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Review

Antibiotic-Associated Encephalopathy in Geriatric Patients: A Neglected Challenge

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Abstract

Background: The aging brain is more vulnerable to many medical drugs, including antibiotics. In geriatrics, the differentiation between symptoms of the infection and adverse effects of the antibiotic therapy can be difficult. Whereas most other drugs are prescribed as lifelong or very long treatments, antibiotics are the drug class most frequently initiated by the largest number of different medical specialties. Since the geriatric rule "start low, go slow" does not apply for antibiotics, the risk of immediate side effects as a consequence of exposure of a geriatric patient to the full drug dose is relatively high. **Method:** For this narrative review we searched PUBMED using defined search terms. **Results:** Age, impaired renal function, and a reduced cognitive reserve are the strongest individual predictors of central nervous toxicity of antibiotics. Antibiotic-associated encephalopathy can be divided into three different forms, which partly overlap: (1) hallucinations and delusions starting within hours to days after the first dose (predominantly associated with fluoroquinolones and macrolides, rarely with sulfamethoxazole/trimethoprim or other antibiotics); (2) myoclonus and epileptic seizures starting within hours to days after the first dose (mainly caused by cephalosporines, penicillins, and carbapenems); (3) vertigo, nystagmus and ataxia caused by metronidazole and optical neuropathy, vertigo, mental obtundation and epileptic seizures as a consequence of the functional antagonism of isoniazid and vitamin B6. **Conclusions:** The contribution of antibiotics to the development of delirium, myoclonus and epileptic seizures is likely underestimated. Renal failure and neurological or psychiatric abnormalities prior to infection are the main predisposing factors for antibiotic-associated encephalopathy in old age.

Keywords: fluoroquinolones; penicillins; cephalosporins; carbapenems; macrolides; sulfamethoxazole/trimethoprim; metronidazole; isoniazid; psychosis; delirium; myoclonus; epileptic seizures; renal dysfunction; cognitive reserve; old age

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1. Introduction

Antibiotics belong to the most frequently prescribed drugs worldwide. In general, antibiotics are well tolerated. Among other adverse events, they can cause antibiotic-associated encephalopathies (AAE) [1–4]. Diagnosis of AAE is difficult, because (a) severe infections can cause septic encephalopathy or septic-embolic or septic-metastatic encephalitis and

(b) in critically ill patients, metabolic encephalopathies can occur. Both conditions can resemble AAE [5].

As a consequence of immunosenescence, geriatric patients are highly susceptible to infections [6]. AAE is particularly relevant in aging populations due to an increased need for antibiotics. At the same time, AAE is harder to diagnose in this population because of the higher incidence of central nervous system (CNS) dysfunction from several causes unrelated to antibiotics.

We undertook this review to examine the incidence, risk factors and outcome of AAE and to help to identify AAE in geriatric clinical practice.

2. Materials and Methods

For this narrative review, we performed a PUBMED search on 17 May 2026, with the following search terms: 1. "antibiotic(s) associated encephalopathy" (n = 5338) **and** ["geriatric" (n = 67) or "old age" (n = 91)]; 2. "Seizure(s)" **and** "antibiotic*" (n =1671) **and** ["geriatric*" (n = 16) or "old age" (n = 52)]. Thereafter, all publications retrieved were assessed by one of the authors with respect to their utility for this narrative review.

In the following weeks, additional PUBMED searches were performed using the names of individual antibiotics and the search terms "adverse effects", "encephalopathy", "seizure(s)", "delirium", "psychosis" or "toxicity" or "pharmacokinetics". Additional PUBMED searches were performed to assess the relevance of drug interactions promoting or mimicking AAE in old patients.

3. Results

The true incidence of AAE is unknown. Generally, severe CNS adverse reactions induced by antibiotics are estimated to occur at a frequency below 1% [4,7]. In a large retrospective multicenter Korean study evaluating in-patients receiving antibiotics, the incidence of AAE was 1.0% [8]. In a retrospective study, 12 out of 117 (10%) patients with status epilepticus had a temporal association with antibiotic administration [9].

AAE probably is under-recognized, because mild forms may have nonspecific clinical symptoms. The differential diagnosis between sepsis-associated encephalopathy and AAE can be difficult. The United States Food and Drug Administration Adverse Event Reporting System (FAERS), a publicly available database containing adverse event reports, medication error reports. and product quality complaints resulting in adverse events, identified from January 2004 to December 2024, i.e., in 21 years, a total of 13,698 patients with AAE. FAERS relies on spontaneous reporting and contains adverse event reports from manufacturers as required by regulation and reports received directly from consumers and healthcare professionals. Reporting bias, notoriety bias and confounding by indication have to be considered when interpreting these data. The five most frequently listed antibiotics were metronidazole (1464), levofloxacin (1447), ciprofloxacin (1290), ertapenem (825), and imipenem/cilastatin (788 cases). The reported proportion of AAE strongly increased with age [4,7]. Approx. 40% of all cases reported in FAERS were 65 years and older (in 17% age was not specified) [4]. According to the reported proportions, sex did not constitute a risk factor for AAE [4,10].

