GIFTIGER SAMSTAG

10.06.2017	**Nebenwirkungen von A bis Z**
10.06.2017	… von Haut- und Hautanhangsgebilde
10.06.2017	… von Leber und Niere
10.06.2017	… von Herz und Lunge
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GIFTIGER SAMSTAG

10.06.2017 **Nebenwirkungen von A bis Z**

Antibiotika: Nebenwirkungen und Interaktionen
Antibiotika und das Gehirn
Antibiotika und das **periphere** Nervensystem

Erich Schmutzhard, Innsbruck

10.06.2017 **… von Gehirn und Nerven**

Eur J Clin Pharmacol (2004) 60: 373–375
DOI 10.1007/s00228-004-0787-3

SHORT COMMUNICATION

G. Brössner · K. Engelhardt · R. Beer · B. Pfausler
A. Georgopoulos · E. Schmutzhard

Accidental intrathecal infusion of cefotiam: clinical presentation and management

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Generalised **myocloni**
Agitated **psychosis**
Respiratory insufficiency – hypercapnia, hypoxemia
Rhabdomyolysis

➔ 5 Wochen NICU

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➔ 5 Wochen NICU **extra**

Antibiotic-Associated Delirium ➔ Seldom Identified, Now Categorized

Dr. **Shamik Bhattacharyya**, Department of Neurology, **Brigham and Women's Hospital** and **Harvard Medical School Boston**, MA 2016

VIEWS & REVIEWS

Antibiotic-associated encephalopathy

Neurology® 2016;86:963-971

Shamik Bhattacharyya, MD*
R. Ryan Darby, MD*
Pooja Raibagkar, MD
L. Nicolas Gonzalez Castro, MD, PhD
Aaron L. Berkowitz, MD, PhD

ZNS **Z**entrales **N**erven-**S**ystem

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.

Review of the clinical, radiologic, and electrophysiologic features of antibiotic-associated encephalopathy (AAE).

Antibiotika-assoziiertes Delirium
Antibiotika-assoziierte Enzephalopathie

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Antibiotika-assoziierte Enzephalopathie: 3 Phänotypen (entsprechend den klinischen Haupt-Symptomen)

antibiotic-associated encephalopathy 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 (mainly **metronidazole**).

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Antibiotika-assoziierte Enzephalopathie:

3 P (entsprechend den klinischen Haupt-Symptomen)

1. Ceph Pen
Epilept.Anfälle
Myocloni
Tage

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2. Gyrase-Hemmer
Makrolide
Procain-Pen
Psychot.Sy.
Tage

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3.
Metronidazol
Zerebell , MR
Wochen

Three clinical phenotypes:

Correlation with underlying pathophysiologic mechanisms of antibiotic neurotoxicity.

Familiarity with these **(pheno)types** of antibiotic toxicity can
-improve **timely diagnosis** of AAE and
-prompt **antibiotic discontinuation**,
-**reducing the time** patients spend in the delirious state

Thre **henoty**

Co ind hy nisms of
anti toxicit

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Delirium occurs in up to **half** of hospitalized patients (in part in elderlies) and up to **80%** of patients in **intensive care units**.

Delirium is associated with
- increased length of hospital stay,
- in-hospital complications,
- discharge to long-term care facilities,
- re-hospitalization from long-term care facilities,
- subsequent cognitive impairment,
- subsequent dependence, and
- increased in-hospital and 1-year mortality.

!

This has led to ongoing efforts to
- **recognize**,
- **prevent**, and
- **treat** delirium

to improve patient outcomes and reduce health care costs.

Although medications are a commonly considered reversible cause of encephalopathy, **antibiotics** are an **underrecognized etiology.**

Inouye et al 2014;
Ely et al 2001;
Ely et al 2004;
Girard et al 2008;
Marcantonio et al 2005;
Albelha et al 2013;
Leslie et al 2005;

Clinical Review & Education

RESULTS Ramelteon was associated with a lower risk of delirium (3% vs 32%; *P* = .003), with a relative risk of 0.09 (95% CI, 0.01-0.69). Even after risk factors were controlled for, ramelteon

From The JAMA Network

Ramelteon for Prevention of Delirium in Hospitalized Older Patients

Stany M. T. Perkisas, MD; Maurits F. J. Vandewoude, MD, PhD
JAMA May 5, 2015 Volume 313, Number 17

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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.

