Antibiotic-associated encephalopathy

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ABSTRACT

Delirium is a common and costly complication of hospitalization. Although medications are a known cause of delirium, antibiotics are an underrecognized class of medications associated with delirium. In this article, we comprehensively review the clinical, radiologic, and electrophysiologic features of antibiotic-associated encephalopathy (AAE). AAE can be divided into 3 unique clinical phenotypes: encephalopathy commonly accompanied by seizures or myoclonus arising within days after antibiotic administration (caused by cephalosporins and penicillin); encephalopathy characterized by psychosis arising within days of antibiotic administration (caused by quinolones, macrolides, and procaine penicillin); and encephalopathy accompanied by cerebellar signs and MRI abnormalities emerging weeks after initiation of antibiotics (caused by metronidazole). We correlate these 3 clinical phenotypes with underlying pathophysiologic mechanisms of antibiotic neurotoxicity. Familiarity with these types of antibiotic toxicity can improve timely diagnosis of AAE and prompt antibiotic discontinuation, reducing the time patients spend in the delirious state. *Neurology*® 2016;86:963–971

GLOSSARY

AAE = antibiotic-associated encephalopathy; **GABAAR** = γ-aminobutyric acid class A receptor; **IPSP** = inhibitory postsynaptic potential.

Delirium occurs in up to half of hospitalized patients and up to 80% of patients in intensive care units.[1] Delirium is associated with increased length of hospital stay,[2–4] in-hospital complications,[5] discharge to long-term care facilities,[6] rehospitalization from long-term care facilities,[7] subsequent cognitive impairment,[4] subsequent dependence,[8] and risk of in-hospital[2,9] and 1-year mortality.[10] This has led to ongoing efforts to recognize, prevent, and treat delirium to improve patient outcomes and reduce health care costs.[11] Although medications are a commonly considered reversible cause of encephalopathy, antibiotics are an underrecognized etiology.[12] Serious CNS adverse effects of antibiotics are generally reported with a frequency of less than 1%, with encephalopathy representing a small proportion of those adverse effects.[13,14] However, a recent retrospective study of 100 critically ill patients reported a 15% rate of encephalopathy associated with use of the fourth-generation cephalosporin cefepime, suggesting that antibiotic-associated encephalopathy (AAE) may be underdiagnosed.[12]

Identification of AAE as a cause of delirium is challenging since patients receiving antibiotics often have multiple potential causes of altered cognition, and data describing the clinical features of and risk factors for AAE are limited to case reports and small series.[14,15] Here we present the results of a comprehensive review of reported cases of AAE to define the specific clinical features, EEG changes, and neuroimaging findings associated with encephalopathy from particular antibiotic classes and individual antibiotics. Our synthesis of this data reveals 3 distinct clinical subtypes of AAE, each with unique pathophysiologic mechanisms.

SEARCH METHODS AND CRITERIA We comprehensively searched PubMed using terms for antibiotics (antibiotic or "anti-bacterial agents" [MeSH] or "anti-bacterial agents" [pharmacologic action] or

Supplemental data at Neurology.org

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2,4-diacetylphloroglucinol or 2-deoxystreptamine or acedapsone or actinonin or actinorhodin … or tinidazole) (see supplemental data on the *Neurology*® Web site at Neurology.org for all antibiotic terms) and the search terms encephalopathy, confusion, delirium, seizure, neuropathy, neurotoxicity, mania, hallucination, or psychosis. The term neuropathy was included to increase sensitivity since some antibiotics such as metronidazole cause concurrent neuropathy and encephalopathy. We searched from the beginning of indexing to October 16, 2013, in English, French, and Spanish. Results were screened by the authors to meet the following inclusion criteria: (1) The article must present a case report or case series describing individual patients experiencing alteration of cognition/consciousness after administration of antibiotics and improvement after cessation. We therefore excluded series not describing individual patient data, but reference lists from such articles were screened for additional case reports and series. (2) Case reports in which altered cognition/consciousness was due to a postictal state after a clinically apparent seizure were excluded, but cases in which patients presented with encephalopathy accompanied by seizures or in whom nonconvulsive seizures were determined to be the cause of encephalopathy were included.

For each described case, we extracted data on demographics (age, sex), antibiotic used, comorbidities (renal dysfunction, hepatic dysfunction, history of psychiatric disease), clinical symptoms accompanying encephalopathy (seizures, myoclonus, focal neurologic deficits), temporal evolution of onset and improvement of toxicity, and laboratory investigations (EEG, MRI, serum or CSF drug levels). We calculated a Naranjo score for each case described (see supplemental data for Naranjo score table) assessing the likelihood of causality of the association described.[16]

CLINICAL CHARACTERISTICS OF AAE Our search yielded 292 articles describing 391 individual cases

Table 1 Baseline characteristics and risk factors in patients with antibiotic-associated encephalopathy

