

CKJ REVIEW

Drugs with a negative impact on cognitive functions (part 3): antibacterial agents in patients with chronic kidney disease

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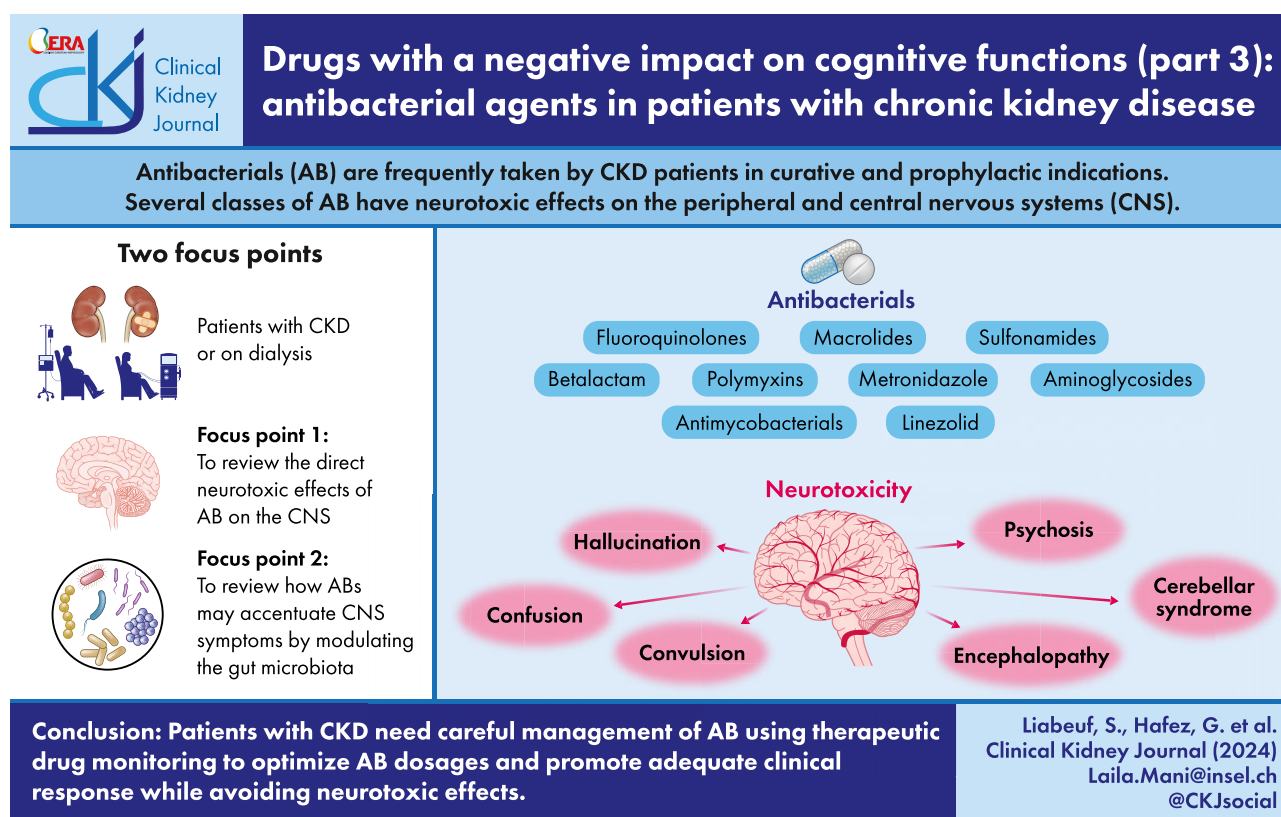
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ABSTRACT

The relationship between chronic kidney disease (CKD) and cognitive function has received increased attention in recent years. Antibacterial agents (ABs) represent a critical component of therapy regimens in patients with CKD due to increased susceptibility to infections. Following our reviewing work on the neurocognitive impact of long-term medications in patients with CKD, we propose to focus on AB-induced direct and indirect consequences on cognitive function. Patients with CKD are predisposed to adverse drug reactions (ADRs) due to altered drug pharmacokinetics, glomerular filtration decline, and the potential disruption of the blood–brain barrier. ABs have been identified as a major cause of ADRs in vulnerable patient populations. This review examines the direct neurotoxic effects of AB classes (e.g. beta-lactams, fluoroquinolones, aminoglycosides, and metronidazole) on the central nervous system (CNS) in patients with CKD. We will mainly focus on the acute effects on the CNS associated with AB since they are the most extensively studied effects in CKD patients. Moreover, the review describes the modulation of the gut microbiota by ABs, potentially influencing CNS symptoms. The intricate brain–gut–kidney axis emerges as a pivotal focus, revealing the interplay between microbiota alterations induced by ABs and CNS manifestations in patients with CKD. The prevalence of antibiotic-associated encephalopathy in patients with CKD undergoing intravenous AB therapy supports the use of therapeutic drug monitoring for ABs to reduce the number and seriousness of ADRs in this patient population. In conclusion, elucidating AB-induced cognitive effects in patients with CKD demands a comprehensive understanding and tailored therapeutic strategies that account for altered pharmacokinetics and the brain–gut–kidney axis.

GRAPHICAL ABSTRACT



Keywords: adverse drug reactions, antibacterial agents, chronic kidney disease, cognitive impairment, drugs

INTRODUCTION

Patients with chronic kidney disease (CKD) have a high comorbidity burden and are frequently admitted to hospital for the management of an acute illness [1]. Hence, these patients have a high long-term medication load and are frequently exposed to drugs for acute care, including antibacterial agents

(ABs). The number of prescription drugs and the complexity of drug management increases as CKD progresses [2]. First, CKD-associated metabolic disturbances (such as the accumulation of uremic toxins) modify drug pharmacokinetics (PK) and pharmacodynamics (PD) (especially for drugs cleared by the kidneys) and therefore require dose adjustments or drug withdrawal to prevent adverse drug reactions (ADRs).

Second, drug dose levels may also need to be adjusted in dialyzed patients (see associated review, part 1) [3]. Third, kidney transplant recipients have the most complex drug regimens, with immunosuppressants, prophylactic treatments, and drugs taken for comorbid conditions and complications such as infections [4]. Finally, considering the high number of prescription drugs in CKD patients, the risk of pharmacokinetic and pharmacodynamic interactions with drugs, including AB, is elevated and may lead to an enhancement of drug side effects.