AAE is not a homogeneous syndrome [11]. Generally, AAE is divided into three types depending on the prevailing symptoms (Type 1: myoclonus or epileptic seizures; Type 2: psychosis including delirium; Type 3: delayed, often with focal neurological signs [3,4]) (Figure 1). There is considerable overlap between Type 1 and Type 2: β-lactam antibiotics usually inducing seizures less frequently cause psychosis, and fluoroquinolones, typically inducing hallucinations and psychosis, less frequently can also cause epileptic seizures.

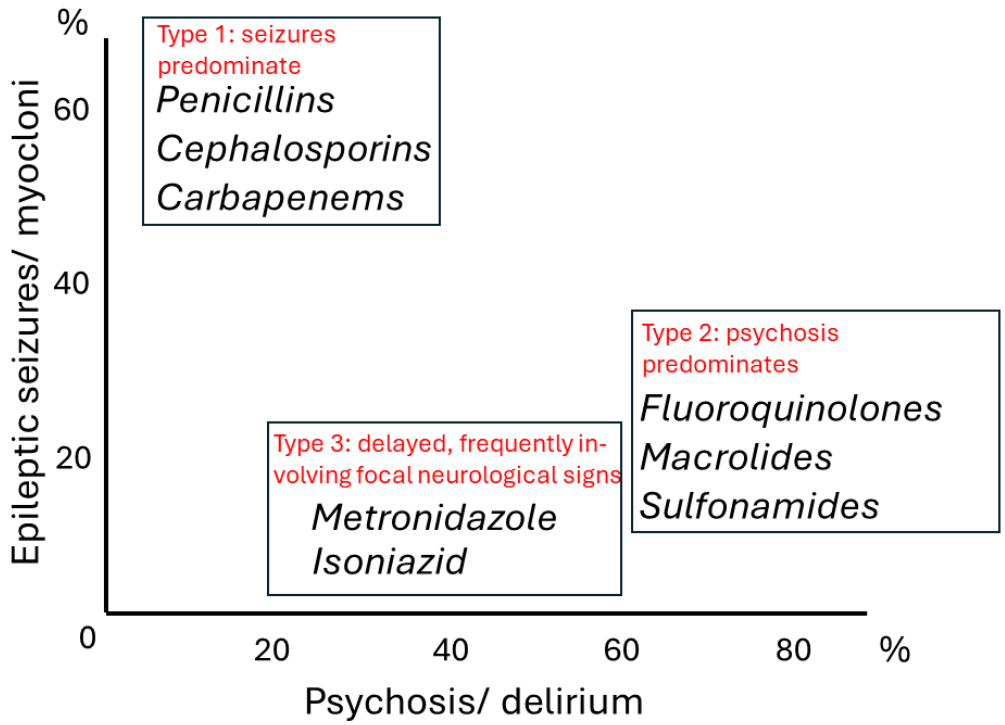


Figure 1. Types of antibiotic-associated encephalopathy (AAE). (1) Seizures predominate. (2) Psychosis, delirium and hallucinations predominate. (3) Delayed development of focal neurological signs associated with metronidazole; delayed optic neuropathy, psychosis and seizures caused by the functional antagonism of isoniazid on vitamin B6 metabolism. The percentages do not represent the absolute risks among treated patients but the frequency of symptoms in patients diagnosed with the respective type of AAE [3,4].

3.1. Types of Antibiotic-Associated Encephalopathy (AAE)

3.1.1. Type 1: Myoclonus and Epileptic Seizures Predominate

The typical adverse CNS effects of β-lactam antibiotics are myoclonus and epileptic seizures [12]. Central nervous system pathology, neurological diseases, history of epilepsy or seizures, and critical illness together with increased age increases the susceptibility to seizure development as a consequence of antibiotic therapy [12].

In the aforementioned retrospective study, the antibiotics administered in relation to a status epilepticus (8× convulsive status epilepticus, 4× non-convulsive status epilepticus) were the β-lactam antibiotics ceftazidime (n = 5), amoxycillin/clavulanic acid (n = 2), piperacillin (n = 2), cefepime (n = 1) and the fluoroquinolones levofloxacin (n = 3), ofloxacin (n = 1), and ciprofloxacin (n = 2) alone or in combinations. Five of these patients had hepatic (42%) and six renal (50%) failure; in the patients with renal failure, the observed dose of the antibiotic was higher than the dose adjusted according to the renal function [9].

Cefepime is considered the β-lactam antibiotic most frequently associated with epileptic seizures and altered mental status. In a systematic review on 135 patients experiencing cefepime-associated neurotoxicity, the majority were elderly (median 69 years), had renal dysfunction (80%), and required intensive care (81%). Many patients with sufficient information available (48%) received cefepime regimens excessive for their reported renal function. However, 26% were dosed appropriately, and another 26% could not be assessed because of incomplete information. Among the 26% of patients experiencing neurotoxicity and considered to be dosed appropriately for renal function, seven patients had measured serum concentrations, and all were elevated (≥20 mg/L) [13]. All 135 patients had altered mental status, and reduced consciousness was reported in 47% of cases. Other frequent clinical findings were myoclonus (n = 57, 42%), confusion (n = 57, 42%), aphasia (n = 20,

15%), seizures (n = 17, 13%), and agitation (n = 15, 11%). All patients who received an electroencephalogram (98 patients, 73%) showed abnormalities (25% non-convulsive status epilepticus, 7% myoclonic status epilepticus, 40% triphasic waves, 39% focal sharp waves) [13].

