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β-Lactam Antibiotics

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INTRODUCTION

The β-lactam antibiotics are a large class of diverse compounds used clinically in both the oral and parenteral forms. The β-lactam antibiotic agents have become the most widely used therapeutic class of antimicrobials because of their broad antibacterial spectrum and excellent safety profile. Reports of drug–drug interactions with the β-lactam antimicrobials are a relatively rare phenomenon, and when interactions do occur, they are generally minor. This chapter describes the drug–drug interactions of the β-lactam antibiotics: penicillins, cephalosporins, carbapenems, and monobactams.

As an overview, each β-lactam drug interaction has been categorized as major, moderate, or minor and is presented in Table 1. Interactions classified as major are considered well documented and have the potential to be life threatening or dangerous. Moderate interactions are those for which more documentation is needed or potential harm to the patient is less. Minor interactions are poorly documented, present minimal potential harm to the patient, or occur with a low incidence.

The clinical significance of drug–drug interactions associated with the β-lactam antibiotics and understanding of the management of these drug–drug interactions are presented.

PENICILLIN DRUG INTERACTIONS

Acid-Suppressive Agents

The combination of various penicillins (ampicillin, amoxicillin, bacampicillin, and amoxicillin/clavulanate) and H_2-receptor antagonists (cimetidine and ranitidine) or omeprazole has been evaluated for effects on the bioavailability of the specific penicillin investigated *(1–5)*. With the exception of bacampicillin, the bioavailability of the penicillins was unaffected. The area under the curve (AUC) of bacampicillin was reduced in the presence of food, ranitidine, and sodium bicarbonate *(5)*; however, another study did not demonstrate a difference in AUC with coadministration of omeprazole and bacampicillin *(2)*. The concurrent administration of most penicillins and acid-suppressive agents poses no problems except possibly with bacampicillin.

From: *Infectious Disease: Drug Interactions in Infectious Diseases, Second Edition*
Edited by: S. C. Piscitelli and K. A. Rodvold © Humana Press Inc., Totowa, NJ

Table 1
Significance of β-Lactam Drug Interactions

	Penicillins	Cephalosporins	Carbapenems	Monobactam
Major	In vitro aminoglycoside inactivation Contraceptives, oral estrogen Methotrexate	Contraceptives, oral estrogen Methotrexate		
Moderate	In vivo aminoglycoside inactivation Aminoglycoside inactivation in sampling serum concentrations Neomycin (oral) Probenecid Warfarin	Acid suppressive agents Iron Ethanol Probenecid Warfarin	Probenecid Ganciclovir	Probenecid Inducers of β-lactams
Minor	Acid-suppressive agents Allopurinol Aspirin β-Adrenergic blockers Calcium channel blockers Chloramphenicol Chloroquine Ciprofloxacin Cyclosporine Heparin Interferon-γ Guar gum Khat Metformin Phenytoin Proguanil Tetracyclines Vecuronium	Aminoglycoside nephrotoxicity Calcium channel blocker Cholestyramine Colistin Furosemide Metoclopramide Nonsteroidal anti-inflammatory drugs Phenytoin Propantheline Theophylline	Cyclosporine Theophylline Valproic acid	

Allopurinol

An increased incidence of skin rash has been reported in patients receiving either ampicillin or amoxicillin concomitantly with allopurinol. In an analysis of data collected in 4686 patients receiving ampicillin, 252 of which were also receiving allopurinol, rash was reported in 5.7% of the patients receiving ampicillin compared to 13.9% of patients receiving both ampicillin and allopurinol ($p = 0.0000001$) *(6)*. There were no differences in age, sex, diagnosis, or admission laboratory value of serum urea nitrogen (BUN) that could be identified between the two groups. Similar results of an increased incidence of a rash have also been reported in patients receiving both amoxicillin and allopurinol (22%) vs amoxicillin alone (5.9%) *(6)*.

Fessel attempted to determine the possible reasons for the higher incidence of rash in patients receiving allopurinol and ampicillin *(7)*. Fessel compared the history of allergies to penicillin, allergies to other antibiotics, presence of hay fever, use of antihistamine medications, and the prevalence of asthma in 124 asymptomatic hyperuricemic individuals compared to 224 matched normouricemic controls. The following results were considered significant in asymptomatic hyperuricemic subjects vs the control subjects: history of penicillin allergy (14.1 vs 4.9%), hay fever (18.8 vs 8.0%), and use of antihistamine medications (9.9 vs 2.7%). The incidence of allergies to antibiotics excluding penicillin and prevalence of asthma were not significant between groups. The author hypothesized that hyperuricemic individuals tend to have a higher frequency of allergic reactions; therefore, this altered immunologic state may explain the increased incidence of ampicillin rashes rather than an ampicillin–allopurinol interaction.

The significance of this pharmacodynamic interaction tends to be minor. Clinicians may continue to prescribe these agents concomitantly. Patients should be monitored and counseled regarding this potential increased incidence of skin rashes when these two agents are prescribed concurrently.

Aminoglycosides

Penicillins and aminoglycosides are commonly used in combination to treat a variety of infections. However, concomitant use of the extended-spectrum penicillin antimicrobials may result in inactivation of the aminoglycosides. Although the majority of interactions are reported in vitro, the potential for in vivo interactions are of concern, especially in those patients with end-stage renal failure *(8–16)*.

In Vivo Aminoglycoside Inactivation

McLaughlin and Reeves reported a case report of a patient undergoing hemodialysis and receiving gentamicin for 8 day for the treatment a soft tissue infection *(9)*. Carbenicillin therapy was added on day 8. The authors reported that therapeutic serum concentrations for gentamicin could not be achieved despite administration of high doses following the addition of carbenicillin. Of note, the patient received more frequent dialysis sessions during this period, which may have also contributed to subtherapeutic gentamicin concentrations. Uber et al. noted similar pharmacokinetic findings when tobramycin and piperacillin were administered concomitantly in a chronic hemodialysis patient *(10)*. McLauglin and Reeves also studied this interaction in an animal model *(9)*. Rabbits that received only gentamicin were reported to have normal gentamicin concentrations ($n = 2$); rabbits receiving carbenicillin and gentamicin had undetectable levels at 30 hours ($n = 3$).

Other investigators have described a reduction in aminoglycoside concentration when coadministered with extended-spectrum penicillins, particularly in patients with end-stage renal failure *(11–16)*. Davies et al. evaluated gentamicin half-lives in the presence of therapeutic doses of ticarcillin or carbenicillin in eight patients with end-stage renal failure *(12)*. In patients receiving gentamicin concomitantly with ticarcillin, the gentamicin half-life was reduced from 31 to 22 hours, whereas gentamicin half-life was reduced from 50 to 8 hours in patients receiving carbenicillin and gentamicin.

Halstenson et al. assessed the effect of piperacillin administration on the disposition of netilmicin and tobramycin in 12 chronic hemodialysis patients *(11)*. The half-life of netilmicin was not significantly altered when netilmicin was given concurrently with piperacillin. In comparison, the half-life of tobramycin was considerably reduced in the presence of piperacillin (59.62 ± 25.18 vs 24.71 ± 5.41 hours). Lau et al. were unable to document any such drug–drug interaction between piperacillin and tobramycin in subjects with normal renal function (defined as creatinine clearances of greater than or equal to 60 mL/minute) *(17)*. Hitt and colleagues reported no differences in pharmacokinetic parameters of once-daily gentamicin with the coadministration of several piperacillin/tazobactam regimens in subjects with normal renal function *(18)*. Similarly, Dowell et al. were unable to demonstrate differences in the pharmacokinetic parameters of tobramycin when administered alone or with piperacillin/tazobactam in subjects with moderate renal impairment (creatinine clearance between 40 and 59 mL/minute), mild renal impairment (creatinine clearance between 20 and 39 mL/minute), or normal renal function (creatinine clearance greater than 90 mL/minute) *(19)*.

