Infectious Disease
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Manjunath P. Pai
Jennifer J. Kiser
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Drug Interactions in Infectious Diseases: Antimicrobial Drug Interactions

Fourth Edition

Humana Press

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Series Editor

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Foreword

In the 1950s and 1960s, there was euphoria that antibacterial drugs had been discovered, which seemed to have the potential to eliminate the major role infectious diseases had in reducing the quality and duration of human life. Penicillins, cephalosporins, macrolides, tetracyclines, and aminoglycosides were a small but manageable armamentarium, which seemed destined to solve many human challenges.

Since the 1960s and 1970s, we have recognized how readily most infectious agents learn to become resistant to the anti-infective agents to which they are exposed. Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), carbapenemase-producing *Klebsiella* (KPC), azole-resistant *Candida*, and acyclovir-resistant herpes simplex have been examples of how much urgency there is to create new drugs which will have activity against organisms that have learned to evade currently available anti-infective agents.

We have also developed new classes of drugs for more recently recognized pathogens such as human immunodeficiency virus (HIV) and hepatitis C. These older and newer drugs are given to patients who are receiving a rapidly expanding armamentarium of molecules to treat their chronic and acute underlying conditions.

Healthcare providers are well aware that drugs are only effective and safe if administered with tactical and strategic planning. The right dose, given at the right time, to the right patient is a foundation for effective and safe care. However, as patients are administered more and more agents for a wide range of health challenges, interactions among drugs become more and more likely.

Every experienced clinician has anecdotes of unanticipated drug interactions that affected clinical outcome. Drug interactions can have a major negative impact on drug efficacy and can greatly enhance toxicity for the antimicrobial agent being focused on or for concurrent drugs that may be life-sustaining.

This fourth edition of *Drug Interactions in Infectious Diseases* provides healthcare providers with a unique resource for both understanding basic principles and finding important information. Volume 1 on Mechanisms and Models of Drug

Interactions and Volume 2 on Antimicrobial Drug Interactions are well organized for providers to quickly find practical information. This resource maximizes the likelihood that the healthcare team can optimize efficacy and safety in this era when patients are so often receiving multiple drugs.

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Editors' Preface

The benefits of new medical therapies in infectious diseases cannot be appreciated without understanding and mitigating risk. Drug interactions in infectious diseases are a major source of medical harm that can be prevented. Over the past two decades, we have witnessed a major expansion in our anti-infective armamentarium. This expansion has been coupled with an improved understanding of drug interaction mechanisms and scientific approaches to measure them. Our transformation of the fourth edition of this text to a two-volume series is a direct reflection of the growing knowledge in this domain. Volume 1 provides a mechanistic profile of drug interactions as well as in vitro, in vivo, in silico, and clinical methods to evaluate these interactions. Volume 2 is structured by anti-infective class to provide clinicians, researchers, and academicians a useful resource to meet their practical needs.

Given the scale of this field of study, no comprehensive reviews on antimicrobial drug-drug interactions can be easily published through journals. Software programs and deep learning algorithms that can integrate the effects of all known covariates of drug-drug interaction are in development but have as yet not entered clinical practice. Hence, clinical intuition and vigilance remain key defenses against untoward drug-drug interactions. Since the last publication in 2011, several new antimicrobials have received regulatory approval. The chapters have been updated to reflect these new additions. Three distinct chapters related to the pharmacologic management of human immunodeficiency virus- and hepatitis C virus-related infections have been added in response to recent drug approvals.

The strength of the textbook lies not only in the fact that it is a comprehensive reference book on drug interactions but it also has chapters that provide insights that are difficult to find in the medical literature. We are confident that the information provided in the detailed tables and text will increase the acumen of the practicing clinician, the academic instructor, and the infectious disease researcher.