The convulsant action of β-lactam antibiotics has been related to the reduction in the release of GABA from nerve terminals or to the concentration-dependent competitive inhibition of γ-aminobutyric acid (GABA) binding to its receptor sites [13,14]. In experimental rats after intracerebroventricular administration, cefazolin was the most powerful epileptogenic antibiotic among the compounds tested. It was approximately three times more potent than benzylpenicillin in generating a response and much more potent than other cephalosporins, such as ceftriaxone, cefoperazone, and cefamandole. Very low epileptogenic activity was observed with equimolar doses of cefixime in this model. Cefotaxime and ceftizoxime also had low pro-convulsive activity at low concentrations. At high concentrations of 3.3 µmol/L (approx. 1.50 mg/L and 1.27 mg/L), cefotaxime and ceftizoxime also had strong epileptogenic activity in the intracerebroventricular rat model [14]. In rats, the carbapenem imipenem was more potent than meropenem in inducing epileptic seizures, its convulsant potency being similar to those of ceftezole and benzylpenicillin. The monobactam aztreonam possessed convulsant properties more potent than those of cefoperazone and cefamandole. In this model, cefepime, amoxicillin/clavulanate and flucloxacillin were not tested [14]. Based on this publication and more recent data [15,16], the French Societies of Pharmacology and Therapeutics and Anaesthesia and Intensive Care Medicine published a list of the relative pro-convulsive activity of β-lactam antibiotics, using penicillin G (=100) as the reference compound [17] (Table 1). Table 1 and Figure 2 suggest that cefazolin, cefepime, penicillin G and imipenem should be used with caution in geriatric patients, and doses should be strictly adjusted to renal function. For cefepime, penicillin G and imipenem less pro-convulsive alternative compounds are available. Apart from a few case reports mainly in patients with impaired renal function (e.g., [18]), intravenous cefazolin in humans does not appear to have a high risk of inducing epileptic seizures. In a large randomized trial analyzing infections caused by methicillin-susceptible *Staphylococcus aureus*, cefazolin was equally effective, but less nephrotoxic than the anti-staphylococcal penicillins flucloxacillin or cloxacillin [19]. In geriatric patients, the possibly higher risk of epileptic seizures with cefazolin must be balanced against the increased risk of renal failure with (flu)cloxacillin. For β-lactam antibiotics with high pro-convulsive activity, dose adjustment to the renal function and therapeutic drug monitoring (TDM) is of particular importance to avoid drug toxicity.

Table 1. Pro-convulsive activity of several β-lactam antibiotics frequently used in the care of older people compared with penicillin G (modified from Guilhaumou and co-workers [17], reproduced under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/, 22 October 2026) with kind permission of Springer Nature, Heidelberg, Germany).

β-Lactam Antibiotic	**Relative Pro-Convulsive Activity (Reference: Penicillin G = 100)**
Cefazolin	294
Cefepime	160
Penicillin G	100
Imipenem	71
Aztreonam	42
Ampicillin	21

Table 1. *Cont.*

β-Lactam Antibiotic	Relative Pro-Convulsive Activity (Reference: Penicillin G = 100)
Ceftazidime	17
Meropenem	16
Ceftriaxone	12
Piperacillin	11
Cefotaxime	8.8
Cefoxitin	1.8