Because of polypharmacy due to high comorbidity burden and complex drug regimens, patients with CKD are prone to ADRs [5]. The incidence of ADRs increases as kidney function deteriorates, as a result of drug-related nephrotoxicity, drug accumulation, and drug interactions [6].

Similarly, CKD is a risk factor for adverse reactions to drugs acting on the central nervous system (CNS). For example, disruption of the blood–brain barrier (BBB) is associated with CKD and may further modify the effectiveness of some drugs by increasing their penetration into the brain parenchyma [3]. In turn, this might induce major CNS-related ADRs. In our previous work, we reviewed the most common medications associated with cognitive impairment (in both the general population and patients with CKD) and described their effects [7]. Most of the reviewed drugs are taken over the long term. However, ABs deserve further attention because they are widely used among patients with CKD and potentially associated with specific CNS toxicity. We will mainly focus on the acute effects on the CNS associated with AB since they are the most extensively studied effects in CKD patients. Furthermore, evidence for chronic effects on cognition in general is scarce. Nevertheless, investigating whether chronic or repeated antibiotic use could be linked to long-term alterations in cognitive function in CKD patients warrants further research. Indeed, a prospective population-based cohort study among 14 542 participants in the Nurses' Health Study II suggested that the long-term antibiotic use in midlife is associated with small decreases in cognition assessed 7 years later [8]. In the same line, the effects of long-term/recurrent use of AB in childhood on developing cognitive impairment in middle and old age have been evaluated in the UK Biobank Database. The authors demonstrated that the likelihood for the development of cognitive impairment increased by 18% among AB users compared to non-users, independently of factors such as age, sex, educational qualification, ethnicity, income, smoking status, alcohol consumption, body mass index, history of hypertension, and history of diabetes [9]. In addition, the association between dementia incidence and AB use was retrospectively analyzed in a population-based South Korean cohort [10]. The used AB classes included penicillin, cephalosporins, macrolides, fluoroquinolones, sulfonamides, lincosamides, tetracyclines, and vancomycin. The authors showed an increased risk for overall dementia, Alzheimer's disease, and vascular dementia with long-term AB use as well as for overall dementia and Alzheimer's disease with use of more than five AB classes as compared to non-AB users. Results were adjusted for age, sex, body mass index, smoking status, alcohol consumption, physical activity, income, comorbidity burden, fasting blood sugar, systolic blood pressure, total cholesterol, and antidepressant use.

Here, we shall first review the direct neurotoxic effects of different AB classes on the CNS in CKD and then describe how ABs may accentuate CNS symptoms by modulating the gut microbiota.

Antibacterial agents and CKD

Antibacterials (AB) are among the most commonly prescribed medicines worldwide [11]. Patients with CKD are at increased risk for infectious complications due to comorbidities, presence of vascular or peritoneal access as well as immunosuppression secondary to immunosuppressive therapy and to renal dysfunction *per se* [12–14]. Indeed, both humoral immunity and cellular immunity are affected in CKD, with low immune cell activity and low antibody levels. This immune dysfunction is present at the onset of CKD but intensifies as kidney disease progresses and is most prominent in patients on dialysis [15]. After kidney transplantation, infections constitute a major cause of morbidity and mortality in immunosuppressed patients. Thus, ABs are frequently prescribed to CKD patients for treatment and prophylaxis.

However, AB therapy in patients with CKD has a number of specific aspects to consider: (i) renal excretion of most ABs; (ii) enhanced drug clearance through extracorporeal therapies; (iii) decreased plasma protein binding in the context of hypoalbuminemia and uremia; (iv) the role of tubular secretion to achieve local therapeutic drug levels (e.g. in urinary tract infections); and (v) interactions with chronic therapeutic regimens (e.g. clarithromycin with calcineurin inhibitors, fluoroquinolones with metallic phosphate binders and iron preparations) [16, 17].

ABs have previously been identified as important causes of adverse drug events in vulnerable patient populations [18]. Several classes of AB have neurotoxic effects on the peripheral and central nervous systems, with clinical manifestations such as antibiotic-associated encephalopathy (AAE) [19]. CKD is a known risk factor for the occurrence of AAE, which in turn is regarded as one of the commonest AB-induced ADRs in CKD patients [20, 21]. The overall prevalence of AAE has been estimated at 4.4% in hospitalized end-stage kidney disease (ESKD) patients receiving intravenous AB therapy, but is likely to be underestimated given the difficulty in inferring causality in sepsis and with comorbidities [21]. Distinct clinical phenotypes of AAE have been described with the use of different AB classes (Table 1) [20].

Role of therapeutic drug monitoring

Therapeutic drug monitoring (TDM) measures the amount of drug in various compartments, such as blood, serum, and/or plasma, and interstitial or other fluids to ensure the amount of drug taken by a patient is safe and effective. TDM as a discipline has evolved from monitoring a few classical anticonvulsants in the 1970s to routine monitoring of a number of drugs in different classes, including AB [22]. The role of TDM as an adjunct to clinical decision making is based on limited data from prospective randomized-controlled studies, as well as on data from systemic reviews and a general consensus on the value of PK/PD surrogacy [7, 23–27]. As discussed in our partner review, CKD-associated changes in drug PK and PD are relevant for dose adjustments and illustrate the use of TDM in the setting of altered PK (Table 2) [3]. The specific TDM targeted ranges are out of scope for this review although some general observations might be useful. Overall, methods in TDM, typically based on liquid chromatography coupled to tandem mass spectrometry, range from single measurements at a specific timepoint (e.g. at trough concentration or maximum concentration for vancomycin or gentamicin) to several measurements at specific timepoints after the administration to comprehensively assess drug exposure by calculating the area under the curve. Based on our clinical

Table 1: Antimicrobial agents. Mechanisms of neurotoxicity and clinical picture.

