common cold in a pneumonia trial would bias a noninferiority trial toward concluding that the two interventions are similar in the treatment of pneumonia, whereas a superiority trial would correctly conclude that the test intervention lacks effect, compared with the control group.

Design of Noninferiority Trials

After meeting the criteria for selection of noninferiority as the ethical and appropriate hypothesis, appropriate design of noninferiority trials entails four considerations.[28,45] First, there must be reliable and reproducible comprehensive quantitative evidence of the effect of the control intervention compared with placebo or no specific therapy in comparable patients, taking into account the variability of that estimate. Prior use in clinical practice or the investigator's belief in effects alone does not justify a noninferiority design. For instance, in nonfatal diseases such as acute bacterial sinusitis, antimicrobials routinely fail to show superiority to placebo; therefore there is a lack of justification for noninferiority trials in this setting.[46] It is irrelevant to show that a new regimen is "not too much worse" than a standard regimen if the standard regimen is ineffective or does not have reliably reproducible effectiveness under the conditions of the planned study.[47] For instance, clinical trials in acute bacterial sinusitis, acute otitis media, and acute exacerbations of chronic obstructive pulmonary disease routinely show "noninferiority" of one antimicrobial to another, yet the effects of the control drug compared with placebo on patient-centered outcomes are unclear in these diseases.[46,48,49] It is insufficient to merely know that a control intervention "works." It is also necessary to know the magnitude of the effect of the control intervention compared with placebo or no specific therapy on specific measureable patient-centered outcomes. Such an analysis should include all information from adequate and well-controlled studies, not only studies that showed favorable effects of the control intervention.

Second, similar to maintaining the conditions of a laboratory test as constant as possible when repeating the test, the design of the planned noninferiority study should be similar in all important aspects (enrollment criteria, dose of the control intervention, comedications and other cointerventions, definition and timing of outcome measures) to the designs of studies that showed the effect of the control intervention. This is done to increase the likelihood that the control intervention will have similar effects in the current study as it did in past studies. For instance, if the timing of an outcome in an acute self-resolving disease that showed the effect of a control drug was seen at 3 days in placebo-controlled trials, moving the timing of the end point to 3 months in a subsequent noninferiority trial may make ineffective drugs appear "noninferior." Similarly in life-threatening diseases, measuring an outcome "too soon" may make interventions appear similar when they differ with longer follow-up.[50] The lack of difference between the groups would be due to natural history of the disease rather than the drug's effects because the patients' disease would resolve spontaneously over this period or because of delayed treatment effects that accrue over time in life-threatening disease.

Third, the investigators must choose a value for how much inferior the test intervention might be while still being considered clinically useful. This value, called the *noninferiority margin,* or *delta,* cannot exceed the magnitude of the effect of the control intervention over placebo in previous studies (a value termed *M1*) and should be somewhat smaller than that value to preserve the important effects of the control intervention (a value called *M2*). The magnitude of the effect of the control drug over placebo or no specific therapy may change based on the types of patients studied owing to heterogeneity of treatment effects.[51] For example, the treatment effect of older effective antimicrobials on mortality in treatment of pneumococcal pneumonia, compared with no specific therapy, in nonbacteremic patients older than 50 years is a 33% absolute reduction in death, with 95% confidence intervals (CIs) from 26% to 40% (M1). In nonbacteremic patients aged 30 to 49 years, the treatment effect on mortality is 10%, with 95% CIs from 5% to 14% (M1).[45] The amount of inferiority for a planned noninferiority trial comparing a new antimicrobial with an older antimicrobial in patients older than 50 years should be less than 26%, but in patients aged 30 to 49 years it should be smaller than 10%—for instance, 5% (M2)—to ensure that a new intervention has any effect at all compared with placebo. Because the goal of noninferiority trials is to preserve the important effects of the control intervention, the chosen margin should be smaller than the total effect of the control. The amount of preservation of the effect of the control intervention should be based on what is clinically meaningful rather than sample size considerations alone or some fixed value, such as half the effect of the control. For instance, in nonbacteremic patients older than 50 years, the margin (M2) would be substantially smaller than 26%, to ensure that patients receiving the new intervention do not have substantially increased probability of death compared with patients receiving the control treatment. The overall margin (M2) in such a case might be 10% or smaller because a 20% increase in death would show the drug has some effect, but it would be clinically unacceptable to allow an increase in death in 1 of every 5 patients treated with the new drug. Smaller noninferiority margins result in larger sample sizes; however, patients in noninferiority trials already have available effective options and therefore cannot ethically be subjected to greatly increased risk of poor outcomes. For instance, for control interventions that decrease mortality, larger noninferiority margins would expose patients to excess mortality in the setting of the trial and in clinical practice. The noninferiority margin should be developed based on patient preferences regarding the inherent trade-offs in noninferiority trials—for example, based on patient interviews of persons with the disease, how much loss of effectiveness is acceptable to them in a trade-off with how much gain in nonefficacy benefits?[43,47]

Fourth, the conduct of noninferiority trials must minimize loss to follow-up and nonadherence to decrease bias toward showing no difference.[52]

SELECTION OF STUDY PARTICIPANTS

Selection of study participants is based on the goals of the study.[53] In explanatory trials, investigators often ensure that patients have a high probability of a diagnosis for the disease under study. In pragmatic trials, investigators may use less stringent criteria that more closely match those that are used in general practice. In diagnostic studies, investigators choose participants who do and do not have the disease, based on some reference standard. In case-control studies, investigators select participants based on the presence or absence of a chosen outcome. In cohort studies, investigators select participants on the basis of presence or absence of the chosen exposure, which can be a drug, a behavior such as smoking, or an environmental factor such as being in a hospital.

When studying interventions in clinical trials to evaluate their treatment effects in treating disease, one must first define the disease and then select a subset of the population for study from the population of patients with that disease. Clear definitions of the disease under study allow (1) consistency among investigators about the types of patients they enroll in a trial, (2) generalization of the results to patients outside the trial, (3) accurate description by regulatory agencies of the intended use of the drug in prescription drug labeling, and (4) appropriate application of the information presented in the trial in clinical practice.

The availability of rapid diagnostics with adequate positive and negative predictive values for the disease under study greatly aids selection of participants. In some situations, the lack of rapid diagnostics has hindered development of new therapies—for instance, in disease caused by resistant pathogens. In this setting, criteria based on signs and symptoms alone lack sufficient sensitivity and specificity, and culture data often are too slow in providing results that would influence study enrollment.