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.**

Review Article
Arun Mattappalil, Kari A. Mergenhagen **Neurotoxicity with Antimicrobials in the Elderly: A Review** Clinical Therapeutics, Volume 36, Issue 11, 1 November 2014, Pages 1489–1511

Fugate et al 2013
Owens et al 2014
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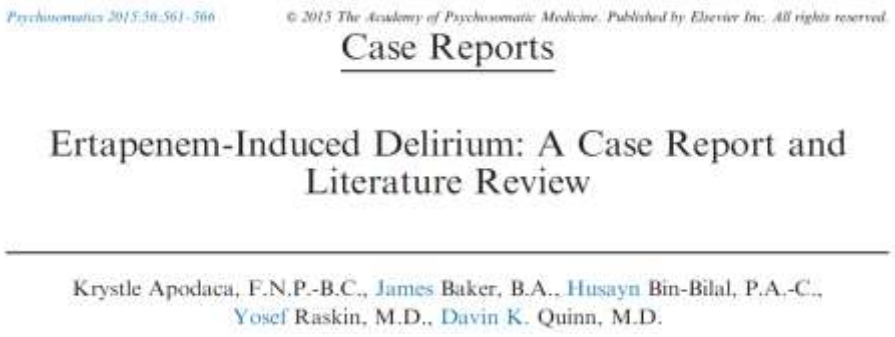
Apodaca et al 2015



Case Reports

Ertapenem-Induced Delirium: A Case Report and Literature Review

Krystle Apodaca, F.N.P.-B.C., James Baker, B.A., Husayn Bin-Bilal, P.A.-C., Yosef Raskin, M.D., Davin K. Quinn, M.D.

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Psychosomatics 2015:56:561–566

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Zur Erinnerung: bis zu 80% der (älteren) ICU PatientInnen entwickeln ein Delirium➔ bei 15/80 (= bei ca jedem/-r 5. bzw 6. ICU PatientIn) ist das Delir **antibiotika-assoziiert**

elderlies!

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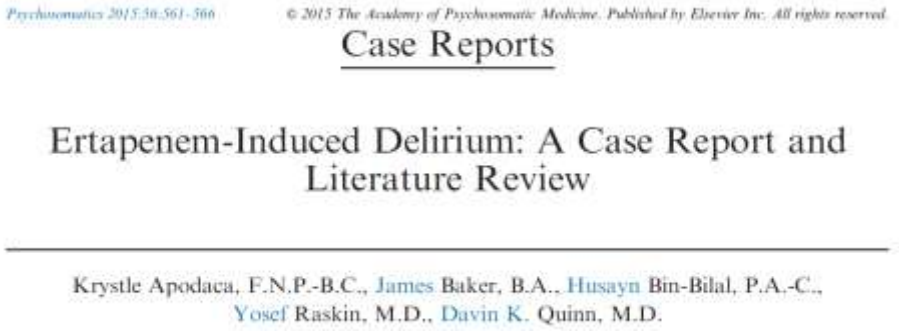

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Identification of AAE as a cause of delirium is **challenging** since **patients receiving antibiotics** often have

➔ **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.

In two comprehensive reviews of reported cases of AAE the

- **specific clinical features,**
- **EEG changes, and**
- **neuroimaging findings**

associated with encephalopathy from particular antibiotic classes and individual antibiotics are described.

AAE = Antibiotika Assoziierte Enzephalopathie

Three distinct clinical subtypes of AAE, each with unique pathophysiologic mechanisms can be differentiated

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VIEWS & REVIEWS

Antibiotic-associated encephalopathy

Neurology® 2016;86:963-971

CLINICAL CHARACTERISTICS OF AAE

In 391 individual cases from 1946 through 2013 inclusive, 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).

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VIEWS & REVIEWS

Antibiotic-associated encephalopathy

Neurology® 2016;86:963-971

plus ALTER

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).

In 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 **metabolic encephalopathy** or **exacerbation of psychiatric illness** in the setting of medical illness

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.

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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)
illin	7 (29)	9 (38)	0 (0)	17 (71)	0 (0)	2 (1-8)	2 (1-8)
	10 (71)	2 (14)	0 (0)	2 (14)	1 (7)	2 (1-23)	3 (1-25)
	9 (13)	24 (35)	13 (54)	28 (41)	0 (0)	3 (1-28)	3 (1-72)
	1 (3)	10 (30)	6 (60)	11 (33)	0 (0)	4 (1-28)	2 (1-72)
	2 (17)	6 (50)	4 (67)	6 (50)	0 (0)	4 (1-25)	4 (2-7)
	6 (25)	8 (33)	3 (38)	11 (46)	0 (0)	3 (1-7)	3 (1-47)
rals	30 (46)	2 (3)	0 (0)	1 (2)	4 (6)	14 (1-360)	5 (1-180)
azid	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.

2. Chin Macr
ProcPen
Psychot.Sy.
Tage

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)
[illegible]zid	23 (47)	1 (2)	0 (0)	1 (2)	3 (6)	21 (1-360)	5 (1-180)
	7 (44)	1 (6)	0 (0)	0 (0)	1 (6)	7 (1-180)	10 (2-60)
	42 (67)	6 (10)	2 (33)	6 (10)	2 (3)	2 (1-10)	3 (1-20)
	17 (65)	3 (12)	1 (33)	4 (15)	0 (0)	2 (1-8)	4 (1-14)
	7 (64)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1-3)	2 (1-20)
	18 (69)	3 (12)	1 (33)	2 (8)	2 (8)	2 (1-10)	3 (1-15)
	34 (63)	1 (2)	0 (0)	1 (2)	1 (2)	2 (1-10)	3 (1-30)
[illegible]romycin	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.