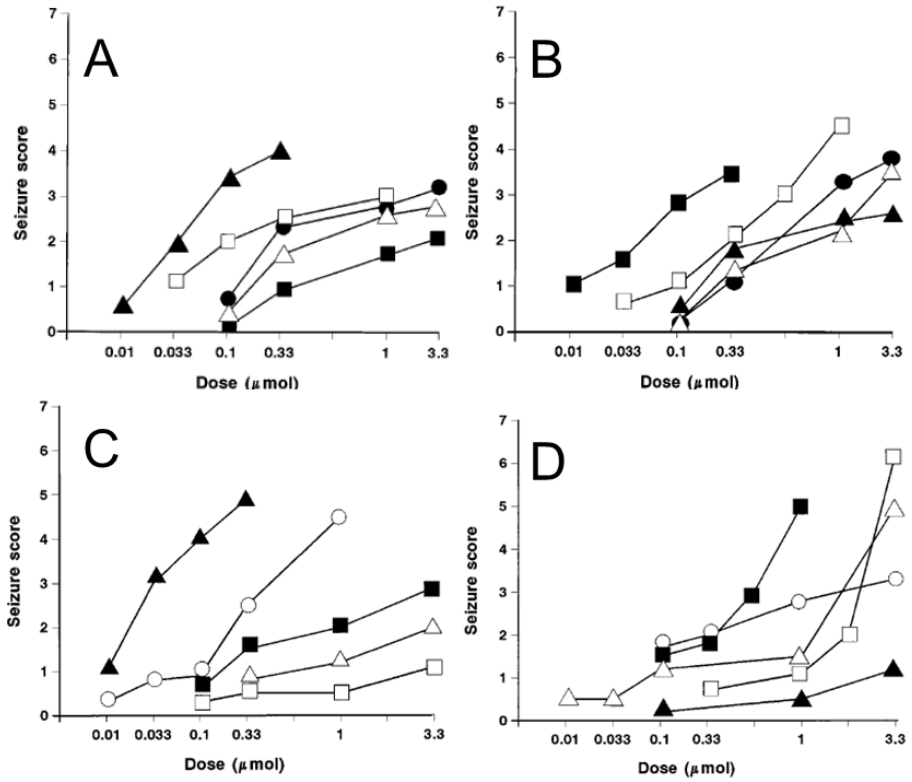


Figure 2. Dose–response curves of seizure intensity score determined from behavioral changes after intracerebroventricular injection of β-lactam antibiotics in rats (de Sarro and co-workers [14]), reproduced with kind permission of the American Society for Microbiology, Washington, DC, USA. (**A**) Filled triangles—benzylpenicillin; open squares—aztreonam; open triangles—amoxicillin; filled circles—ampicillin; filled squares—sulbenicillin. (**B**) Open squares—azlocillin; open triangles—piperacillin; filled squares—imipenem; filled triangles—mezlocillin; filled circles—meropenem. (**C**) Filled triangles—cefazolin; open circles—cefoperazone; open triangles—cefuroxime; open squares—cephradine; filled squares—Ro 23-9424 (fused compound containing fleroxacin combined with desacetylcefotaxime). (**D**) Filled squares—ceftriaxone; open circles—ceftazidime; open triangles—cefotaxime; open squares—ceftizoxime; filled triangles—cefixime.

The pro-convulsive activity of the individual compounds was established by expert consensus considering animal and clinical data [14–16].

3.1.2. Type 2: Psychosis Predominates

As a consequence of the CNS excitatory effects of fluoroquinolones, elderly patients should be monitored carefully for such symptoms. Probably many signs of possible adverse

reactions, such as confusion, weakness, loss of appetite, tremor or depression, are often mistakenly attributed to old age and remain unreported [20].

A review evaluating FAERS data identified 15 antibiotics associated with a significantly increased odds of psychosis (OR = 1.67–9.48), including fluoroquinolones, macrolides, cephalosporins, doxycycline and penicillins. The proportion of adverse drug reports referring to psychosis as a consequence of treatment with antibiotics ranged from 0.3 to 3.8%. The antibiotics with the greatest increased odds of psychosis were the macrolide clarithromycin, the fluoroquinolones ciprofloxacin and levofloxacin and the nitroimidazole metronidazole [10]. These drugs are characterized by a moderate to high lipophilicity and readily enter the brain and CSF [21–23]. The free fluoroquinolone concentrations in the cerebral extracellular fluid are close to the respective free concentrations in CSF [24].

Fluoroquinolone-induced psychosis involves the inhibition of GABA receptors and the activation of glutaminergic N-methyl-D-aspartate (NMDA) receptors [25]. Fluoroquinolones also can cause peripheral neuropathy [26]. In a univariate analysis, the risk factor with the highest link to encephalopathy and peripheral neuropathy was age > 60 years, reported in 69.5% of the cases, followed by renal failure [27]. In a study among US veterans (mean age 71.5 years, range 22–95), psychosis including delirium occurred in 3.6% of ciprofloxacin-treated (n = 14/391), 4.5% of moxifloxacin–treated (n = 9/200), and 0% of levofloxacin-treated patients (n = 0/40) [28]. In a retrospective pharmacovigilance study using FAERS data from Q1 2004 to Q4 2023 (84,777 reports associated with fluoroquinolones), ciprofloxacin was most frequently linked to depression and suicidal thoughts, whereas moxifloxacin "showed a robust correlation with delirium". The risk of the individual neuropsychiatric adverse drug reactions varied by age group: affective disorders were more prevalent in adults under 65, psychosis and delirium most frequent in those over 65 [29]. In patients receiving a fluoroquinolone, a 10-year increase in age was associated with a 1.8-fold greater likelihood of psychosis [28]. In addition to age, a history of neurologic or psychiatric disorders increased the AAE incidence of ciprofloxacin [30].

Which of the frequently used fluoroquinolones has the highest risk of inducing psychosis is still unclear. In a Czech retrospective study in a nephrological department (high prevalence of patients with impaired renal function), the overall incidence of neurological adverse drug reactions for ciprofloxacin was 3.6%. No neurological adverse drug reactions occurred in patients ≤70 years [30]. In the absence of meningeal inflammation, ofloxacin and levofloxacin enter the brain more readily than ciprofloxacin and moxifloxacin [21–23,31,32]. Ofloxacin in relation to its low prescription rate has been reported a high frequency of CNS adverse effects. Levofloxacin, the antibacterially active L-isomer of ofloxacin, is considered safer, but in a recent Spanish review appeared the second most frequent (after ciprofloxacin) fluroquinolone involved in CNS adverse effects [33]. The inhibitory effects of the fluoroquinolones on [^{3}H]muscimol binding to GABA receptors on synaptic plasma membranes of mouse brains were most pronounced with prulifloxacin and norfloxacin followed by ciprofloxacin, enoxacin, gatifloxacin, ofloxacin, tosufloxacin, lomefloxacin, levofloxacin, sparfloxacin, pazufloxacin and fleroxacin [34].