It has been suggested that the extended-spectrum penicillins interact chemically with the aminoglycosides to form biologically inactive amides. The degree of inactivation is dependent on the specific aminoglycoside and β-lactam used *(12,20)*. In vivo inactivation of aminoglycosides occurs at such a slow rate that it appears to be clinically insignificant in patients with normal renal function *(17,20)*. Some investigators have stated that this interaction could possibly be relevant for patients with renal failure who have high serum concentrations of penicillins *(11,12,21)*; therefore, close therapeutic monitoring of aminoglycosides is warranted in this specific clinical situation.

Neomycin

Concomitant administration of oral neomycin and penicillin V has been reported to reduce serum concentrations of penicillin *(22)*. In healthy volunteers, penicillin V concentrations decreased by over 50% following the administration of oral neomycin concomitantly with penicillin V *(22)*. Because of the significant decrease in penicillin exposure, oral neomycin should not be coadministered with penicillin V.

In Vitro Aminoglycoside Inactivation

McLaughlin and Reeves described undetectable gentamicin concentrations and clinical failure in a patient who received an infusion of carbenicillin and gentamicin for *Pseudomonas* bacteremia *(9)*. In vitro inactivation of aminoglycosides can be significant when these agents are prepared in the same intravenous mixture for administration *(20)*. Within 2 hours of admixing at room temperature, an intravenous fluid mixture containing ampicillin (concentration equivalent to 12 g/day) and gentamicin resulted in a 50% decline in the gentamicin activity. After 24 hours, no measurable gentamicin

activity was noted *(20)*. An intravenous fluid mixture containing gentamicin and carbenicillin demonstrated a 50% reduction in activity between 8 and 12 hours after admixing at room temperature. Aminoglycosides and penicillins should not be mixed together prior to infusion.

In Vitro Inactivation Aminoglycoside in Sampling Serum Concentrations

If high concentrations of penicillins are present in serum samples that are to be assayed for aminoglycoside concentrations, inactivation of the aminoglycosides by the penicillins can result in falsely decreased aminoglycoside concentrations *(8)*. Penicillin concentration, period of time prior to sampling, and storage temperature of the sample are factors that affect the extent of inactivation *(8)*. When measuring aminoglycoside serum concentrations through intravenous tubing, one should flush 5–10 mL of either normal saline or 5% dextrose in water (based on drug compatibilities) through the tubing before withdrawing blood to minimize the amount of β-lactam present in the intravenous tubing prior to sampling.

Aminoglycosides—Synergy

The concomitant use of β-lactam and aminoglycoside antimicrobials has been described as synergistic for several Gram-positive and Gram-negative organisms *(23–26)*. By inhibiting the cell wall synthesis, β-lactams increase the porosity of the bacterial cell wall, resulting in greater aminoglycoside penetration and access to target ribosomes *(27)*.

The use of penicillin or ampicillin in combination with an aminoglycoside has been documented to be advantageous in the treatment of enterococcal infections *(28)*. Moellering et al. also noted that whereas penicillin exhibits only bacteriostatic activity against enterococci, the combination of penicillin and streptomycin possesses bactericidal activity *(23)*. As a result, most severe enterococcal infections are routinely treated with penicillin or ampicillin plus an aminoglycoside.

Despite the well-documented in vitro synergy between β-lactams and aminoglycosides, limited clinical data are available supporting superior efficacy of synergistic vs nonsynergistic combinations for the treatment of Gram-negative infections. Anderson et al. retrospectively evaluated Gram-negative bacteremias to determine if the treatment with one or two antimicrobials effected outcome and whether in vitro synergy correlated with superior efficacy *(29)*. Of the 173 patients treated with two drugs, the clinical response rate was 83% in patients who received synergistic vs 64% with nonsynergistic antimicrobial regimens ($p < 0.05$). The use of synergistic antimicrobial combinations (aminoglycoside plus ampicillin or carbenicillin) was associated with better clinical response in patients with neutropenia ($p < 0.001$), shock ($p > 0.001$), *Pseudomonas aeruginosa* bacteremias ($p < 0.05$), and "rapidly or ultimately fatal" conditions ($p < 0.005$). In critically ill patients with Gram-negative bacteremia, the combination of an extended spectrum penicillin and aminoglycoside is a reasonable therapeutic approach.

Anticoagulants

Heparin

A number of case reports have suggested that parenteral penicillins in combination with heparin have caused coagulopathies *(30–36)* and may predispose patients to clini-

cally significant bleeding *(33–35,37)*. The exact mechanism of this interaction is unknown but may be a result of a direct effect on platelet function by penicillins, which may have an additive anticoagulant effect when combined with heparin *(31–32,37)*.

Wisloff et al. evaluated the bleeding time of patients receiving heparin and penicillins compared to heparin alone *(36)*. Fifty patients were placed on heparin (5000 IU sc for 7 days) following an elective vascular surgery procedure and were also randomly assigned to receive a combination of ampicillin and cloxacillin or no antibiotics. The patients who were receiving heparin along with the penicillins had a slightly longer bleeding time; however, this was still within an acceptable range in most cases.

Because patients receiving heparin are routinely monitored closely for coagulopathies and clinically significant bleeding, the potential interaction between these two drugs does not warrant further precautions.

Warfarin

A decreased anticoagulant effect for warfarin has been documented when given concomitantly with nafcillin *(38–41)* or dicloxacillin *(38,42,43)*. Some clinicians have postulated that these antibiotics induce the cytochrome P450 system and may increase the metabolism of warfarin *(40,44,45)*. Another possible explanation may involve the ability of these highly protein-bound agents to displace warfarin. However, Qureshi et al. performed an in vitro study and demonstrated that nafcillin did not affect the protein binding of warfarin *(40)*.

Krstenansky et al. studied the effect of dicloxacillin in seven patients stabilized on warfarin therapy *(42)*. Prothrombin times (PTs) were obtained prior to treatment and on days 1, 3, 6, and 7 of dicloxacillin administration. A decrease in the PT was observed in all patients on day 6 or 7 compared to baseline PT values. The decrease in PT ranged from 0.3 to 5.6 seconds (mean ± SD of –1.9 ± 1.8 seconds) and was statistically significant ($p < 0.05$).

Brown et al. presented a case report of a patient on 2.5 mg warfarin daily who developed an increased hypoprothrombinemic response after receiving high-dose intravenous penicillin (24 million units/day). On withdrawal of the penicillin, the patient's PT subsequently returned to his baseline *(46)*. Davydov et al. reported a case of a 58-year-old woman with an interaction of warfarin with amoxicillin/clavulanate, resulting in an elevated international normalized ratio (INR) and hematuria *(47)*. Although the exact mechanism of this interaction remains unknown, it has been proposed that broad-spectrum antibiotic use may lead to a decrease in vitamin K-producing bacteria within the gastrointestinal tract. This may then result in a vitamin K-deficient state (especially in patients with low dietary intake of vitamin K), potentially leading to an increased effect of warfarin. Clinicians should be aware of the potential interaction between penicillins and oral anticoagulants and monitor the PT and INR in patients receiving these agents concurrently.

Aspirin

Large doses of aspirin may increase the serum concentrations and half-lives of penicillin, oxacillin, nafcillin, cloxacillin, and dicloxacillin when administered concurrently *(48,49)*. Eleven patients with arteriosclerotic disorders received penicillin G before and after high doses of aspirin (3 g/day) *(48)*. During aspirin administration, penicillin half-life increased from 44.5 ± 15.8 minutes to 72.4 ± 35.9 minutes ($p < 0.05$) *(48)*. The

mechanism of this interaction remains unknown. Some have speculated that this interaction may occur as a result of aspirin displacing penicillin from protein-binding sites or of aspirin competing with penicillins for the renal tubular secretory proteins *(48–52)*. Avoidance of this combination is unnecessary.