Diagnostic tests with both high sensitivity and high specificity are always preferable in both clinical trials and clinical practice. However, when diagnostic testing is less than optimal and one must choose between high sensitivity or high specificity, the desirable characteristics of a diagnostic test differ significantly between clinical practice and clinical trials. In clinical practice, clinicians may choose to use a diagnostic test with high sensitivity so that clinicians do not fail to diagnose patients with the disease, especially for infections with high morbidity and mortality. In the setting of an explanatory clinical trial, however, tests

with high specificity are needed to ensure that patients enrolled in the trial actually have the disease under study, especially in the setting of noninferiority trials, where inappropriate diagnosis can bias toward a false conclusion of noninferiority. For instance, practice guidelines recommend treating patients with symptoms of uncomplicated urinary tract infections and colony counts as low as 10^2 colony-forming units (CFUs)/mL of urine.[54,55] However, to increase specificity, clinical trials usually enroll only patients with at least 10^5 CFUs/mL of urine, to more accurately differentiate patients with true uncomplicated urinary tract infection from those with symptoms of dysuria caused by other conditions with potentially contaminated urine specimens. In noninferiority trials, investigators must use the same definition of disease as that used in the historical studies that demonstrated the effect of the control intervention compared with no specific therapy.[56]

In some diseases, microbiologic information is not available or helpful in making diagnoses—for instance, in settings wherein culture data have low sensitivity and specificity (e.g., cellulitis) or in culture data from nonsterile body sites where differentiation of colonization from disease is challenging.

Selecting the appropriate patient population often entails striking a balance between including enough different types of patients so that one may extrapolate the results of the trials to clinical practice but not be so inclusive as to blur important distinctions in drug efficacy or safety across patient subgroups. Inclusion of patients with various types of infections caused by the same organism but with differing pathophysiologic features, patient characteristics, and outcome measures could result in uninterpretable results for any type of infection. For example, both sinusitis and pneumonia are respiratory tract infections but differ substantially in pathophysiology and outcomes. Conversely, skin infection studies often include patients with both cellulitis and wound infections, given the similar pathophysiologic features of the diseases. However, investigators wish to be inclusive enough that results of the trial are useful in making treatment decisions for a broad range of patients. For instance, clinical trials often include patients who are elderly or who have mild renal or hepatic insufficiency in an attempt to determine outcomes in these patient populations.

MINIMIZING ERROR IN STUDIES

Two types of error can affect the validity of study results. *Random error* refers to variability that occurs because of chance alone. Common statistical tests are used to evaluate the impact of random error on study results, and studies are designed to minimize random error as much as possible. Increasing the sample size of studies, studying a more homogeneous population, or using more precise measurement tools decreases random error.

Two types of random error exist in trials. *Type 1 error,* or alpha, is the probability of concluding false-positive results. This means rejecting the null hypothesis when, in fact, the null hypothesis of lack of effect of the test intervention is true.[57] This value is conventionally set at 5% for most studies, meaning an error rate of 1 in 20. If one considers the thousands of studies conducted each year, an error rate of 1 in 20 studies is actually a low standard of evidence.

Therefore, independent confirmation of evidence from similar studies is important because a confirmatory study with a type 1 error rate of 5% lowers the overall type 1 error rate of the two studies to 0.25% (5% times 5%). An error rate of 1 in 20 is still substantial, and the inability to confirm results of many studies using *P* values of .05 has led some authors to suggest lowering the threshold for "statistical significance" to .005.[58]

Type 2 error, or beta, is the probability of a false-negative result—that is, not rejecting the null hypothesis when, in fact, the alternative hypothesis is true. This value is usually set at 10% to 20% for most studies.[59]

Power is the ability of the study to detect a difference, should such a difference exist, and is defined as 100% minus the type 2 error. For a study with a type 2 error rate of 10%, the study has 90% power to be able to detect a difference. It is not appropriate to calculate "power" after a study is complete, because power is only the prestudy probability of detecting a difference. Once the study is complete, a difference was detected or it was not.[60]

The type 1 and type 2 error rates are values selected before the study in order to choose a sample size (the number of participants needed for enrollment) for the study.[61,62] In addition, two other variables affect sample size. The first is the hypothesized difference in effect size between the test and control groups, called delta, based on available evidence from similar studies and what is a clinically meaningful difference. This value often represents the investigators' best guess, and the actual measured difference between study groups cannot be known until after the study is over. A common error is selecting a larger difference between study groups than is justifiable based on available evidence or what is clinically meaningful in order to decrease the sample size of the study. However, if the true difference between groups is smaller, then the study will have an insufficient sample size to detect differences. Conversely, investigators may choose a large sample size to be able to detect small differences even if those differences are not clinically meaningful.

The appropriate number of participants to enroll (sample size) for a study is the number that allows one to answer the chosen research question while minimizing random error and achieving adequate precision of the results. Larger sample sizes, however, expose more participants to potential risk and cost more in terms of time, manpower, and money. Therefore the sample size of a study should be carefully chosen before the trial, to maximize valid results while achieving the greatest efficiency. Interim blinded preplanned analyses during the course of a study may show that initial assumptions affecting sample size were incorrect and require adjustment for valid reasons during the study. However, it is ethically and scientifically questionable to start with a sample size in mind and then choose hypotheses that are not clinically meaningful but for which data can be acquired with the chosen sample size. For instance, one could choose to use a laboratory test as an outcome measure because of the ability to show differences between study groups with smaller sample sizes. However, this approach is questionable if the laboratory test does not validly reflect differences on the true outcome of interest, such as mortality, patient function, or patient symptoms. Smaller trials require greater planning and foresight than larger trials.[63]

The second type of error in studies is *systematic error.*[64] Systematic error is any type of error at any point of inference in a study that causes the results to not provide valid inferences related to the research question. Systematic error can be divided into bias and confounding. *Bias* is any type of systematic error at any point in the study that gives results or conclusions that differ systematically from the true values.[65] In other words, the measured values are incorrect. For example, a nonrandomized, nonblinded, placebo-controlled clinical trial of the drug patulin, prescribed for the common cold in the 1940s, showed a 48% (95% CI, 35%–60%; $P = .002$) absolute reduction in symptoms with the drug.[66] However, a subsequent randomized, blinded trial with better definitions of outcomes showed a treatment effect of zero (95% CI, −4% to +4%; $P = .96$).[67] The difference between these two results is due to bias inherent in the design of the first study. *Confounding* is the presence of factors associated with both exposure and outcome that influence causal conclusions related to the interventions resulting from imbalances in the confounding factors between the study groups.[68] With confounding, the measured values are correct, but confounding means the observed effects may be due to factors other than those measured. For instance, in nonrandomized studies of interventions, if there are baseline differences between groups with factors known to influence outcomes, such as age and severity of illness (selection bias), then outcomes may be confounded by those factors and not be due to the interventions under study. The process of randomization addresses the problem of confounding at the time of randomization, but does not address confounding that may occur before randomization (e.g., prior effective therapy) or after randomization (concomitant effective therapy).[69]