AB class	Mechanism neurotoxicity	Clinical picture
Beta-lactam Penicillins	Inhibition of GABA neurotransmission Non-competitive binding to GABA-A receptors	Increased excitability (high doses) Confusion, disorientation, hallucinations, myoclonus, and convulsions. Coma in high doses. Hoigne's syndrome (acute psychosis associated with IM procaine benzylpenicillin)
Cephalosporins	Competitive binding to GABA-A receptors High drug penetration in CNS Enhanced glutaminergic activity	Confusion, disorientation, hallucinations, myoclonus, and convulsions. Non-convulsive status epilepticus and language dysfunction potentially mimicking stroke. Cefazolin —headache, dizziness, drowsiness, confusion; Cefuroxime (<1%)—chills, headache, dizziness, drowsiness, irritability, trismus; Ceftazidime —seizures; Ceftriaxone (<1%)—chills, headache, dizziness, seizure; Cefepime (very frequent): encephalopathy, aphasia, myoclonus, seizure, non-convulsive status epilepticus 2 to 4 days after initiation.
Carbapenems	High tissue penetrance Antagonism of GABA-A receptor binding site Interaction with antiepileptic drugs	Seizures, encephalopathy, hallucinations. Neuropsychiatric features (altered mental status) 5 to 7 days after initiation Ertapenem —lower seizure risk (small volume of distribution + high protein binding); Meropenem —lower seizure risk. Additionally causes delirium and myoclonic jerking.
Fluoroquinolones	Inhibition of GABA neurotransmission (structural similarity to GABA) Interference with NMDA	Common: confusion, agitation, insomnia, drowsiness. Less common: hallucinations, suicidal ideation and toxic psychosis; dizziness, restlessness, Rare: seizures 2 to 3 days after initiation
Sulfonamides	Unknown (proposed deficiency in glutathione, secondary deficiency in dopamine and serotonin)	Apathy, depression, aseptic meningitis, ataxia, chills, headache, insomnia, seizures
Macrolides	Unknown (proposed metabolism involving cytochrome P450 3A4)	<1%: Acute psychosis, vertigo, dizziness, drowsiness, headache. Erythromycin—seizures
Metronidazole	Unknown (proposed interference with thiamin pathway, free radical formation). Usually long-term users	Cerebellar symptoms Altered mental status, seizures, peripheral neuropathies and psychosis.
Linezolid	Non-dose-related, weak nonselective monoamine oxidase inhibitor, leading to inhibition of serotonin metabolism Mitochondrial toxicity due to reduced protein synthesis inhibition of monoamine oxidase. Interaction with anticholinergic medications	Serotonin syndrome (agitation, confusion, hyperreflexia), delirium. Peripheral (pain, numbness, paresthesia, weakness) and cranial nerve (optical) neuropathies, when used for >27 days
Aminoglycosides	Activation of NMDA receptors	Numbness, seizure, abnormal gait, ataxia, confusion, headache, lethargy, seizure, vertigo, pseudotumor cerebri Ototoxicity
Polymyxins	Unknown, but dose dependent	Oral paresthesia (streptomycin), ataxia and visual disturbances. Seizures, confusion, hallucinations, vertigo
Isoniazid	Reversible, preventable with pyridoxine supplementation, and dose-related—formation of pyridoxal isonicotinyl hydrazine that leads to competitive inhibition of vitamin B6 action	Peripheral neuropathy (most frequent), paresthesia, sensory impairment, seizures, encephalopathy. Optical neuritis.
Ethambutol	Probable formation of pyridoxal isonicotinyl hydrazine that leads to competitive inhibition of vitamin B6 action	Confusion, dizziness, hallucination, headache, peripheral neuritis. Depression and suicidal ideation. Optical neuritis (irreversible blindness reported)

