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The Challenge of Drug-Induced Aseptic Meningitis Revisited

Cases of drug-induced aseptic meningitis (DIAM) are likely underreported, and only a few reviews of the literature have been performed. We have updated (to February 2014) a previous review (1999)[1] to identify newer agents associated with DIAM, as well as distinctive new features.

Methods | Using the MEDLINE database, we searched the literature to February 2014 and included those cases with cerebrospinal fluid (CSF) findings and reviews added to the literature from 1999 to date. Tables have been assembled from information derived from 192 studies (these data are available from the authors on request).

Results | Four groups of drugs continue to be associated with DIAM (**Table 1**): nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, immunosuppressive-immunomodulatory (IS-IM), and antiepileptic drugs.[1] Prior exposure to the associated drug was present in 26% to 35% of cases (Table 1). The interval between exposure and meningitis ranged from minutes to 5 months (Table 1). Most patients presented with headache, fever, meningismus, and mental status changes (**Table 2**). Underlying systemic disorders were often present, particularly systemic lupus ery-

Table 1. Drugs Involved in Drug-Induced Aseptic Meningitis (DIAM)[a]

Drugs Involved (No. of Cases)	Female Sex, %	Age, Mean (SD) [range], y	Range of Latency (Median)	Prior Exposure to Drug, %
NSAIDs (n = 72 cases): Ibuprofen (46), sulindac (7), naproxen sodium (7), tolmetin (1), diclofenac sodium (2), ketoprofen (1), celecoxib (1), dexibuprofen (1), piroxicam (1), ketorolac (1), rofecoxib (4)	62	39 (15) [21-73]	30 min-4 mo (8 h)	35
Antibiotics (n = 69 cases): Trimethoprim-sulfamethoxazole (32), trimethoprim (11), amoxicillin (8),[b] sulfamethoxazole (1), isoniazid (1), ciprofloxacin (2), penicillin (1), metronidazole (3), cephalosporin (2), pyrazinamide (1), sulfisoxazole (1), fumagillin (1), minocycline (1), ornidazole (1), rifampicin (1), valacyclovir (2)	59	46 (23) [1-90]	10 min-3 mo (6 h)	33
IS-IM agents (n = 19 cases): Cetuximab (5), efalizumab (2), infliximab (4), adalimumab (1), leflunomide (1), methotrexate (1), salazopyrin (1), sulfasalazine (3), etanercept (1)	53	51 (11) [31-78]	3 h-5 mo (48 h)	26
Antiepileptic drugs[c] (n = 34 cases): Lamotrigine (30), carbamazepine (4)	82	33 [15-79]	1-42 d (14)	NA
SLE group[d] (n = 29 cases): Ibuprofen (17), tolmetin (1), sulindac (1), naproxen (1), diclofenac (1), dexibuprofen (1), trimethoprim-sulfamethoxazole (3), trimethoprim (1), sulfisoxazole (1), rifampicin (1), lamotrigine (1)	89	38 (14) [21-73]	20 min-2 wk (35 h)	32

Abbreviations: IS-IM, immunosuppressive or immunomodulatory; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

[a] Data were pooled and updated from reference.[1] One patient can develop various DIAM episodes in relation with more than 1 drug.

[b] Five patients were receiving therapy with amoxicillin plus clavulanic acid.

[c] Estimated data from recent series.[2]

[d] The SLE group comprised all the patients with SLE irrespective of the associated drug.

Table 2. Percentages of Clinical Signs and Symptoms of Drug-Induced Aseptic Meningitis

Sign or Symptom	NSAIDs	ATB	IS-IM	SLE	Total
Fever	91	88	72	88	88
Headache	81	84	83	83	82
Meningeal signs	73	71	67	75	72
Nausea and vomiting	60	49	11	67	49
Rash	16	11	11	30	13
Abdominal pain	6	6	6	17	5
Arthromyalgias	16	13	17	25	15
Hypotension	15	3	6	29	9
Facial edema	16	16	6	17	14
Abnormal conciousness[a]	49	55	11	58	47
Focal neurologic deficit	10	7	NA	9	10
Seizures	4	7	NA	9	5
Papilledema	5	6	NA	8	5
Lymphadenopathies	3	7	NA	4	4
Abnormal liver function	5	11	22	12	11
Photophobia	9	11	16	12	11
Phonophobia	NA	2	11	NA	2

Abbreviations: ATB, antibiotics; IS-IM, immunosuppressive or immunomodulatory; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

[a] Includes somnolence-coma and confusional states.

thematosus (SLE). The CSF showed pleocytosis with neutrophilic predominance, normal-to-low glucose values, and increased proteins. Neuroimaging results were normal in most patients. Complete recovery in several days after drug discontinuation was the rule.