3. Metronidazol
Zerebell Sy., MR
Wochen

Clinical features associated with 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).

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, so it should be noted that we excluded cases of metronidazole-associated cerebellar toxicity that did not cause accompanying encephalopathy.

Kuriyama et al 2011

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**.

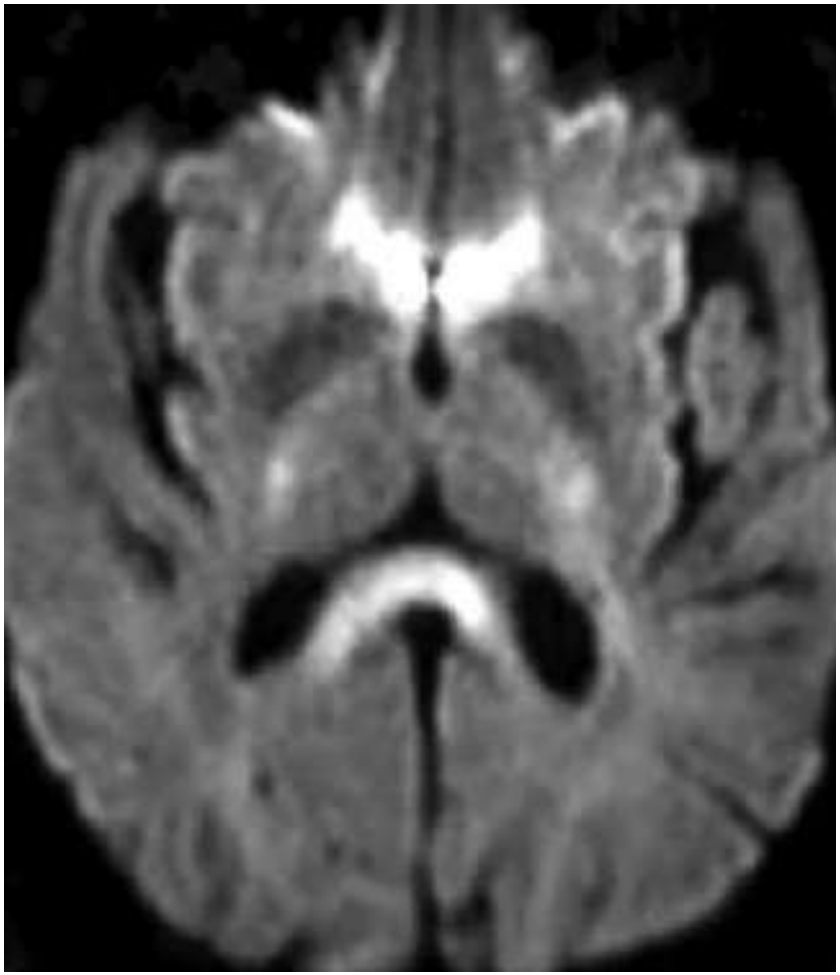
However, a broad range of times to AAE onset were seen across all antibiotics, from first dose effects to emergence months after initiation of treatment.

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.

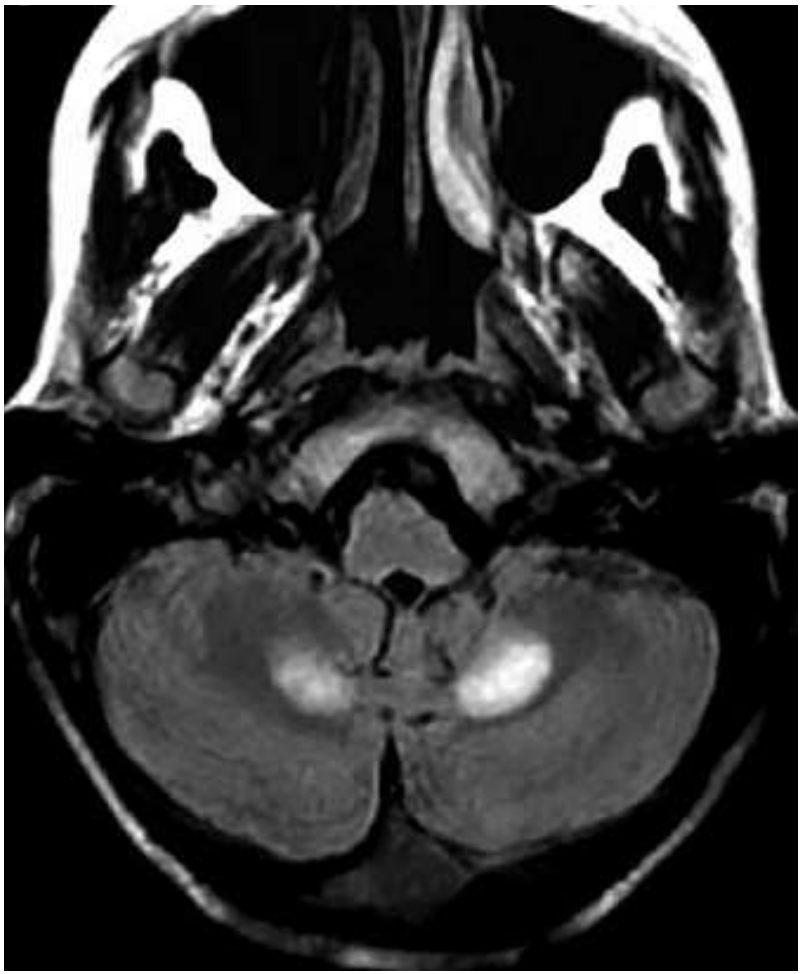
Table 3 Brain MRI and EEG abnor ties in antibiotic-associated encephalopathy