Many types of bias can affect the results of clinical studies, and authors have divided bias into various types.[65] *Selection bias* means that subjects in one study group systematically differ from subjects in another group by factors that influence outcomes.[70] One of the major issues with nonrandomized trials is that even when attempting to control for known factors influencing outcomes, one cannot account for unknown factors or the various combinations of known and unknown factors that influence outcomes. Randomization addresses this issue as discussed

later. *Observer bias* is the process by which persons who assess outcomes can influence the measurement of those outcomes. Blinding participants, investigators, and outcome assessors to study group assignment can address this issue. Studies that are not blinded to treatment assignment are called "open label." *Misclassification bias* is related to observer bias and occurs when a value is defined in error—for instance, when participants who experience failure of a study medication are coded as successes and vice versa. Blinding addresses this issue in part, but clearly defined study measures and procedures also help minimize this bias. *Instrument bias* is when the instrument, scoring system, laboratory test, or other measure is systematically incorrect. For example, one study asked clinicians to measure marbles of the same and different sizes used as a substitute for tumors in a blinded manner. The results of the study showed that clinicians systematically erred in measuring marbles of the same size such that there would be a large "treatment effect" on tumor shrinkage, when, in fact, they were measuring marbles of identical size.[71] In infectious diseases, lack of reliability of measurements, such as the Clinical Pulmonary Infection Score (CPIS), could result in biased measurements.[72,73]

Bias is most problematic because there is no way to specifically test for it. Bias cannot be addressed or measured by statistical testing alone, and increasing sample size actually magnifies the effects of bias on outcomes. Therefore, a larger trial will minimize random error but give a more precisely incorrect answer to the research question in the presence of biases. Bias is addressed most effectively at the design and conduct stages of a study. Appropriate design of a study helps to minimize the occurrence of bias before initiation of the study. Appropriate conduct, such as minimizing loss to follow-up, helps control bias during the study. Appropriate analysis, such as including all randomized patients in the primary analysis, also is an important way to minimized bias. Controlling bias is also an important ethical issue in studies. Studies cannot contribute to generalizable knowledge if their results are not valid and free from bias.

BASELINE COMPARABILITY BETWEEN STUDY GROUPS

With some research questions, the goal is to evaluate the differences in baseline factors that influence outcomes between groups. For instance, when evaluating risk factors for disease acquisition or prognostic factors for outcomes, the goal of the research is to find the baseline differences between the groups that may or may not be causal but still bear some relationship to each other. For instance, hospitalization is a risk factor for acquisition of resistant pathogens, but hospitalization alone does not cause colonization with resistant pathogens because other factors may be equally or more important, or hospitalization may be a marker for the presence of other factors.

However, when attempting to evaluate causal relationships between exposures and outcomes, one of the most important aspects of study design and analysis is ascertaining that study groups are as comparable as possible so that investigators can draw valid conclusions about relationships between study groups.[74]

In nonrandomized trials, investigators can attempt to evaluate baseline comparability of known factors that influence outcomes, but it is challenging, if not impossible, to ascertain the influence of selection bias due to unmeasured factors on outcomes. For this reason, nonrandomized studies are often used as a basis for hypothesis generation for future randomized trials, and randomized trials have become the gold standard for evaluating medical interventions.[75] A study that evaluated the importance of randomization and blinding on potential bias in study results showed that at least one prognostic factor was not distributed equally between arms of the trial in 14% of trials that were blinded and randomized, in 26.7% of open-label randomized trials, and in 58.1% of the open-label observational trials. The authors found statistically significant differences in case-fatality rates between the treatment and control groups in 8.8% of the blinded and randomized trials, 24.4% of the open-label randomized studies, and 58.1% of open-label observational trials.[76]

The process of randomization is a systematic way of assigning participants to study groups.[77] These include processes as simple as flipping a coin or using computer-generated number tables. Nonsystematic ways of assignment to study groups, such as alternately assigning participants to study groups or enrollment in groups based on admission date or social security numbers are not random processes and are not defined as randomization. Randomization in studies of sufficient sample size results in an equal probability of similar distribution of both measured and unmeasured factors and thereby minimizes confounding. This addresses the issue of confounding resulting from baseline imbalances between groups and obviates discussion of confounding in randomized superiority trials. As noted previously, confounding is often confused with effect modification in the setting of randomized trials, wherein the effect of interventions may differ in different types of patients or clinical settings. The minimization of selection bias and confounding by randomization allows causal inferences between the interventions studied and outcomes. Differences between study groups in the randomized population causally relate the interventions to observed outcomes, as long as other sources of bias that can occur after randomization are minimized.

It is still possible for baseline imbalances to remain in randomized trials, especially in trials with small sample sizes. Randomization provides a *probability* of equally distributing important variables between arms of a trial prior to enrollment. When important variables are not equally distributed across arms of the trial once the study is complete, randomization has not "failed" because the process of random distribution did occur as planned but without the desired result. However, unequal distribution of factors between the arms of a trial may have an impact on the interpretation of the results. The importance of unequal distribution of various factors depends not on the statistical significance of the difference in the distribution of the factor between the study arms but on the strength of the association of the outcome with that factor.[78,79] In other words, one should consider small differences in the distribution of factors between study arms as clinically significant if the factor has a known large impact on outcomes, even though the baseline differences in patient characteristics are not statistically significant.[80]

The randomization code also should remain blinded so that investigators cannot consciously or unconsciously influence assignment to study groups. This process of blinding of the randomization code is called *allocation concealment*. On average, studies without allocation concealment show larger treatment effects than do those with allocation concealment, indicating the potential for bias influencing results.[81]

Stratification may be used along with randomization to ensure baseline comparability between groups, especially when sample sizes are small.[82] Stratification entails dividing the study group before randomization by the important baseline variables that affect outcomes and then randomizing separately in each stratum. For instance, patients could be divided by age category before randomization and then randomized to study groups within each age category. Stratification ensures equal numbers of participants in each stratum; but unless there are separate hypotheses, sample size calculations, and appropriate adjustment for increasing the false-positive error rate (type 1 error), stratification alone does not allow confirmatory conclusions in each stratum. Keeping the number of strata to a minimum of important categories known to affect outcomes helps simplify trial operations.

The benefit of randomization on decreasing selection bias relies on participants remaining in their assigned study groups and analysis of results based on the randomized groups. Eliminating participants from the analysis or performing analyses that evaluate only subgroups of participants may still involve selection bias. Missing data are an important consideration in clinical studies and an important cause of bias.[83] Minimizing missing data in terms of loss to follow-up or elimination of participants from analyses requires careful study planning. Although the best way to address the situation of missing data is to avoid it, imputation methods are available to perform analyses based on various assumptions related to the reason for missing data. The challenge is that these assumptions are often unverifiable based on the available evidence in the study.[84]

OUTCOME ASSESSMENTS

The specific definitions of outcomes, who does the measuring, when assessments are performed, and how to analyze the outcomes depend on the clinical context and the research questions of the study initiation. In case-control studies, investigators choose the outcomes first and then

look backward in time to examine differences in exposures. In cohort studies and clinical trials, investigators choose exposures and then follow patients forward in time to examine outcomes. In clinical trials, outcomes are used to define *end points.* An end point is the outcome measure used to examine differences between study groups at specific points in time using specific predefined analysis methods, such as differences in proportion of mortality between groups treated with different antimicrobials at 30 days after randomization.