Compared with fluoroquinolones, clarithromycin and metronidazole, the association with psychosis was low with sulfamethoxazole/trimethoprim, nitrofurantoin, doxycycline, azithromycin, erythromycin, cefuroxime, ceftriaxone and cephalexin. No significant disproportionality concerning psychosis was reported for tetracycline, penicillin, piperacillin, meropenem, vancomycin, ceftriaxone or aminoglycosides [10] (Table 2).

Table 2. Odds ratios for psychosis adverse drug reactions for individual antibiotics and antibiotic classes, relative to minocycline according to the United States (US) Federal Drug Administration (FDA) Adverse Event Reporting System (FAERS) (according to Essali & Miller [10], reproduced with kind permission of Elsevier B.V., Amsterdam, The Netherlands).

Drug		Adverse Event									
Class	Agent	Total	Psychotic Symptoms					Hallucinations			
			% ADR	N	Male (n)	OR	95% CI	N	Male (n)	OR	95% CI
Tetracycline	Minocycline	5149	0.4	21	6	1.00	Reference	13	4	1.00	Reference
	Doxycycline	6237	0.9	59	31	**2.32**	**1.41–3.82**	32	11	**2.03**	**1.07–3.88**
	Tetracycline	996	0.7	7	0	1.72	0.73–4.06	4	0	1.59	0.52–4.89
	All Tetracyclines	7233	0.9	66	31	**2.23**	**1.36–3.66**	36	11	**1.97**	**1.04–3.72**
Sulfonamides	SMX/TMP	22,697	0.7	168	80	**1.81**	**1.15–2.86**	134	62	**2.34**	**1.32–4.14**
Nitrofurantoin	Nitrofurantoin	3300	0.9	32	8	**2.38**	**1.37–4.13**	25	8	**3.00**	**1.53–5.87**
Penicillin	Penicillin	877	0.5	5	1	1.40	0.53–3.72	3	0	1.35	0.39–4.76
	Amoxicillin	10,658	1.2	129	51	**2.97**	**1.87–4.71**	86	34	**3.20**	**1.78–5.73**
	Amoxicillin/Clavulanate	15,552	0.6	106	46	**1.67**	**1.05–2.67**	74	27	**1.88**	**1.04–3.40**
	Piperacillin	530	0.5	3	0	1.39	0.41–4.67	1	0	0.75	0.10–5.72
	All Penicillins	27,617	0.8	243	98	**2.15**	**1.38–3.37**	164	61	**2.35**	**1.33–4.14**
Fluoroquinolone	Levofloxacin	26,957	2.2	619	193	**5.63**	**3.64–8.71**	421	126	**6.19**	**3.56–10.75**
	Ciprofloxacin	18,042	2.7	503	225	**6.84**	**4.41–10.59**	348	159	**7.64**	**4.39–13.30**
	All Fluoroquinolones	44,999	2.0	1122	418	**6.11**	**3.96–9.42**	769	285	**6.76**	**3.90–11.71**
Macrolides	Azithromycin	5272	0.8	46	21	**2.14**	**1.27–3.59**	31	15	**2.33**	**1.22–4.46**
	Erythromycin	4254	1.0	45	22	**2.59**	**1.54–4.36**	37	20	**3.44**	**1.83–6.49**
	Clarithromycin	18,356	3.8	710	271	**9.48**	**6.14–14.65**	439	169	**9.47**	**5.45–16.46**
	All Macrolides	27,882	2.8	801	314	**7.04**	**4.56–10.87**	507	204	**7.20**	**4.14–12.49**
Glycopeptides	Vancomycin	9787	0.3	32	21	0.80	0.46–1.39	24	16	0.97	0.49–1.91
Nitroimidazoles	Metronidazole	11,168	2.5	283	110	**6.21**	**3.98–9.69**	182	74	**6.45**	**3.67–11.34**
Lincosamide	Clindamycin	4604	0.4	19	9	1.01	0.54–1.88	16	7	1.38	0.66–2.86
Aminoglycoside	Gentamicin	2432	0.3	8	7	0.81	0.36–1.82	7	6	1.14	0.45–2.86
	Amikacin	1556	0.5	8	6	1.26	0.56–2.85	7	6	1.78	0.71–4.47
	All Aminoglycosides	3988	0.4	16	13	0.98	0.52–1.88	14	12	1.39	0.65–2.96
Carbapenem	Meropenem	3354	0.5	20	11	1.46	0.79–2.70	12	7	1.42	0.65–3.11
Cephalosporins	Cefuroxime	2352	0.5	41	16	**2.92**	**1.72–4.95**	29	13	**3.34**	**1.73–6.42**
	Ceftriaxone	6059	0.6	42	27	**1.70**	**1.01–2.87**	27	18	1.76	0.91–3.42
	Cefepime	1334	1.7	23	9	**4.23**	**2.33–7.66**	22	9	**6.53**	**3.28–13.00**
	Cephalexin	5799	0.8	47	8	**1.99**	**1.19–3.33**	35	4	**2.39**	**1.26–4.52**
	All Cephalosporins	16,636	0.9	153	60	**2.25**	**1.42–3.56**	113	44	**2.69**	**1.51–4.78**

ADR—adverse drug reaction. OR—odds ratio. CI—confidence interval. Significant differences versus minocycline are written in bold letters. FAERS relies on spontaneous reporting of adverse event reports from manufacturers and reports received directly from consumers and healthcare professionals. For the interpreting of these data, reporting bias, notoriety bias and confounding by indication must be considered.