β-Adrenergic Blockers

Coadministration of ampicillin and atenolol may lead to a decrease in the serum concentration of atenolol. In a crossover study, six healthy subjects were orally administered 100 mg atenolol alone and with 1 g ampicillin. Atenolol pharmacokinetics were assessed after a single dose and after reaching steady state. These subjects previously received intravenous atenolol in another study, which was utilized to determine oral bioavailability in the present study. The bioavailability of atenolol was reduced from 60 (atenolol alone) to 36 (single-dose atenolol and ampicillin, $p < 0.01$) to 24% (steady-state concentrations of atenolol and ampicillin, $p < 0.01$) *(53)*. Other atenolol pharmacokinetic parameter values for AUC, C_{max}, and mean steady-state concentrations were also significantly reduced ($p < 0.01$). Despite the differences in atenolol serum concentration, blood pressure measurements did not differ between the groups over a 4-week treatment period.

McLean and colleagues also performed a crossover study administering oral atenolol and ampicillin to six volunteers *(54)*. Unlike the previous study, these investigators dosed ampicillin at clinically applicable doses of 250 mg four times a day as well as at higher doses of 1 g. The mean reduction of AUC was lower in the former dosing regimen compared to the latter one (18.2 vs 51.5%).

Although the clinical significance of this interaction is questionable, it would seem reasonable that patients should be monitored for this interaction when higher doses of ampicillin are used, especially in the presence of renal dysfunction; however, no empiric dosage alterations are recommended at this time.

Calcium Channel Blockers

Nifedipine appears to increase the bioavailability of amoxicillin by facilitating its active transport mechanism within the gastrointestinal tract *(55)*. In a randomized crossover study conducted in eight healthy volunteers, each subject received 1 g oral amoxicillin with 20 mg nifedipine or placebo. The absolute bioavailability of amoxicillin was noted to increase from 65.25 to 79.2% with the addition of nifedipine ($p < 0.01$) *(55)*. The AUC also increased from 29.7 ± 5.3 mg · hours/L (amoxicillin alone) compared to 36.26 ± 6.9 mg · hours/L (amoxicillin and nifedipine) ($p < 0.01$). Because no adverse events were associated with the alterations of these pharmacokinetic parameters, no dosage adjustments are recommended.

Nafcillin has been postulated to enhance the elimination of agents metabolized through the cytochrome P450 system *(44,45)*. A crossover study was conducted to evaluate the induction potential of nafcillin on nifedipine, a substrate of the cytochrome P450 3A4 enzyme *(56)*. Healthy volunteers were randomly assigned to receive 5 days of oral nafcillin (500 mg four times daily) or placebo, which was followed by a single dose of nifedipine. The subjects who received nafcillin along with nifedipine were found to have a significant reduction in the nifedipine $AUC_{0-\infty}$ (80.9 ± 32.9 vs 216.4 ± 93.2 μg · hours/L; $p < 0.001$) and enhanced plasma clearance (138.5 ± 42.0 vs 56.5 ±

32.0 L/hour; $p < 0.002$) compared to the nifedipine-placebo group. Because of the limited available data, the clinical significance of this interaction is unknown.

Chloramphenicol

The administration of a bacteriostatic agent such as chloramphenicol may antagonize the bactericidal activity of β-lactam antimicrobials *(57,58)*. β-Lactam antimicrobials exhibit their bactericidal effect by binding to penicillin-binding proteins and inhibiting bacterial cell wall synthesis. For β-lactams to exert optimal bactericidal effects, bacteria should be actively growing and dividing. However, bacteriostatic agents such as chloramphenicol, which may inhibit protein synthesis, may interfere with the bactericidal activity of penicillins.

In vitro studies have demonstrated the concomitant use of penicillin and chloramphenicol to be antagonistic *(57,59)*. However, human data do not support these findings *(60,61)*. Patients with gonococcal infections who were treated with a combination of penicillin and chloramphenicol had better clinical outcomes than patients treated with penicillin alone *(60)*. Superior outcomes were also reported among patients infected with typhoid fever who were treated with chloramphenicol plus ampicillin compared to chloramphenicol alone *(61)*.

Relevant clinical information is limited for this drug–drug interaction. Because the in vivo and in vitro data concerning this interaction are contradictory, it is unnecessary to avoid the concurrent use of these antimicrobials.

Chloroquine

Investigators conducted a study in healthy volunteers to evaluate the coadministration of chloroquine and ampicillin on the pharmacokinetics of ampicillin *(62)*. Ampicillin pharmacokinetics alone or in the presence of chloroquine was determined by characterizing the drug's renal elimination. The mean percentage of dose excreted was 29% for ampicillin alone vs 19% for the ampicillin/chloroquine combination ($p < 0.005$). The coadministration of ampicillin and chloroquine resulted in a significant reduction in ampicillin bioavailability but not in time of maximal excretion *(62)*. Based on limited data, coadministration of these agents may lead to a reduction in ampicillin concentrations. Although the clinical significance of this interaction remains unknown, concomitant administration of chloroquine and ampicillin should be avoided.

Ciprofloxacin

Interactions between the penicillins and fluoroquinolones have been rarely documented *(63,64)*. Barriere et al. assessed the effect of the concurrent administration of ciprofloxacin and azlocillin in a crossover trial *(63)*. Six subjects were administered single doses of ciprofloxacin and azlocillin alone and in combination. Similar pharmacokinetic profiles were noted with azlocillin; however, when coadministered with azlocillin, a statistically significant reduction in total clearance and renal clearance of ciprofloxacin was noted. Based on limited data, coadministration of these agents need not be avoided.

Contraceptives: Oral Estrogen

Several case reports of breakthrough bleeding and pregnancies have been reported in patients receiving oral contraceptives and antibiotics concomitantly *(65–69)*. It has

been postulated that antibiotics interfere with the enterohepatic circulation of oral estrogens, resulting in subtherapeutic estrogen concentrations *(67–69)*. After oral estrogens are absorbed, they undergo hepatic metabolism to glucuronide and sulfate conjugates and are excreted into the bile. Bacteria residing in the gut hydrolyze the conjugates to active drug, which is then reabsorbed by the body *(67)*. The proposed mechanism of this interaction involves the ability of antibiotics to destroy the gut bacteria required to hydrolyze the conjugated estrogen to their active form.

Studies in animal models assessing this interaction have shown mixed results *(70,71)*. One investigation demonstrated no alterations in the pharmacokinetics of ethinylestradiol when administered with ampicillin *(70)*. Another study found differences in both AUC and plasma clearance in the group that received antibiotics compared to those that received ethinylestradiol alone *(71)*.

Several studies have been performed in humans to determine if the case reports and animal data represent significant findings *(72–74)*. Freidman and colleagues prospectively evaluated the serum concentrations of gonadotropins and other hormones in 11 volunteers receiving Demulen® (50 μg ethinylestradiol and 1 mg ethynodiol diacetate) plus ampicillin or placebo during two consecutive menstrual cycles *(73)*. Progesterone concentrations were similar between the Demulen-ampicillin and Demulen-placebo groups. Follicle-stimulating hormone and luteinizing hormone appeared to be similar between the two groups. None of the 11 patients underwent ovulation. Freidman and colleagues concluded that ampicillin should not reduce the effectiveness of Dumulen. Other researchers have criticized the results of this study because of its study design, which included a small number of subjects, a short duration of antimicrobial therapy, and a relatively high dose of estrogens (present in Demulin) *(68)*.

Back and colleagues evaluated seven women receiving oral contraceptives (all containing ≥ 30 μg ethinyloestradiol) for at least 3 months who presented to their clinic with an infection that required the administration of ampicillin for 8 days *(72)*. Blood samples were taken during concomitant oral estrogen and ampicillin therapy and during the next menstrual cycle without ampicillin. Six female volunteers receiving only oral contraceptives for at least 3 months were similarly evaluated for the potential drug interaction. Plasma concentrations of ethinyloestradiol, levonorgestrel, follicle-stimulating hormone, and progesterone were not significantly different between the two groups (oral contraceptive-ampicillin vs oral contraceptive alone). Despite the fact that a lower concentration of ethinyloestradiol was seen with two women on ampicillin, the authors concluded that alternative methods of protection are not necessary in most women *(67)*.