	No. of reports	Median (range) age, y	Men, n (%)	Renal insufficiency, n (%)	Hepatic dysfunction, n (%)	Psychiatric history, n (%)
Penicillins	72	41 (4–87)	40 (56)	12 (17)	0 (0)	2 (3)
Penicillin G procaine	34	28 (11–75)	20 (59)	0 (0)	0 (0)	0 (0)
Penicillin	24	53 (10–84)	15 (63)	7 (29)	0 (0)	0 (0)
Other	14	52 (4–87)	5 (36)	5 (36)	0 (0)	2 (14)
Cephalosporins	69	65 (8–88)	35 (54)	50 (72)	2 (3)	2 (3)
Cefepime	33	70 (14–86)	16 (55)	23 (70)	2 (6)	1 (3)
Ceftazidime	12	71 (34–80)	7 (58)	11 (92)	0 (0)	0 (0)
Other	24	61 (8–88)	12 (50)	16 (67)	0 (0)	1 (4)
Antimycobacterials	65	40 (14–80)	40 (62)	8 (12)	1 (2)	4 (6)
Isoniazid	49	43 (14–80)	30 (61)	8 (16)	1 (2)	4 (8)
Other	16	32 (15–60)	10 (63)	0 (0)	0 (0)	0 (0)
Quinolones	63	57 (<1–89)	27 (43)	14 (22)	0 (0)	9 (14)
Ciprofloxacin	26	55 (<1–88)	13 (50)	8 (31)	0 (0)	2 (8)
Ofloxacin	11	50 (5–75)	2 (18)	0 (0)	0 (0)	5 (45)
Other	26	61 (17–89)	12 (46)	6 (23)	0 (0)	2 (8)
Macrolides	54	51 (3–94)	32 (59)	4 (7)	2 (4)	11 (20)
Clarithromycin	44	51 (3–94)	23 (52)	2 (5)	0 (0)	10 (23)
Other	10	53 (4–81)	9 (90)	2 (20)	2 (20)	1 (10)
Metronidazole	29	48 (19–75)	19 (66)	1 (3)	4 (14)	0 (0)
Sulfonamides	19	54 (19–88)	11 (58)	4 (21)	0 (0)	3 (16)
Trimethoprim-sulfamethoxazole	15	55 (19–88)	8 (53)	4 (27)	0 (0)	3 (20)
Other	4	36 (23–55)	3 (75)	0 (0)	0 (0)	0 (0)

The table shows antibiotic classes and antibiotics (listed under each class) for which 10 or more clinical reports were available. Other antibiotics are aggregated under the subtitle "other." The "other" category includes the following antibiotics: penicillins: amoxicillin (5 cases), piperacillin (4), ampicillin (1), cloxacillin (1), oxacillin (1), mix of procaine penicillin and benzathine penicillin (1), ticarcillin (1); cephalosporins: cefuroxime (5), ceftriaxone (4), cefazolin (3), cephalexin (3), cefixime (2), cefotaxime (2), cefditoren pivoxil (1), cefoperazone (1), cefoxitin (1), cephaloridine (1), cephalothin (1); antimycobacterials: dapsone (5), streptomycin (3), cycloserine (2), ethambutol (2), ethionamide (2), rifampin (2); quinolones: levofloxacin (9), gatifloxacin (7), norfloxacin (3), naldixic acid (2), pefloxacin (2), gemifloxacin (1), moxifloxacin (1), trovafloxacin (1); macrolides: azithromycin (5), erythromycin (5); sulfonamides: sulfadiazine (3), sulfanilamide (1).

from 1946 through 2013 inclusive.[e1–e292] Toxicity was reported with 54 different antibiotics from 12 different classes of antibiotics. Of the 391 cases, 54% were male, and the median age was 54 years (range <1–94 years). Tables 1–3 show results by antibiotic class and individual antibiotics for which 10 or more cases of AAE were reported. Antibiotics with fewer than 10 reported cases of AAE were compiled under the heading "other" for each antibiotic class.

Baseline characteristics and risk factors. Table 1 shows baseline characteristics of reported cases of AAE. Renal insufficiency was present in 25% of all cases. Baseline renal insufficiency was particularly common in cases of cephalosporin-associated encephalopathy (72% overall for cephalosporins, 70% cefepime, 92% ceftazidime), but was present in only 3%–22% of cases reported for other antibiotic classes. Baseline hepatic dysfunction (14% for metronidazole, <5% for other classes of antibiotics) and psychiatric history (≤20% for all classes) were uncommon. It is possible that AAE is underreported in such patients since encephalopathy may be misattributed to hepatic encephalopathy or exacerbation of psychiatric illness in the setting of medical illness.

Clinical features associated with AAE. Table 2 shows the clinical characteristics of AAE. Psychosis (defined as presence of delusions or hallucinations) was present in 47% of cases overall and was most common among cases of encephalopathy associated with sulfonamides (68%), quinolones (67%), macrolides (63%), and penicillin procaine (68%). Psychosis was much less common in cases of encephalopathy associated with cephalosporins (13%) and metronidazole (24%).

Seizures were present in 14% of cases overall and were most common in AAE reported in association with penicillin (as an individual antibiotic) (38%) and cephalosporins (35%). For anti-mycobacterials, quinolones, macrolides, and metronidazole, 10% or fewer reported cases had seizures accompanying AAE. Seizures associated with cephalosporin-associated encephalopathy were nonconvulsive in 54% of patients, whereas nearly all other reported seizures were clinically apparent (with the exception of 2 cases of nonconvulsive seizures associated with quinolone-associated encephalopathy).