The principles of terminology, development, and application of outcome assessments as end points in clinical trials have been explored.[85] The variables that make up an end point should be clearly defined and reliably measured. Terms such as "clinical response" or "success" and "failure" are meaningful only if the defining of specific variables allows one to determine what is actually measured. In addition, if end points have components related to judgment in measuring or interpreting the variables, there may be substantial variability in the measurements, with resulting misclassification bias.[72,73]

The definitions of end points for trials should be clinically relevant to patients: measuring how patients feel in terms of their symptoms, function in their daily lives, or survive.[86] Direct measures of how patients feel, function, or survive have previously been defined as "clinical" end points; however, in trials the term "clinical" is often misunderstood to mean any measure obtained as part of patient care.[87] Recent guidance has suggested the term "clinical outcome assessments" to encompass both direct and indirect measures of patient benefit.[85] Patient-reported outcomes (PROs) are direct measures of patient benefit, whereas clinician observations including physical signs are indirect measures of patient benefit. Direct measures of patient benefit include resolution or improvement of impaired functioning or symptoms that cause patients to seek medical care, in addition to survival.[88]

Investigators sometimes are concerned about "specificity" of symptom-based outcome measures; however, appropriate diagnosis ensures that patients' symptoms are due to the disease. For instance, many patients with cough do not have pneumonia, but after radiographic confirmation of the diagnosis, cough is no longer a "nonspecific" outcome measure but due to pneumonia. In addition, randomization addresses baseline comparability and balances groups for outcomes unaffected by the intervention such that any remaining differences between groups are causally related to the interventions tested. Examining "all-cause" outcomes is important because interventions may worsen symptoms, function, or survival as a result of off-target effects. For instance, all-cause mortality evaluates the net benefits and harms of an intervention, whereas cause-specific mortality does not because all-cause mortality takes into account adverse effects of interventions that may cause death even if the test intervention "works" according to its specified mechanism of action. In addition, the tools and judgments used to evaluate cause-specific mortality lack sensitivity and specificity. For instance, current diagnostic tools used to diagnose fungal infections are not sufficiently sensitive or specific.[86] Autopsy studies show substantial misclassification of clinicians' judgments regarding causes of death.[89]

Often, more than one manifestation of a disease is clinically relevant, and/or different outcomes may occur at different rates. In these cases it may be appropriate to evaluate relevant symptoms in addition to mortality in a composite end point, either by combining outcomes into a single measure or by ranking outcomes on an ordinal scale.[90,91] For types of diseases or stages of diseases in which mortality is low, a measure of symptoms plus survival may be most useful. The use of a composite end point can provide a comprehensive evaluation of the efficacy of interventions.[89] For example, in clinical trials of patients at low risk of death with community-acquired pneumonia, an appropriate end point may evaluate resolution or improvement of cough, shortness of breath, and chest pain, in addition to mortality.[92] Survival is always measured because it is not possible to evaluate symptoms in patients who do not survive. However, composite end points are driven by the most common outcomes in the composite, so similarity of symptoms may mask differences in outcomes between groups regarding mortality if mortality in the study population is low. Composite end points should be derived from outcomes that are similarly meaningful for patients. For example, combining death and complications of disease is more clinically meaningful than combining death and a surrogate end point of culture results. In noninferiority trials, investigators are limited to using the same definition and timing of end points used in previous studies that demonstrated the effect of the control intervention.[16]

End points in clinical trials also can measure indirect outcomes that are hypothesized to reflect how patients feel, function, and survive. These indirect end points can be events determined by clinician judgment (termed *clinician-reported outcomes* [ClinROs]), such as decisions to switch medications, prescribe additional medications, or decisions on hospital admission or discharge.[93] Such end points assume that the reasons for the event are related to patient symptoms. Biomarkers, defined as laboratory measurements (e.g., radiography, cultures, polymerase chain reaction [PCR] assays, and serologic testing) or physical signs, used as a substitute for direct measures of how patients feel, function, or survive, can also be used as indirect outcomes or "surrogate" end points.[88] Microbiologic end points that measure the suppression of pathogenic organisms below some level of detection are surrogate end points because they do not measure patient outcomes directly. The most useful indirect measures in clinical trials are those that are reproducible (analytically valid), are on the causal pathway of the disease, and have relationships to direct outcomes of interest that are well known.[87,94] Indirect measures that are not on the causal pathway of disease are less useful because they can be affected by interventions other than those that affect the disease process. For instance, in pneumonia, fever is not on the causal pathway of disease because pneumonia causes fever rather than fever causing pneumonia. Therefore, interventions such as antipyretics can lower body temperature without affecting the course of pneumonia. Measurements of pathologic organisms that are on the causal pathway of the disease may be candidates for potential surrogate end points. Surrogate end points are most useful in chronic diseases when direct outcomes cannot be measured for a prolonged period of time.

However, the major issue with surrogate end points is that they may not reflect the outcomes of how patients feel, function, or survive because of off-target benefits or harms or pathways of disease not captured by the indirect measures. Correlation between an indirect outcome and a direct outcome, such as mortality, is necessary but not sufficient to evaluate an indirect measure as a surrogate end point.[95] Correlations often compare patients with and without the indirect measure and then evaluate the relationship to the direct outcome measure independent of the interventions received. However, such *patient-level* evaluations may be measuring differences in patient characteristics rather than differences in the treatment effects of the interventions the patients receive.[96] Of note, such patient-level evaluations are independent and may not be mediated by treatment—that is, they may reflect the natural history in different types of patients rather than the effects of interventions. In addition, correlations often evaluate only one side of the relationship between the direct and indirect measures. For instance, a microbiologic outcome of negative cultures may "correlate" with resolution of symptoms. However, one must also evaluate whether positive cultures also correlate with lack of resolution of symptoms. Therefore, microbiologic success should predict clinical success, and microbiologic failure should predict clinical failure. Although it seems intuitive that suppression of pathogenic organisms below some level of detection should reflect direct outcomes, this is not always the case. Antimicrobials may exert direct effects on the immune system that may affect direct outcomes.[97–99] Antimicrobials may also have effects on organisms, such as rapid lysis with subsequent stimulation of the immune system, which also may influence direct outcomes. The recommendation to administer steroids before antimicrobials in acute bacterial meningitis is based on this phenomenon.[76,77] Immune reconstitution inflammatory syndrome in HIV is another such example. Because these effects are the result of administration of the antimicrobial, they are not solely effects related to the host. In addition, host inflammatory reactions may continue to cause disease manifestations even after decreasing organism burden, thereby contributing to discordance between indirect microbiologic outcomes and direct outcome measures. Measuring direct outcomes is the only way to capture such effects.

A *trial-level* surrogate is when an intervention-mediated treatment effect (the difference between the test and control group) on the surrogate end point also reflects a treatment effect on the direct patient-centered

outcome of interest (symptoms, function, or survival).[96,100,101] This entails comparison of treatment differences between the test and control groups regarding the indirect measure and the direct measure. Biomarkers or clinical outcome assessments that are patient-level correlates are not necessarily trial-level surrogates. This also requires clearly defining the direct measure, in terms of symptoms, function, or survival, for which the indirect measure is a substitute.