Another study in volunteers analyzed the effect of administering ampicillin or metronidazole with an oral contraceptive preparation *(74)*. This summary is limited to the group using ampicillin ($n = 6$). Subjects initially received a low-dose oral contraceptive (1 mg norethisterone acetate and 30 μg ethinyl estradiol). On days 6 and 7, plasma concentrations of ethinylestradiol and norethisterone were obtained. Subsequently, subjects were administered ampicillin (500 mg twice daily orally for 5–7 days) and the contraceptive steroid. Following antibiotic treatment, serum hormones, ampicillin, and progesterone concentrations were measured in the subjects. The concentrations of norethisterone and ethinylestradiol were not altered in the presence of ampicillin, and progesterone concentrations were in the appropriate range to suppress ovulation *(74)*.

It is difficult to determine the clinical significance of this interaction because of the small number of clinical trials, small number of patients, minimal number of case reports, and the limited number of oral contraceptives studied. A review article suggested that the possibility of a clinically significant interaction between antibiotics and oral contraceptives is likely less than 1% *(75)*. The author stated that women with a greater extent of enterohepatic circulation, previous breakthrough bleeding, or contraceptive failure may have a higher risk for this interaction *(75)*. Because of the potential risk of contraceptive failure, clinicians should still counsel patients on this potential interaction and suggest alternative method(s) of contraception if antimicrobial therapy is necessary.

Cyclosporine

Although nafcillin is not well established as an inducer of the cytochrome P450 system, the following case report suggests that nafcillin may reduce the serum concentrations of cyclosporine via induction of the cytochrome P450 system *(76)*.

Case Study 1

On two separate occasions, a 34-year-old woman, status postrenal transplant, experienced a reduction in cyclosporine serum concentration following nafcillin administration *(76)*. The patient received 2 g nafcillin intravenously every 6 hours for a positive culture of methicillin-susceptible *Staphylococcus aureus* from a perinephric abscess. On admission, the patient was receiving 400 mg cyclosporine daily with a corresponding trough serum concentration of 229 ng/mL. After initiation of nafcillin, her cyclosporine concentrations decreased to 119 ng/mL and 68 ng/mL on days 3 and 7 of nafcillin, respectively, despite stable daily doses of 400 mg cyclosporine. On discontinuation of nafcillin, trough serum concentrations of cyclosporine increased to 141 ng/mL and 205 ng/mL on days 2 and 4 without nafcillin therapy, respectively. No change in renal or hepatic function was noted throughout this entire treatment period. The second cyclosporine–nafcillin interaction occurred when the patient was later readmitted for drainage of retroperitoneal fluid collection. The patient experienced a similar decline in cyclosporine concentrations during concomitant therapy and subsequent increases in cyclosporine concentrations following discontinuation of nafcillin. Based on the findings of this case report, cyclosporine concentrations should be closely monitored during concomitant nafcillin administration.

Erythromycin

The concurrent administration of erythromycin and penicillin may result in antagonism, synergy, or no effect (indifference) on the antibacterial activity of penicillin. β-Lactams exert their cidal effects on bacteria by binding to penicillin-binding proteins and inhibiting cell wall synthesis. For β-lactams to exercise their optimal bactericidal activity, bacteria should be actively growing and dividing; therefore, erythromycin can interfere with the bactericidal activity of penicillin by inhibiting protein synthesis.

In vitro studies have demonstrated the concomitant administration of penicillin and erythromycin to be synergistic, antagonistic, additive, or indifferent *(77–84)*. These differences may be caused by such factors as the specific microorganism involved,

susceptibility patterns to both agents, antibiotic concentrations, the inoculum effect, and time of incubation *(77,79,81,83–86)*. Similar to the disparate results demonstrated in vitro, case reports have shown penicillin and erythromycin antagonism in the treatment of scarlatina *(87)* and *Streptococcus bovis* septicemia *(88)*, whereas clinical improvement has been reported with the concurrent use of ampicillin and erythromycin in the treatment of pulmonary nocardiosis *(89)*.

Although there has been concern about the use of the combination of β-lactams and macrolides because of the possibility of antagonism, they have gained favor for the treatment of community-acquired pneumonia in the hospitalized patient. Several studies found that patients with bacteremic pneumococcal pneumonia treated with a β-lactam plus a macrolide had a lower mortality rate compared to those treated with a single agent *(90–92)*. As such, treatment guidelines for community-acquired pneumonia recommend a penicillin and macrolide as a preferred treatment option for hospitalized patients *(93)*. As evident from these clinical reports and in vitro testing, the antagonism risk between β-lactams and macrolides appears to be minimal.

Guar Gum

Guar gum, which may be utilized as a food additive, has been reported to reduce serum concentrations of phenoxymethyl penicillin *(94)*. In a double-blind study, 10 healthy volunteers received guar gum or placebo granules along with 3 million units of phenoxymethyl penicillin. The peak penicillin concentration decreased significantly from 7560 ± 1720 to 5680 ± 1390 ng/mL ($p < 0.01$) when administered with placebo compared to guar gum. The $AUC_{0–6\ hours}$ of penicillin decreased significantly from 14,500 ± 1860 to 10,380 ± 2720 ng/mL · hour ($p < 0.001$) when administered with guar gum. The time to peak concentration was not altered significantly. As a result of the significant decrease in the peak serum concentrations and $AUC_{0–6\ h}$, phenoxymethyl penicillin should not be administered concomitantly with guar gum.

Interferon-γ

Data suggested that penicillin may interact with a variety of cytokines by conjugating these biological proteins *(95,96)*. Benzylpenicillin has been shown to conjugate interferon (IFN)-γ, interleukin (IL)-1β, IL-2, IL-5, IL-13, and tumor necrosis factor (TNF)-α; however, based on a series of in vitro experiments, benzylpenicillin only appears to alter the biological activity of IFN-γ *(95)*. Using an in vitro bioassay, Brooks et al. noted that benzylpenicillin inhibited the ability of IFN-γ to induce CD54 expression on epithelial cells. Additional preclinical studies suggested that other regulatory functions of IFN-γ may also be modulated by benzylpenicillin *(96)*. Because IFN-γ promotes Th1 responses and inhibits Th2 and immunoglobulin E-mediated responses, disruption of IFN-γ activity by benzylpenicillin may result in clinically significant immunomodulatory effects, which promote allergy. Referred to Chapter 13 for additional information on drug–cytokine interactions.

Khat

The chewing of khat (a natural substance obtained from shrubs grown in East Africa and Yemen) may reduce the bioavailability of ampicillin and amoxicillin *(97)*. In a crossover design, eight healthy adult male Yemeni subjects received ampicillin or

amoxicillin under various conditions of khat chewing *(97)*. The urinary excretion method was utilized to determine the bioavailabilities of ampicillin and amoxicillin under the following conditions: antibiotic alone, 2 hours before khat chewing, immediately prior to khat chewing, immediately prior to khat chewing with a meal, midway through khat chewing, and 2 hours after khat chewing. The bioavailability of ampicillin (measured by percentage of ampicillin excreted unchanged in the urine, peak excretion, and time to peak excretion) was significantly decreased during all conditions except when administered 2 hours after khat chewing. In contrast, amoxicillin's bioavailability was only affected when amoxicillin was taken midway through khat chewing. Considering the limited use of khat in the developed countries, this should not be considered a clinically relevant drug–drug interaction. However, if ampicillin and amoxicillin are administered to an individual using khat, these agents should be taken at least 2 hours following khat chewing.

Metformin

In a crossover study, healthy volunteers were randomly assigned to receive metformin alone or metformin along with cephalexin *(98)*. The coadministration of metformin and cephalexin led to an increase in C_{max} and AUC of metformin by approx 30%. It appears that cephalexin interferes with renal clearance of metformin, which may be because of competition for renal transport proteins such as organic anion or cation transporter *(98,99)*. Limited data are available on the clinical significance of this interaction. Clinicians should exercise caution when using these two agents together.