As the editors of the fourth edition of *Drug Interactions in Infectious Diseases*, we are thrilled to deliver a text that will enhance your clinical knowledge of the complex mechanisms, risks, and consequences of drug interactions associated with antimicrobials, infection, and inflammation. The quality and depth of the information provided would not be possible without the contributions of an excellent

number of authors. We are indebted to our authors for their time and diligence to ensure that this textbook remains a primary reference for those engaged in the field of infectious diseases. Finally, we thank our families for their support and encouragement throughout this endeavor.

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Author's Preface

It is well known that drug interactions pose a major risk to patients. Even a cursory look at approved drug product labels for anti-infective drugs, such as HIV drugs, direct-acting antivirals for HCV, azole antifungal drugs, and anti-mycobacterial agents, reveals that drug interactions present a huge challenge for patients and their healthcare providers. However, before a drug reaches patients, drug development scientists have the opportunity to define the potential for drug interactions. The work of these scientists and the regulatory scientists responsible for drug approval results in information available to healthcare providers and patients.

Concerns related to drug interactions grow as the knowledge of pharmacology advances. The interactions may be due to CYP enzymes, non-CYP enzymes, the ever-growing list of drug transporters, changes in gastric pH, and more. It is easy to be overwhelmed by the scope of the issue. How do you develop an informative and efficient drug interaction program? What drugs are likely perpetrators or victims of interactions? Do you have to study all potential interactions? This textbook helps answer those questions. The chapters address general drug interaction concepts, specific classes of anti-infective drugs, and application of the concepts to drug development. Together, the information helps one focus on the overarching goals of a drug interaction program, determine the potential for clinically significant drug interactions, and develop management strategies for the interactions. The first goal can be divided into four questions. Does the investigational drug alter the pharmacokinetics of other drugs? Do other drugs alter the pharmacokinetics of the investigational drug? What is the magnitude of the change? Is the change clinically significant?

As indicated in the initial chapters of this book, there are many potential mechanisms for drug interactions. Also, concerns go beyond interactions between small molecules. Other considerations include interactions due to biologic products, food components, and herbal medications. However, the bulk of drug interaction evaluations involve investigation of CYP enzyme- or transporter-based interactions. Drug development programs include multiple steps to evaluate the potential for these interactions. For both CYP enzyme and transporter interactions, programs often begin with in vitro evaluations that screen for interactions. If the in vitro evaluations

reveal potential interactions, additional evaluations, usually clinical studies with pharmacokinetic endpoints, follow. In some situations, model-based simulations can replace clinical studies or help refine their design [1]. Scientific quality and rigor is essential for all studies. The methods and interpretation of in vitro metabolism and transporter studies must follow best practices because the results may screen out the need for clinical evaluations [2]. Each clinical study should be designed to address the goal of the study. Some clinical studies, referred to as index studies, use perpetrators (inhibitors or inducers) or substrates (victims) with well-known pharmacokinetic and drug interaction properties [1]. Results of the index studies can be extrapolated to other drug combinations and inform the need for additional studies. The design of index studies should maximize the potential to detect an interaction. In contrast to index studies, concomitant use studies investigate drug interactions between the investigational drug and other drugs used in the target population [2]. Results of concomitant use studies provide useful information for the healthcare provider and patient.

The progression from in vitro to index and then concomitant use studies is a common drug development path. However, there are other options. In silico studies that use physiologically based pharmacokinetic (PBPK) methods may substitute for some clinical studies [1]. Instead of dedicated drug interaction studies, prospectively planned evaluations nested within a larger clinical trial may provide useful drug interaction information in the intended patient population. The nested studies often use population pharmacokinetic methods. The in silico and population PK evaluations should be carefully designed to address their specific goals.

Two draft guidance documents from the US Food and Drug Administration provide more details about in vitro and in vivo drug interaction studies: In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies Guidance for Industry [3] and Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications Guidance for Industry [4].

The progression of drug interaction evaluations that determine the presence and magnitude of pharmacokinetic changes forms the foundation for the next questions: Is the interaction clinically significant? How are clinically significant interactions managed? Thus, solid knowledge regarding general drug interaction concepts, issues related to specific classes of anti-infective drugs, and application of the concepts to drug development are essential to the development of anti-infective drugs.