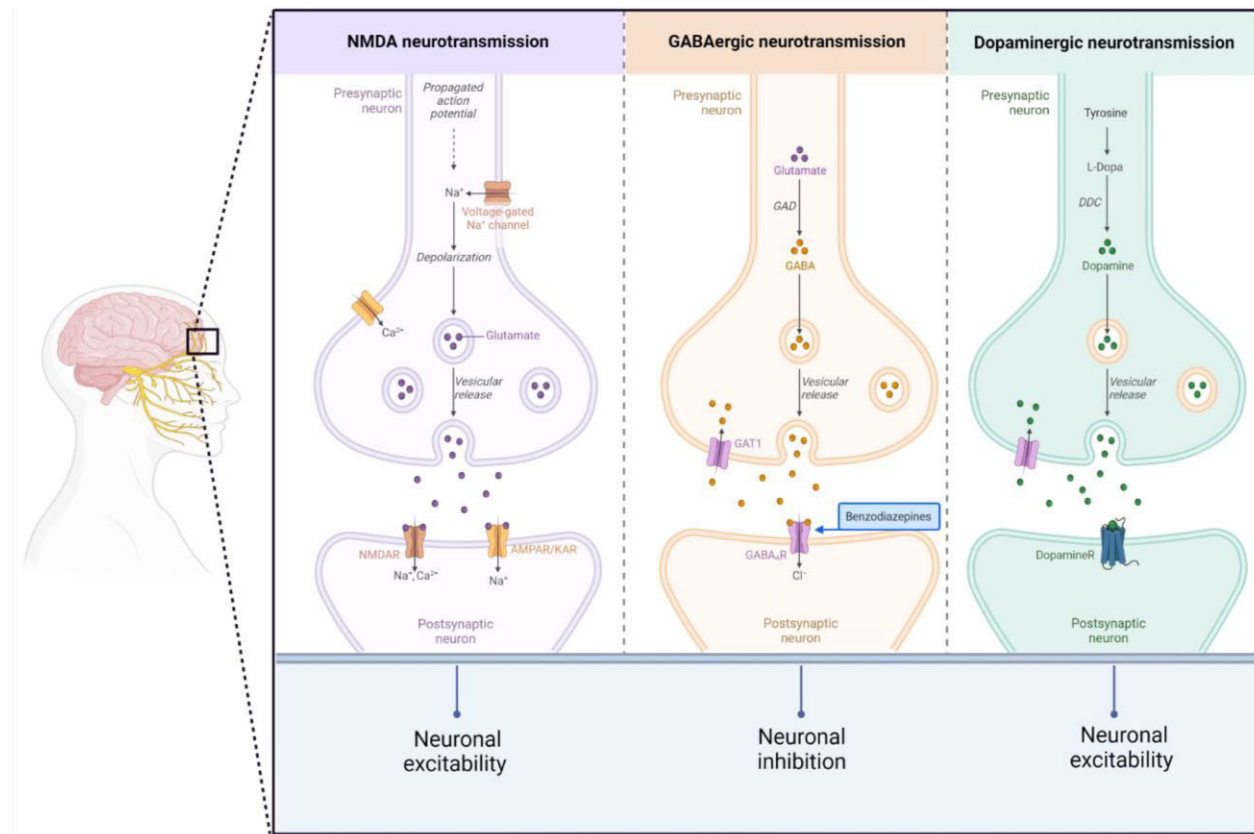


Figure 1: Central neuro-transmitter systems (created by BioRender.com). NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor; AMPAR/KAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor/kainate receptor; GABA, γ -Aminobutyric acid; GAD, Glutamate decarboxylase; GAT1, GABA transporter 1; GABA A R, γ -Aminobutyric acid-A receptor; DDC, DOPA decarboxylase.

experience, there are several key messages to remember before using TDM in daily practice: (i) The preferred TDM approach is proactive (regardless of clinical situation and based on risk factors for altered individual PK) as opposed to reactive (in response to clinical deterioration). (ii) TDM should be performed at the time of drug initiation or changed dosage regimen. (iii) For TDM purposes, a system should be in place assuring compliance with precise timing and handling according to laboratory instructions.

Antibacterials and direct neurotoxic effects

In the following, data on AAE in CKD patients will be presented according to different AB classes.

Beta-lactam-antibiotics

Beta-lactam antibiotics have classically been associated with neurotoxic effects [28]. CNS manifestations are mainly attributed to inhibition of the gamma-aminobutyric acid (GABA)-mediated neurotransmission leading to increased excitability. The interaction is linked to the core beta-lactam ring that is structurally similar to GABA, leading to non-competitive (e.g. penicillins) or competitive (e.g. cephalosporins) binding to the GABA-A receptor [29, 30]. The binding affinity is increased by predominantly basic C-2 side chain structures, e.g. in imipenem as compared with other carbapenems. In addition, inhibition of GABA-mediated neurotransmission also occurs through interac-

tion with the benzodiazepine receptor and decrease in number of benzodiazepine receptors (Fig. 1) [29].

Penicillins. Despite their large therapeutic window and different structural characteristics, virtually all penicillin molecules may exhibit neurotoxic effects at high serum levels [31]. Clinical manifestations include confusion, disorientation, hallucinations, myoclonus, and convulsions with onset within days of starting treatment and potential reversibility after drug cessation. A particular case concerns the acute psychotic picture associated with the intramuscular administration of procaine benzylpenicillin referred to as Hoigne's syndrome, mainly attributed to the procaine component influencing central dopaminergic neurotransmission analogous to other local anesthetics (Fig. 1) [32]. By contrast, chronic effects on cognitive function are not part of the typical clinical picture, although penicillins were among the AB classes associated with dementia risk in the population-based cohort mentioned earlier [10].

In the non-CKD population, penicillin central neurotoxicity has mainly been described in the setting of direct intraventricular application and high-dose-treatment [28, 33–43]. However, impaired renal function represents the chief risk factor and a relevant number of reported cases had preexisting stable CKD or acutely worsening kidney function. Encephalopathy occurred as consequence of failed dose adaptation, but also despite adapted dose regimens [38, 43–49]. In hemodialysis patients, two cases of encephalopathy induced by piperacillin-tazobactam have been reported [50, 51]. Neves et al. describe clinical improvement

Table 2: Antimicrobial agents and TDM

Drug class	Role of TDM for toxicity
Aminoglycosides	Ototoxicity [166] AMK: $C_{\min} > 5$ mg/l GEN: $C_{\min} > 1$ mg/l TOB: $C_{\min} > 1$ mg/l
Beta-lactams	Neurotoxicity [24, 56, 166] PIP: $C_{\min} > 361.4$ mg/l MEM: $C_{\min} > 44.5$ – 64.2 mg/l FLX: $C_{\min} > 125.1$ mg/l FEP: $C_{\min} > 20$ mg/l, $C_{ss} > 60$ mg/l
Fluoroquinolones	General toxicity [166, 167] Unclear
Oxazolidinones	Neurotoxicity [168] LZD: $C_{\min} > 2$ mg/l, >4 weeks treatment duration
Polymyxins	Nephrotoxicity [166] COL: $C_{\min} > 2.4$ mg/l PMB: AUC ₂₄ > 100
Sulfonamides	General toxicity [169] SXT: SMX > 150 mg/l

AMK: amikacin; AUC₂₄—area under the concentration–time curve during a 24-hour period (estimation based on one or several samples taken, measured in mg/l \times h); C_{\min} : minimum steady-state concentration monitoring for intermittent infusions (sample obtained prior to next dose); C_{ss} : steady-state concentrations for continuous infusions (sample obtained at any time during infusion); COL: colistin; FEP: cefepime; FLX: flucloxacillin; GEN: gentamycin; LZD: linezolid; MEM: meropenem; PIP: piperacillin; PMB: polymyxin B; SMX: sulfamethoxazole; SXT: co-trimoxazole (trimethoprim/sulfamethoxazole); TOB: tobramycin.

after two hemodialysis sessions with a switch to a high flux filter. In peritoneal dialysis patients, rapid improvement after one hemodialysis session has been noted, whereas another case showed resolution after drug cessation and with continued peritoneal dialysis [52, 53]. Kidney replacement therapy (continuous in roughly one-third) or creatinine clearance <10 ml/min were predictors of overdosing with oxacillin and cloxacillin in ICU patients with severe infections [43].