	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)

Metronidazol - Toxizität

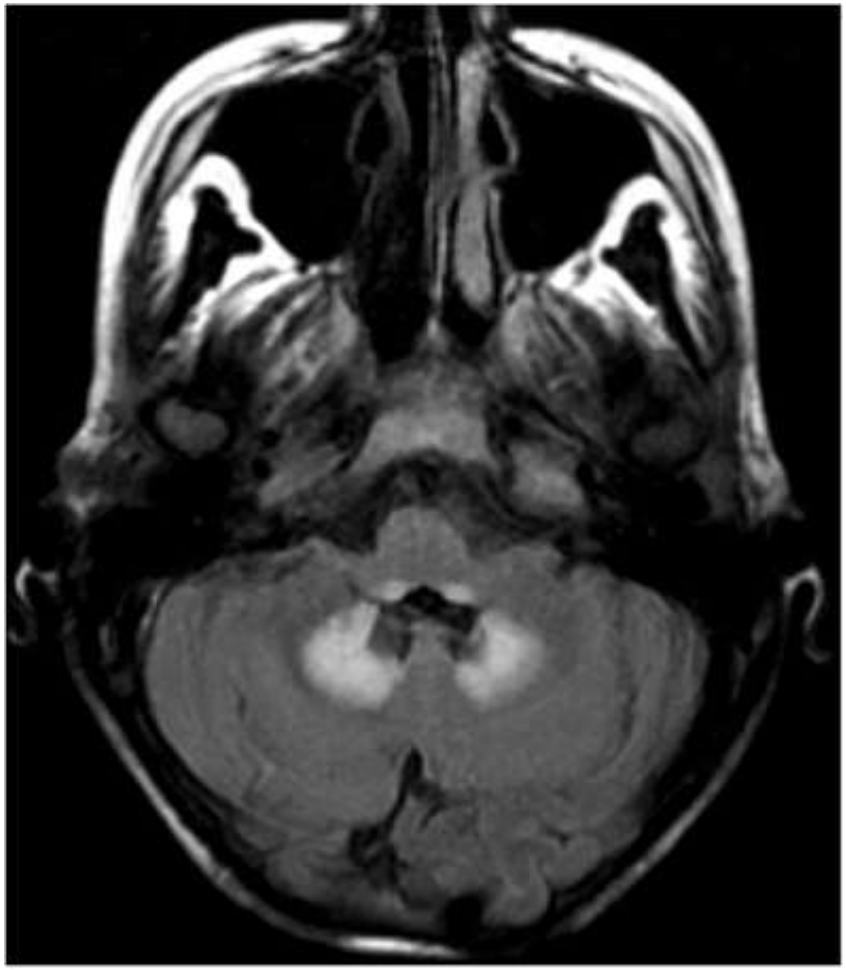


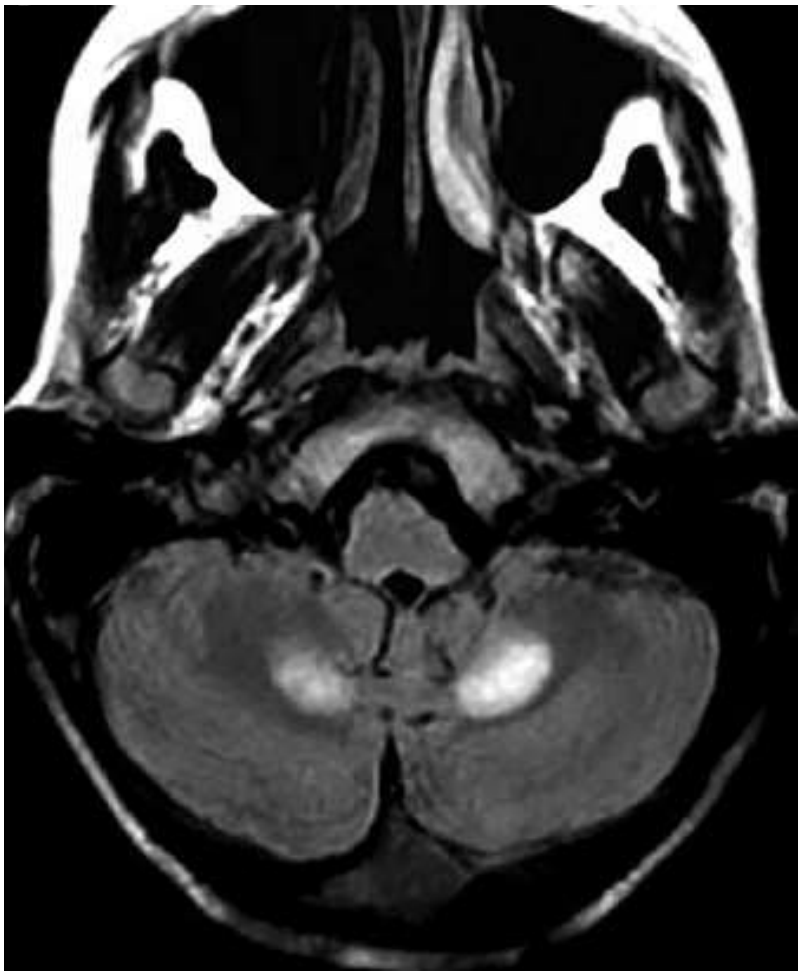
Diffusions-Wichtung



FLAIR

Metronidazol - Toxizität





FLAIR

Laboratory investigations in 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.

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.

Kim et al 2012;
Gupta et al 2003;
Fernandez-Torre et al 2004

The isolated case of cefditoren pivoxil toxicity reported bilateral frontal subcortical T2 MRI hyperintensities. CT of the brain was normal in all cases except for one case of cerebellar hypodensity with