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Adverse Antibiotic Effects Associated with Renal Insufficiency

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We review the English-language literature on antibiotic-associated adverse reactions in patients with renal insufficiency in order to highlight this important but often overlooked clinical problem. Because many adverse reactions to antibiotics are not dependent on renal function, we have attempted to review only those reactions that are believed to be associated with renal insufficiency or that have been reported in patients with impaired renal function. Adverse effects of antibiotics in this setting can be divided into six major categories: neurologic toxicity, coagulopathy, nephrotoxicity, hypoglycemia, hematologic toxicity, and aminoglycoside inactivation by penicillins. Neurologic toxicity can be further divided into central nervous system toxicity consisting primarily of encephalopathy and seizures, ototoxicity, peripheral neuropathy, and neuromuscular blockade/respiratory depression. We explore the factors in uremia that may contribute to the susceptibility of patients with renal insufficiency to the adverse effects of antibiotics. Moreover, we make general recommendations regarding the use of the discussed antibiotics in patients with compromised renal function.

Infections cause significant morbidity in renal insufficiency, occurring in up to 88% and 60% of patients with acute and chronic renal failure, respectively [1]. Infections are also the leading cause of death in acute renal failure and the second most common cause of death in patients undergoing hemodialysis [2]. Hence, many patients with impaired renal function can be expected to be exposed during their lifetime to a multitude of antibiotics, some of which may be more likely than others to cause adverse effects in renal insufficiency. The literature abounds with case reports and isolated reviews of adverse reactions to antibiotics in patients with renal insufficiency, but a comprehensive review of this subject has been lacking. Our recent experience with several patients with renal impairment who had antibiotic-related adverse reactions prompted us to review the literature on this subject in hopes of heightening the awareness of this important but often overlooked clinical problem.

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Materials and Methods

The literature search was confined to English-language publications and was facilitated by computerized service from MEDLAR II of the National Library of Medicine for publications since 1966. Only those antibiotics that are currently used for their antimicrobial properties were considered. Neither older antibiotics that are currently not in use nor antiprotozoal, anthelmintic, or antineoplastic agents with antimicrobial activity were included. An antibiotic-associated adverse effect was defined as an untoward reaction in which an antimicrobial agent has been strongly implicated. Because many adverse effects of antibiotics are not dependent on renal function, an attempt was made to review only those reactions specifically reported in patients with renal insufficiency or thought to occur more frequently in such patients. Allergic adverse reactions, such as rash and drug fever, were excluded. Criteria for renal insufficiency were a blood urea nitrogen (BUN) level of >20 mg/dL, a serum creatinine level of >1.5 mg/dL, or a creatinine clearance rate of <70 mL/min.

Review of the Literature

Adverse reactions caused by antibiotics in renal insufficiency can be divided into six major categories: neurotoxicity, coagulopathy, nephrotoxicity, hypoglycemia, hematologic toxicity, and aminoglycoside

inactivation by penicillins. Each of these categories will be considered separately.

Neurotoxicity

Neurotoxicity associated with antibiotics can be subdivided into four types: CNS toxicity, ototoxicity, peripheral nerve toxicity, and neuromuscular blockade/respiratory depression.

CNS toxicity. CNS toxicity is one of the most frequent adverse reactions caused by antibiotics in patients with impaired renal function. A wide spectrum of reactions, including confusion, dysarthria, psychosis, myoclonus, seizures (focal motor or generalized), and coma, have been reported [3–29] (see Appendix). These neurologic findings are often attributed to other processes, a mistake that results in delay in the correct diagnosis. Antibiotics reported to cause CNS toxicity in renal insufficiency are listed in table 1.

Table 1. Antibiotics associated with CNS toxicity in renal insufficiency.

Antibiotic	Reference(s)
Acyclovir	4
Amantadine	5
Cephalosporins*	
Cefazolin	6, 7
Cefuroxime	8
Cephalexin	9
Cephalothin	10
Moxalactam	11
Colistimethate	12–15
Cycloserine	16
Erythromycin	17, 18
Imipenem/cilastatin	19
Isoniazid	20–22
Penicillins*	
Ampicillin	23
Dicloxacillin	Appendix
Oxacillin	3, Appendix
Penicillin G	24–26
Ticarcillin	27
Nalidixic acid	28
Tetracycline	29

* Potentially, any β-lactam antibiotic at high serum levels may be associated with CNS toxicity.