Table 2 Clinical features of antibiotic-associated encephalopathy

	Psychosis, n (%)	Seizure, n (%)	Nonconvulsive seizures, n (%)[a]	Myoclonus, n (%)	Cerebellar, n (%)	Median (range) days to toxicity	Median (range) days to resolution
Penicillins	40 (56)	11 (15)	0 (0)	19 (26)	0 (0)	1 (1-69)	1 (1-25)
Penicillin G procaine	23 (68)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1-69)	1 (1-2)
Penicillin	7 (29)	9 (38)	0 (0)	17 (71)	0 (0)	2 (1-8)	2 (1-8)
Other	10 (71)	2 (14)	0 (0)	2 (14)	1 (7)	2 (1-23)	3 (1-25)
Cephalosporins	9 (13)	24 (35)	13 (54)	28 (41)	0 (0)	3 (1-28)	3 (1-72)
Cefepime	1 (3)	10 (30)	6 (60)	11 (33)	0 (0)	4 (1-28)	2 (1-72)
Ceftazidime	2 (17)	6 (50)	4 (67)	6 (50)	0 (0)	4 (1-25)	4 (2-7)
Other	6 (25)	8 (33)	3 (38)	11 (46)	0 (0)	3 (1-7)	3 (1-47)
Antimycobacterials	30 (46)	2 (3)	0 (0)	1 (2)	4 (6)	14 (1-360)	5 (1-180)
Isoniazid	23 (47)	1 (2)	0 (0)	1 (2)	3 (6)	21 (1-360)	5 (1-180)
Other	7 (44)	1 (6)	0 (0)	0 (0)	1 (6)	7 (1-180)	10 (2-60)
Quinolones	42 (67)	6 (10)	2 (33)	6 (10)	2 (3)	2 (1-10)	3 (1-20)
Ciprofloxacin	17 (65)	3 (12)	1 (33)	4 (15)	0 (0)	2 (1-8)	4 (1-14)
Ofloxacin	7 (64)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1-3)	2 (1-20)
Other	18 (69)	3 (12)	1 (33)	2 (8)	2 (8)	2 (1-10)	3 (1-15)
Macrolides	34 (63)	1 (2)	0 (0)	1 (2)	1 (2)	2 (1-10)	3 (1-30)
Clarithromycin	26 (59)	0 (0)	0 (0)	1 (2)	1 (2)	3 (1-10)	3 (1-30)
Other	8 (80)	1 (10)	0 (0)	0 (0)	0 (0)	2 (1-7)	4 (1-21)
Metronidazole	7 (24)	3 (10)	0 (0)	0 (0)	14 (48)	19 (1-180)	13 (1-365)
Sulfonamides	13 (68)	3 (16)	0 (0)	0 (0)	0 (0)	3 (1-16)	2 (1-5)
Trimethoprim-sulfamethoxazole	10 (67)	2 (13)	0 (0)	0 (0)	0 (0)	3 (1-16)	1 (1-5)
Other	3 (75)	1 (25)	0 (0)	0 (0)	0 (0)	9 (2-15)	5 (4-5)

Symptoms associated with encephalopathy on clinical presentation or during course of antibiotic-associated encephalopathy. Days to resolution refers to time from stopping antibiotics to return to baseline cognition.

[a] Percentage refers to proportion of seizures that are nonconvulsive.

Myoclonus was found in 15% of cases overall. Myoclonus was most common in cases of encephalopathy associated with penicillin (71%) and cephalosporins (41%), but infrequent (≤10%) with other antibiotic classes. Cerebellar symptoms (defined as presence of ataxia or dysmetria) were seen in 5% of cases overall. They were most common with metronidazole-associated encephalopathy (48%) and reported in fewer than 6% of cases of AAE associated with other antibiotic classes. A cerebellar syndrome is well-described with metronidazole neurotoxicity,[17] so it should be noted that we excluded cases of metronidazole-associated cerebellar toxicity that did not cause accompanying encephalopathy. Language dysfunction was present in 3% of cases overall, and was most commonly seen with cefepime-associated encephalopathy, in which 27% of cases were described as having aphasia accompanying AAE.

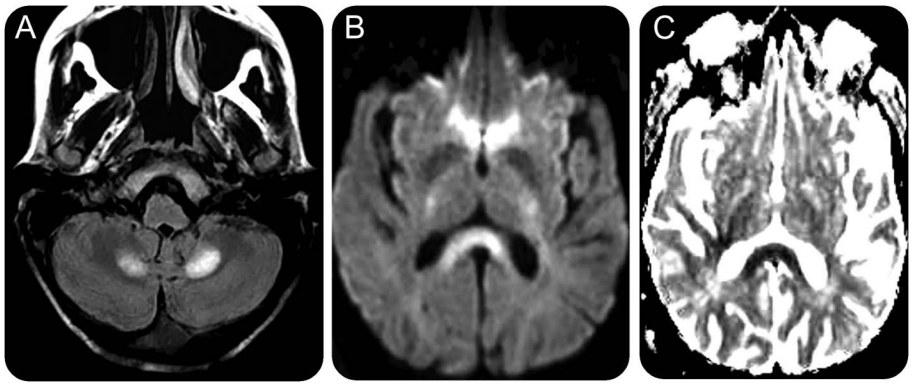
Time to onset and resolution of AAE. AAE is apparent within a median time of 5 days after antibiotic initiation for all individual antibiotics except isoniazid and metronidazole, for which the median length of time from antibiotic initiation to emergence of encephalopathy was approximately 3 weeks. However, a broad range of times to AAE onset were seen across all antibiotics, from first dose effects to emergence months after initiation of treatment. Time to resolution of encephalopathy after antibiotic discontinuation was within a median of 5 days for most antibiotic classes, with the exception of metronidazole, for which median time to resolution was 13 days.

Laboratory investigations in AAE. Table 3 shows the results of investigations performed in reported cases of AAE. MRI of the brain was abnormal in all cases of metronidazole-associated encephalopathy, but normal in all others, with the exception of one case of cefditoren pivoxil toxicity in the setting of acquired carnitine deficiency.[18] The typical pattern of MRI changes in metronidazole-associated neurotoxicity is T2 hyperintensities in the dentate nuclei of the cerebellum with variable involvement of the brainstem, corpus callosum, or other regions (figure 1).[17] The isolated case of cefditoren pivoxil toxicity reported bilateral frontal subcortical T2 MRI hyperintensities.[18] CT of the brain was normal in all cases except for one case of cerebellar hypodensity with metronidazole toxicity[19] and one report of left thalamic hypodensity with imipenem toxicity associated with generalized seizures and epileptiform discharges on EEG.[20]