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Chapter 1
Beta-Lactam Antibiotics

Larry H. Danziger and Karolyn S. Horn

1.1 Beta-Lactam Antibiotics

The beta-lactam antibiotics are a large class of diverse compounds used clinically in oral, parenteral, and inhaled dosage formulation. The beta-lactam antibiotic agents have become the most widely used therapeutic class of antimicrobials because of their broad antibacterial spectrum and wide therapeutic index. Reports of drug-drug interactions with the beta-lactam antimicrobials are a relatively rare phenomenon, and when they do occur, they are generally of minor clinical significance. This chapter describes the drug-drug interactions of the beta-lactam class of antibiotics: penicillins, cephalosporins, carbapenems, and monobactams.

This chapter serves as a review and clinical assessment of the literature regarding beta-lactam drug interactions. After reading this chapter, the reader will recognize the clinical significance of drug-drug interactions associated with the beta-lactam antibiotics and understand the management of these drug-drug interactions.

1.2 Penicillin Drug Interactions

1.2.1 Acid-Suppressive Agents

The combination of various penicillins (ampicillin, amoxicillin, bacampicillin, amoxicillin/clavulanate) and H_2-receptor antagonists (cimetidine and ranitidine) and the proton pump inhibitors (omeprazole, esomeprazole, and lansoprazole) has

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been evaluated for effects on the bioavailability of different penicillins [1–9]. 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 [3]. The concurrent administration of most penicillins and acid-suppressive agents poses no problems except possibly with bacampicillin.

1.2.2 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 5.9% of the patients receiving ampicillin compared to 13.9% of patients receiving both ampicillin and allopurinol ($p = 0.0000001$) [10]. There were no differences in age, sex, diagnosis, or admission laboratory value of blood urea nitrogen (BUN) that could be identified between the two groups. Another study identified 1324 patients who received ampicillin, with 67 also receiving allopurinol. The frequency of skin rashes was higher in the ampicillin-allopurinol combination than ampicillin alone (22.4% vs. 7.5%, $p < 0.00005$). The incidence of rash in those on allopurinol alone was 2.1% [11].

Fessel and colleagues attempted to explain why there is a higher incidence of rash in patients receiving allopurinol and ampicillin [12]. They 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 significant in asymptomatic hyperuricemic subjects versus the control subjects: history of penicillin allergy (14.1% versus 4.9%), hay fever (18.8% versus 8.0%), and use of antihistamine medications (9.9% versus 2.7%). The incidence of allergies to antibiotics excluding penicillin and prevalence of asthma were not significant between groups. The authors 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 [12].

Fredj and colleagues reported a case of amoxicillin hypersensitivity 2 years after a drug rash with eosinophilia and systemic symptoms (DRESS) induced by allopurinol therapy [13]. Another case of erythema multiforme and allopurinol hypersensitivity syndrome in a patient on concomitant allopurinol and amoxicillin has also been reported [14].

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. As with any patient who develops DRESS or

another severe medication-induced rash, the clinician and patient should be cognizant of the potential for future medication-induced reactions.

1.2.3 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. Henderson et al. reported on the in vitro inactivation of tobramycin, gentamicin, and netilmicin, when combined with azlocillin, carbenicillin, and mezlocillin in plasma samples incubated at 37° from 1 to 9 days. They noted that each of the penicillins studied decreased the concentrations of the aminoglycosides. The amount of aminoglycoside inactivation was related to temperature, contact time, and penicillin concentration [15]. Although the majority of interactions are reported in vitro, the potential for in vivo interactions is of concern, especially in those patients with end-stage renal failure [16–23].