Cephalosporins. Cephalosporin-induced neurotoxic effects are well known and tend to occur more frequently with cefepime and ceftazidim [29, 54]. Neurotoxicity might be favored by high drug penetration into the CNS and competitive binding to GABA-A receptors, in contrast to non-competitive binding of penicillins. Clinical symptoms mirror those observed from other beta-lactam AB, but also include non-convulsive status epilepticus and language dysfunction potentially mimicking stroke [20]. Furthermore, cephalosporins were among the AB classes studied in a retrospective cohort analysis, which showed an increased risk for overall dementia in a cumulative and duration-dependent manner [10]. In a retrospective cohort study that included 319 in-hospital patients undergoing TDM for cefepime, the incidence of neurotoxicity was 23.3% and correlated with plasma trough levels. Median onset of symptoms after treatment commenced was 2 days with 81% of patients recovering after drug cessation within 2 days [55]. The overwhelming majority of cases has been described in patients with impaired kid-

ney function [56]. Reports on the effectiveness of hemodialysis as therapy for cefepime-induced neurotoxicity have shown conflicting results [56].

Carbapenems. Despite seizures regarded as the most prominent manifestation of carbapenem-associated neurotoxicity, neuropsychiatric features may also occur with these antibiotics [57]. However, this spectrum does not include chronic effects on cognitive function. In comparison with benzylpenicillin, carbapenems have been shown to exhibit higher neurotoxic potential due to high tissue penetrance that may be potentiated due to specific molecule properties as outlined above [58, 59]. In addition, the interaction with antiepileptic drugs increases the risk for seizure occurrence [60]. Among carbapenems, meropenem exhibits less neurotoxic effects than imipenem or ertapenem [61]. Neurotoxic effects are mainly described in the context of high-dose-treatment, preexisting CNS lesions, as well as renal impairment [62, 63]. However, these effects have been reported even with kidney function-adjusted regimens [48]. For example, among 26 reviewed cases of neurotoxicity associated with the use of ertapenem, 69% had acutely or chronically decreased kidney function [63]. Symptoms occurred between two and ten days and were reversible after drug discontinuation with or without hemodialysis treatment. However, long-lasting effects of up to two weeks have also been reported [64]. In patients undergoing chronic hemodialysis treated with ertapenem, an incidence of 10% for neurotoxic effects was described [65]. Drug elimination through hemodialysis sessions has been reported at 30% and up to 72% using low flux and high flux filters, respectively [64, 66]. In kidney transplant recipients, two reports have suggested an interaction between imipenem/cilastatin and cyclosporine A, leading to increased neurotoxicity [67, 68]. Given its lower neurotoxic potential, meropenem may be the preferred carbapenem to use in CKD patients at high risk of neurotoxicity.

Fluoroquinolones

ADRs affecting the CNS are well known among this drug class with an incidence of 1.1%–6.6% reported for ciprofloxacin [69, 70]. Manifestations include a wide range of neurological and psychiatric symptoms with a predominance of psychotic syndromes and a rare occurrence of seizures [71, 72]. In addition, epilepsy and serious cognitive impairment following the use of intravenous levofloxacin injection have been described in a single case. Improvement of the disorder after drug withdrawal was noted, which may be considered a rare adverse effect of levofloxacin [73].

Several molecules have been shown to cross the BBB despite non-lipophilic properties [74]. Neurotoxic reactions are ascribed to inhibition of GABA neurotransmission given the structural similarity to GABA with displacement of GABA from its receptor [75]. However, interference with N-methyl-D-aspartate (NMDA) neurotransmission has also been demonstrated in vitro (Fig. 1) [76]. In addition, drug interactions with xanthine derivatives and non-steroidal anti-inflammatory drugs can potentially increase neurotoxicity [75]. Additional risk factors for the development include high dosage and renal impairment [77]. Among 63 reviewed cases of quinolone-associated AAE, 22% had underlying kidney impairment [20]. Few cases of quinolone neurotoxicity have been reported in patients on hemodialysis and peritoneal dialysis, some but not all following overdosing [78–82].

Sulfonamides

Sulfonamide-induced neurotoxic effects have been recognized early after the discovery of this AB class with acute psychosis as a main manifestation [83]. However, sulfonamides were included in a retrospective cohort analysis showing an increased risk with cumulative or long-term AB use [10]. The incidence of this ADR has been estimated up to 23.5% in HIV-infected patients, but it might be difficult to evaluate given the comorbid condition and frequent co-medication with steroids in the setting of *Pneumocystis jiroveci* pneumonia [84]. Despite high penetration into the CNS, the mechanisms underlying these effects are unknown [85]. Deficiency in glutathione as well as reduced tetrahydrobiopterin synthesis with secondary deficiency in dopamine and serotonin have been proposed [86, 87]. Neurotoxic effects occur in a dose-dependent manner [84]. No impaired renal function was noted in a cohort of HIV-infected patients developing acute psychosis under treatment with co-trimoxazol [84]. In another retrospective cohort of 20 kidney transplant recipients treated for *Pneumocystis jiroveci* pneumonia, four patients developed acute psychosis that resolved within 24 hours after discontinuing the drug [88].

Macrolides

The main neurotoxic manifestation induced by macrolide AB is an acute psychosis-like syndrome; however, CNS effects may include dizziness, vertigo, insomnia, tinnitus, confusion, and disorientation [20, 89]. In addition, macrolides were one of the seven classes of ABs analyzed in a population-based cohort showing that AB exposure may increase the risk for dementia in a cumulative duration-dependent manner [10]. In an early small cohort of elderly patients treated with clarithromycin, side effects affecting the CNS occurred in more than half of the patients [90]. The pathophysiological substrate of these neuropsychiatric effects is currently not known [91]. However, given the metabolism involving cytochrome P450 3A4, the co-administration of other molecules metabolized through this pathway may lead to increased risk for neurotoxicity [89]. Importantly, CYP 3A4 activity has been reported to be reduced in uremia and to be partly restored after hemodialysis treatment [92]. However, among 54 and 38 reviewed cases of macrolide- and clarithromycin-induced neurotoxicity, only four and two cases had preexisting kidney impairment, respectively [20, 89]. Several cases of clarithromycin-induced hallucinations in peritoneal dialysis patients have been published so far, in one case despite the use of kidney-adapted dosing regimens [93–95]. On the other hand, a neuroprotective potential of erythromycin has been suggested. Thus, in a mouse model for Alzheimer's disease, erythromycin showed high anti-amyloid effects [96]. Furthermore, in a clinical randomized-controlled trial, perioperative use of erythromycin led to improved cognitive performance after coronary artery bypass grafting surgery compared to standard of care therapy [97]. However, although a candidate drug for exploring the potential to prevent cognitive decline and progression to dementia based on benefits to synaptic impairment, erythromycin was excluded as it passes the BBB only if used in high doses potentially causing hematological complications [98].