Table 3 Brain MRI and EEG abnormalities in antibiotic-associated encephalopathy

	Total MRI (% abnormal)	Total EEG (% abnormal)	EEG with seizures or epileptiform discharges, n (% of abnormal EEG)	EEG with slowing/ triphasic, n (% of abnormal EEG)
Penicillins	5 (0)	11 (55)	2 (33)	6 (100)
Penicillin G procaine	3 (0)	1 (0)	0 (0)	0 (0)
Penicillin	0 (0)	6 (83)	2 (40)	5 (100)
Other	2 (0)	4 (25)	0 (0)	1 (100)
Cephalosporins	11 (9)	42 (95)	22 (55)	23 (58)
Cefepime	6 (0)	22 (100)	12 (55)	14 (64)
Ceftazidime	1 (0)	7 (100)	6 (86)	1 (14)
Other	4 (25)	13 (85)	4 (36)	8 (73)
Antimycobacterials	3 (0)	15 (67)	1 (10)	8 (80)
Isoniazid	2 (0)	13 (69)	1 (11)	7 (78)
Other	1 (0)	2 (50)	0 (0)	1 (100)
Quinolones	16 (0)	19 (47)	4 (44)	6 (67)
Ciprofloxacin	4 (0)	6 (83)	2 (40)	3 (60)
Ofloxacin	4 (0)	4 (0)	0 (0)	0 (0)
Other	8 (0)	9 (44)	2 (50)	3 (75)
Macrolides	6 (0)	8 (25)	0 (0)	2 (100)
Clarithromycin	4 (0)	6 (33)	0 (0)	2 (100)
Other	2 (0)	2 (0)	0 (0)	0 (0)
Metronidazole	15 (100)	4 (50)	0 (0)	2 (100)
Sulfonamides	2 (0)	1 (100)	0 (0)	1 (100)
Trimethoprim-sulfamethoxazole	2 (0)	1 (100)	0 (0)	1 (100)
Other	0 (0)	0 (0)	0 (0)	0 (0)

Figure 1 MRI in metronidazole neurotoxicity



(A) Fluid-attenuated inversion recovery sequence shows characteristic hyperintensities in bilateral deep cerebellar nuclei. Restricted diffusion in splenium of corpus callosum with metronidazole toxicity is shown in diffusion-weighted imaging (B) and apparent diffusion coefficient (C) sequences.

EEG was abnormal in 70% of cases of AAE in which EEG was performed. EEG was abnormal in nearly all cases of cephalosporin-associated encephalopathy in which EEG was obtained (95%). EEG abnormalities were also common with penicillin (83%), ciprofloxacin (83%), and isoniazid (69%), but EEG was performed much less frequently in patients with encephalopathy associated with these antibiotics, limiting interpretation. The most common EEG abnormalities were nonspecific signs of encephalopathy such as slowing and generalized periodic discharges with triphasic morphology. EEG revealed epileptiform discharges or seizures in 28% of cases in which EEG was performed, including 55% of cases of cephalosporin-associated encephalopathy, 44% of quinolone-associated encephalopathy, and 40% of penicillin-associated encephalopathy, but in no cases of macrolide-, metronidazole-, or sulfonamide-associated encephalopathy.

Cefepime was the only antibiotic for which more than 10 reports of serum drug concentration during toxicity were reported alongside detailed clinical reports. From manufacturer-reported pharmacokinetic data to the United States Food and Drug Administration, cefepime trough levels in healthy individuals are generally between 0.2 and 1.1 mg/L depending on the dose.[21] The median serum cefepime concentration during toxicity was 38 mg/L (range 15–284 mg/L from 13 reports). The CSF level during toxicity was measured in 2 cases with values of 2.4 mg/L (serum concentration of 81 mg/L) and 18 mg/L (serum concentration of 284 mg/L). In a study correlating cefepime trough levels with neurotoxicity, the 50% probability of neurologic toxicity occurred at trough level of 22 mg/L.[22]

Strength of association of antibiotic and AAE. The median Naranjo scale score for all antibiotic classes was 4, indicating that the association described is possible in most cases. The median score was low since all reported cases by definition had an active infection that could not be definitively excluded as a potential cause of encephalopathy; if this strict interpretation of the Naranjo scale is loosened for patients with non-CNS infections, the median score would be 5, indicating probable association.

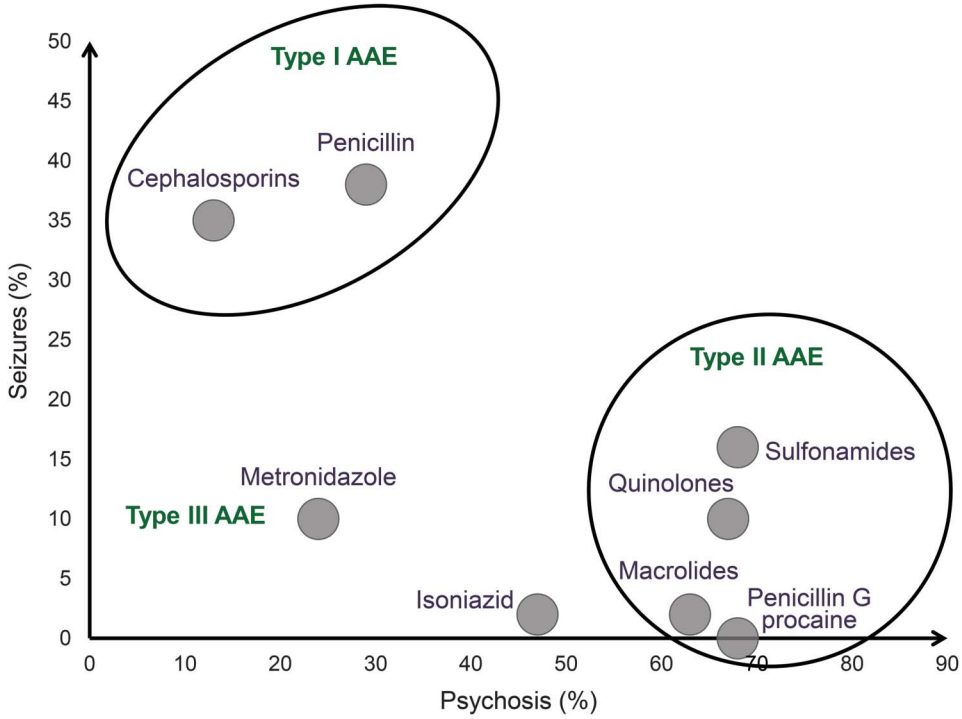
Three distinct clinical phenotypes of AAE. Based on the above data, 3 clinical phenotypes of AAE emerge with respect to clinical symptoms, temporal evolution, and laboratory abnormalities (figure 2). We classify these here as type 1, type 2, and type 3 AAE. These clinical phenotypes not only are useful in improving diagnostic recognition of AAE associated with particular antibiotics but also provide clinical grounds for an understanding of the pathophysiology underlying encephalopathy caused by different antibiotics (see Pathophysiology of AAE).