1.2.3.1 In Vivo Aminoglycoside Inactivation

Animal models have demonstrated interactions between various penicillins and aminoglycosides. In bilaterally nephrectomized canines administered carbenicillin and tobramycin, gentamicin, and amikacin, the serum concentrations of all the aminoglycosides were decreased at 24 h and 7 days [24]. Additionally, it was noted that carbenicillin reduced serum half-lives of gentamicin and tobramycin by 40% ($P < 0.05$). In another study, a decrease in plasma concentrations as well as a variation in volume of distribution and half-life was shown with coadministration of piperacillin and netilmicin in rabbits, but renal accumulation and renal damage were similar between rabbits treated with the combination and only netilmicin [25]. McLaughlin and Reeves noted that rabbits that received only gentamicin were reported to have normal gentamicin concentrations, while rabbits receiving carbenicillin and gentamicin had undetectable concentrations at 30 h [17].

Evidence for an interaction between penicillins and aminoglycosides in humans is primarily restricted to coadministration with extended-spectrum penicillins, particularly in patients with end-stage renal failure [17–23, 26, 27]. McLaughlin and Reeves reported their experience in two patients [17]. In the first patient, they reported undetectable gentamicin concentrations and clinical failure in a 12-year-old patient who received an infusion of carbenicillin and gentamicin for *Pseudomonas* bacteremia. The second patient was undergoing hemodialysis and receiving gentamicin for 8 days for the treatment of a soft tissue infection. 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 findings when tobramycin and piperacillin where administered concomitantly in a chronic hemodialysis patient [18]. 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 [20]. In patients receiving gentamicin concomitantly with ticarcillin, the gentamicin half-life was reduced from 31 to 22 h, whereas gentamicin half-life was reduced from 50 to 8 h in patients receiving carbenicillin and gentamicin. Blair et al. also documented a significant interaction between carbenicillin and gentamicin. The mean gentamicin serum half-life was significantly impacted by the presence of carbenicillin (18.4 ± 8.2 versus 61.6 ± 30.7 h, respectively) [22]. However, these authors reported that amikacin serum concentrations and clearance were not altered by concomitant carbenicillin administration. Lastly, Riff and Jackson reported on four patients on chronic hemodialysis receiving gentamicin and carbenicillin concomitantly, noting that the half-life of gentamicin was reduced by over 50% and that serum concentration was also reduced by 20–40% [23].

However, Halstenson et al. assessed the effect of piperacillin administration on the disposition of netilmicin and tobramycin in 12 chronic hemodialysis patients [19]. The half-life of netilmicin was not significantly altered when given concurrently with piperacillin. In comparison, the half-life of tobramycin was considerably reduced in the presence of piperacillin (59.62 ± 25.18 versus 24.71 ± 5.41 h). 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/min) [28]. One report of healthy subjects who received 1 g of aztreonam both alone and combined with 0.5 g of amikacin showed no difference in overall exposure between monotherapy and combination therapy [29]. 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 [30]. 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/min), mild renal impairment (creatinine clearance between 20 and 39 mL/min), or normal renal function (creatinine clearance greater than 90 mL/min) [31].

Roberts and colleagues evaluated 18 healthy, cystic fibrosis patients administered either tobramycin alone or tobramycin plus ticarcillin. They noted that the clearance and volume of distribution of tobramycin increased by 13% ($P < 0.001$) and 14% ($P < 0.001$), respectively, with the coadministration of ticarcillin. They also noted that the concentration of tobramycin was decreased significantly (by 13%) when measured out to 330 min, in the presence of ticarcillin. The authors felt this difference was unlikely to be of any clinical significance [32].

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 beta-lactam used [20, 33]. In vivo inactivation of aminoglycosides occurs at such a slow rate that it appears to

be clinically insignificant in patients with normal renal function [28, 33]. Some investigators have stated that this interaction could possibly be relevant for patients with renal failure who have high serum concentrations of penicillins [19, 20, 34]; therefore, close therapeutic monitoring of aminoglycosides is warranted in this specific clinical situation.

Concomitant administration of oral neomycin and penicillin VK has been reported to reduce serum concentrations of penicillin [31]. In healthy volunteers, penicillin VK concentrations decreased by over 50% following the administration of oral neomycin concomitantly with penicillin VK [31]. Due to the significant decrease in penicillin exposure, penicillin VK should not be administered to patients receiving oral neomycin.