Biomarkers have been successful in some settings, such as treatment effects on viral load measurements in trials of HIV/AIDS, reflecting treatment effects on mortality and AIDS-defining opportunistic infections. On the other hand, surrogate end points often fail to reflect direct outcomes. For instance, improved microbiologic outcomes with clarithromycin in *Mycobacterium avium* complex bacteremia showed increased mortality in trials in patients with HIV/AIDS.[102] This reinforces the idea that the utility of surrogate end points is contextual, requiring reevaluation when used in different patient populations or with different interventions.[103]

Biomarkers as surrogate end points are useful in hypothesis-generating studies to demonstrate proof of principle that an intervention has biologic activity. Such trials are appropriate for selecting candidate interventions and to generate hypotheses for further trials that demonstrate that the effect of the biomarker translates into treatment effects on direct measures of symptoms, function, or survival.

The timing of end-point measurements also is important.[104] Investigators should time the measurements based on the natural history of the disease and the timing of clinically relevant treatment effects. For example, placebo-controlled trials show that most cases of traveler's diarrhea will resolve spontaneously within a few days.[105] Therefore, measuring resolution of diarrhea several weeks after the start of symptoms would not allow one to differentiate the effects of antimicrobial therapy from placebo in a superiority trial or would make two agents appear similar in a noninferiority trial. Often in spontaneously resolving diseases, the time to resolution of symptoms may be a more clinically meaningful end point than measurement of clinical outcomes at some fixed time point. However, in life-threatening acute diseases in which death occurs in days to weeks, a fixed time point may be more informative because whether the patient dies earlier or later in the course of a short illness may not be clinically relevant. Also, it is important to follow patients for long enough to evaluate the durability of treatment effects. Again, in noninferiority trials, the timing of the end point should reflect the timing used in prior superiority trials that demonstrated the effect of the control regimen.

When measuring outcomes in diseases that tend to recur, such as diarrhea caused by *Clostridioides difficile* (formerly *Clostridium difficile*) studies should evaluate outcomes in the entire randomized population and not recurrence only in the subgroups of patients who experience resolution of diarrhea. Outcome measures should include both patients in whom interventions initially fail combined with those in whom disease recurs. Evaluating only subjects who are initially cured and then following that subgroup alone for recurrence gives biased estimates when initial cure rates differ between the two interventions. The "recurrence rate" in an intervention that cures no one is zero, but this means the intervention is "preventing" recurrence through being ineffective.[106]

ANALYSIS OF STUDY RESULTS

Investigators and consumers of trial results should evaluate the results in light of the primary research questions posed by the study. Secondary hypotheses or subgroup analyses may pose interesting questions, but the primary analysis is of primary importance, as reflected by the design of the trial.

In addition to presentation of estimates of difference between test and control groups, investigators use statistical tests to examine the likelihood that the results of the trial could have occurred by chance alone (random error), to examine the direction and magnitude of treatment effects, and to determine the precision of the results. If the likelihood of accepting a chance result is low and bias is minimized, as determined by the error rates set up before initiation of the trial and design and conduct of the study, then investigators conclude that the evidence is strong enough to reject the null hypothesis. They then can assume that the alternative hypothesis is likely true.[107]

Analysis of Populations

Before performing statistical calculations, investigators must first decide on the population of patients in the trial that they wish to analyze. In the *intention-to-treat* (ITT) population, patients are assigned according to the group to which they were initially randomized, regardless of whether the patient received the drug, discontinued therapy, or switched to a different therapy.[108] In other words, investigators evaluate patients by the treatment they intended to give. This population preserves the protection from selection bias that randomization offers. It also provides the most clinically meaningful results because in practice patients and clinicians often do not use interventions as prescribed, and the reasons for not adhering to the intervention may be related to the intervention itself, such as adverse effects and tolerability. The ITT analysis also allows appropriate statistical testing based on the principle of randomization. Investigators can use a *modified intention-to-treat* (mITT) population of patients who received at least one dose of the study medication and who have the disease under study. This analysis is valid only if the difference in the number of patients between the mITT and ITT populations is small—for instance, less than 5%. The *per-protocol* (PP) population (sometimes called the "clinically evaluable" population) is a subgroup analysis composed of patients who follow the protocol as specified—for instance, those who received some minimal amount of the study or control drug and returned for an assessment of their outcome. Such analyses may lack the protection of randomization from selection bias if patients are excluded from analyses based on events that occur after randomization and/or if those who drop out of the study systematically differ from those who complete the study. Exclusion of participants from the PP population assumes that the missing data are uninformative, a conclusion that is usually not verifiable or justifiable. Exclusion of subjects based on lack of receiving a "sufficient" duration of the study intervention is not scientifically justifiable and is based on the notion that antimicrobials take some fixed amount of time to exert an effect. Also, excluding participants after randomization may mitigate the protection of randomization from selection bias because investigators are selectively choosing which patients to analyze. Exclusions based on receipt of concomitant medications during the study are also problematic, especially if the subjects received additional antimicrobials because of spread of their disease or new disease elsewhere in the body.

In superiority trials, the ITT population is usually the most appropriate patient population used for analysis of the primary end point because it provides the least likelihood of coming to a false-positive conclusion.[109] However, in a noninferiority trial, if there are large numbers of participants excluded or missing data, then the analysis of the ITT population may make the test and control interventions appear more similar, although more recent studies have demonstrated that this concern may be more theoretical than practical.[110,111] The theoretical concern is that ITT analyses may lead to a false-positive conclusion that the drugs are similar in efficacy when there may be important differences between the drugs. Because the benefits of randomization may be lost in the PP population, this population also may not reflect the true efficacy of drugs in a noninferiority trial. Given the limitations of both the ITT and the PP population in noninferiority trials, it is often most informative to examine analyses of the primary end point in both populations. Differences in the comparative efficacy of the study and control drugs between the ITT and PP populations in a noninferiority trial would require an examination of the reasons for such differences. Trial results are most convincing in noninferiority studies when ITT, mITT, and PP analyses reach similar conclusions.

Examining Baseline Comparability

Although randomization gives a probability of equal distribution of measured and unmeasured baseline factors before trial initiation, it is still necessary to evaluate whether randomization produced such balance once a trial is complete. One should examine baseline variables that can influence outcomes to assess their balance between the test and control groups. Using *P* values to evaluate balance on baseline variables is not appropriate.[79] Factors with "insignificant" *P* values can still affect outcomes, and factors with "significant" *P* values may have no effect on outcomes. *P* values are measures of hypothesis testing, and no

hypothesis is being tested regarding baseline variables in a trial, and any differences are by definition due to chance.