metronidazole toxicity and one report of left thalamic hypodensity with imipenem toxicity associated with generalized seizures and epileptiform discharges on EEG.

EEG was **abnormal** in 70% of cases of AAE in which EEG was performed.

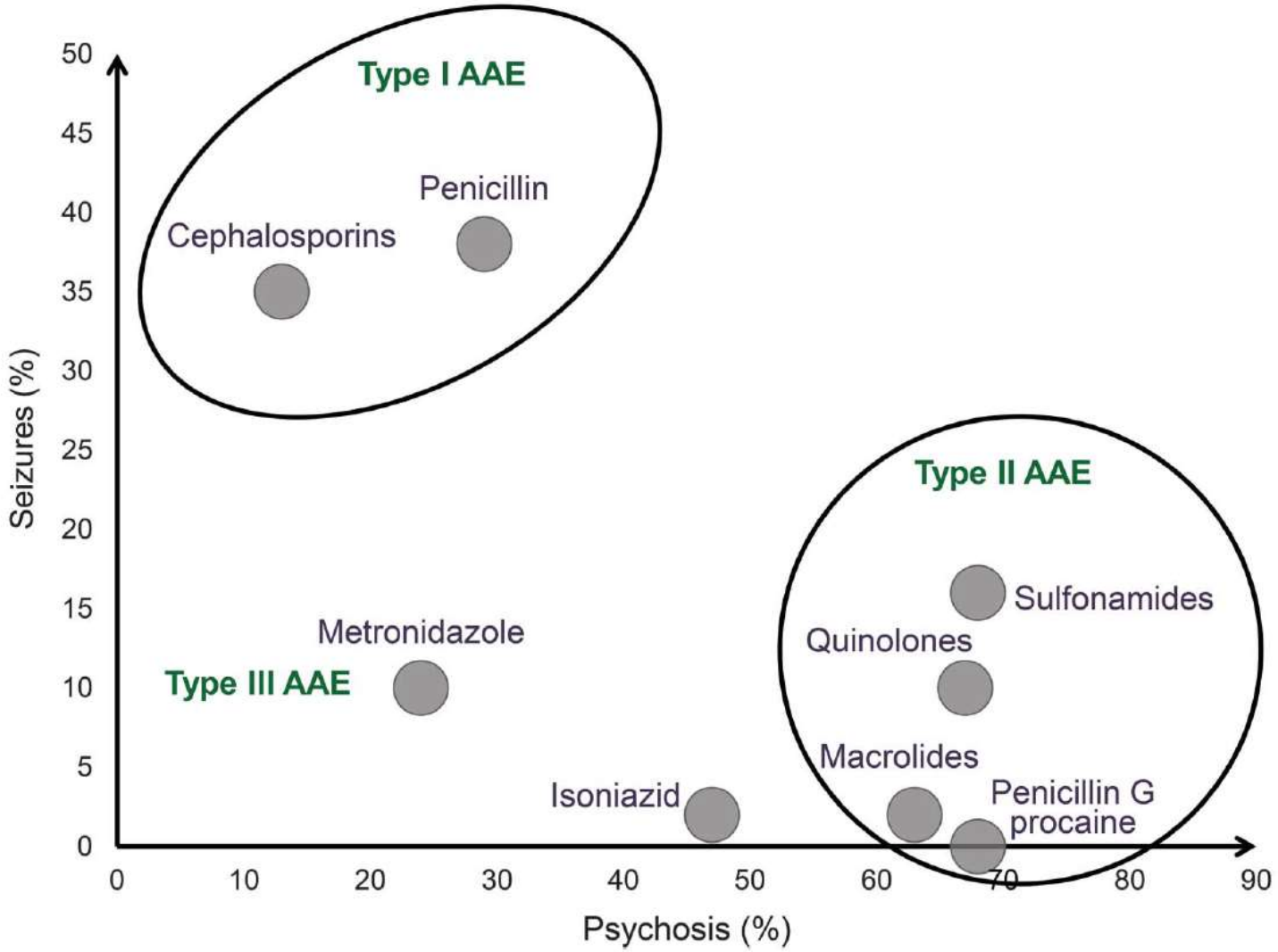
EEG was **abnormal** in nearly all cases of **cephalosporin-associated** encephalopathy in which EEG was obtained (95%).
EEG abnormalities were also common with **penicillin** (83%), **ciprofloxacin** (83%), and **isoniazid** (69%),
but EEG was performed much less frequently in patients with encephalopathy 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.