Type 1 AAE is characterized by onset within days of antibiotic initiation, common occurrence of myoclonus or seizures, abnormal EEG, normal MRI, and resolution within days. This is the clinical phenotype seen with penicillin (as an individual antibiotic) and cephalosporins. Cephalosporin-associated encephalopathy was reported most commonly in the setting of renal insufficiency.

Type 2 AAE is marked by onset within days of antibiotic initiation, frequent occurrence of psychosis, rare occurrence of seizures, infrequently abnormal EEG (which is more commonly nonspecific rather than epileptic), normal MRI, and resolution within days. This is the clinical phenotype seen in association with procaine penicillin, sulfonamides, fluoroquinolones, and macrolides.

Type 3 AAE, seen only with metronidazole, is characterized by onset weeks after initiation, frequent occurrence of cerebellar dysfunction, rare seizures,

Figure 2 Types of antibiotic-associated encephalopathy



Antibiotic classes and individual antibiotics (penicillin, procaine penicillin, metronidazole, and isoniazid) plotted in a graph that shows the relationship between presence of seizures (vertical axis, percentage of cases) and presence of psychosis (horizontal axis, percentage of cases). The types of toxicity are circled on the graph showing distinct characteristics of types I, II, and III antibiotic-associated encephalopathy (AAE). Isoniazid does not fit into any of the 3 subtypes.

rare and nonspecific EEG abnormalities, and omnipresence of abnormal MRI.

Isoniazid did not fit clearly into any of these categories: time to onset is weeks to months as with metronidazole, psychosis is common, seizures are rare, and EEG is frequently abnormal but nonspecifically so. We did not include cases of isoniazid intoxication due to overdose, in which the encephalopathy begins immediately and seizures are common.

PATHOPHYSIOLOGY OF AAE

Type 1 AAE (seizure/myoclonus). Type 1 AAE is thought to be caused by disruption of inhibitory synaptic transmission leading to excitotoxicity. The most commonly implicated receptor is the ligand-gated ion channel γ-aminobutyric acid class A receptor ($GABA_AR$). Activation of $GABA_AR$ by endogenous GABA results in intracellular influx of chloride ions creating an inhibitory postsynaptic potential (IPSP) that increases the threshold for generation of an action potential.[23] β-lactams impede inhibitory neurotransmission at $GABA_AR$ through a variety of mechanisms, causing central excitotoxicity.[15,24–26] β-lactams can bind either noncompetitively (e.g., penicillins) or competitively (e.g., cephalosporins) to $GABA_AR$.[27,28] In animal models, direct cortical application of penicillins leads to decreased IPSPs and increased burst properties of excitatory neurons, which is the likely pathophysiologic basis of encephalopathy, myoclonus, and seizures related to β-lactam neurotoxicity.[29–33] The affinity of β-lactams for $GABA_AR$ is dependent on the β-lactam ring, since cleavage of this ring with penicillinase abolishes the excitatory effects of penicillin applied directly to the cortex in vivo.[34] Other chemical structural differences between antibiotics also affect whether a given antibiotic will cause neurotoxicity. For example, carbapenems with more basic amino acid side chains at the C2 position (e.g., imipenem) more strongly inhibit $GABA_AR$ and may be more epileptogenic.[35]

Type 2 AAE (psychosis predominant). The distinct neuropsychiatric features found in type 2 AAE closely resemble drug-induced psychotic syndromes caused by perturbations of the D2 dopamine and NMDA glutamate receptors (e.g., cocaine, amphetamines, and phencyclidine). Studies of neurotoxic effects of quinolones and macrolides are limited. In an in vitro study examining rat hippocampal slices treated with quinolones at therapeutic concentrations, neuronal population spikes appeared to be modulated primarily through the NMDA glutamate receptor in a concentration-dependent manner.[36] No direct evidence exists for the effects of quinolones on the dopaminergic system, although a Tourette-like syndrome has been reported with ofloxacin, suggesting a potential

interaction with the dopaminergic system.[37] In Type 2 AAE caused by procaine penicillin, also termed Hoigne syndrome,[38] procaine is likely responsible for the neurotoxic effects rather than penicillin. Procaine is pharmacologically similar to cocaine and, in addition to blocking sodium channels, has been shown to partially block the presynaptic dopamine transporter, leading to increased dopamine levels in the synapse.[39] Procaine administration induces anxiety and somatization in normal patients,[40] is experienced as similar to cocaine in cocaine addicts,[41] and causes increased blood flow on SPECT imaging in reward-processing areas such as the ventral striatum in a pattern similar to cocaine administration.[42,43]

Type 3 AAE (encephalopathy with cerebellar signs). Unlike the other subtypes of AAE, metronidazole toxicity results in characteristic reversible MRI signal abnormalities in the cerebellar dentate nuclei, dorsal brainstem, or splenium of the corpus callosum.[44] Both increased and decreased diffusivity have been observed in MRI, suggesting the variable presence of both vasogenic and cytotoxic edema, respectively.[44] The pathophysiologic basis of metronidazole neurotoxicity appears to be related to free radical formation and altered thiamine metabolism. Derivatives of 5-nitroimidazole such as metronidazole interact in rat adrenal tissues to form nitrogen anion radicals, supraoxide free radicals, and hydrogen peroxide, which may be neurotoxic.[45] However, this mechanism does not explain the region-specific neurotoxicity of metronidazole, which may be better explained by effects on the thiamine pathway. Metronidazole is enzymatically converted into a thiamine analog that impairs thiamine phosphorylation in vitro.[46] Rats treated with toxic doses of metronidazole show lesions in the cerebellum, superior olive, and pons that histopathologically appear identical to thiamine-deficient rat brains.[47] There is also overlap between the neuroimaging features in metronidazole toxicity and those observed in malnourished patients with nonalcoholic Wernicke encephalopathy.[48,49] In particular, unlike in alcoholic Wernicke encephalopathy, mammillary body imaging abnormalities tend to be less frequent in Wernicke encephalopathy from non-alcohol-related etiologies, similar to metronidazole toxicity.[49] However, other characteristic lesions found in all types of Wernicke encephalopathy such as medial thalamic lesions are usually not found in metronidazole toxicity, suggesting likely differences in pathophysiology as well.