Metronidazole

Metronidazole neurotoxicity produces a distinctive clinical phenotype. In an incidental cohort of 336 425 elderly patients

treated with metronidazole for the first time, 0.2% developed CNS symptoms within 100 days of therapy start [99]. The clinical picture is characterized by encephalopathy with cerebellar symptoms and typical MR imaging signs occurring with a latency of weeks after treatment begins, rather than within days as described for other AB [20, 100, 101]. However, neuropsychiatric patterns including altered mental status and seizures, as well as peripheral neuropathies, psychosis, and rapid, reversible cognitive decline, can also occur [101–104]. Time to resolution typically is longer than that described for other AB and might be incomplete in rare cases [20, 101, 102]. Despite metronidazole readily crossing the BBB, the mechanism by which it exerts its neurotoxic effects is unknown [85]. Among other hypotheses, interference with the thiamine pathway and free radical formation has been discussed [105–107]. At least 15% of the 136 patients collected by Sorensen *et al.* exhibiting metronidazole-induced neurotoxicity had preexisting hepatic dysfunction, whereas 7% had CKD [101]. Conflicting data exist concerning the acute and cumulative dose-dependency of metronidazole neurotoxicity, which has been suggested by some authors, based on single case reports, but has not been confirmed by others reporting larger cohorts [99, 101, 108, 109]. Indeed, such a finding could be of relevance in the immunosuppressed and aged CKD patient population. Data on patients undergoing dialysis treatment are scarce. Hemodialysis has been used in the context of metronidazole-induced neurotoxicity and accidental overdose in hemodialysis patients, respectively [110, 111]. In kidney transplant recipients, metronidazole-induced neurotoxicity has been reported after variable treatment duration and with complete resolution of symptoms after drug discontinuation [112, 113].

Linezolid

Besides more common neurotoxic effects, including peripheral and cranial nerve neuropathies and serotonin syndromes, very few data exist on the potential occurrence of linezolid-induced encephalopathy [114–116]. Symptoms in these cases resolved after drug discontinuation. In contrast, no long-term effects on cognition have been described to our knowledge. Linezolid penetrates the BBB [85]. One postulated mechanism of injury is mitochondrial toxicity due to reduced protein synthesis [117]. In addition, inhibition of monoamine oxidase by linezolid might explain some of the CNS effects, including 'serotonin syndrome', delirium and interaction with anticholinergic medications [118]. However, comorbid conditions, including electrolyte abnormalities and alcoholism, as well as co-medications do not allow for any firm conclusion. In only one case was reduced kidney function reported [114].

Aminoglycosides

Neurotoxic effects associated with the use of aminoglycosides are known to affect the cochlea, neuromuscular and autonomic transmission, as well as the peripheral nervous system. However, very limited data suggest the occurrence of encephalopathy after exposure to gentamicin with ultrastructural evidence of lysosomal pathology, whereas distinctive reproducible lesions of the brain stem have also been reported in an animal study after high-dose intracisternal gentamicin administration [119, 120]. However, no chronic effects on cognitive functions have been described. As demonstrated for ototoxicity, activation of NMDA receptors has been shown to be involved with direct intraatrial application of neomycin [121].

Polymyxins

Polymyxins such as colistin are known to exhibit neurotoxic effects comprising neuromuscular blockade (after intramuscular administration), paresthesia, ataxia, and visual disturbances [122]. However, the occurrence of seizures, confusion, and hallucinations, as well as severe encephalopathy, have also been reported [122–124]. By contrast, to our knowledge, no lasting effects on cognitive functions have been reported. CNS effects are thought to be facilitated by the lipophilic structure of polymyxins [125]. However, the exact mechanism for central neurotoxicity is still unknown. Kidney impairment has not been described as a risk factor for the occurrence of CNS neurotoxicity [122]. Polymyxin use was nevertheless associated with a high frequency of overall neurotoxic events in a cohort of 213 kidney transplant recipients with mainly paresthesiae, but also hallucinations in 3.4% [126].

Antimycobacterials

Active tuberculosis, caused by the *Mycobacterium tuberculosis* bacteria, remains one of the main infectious causes of death worldwide, with variable geographical prevalence. Recommended treatment for active tuberculosis relies on quadritherapy with isoniazid, rifampicin, pyrazinamide, and ethambutol [127]. CKD is known to be associated with a higher prevalence of tuberculosis, but very few data are available in CKD patients on the frequency of prescription and tolerance of antimycobacterials [128].

Isoniazid. Isoniazid is the main antimycobacterial associated with neurotoxicity and causes peripheral neuropathy. Described effects on the CNS mainly include encephalopathy; however, in a prospective cohort of 100 patients receiving isoniazid for treatment of latent tuberculosis, nine suffered from cognitive impairment of unspecified duration [129]. An American study assessed the cognitive function of 25 adolescents who received isoniazid for at least 6 months before the treatment, during, and after its cessation and did not find significant impact on attentional function [130]. Isoniazid neurotoxicity is mainly due to altered metabolism of pyridoxine (vitamin B6). High-dose pyridoxine supplementation is recommended if signs of isoniazid-induced peripheral neuropathy appear. Some case reports and case series suggested increased isoniazid neurotoxicity in ESKD due to altered pyridoxine metabolism, resulting in severe deficiency in pyridoxal phosphate (active form of pyridoxine), as well as an important removal of pyridoxal phosphate by renal replacement therapies, including hemodialysis and peritoneal dialysis [131, 132]. Despite the rarer occurrence of isoniazid neurotoxicity affecting the CNS, CNS toxicity seems to be more frequent in CKD patients and cases of encephalopathy (presenting mainly as consciousness disorders, seizures, or cerebellitis) were reported in these patients [133, 134]. It is therefore recommended to prescribe pyridoxine supplementation to CKD patients taking isoniazid (minimum dosage 100 mg/day) for the duration of treatment to prevent its neurotoxicity.