Methotrexate

Weak organic acids such as penicillins can compete with methotrexate (MTX) for renal tubular secretion *(100,101)* and reduce the renal elimination of MTX. Various studies in rabbits have demonstrated a reduction in the renal clearance of MTX and 7-hydroxymethotrexate *(100–103)*. One of the studies demonstrated nearly 50% reduction in MTX clearance when piperacillin was administered 10 minutes before and 4 hours after a single dose of MTX ($p \leq 0.05$) *(101)*. The AUC of MTX and its 7-hydroxymethotrexate metabolite also differed significantly from the control ($p \leq 0.05$).

Despite the rather significant results reported from animal studies, few case reports have documented this potential interaction *(104–109)*. Bloom and colleagues reported four cases in which the administration of various penicillins concomitantly with MTX resulted in the decreased clearance of MTX *(105)*. MTX clearance before and after the addition of the following antimicrobial agents was as follows: penicillin, 2.8 vs 1.8 L/hour; piperacillin, 11 vs 3.6 L/hour; ticarcillin, 5.8 vs 2.3 L/hour; and dicloxacillin/indomethacin, 6.4 vs 0.45 L/hour, respectively. Because of reduction in clearance, these patients required an extended leucovorin rescue. A case report described severe MTX toxicity following the concomitant administration of high-dose MTX and oxacillin, which led to a series of complications and ultimately the death of the patient *(109)*. In contrast, Herrick and colleagues reported no differences in renal clearance of MTX administered alone or with flucloxacillin in 10 patients *(110)*.

Avoiding the concomitant use of penicillins and MTX is justified to avoid potential toxicity. If the concomitant administration of penicillins and MTX is necessary, close monitoring of MTX concentrations and signs of toxicity is warranted.

Oseltamivir

A pharmacokinetic study conducted in healthy volunteers evaluated the concurrent administration of oseltamivir (a prodrug) and amoxicillin *(111)*. No differences in the pharmacokinetic parameters of oseltamivir's active metabolite, Ro 64-0802, were noted when administered alone compared to coadministration with amoxicillin. Also, no pharmacokinetic differences were noted for amoxicillin with or without the administration of oseltamivir *(111)*. Based on these finding, oseltamivir may be prescribed with amoxicillin.

Phenytoin

Highly protein-bound antibiotics such as nafcillin and oxacillin (both approx 90% bound to plasma proteins) *(112)* have the potential to interact with other highly protein-bound agents such as phenytoin *(113,114)*. Because of drug displacement from protein-binding sites, high doses of nafcillin or oxacillin may increase unbound concentrations of phenytoin in certain patient populations *(113,114)*.

Dasgupta et al. conducted an in vitro study to determine the potential drug interaction between oxacillin and phenytoin *(113)*. Serum was collected from three separate patient populations (A, B, and C). Serum for Group A was collected from healthy patients receiving phenytoin. Sera for Groups B and C were obtained from hypoalbuminemic and hyperuremic individuals, respectively. Subjects in these last two groups were not receiving phenytoin; therefore, the sera were supplemented with phenytoin. Each group was tested for total and unbound phenytoin concentrations with and without 15 or 50 μg/mL oxacillin, which represented estimated peak oxacillin concentrations following a 500-mg oral dose and a 1-g iv dose, respectively. Serum from Group A showed no statistical difference in unbound phenytoin concentrations with 15 μg/mL oxacillin; however, a significantly higher unbound phenytoin concentration with 50 μg/mL of oxacillin was observed when compared to serum not containing oxacillin (1.67 vs 1.47 μg/mL) ($p < 0.05$). Sera from subjects in Groups B and C also demonstrated a statistically significant increase in unbound phenytoin concentrations for both oxacillin concentrations compared to the group without oxacillin.

Dasgupta and colleagues performed another study to determine the potential effect of nafcillin on unbound phenytoin concentrations *(114)*. The study consisted of both in vitro and in vivo components. The authors observed both in vitro and in vivo displacement of phenytoin with the addition of nafcillin to serum. Although increases in unbound phenytoin appeared to be minor for the in vitro portion of the experiment, a significant increase in unbound phenytoin concentrations was noted in all groups compared to the control group ($p < 0.05$). Unbound phenytoin concentrations were also measured in four patients receiving phenytoin and nafcillin concurrently *(114)*. The investigators obtained unbound phenytoin concentrations during and after nafcillin therapy. Unbound phenytoin concentrations decreased following the discontinuation of nafcillin, although baseline phenytoin concentrations were not obtained.

Patients receiving antimicrobials with a high percentage of protein binding (90% or greater) and concomitant phenytoin should be monitored closely for signs of phenytoin toxicity. Furthermore, patients receiving high doses of any penicillin should have their unbound and total phenytoin concentrations monitored closely. Phenytoin dosage adjustments should be made according to extent of the interaction.

Probenecid

The interaction of probenecid and penicillins (weak organic acids) occurs primarily as a result of the inhibition of the tubular secretion of penicillin, although other mechanisms may be possible as well *(115,116)*. The decrease in renal elimination results in increased penicillin serum concentrations. Studies have shown that the AUCs of amoxicillin, ampicillin, ticarcillin, and nafcillin may increase by approx 50 to 100% when coadministered with probenecid *(48,116–119)*. Other β-lactams such as penicillin and dicloxacillin have also demonstrated increased serum concentrations in the presence of probenecid *(48,120–123)*. Although probenecid significantly affects renal clearance of piperacillin/tazobactam, it does not significantly effect area under the curve or half-life of piperacillin/tazobactam *(124)*.

This drug–drug interaction may be clinically beneficial in certain situations in which higher penicillin serum concentrations are necessary (e.g., in the treatment of meningitis or endocarditis). However, careful monitoring or avoidance of this combination should be considered in certain patient populations in whom drug accumulation may occur (e.g., elderly patients or patients with impaired renal function).

Proguanil

Babalola et al. conducted a study in healthy volunteers to evaluate the coadministration of proguanil and cloxacillin on the pharmacokinetics of cloxacillin *(125)*. Differences in pharmacokinetic parameter values for cloxacillin alone or in the presence of proguanil were determined by assaying urinary samples. Both the maximum excretion rate and total amount of excreted unchanged cloxacillin were reduced by approx 50% when taken with proguanil compared to proguanil alone ($p < 0.0001$). No differences were noted in cloxacillin half-life or T_{max}. The authors suggested that separating these two agents by 1–2 hours may avoid this potential interaction.

Sulfonamides

The concurrent administration of penicillins and sulfonamides was evaluated in a pharmacokinetic study *(49)*. The unbound concentrations of penicillin G, penicillin V, nafcillin, and dicloxacillin were increased with the concurrent administration of several sulfonamides. The researcher postulated that this interaction occurred as a result of the displacement of penicillins from protein-binding sites *(49)*. In a separate study, Kunin reported that the coadministration of oral oxacillin and sulfonamides caused a decrease in oxacillin serum concentrations. The author postulated that perhaps the sulfonamides may cause reduced absorption of oral oxacillin; however, additional mechanisms cannot be ruled out *(49)*. Based on these limited clinical data, avoidance of penicillins and sulfonamides is not warranted.

Tetracyclines

As stated in the Chloramphenicol section, the administration of a bacteriostatic agent, such as tetracycline or related compounds, may antagonize the bactericidal activity of β-lactams. Nonetheless, both antagonism and synergy between penicillins and tetracyclines has been documented in in vitro and in vivo studies *(126–130)*.

Lepper and Dowling reported the outcome of 57 patients diagnosed with pneumococcal meningitis who were treated with high-dose penicillin ($n = 43$) or high-dose

penicillin along with the tetracycline antibiotic aureomycin (n = 14) *(131)*. Although the severity of illness appeared similar between the treatment groups, mortality rates were significantly higher in the patients who received combination therapy compared to penicillin alone (79 vs 30%). Olsson and colleagues also noted a trend toward increased mortality in patients with pneumococcal meningitis treated with penicillin in combination with a tetracycline derivative (85%; n = 7) vs penicillin alone (52%; n = 23) or erythromycin alone (50%; n = 6) *(132)*. Strom noted that treatment of hemolytic streptococci with penicillin in combination with chlortetracycline compared to penicillin alone had similar initial clinical response, but the penicillin/chlortetracycline group experienced a higher incidence of reinfection *(133)*.