The fact that isoniazid-associated encephalopathy does not fit clearly into any of the 3 proposed phenotypes may reflect the unique pathogenesis of isoniazid neurotoxicity, which impairs presynaptic production of GABA over time.[50]

Pharmacokinetics and patient-specific factors. In addition to the mechanisms outlined above, pharmacokinetics of individual antibiotics and patient comorbidities also play a role in the development of AAE. In animal models, hydrophobic penicillins more readily cross into the brain and result in neurotoxicity.[51] Imipenem, compared to other carbapenems, has slower rate of clearance from CSF, which may contribute to increased neurotoxicity with imipenem compared to other carbapanems.[52] Patient characteristics such as age, renal failure, and pre-existing cerebral disease (e.g., Parkinson disease, stroke, or head trauma) increase the risk of antibiotic-associated neurotoxicity for some though not all antibiotics.[14,15,50] Renal insufficiency can increase the risk of antibiotic neurotoxicity not only by increasing serum antibiotic concentrations but also by causing proteinuria leading to lower serum protein levels and increased antibiotic bioavailability.[53] Decreased serum protein levels from proteinuria in renal insufficiency also decrease protein glycation and carbamylation leading to alterations in the integrity of the blood–brain barrier, which increases antibiotic entry into the CNS.[54] The use of iron, calcium, and aluminum supplements in patients with renal insufficiency can also increase gastrointestinal absorption of certain antibiotics such as quinolones.[54]

LIMITATIONS Our review has several limitations. First, a review relying solely on case reports and small series is subject to selection and publication bias. This may be one reason why the median age for AAE in reported cases is relatively young at 54 years whereas it would be expected that an older population would be even more susceptible to adverse effects from antibiotics. Antibiotics may be an underrecognized factor in delirium in the elderly labeled as multifactorial, and therefore cases of AAE in the elderly may be underreported. Second, since different case reports and series described patients in varying degrees of detail, missing information may lead to imprecise estimates of the prevalence of symptoms and laboratory findings reported. However, by reviewing a large number of cases, we sought to decrease the effects of such variability on our analysis. Missing information may have also contributed to the designation of possible association between antibiotic and encephalopathy for the majority of reported cases based on the Naranjo score since there was often not enough clinical information to definitively exclude another potential contributing factor to encephalopathy in such patients (see Strength of association of antibiotic and AAE). Fourth, although we have attempted to group antibiotics into categories (types I, II, and III), statistical comparisons between antibiotic classes were not possible due to the heterogeneity in reported cases with respect to both clinical factors and level of detail reported in individual reports. Finally, we restricted the analyses to cases describing altered

cognition with antibiotics. There is also a substantial literature on seizures associated with antibiotics. It is possible that many reports focusing on seizures with antibiotics (such as with carbapenems) underreport encephalopathy and hence were excluded from our analysis.

DISCUSSION AAE is an underrecognized cause of altered mental status in hospitalized patients, and should be considered in all patients who develop delirium after initiation of antibiotics. Although the clinical features of AAE are diverse, they can be divided into 3 core clinical syndromes associated with particular antibiotics and unique underlying pathophysiologic mechanisms of neurotoxicity. Increased recognition of AAE can lead to earlier discontinuation of causative medications, reducing time spent in a delirious state and thereby improving outcomes in patients with delirium.

AUTHOR CONTRIBUTIONS

S.B.: performed all statistical analyses, conception of study, acquisition of data, analysis of data, writing of manuscript. R.R.D.: acquisition of data, analysis of data, writing of manuscript. P.R.: acquisition of data, analysis of data, writing of manuscript. L.N.G.C.: acquisition of data, analysis of data, writing of manuscript. A.L.B.: conception of study, acquisition of data, analysis of data, writing of manuscript.