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.

Type 1 antibiotic associated encephlopathy (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.**

PATHOPHYSIOLOGY of 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.

Beta-lactams
- impede inhibitory neurotransmission at $GABA_AR$ through a variety of mechanisms,
- causing central excitotoxicity.

Beta-lactams can bind either noncompetitively (e.g., penicillins) or competitively (e.g., cephalosporins) to $GABA_AR$.

Chow et al 2005
De Sarro & De Sarro 2001
Akahane et al 1994
Sugimoto et al 2002
Lindquist et al 2004
Davidoff 1072;
Dingledine & Gjerstad 1979
Meyer & Prince 1973
Wong & Prince 1979
Van Duijn et al 1973
Gutnik & Prince 1971

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Van Duijn et al 1973
Gutnik & Prince 1971

PATHOPHYSIOLOGY OF AAE

Type 1 AAE (seizure/myoclonus).

In animal models, **direct cortical application of penicillins** leads to

- decreased **inhibitory postsynaptic potentials** (**IPSPs**) and
- **increased burst properties of excitatory neurons**, which is the likely **pathophysiologic basis** of
  - encephalopathy,
  - **myoclonus, and**
  - **seizures**

  related to β-lactam neurotoxicity.

Chow et al 2005
De Sarro & De Sarro 2001
Akahane et al 1994
Sugimoto et al 2002
Lindquist et al 2004
Davidoff 1072;
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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.
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.**

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 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.

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.

Schmuck et al 1998
Thomas & Reagan 1996
Hoigne & Schöch 1959
Graham et al 1995
Adinoff et al 2009
Adinoff et al 1998
Adinoff et al 1999
Adinoff et al 2001

Type 2 AAE (psychosis predominant)

In Type 2 AAE caused by **procaine penicillin**, also termed Hoigne syndrome, **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.

Procaine administration induces

- anxiety and
- somatization in normal patients is experienced as similar to cocaine in cocaine addicts, and
- causes increased blood flow on SPECT imaging in reward-processing areas such as the ventral striatum in a pattern similar to cocaine administration.

Schmuck et al 1998
Thomas & Reagan 1996
Hoigne & Schöch 1959
Graham et al 1995
Adinoff et al 2009
Adinoff et al 1998
Adinoff et al 1999
Adinoff et al 2001

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 s
- plenium of the corpus callosum.

Both increased and decreased diffusivity have been observed in MRI, suggesting the variable presence of both **vasogenic** and **cytotoxic edema**, respectively.

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.

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 analogue** that **impairs thiamine phosphorylation in vitro.**

Kim et al 2007
Rao & Mason 1987
Alston & Abeles 1987

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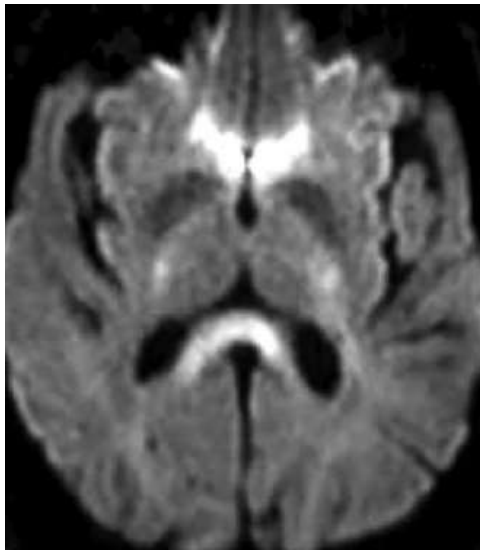
Rao & Mason 1987
Alston & Abeles 1987

Type 3 AAE (encephalopathy with cerebellar signs).