1.2.3.2 In Vitro Aminoglycoside Inactivation

In vitro inactivation of aminoglycosides can be significant when these agents are prepared in the same intravenous mixture for administration [17, 23, 33]. Noone and Pattison showed that within 2 h of admixing at room temperature, an intravenous fluid mixture containing ampicillin (concentration equivalent to 12 g/d) and gentamicin resulted in a 50% decline in the gentamicin activity. After 24 h, no measurable gentamicin activity was noted [33]. An intravenous fluid mixture containing gentamicin and carbenicillin demonstrated a 50% reduction in activity between 8 and 12 h after admixing at room temperature. Aminoglycosides and penicillins should not be mixed together prior to infusion.

1.2.3.3 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 [16, 35]. Penicillin concentration, period of time prior to sampling, and storage temperature of the sample are factors that affect the extent of inactivation [16]. 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 beta-lactam present in the intravenous tubing prior to sampling.

1.2.3.4 Aminoglycosides: Synergy

The concomitant use of beta-lactam and aminoglycoside antimicrobials has been described as synergistic for several Gram-positive and Gram-negative organisms [36–39]. By inhibiting the cell-wall synthesis, beta-lactams increase the porosity of

the bacterial cell wall resulting in greater aminoglycoside penetration and access to target ribosomes [40].

The use of penicillin or ampicillin in combination with an aminoglycoside has been documented to be advantageous in the treatment of streptococcal and enterococcal infections [41–47]. As a result of increased efficacy with combination therapy, many severe streptococcal and enterococcal infections are routinely treated with penicillin or ampicillin plus an aminoglycoside [46].

Despite the well-documented in vitro synergy between beta-lactams and aminoglycosides, limited clinical data are available supporting superior efficacy of synergistic versus 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 [48]. Of the 173 patients treated with two drugs, the clinical response rate was 83% in patients who received synergistic versus 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 ($p < 0.005$). However, the data from several meta-analyses do not support the use of concomitant antimicrobial therapy for definitive treatment of Gram-negative bacterial infections [49]. In critically ill patients with severe sepsis associated with Gram-negative bacteremia, the combination of an extended-spectrum penicillin and aminoglycoside is a reasonable therapeutic approach [49].

1.2.4 Anticoagulants

1.2.4.1 Heparin

A number of case reports have suggested that parenteral penicillins in combination with heparin have caused coagulopathies [50–56] and may predispose patients to clinically significant bleeding [53–55, 57]. 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 [51, 52, 57].

Wisloff and colleagues evaluated the bleeding time of patients receiving heparin and penicillins compared to heparin alone [56]. Fifty patients were placed on heparin (5000 IU subcutaneously for 7 days) following an elective vascular surgery procedure and were also randomized to receive a combination of ampicillin and cloxacillin or no antibiotics. The patients that were receiving heparin along with the penicillins had a slightly longer bleeding time; however, this was still within an acceptable range in most cases.

Since 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.

1.2.4.2 Warfarin

A decreased anticoagulant effect for warfarin has been documented when given concomitantly with nafcillin [58–63], dicloxacillin [58, 64, 65], cloxacillin [66], and flucloxacillin [67, 68]. This interaction can be significant, necessitating up to a two- to fourfold increase in warfarin dose during concomitant therapy. In addition to decreasing INR levels, cloxacillin has also been described as increasing INR in a patient on chronic warfarin therapy [69].

It has been postulated that these antibiotics induce the cytochrome P450 system and may increase the metabolism of warfarin [60, 63, 70, 71]. 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 [60]. Cropp and Busey reported that the usual onset of this interaction between nafcillin and warfarin is within 1 week after initiation of nafcillin therapy and with warfarin requirements returning to baseline usually within 4 weeks after the discontinuation of the nafcillin [72].