3.1.3. Type 3: Delayed Toxicity, Often Focal Neurological Signs Predominate

The prototype of this form of antibiotics-associated encephalopathy is caused by metronidazole. Metronidazole occasionally can affect the cerebellum, causing ataxia, dysmetria in finger-to-nose and heel-to-knee tests, gait instability, dizziness, vertigo and spontaneous nystagmus and producing typical MRI findings in the cerebellar dentate nuclei (Figure 3). The MRI findings resemble images found in Wernicke's encephalopathy [35,36]. Neurotoxicity of metronidazole also can manifest as peripheral neuropathy, epileptic seizures and headache [35,36]. Termination of metronidazole treatment can but not always does result in rapid clinical improvement and resolution of signal changes (Figure 3). The incidence of metronidazole-induced encephalopathy is unknown. Metronidazole can cause a disulfiram-like reaction when consumed together with alcohol. The interaction of metronidazole and alcohol occurs with unclear frequency, and, when it occurs, it manifests with varying severity [37]. The mechanism of this interaction is unknown. Early studies suggested an inhibition of the alcohol dehydrogenase in the liver by metronidazole or its metabolites. Recent studies were unable to confirm this mechanism [37].

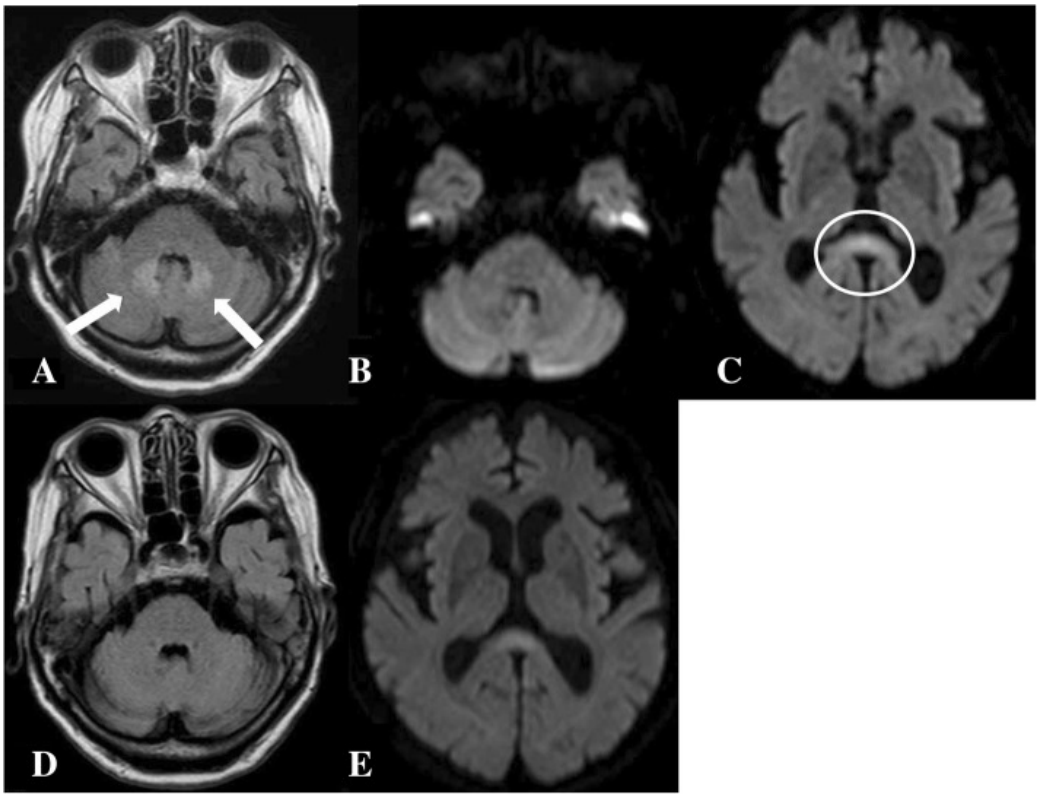


Figure 3. Cerebral magnetic resonance imaging of a patient with metronidazole-induced encephalopathy. (**A**) T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging performed at 4 days after the onset of symptoms: hyperintense areas in the bilateral cerebellar dentate nuclei (white arrows). (**B**) Diffusion-weighted imaging (DWI) also performed 4 days after onset of symptoms: almost normal intensity in the bilateral basal dentate nuclei. (**C**) DWI recorded 4 days after the onset of symptoms revealed a hyperintense T2 signal compatible with cytotoxic edema in the posterior commissure (white circle). (**D**) Fourteen days after stopping oral metronidazole, the abnormal findings on T2-weighted FLAIR imaging had completely disappeared. (**E**) Fourteen days after stopping metronidazole, the signal intensities in the posterior commissure on DWI had almost disappeared (Mizuta and co-workers [36], reproduced under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/, 22 October 2026) with kind permission of Springer Nature, Heidelberg, Germany).