The epileptogenic properties of penicillin administered directly into the cerebral cortex, ventricular space, or subarachnoid space were demonstrated more than 4 decades ago [30–32]. Related β-lactam antibiotics, including other penicillins, cephalosporins, and imipenem, comprise the major group of neurotoxic agents. In most instances, this toxicity appears to be related to high concentrations of drug in serum. Other factors, such as decreased protein binding of drugs in uremia [33, 34] (which results in an increased free fraction of highly protein-bound drugs in the serum, and therefore in the CNS), altered blood-brain barrier in uremic patients [35], and underlying anatomic and physiologic cerebral abnormalities associated with uremia [14, 36], may contribute to the susceptibility of these patients to antibiotic-related CNS reactions. Because of these factors, even those antibiotics that reach only low CSF concentrations under ordinary circumstances (e.g., cefazolin and cephalexin) can cause CNS toxicity. Resolution of symptoms may be slow even after discontinuation of therapy [10, 24, 27], possibly because of the slow clearance of antibiotics from CSF [24, 27].

Imipenem/cilastatin-related seizures have also been associated with renal insufficiency, particularly when an appropriate dosage reduction is not made [19].

Ototoxicity. Antibiotic-associated ototoxicity may affect vestibular and/or cochlear function. Vestibular toxicity presents as dizziness, vertigo, and ataxia. Auditory toxicity can be associated with tinnitus and encompasses a spectrum of hearing impairment ranging from high-frequency subclinical hearing loss to complete deafness. Uremic polyneuropathy associated with dysfunction of the eighth cranial nerve [36] may contribute to susceptibility to drug-induced ototoxicity. Antibiotics associated with ototoxicity in renal insufficiency include aminoglycosides [37–51], erythromycin [17, 52–56], cephalexin [57], and vancomycin [58]. Because of quantitative and qualitative differences in the ototoxicity of these groups of antibiotics, each will be considered separately.

(1) Aminoglycosides. Aminoglycoside-induced ototoxicity is generally thought to occur more commonly in patients with renal impairment than in other patients [37, 39, 48], but renal insufficiency may not necessarily be an important risk factor for ototoxicity as long as serum drug levels are closely monitored [59]. Important features of aminoglycoside ototoxicity include the following. (a) It may be unilateral or bilateral [39]. (b) High-frequency sound perception is affected first and lower-frequency hearing loss next [39]. (c) Ototoxicity may occur days to weeks after therapy has been discontinued [39, 50]. (d) Concomitant use of "loop" diuretics potentiates

toxicity [37, 46, 60]. (e) Auditory toxicity is generally irreversible [39, 40, 50, 59, 61]. (f) Aminoglycoside-induced ototoxicity may occur independent of nephrotoxicity [62–64]. (g) The cumulative dose of aminoglycoside and duration of therapy are more important than serum concentrations [41, 43, 49, 50]. Although the mechanism for the predisposition of renally impaired patients to aminoglycoside ototoxicity is unknown, drug accumulation with persistently high concentrations in the perilymph and endolymph [43, 49, 65], repeated exposure to ototoxic drugs [37], and eighth-cranial-nerve dysfunction in uremia [36] may be operative. Concomitant proprioceptive defects due to uremic polyneuropathy may also exacerbate the clinical manifestations of vestibular toxicity in these patients [42, 66, 67].

Ototoxicity caused by gentamicin is principally vestibular but may also be cochlear [37, 44]. In a study of vestibular toxicity in patients undergoing chronic hemodialysis and receiving gentamicin, clinically significant vestibular toxicity developed in 30% of cases [43], with a cumulative dose of >17.5 mg/kg being predictive of ototoxicity. However, as little as 410 mg of gentamicin [50] has been associated with vestibular toxicity in a patient with renal failure.

Tobramycin has also been associated with an increased risk of ototoxicity in renal insufficiency and is generally thought to be associated with an equivalent risk of auditory and vestibular toxicity [47]. However, in a study by Brogard et al. [65], six of 10 patients on maintenance hemodialysis who received prolonged courses of tobramycin (total dose, 500 mg over a 15-day period) developed subclinical vestibular dysfunction detected by vestibulometry, with no evidence of significant cochlear impairment. In contrast, in persons with normal renal function who received 150–225 mg of tobramycin daily for 15 days, subclinical ototoxicity was generally either absent or mild. No clear relation between serum drug concentrations and ototoxicity was established. In another study, a high total dose, an extended period of therapy (>10 days), and treatment with other possibly ototoxic drugs were associated with the development of ototoxicity in renal insufficiency [47].

Although several studies in animals and humans have found tobramycin to have less ototoxic potential than gentamicin [47, 64, 68, 69], other investigations have not corroborated such findings [70]. In the absence of well-designed prospective studies, the comparative risk of ototoxicity of these two aminoglycosides in renal insufficiency remains speculative.

Amikacin-induced ototoxicity primarily affects auditory function [71–74], with an associated risk of ototoxicity similar to that for other commonly used aminoglycosides [38, 61, 75]. In contrast, streptomycin causes primarily vestibular toxicity that can be particularly disabling in renally impaired patients [40].

