargy and stupor, continuous vomiting	1	1 h	1 wk	26
30	33	F	SLE	T	NS—patient told to avoid sulfa drugs owing to allergy	UTI	f, nuchal rigidity, back pain, my, pruritus	2	10 d → 1 h	4 d	26
31	61	F		T	yes—arthralgia	UTI	f, HA, ci, n/v, back pain, perimyocarditis	2	10 min → 5–10 min	few days	26
32	63	F	SS, hypothyroid	TS	NS	UTI	f, co, lethargic	1	within hours	3 d	26
32	63			T	yes—case above	UTI	f, HA, co, n/v	1	1 h	NS	26
33	17	F	asthma and eczema	T	NS	UTI	f, HA, nuchal rigidity, n/v, ci	2	1 h → 1 h	2 d	26
34	72	M	prostate cancer s/p radical prostatectomy	TS	yes—hospitalized with presumed urosepsis ×2	UTI	f, HA, meningismus, malaise	2	<12 h → 6 h	1 d	27
35	43	F		TS	no	UTI	f, rash, co, n/v, diarrhea, myoclonic jerks of hand and facial muscles	1	6 d	2 d	28
36	37	M		TS	no	UTI	f, HA, co, np, maculopapular rash, itching, difficulty speaking, weakness, hepatitis, orthostatic hypotension, hemolytic anemia (2/2 G6PD)	1	8 d	5 d	29
37	15	M	migraines	T	yes—HA, np, p, co—stopped medicine—no medical treatment	acne	f, HA, np, n/v, p, ci, numbness in extremities	2	<12 h	3 d	30
38	76	F		T	yes—no symptoms	UTI	f, HA, nuchal rigidity, co, dysphagia, speech disturbance, abnormal EEG	2	<12 h → 1 h	1 d	31
39	18	F		T	yes—f, HA, ci, eye pain—seen in ED, abx changed	UTI	HA, np, Kernig sign, ci, p, diagnosed with uveitis (b/l anterior), arthralgia	1	4 h	unknown	32
40	23	F		SM	yes—f, HA, abdominal pain—diagnosed with streptococcal pharyngitis	UTI	f, HA, nuchal rigidity, ci, pruritus, hypotension (66/44 mmHg), severe abdominal pain, hepatitis, pancreatitis	2	8 h → 30 min	2 d	33
41	33	F		TS	no	MRSA skin infection	f, HA, np, n/v, p	1	3 d	18 h	34

Abbreviations: abx, antibiotics; AML, acute myeloid leukemia; ARF, acute renal failure; b/l, bilateral; ci, conjunctival injection; CMV, cytomegalovirus; co, confusion; cx, culture; ED, emergency department; EEG, electroencephalogram; ESRD, end-stage renal disease; F, female; f, fever; G6PD, glucose-6-phosphate dehydrogenase; HA, headache; HIV, human immunodeficiency virus; IVDU, intravenous drug user; LOC, loss of consciousness; M, male; MRSA, methicillin-resistant *Staphylococcus aureus*; my, myalgia; n/v, nausea/vomiting; np, neck pain; NS, not stated; OM, otitis media; p, photophobia; PCP, pneumocystis pneumonia; PNA, pneumonia; proph, prophylaxis; RA, rheumatoid arthritis; S, sulfamethizole; s/p, status post; SLE, systemic lupus erythematosus; SS, Sjögren syndrome; ST, sore throat; T, trimethoprim; T/C seizure, tonic-clonic seizure; TS, trimethoprim plus sulfamethoxazole.