In observational trials, there may be imbalances on both measured and unmeasured baseline factors that affect outcomes independent of the intervention or exposure. There are multiple methods that attempt to balance for such factors after data have been collected. Of increasing interest is the use of *propensity scores* in observational studies, which attempt to evaluate the effect of interventions or exposures on outcomes.[112] The scores are used to fit a statistical model to estimate the individual likelihood that patients would be prescribed a specific intervention or have a specific exposure based on their observed baseline characteristics. The score is derived by combining baseline preintervention characteristics rather than using individual variables as in multivariable logistic regression. The variables used to derive the scores are estimated by logistic regression with treatment or exposure as the dependent variable and the observed potential confounding variables as the independent variables. The propensity "scores" range from 0 to 1.0. Investigators can then "match" patients by their propensity scores using various methods of matching (identical vs. "close enough").[113] It is unclear if propensity score matching is a better method of controlling bias than other methods of adjustment for baseline variables in observational studies. Studies comparing propensity scoring in observational trials versus randomized trials in the same topic area have shown either larger or erroneous treatment effects with use of propensity scores.[114] No method of adjustment can account for unmeasured confounding.[115]

Calculating Differences Between Groups

Once investigators decide which population to analyze, they calculate the *point estimate* for successful outcomes for the primary end point in the study drug and control groups.[116] The point estimate represents the average value in the sample studied, but not necessarily the average value in the population from which the sample was taken. The point estimate is the number of patients with successful outcomes divided by the total number of patients in the analyzed population. For instance, consider an example of a trial in which the primary analysis population contains 300 patients in each arm of the trial, where 225 and 240 patients have successful outcomes in the study drug and control drug arms, respectively. In this case, the point estimates of successful outcomes are 75% (225/300) in the study drug arm and 80% (240/300) in the control arm. Investigators should present numerator and denominator data rather than summaries alone so that readers can perform these calculations on their own.

However, in experimental studies, the *differences* between the test and control groups are of primary importance rather than solely "success rates" in the individual study groups. Clinical trials are comparative, and "success rates" can vary from study to study by random variation alone or because of differences in patient groups between studies. This makes cross-study comparisons challenging.

Investigators can present comparisons of the differences between the test and control groups as absolute differences, relative differences, or odds. *Absolute differences* are the difference between proportions between the groups.[116] In our example, the absolute difference in outcomes between the study and control drugs is 75% minus 80% or a difference of −5%. Absolute differences are easy to calculate and interpret and are symmetrical (number of successes and number of failures sum to 100%). However, when percentages are small (below 1%) these differences are challenging for patients and clinicians to understand.

The inverse of the absolute difference (1 divided by the absolute difference) is the *number needed to treat* (NNT).[117] This value shows the number of patients who are exposed in order to benefit or harm one person. In our example, 1 divided by the 5% absolute difference gives an NNT of 20. This means that 20 patients must be treated with the drug for one person to benefit. This provides a basis for numerically comparing benefits and harms in a single study but does not provide a context for the numbers because the nature of the benefits and harms may differ. For instance, a smaller number needed to treat to harm (NNTH) regarding nausea may be justified if the benefit is a larger NNT regarding mortality, given that nausea would be a tolerable adverse effect in order to achieve benefits in mortality. However, NNT is useful when the nature of benefits is similar to the nature of harms, such as the benefit of decreasing symptoms compared with the harms of headache, skin rash, or diarrhea. There is no single "good" NNT number, and comparing across therapeutic areas and between treatment and prevention studies is challenging, given the different contexts and different balances between benefits and harms. Several studies have shown that patients and clinicians more readily understand absolute differences and the NNT.

Relative differences express the event rates in the test group as a proportion of those measured in the control group, with a range of values between 0 and +1.0 or −1.0. In our example, the rate of unsuccessful outcomes is 25% for the study drug and 20% for the control. Therefore the relative reduction in unsuccessful outcomes is a 20% decrease in treatment failures for the control drug relative to the study drug (1 minus 20% divided by 25%). Relative differences do not reflect the baseline rate of events in the control group. Hence, decreases in the absolute event rate, from 2% to 1% and from 20% to 10%, are both 50% relative decreases. The clinical meaning may differ substantially, however, and may overestimate or underestimate the actual impact of an intervention when event rates are very high or very low. Presentation of relative differences can lead to overinterpretation of treatment benefits.[117]

Odds are expressed as the number of persons experiencing an event divided by the number of persons not experiencing an event. For instance, if 8 of 10 people develop a disease in a test group, the odds are 8 divided by 2, which equals 4. The odds ratio is the odds in the test group divided by the odds in the control group. For instance, if 6 people develop a disease in the control group, the odds in the control group is 6 divided by 4, which is 1.5, and the odds ratio is 4 divided by 1.5, which is 2.7. Odds are intrinsically more challenging to understand. They are not the same as relative risk, but they are often misinterpreted in this way. Odds can range from zero to infinity, unlike relative risks. Odds and relative risks are similar when event rates are less than 20%, but they give different results when events rates exceed this value. Odds are useful in case-control studies in which the denominator of events is unclear. They are also the output of logistic regression analyses and provide a greater "dynamic range" of values than relative risks because they can extend beyond a value of 1.

Examining the Evidence: *P* Values and Confidence Intervals

Investigators use inferential statistical testing to examine the precision and variability of the difference between the test and control groups and the probability that the difference could have occurred by chance alone. The actual statistical tests used depend on the types of data examined. A discussion of various statistical tests and their appropriate use is beyond the scope of this chapter. Investigators commonly use tests such as the chi-square to examine dichotomous variables (cure vs. success) and the Student *t* test to examine continuous variables (e.g., weight and age).[118,119] However, at a minimum, readers of clinical trials and peer reviewers for journals should ensure that investigators identify the appropriate statistical tests used in examining the results of a trial.

One of the most commonly used results in statistical testing is the *P* value.[120,121] Unfortunately, it is often misused and misinterpreted.[122] In one study, only about one-fifth of respondents to a multiple-choice questionnaire understood the meaning of the *P* value.[123] The *P* value is a measure of hypothesis testing. If the *P* value is less than the specified type 1 error, usually set at .05, the result is called "statistically significant." A *P* value of less than .05 means that there is a less than 5% chance that results as extreme as those observed in the trial are due to chance or random error.[124] Therefore the *P* value is not a measure of clinical significance. *P* values do not measure bias that may be inherent in the design of a study or occur during the study. Increasing sample size decreases the *P* value for a given difference while increasing the effects of bias on the results. Authors have pointed out that the view of dichotomizing *P* values above and below .05 as "positive" and "negative" studies often clouds issues related to clinical meaningfulness of the results of studies. A *P* value of .01 does not mean that there is only a 1% chance that the intervention tested is ineffective or that there is a 99% chance that the intervention is effective. As discussed previously, given the thousands of trials performed each year, a *P* value of .05 is

actually a low standard of evidence. The *P* value does reflect the "strength" of the evidence in that it provides evidence toward whether the study (in the absence of other forms of bias) is likely to be confirmed in follow-up studies. A study with a *P* value of .05 has a probability of confirmation in 57% of follow-up studies, meaning that one in every two to three subsequent trials will fail to confirm the original findings.[125] *P* values also are affected by the size of the between-group difference and the sample size. The larger the difference between the study and control drugs, then the smaller the sample size needed to demonstrate statistical significance. Therefore, less effective interventions require larger sample sizes to demonstrate effects. Because *P* values are a unitless measure, they do not directly evaluate the magnitude or the clinical meaning of the treatment effect. Therefore, larger sample sizes may result in statistically significant *P* values but do not necessarily translate into meaningful clinical effects.