In one study, netilmicin was less ototoxic than tobramycin in patients with serum creatinine levels of ≤2.4 mg/dL [76]. Barza et al. [38] reported that two of three patients with netilmicin-related auditory toxicity had prior renal failure. Insignificant differences in ototoxicity between netilmicin and amikacin have been reported [38, 61].

Use of neomycin in renally impaired patients is associated with a high risk of ototoxicity regardless of the mode of administration (i.e., oral, intraperitoneal, or topical on open wounds) [39, 45, 51]. We have also observed ototoxicity from prolonged neomycin bladder irrigation in uremic patients (authors' unpublished observations). Although neomycin absorption by these routes may seem trivial, ototoxic blood levels can easily be achieved in renal insufficiency, particularly during extended therapy [39].

(*2*) *Erythromycin.* Ototoxicity caused by erythromycin was first reported in 1973 in two patients with normal renal function [55]. Subsequently, several cases of erythromycin-induced ototoxicity have been reported in patients with renal insufficiency [53]. Although auditory function is most affected, vestibular dysfunction may also occur [17]. Several formulations of the drug—including lactobionate, ethylsuccinate, and stearate given orally, intravenously, or intraperitoneally—have been implicated [17, 52, 53, 55, 56]. Ototoxicity caused by erythromycin is reversible and dose related, with many affected patients having received daily doses of ≥4 g [53]. Serum concentrations of erythromycin in these patients have been severalfold higher than therapeutic concentrations [18, 53]. It should be emphasized that although erythromycin is excreted primarily via the hepatic route, its serum half-life is prolonged in anuria [53, 77].

(*3*) *Vancomycin.* Vancomycin-induced ototoxicity primarily affects auditory function [58]. The risk of vancomycin ototoxicity in renal insufficiency is unknown, but high serum concentrations (>30 mg/mL) during parenteral therapy have been associated with this adverse reaction [58, 78]. Because of the drug's primary renal excretion, patients with renal impairment may be particularly susceptible to

vancomycin-induced ototoxicity unless serum drug concentrations are closely monitored. Concomitant therapy with other ototoxic agents (such as aminoglycosides) may have an additive effect [78].

Although not appreciably absorbed in healthy individuals [79], oral vancomycin has reached detectable—at times significant—serum levels (>10 mg/mL) in patients with renal insufficiency and antibiotic-induced colitis [79, 80]. However, no apparent adverse reaction has been attributed to such drug levels. Routine monitoring of serum vancomycin levels in renally impaired patients receiving oral vancomycin is probably not necessary but may have to be considered in patients receiving a high dose (>2 g daily) or a prolonged course (>10 days) [79].

(*4*) *Cephalexin.* Reversible ototoxicity due to cephalexin was reported in two patients with impaired renal function who presented with dizziness and vertigo after having received "usual doses" of the drug for ≥10 days [57]. Cochlear function was not clinically affected. Although cephalexin is effectively removed by hemodialysis and peritoneal dialysis, one of the reported ototoxic patients was undergoing maintenance hemodialysis when ototoxicity developed.

Peripheral nerve toxicity. Nitrofurantoin has caused peripheral nerve toxicity in patients with renal insufficiency [81]; this reaction is manifested by paresthesias and weakness in the extremities associated with high serum drug concentrations. Renal failure has also been reported to be a risk factor for isoniazid-induced peripheral neuropathy [82] that appears to be related to pyridoxine deficiency and resolves after administration of this vitamin. Uremic polyneuropathy [36] may contribute to this toxicity.

Neuromuscular blockade/respiratory depression. Two major groups of antibiotics cause neuromuscular blockade with resultant respiratory depression in renal insufficiency: aminoglycosides [83–88] and polymyxins [85, 87, 89, 90]. Although this adverse reaction may occur in patients with normal renal function as well, renal impairment—with its associated drug accumulation and possible hypocalcemia [91]—appears to be an important contributing factor. Concurrent administration of other neuromuscular blocking agents, such as *d*-tubocurarine, pancuronium, and succinylcholine, may produce an additive effect [83, 86, 88]. Aminoglycosides act primarily on the presynaptic sites of the neuromuscular junction, with resultant suppression of the release of acetylcholine at nerve endings [87]. This action is effectively reversed by calcium, with only a partial response to neostigmine. Polymyxins appear to act primarily on postsynaptic sites of the neuromuscular junction [87]. In contrast to the condition induced by aminoglycosides, polymyxin-induced neuromuscular blockade has generally not been reversed by neostigmine and has been only partially reversed by calcium.

Coagulopathy

Patients with renal insufficiency may be particularly susceptible to antibiotic-induced coagulopathy because of several potential preexisting defects in their coagulation function: (1) uremic platelet dysfunction, including decreased platelet adhesion, clot retraction, and aggregation [92–97]; (2) frequent baseline vitamin K deficiency [95, 96, 98, 99]; and (3) heparinization during hemodialysis [100].