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.
There is also overlap between the neuroimaging features in metronidazole toxicity and those observed in malnourished patients with nonalcoholic **Wernicke encephalopathy.**
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.
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.



von Rogulja et al 1973
Zuccoli et al 2008
Zuccol & Pipitone 2009
Snavely & Hodges 1984

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.

Pharmacokinetics and patient-specific factors

In addition to all these mechanisms,
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.**
- **Imipenem**, compared to other carbapenems, **has slower rate** of **clearance from CSF**, which may contribute to increased neurotoxicity with imipenem compared to other carbapanems.

Patient characteristics such as
-age,
-renal failure, and
-preexisting cerebral disease (e.g., Parkinson disease, stroke, or head -/ brain trauma)
increase the risk of antibiotic-associated neurotoxicity for some though not all antibiotics.

Weihrauch et al 1975de Sarro et al 1995
Manian et al 1990
Chow et al 2004Grill %
Maganti 2008
Mattappalil & Mergenhagen 2014

Pharmacokinetics and patient-specific factors

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.**

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**.

The use of iron, calcium, and aluminum supplements in patients with renal insufficiency can also increase gastrointestinal absorption of certain antibiotics such as quinolones.

Weihrauch et al 1975de Sarro et al 1995
Manian et al 1990
Chow et al 2004Grill %
Maganti 2008
Mattappalil & Mergenhagen 2014

Antibiotic-Antiepileptic Interactions

Antibiotics can alter the **serum concentrations of antiepileptics**, resulting in

- **seizures or**
- **antiepileptic drug toxicity.**

Signs of antiepileptic drug toxicity include

- encephalopathy,
- nystagmus,
- imbalance, and/or
- ataxia.

While the possible pharmacologic interactions between antibiotics and antiepileptics are numerous, only a few are clinically significant.

Antibiotic-Antiepileptic Interactions

One of the more commonly reported significant interactions is a marked **reduction** in **serum valproic acid** concentration **following carbapenem** administration, which can lead to **seizures** in **epileptic patients**.
Mechanisms of this interaction include decreased intestinal transport of valproic acid and sequestration of valproic acid in erythrocytes .

Serum valproic acid concentration has been reported to fall by as much as 66 % in the presence of meropenem, though the degree of change is highly variable. Animal data suggest that imipenem likely has the same effect.
Carbapenems should therefore ideally be **avoided** in patients **receiving valproic acid**.
If carbapenems are essential for a particular infection in a patient on valproic acid therapy,
- serum valproic acid levels should be followed closely, and
- an additional antiepileptic medication could be considered if therapeutic levels of valproic acid are difficult to maintain.

Antibiotic-Antiepileptic Interactions

Antibiotic-antiepileptic combinations that have been reported to **increase** **antiepileptic drugs to toxic levels** include

- chloramphenicol with phenytoin
- clarithromycin , erythromycin with phenytoin
- isoniazid with carbamazepine.

Given potential interactions between antiepileptics and antibiotics, a **serum antiepileptic drug level** should be drawn **at the time of initiation of antibiotic therapy,** and the patient should be **closely monitored for seizures or antiepileptic drug toxicity**.

The development of either warrants a repeat serum antiepileptic drug level to compare with the initial level

Peripheral Nervous System (PNS)

Optic Neuropathy

Optic neuropathy caused by antibiotics generally presents as painless, progressive, symmetric visual loss with decrease in color vision (especially red-green discrimination). Visual field testing typically reveals centrocecal defects (loss of vision between the point of fixation and blind spot) and/or bitemporal defects (loss of bilateral peripheral vision).

The antibiotics most frequently associated with **optic neuropathy** are
- **ethambutol** and
- **linezolid**

although individual case reports have described **optic neuropathy** with other antibiotics including
- ciprofloxacin ,
- levofloxacin ,
- chloramphenicol,
- metronidazole ,
- sulfonamides,
- isoniazid, and
- streptomycin .

Optic Neuropathy

Ethambutol is estimated to cause optic neuropathy in 1 % of patients taking standard doses (15 mg/kg/day), but in as many **50 % in patients** taking doses in **excess of 60 mg/kg/day.**

Optic neuropathy is thought to be secondary to ethambutol-induced mitochondrial dysfunction , and pathology has demonstrated demyelinating lesions in the optic nerve and chiasm.
Risk factors for developing optic neuropathy due to ethambutol include

- older age,
- hypertension,
- renal disease,
- prolonged duration of therapy (greater than 2 months), and
- higher doses (above 15–20 mg/kg/day).

Patients who require ethambutol for **prolonged periods** should undergo a **screening ophthalmological examination** prior to initiation of therapy and **follow-up** examinations every 1 to 3 months (though practice varies across centers) to test for subclinical development of visual dysfunction.
If optic neuropathy develops, ethambutol should ideally be discontinued in favor of an alternative antibiotic.
Vision loss is generally reversible, although permanent visual loss may occur after prolonged treatment.