Table 2
Immunologic testing

Study	Patient number	Immunologic testing
Kremer et al ¹²	1	negative nephelometric result and lymphocyte transformation
Joffe et al ⁴	3	increased circulating immune complexes in serum but not CSF, mildly decreased CH50, IgA undetectable
Joffe et al ⁴	4	circulating immune complexes detected in serum but not in CSF by Raji assay
Joffe et al ⁴	5	normal ANA, RF, and CH50
Auxier ⁷	8	normal quantitative immunoglobulins, total serum complement, and urine electrophoresis
Haas ⁸	9	peripheral eosinophilia 26%
Gordon ⁹	10	2 eosinophils in CSF at 3 different LPs, CSF immune complexes (IgG, IgM and IgA) found; CSF TMP-SMX level 0.9 µg/mL (below therapeutic level)
Pashankar et al ¹²	13	serum immunoglobulins and complement nl except slight increase in C3
Jurado et al ¹³	14	eosinophils present in CSF ×2
Patey et al ¹⁵	17	CSF with 14% eosinophils, peripheral eosinophilia appeared a few days later (22.4%–35.55%)
Escalante and Stimmler ¹⁸	20	normal cryoglobulin, C3 and C4 normal
Wambulwa et al ²¹	23	CD4 count 95/mm ³ (low)
Capra et al ²²	24	gas chromatography showed presence of TMP in blood
Therrien ²³	25	patient taking TMP-SMX M/T/W, had HA worsening on Mondays; LP on Monday: CSF 56 WBCs, 1% PMNs, 3% eosinophils; LP on Wednesday: WBCs 427, 95% PMNs, no eosinophils reported on repeat
River et al ²⁴	26	patient with positive ANA, positive anti-DNA, and low C3 level (43 mg/dL, nl >60); patient developed typical SLE manifestations 2 y later
River et al ²⁴	27	normal C3 and protein electrophoresis, negative ANA
Derbes ²⁵	28	elevated C1q precipitin in serum on day 3 (500–1000 mg/L, normal 0 mg/L), negative C1q precipitin in CSF (although LP performed 7 d later)
Carlson ²⁶	31	positive ANA, positive RF, interstitial cystitis on bladder biopsy
Carlson ²⁶	32	positive ANA, positive RF, and positive Shirm test result; diagnosed with Sjögren syndrome
Hedlund et al ³¹	38	serum/CSF electrophoresis showed “barrier injury” but no intrathecal antibodies, repeat electrophoresis day 3 normal
Gilroy et al ³²	39	ANA negative, nl RF

Abbreviations: ANA, antinuclear antibody; CSF, cerebrospinal fluid; HA, headache; LP, lumbar puncture; M/T/W, Monday/Tuesday/Wednesday; nl, normal; PMN, polymorphonuclear lymphocytes; RF, rheumatoid factor; SLE, systemic lupus erythematosus; SMX, sulfamethoxazole; TMP, trimethoprim; WBC, white blood cell.

English and humans. Cases were included that fit the case definition of headache, neck pain, or change in mental status with elevated cerebrospinal fluid (CSF) white blood cell count or protein attributable to TMP-SMX. Included were patients who reacted solely to TMP or SMX as the case presentations and whose laboratory findings were identical to reactions with TMP-SMX, and there was the expectation these patients would have the same reaction if given the TMP-SMX combination. Thirty-three articles were found that were consistent with the case definition.^{2–34} One case described by Blumenfeld et al²⁸ was not used because the patient was taking erythromycin and sulfisoxazole in combination and the symptoms could not be attributed to just 1 drug. Also, a case by Anttonen et al³⁵ was not included because the patient did not have characteristic CSF findings, but is listed as an atypical case because the clinical picture is suggestive of the diagnosis.

Results

In the 33 articles evaluated, 41 patient cases were described (Table 1). Thirty patients developed aseptic meningitis to TMP-SMX, 4 patients to TMP-SMX and TMP, 6 to TMP alone, and 1 to sulfamethizole alone. Patients' ages ranged from 6 to 90 years old, and 22% (9 cases) were pediatric patients younger than 20 years. There was a female predominance of 61% (25 cases), 27% of patients (11 cases) held a diagnosis of an autoimmune disease, 6 patients (15%) had human immunodeficiency virus, 1 had acute myeloid leukemia and undergone chemotherapy, and 1 had undergone renal transplantation for systemic lupus erythematosus (SLE). Patients were prescribed TMP-SMX for multiple reasons, most commonly for urinary tract infections (UTIs), UTI prophylaxis, pneumocystis pneumonia (PCP), and PCP prophylaxis. It was not necessary for patients to have been previously exposed to the medication before developing aseptic meningitis in response to it. Nine patients (22%) developed TSIAM at their first exposure. The longest a patient had been on TMP-SMX before developing symptoms was 3 months. Only 1 patient had a history of aseptic meningitis to an unrelated medication (patient 12 to ibuprofen).¹¹