Penicillin G–associated hemorrhagic complications have occurred in patients with renal impairment who have received 10 million units/d [101]; platelet dysfunction, decreased conversion of fibrinogen to fibrin, and increased antithrombin III activity have been documented. These adverse effects are considered dose related because similar complications with penicillin G have been observed only with very high doses (30–40 million units/d) in patients with normal renal function [101]. Dose-related coagulopathy has been reported with the use of carbenicillin in renal failure and has been associated with platelet dysfunction, increased antithrombin III activity, and prolonged thrombin and prothrombin times [100, 102–105]. Andrassy et al. [100] have noted induction of a "heparin-like substance" by carbenicillin in uremia, with cessation of bleeding achieved through protamine chloride administration.

Ampicillin-associated platelet dysfunction has not been reported in patients with renal insufficiency but has occurred in those with normal renal function who have received high doses (20 g/d) [106]. Because of the primary renal excretion of ampicillin, failure to adjust its dosage appropriately in renally impaired patients could potentially cause this adverse effect. Similarly, severe bleeding due to ticarcillin has not been reported in renally impaired patients but can occur at high doses (24 g/d) in those with normal renal function [107]. Because of its structural similarity to carbenicillin (both are carboxypenicillins) and its well-known inhibition of platelet function even at therapeutic concentrations [108, 109], ticarcillin

may be expected to cause clinically significant coagulopathy in patients with renal insufficiency unless its dose is appropriately adjusted. Other broad-spectrum penicillins (e.g., piperacillin, azlocillin, and mezlocillin) would be less likely to cause clinically significant bleeding in this setting because of their lower propensity to cause platelet dysfunction [110].

Cephalosporins with the *N*-methyl-thiotetrazole (NMTT) side chain (e.g., cefamandole [111], cefoperazone [112], moxalactam [113], and cefotetan [114]) have been associated with clinically significant coagulopathy in renal insufficiency. The NMTT side chain may directly inhibit vitamin K–dependent γ-carboxylation of clotting factors [115]. In a study by Cohen et al. [116], none of nine well-nourished patients (including four with renal impairment) who had normal serum vitamin K1 levels and were receiving a 7-day course of cefotetan developed hypoprothrombinemia when the dose of antibiotic was adjusted for decreased renal function. In contrast, when surgical patients (many of whom were malnourished and had low serum vitamin K levels) were treated with cefotetan or other antibiotics not containing the NMTT side chain, 11 of 20 (seven given cefotetan and four given other drugs) developed hypoprothrombinemia despite normal renal function. Aronoff et al. [117] demonstrated that vitamin K–deficient, anephric rats treated with moxalactam have a prothrombin time that is more prolonged than that in vitamin K–replete rats with normal renal function. No such prolongation of prothrombin time was observed in vitamin K–replete, anephric rats. These data suggest that concomitant vitamin K deficiency, rather than renal insufficiency per se, is the determining factor for the development of coagulopathy in renal patients treated with antibiotics containing the NMTT side chain. In addition to hypoprothrombinemia, platelet dysfunction and prolongation of bleeding time have been associated with moxalactam treatment [113, 118].

Two non-NMTT-containing antibiotics, cefoxitin [112] and ceftriaxone [119], have also been associated with clinically significant bleeding in patients with renal insufficiency. Enhanced destruction of the vitamin K–producing intestinal flora due to a compensatory increase in biliary excretion of these drugs may be contributory [111]. However, other factors, such as subclinical vitamin K deficiency, probably play a more important role since (as previously suggested [116]) other antibiotics that eliminate the intestinal flora (e.g., tetracycline) have not been associated with this complication.

Cefazolin-induced clinical bleeding has been documented in a uremic patient with increased thrombin, prothrombin, and partial thromboplastin times [120]. Although several other β-lactam antibiotics have been shown to inhibit platelet function in vitro at very high concentrations [118], the clinical relevance of these findings in renal insufficiency remains uncertain.

Nephrotoxicity

The nephrotoxic potential of antibiotics has been reviewed in detail elsewhere [121–123]. Although antibiotic-associated nephrotoxicity is often reversible after discontinuation of therapy, it may cause significant morbidity and prolonged hospitalization. It is reasonable to hypothesize that patients with underlying renal insufficiency will be at higher risk of renal function deterioration when exposed to nephrotoxic antibiotics. The nephrotoxic potential of the commonly used and the especially toxic, infrequently used antibiotics in renal insufficiency is discussed below.

Aminoglycosides. Preexisting renal disease is a risk factor for worsening renal function during aminoglycoside therapy [37, 73, 124, 125]. By far the most nephrotoxic aminoglycoside is neomycin, which may reach levels in the renal cortex that are 70-fold higher than those in blood [126]. The nephrotoxic potential of neomycin should be kept in mind when the drug is used in renally impaired patients, regardless of the route of administration, because of the possibility of significant drug accumulation. Streptomycin is the least nephrotoxic aminoglycoside, but because of its poor bactericidal activity against many gram-negative bacilli, it can rarely be substituted for the other, more commonly used aminoglycosides.