Peripheral Neuropathy

The antibiotics most commonly associated with peripheral neuropathy are
- metronidazole,
- **linezolid**, and
- dapsone,

though neuropathy has also been described in patients taking
- chloramphenicol,
- chloroquine,
- ethambutol,
- fluoroquinolones,
- isoniazid,
- nitrofurantoin, and
- sulfasalazine.

The mechanism of antibiotic-induced neuropathy is thought in most cases to be axonal injury caused by effects on DNA repair, cell metabolism, and mitochondrial function.

Peripheral Neuropathy

Antibiotic-induced peripheral neuropathies are most commonly **length-dependent** sensorimotor neuropathies, although autonomic neuropathy has been reported with metronidazole, pure motor neuropathy with dapsone, and optic neuropathy with linezolid

The majority of cases of antibiotic-induced peripheral neuropathy occur in patients with **prolonged antibiotic exposure** (i.e., months in duration) with incidence reported to be as high as **50 % in patients** with **long-term use** of **metronidazole** or **linezolid**.

In most patients, recovery occurs over weeks to months after cessation of antibiotics, although neuropathy may rarely persist.

In some patients, the neuropathy may continue to progress for several weeks following discontinuation of antibiotics before beginning to improve, a phenomenon referred to as “coasting”.

Antibiotic-Induced Exacerbation of Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder in which antibodies against postsynaptic receptors at the neuromuscular junction cause fluctuating weakness in ocular, bulbar, proximal limb, and respiratory muscles.
Signs and symptoms include

- diplopia,
- ptosis,
- dysarthria,
- dysphagia, and
- proximal limb weakness,
- all of which may become more prominent at the end of the day or after activity.

The majority of patients have measurable serum antibodies against the acetylcholine receptor (AChR) or, less commonly, the muscle-specific receptor tyrosine kinase (MuSK), and 10–15 % will have thymomas.

Electromyogram (EMG) demonstrates decrement in amplitude of compound motor action potentials (CMAP) with repetitive stimulation and increased jitter (variability of the interval between muscle potentials) with single muscle fiber EMG.

Antibiotic-Induced Exacerbation of Myasthenia Gravis

The antibiotics most commonly reported to precipitate flares of MG are
- aminoglycosides,
- fluoroquinolones, and
- macrolides.

Individual case reports have described MG exacerbations with
- clindamycin,
- colistin,
- tetracyclines,
- ampicillin,
- imipenem, and
- paromyxin B.

The proposed mechanisms of antibiotic-induced exacerbations of MG include **presynaptic** interactions with voltage-gated calcium channels and calcium-sensitive receptors as well as **postsynaptic** interactions with acetylcholine receptors .

Aminoglycosides, fluoroquinolones, and macrolides should therefore ideally be **avoided** in patients with MG. If one or more of these antimicrobial agents is necessary for treatment of a particular infection in a patient with MG, patients should be **monitored** closely for any worsening MG-related symptoms (e.g., weakness, dysarthria, dysphagia, shortness of breath).

CONCLUSION I

Onset of **new neurologic symptoms or signs after the initiation** of antibiotics should raise suspicion for potential antibiotic neurotoxicity.

Careful **selection of antibiotics and dosages** is essential in

- **old, very old** patients,
- patients with **renal insufficiency**,
- patients with **epilepsy**, or
- patients with **myasthenia gravis**

in order to **prevent** avoidable iatrogenic neurologic complications.

CONCLUSION II

If patients in these at-risk populations are infected with organisms requiring a specific antibiotic regimen that has been associated with neurotoxicity, appropriate **monitoring** should be initiated to facilitate early identification of neurotoxicity.

Such monitoring may include

- **long-term EEG monitoring** in hospitalized patients who develop encephalopathy after initiation of antibiotics,
- **serum antiepileptic drug concentrations** in patients with epilepsy taking antiepileptic medications initiated on antibiotics, and
- **serial ophthalmologic examinations** in patients receiving antibiotics known to cause optic neuropathy
- **Clinical** and **electrophysiological monitoring for** neuropathy and/or myasthenic signs and symptoms.

Given that **antibiotic neurotoxicity is likely under-recognized**, **continued reporting** is essential to understand more fully which patients are at the highest risk for neurologic complications of antibiotic therapy.

CONCLUSION III

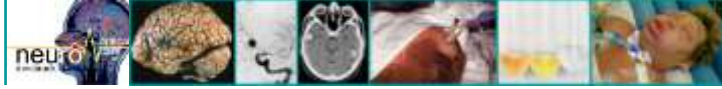
AAE is an **underrecognized** cause of **altered mental status in hospitalized patients,** and should be considered in all patients who develop **delirium after initiation of antibiotics.**

Although the clinical features of AAE are diverse, they can be divided into **3 core clinical syndromes** associated with particular antibiotics and uniqu underlying pathophysiologic mechanisms of neurotoxicity.

Epilept. Anfälle, Myoklonien
Psychot. Sy.
Zerebell.Sy.

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.

Vielen Dank für Ihre Aufmerksamkeit



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