Unlike the case studies involving meningitis, Ahern and Kirby reported similar clinical outcomes in patients treated with penicillin alone vs penicillin in combination with aureomycin for pneumococci pneumonia (*134)*. The authors suggested that the role of rapid, bactericidal activity of penicillin is of more clinical significance in treating meningitis compared to less-severe infections such as pneumonia. Adhern and Kirby stressed the importance of penicillin's role in treating meningitis because of the relatively limited phagocytic activity in the subarachnoid space compared to nonmeningeal infections such as pneumonia.

Avoiding the combination of penicillin and tetracycline derivatives appears appropriate in severe infections requiring rapid bactericidal activity such as meningitis. In less-severe infections, the use of these drugs in combination has not been documented to affect outcomes adversely.

Vecuronium

The concurrent administration of vecuronium and acylaminopenicillins has been reported to prolong muscle paralysis in both humans and animals *(135–138)*. Condon et al. conducted a double-blind clinical trial to determine the ability of piperacillin or cefoxitin (control agent) to prolong the muscular blockade of vecuronium *(139)*. Patients were eligible for study enrollment if they were undergoing an elective operation with general anesthesia that required antibiotic prophylaxis. Patients were subsequently randomly assigned to receive piperacillin or cefoxitin as the prophylactic antibiotic prior to the operation. All patients received vecuronium for muscle relaxation. Prolongation of neuromuscular blockade was determined before and after the administration of the antibiotic by the electromyographic twitch response. Of the 27 evaluable patients enrolled in the study, 5 patients (2 on piperacillin and 3 on cefoxitin) exhibited a nonclinically significant prolongation of neuromuscular blockade. Otherwise, the rate and extent of neuromuscular blockade was similar between groups. It appears that this interaction is clinically insignificant, although knowledge of this potential prolongation may be useful in certain surgical settings.

Miscellaneous Agents

The concomitant administration of penicillins and acidic drugs such as phenylbutazone, sulfinpyearazone, indomethacin, and sulfaphenazole may prolong the half-life of penicillin. This is postulated to occur as a result of competition between the acidic drugs and penicillin for renal tubular secretory proteins *(48)*. In this investigation, the half-life of penicillin was not noted to change significantly with concomitant administration of chlorothiazide, sulfamethizole, and sulfamethoxypyearidazine *(48)*.

Potential drug–drug interactions between the penicillins and theophylline have also been investigated. The coadministration of amoxicillin, ampicillin, ticarcillin/clavulanic acid, or ampicillin/sulbactam with theophylline was not noted to alter theophylline's properties *(140–144)*.

Deppermann et al. assessed the effect of the coadministration of pirenzepine, an antimuscarinic, with various antibiotics including amoxicillin in a double-blind, randomized crossover study *(4)*. Coadministration of pirenzepine with amoxicillin did not significantly alter the pharmacokinetics of amoxicillin.

CEPHALOSPORIN DRUG INTERACTIONS

Acid-Suppressive Agents

Ranitidine and Famotidine

Concomitant administration of the prodrugs cefpodoxime proxetil, cefuroxime axetil, and cefditoren pivoxil with agents that increase gastric pH, such as ranitidine, results in a reduction of the antibiotic serum concentrations *(5,145)*. The bioavailability of the cefpodoxime proxetil has been reported to decrease by approx 30–40% with concurrent administration of an H_2-receptor antagonist *(145,146)*. However, no impact on the bioavailability of cefpodoxime was noted when famotidine administration was separated from cefpodoxime by 2 hours. Similarly, the AUC of cefuroxime axetil was reduced by approx 40% with pretreatment of ranitidine and sodium bicarbonate *(5)*. The C_{max} and AUC of cefditoren pivoxil were reduced by approx 25% with the concurrent administration of famotidine *(147)*. Other studies have found no significant effect on the bioavailability of cephalexin and cefaclor AF when administered concomitantly with H_2-receptor antagonists *(4,148)*. Based on the results from these studies, concurrent administration of H_2-receptor antagonists and cefuroxime axetil, cefpodoxime proxetil, and cefditoren pivoxil should be avoided. If these agents need to be administered concurrently, the cephalosporins should be given at least 2 hours after the H_2-receptor antagonist.

Antacids

The coadministration of antacids and certain cephalosporins, including Cefaclor CD®, cefdinir, cefpodoxime, and cefditoren may lead to decreased concentrations of the antibiotics (*145–149*). A variety of studies have reported decreases in cephalosporin AUC and C_{max} to be in the range of 20–40% for cefaclor, cefdinir, and cefpodoxime when administered with an antacid *(145,148,149)*. A minimal reduction in C_{max} (14%) and AUC (11%) was noted with the concurrent administration of cefditoren with an antacid *(147)*. Other investigators have found no effect with cephalexin *(4)* or cefixime *(150)* when administered concomitantly with antacids. Certain cephalosporins, including Cefaclor CD, cefdinir, cefpodoxime, and cefditoren, should not be coadministered with antacids. If antacids are required during therapy, the cephalosporins should be separated from the antacid administration by at least 2 hours.

Calcium Channel Blockers

Variable data exist regarding the effects of nifedipine on cephalosporin pharmacokinetics *(151,152)*. In a randomized crossover study, each healthy volunteer received cefixime with nifedipine or placebo *(152)*. The absolute bioavailability of cefixime

was increased from 31 (cefixime alone) to 53% (cefixime and nifedipine) ($p < 0.01$). The $AUC_{0-\infty}$ also increased from 16.1 mg · (cefixime alone) compared to 25.4 mg · hours/L (cefixime and nifedipine) ($p < 0.01$) *(152)*. These investigators have also shown increased cephalexin concentrations with coadministration of nifedipine or diltiazem in an animal model *(153)*. The authors concluded that nifedipine can increase the absorption of these cephalosporins by enhancing the active transport mechanism in the intestine. In contrast, another study demonstrated that the pharmacokinetics of cefpodoxime did not change when coadministered with nifedipine *(151)*. Because of differences in specific antimicrobials and lack of adverse events seen with calcium channel blocker and cephalosporin combinations, no dosage changes are recommended when these agents are coadministered.

Cholestyramine

The coadministration of cholestyramine with cefadroxil or cephalexin has been shown to cause a delay in absorption associated with a prolonged T_{max} and reduction in C_{max} *(154,155)*. Despite these pharmacokinetic alterations, other important parameters such as AUC or amount of drug excreted in the urine were minimally affected. Although data for this interaction are limited, the clinical significance is doubtful, particularly considering that cholestyramine does not appear to alter cephalosporin exposure.

Contraceptives: Oral Estrogen

Refer to this topic in the discussion of penicillin.

Ethanol: Disulfiramlike Reactions

Semisynthetic cephalosporins containing a methyltetrazolethiol (MTT) side chain, such as cefamandole, cefoperazone, cefmenoxime, cefotetan, and moxalactam, have been documented to cause disulfiramlike reactions in patients who consume ethanol during antibiotic treatment *(156–158)*. Cephalosporins with an MTT side chain inhibit acetaldehyde dehydrogenase, which results in the accumulation of acetaldehyde, a toxic metabolite of ethanol. Patients should be instructed not to consume alcohol during and for several days following antibiotic therapy. Refer to Chapter 12 regarding antimicrobials and food interactions for a more detailed review of this topic.

Iron

Coadministration of ferrous sulfate appears to cause a chelation complex and reduce the absorption of cefdinir *(159)*. In a randomized three-way crossover study, six healthy male subjects received the following regimens: 200 mg cefdinir alone, 200 mg cefdinir plus 1050 mg ferrous sulfate sustained release, or 200 mg cefdinir followed by 1050 mg ferrous sulfate sustained release 3 hours later *(159)*. The $AUC_{0-12} \pm SD$ (μg · hours/mL) was significantly lower in the groups that received cefdinir concomitantly with ferrous sulfate (0.78 ± 0.25 μg · hours/mL) or at 3 hours following the dose of cefdinir (6.55 ± 1.61 μg · hours/mL) compared to cefdinir alone (10.3 ± 1.35 μg · hours/mL) ($p < 0.05$). To avoid the potential for therapeutic failure of cefdinir, it should not be taken together with ferrous sulfate.