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REFERENCES

1. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet 2014;383:911–922.
2. Pompei P, Foreman M, Rudberg MA, Inouye SK, Braund V, Cassel CK. Delirium in hospitalized older persons: outcomes and predictors. J Am Geriatr Soc 1994;42:809–815.
3. Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001;27:1892–1900.
4. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753–1762.
5. Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. Crit Care 2008;12(suppl 3):S3.
6. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to Poor hospital outcomes? J Gen Intern Med 1998;13:234–242.
7. Marcantonio ER, Kiely DK, Simon SE, et al. Outcomes of older people admitted to postacute facilities with delirium. J Am Geriatr Soc 2005;53:963–969.
8. Abelha FJ, Luís C, Veiga D, et al. Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. Crit Care 2013;17:R257.
9. Lin SM, Liu CY, Wang CH, et al. The impact of delirium on the survival of mechanically ventilated patients. Crit Care Med 2004;32:2254–2259.
10. Leslie DL, Zhang Y, Holford TR, Bogardus ST, Leo-Summers LS, Inouye SK. Premature death associated with delirium at 1-year follow-up. Arch Intern Med 2005;165:1657–1662.
11. Inouye SK, Bogardus ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340:669–676.
12. Fugate JE, Kalimullah EA, Hocker SE, Clark SL, Wijdicks EF, Rabinstein AA. Cefepime neurotoxicity in the intensive care unit: a cause of severe, underappreciated encephalopathy. Crit Care 2013;17:R264.
13. Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis 2005;41(suppl 2):S144–S157.
14. Mattappalil A, Mergenhagen KA. Neurotoxicity with antimicrobials in the elderly: a review. Clin Ther 2014;36:1489–1511.e4.
15. Grill MF, Maganti R. Cephalosporin-induced neurotoxicity: clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. Ann Pharmacother 2008;42:1843–1850.
16. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–245.
17. Kuriyama A, Jackson JL, Doi A, Kamiya T. Metronidazole-induced central nervous system toxicity: a systematic review. Clin Neuropharmacol 2011;34:241–247.
18. Kim H, Chu K, Jung KH, Lee ST, Kim JM, Lee SK. Acquired encephalopathy associated with carnitine deficiency after cefditoren pivoxil administration. Neurol Sci 2012;33:1393–1396.
19. Gupta AK, Agarwal MP, Avasthi R, Bhadoria DP, Rohatgi N. Metronidazole-induced neurotoxicity. J Assoc Physicians India 2003;51:617–618.
20. Fernández-Torre JL, Velasco M, Gutiérrez R, Fernández-Sampedro M. Encephalopathy secondary to imipenem therapy. Clin EEG Neurosci 2004;35:100–103.
21. Drugs@FDA. FDA Approved Drug Products [Internet]. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/050679s031lbl.pdf. Accessed May 24, 2015.
22. Lamoth F, Buclin T, Pascual A, et al. High cefepime plasma concentrations and neurological toxicity in febrile neutropenic patients with mild impairment of renal function. Antimicrob Agents Chemother 2010;54:4360–4367.
23. Chow KM, Hui AC, Szeto CC. Neurotoxicity induced by beta-lactam antibiotics: from bench to bedside. Eur J Clin Microbiol Infect Dis 2005;24:649–653.
24. De Sarro A, De Sarro G. Adverse reactions to fluoroquinolones. an overview on mechanistic aspects. Curr Med Chem 2001;8:371–384.
25. Akahane K, Tsutomi Y, Kimura Y, Kitano Y. Levofloxacin, an optical isomer of ofloxacin, has attenuated epileptogenic activity in mice and inhibitory potency in GABA receptor binding. Chemotherapy 1994;40:412–417.
26. Akahane K, Sekiguchi M, Une T, Osada Y. Structure-epileptogenicity relationship of quinolones with special reference to their interaction with gamma-aminobutyric acid receptor sites. Antimicrob Agents Chemother 1989;33:1704–1708.

27. Sugimoto M, Fukami S, Kayakiri H, et al. The beta-lactam antibiotics, penicillin-G and cefoselis have different mechanisms and sites of action at GABA(A) receptors. Br J Pharmacol 2002;135:427–432.
28. Lindquist CEL, Dalziel JE, Cromer BA, Birnir B. Penicillin blocks human alpha 1 beta 1 and alpha 1 beta 1 gamma 2S GABAA channels that open spontaneously. Eur J Pharmacol 2004;496:23–32.
29. Davidoff RA. Penicillin and inhibition in the cat spinal cord. Brain Res 1972;45:638–642.
30. Dingledine R, Gjerstad L. Penicillin blocks hippocampal IPSPs, unmasking prolonged EPSPs. Brain Res 1979;168:205–209.
31. Meyer H, Prince D. Convulsant actions of penicillin: effects on inhibitory mechanisms. Brain Res 1973;53:477–482.
32. Wong RK, Prince DA. Dendritic mechanisms underlying penicillin-induced epileptiform activity. Science 1979;204:1228–1231.
33. Van Duijn H, Schwartzkroin PA, Prince DA. Action of penicillin on inhibitory processes in the cat's cortex. Brain Res 1973;53:470–476.
34. Gutnick MJ, Prince DA. Penicillinase and the convulsant action of penicillin. Neurology 1971;21:759–764.
35. Sunagawa M, Matsumura H, Sumita Y, Nouda H. Structural features resulting in convulsive activity of carbapenem compounds: effect of C-2 side chain. J Antibiot (Tokyo) 1995;48:408–416.
36. Schmuck G, Schürmann A, Schlüter G. Determination of the excitatory potencies of fluoroquinolones in the central nervous system by an in vitro model. Antimicrob Agents Chemother 1998;42:1831–1836.
37. Thomas RJ, Reagan DR. Association of a Tourette-like syndrome with ofloxacin. Ann Pharmacother 1996;30:138–141.
38. Hoigne R, Schoch K. Anaphylactic shock and acute nonallergic reactions following procaine-penicillin. Schweiz Med Wochenschr 1959;89:1350–1356.
39. Graham JH, Maher JR, Robinson SE. The effect of cocaine and other local anesthetics on central dopaminergic neurotransmission. J Pharmacol Exp Ther 1995;274:707–717.
40. Adinoff B, Devous MD, Cooper DC, Best SE, Harris TS, Williams MJ. Neural Response to Lidocaine in healthy subjects. Psychiatry Res 2009;173:135–142.
41. Adinoff B, Brady K, Sonne S, Mirabella RF, Kellner CH. Cocaine-like effects of intravenous procaine in cocaine addicts. Addict Biol 1998;3:189–196.
42. Adinoff B, Devous MD, Best S, George MS, Alexander D, Payne K. SPECT following intravenous procaine in cocaine addiction. Ann NY Acad Sci 1999;877:807–810.
43. Adinoff B, Devous MD, Best SM, George MS, Alexander D, Payne K. Limbic responsiveness to procaine in cocaine-addicted subjects. Am J Psychiatry 2001;158:390–398.
44. Kim E, Na DG, Kim EY, Kim JH, Son KR, Chang KH. MR imaging of metronidazole-induced encephalopathy: lesion distribution and diffusion-weighted imaging findings. AJNR Am J Neuroradiol 2007;28:1652–1658.
45. Rao DN, Mason RP. Generation of nitro radical anions of some 5-nitrofurans, 2- and 5-nitroimidazoles by norepinephrine, dopamine, and serotonin: a possible mechanism for neurotoxicity caused by nitroheterocyclic drugs. J Biol Chem 1987;262:11731–11736.
46. Alston TA, Abeles RH. Enzymatic conversion of the antibiotic metronidazole to an analog of thiamine. Arch Biochem Biophys 1987;257:357–362.
47. von Rogulja P, Kovac W, Schmid H. Metronidazole encephalopathy in rats. Acta Neuropathol 1973;25:36–45.
48. Zuccoli G, Pipitone N, Santa Cruz D. Metronidazole-induced and Wernicke encephalopathy: two different entities sharing the same metabolic pathway? AJNR Am J Neuroradiol 2008;29:E84; author reply E85.
49. Zuccoli G, Pipitone N. Neuroimaging findings in acute Wernicke's encephalopathy: review of the literature. AJR Am J Roentgenol 2009;192:501–508.
50. Snavely SR, Hodges GR. The neurotoxicity of antibacterial agents. Ann Intern Med 1984;101:92–104.
51. Weihrauch TR, Köhler H, Höffler D. Cerebral toxicity of penicillins in relation to their hydrophobic character. Naunyn Schmiedebergs Arch Pharmacol 1975;289:55–64.
52. de Sarro A, Imperatore C, Mastroeni P, de Sarro G. Comparative convulsant potencies of two carbapenem derivatives in C57 and DBA/2 mice. J Pharm Pharmacol 1995;47:292–296.
53. Manian FA, Stone WJ, Alford RH. Adverse antibiotic effects associated with renal insufficiency. Rev Infect Dis 1990;12:236–249.
54. Chow KM, Szeto CC, Hui ACF, Li PKT. Mechanisms of antibiotic neurotoxicity in renal failure. Int J Antimicrob Agents 2004;23:213–217.