Krstenansky et al. studied the effect of dicloxacillin in seven patients stabilized on warfarin therapy [64]. 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 s (mean ± SD of −1.9 ± 1.8 s) and was statistically significant ($p < 0.05$). This interaction is described in case reports for patients being treated with dicloxacillin and warfarin [58, 69, 73]. Similar to nafcillin and warfarin, the effects of the interaction on international normalized ratio (INR) often last for up to 3 weeks after discontinuation of dicloxacillin.

Brown and colleagues presented a case report of a patient on warfarin 2.5 mg daily who developed an increased hypoprothrombinemia response after receiving high-dose intravenous penicillin (24 million units/day). Upon withdrawal of the penicillin, the patient's prothrombin time subsequently returned to his baseline [74].

Davydov et al. reported a case of a 58-year-old woman, in which warfarin interacted with amoxicillin/clavulanate resulting in an elevated international normalized ratio (INR) and hematuria [75]. More recently, amoxicillin, amoxicillin-clavulanate, and cloxacillin have all been implicated in case reports as interacting with warfarin to increase INR [76, 77]. It is important to note that some of these reports also describe clinically significant bleeding that occurred as a result of this interaction [75, 77].

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.

1.2.4.3 Direct Oral Anticoagulants

To date no studies have been published regarding drug interactions between the penicillin antibiotics and the direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, and edoxaban). However, Lippi et al. described that a review of the Web site of eHealthMe reported cerebral hemorrhage in two patients, rectal hemorrhage in six patients, and ten episodes of hematemesis in patients receiving amoxicillin and dabigatran concomitantly [78]. According to these reports, it would seem prudent that patients concomitantly administered amoxicillin and the DOACs require close follow-up.

1.2.4.4 Aspirin

Large doses of aspirin may increase the serum concentrations and half-lives of penicillin, oxacillin, nafcillin, cloxacillin, and dicloxacillin when administered concurrently [79, 80]. Eleven patients with arteriosclerotic disorders received penicillin G before and after high doses of aspirin (3 g/d) [79]. During aspirin administration, penicillin half-life increased from 44.5 ± 15.8 m to 72.4 ± 35.9 m ($p < 0.05$) [79]. 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 [79–83]. Avoidance of this combination is unnecessary.

1.2.5 Beta-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 with 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, $p < 0.01$) [84]. Other atenolol pharmacokinetic parameter values for AUC, Cmax, 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 [85]. Unlike the previous study, these investigators dosed ampicillin at clinically applicable doses of 250 mg four times a day, as well as higher doses of 1 g. The mean reduction of AUC was lower in the former dosing regimen compared to the latter one (18.2% versus 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.

1.2.6 Calcium Channel Blockers

Nifedipine appears to increase the bioavailability of amoxicillin by facilitating its active transport mechanism within the gastrointestinal tract [86]. 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 ($p < 0.01$) [86]. The AUC also increased from 29.7 ± 5.3 mg · h/L (amoxicillin alone) compared to 36.26 ± 6.9 mg · h/L (amoxicillin and nifedipine) ($p < 0.01$). Since 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 [63, 70]. A crossover study was conducted to evaluate the induction potential of nafcillin on nifedipine, a substrate of the cytochrome P450 3A4 enzyme [71]. Healthy volunteers were randomized 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 μg · l/h versus 216.4 μg · l/h; $p < 0.001$) and enhanced plasma clearance (138.5 ± 42.0 l/h versus 56.5 ± 32.0 l/h; $p < 0.002$) compared to the nifedipine-placebo group. Due to the limited available data, the clinical significance of this interaction is unknown.

In an animal model, the total exposure of amlodipine was increased by 42 and 133% greater when it was coadministered with ampicillin at doses of 10 mg/kg and 20 mg/kg, respectively, compared to amlodipine alone ($p < 0.001$). The authors postulated that ampicillin (and possibly other antibiotics) increases amlodipine exposure by suppression of gut microbes responsible for metabolism of amlodipine [87].