Metoclopramide

A healthy volunteer, crossover study evaluated the effect of food, metoclopramide, propantheline, and probenecid on the pharmacokinetics of cefprozil *(160)*. In the metoclopramide arm of the study, volunteers received cefprozil alone or cefprozil given 0.5 hours after a dose of metoclopramide. Both isomers of cefprozil, *cis* and *trans*, were assayed in blood and urine. Cefprozil's isomers demonstrated a statistically significant reduction in mean residence time when administered after metoclopramide; however, there was no difference in $AUC_{0-\infty}$ or half-life of cefprozil among the treatment groups. Administration of metoclopramide prior to cefprozil did not affect its extent of absorption. Concurrent administration of these agents need not be avoided.

Methotrexate

Rabbits receiving concomitant infusions of MTX and a cephalosporin (ceftriaxone, ceftazidime, ceftizoxime, or cefoperazone) have been demonstrated to have an increased renal elimination of MTX and 7-hydroxymethotrexate *(100,101)*.

In a case report, an 8-year-old boy receiving MTX for non-Hodgkin's lymphoma experienced a decrease in MTX clearance when MTX was coadministered with piperacillin *(104)*. The patient subsequently received MTX along with ceftazidime without any impact on MTX clearance. The differences seen in MTX renal elimination between cephalosporins and piperacillin may be because of the extent of tubular secretion (penicillins > cephalosporins) *(100,161)*.

Based on the limited data available, there have been no documented interactions resulting in decreased renal elimination of MTX with the concurrent administration of cephalosporins. However, because of the documented interaction between some penicillins and MTX, close monitoring of MTX concentrations and signs of toxicity (e.g., bone marrow suppression, nephrotoxicity, mucositis) is suggested during concurrent use of cephalosporins and MTX.

Nonsteroidal Anti-Inflammatory Drugs

Diclofenac has been reported to cause an increase in the biliary excretion of ceftriaxone *(162)*. A study was conducted in patients in whom a cholecystectomy was performed and a drain was placed in the common bile duct *(162)*. The subjects who received ceftriaxone along with diclofenac demonstrated a 320% ($p < 0.05$) increase in the amount of ceftriaxone excreted in the bile and a 56% ($p < 0.05$) reduction in the amount excreted in the urine. Because of limited data, no therapeutic recommendations can be made.

Phenytoin

Highly protein-bound antibiotics such as ceftriaxone (approx 90% bound to plasma proteins) *(112)* have the potential to interact with other highly protein-bound agents such as phenytoin *(114)*. Because of protein displacement, high doses of ceftriaxone may increase unbound concentrations of phenytoin in certain patient populations *(114)*. Dasgupta and colleagues performed an in vitro study to determine the effect of ceftriaxone in displacing phenytoin from protein-binding sites *(114)*. Estimated peak ceftriaxone concentrations (270 and 361 μmol/L) were added to pooled sera from

patients receiving phenytoin. Three groups with varying albumin concentrations were evaluated. The greatest ceftriaxone-induced displacement effect was seen the group with the lowest albumin concentration (25 g/L). In this group, the unbound phenytoin concentrations (μmol/L) (SD) were 8.12 (0.28) for the control, 9.39 (0.12) for 270 μmol/L ceftriaxone, and 9.93 (0.36) for 361 μmol/L ceftriaxone. Although the increases appear minor, significant increases in unbound phenytoin concentrations were noted in all groups compared to the control group ($p < 0.05$). In patients receiving ceftriaxone concomitantly with phenytoin, monitoring of unbound and total serum concentrations of phenytoin in addition to watching for signs of phenytoin toxicity is warranted.

Oral Anticoagulants

Semisynthetic cephalosporins containing an MTT substituent at the 3-position, such as cefamandole, cefoperazone, cefmenoxime, cefotetan, and moxalactam, have been associated with the development of a hypoprothrombinemia *(163)*. Several case reports have implicated these agents in prolonged PT or bleeding episodes in patients *(164–170)*. Angaran and colleagues retrospectively assessed the effect of prophylactic administration of cefamandole or vancomycin on the warfarin anticoagulation response in 60 postsurgical patients *(171)*. Patients who received cefamandole had a higher proportion of elevated PTs compared with those who received vancomycin (14 vs 1, $p < 0.05$). In another study, these same investigators characterized the effect of cefazolin, cefamandole, and vancomycin on warfarin anticoagulation in patients after cardiac valve replacement *(172)*. They noted that the greatest number of patients ($n = 6$) with elevated PTs received cefamandole compared to cefazolin ($n = 1$) and vancomycin ($n = 1$). In addition, cefamandole therapy was associated with a 15–20% greater change in PTs compared to the cefazolin and vancomycin ($p < 0.01$). Patients who are malnourished or who have renal insufficiency may be at higher risk for this interaction *(164)*. The exact mechanism of the hypoprothrombinemic phenomenon is unknown, although several mechanisms have been proposed *(97,173–176)*. Clinicians are cautioned to monitor for signs and symptoms of bleeding, PT, and activated partial thromboplastin time in patients receiving cephalosporins with an MTT side chain and concomitant therapy with oral anticoagulants.

Probenecid

Probenecid can increase the serum concentrations of most renally eliminated cephalosporins *(148,160,177–191)*. Although other mechanisms may contribute, probenecid appears to inhibit tubular secretion of cephalosporins, resulting in their decreased renal elimination *(115,116)*. The AUCs of ceftizoxime, cefoxitin, cefaclor, and cefdinir have been reported to increase by approx 50–100% with the coadministration of probenecid *(115,179,180)*. Probenecid has been documented to prolong the half-life and increase the serum concentration of many other cephalosporins as well *(148,149,160,177–192)*. Certain cephalosporins, such as ceforanide, ceftazidime, ceftriaxone, and moxalactam, are eliminated through a different pathway, and their pharmacokinetics are not significantly altered by probenecid *(177,178,193–198)*.

Achieving high cephalosporin concentrations may be clinically beneficial in certain situations (e.g., in the treatment of meningitis or endocarditis); however, caution or avoidance of this combination should be considered in certain patient populations in

which drug accumulation may occur (e.g., elderly patients or patients with impaired renal function).

Propantheline

A healthy volunteer, crossover study evaluated the effect of food, metoclopramide, propantheline, and probenecid on the pharmacokinetics of cefprozil *(160)*. In the propantheline arm of the study, volunteers received cefprozil alone or cefprozil given 0.5 hours after a dose of propantheline. Both isomers of cefprozil, *cis* and *trans*, were assayed in blood and urine samples. There was no difference in cefprozil $AUC_{0-\infty}$ or half-life in either treatment group. The administration of propantheline prior to cefprozil does not affect the extent of cefprozil absorption. No special precautions seem necessary for this combination.

Theophylline

The coadministration of cephalexin or cefaclor with theophylline has not been documented to significantly alter any pharmacokinetic parameters of theophylline *(199–201)*. However, Hammond and Abate reported a case of a possible interaction between theophylline and cefaclor, which resulted in theophylline toxicity *(202)*. It was unclear whether this was an actual drug–drug interaction or the effect of an acute viral illness on theophylline disposition. Based on these limited data, no dosage recommendations are necessary.

Miscellaneous Agents

Older cephalosporins such as cephalothin and cephaloridine have been reported to cause nephrotoxicity *(203,204)*. The coadministration of these older cephalosporins with other potential nephrotoxic agents, including colistin *(204,205)*, various aminoglycosides *(203,206–212)*, and furosemide *(213–216)*, has been associated with an increased incidence of nephrotoxicity. The clinical impact of this interaction is limited because these cephalosporins are rarely used in current clinical practice; however, careful monitoring of renal function is warranted if such combinations are prescribed. These drug–drug interactions have not been documented as a clinically significant problem for any of the newer cephalosporins *(217–219)*.