All patients complained of headache or neck pain unless they had altered consciousness, in which case pain often was not localized. All but 3 patients had fever and 50% had associated nausea and vomiting. Eye symptoms of conjunctival injection and photophobia were reported in 6 and 7 of 41 patients, respectively. Five patients were noted to have a rash and 2 patients had facial flushing. Neurologic changes such as generalized weakness and/or speech changes were reported in 8 patients, generalized tonic-clonic seizure was reported in 3 patients, and 1 patient had myoclonic jerks. Severe complications including unconsciousness or coma occurred in 4 patients and hypotension requiring pressor support occurred in 3 patients. Two patients had laboratory evidence of hepatitis and 2 patients had acute renal failure that resolved quickly after withdrawal of TMP-SMX. Of note, all symptoms characteristically resolved spontaneously once the offending drug was withdrawn, with patients becoming afebrile over 24 to 48 hours and regaining consciousness within 1 to 3 days. One patient had permanent neurologic sequelae of paraparesis (patient 26).²⁴

Laboratory and Imaging Characteristics and Diagnosis

Cerebrospinal fluid evaluation typically showed an elevated white blood cell count (93%; range 0–5,750/µL, most in the 100–1,000/µL range), with neutrophil predominance seen in 80%. The CSF protein was typically elevated (70%) with normal glucose (65%). Eosinophilia was not common; 2 patients were noted to have peripheral eosinophilia and 4 patients had eosinophils found in the CSF (range 2%–14%). Immunologic studies were variably attempted; they are listed in Table 2.

Computed tomography and magnetic resonance imaging of the brain are often obtained with the clinical picture of aseptic meningitis, particularly in recurrent cases, to look for structural abnormality. There are no specific radiologic findings to aid in the diagnosis of TSIAM. Twenty-seven head computed tomograms and 5 brain magnetic resonance images were reported in this case review. Only 1 patient showed related changes at brain imaging; patient 36 showed acute encephalitic changes at computed tomography and magnetic resonance imaging that normalized 4 months later.

Table 3
Drug challenges

Study	Patient number	Medicine	Challenge type	Time onset	Symptoms	Laboratory test
Kremer et al. ²	1	TS	open	3 h	f, HA, np, v	peripheral leukocytosis, patient refused repeat LP
Haas ⁸	9	TS	open	75 min	rigors, co, ci, diffuse achiness	no tests done, investigator judged repeat LP unnecessary, patient recovered in 2 d
Gordon ⁹	10	TS	open	30 min	f, HA, p, ci, meningismus	CSF: WBC count 93/ μ L, 75% PMN, protein 95 mg/dL, glucose 51 mg/dL
Biosca et al. ¹⁰	11	TS	open	30 min	f, co, n/v, combativeness, nuchal rigidity	CSF: WBC count 284/ μ L, 98% PMN, protein 118 mg/dL, recovered in 5 d

Abbreviations: ci, conjunctival injection; co, confusion; CSF, cerebrospinal fluid; f, fever; HA, headache; LP, lumbar puncture; n/v, nausea/vomiting; np, neck pain; PMN, polymorphonuclear lymphocytes; p, photophobia; TS, trimethoprim plus sulfamethoxazole; v, vomiting; WBC, white blood cell.

Given that drug-induced aseptic meningitis is a diagnosis of exclusion, the only way to definitively diagnose this entity is by drug challenge. Four patients underwent open drug challenge with reproduction of their symptoms (Table 3).

Clinical Course

A common clinical course was seen in the cases reviewed. Symptoms persisted and worsened while the patients continued treatment with the offending agent. However, once the medication was withdrawn, some patients continued to worsen clinically over the following 12 to 24 hours while the drug already ingested was absorbed and reached its peak in the serum and tissues. Few patients worsened after that time; those who did are listed in Table 4 as examples of atypical cases. Patients typically became afebrile, with resolution of headache and return of normal mentation within 2 to 3 days of stopping the offending medication, which correlates with 5 to 7 half-lives of the drug, when 95% to 99% of the medication has been eliminated.

Treatment

Treatment for TSIAM consists primarily of withdrawing the medication. However, given that symptoms and laboratory results are indistinguishable from partially treated bacterial meningitis, most patients were treated with intravenous antibiotics of another class and sometimes antivirals while awaiting bacterial and viral study results. Variably, some patients completed the course of antibiotics despite negative cultures, whereas others stopped antibiotics once cultures were negative. No patient had relapse of symptoms after stopping antibiotics that would have indicated incompletely treated bacterial meningitis. Several patients were placed on intravenous corticosteroids during the acute phase of their illness; however, this did not significantly shorten recovery time. No patients were treated with epinephrine, and antihistamines were not typically used. When the aseptic meningitis trigger was not correctly identified, many patients were instructed to restart their TMP-SMX for treatment or prophylaxis of their initial condition, with rapid recurrence of symptoms, which aided in the final diagnosis of TSIAM. Twenty-three patients experienced multiple TSIAM reactions to the medication. In all cases, onset of TSIAM symptoms occurred as fast if not significantly faster than the previous episode.