In our example, the *P* value for the difference between a study drug with a success rate of 75% and a control drug with a success rate of 80%, with 300 patients per arm, is .14. If one studies 1000 patients per arm and the success rates remain at 75% and 80% for the study and control drugs, respectively, the *P* value decreases to .007, even though the difference in point estimates remains at −5%. However, if the study drug success rate remains at 75% and the success rate in the control increases to 85%, with 300 patients per arm in the trial, the *P* value is .002. The assumption that point estimates will remain constant with increased sample size is often erroneous because the principle of regression to the mean indicates that point estimates will change toward the true value with increasing sample size. Therefore, it is often erroneous to propose that increasing sample size would yield a "significant" result in trials that "just miss" demonstrating statistical significance, or that show a "trend" toward statistical significance (e.g., *P* values of .6 to .9). This is an empirical question that needs evaluation in future studies.

P values as traditionally calculated are of little utility in noninferiority trials because they are based on difference around zero rather than difference around the noninferiority margin. Interventions that meet a noninferiority margin and those that do not will both have *P* values of greater than .05, as traditionally calculated, whenever the interventions are not frankly superior or inferior.

A *P* value of .05 means that 1 in 20 studies will demonstrate a false-positive result. Also it reflects that 1 in 20 comparisons made in a clinical trial may represent a false-positive result. If an investigator makes more than one comparison in a clinical trial, the chance of drawing a false conclusion increases. For 5 independent comparisons the type 1 error increases from 5% to 20%, and for 10 comparisons to 40%. For 20 comparisons, the type 1 error increases to 64%.[124] In other words, by making multiple comparisons with *P* values at a .05 level of statistical significance, one is more likely than not to find a statistically significant result that is false. This is called the problem of *multiplicity*. Examining many *P* values without adjustment for multiplicity is appropriate in exploratory hypothesis-generating studies. However, in confirmatory studies testing medical interventions, it often is appropriate to use a lower *P* value to define statistical significance when making multiple comparisons.

Investigators or readers may use methods such as the Bonferroni procedure[126] or other corrections for *P* values. The Bonferroni method is easy for casual readers to use because one divides the *P* value by the number of comparisons to determine the corrected definition for statistical significance. Therefore, if one makes five comparisons, the *P* value used to define statistical significance decreases from .05 to .01. An important caveat is that one should divide by the total number of comparisons made by the investigators, not just the number of comparisons presented. If the comparisons are not independent, some authors feel that the Bonferroni correction is too conservative.[127] Alternatively, investigators can perform "sequential testing" by spelling out a hierarchy of assessments before study initiation, testing each sequential difference at the same .05 significance level, proceeding from one to the next as long as each test reaches statistical significance. For instance if a study has three hierarchic end points of survival, spread of disease to another organ system, and improved symptoms, each can be tested at the .05 significance level. If the *P* value for survival is less than .05, then the investigator can proceed to test the hypothesis related to spread of disease at the .05 significance level. If this hypothesis does not reach statistical significance, then the investigator cannot test the third hypothesis related to symptoms at the .05 level. The important point for readers of clinical trials is that authors should describe what procedure was used when accounting for multiple comparisons. The most common use of multiple comparisons is in subgroup analyses, but it also occurs with multiple secondary end points or a primary end point measured at multiple times.[128]

CIs are another way of analyzing trial results and provide adjunctive information to *P* values.[129] Unfortunately, studies demonstrate that researchers lack understanding of the interpretations of CIs, just as for *P* values.[130] However, understanding CIs is integral to understanding trial results, especially for noninferiority trials. CIs are measured in the same units as the point estimate of the primary end point—for example, percentage of patients with a successful outcome. Therefore, CIs can provide an estimate of the size of the treatment effect. The range of the CI also provides some estimate of the precision of the result in clinically meaningful terms. With larger sample sizes, the range of the CI decreases. A 95% CI is a measure of estimation rather than hypothesis testing, meaning that the investigator attempts to estimate the true difference in a population from the results in a sample from that population. A 95% CI means that if the same trial hypothetically was repeated 100 times, one could expect the observed treatment effects of 95 of those trials to contain the true treatment difference, and 5 studies would not contain the true difference within their confidence bounds. When evaluating a single study, it is not possible to know if that study is one of the 95 that contain the true difference or one of the 5 erroneous studies. This reinforces why confirmation of evidence from independent studies is important. The CI is not a measure of probability (like the *P* value). Any value within the limits of the CI of a single study is equally likely to represent the true value in the population from which the sample is chosen. On average, 5 studies out of 100 will not contain the true mean at all. Data simulations show that the point estimate for one study does not lie within the confidence bounds for a follow-up study in one in six repetitions.[131] Therefore, posing that the point estimate from the studied sample of patients is the most likely "true" value in the population and that the lower and upper bounds of a given single CI are "unlikely" does not represent the true meaning of CIs.[129] In our example, the difference in point estimates is −5%. For a trial with 300 patients in each arm, the lower bound of the 95% CI is −11.7%, and the upper bound is +1.7%. This means that based on the evidence from this single study, the study drug could be somewhere from 11.7% worse to 1.7% better than the control drug for the measured outcome. Increasing the sample size to 1000 patients in each arm would give greater precision to the results by narrowing the CI to −10.0% to +0.002% if the success rates remained the same. However, the success rates usually will not remain fixed but will move toward the true mean, a phenomenon called *regression to the mean*.

CIs aid in the interpretation of "negative" studies that do not reach statistical significance and in the interpretation of noninferiority trials. CIs whose range includes clinically meaningful differences can mean that further larger studies are needed to rule out an important effect. Narrow CIs that rule out clinically meaningful differences may indicate that future studies are not needed. In this way, CIs provide more information than dichotomous evaluations of statistical significance.