Among the traditional compounds of first-line antituberculosis therapy, isoniazid is most often associated with nervous system adverse effects. Peripheral neuropathy is most common followed by psychosis, seizures and optical neuropathy [38]. Since isoniazid interferes with the endogenous vitamin B6 metabolism by inactivation of pyridoxal phosphate, the active form of vitamin B6, patients receiving isoniazid should receive vitamin B6 supplementation (e.g., 50–100 mg/day) to reduce these adverse effects.

4. Discussion

Here, we present the most frequent types of injury of antibiotics to the CNS and their high relevance for the geriatric patient. The main limitations of our study are that a) despite many published retrospective studies and case reports, the true incidence of AAE still is unknown; b) study selection was done without predefined inclusion criteria; and c) our search string may have biased our results towards selected AAE as some search terms were quite specific. At the same time, we may have missed some cases, e.g., by using "seizure(s)" and not also "epileptic" or "epilepsy".

In order to identify the true incidence of AAE, population-based prospective studies with clear diagnostic criteria will be necessary. Less potent, but much easier to be performed would be a case-control study comparing the initiation of antibiotic therapy with the initiation of a drug without any biological plausible mechanism for delirium or epileptic seizures, such as metamizole (dipyrone), using a control group matched on age, comorbidity, and setting (in-patient or out-patient, intensive care unit [ICU]).

Antibiotics can roughly be divided into time- and concentration-dependent drugs. For time-dependent drugs (e.g., β-lactam antibiotics, glycopeptides) the pharmacodynamic goal is to maximize the time that free (unbound) drug concentrations spend above the minimum inhibitory concentration (MIC). For concentration-dependent antibiotics (e.g., aminoglycosides, fluoroquinolones) maximizing the free peak-to-MIC ratio ensures rapid bacterial killing. Time- and concentration-dependent antibiotics require different dosing strategies [39]: time-dependent antibiotics require frequent dosing or even a continuous infusion to optimize time above the MIC, whereas concentration-dependent antibiotics have a strong post-antibiotic effect and require large doses less frequently (e.g., 1× daily).

Pharmacodynamically, β-lactams as time-dependent antibiotics are suitable for old people because of their low general toxicity. By frequent dosing and prolonged infusions, high peak concentrations can be avoided without compromising their antibiotic effect. Conversely, fluoroquinolones require high peak concentrations for an optimum bactericidal activity [40]. Avoidance of high peak concentrations could compromise the antibacterial activity of fluoroquinolones. Since in general the risk to induce psychosis incl. delirium by fluoroquinolones is higher than the risk to induce myoclonus or epileptic seizures by β-lactam antibiotics, several lists of potential inadequate drugs for older people suggest the restriction of the use of fluoroquinolones: the FORTA lists recommends not to use ciprofloxacin in old patients and to administer other fluoroquinolones with caution [41], and the PRISCUS list classifies all fluoroquinolones as potentially inadequate [42]. As a consequence of the unique pharmacokinetic and pharmocodynamic properties of fluoroquinolones, a complete ban of these compounds appears not realistic in geriatric medicine. Because of their high bioavailability, these drugs are established in the long-term and oral treatment of osteoarticular infections including diabetic foot osteomyelitis and joint septic arthritis [43]. Fluoroquinolones in geriatric medicine, however, should be used with great caution. Urinary and respiratory tract infections in geriatric patients should not be treated by fluoroquinolones, as long as less toxic options are available.

The data presented show that age, impaired renal function and a history of neurologic or psychiatric disorders are the strongest indicators of a high risk to develop AAE. Antibiotic

therapy aims at attaining rapidly antibacterial plasma and tissue concentrations while avoiding neurotoxicity. For most of the antibiotics used in geriatrics, the elucidation of the true renal function is the clue to avoid toxicity.

In clinical practice, the assessment of renal function poses severe problems: (a) The determination of the creatinine clearance is cumbersome and requires the 24 h collection of urine. (b) Formulae for the estimation of the glomerular filtration rate (GFR) using the plasma creatinine concentration require the presence of a steady state. These formulae overestimate the GFR during worsening of renal function and underestimate GFR during the resolution of renal failure. (c) In patients with reduced muscle mass, e.g., in frail patients, these formulae overestimate and in persons with a large muscle mass underestimate the true GFR. Cystatin C is a proteinase inhibitor synthesized by eukaryotic cells at a relatively constant rate. It is eliminated from the body exclusively by glomerular filtration, then completely reabsorbed and metabolized by tubular cells. Tubular secretion or re-entry of cystatin C into the bloodstream do not occur. For these reasons, the plasma concentration of cystatin C is the most reliable routine parameter to estimate GFR. Because the GFR estimated by plasma creatinine strongly depends on the muscle mass, and the GFR estimated by cystatin C is independent of the muscle mass, the discrepancy of the GFR estimated by cystatin C and creatinine plasma concentrations has been used as an indicator of frailty [44,45]. Estimating renal function by plasma cystatin C instead of plasma creatinine can help to identify patients at risk of renal function overestimation and subsequent antibiotic overdosing. However, the cystatin C plasma concentrations can be decreased by hypothyroidism and increased by steroid treatment, cigarette smoking, chronic inflammation, obesity and hyperthyroidism. Equations combining plasma creatinine and cystatin C can improve the accuracy of GFR estimation, especially in patients with a moderate impairment of renal function, including older patients [46]. We suggest to determine cystatin C in geriatric patients with an apparently reduced muscle mass or extended hospitalization or ICU stay [47].