Ethambutol. Optic neuropathy is a common complication of ethambutol treatment and can occur early following the initiation of ethambutol. Patients will usually present bilateral central visual acuity loss and dyschromatopsia [135]. However, rare cases of ethambutol-induced psychosis and confusion have also been reported [136–138]. No association has been

reported between ethambutol and chronic cognitive dysfunction. Pathophysiology of ethambutol-induced neurotoxicity is poorly understood, but is suggested to be related to the metal chelating effect of ethambutol through two putative mechanisms: copper chelation disrupting mitochondrial metabolism and zinc chelation inhibiting lysosomal activation [135]. CKD patients are exposed to higher concentrations of ethambutol and are considered at higher risk of ethambutol-induced optic neuropathy, although the evidence is weak [132, 139]. Of note, concomitant administration of isoniazid might increase the risk of ethambutol-induced optic neuropathy.

Rifampicin. Interestingly, experimental murine studies suggested that rifampicin might have neuroprotective effects. Rifampicin decreased apoptosis and increased neuron viability in *in vitro* models of neurotoxicity and decreased the neurotoxicity and aggregation of amyloid beta protein in rat pheochromocytoma cells. [140, 141]. In addition, several experimental studies found that rifampicin improved cognitive performance in models of cognitive impairment in rodents [142]. In humans, the potential beneficial effect of rifampicin is still debated. A randomized-controlled study evaluating daily doxycycline + rifampicine versus placebo in patients with probable Alzheimer's disease found an improvement in cognitive decline in the treated group [143]. However, the subsequent randomized-controlled DARAD trial did not find any effect of rifampicin on cognition in patients with Alzheimer's disease [144]. However, no clinical data have evaluated whether rifampicin might mitigate neurotoxicity induced by isoniazid and ethambutol. An experimental study found that prenatal exposition to ethambutol, isoniazid, and rifampicin could induce cognitive dysfunction in rats [145].

Antibacterials and effects on gut microbiota

Microbiota in CKD

The composition of bacteria, fungi, archaea, and viruses colonizing the GI tract is collectively referred to as gut microbiota. It forms a complex and mutually beneficial relationship with the host, and its composition is considered to play an important role for the maintenance of the host homeostasis, as well as for the development of certain diseases [146]. Since several years, CKD has been associated with dysbiosis, an imbalanced intestinal microbial community with quantitative and qualitative changes in the composition and metabolic activities of the gut microbiota [147]. It is thought that in CKD increasing urea concentrations lead to alterations in the intestinal flora that can increase production of gut-derived toxins [148]. Likewise, changes in microbiota composition and structure produce excessive amounts of uremic toxins and less reno-protective metabolites [149]. Thus, in pathological states, interactions between the kidneys and gut microbiota are bidirectional and current management of dysbiosis in CKD should be considered as a novel focus for the management of CKD (Fig. 2).

It was demonstrated that healthy gut microbiota has reno-protective roles. Short-chain fatty acids (SCFA) are products of microbial fermentation that protect tubular cells against oxidative stress and biogenesis of mitochondria. They can also reduce ischemia-reperfusion kidney injury and inflammation, as well as infiltration of immune and apoptotic cells in the injured kidneys of mice [150–152]. However, in CKD, dysregulation of SCFAs and their receptors has been reported, and CKD-linked dysbiosis

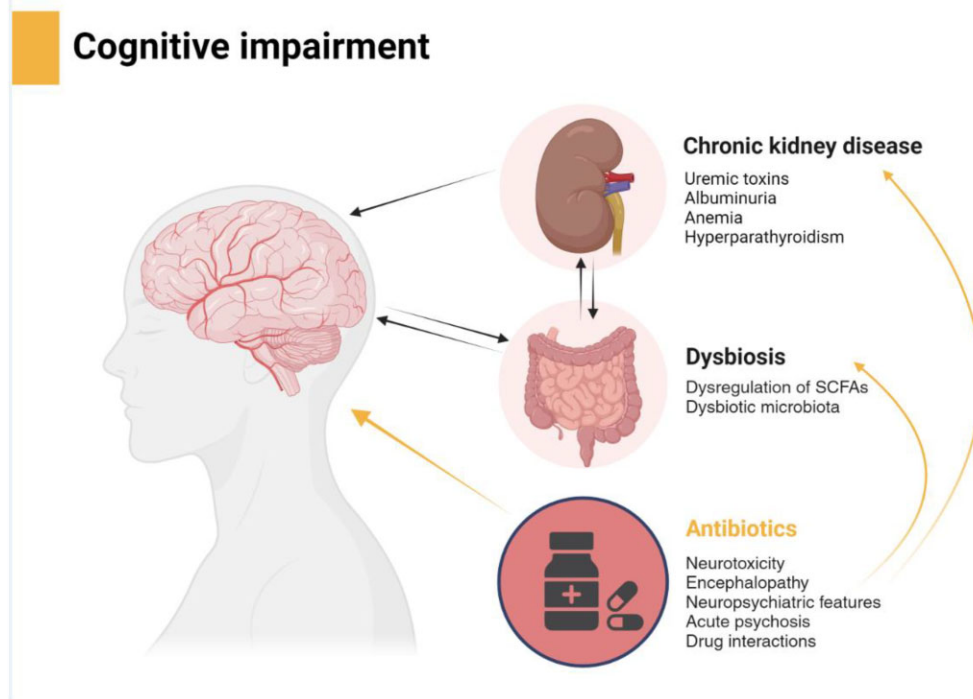


Figure 2: Interaction between antibacterials, microbiota, and kidney function contributing to cognitive impairment (created by BioRender.com). SCFAs, short-chain fatty acids.

increased the microbiota-derived uremic toxins, trimethylamine-*N*-oxide, and activation of aryl hydrocarbon receptors [153, 154]. In patients with stage 3–4 CKD there is also an increase in aerobic and a decrease in anaerobic bacteria [155]. In rats with CKD induced by 5/6 nephrectomy, abundance of bacterial taxa differs significantly compared with controls and the serum levels of uremic toxins in these animals correlated with the abundance of *Clostridia*- and *bacteroidia*-affiliated species in the gut microbiota [156, 157].