Which of the more frequently used aminoglycosides is the least likely to cause further deterioration of renal function in patients with renal impairment? Unfortunately, prospective randomized studies comparing the nephrotoxicity of different aminoglycosides in such patients have not been reported. On the basis of available studies in animals and humans, it is generally agreed that tobramycin has less nephrotoxic potential than gentamicin [70, 127–131]. Because nephrotoxicity may be related to total dose and drug accumulation [124, 126], it may be that tobramycin—with its lower tissue accumulation than gentamicin [126, 132]—is less nephrotoxic to already-compromised kidneys, particularly during prolonged

therapy. However, it is also possible that any significant difference between the nephrotoxic potential of these two aminoglycosides is mitigated by preexisting renal insufficiency. In severely diseased human kidneys, the tissue accumulation of gentamicin and tobramycin is greatly reduced [126], with the latter manifesting slightly but consistently higher levels.

Amikacin is not significantly less nephrotoxic than gentamicin [130, 133]. Similarly, comparison of the nephrotoxicity of netilmicin in humans with that of tobramycin or amikacin has failed to show significant differences [61, 76]. It is clear from the above discussion that until further data become available, none of the aforementioned aminoglycosides can be considered the "aminoglycoside of choice" in patients with renal impairment.

Concomitant administration of cephalosporins may further increase the risk of aminoglycoside-induced nephrotoxicity. This subject is reviewed in more detail below.

Amphotericin B. Although not significantly excreted through the kidneys, amphotericin B is commonly associated with varying degrees of renal insufficiency, even in patients with normal kidneys. Toxicity is dose related and is often associated with tubular necrosis [123]. Although patients with renal insufficiency may be at increased risk of amphotericin B–induced nephrotoxicity, the degree of risk is unknown. It is of note that amphotericin B potentiates the renal toxicity of cyclosporine and aminoglycosides [134].

Cephalosporins. The significant risk of nephrotoxicity associated with cephaloridine, particularly in patients with underlying renal disease [121], eventually led to the withdrawal of this drug from the market in the United States. Cephalothin has been associated with worsening renal function in patients with baseline renal dysfunction [23]. Nephrotoxicity due to cephalothin appears to be potentiated by concurrent aminoglycoside administration, with resulting acute tubular necrosis [135–139]. As many as 26% of older cancer patients who have serum creatinine levels in the high-normal range (1.1–1.5 mg/dL) and are receiving cephalothin and gentamicin develop nephrotoxicity [136]. Because the dose of cephalothin has often been high (12 g/d) in the nephrotoxic patients, the risk of nephrotoxicity in patients with renal impairment who are given lower doses in combination with an aminoglycoside is unknown. Concurrent administration of cephalothin and gentamicin in renal insufficiency should probably be avoided [135]. Other cephalosporins, including cefazolin and cephapirin, may be associated with enhanced nephrotoxicity when administered concurrently with aminoglycosides [140], but their exact risk of toxicity in renal insufficiency has not been defined.

Cefoxitin [141] and cephalexin [142, 143] have also been associated in rare instances with a deterioration of renal function in patients with renal insufficiency. It should be remembered that the interference of cefoxitin and cephalothin with certain assays for serum creatinine concentrations [144, 145] may falsely elevate results, a situation leading to an erroneous diagnosis of drug-induced nephrotoxicity. A lack of concomitant rise in BUN should alert the physician to this artifact.

Penicillins. Like cephalosporins, penicillins are generally regarded as safe in renally impaired patients. Nephrotoxicity is commonly associated with interstitial nephritis, which appears to be related to hypersensitivity [121]. There is no evidence that patients with renal impairment are more likely than patients with normal renal function to develop this complication when treated with appropriately adjusted doses of penicillins. However, at high doses (8 g/d), ampicillin has been associated with nephrotoxicity in some patients with renal insufficiency [23].

Polymyxins. Polymyxins (including polymyxin B and colistimethate) in usual doses have caused worsening renal function in patients with preexisting renal insufficiency [12, 13, 122]. Toxicity appears to be dose related, with acute tubular necrosis developing in some patients. Renally impaired patients receiving colistimethate seem to be at no higher risk of nephrotoxicity than those with normal renal function as long as the dose is appropriately adjusted [13]. The nephrotoxicity of polymyxin is potentiated by the concomitant administration of a cephalosporin [121].

Tetracyclines. Tetracyclines are generally contraindicated in patients with renal insufficiency. Tetracycline and minocycline cause worsening acidosis and azotemia in renal impairment as a result of their anti-anabolic effects [146, 147]. Doxycycline, because of its unique mode of excretion through the gastrointestinal tract, has generally been considered safe in renal insufficiency [147]; only one report to date implicates this antibiotic as a cause of worsening azotemia [148].