In geriatric patients with difficult-to-treat infections, therapeutic drug monitoring (TDM) probably is useful, although without robust clinical data for patient-related outcomes so far. For TDM in intensive care patients, the following suggestions with relevance to geriatric patients have been proposed [17]: (1) Since geriatric patients frequently have low plasma albumin concentrations, plasma albumin must be determined in every patient in order to estimate the unbound ("free") fraction of the antibiotic. (2) To exert a maximum bactericidal effect, the free plasma concentration of β-lactam antibiotics should lie between four and eight times the MIC of the causative bacteria for 100% of the dosing interval. (3) In order to avoid toxicity, the free plasma concentrations of β-lactam antibiotics must not exceed eight times the MIC. Guilhaumou and co-workers [17] provide absolute concentration thresholds considering the unbound fraction of the antibiotic and 8× the epidemiological cut-off values (ECOFF) of susceptible bacteria (except for ceftazidime and *Pseudomonas aeruginosa*). We are of the opinion that for antibiotics there are no absolute concentration thresholds for toxicity. Toxicity does not only depend on the drug and the free drug concentration, but also on the cognitive reserve or epileptogenic foci of the patient treated with the respective antibiotic. Therefore, when the causative pathogen is highly susceptible, effective free drug concentrations can be reached at concentrations substantially lower than those given as toxicity limits by intensive care specialists [17]. In order to further reduce the toxicity of β-lactam antibiotics in old vulnerable persons, we advocate to use the true MIC of the causative pathogen [48] instead of the ECOFF for the adjustment of the free plasma concentrations to four to eight times the MIC. (4) In order to avoid high peak concentrations, β-lactam antibiotics in critically ill patients should be administered as prolonged infusion. A continuous infusion offering some benefit in critically ill intensive care patients [49], in geriatric patients outside of an ICU to us does not appear feasible. (5) Whenever β-

lactam antibiotic-induced toxicity is suspected, the antibiotic plasma concentration should be determined. (6) Steady state or trough concentrations of frequently used antibiotics considered appropriate for intensive care units have been published [17]. Further research is necessary, whether these relatively high concentrations also can be used in geriatric patients. (7) Also in patients with renal failure, the first antibiotic dose(s) should be full dose(s) in order to rapidly achieve therapeutic drug concentrations [50].

Worldwide, a high percentage of the elderly population is exposed to polypharmacy [51]. Therefore, drug interactions between antibiotics and other compounds must be considered. Linezolid seldomly causes a serotoninergic syndrome, particularly when co-administered with other serotoninergic drugs. In a recent study using FAERS data, citalopram, fentanyl, sertraline, escitalopram and tramadol were the most frequently serotonergic agents co-administered with linezolid in cases of serotonin syndrome [52]. In a Canadian retrospective population-based study, co-administration of linezolid and antidepressants, however, did not significantly increase the risk of a serotonin syndrome [53]. Carbapenem co-administration with valproate causes a strong decline in valproate plasma concentrations. In a retrospective study in patients prescribed valproate for its antiepileptic properties, seizures occurred after carbapenem administration in 46.3% of the cases [54]. Clarithromycin interacts with a variety of drugs: it can both decrease and increase the concentrations of other drugs, and other drugs can influence clarithromycin plasma concentrations [55]. In a Danish population-based retrospective study of hospitalized patients, among anti-infectives, meropenem–valproic acid, domperidone–fluconazole, imipramine–terbinafine, agomelatine–ciprofloxacin and clarithromycin–quetiapine were associated with elevated mortality [56]. In total, 62% of patients receiving discouraged drug pairs were 65 years and older. Therefore, physicians caring for older patients must remain vigilant for these and other drug interactions potentially promoting or mimicking AAE [53–56].

5. Conclusions

Age, impaired renal function and pre-existing neurological or psychiatric diseases are the strongest indicators of a high risk to develop antibiotics-associated encephalopathy. In frail patients, the estimation of renal function should not rely on plasma creatinine alone, but should employ a procedure independent of the muscle mass, e.g., cystatin C. With time-dependent, in particular β-lactam antibiotics, short dosing intervals and prolonged infusions should be chosen. Fluoroquinolones should be used with caution and only with mandatory indication. Also in geriatric patients, the first antibiotic dose should be a full dose in order to achieve a rapid bactericidal effect.

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Abbreviations

The following abbreviations are used in this manuscript:

AAE	antibiotic-associated encephalopathies
CNS	central nervous system
CSF	cerebrospinal fluid
FAERS	United States Food and Drug Administration Adverse Event Reporting System
FORTA	Fit for The Aged
GABA	γ-aminobutyric acid
GFR	glomerular filtration rate
ICU	intensive care unit
MIC	minimum inhibitory concentration
NMDA	N-methyl-D-aspartate
PRISCUS	potentially inappropriate medications in the elderly
TDM	therapeutic drug monitoring

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