Discussion

The TMP-SMX combination was approved by the US Food and Drug Administration in 1973. It was approved as a fixed-drug combination given the synergistic effect of the 2 medications producing sequential blockade of microbial dihydrofolate reductase. Each drug is well absorbed after oral ingestion and serum levels approach those achieved with intravenous administration. Each drug is widely distributed in the body and can be detected in most tissues including the CSF. The serum half-life of TMP is 8 to 10 hours and that of SMX is 10 hours.³⁶ It has remained a popular antibiotic owing to its low cost and effectiveness in treating common

infections such as UTI and traveler's diarrhea, although its worldwide use exploded with the rise of the human immunodeficiency virus and its indication for PCP and PCP prophylaxis. There also has been a recent increase in its use owing to methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections.

Aseptic meningitis from TMP-SMX was first described by Kremer et al.² in 1983 (patient 1). They saw a 30-year-old previously healthy woman with aseptic meningitis who had onset of fever, headache, neck pain, nausea, and vomiting 3 hours after taking her first dose of TMP-SMX. In a review of the patient's records, they discovered that she had a history of 2 episodes of culture negative meningitis previously in response to SMX plus phenazopyridine. This suggested that SMX was the offending component of the medication. After the patient's recovery, she was rechallenged with TMP-SMX, with recurrence of symptoms within 3 hours. Derbes²⁵ described the next case of TMP-SMX aseptic meningitis in 1984, describing a 61-year-old diabetic woman with Sjögren syndrome who had 4 episodes of aseptic meningitis temporally related to TMP-SMX. She was given TMP alone because of concerns for sulfa allergy and had recurrent symptoms of lethargy and confusion within 3 hours. This suggested that TMP was the offending component in this patient. Three other patients were given TMP after having TSIAM with TMP-SMX, with recurrence of symptoms.^{19,26} It is important for the allergist to appropriately counsel patients with TSIAM that they must avoid the 2 components of the medication in the future.

The mechanism of reaction in TSIAM is unknown and does not fit neatly into a typical Gell and Coombs classification, although it likely represents an immune-mediated hypersensitivity reaction. TSIAM reactions are not likely mediated by IgE because none of the cases reviewed involved typical findings of urticaria, angioedema, or bronchospasm. Hapten-conjugate formation has been seen with SMX after N-oxidation metabolism, which would allow antibody formation by B cells. It has been proposed that hapten conjugation with meningeal or CSF proteins could cause inflammation and subsequent aseptic meningitis. Hapten conjugation with fixed antigen (meninges) would be a type II reaction, whereas hapten conjugation with soluble antigen would represent a type III reaction.³⁷ Evidence of immune complexes were found in 4 patients. Immune complexes in the peripheral blood but not in the CSF was found in 3 patients,^{4,25} and immune complexes were found in the CSF in 1 patient.⁹ Although the initial reaction to TMP-SMX is typically delayed, starting 3 hours to several days after starting the medication, subsequent reactions do start faster and can be more severe, which could be seen in type II or III reactions at subsequent exposure.³⁷ Type IV reaction also could be involved by the newer concept of T-cell-mediated pharmacologic interactions of drugs with immune receptors (p-i concept). This concept postulates that a chemically inert drug can reversibly bind to an HLA or MHC molecule and to T-cell receptors, enabling it to stimulate a variety of T-cell responses. Depending on the mechanism, these reactions can vary from maculopapular exanthems with eosinophilia (type IVb) to cytotoxic reactions inducing hepatitis (type IVc) to sterile neutrophilia