· *Trimethoprim-sulfamethoxazole (TMP-SMZ).* The nephrotoxic potential of TMP-SMZ, particularly in renal insufficiency, has been the subject of much controversy. While some authors have reported a de-

terioration in renal function resulting from the use of TMP-SMZ in renally impaired patients [149, 150], others have failed to confirm such an association [151, 152]. Although toxicity may be more likely at high or unadjusted doses, Kalowski et al. [150] reported frequent deterioration of renal function even in renally impaired patients receiving modified, presumably properly adjusted doses of TMP-SMZ. They suggested avoiding TMP-SMZ in patients with serum creatinine levels of >2.0 mg/dL or creatinine clearance rates of <40 mL/min. Because of the possibility of accumulation of sulfonamide metabolites, Bergan and Brodwall [153] recommended administering TMP-SMZ to renally impaired patients with creatinine clearance rates of <15 mL/min only when close monitoring of serum levels of total sulfonamide is feasible. Nephrotoxicity due to TMP-SMZ appears to be related to the sulfonamide component, which causes hypersensitivity interstitial nephritis, crystalluria, tubular necrosis, or hemolysis and hemoglobinuria [123, 150]. It should be noted that TMP alone (but not SMZ) can cause serum creatinine elevation without affecting glomerular filtration [154], apparently because of TMP-mediated reduction in tubular secretion of creatinine.

Vancomycin. Although the nephrotoxic potential of vancomycin is not high in patients with normal renal function [122, 155], its exact risk of nephrotoxicity in patients with altered renal function is not known. However, in line with their increased risk of ototoxicity [122], renally impaired patients may also be at higher risk of developing nephrotoxicity due to vancomycin therapy, particularly if high serum concentrations of the drug are maintained.

Hypoglycemia

Sulfonamide-induced hypoglycemia was reported in a patient with severe renal insufficiency (creatinine clearance rate, 5 mL/min) during daily administration of TMP-SMZ (800 mg of TMP and 160 mg of SMZ) [156]. A similar reaction occurred in a chronic hemodialysis patient who was receiving much higher doses of this combination [157]. Inappropriately elevated serum levels of insulin were documented in both instances, and neither patient was diabetic. The mechanism of hypoglycemia was presumed to be due to high serum concentrations of SMZ, which structurally resembles oral hypoglycemic agents (sulfonylureas) and thereby stimulates insulin secretion. In addition to higher serum SMZ concentrations caused by slower body clearance and to lower serum protein binding in uremia [34] resulting in a larger free-drug fraction, uremic patients can also have abnormal carbohydrate metabolism, with impaired glycogenesis and gluconeogenesis [158, 159]; this condition further potentiates the hypoglycemic effects of sulfonamides. Diabetic patients with renal impairment who receive sulfonylureas may also be at particularly high risk of developing TMP-SMZ-related hypoglycemia as a result of the displacement of the oral hypoglycemic agent from serum proteins by SMZ [160].

Hematologic Toxicity

Patients with renal insufficiency who receive chloramphenicol are reported to be at relatively high risk of developing nonaplastic erythropoietic marrow depression [161], probably because of high serum concentrations of "free" chloramphenicol. Because chloramphenicol is hepatically excreted, decreased serum protein binding in uremia [162]—rather than drug accumulation—may be responsible for the higher serum concentration of "free" drug, which may in turn lead to a higher risk of marrow toxicity. In addition, a nearly universal erythropoietic marrow depression in chronic renal failure [163, 164] may render such patients particularly susceptible.

Delayed neutropenia 1 month after discontinuation of vancomycin therapy, with serum drug levels still detectable, has been reported in a patient undergoing chronic hemodialysis [165]. Since vancomycin-related neutropenia is rare [58], the abnormally long half-life of the drug in this patient was suspected as contributory. Although hypersensitivity was implicated, the exact mechanism of vancomycin-induced neutropenia remains unknown.

Renally impaired patients are also at particular risk of developing marrow toxicity due to flucytosine, a renally excreted antifungal drug [166, 167]. Toxic serum concentrations of flucytosine (>100–125 μg/mL) are likely to be reached unless the dosage is adjusted appropriately. Conversion to 5-fluorouracil by the human intestinal flora may be an important intermediate step in the toxicity of flucytosine [168].