CARBAPENEMS

Probenecid

Concomitant probenecid can increase the concentration of the carbapenems. It is proposed that probenecid inhibits tubular secretion of the carbapenems, resulting in their decreased renal elimination. Meropenem's half-life and AUC were increased by 33 and 55%, respectively, when coadministered with probenecid *(220)*. Probenecid has less impact on the renal elimination of ertapenem and imipenem. The combination of ertapenem and probenecid produced a 20% increase in half-life and a 25% increase in the AUC of ertapenem compared to ertapenem alone *(221)*. In contrast, imipenem's half-life and AUC only increased 6 and 13%, respectively, when coadministered with probenecid *(222)*.

Achieving high concentrations of carbapenems may be clinically beneficial in infections in which higher serum concentrations are necessary. However, caution or avoid-

ance of this combination should be considered in patient populations in which drug accumulation may occur (such as elderly patients or patients with impaired renal function). The increased serum concentration noted as a result of this drug–drug interaction may increase the risk of central nervous system toxicity of these agents.

Valproic Acid

Limited data suggest that the coadministration of carbapenems and valproic acid may lead to decreased concentrations of valproic acid. DeTurck and colleagues described two case reports in which valproic acid concentrations were decreased following the administration of meropenem and amikacin *(223)*. Both patients were receiving valproic acid for seizure prophylaxis. The first patient was receiving valproic acid as a continuous infusion following the placement of a ventricular drain to relieve obstructive hydrocephalus secondary to a subdural hemorrhage. Steady-state valproic acid concentrations were maintained between 50 and 100 mg/L; however, the addition of meropenem and amikacin therapy resulted in subtherapeutic valproic acid concentrations within 2 days. In the second case report, the authors described a female patient receiving valproic acid following clipping of multiple cerebral aneurysms. Similar to the previous case, valproic acid concentrations decreased suddenly with addition of meropenem. Other authors have reported data on three cases describing a potential interaction with valproic acid and panipenem/betamipron, a carbapenem *(224)*. Animal models have also found decreased valproic acid concentrations with the concurrent administration of imipenem *(225)*, meropenem *(226)*, or panipenem *(227)* and valproic acid. Monitoring for alteration in valproic acid concentrations during concurrent carbapenem therapy seems reasonable to avoid the possibility of subtherapeutic valproic acid serum concentrations.

IMIPENEM/CILASTATIN

Cyclosporine

Based on case reports, cyclosporine and imipenem/cilastatin may demonstrate additive central nervous system toxicity when administered concomitantly. Bösmuller and colleagues reported five transplant patients experiencing central nervous system toxicity during administration of cyclosporine and imipenem/cilastatin *(228)*. None of these patients reported a history of seizures. Four of the five patients experienced a seizure despite cyclosporine concentrations within normal therapeutic range. The fifth patient experienced myclonia; this was associated with an elevated cyclosporine concentration of 900 ng/mL. Symptoms of central nervous toxicity occurred within 1 day in four patients, and symptoms resolved in all patients with discontinuation of imipenem/cilastatin or dose reduction of cyclosporine.

Zazgornik and colleagues published a case report of a 62-year-old female receiving imipenem/cilastatin and cyclosporine who developed central nervous system toxicity *(229)*. The patient had recently received a renal transplant secondary to interstitial nephritis and was receiving imipenem/cilastatin for a urinary tract infection. Following the second dose of imipenem/cilastatin, the patient experienced confusion, agitation, and tremors, which resulted in the discontinuation of imipenem/cilastatin. The serum cyclosporine concentration, which was obtained 4 days after imipenem/cilastatin therapy, was elevated at 1000 ng/mL compared to a previous level of 400 ng/mL. In

contrast, an investigation in a rat model demonstrated decreased cyclosporine serum concentrations when it was coadministered with imipenem/cilastatin *(230)*.

Because both imipenem and cyclosporine administered alone may have the potential to cause central nervous system side effects, it is difficult to determine what role the combination of these agents may have played in these reports. Based on these limited clinical data, avoidance of imipenem and cyclosporine is not warranted.

Theophylline

Semel and Allen reported three cases of seizures occurring in patients receiving imipenem/cilastatin and theophylline *(231)*. None of the patients had a previous history of neurological or seizure disorder. The authors concluded that the seizures could be caused by both drugs' ability to inhibit γ-aminobutyric acid binding to receptors. It is difficult to differentiate the potential for seizures between the administration of imipenem/cilastatin alone and the combination of imipenem/cilastatin and theophylline. Avoiding coadministration of theophylline and imipenem/cilastatin is not warranted.

Ganciclovir

Patients have experienced generalized seizures during concomitant imipenem/cilastatin and ganciclovir therapy *(232)*. No additional information is available on these patients. Because of these limited data, it is difficult to differentiate the potential for seizures of imipenem/cilastatin alone or the combination of imipenem/cilastatin and ganciclovir. The manufacturer does not recommend coadministration of imipenem/cilastatin and ganciclovir unless the benefits outweigh the risks.

MONOBACTAMS

Inducers of β-Lactams

Antimicrobials that can induce the production of β-lactamases, such as cefoxitin and imipenem, should not be used concurrently with aztreonam in the treatment of certain infections, depending on the causative microorganism *(233)*. This β-lactamase production by certain Gram-negative aerobes, such as *Enterobacter* and *Pseudomonas* species, may lead to the inactivation of aztreonam. Based on the organism isolated and susceptibility results, one should consider this potential interaction when choosing an antimicrobial regimen.

Probenecid

Concomitant probenecid can increase aztreonam concentrations *(234)*. It is proposed that probenecid inhibits tubular secretion resulting in decreased aztreonam renal elimination. In a randomized crossover trial, six healthy men received aztreonam alone or aztreonam along with probenecid *(234)*. Coadministration of probenecid with aztreonam increased aztreonam concentrations from 81.7 ± 3.4 to 86.0 ± 2.2 μg/mL. This interaction seems to carry minimal clinical risk. No recommendation to avoid the concurrent administration of probenecid and aztreonam seems warranted.

CASE STUDY 2

A 72-year-old male with a 10-year history of adult onset diabetes mellitus has been poorly controlled on rosiglitazone, with complications of diabetic retinopa-

thy and multiple episodes of lower extremity infections. He also takes 5 mg warfarin daily status post-pulmonary embolism. Seven days ago, he presented to his local doctor with an infected left baby toe after "bumping it" on the leg of a chair. At that time, his doctor started him empirically on 500 mg dicloxacillin twice daily for 7 days. At his follow-up visit a week later, although his infection was better, it was noted that his INR had changed from 2.2 to less than 1.0.

A decreased anticoagulant effect for warfarin has been documented when given concomitantly with semisynthetic penicillins like nafcillin or dicloxacillin. It has been postulated that, because these antibiotics induce the P450 cytochrome system, this may lead to an increased warfarin metabolism.

Avoiding the concomitant use of dicloxacillin and warfarin is justified in this patient to avert this interaction. Selection of another antimicrobial that does not interfere with warfarin metabolism would be a more reasonable approach in this patient.

Case Study 3

A 45-year-old white male complaining of earache, pressure above his eyebrows, and cough producing thick, white purulent sputum for the last 2 weeks presented to the outpatient clinic for help. The patient also complained of inability to sleep because of feeling hot, having a constant pressure in his ears, and chest soreness. He stated that he has had a productive cough for several months at a time over the last 3 years. He routinely takes one 65-mg aspirin daily and one multivitamin supplemented with extra iron. The clinic doctor prescribed 300 mg cefdinir twice daily for 10 days. Despite taking the medication as directed, he returned to the clinic 5 days later with only minimal improvement of his symptoms and a temperature of 101.1°F. The clinic doctor discontinued the cefdinir and started another antibiotic.

The apparent clinical failure in this patient may have been caused by the coadministration of ferrous sulfate and cefdinir. This combination has been shown to result in a chelation complex that results in reduced absorption of cefdinir.

To avoid the potential for therapeutic failure with cefdinir therapy in this instance, the two drugs should not be taken together. Or, if the cefdinir therapy is considered essential, then the drug should be taken at least 2 hours before administration of the iron-containing product.

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