Table 4
Atypical cases

Study	Patient number	Atypical characteristics
Continued worsening >24 h s/p withdrawal of TMP-SMX River et al ²⁴	26	A 15-y-old boy developed aseptic meningitis and paraparesis that worsened to paraplegia and respiratory failure requiring intubation 3 d after stopping TMP-SMX. Patient gradually recovered but did not recover fully, remained wheelchair bound. Had recurrent symptoms after taking TMP-SMX a second time. Patient later developed typical manifestations of SLE.
Blumenfeld et al ²⁸	35	Patient developed fever and rash on day 4 of TMP-SMX, nausea and diarrhea developed on day 6. Medicine changed to ciprofloxacin but overnight confusion and myoclonic jerks developed, MRI showed b/l supratentorial white matter T2 signal abnormalities without enhancement. EEG showed continuous left-to-right frontotemporal slowing consistent with encephalitis. All neurologic symptoms resolved over 7 d, MRI normalized by 4 mo.
Chisholm-Burns et al ²⁹	36	A 37-y-old man developed typical TSIAM symptoms on day 8 of medication, symptoms worsened over next 4 d with hepatic involvement and hemolysis. Patient was later diagnosed with G6PD.
Initial bacterial meningitis followed by TSIAM Joffe et al ⁴	3	A 57-y-old woman had RA. Before TSIAM episodes, she was treated for <i>Escherichia coli</i> pyelonephritis with intravenous gentamycin $\times 2$ wk. Patient was asymptomatic until started on TMP-SMX at discharge. Within 1 d, had onset of HA, fever, and leg cramps. CSF culture grew <i>E coli</i> . Patient fully treated for <i>E coli</i> meningitis, but symptoms were noted to resolve promptly after change of antibiotic. This episode was not included in the review, although the patient developed 4 further episodes of TSIAM, which were included.
Minimal symptoms, positive CSF Therrien ²³	25	An 18-y-old woman with AML s/p chemotherapy was placed on TMP-SMX for PCP prophylaxis. She was admitted to undergo bone marrow transplantation; however, c/o HA on admission and LP demonstrated elevated WBCs and protein. Her TMP-SMX regimen was Monday through Wednesday once daily. HA was noted to worsen on Mondays. LP initially done on Monday was repeated on Wednesday and showed increased WBC count and protein. TMP-SMX was stopped and HA resolved quickly; repeat LP on day 14 showed normalization. Patient was afebrile and had been on TMP-SMX $\times 3$ mo before symptoms developed.
Positive symptoms, no CSF findings Antonen et al ³⁵	n/a	A 30-y-old previously healthy man developed f, HA, np, p, ci, dizziness, and back pain after 4 d of TMP-SMX for sinusitis. CSF showed 0 WBC and normal protein. Symptoms resolved 24 h after TMP-SMX was withdrawn. Not included in case review because there were no CSF findings of aseptic meningitis; however, clinical picture is consistent with diagnosis.

Abbreviations: AML, acute myeloid leukemia; b/l, bilateral; c/o, complained of; ci, conjunctival injection; CSF, cerebrospinal fluid; EEG, electroencephalogram; f, fever; G6PD, glucose-6-phosphate dehydrogenase; HA, headache; LP, lumbar puncture; MRI, magnetic resonance imaging; n/a, not applicable; np, neck pain; p, photophobia; PCP, pneumocystis pneumonia; RA, rheumatoid arthritis; s/p, status post; SLE, systemic lupus erythematosus; SMX, sulfamethoxazole; TMP, trimethoprim; TSIAM, trimethoprim-sulfamethoxazole-induced aseptic meningitis; WBC, white blood cell.

(type IVd).^{38,39} All these features can be seen in TSIAM.^{8,14,15,18,29,33} Although sulfonamide antibiotics have been implicated in hapten responses and p-i interactions,³⁹ to the authors' knowledge, TMP alone has not been specifically implicated in either of these, which is an important consideration given that TMP can produce the same clinical symptoms of aseptic meningitis as TMP-SMX.

Several cytokines have been studied in regard to TSIAM reactions. Interleukin (IL)-6 was shown to spike acutely in serum and the CSF in TSIAM-like reactions involving fever, headache, and photophobia (but without CSF evidence of meningitis).³⁵ IL-6 levels normalized as symptoms resolved. Tumor necrosis factor- α and IL-1 β levels did not rise. Antonen et al found this cytokine response in vivo in a patient acutely symptomatic³⁵ and in vitro using peripheral blood mononuclear cells of patients with a history of TSIAM-like reactions.⁴⁰ Immunologically, IL-6 induces a T-helper type 17 response, which recruits neutrophilic inflammation and potentially drives the neutrophil predominance seen in aseptic meningitis. T-helper type 17 reactions are typically triggered by bacterial or fungal infections; it is not clear why it is also triggered in aseptic meningitis.^{41,42}