Aminoglycoside Inactivation by Penicillins

Although not truly an adverse effect, inactivation

of aminoglycosides by penicillin may be detrimental in the seriously ill patient with renal insufficiency. Penicillins, including penicillin G, ampicillin, cloxacillin, carbenicillin, ticarcillin, and piperacillin, have been shown to inactivate aminoglycosides in vitro [169–174], with gentamicin being most affected and amikacin least affected [172]. Significant aminoglycoside inactivation has also been demonstrated in patients with renal failure who have been treated simultaneously with gentamicin or tobramycin and carbenicillin or ticarcillin [169–171, 173]. This inactivation is dose dependent and is caused by sustained high serum concentrations of penicillins with the formation of a physicochemical linkage between the β-lactam ring of the latter and the amino sugars of the aminoglycoside [37]. Persistently low serum concentrations of aminoglycoside, despite adequate dosing in patients with renal insufficiency who are concurrently treated with penicillins, should bring this interaction to mind. Conversely, renally impaired patients with stable "therapeutic" levels of an aminoglycoside during concomitant treatment with penicillin may conceivably develop toxic serum levels of aminoglycoside following discontinuation of the β-lactam agent.

Conclusion and Recommendations

Knowledge of the pharmacokinetics of antibiotics, with appropriate dose adjustment, is essential for the prevention of adverse effects in renal insufficiency. Familiarity with ancillary factors in uremia (table 2) should help explain why these patients are often at higher risk of side effects from antibiotic therapy. Awareness of these untoward reactions (table 3) is essential for their early recognition and correction. When a particular antibiotic is considered to be causing an adverse reaction, it should be either discontinued or—if the reaction is thought to be dose related—administered at a reduced dosage. General recommendations regarding the use of antibiotics in renal insufficiency are listed in table 3. Specific recommendations on the appropriate dose of antibiotics in patients with altered renal function have been published elsewhere [175–177]. In light of variations in antibiotic metabolism among renally impaired patients, serum drug levels should be documented whenever possible despite an apparently appropriate dosage, especially if a toxic reaction is suspected. Because total body clearance of many antibiotics is slowed in renal insufficiency, resolution of adverse effects can be delayed. Furthermore, because of the poor dialyzability of many antibiotics [175], toxicity may easily occur in dialysis patients, and adverse reactions may be slow to resolve despite frequent dialysis. Nevertheless, most antibiotics can be used safely in patients with renal insufficiency, and their potential adverse reactions should not interdict their administration when they are clearly indicated.

Table 2. Factors in uremia that may contribute to adverse effects of antibiotics.

Adverse effect	Factor in uremia [reference(s)]
Neurotoxicity	
CNS toxicity	Altered blood-brain barrier [35]
	Altered serum protein binding (higher free-drug concentrations for some drugs) [33, 34]
	Anatomic and physiologic CNS anomalies [14, 36]
Ototoxicity	Uremic polyneuropathy [36, 42, 66, 67]
Peripheral nerve toxicity	Uremic polyneuropathy [36, 42, 60, 67]
Neuromuscular blockade	Hypocalcemia [91]
Coagulopathy	Uremic platelet dysfunction [92–97]
	Vitamin K deficiency
	Baseline [95, 96, 98, 99]
	Compensatory increase in antibiotic biliary excretion [111]
	Heparin (hemodialysis patients) [100]
Nephrotoxicity	Underlying renal disease
Hypoglycemia	Abnormal carbohydrate metabolism [158, 159]
	Altered serum protein binding (sulfonamides) [34]
Hematologic toxicity	Marrow depression [163, 164]
	Altered serum protein binding (chloramphenicol) [162]

NOTE. High serum concentrations of antibiotic and slow rates of body clearance in renal insufficiency are important in the development of many adverse effects.

Appendix: Case Report

A 46-year-old man undergoing chronic hemodialysis was admitted to the hospital with documented *Staphylococcus aureus* bacteremia and multiple septic joints. Initially, he responded favorably to iv vancomycin; later, because of the recurrence of fever and CSF pleocytosis with negative smears and cultures, oxacillin (1 g iv every 6 hours) was added to the regimen. Because of continued fever, the dose of oxacil-

Table 3. Adverse effects of antibiotics associated with renal insufficiency.