Antibacterials and Microbiota

Prescribed ABs are considered a major risk factor for alteration of gut microbiota composition, diversity, and abundance. Even short-term AB treatment can shift the gut microbiota to a long-term dysbiotic state. The post-antibiotic dysbiosis includes loss of bacterial diversity and reduced colonization resistance against pathogens. Furthermore, one of the major concerns of AB use is the long-term alterations of the healthy gut microbiota and horizontal transfer of resistance genes that could result in accumulation of bacteria with multidrug resistance genes. Unfortunately, CKD patients are frequently exposed to ABs for curative or prophylactic indications. Thus, the already altered composition and function of gut microbiota are further worsened by AB treatment.

A systematic review of AB-induced changes in human gut microbiota from published data between 1979 until 2017 revealed that dysbiosis rapidly develops under AB administration. After AB treatment, composition of the gut microbiota generally returns to similar pretreatment state within several weeks, but not in all cases [158]. For example, prescribed amoxicillin induced an increase in *Enterobacteria*, a decrease or no change in anaerobic bacteria, *Lactobacillus* and *Bifidobacteria*, as well as an increase in *Bacterioides* and overgrowth of *Candida* in some

cases. Amoxicillin with clavulanic acid induced an increase in aerobic gram-positive cocci and *Enterobacteria*, including *Escherichia coli*, a decrease in *Lactobacillus* and *Bifidobacteria*, as well as overgrowth of *Clostridium*. This review from a UK primary care setting suggests that once treatment has been stopped, gut bacteria are capable of recovery to their pretreatment state. However, the fact that the microbiota may not have fully recovered suggests that some ABs have a persistent effect on certain bacterial species.

Antibacterials, microbiota, and effects on the CNS

The association of long-term AB use with cognitive function is controversial. A prospective, population-based cohort study was conducted on >14 000 women to investigate whether at least 2 months of AB exposure is associated with cognitive scores [8]. It was concluded that long-term ABs use in midlife was associated with a small decrease in cognition assessed seven years later. Assessment included global cognition, learning and working memory, psychomotor speed, and attention. On the other hand, short-term AB use can be linked to extreme neurological changes such as encephalopathy or psychosis that have been attributed to direct neurotoxic effects (see previously). However, at present it is unclear whether AB effects on microbiota composition play an additional role in these cases.

Conversely, psychotropic agents do have an effect on gut microbiota and prolonged exposure to such agents is often associated with marked gastrointestinal changes, including altered food intake, bowel motility, gastric emptying, and transit time. In addition, mounting evidence suggests that physical and mental disturbances lead to changes in gastrointestinal motility in both animals and humans. In the experimental model of depressive-like behavior in rats, treatment with oxytocin exerted anxiolytic and antidepressant effects, but also induced a strong shift in

microbiota composition. The magnitude of that shift was associated with behavioral tests scores [159]. Furthermore, this study showed that a specific bacterial genus, *Mogibacterium*, which increased in abundance, was associated with low-anxiety behavior in rats.

Therefore, it might be concluded that the relation between gut and CNS is bidirectional and that drugs affecting CNS affect gut microbiota, while AB when affecting gut microbiota have effects on CNS and cognitive functions (Fig. 2).

Antibacterials and the brain-gut-kidney axis

The term 'brain-gut-kidney axis' was introduced by Yang in a review on the relationship between gut microbiota and hypertension in CKD [160]. However, considering CKD patients and the negative impact of ABs on gut microbiota that may lead to, or at least add to, cognitive decline, we should think about the brain-gut-kidney axis as an important pathogenic in patients with kidney disease.

In addition, several risk factors may contribute to cognitive impairment such as cardiovascular disease, inflammation, and head injury, but other CKD-related factors such as anemia, hyperparathyroidism, uremic toxins, or albuminuria may also contribute [161, 162].

Finally, kidney dysfunction and uremia have implications for the BBB and gut-blood barrier through reduced expression of tight-junction proteins in both barriers. In addition, gut-derived uremic toxins are associated with increased inflammation and oxidative stress that may be associated with anemia and mineral metabolism disorders. Kidney-dependent gut dysbiosis is also linked to decreased SCFAs, barrier damage, and Th17 polarization. Taken together, these factors affect brain and cognitive functions. Furthermore, dysregulation of the tryptophan kynurenine pathway of CKD might also be associated with the cognitive impairment as part of the brain-gut-kidney axis [160, 163].

Where do AB-dependent microbiota changes or dysbiosis stand in relation to other factors? It seems particularly challenging to distinguish what comes first and how original disruption of cognitive functioning by ABs is associated with its effects on the gut microbiota already changed by CKD. More studies should be conducted analyzing the impact of prescribed ABs on cognitive impairment in CKD patients. Moreover, therapeutic approaches to AB prescribing involving prebiotic, probiotic, and symbiotic supplementation CKD patients should be considered to restore gut microbiota balance.

CONCLUSION

In conclusion, AB dosing in CKD patients involves regimen adaptations taking into account the altered pharmacokinetics. Moreover, caution is required to detect acute changes in kidney function in these patients in the clinical setting of infection. In addition, the AB drug mechanism of action (time- vs concentration-dependent), therapeutic window, severity of infection, microbial sensitivity, infection site, and host immunodeficiency have all to be considered to ensure adequate dosing and avoid under-dosing [164]. In particular, and in most cases, the administration of loading doses in the normal range is possible [165]. To avoid ADRs affecting the CNS, AB dose levels must be measured and adjusted using TDM.

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AUTHORS' CONTRIBUTIONS

L.-Y.M., S.L., and G.H. were responsible for the research idea. L.-Y.M. was responsible for the writing and the supervision of review writing. L.-Y.M., V.P., G.S., M.B., R.M., I.A.B., M.P., and Z.A.M. contributed to writing parts of the manuscript. R.M., I.A.B., A.C.F., A.F., and J.M. contributed to table preparation. G.H. and S.L. contributed to figure preparation. All authors critically revised the manuscript. All authors reviewed and approved the manuscript for publication.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

CONFLICT OF INTEREST STATEMENT

Robert Unwin is currently working as a Chief Scientist (Kidney Diseases) in Translational Science and Experimental Medicine, Early CVRM (Cardiovascular, Renal and Metabolism), BioPharmaceutical R&D, AstraZeneca, Cambridge, UK. Other authors declare no conflicts of interest related to this work.

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