Previous reports have suggested that TSIAM (or TIAM) most commonly occurs in patients with connective tissue disease such as SLE or Sjögren syndrome; indeed, these patients represented 20% of the cases reviewed. It is interesting that some p-i reactions have been linked to specific HLA types,³⁹ and perhaps future studies might find that individual characteristics that predispose a person to connective tissue disease also may increase the risk for TSIAM reaction. There have been concerns that flares of SLE or Sjögren syndrome might produce aseptic meningitis symptoms and that reports of TSIAM in these patients may actually be part of the patients' underlying disease.⁴³ This is not likely, however, because all cases in this review of patients with SLE or Sjögren syndrome experienced multiple reactions to TMP-SMX (or TMP alone), with

onset of classic symptoms from 30 minutes to a few hours and quick resolution of symptoms after stopping the offending medication. Such abrupt onset and resolution would not be characteristic of an autoimmune flare associated with aseptic meningitis.

There has been a predominance of female patients reported with this condition, which the authors also found at 61%. The authors suspect this reflects the fact that female patients have significantly more UTIs than male patients, for which TMP-SMX is a first-line treatment. Indeed, all but 2 female patients in this review were prescribed TMP-SMX for UTI, and UTI was the most common complaint for which it was prescribed overall (61% of cases).

For the allergist seeing a patient with suspected TMP-SMX-induced aseptic meningitis, diagnosis of this condition is primarily clinical. It is important to start with a detailed history of the patient's reaction, including the symptoms involved, the time elapsed from ingestion of the drug to the appearance of symptoms, the dose and route of drug intake, and time to resolution of symptoms. If available, previous records from hospitalizations or emergency department visits associated with the previous reaction may be invaluable to evaluate the patient's vital signs, laboratory values, and detailed history during the time of reaction. Diagnostic testing options are limited because no testing techniques have proved to be reliable, valid, and practical for clinical use.⁴⁴ Skin prick or intradermal testing is not recommended in TSIAM evaluation given its non-IgE-mediated mechanism of reaction. Delayed-reading intradermal tests and patch testing have been discussed in evaluating delayed-type reactions to sulfonamides.⁴⁵ These tests have been used primarily in patients with non-immediate drug eruptions and have had limited success.⁴⁶ Given that skin findings are not a dominant feature of TSIAM reactions, these tests are not likely to be beneficial in evaluation. In vitro testing, such as lymphocyte transformation testing, may provide benefit in the

future but has not yet been fully validated, and the ability to perform this test is limited because it must be performed by skilled personnel with specific experience.^{45,47}

The only way to objectively confirm the diagnosis of TSIAM is to reproduce the symptoms with drug challenge, which some would consider unethical if there is a true concern for TSIAM given the possibility of inducing a severe reaction such as coma or seizure. For the patient with an unconvincing clinical history of only a mild reaction or in the case in which there is no alternative antibiotic choice and the risk outweighs the benefit, drug challenge or graded test dosing could be considered. Four patients in this review were openly challenged with TMP-SMX (Table 3). No patient in this review underwent attempted drug desensitization. The authors would not recommend attempting desensitization because these protocols are designed primarily for patients with typical cutaneous reactions rather than potentially severe neurologic reactions.⁴⁸ For the case in which drug challenge is attempted, the authors would recommend doing so in a supervised setting with prolonged observation after obtaining informed consent. Time of observation should be based on the time to the previous reaction, because no patient in this review showed a longer interval to reaction on repeat dosing. If time to reaction is unknown, the data in this review showed 65% (15 of 23) of patients with repeat reactions reacted within 2 hours, and 91% (21 of 23) reacted within 6 hours. All patients with repeat reactions reacted within 24 hours of the repeat dose even when the initial reaction did not occur for 1 to 2 weeks after starting TMP-SMX.

Conclusion

Drug-induced aseptic meningitis is a clinical syndrome familiar to the allergist but typically encountered with drugs such as nonsteroidal anti-inflammatory drugs and intravenous immunoglobulin. TMP-SMX is the most common antibiotic reported to cause aseptic meningitis but it is not a widely known adverse drug reaction among clinicians. As seen in this review, multiple patients developed multiple episodes of TMP-SMX–induced aseptic meningitis before the reaction was recognized. It is an entity that may be encountered by the allergist in an evaluation for antibiotic allergy, and by being aware of it, the allergist may be able to prevent future reoccurrences for the patient. Further research is needed to elucidate the mechanism of TSIAM reactions and to help identify factors that place patients at increased risk for reaction.

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