Antibiotic	Adverse effect [reference(s)]	Recommendations*
Acyclovir	CNS toxicity† [4]	Adjust dose appropriately
Amantadine	CNS toxicity [5]	Adjust dose appropriately
Aminoglycosides‡	Nephrotoxicity [37, 73, 124, 125, 136–140], enhanced by cephalothin [136–140]	Monitor serum levels; monitor renal function; avoid prolonged therapy and concurrent cephalothin; avoid other ototoxic drugs and neuromuscular blocking agents; administer calcium and neostigmine for reversal of neuromuscular blockade; avoid neomycin
	Ototoxicity [37–51], enhanced by "loop" diuretics [37, 46]	
	Neuromuscular blockade/respiratory depression [83–88]	
	Inactivation by penicillins [169–173]	
Amphotericin B	Nephrotoxicity§ [123]	Avoid use unless absolutely indicated; monitor renal function
Cephalosporins		
General	CNS toxicity [6–11]	Adjust dose appropriately
Selected		
Cefazolin	Coagulopathy [120]	Adjust dose appropriately
Cefamandole	Coagulopathy [111]	Administer vitamin K supplement
Cefoperazone	Coagulopathy [112]	Administer vitamin K supplement
Cefoxitin‖	Coagulopathy [112]	Administer vitamin K supplement; adjust dose appropriately
	Nephrotoxicity [141]	Monitor renal function
Ceftriaxone	Coagulopathy [119]	Administer vitamin K supplement
Cephalexin	Vestibular toxicity [9]	Adjust dose appropriately
	Nephrotoxicity [142, 143]	
Cephalothin‖	Nephrotoxicity, enhanced by aminoglycosides [23, 136, 138, 139]	Avoid use
Moxalactam	Coagulopathy (platelet dysfunction and vitamin K deficiency) [113]	Avoid use
Chloramphenicol	Marrow suppression [161]	Monitor peripheral blood count
Cycloserine	CNS toxicity [16]	Avoid use if possible; when indicated, adjust dose appropriately and monitor serum levels
Erythromycin	CNS toxicity [17]	Avoid daily dose of >2 g in severe renal insufficiency
	Ototoxicity [17, 52–56]	
Flucytosine‖	Marrow suppression [166, 167]	Avoid use if possible; adjust dose appropriately; monitor serum levels; monitor peripheral blood count
Imipenem/cilastatin	CNS toxicity [19]	Adjust dose appropriately; avoid daily dose of >2 g
Isoniazid	CNS toxicity [20–22]	Decrease daily dose to 200 mg in severe renal insufficiency; administer routine pyridoxine supplement; monitor drug levels; treat toxicity with high-dose pyridoxine and hemodialysis
	Peripheral nerve toxicity [82]	
Nalidixic acid	CNS toxicity [28]	Avoid use
Nitrofurantoin	Peripheral nerve toxicity [81]	Avoid use
Penicillins	CNS toxicity [3, 23–27]**	Adjust dose appropriately; monitor serum levels when possible; avoid carbenicillin or ticarcillin in patients with clinically evident coagulopathy or bleeding
	Aminoglycoside inactivation [169–173]	
	Coagulopathy (platelet inhibition, particularly with carbenicillin and ticarcillin) [100–105]	
	Nephrotoxicity at high doses (ampicillin) [23]	
Polymyxins	Nephrotoxicity [12, 13, 122]	Avoid use if possible; adjust dose appropriately
	Neuromuscular blockade/respiratory depression [85, 87, 89, 90]	
	CNS toxicity [12–15]	
Tetracyclines	Worsening uremia and acidosis [146–148]	Avoid tetracycline and minocycline; use doxycycline when a tetracycline is indicated
TMP-SMZ	Nephrotoxicity [149, 150]	Adjust dose appropriately; monitor renal function
	Potential false increase in serum creatinine [154]	
	Hypoglycemia [156, 157]	
Vancomycin	Ototoxicity [58, 78]	Adjust dose appropriately; monitor serum levels, even in hemodialysis patients††; monitor renal function
	Delayed-onset neutropenia [165]	
	Nephrotoxicity, particularly with concurrent aminoglycoside use [122]	

* For specific dosage adjustments, see [175–177].
† Includes encephalopathy and seizures.
‡ Includes neomycin, streptomycin, gentamicin, tobramycin, amikacin, and netilmicin.
§ Probable increased risk of toxicity in renal insufficiency.
‖ May falsely elevate serum creatinine measurement by certain assays [144, 145, 178].
See [179].
** See also Appendix.
†† See [180].

lin was increased to 2 g every 6 hours. Following this dose adjustment, the patient became encephalopathic, with increasing confusion and new onset of myoclonus in his extremities. Repeat CSF examination showed reduced pleocytosis. An electroencephalogram was consistent with drug-induced encephalopathy, and a nuclear brain scan was normal. Antibiotic-induced encephalopathy and myoclonus were suspected, and oxacillin treatment was stopped. The patient's neurologic symptoms resolved promptly (i.e., within 24 hours).

Because of recurrent fever during treatment with vancomycin alone, oxacillin therapy was restarted (1 g iv every 12 hours). Ten days later the patient had a grand mal seizure shortly after receiving a dose of the antibiotic. CNS evaluation, including computed tomography of the head and repeat lumbar puncture, was noncontributory, as were blood tests (including electrolytes and calcium). The peak serum concentration of oxacillin (1 hour after completion of iv infusion) was 50 μg/mL (upper limit of therapeutic range, 25 μg/mL). The dose of oxacillin was decreased to 500 mg iv every 12 hours, with no further recurrence of seizure activity. The patient became more confused when oxacillin therapy was subsequently changed to dicloxacillin treatment (500 mg orally every 6 hours). The peak serum level of dicloxacillin was 24 μg/mL (upper limit of therapeutic range, 11 μg/mL). Symptoms resolved following discontinuation of dicloxacillin.

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