The term ictal epileptic headache,[5] instead of HE, should be used to define a migraine of epileptic origin in order to provide a framework for clinical diagnosis, investigation, and therapeutic approaches for each patient and to facilitate communication among clinicians.

Author Response: Zubeda Sheikh, East Rutherford; David Marks, Newark, NJ: We appreciate the comments of Belcastro et al. regarding our recent report.[1] In the ICHD-3 classification, headaches secondary to seizures were classified as HE or postictal headache.[6] Belcastro et al. suggested the term ictal epileptic headache for a headache that is the only ictal clinical manifestation of an epileptic seizure, is synchronous with the ictal EEG discharge, and responds to IV antiepileptic medications.[3,7] Belcastro et al. differentiate an ictal epileptic headache from HE, which they propose should be reserved for an epileptic headache either associated with or having synchronous or sequential sensorimotor manifestations.[8]

The patient described had prominent visual hallucinations, hemianopsia, and epileptic nystagmus accompanying the headache.[1] Due to the presence of these sensorimotor manifestations affecting the visual system, the diagnosis is more consistent with the diagnostic criteria outlined for HE rather than the criteria proposed for ictal epileptic headache. Until a better classification system for headaches caused by seizures is available, we propose the continued use of the ICHD-3 classification.

1. Sheikh Z, Georgsson H, Marks D. Pearls & Oy-sters: hemicrania epileptica: unfolding the mystery of an unremitting migraine. Neurology 2015;85:e190–e192.
2. Belcastro V, Striano P, Pierguidi L, Calabresi P, Tambasco N. Ictal epileptic headache mimicking status migrainosus: EEG and DWI-MRI findings. Headache 2011;51:160–162.
3. Parisi P, Verrotti A, Costa P, et al. Diagnostic criteria currently proposed for "ictal epileptic headache": perspectives on strengths, weaknesses and pitfalls. Seizure 2015;31:56–63.
4. Perucca P, Terzaghi M, Manni R. Status epilepticus migrainosus: clinical, electrophysiologic, and imaging characteristics. Neurology 2010;75:373–374.
5. Parisi P, Striano P, Trenite DG, et al. "Ictal epileptic headache": recent concepts for new classifications criteria. Cephalalgia 2012;32:723–724.
6. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 2013;33:629–808.
7. Belcastro V, Striano P, Kasteleijn-Nolst Trenite DG, Villa MP, Parisi P. Migralepsy, hemicrania epileptica, post-ictal headache and "ictal epileptic headache": a proposal for terminology and classification revision. J Headache Pain 2011;12:289–294.
8. Parisi P, Striano P, Villa MP, Belcastro V. Ictal epileptic headache: terms do matter in clinical practice! reply to Cianchetti et al. Cephalalgia 2013;33:426.

CORRECTIONS

Antibiotic-associated encephalopathy

In the Views & Reviews article "Antibiotic-associated encephalopathy" by S. Bhattacharyya et al. (Neurology 2016;86:963–971), there is an error in the paragraph prior to "Limitations." The last sentence should read "The use of iron, calcium, and aluminum supplements in patients with renal insufficiency can also alter gastrointestinal absorption of certain antibiotics such as quinolones[54]" rather than "increase" as originally published. The authors regret the error.

Use of amyloid-PET to determine cutpoints for CSF markers: A multicenter study

In the article "Use of amyloid-PET to determine cutpoints for CSF markers: A multicenter study" by M.D. Zwan et al. (Neurology 2016;86:50–58), concordance was incorrectly defined in the Methods section. The correct definition is "the proportion of individuals with an identical classification of both biomarkers, e.g., normal CSF biomarkers (not Alzheimer-like) (either $A\beta_{42}$ alone or $A\beta_{42}$/tau) and normal (negative) amyloid-PET or abnormal (Alzheimer-like) CSF biomarkers (either $A\beta_{42}$ alone or $A\beta_{42}$/tau) and abnormal (positive) amyloid-PET." In addition, the patient numbers described in the Results section under "Concordance between CSF $A\beta_{42}$/tau ratio and amyloid-PET" are incorrect and should have been 140, 218, 39, and 17, respectively, as shown in table 5. The authors regret the errors.

Author disclosures are available upon request (journal@neurology.org).