NSAID-induced meningitis was most common after ibuprofen exposure, and antibiotic-related DIAM was most often caused by trimethoprim with or without sulfamethoxazole, followed by amoxicillin (Table 1). Both were more frequent in women. The IS-IM group did not show sex predilection. After DIAM induced by the OKT3 antibody was recognized in 1% to 5% of renal transplant patients, monoclonal antibodies, and intravenous immunoglobulins have become the leading agents of this group. Monoclonal antibodies represent a new causative group, mainly tumor necrosis factor inhibitors, such as infliximab,[3,4] adalimumab and etanercept. Three cases of DIAM have been associated to the use of efalizumab, a humanized monoclonal antibody binding to the CD11 molecule on the T-cell surface. Cetuximab, a chimeric monoclonal antibody against epidermal growth factor receptor used for cancer treatment, has also been associated with a few cases of DIAM.[5]

Lamotrigine is the main antiepileptic agent associated with DIAM. Forty cases of suspected lamotrigine-associated aseptic meningitis have been reported, although only 25 had a CSF profile consistent with meningitis.[2] Chemotherapeutic agents associated with DIAM include pemetrexed[6] and cytarabine. There were 48 patients with recurrent DIAM, totaling 115 episodes, with a mean age of 45 years and female predominance and were mainly due to NSAIDs and antibiotics. The mechanisms of DIAM are not fully understood but are likely diverse, the most invoked being hypersensitivity. Why such reactions are mainly confined to the CSF compartment in some patients is intriguing.

Discussion | Aside from the classical NSAIDs and antibiotics, lamotrigine and a number of monoclonal antibodies stand out as new drugs associated with DIAM. The clinical profiles do not allow for a distinction between drugs, and the CSF profile, often with neutrophilic pleocytosis, may cause confusion with infectious meningitis. Many patients with DIAM have an underlying disorder, particularly SLE, which may also cause meningitis. Meningitis can be associated with a variety of other systemic disorders. A rapid onset and resolution of the signs and symptoms (1-5 days) with consistent CSF findings, together with a lack of systemic activity, suggest DIAM. The only confirmatory test would be drug rechallenge but is unethical; thus, the history of drug intake and clinical judgment remain critical.

A thorough history on drug intake must be performed in patients with meningitis to avoid expensive diagnostic procedures and unnecessary antibiotic therapy. Until an infectious etiology is ruled out, the use of a third-generation cephalosporin is advised given their low frequency of association with DIAM.

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Women's Clinical Preventive Services in the United States: Who Is Doing What?

A well-woman preventive care visit is a core service supported by the Human Resources and Services Administration,[1] yet it is unclear which preventive services are provided by primary care physicians (PCPs) and which are provided by obstetrician/gynecologists (OB/GYNs).[2,3] We examined patterns of selected age-appropriate preventive care visits across a woman's lifespan, focusing on the wide range of preventive services provided to nonpregnant women.

Methods | The study was considered exempt for institutional review board approval by the Centers for Disease Control and Prevention because these were considered public use data and there were no identifiable data. We used abstracted data from medical records of national representative visits occurring from 2007 to 2010 to office-based physicians collected through the National Ambulatory Medical Care Survey (NAMCS) and visits to outpatient departments collected through the National Hospital Ambulatory Medical Care Survey (NHAMCS).[4] The sample was limited to preventive care visits among nonpregnant women 18 years or older (N = 14 075 visits). Applicable use of preventive services was determined using survey encounter forms; see the **Table** for complete listing and target population age. Since data collection for contraceptive care counseling was available only for 2009 to 2010, the estimates were excluded from our study.