An examination of the upper and lower bounds of the CI allows one to determine, as with *P* values, whether a study drug is statistically superior, inferior, or noninferior to a control drug (Fig. 52.1). The *P* value and the CI are related in that if the 95% CI excludes zero, then the *P* value is less than .05. A statistically superior drug has a lower bound of the 95% CI that is greater than zero for absolute differences. A statistically inferior drug has an upper bound of the 95% CI that is less than zero. To determine whether a study drug is "noninferior" to a control drug, one must compare the bound of the 95% CI to some prespecified margin of noninferiority. In our example, the lower bound of the 95% CI is −11.7%. If the noninferiority margin selected before initiation of the trial was −15%, then one can conclude that the study drug is statistically noninferior to the control. If the prespecified noninferiority margin was −10%, then the study drug fails to meet the statistical definition of noninferiority. Hence, the incentive for some

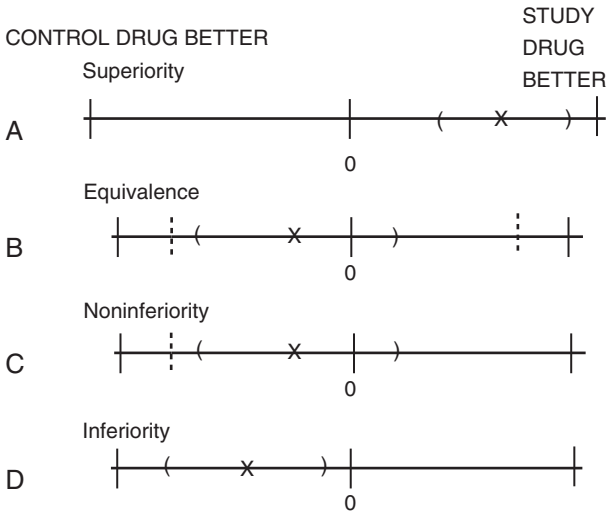

FIG. 52.1 Interpretation of results using confidence intervals (CIs) in clinical trials. *X* represents the difference in the point estimates of two therapies. The central zero mark indicates no difference between drugs. The parentheses represent the upper and lower bounds of the 95% CIs. The dashed lines are the noninferiority and equivalence margins. (A) A study drug that demonstrated superiority over the control has a point estimate and the upper and lower bounds of the 95% CIs greater than zero. (B) A study drug that demonstrates equivalence to a control drug has upper and lower bounds of the 95% CIs within a prespecified margin. The point estimate can be greater or less than zero. (C) A study drug that demonstrates noninferiority to a control drug has a lower bound of the 95% CI greater than some prespecified margin. If the lower bound is more negative than the prespecified margin, the study drug is said not to meet the definition of noninferiority. (D) A drug that is inferior to the control drug has the upper bound of the 95% CI less than zero. (See text for further explanation.)

investigators is to push for larger noninferiority margins to both decrease the sample size of trials and increase the likelihood of "positive" results. However, as discussed previously, investigators should choose noninferiority margins based on ruling out clinically meaningful differences in loss of effect with the test intervention compared with the control intervention rather than sample size considerations alone. For instance, allowing a new drug to potentially increase mortality by 15% to 20%, or 1 in every 5 to 6 patients treated with the new drug, compared with having received the older drug, seems hard to justify.

Measurement of Harms

Many clinical trials are designed to evaluate both the harms and the benefits of an intervention. However, studies often have no specified hypotheses related to harms and do not have a large enough sample size to rule out many adverse events, especially those that are less common. Reporting of harms is usually descriptive only, because often no specific hypotheses are tested, and often inadequate, with more space devoted to authors' affiliations[132] than description of harms. Absence of evidence of a difference is not the same as evidence of absence of a difference between interventions. When a clinical trial shows no cases of a particular adverse event, one can only rule out a rate of 1 in the number of patients examined divided by 3.[133] For example, if one sees no cases of a particular adverse event in 300 patients, that rules out a risk of 1 in 100 or, in other words, a rate greater than 1%. If one does not see an adverse event in 3000 patients, that observation rules out a risk of 1 in 1000, or greater than 0.1%. When there are no specified hypotheses or chosen sample size related to demonstration of harms, use of *P* values is less helpful, and nonsignificance of *P* values does not mean that no difference exists between groups. The goal of analysis of harms is to evaluate signals for toxicity along with data from preclinical, early clinical, and other studies. Spontaneous reporting of harms from postmarketing databases often detects only a small proportion of the total number of harms, estimated at 1% to 10% of the true total. Spontaneous reporting may be helpful in assessing causality to the intervention when the adverse rarely occurs spontaneously—for example, liver failure in otherwise healthy people. Spontaneous reporting is less helpful in assessing causality related to the effects of interventions on common events such as myocardial infarctions or death in seriously ill populations. Therefore, comparisons of rates of adverse events are challenging when the denominators are not known.

Subgroup Analyses

Although the overall results based on the primary research question are the most valid, investigators often express an interest in examining whether differences observed in the overall population are also present in specific subgroups of patients in the study. However, there are several pitfalls that may decrease the validity of subgroups.[134]

Valid subgroups analyses in confirmatory trials are those that (1) are spelled out before the study begins ("prespecified"), (2) have separate hypotheses (delineating what differences are expected in the subgroup compared with the entire study population) and sample size calculations, (3) have appropriate adjustment for multiple comparisons in the study, and (4) perform tests for interactions. Prespecification alone is not sufficient for valid analysis of subgroup analyses. Testing for interaction means comparing the observed differences between the test and the control groups in the subgroup of interest with the observed differences in the complementary subgroup, rather than presenting only the statistical significance of the difference between the test and control groups for the individual subgroup—in other words, evaluating a difference of differences. For instance, if a drug shows a larger effect in older patients than in younger patients, a test for interaction would compare the treatment effects in the test versus control group of older participants with the treatment effects in the test versus control group of younger participants, rather than just evaluating the statistical significance of the test versus control group of older participants.

The issue with subgroup analyses is that the protection of randomization from selection bias applies to the total randomized population but may not apply to specific subgroup analyses. Subgroups chosen based on factors that occur *after randomization,* such as adherence, drug concentrations used in pharmacodynamic analyses, exposure to medication, or treatment success or failure, are particularly problematic.[135] In these types of subgroup analyses, the patients comprising the groups may differ substantially for other factors that influence outcomes. For instance, drug exposure is influenced by severity of illness and concomitant medications. Therefore, comparing outcomes in subgroups of patients with higher drug exposures versus those with lower drug exposures may not be measuring treatment effects of the drugs, and observed differences may reflect baseline differences between patients. The same issues apply to comparing patients who adhere to a medication regimen with less adherent patients because baseline differences exist between such patients. Prior studies show decreased mortality when comparing adherent with nonadherent patients within the placebo group, demonstrating that such differences in patient characteristics influence the observed outcomes rather than effects of the interventions.[136,137] Finally, there is the issue of multiple comparisons discussed previously. The adjustment for multiple comparisons should be based on the number of comparisons made rather than the number of comparisons presented. There is an incentive to present only the "positive" subgroups in publication rather than all the subgroups evaluated. It is common, when subgroup analyses are performed without following the three criteria outlined earlier, that follow-up randomized trials in the subgroup population fail to confirm the results in the subgroup analyses. The results of subgroup analyses are most useful when they confirm the primary findings of the study.

EXAMINING THE CONCLUSIONS

In the discussion section of published studies, investigators summarize the results, discuss the strengths and limitations of the data, and relate the results to other studies of the disease in the field.[138] However, previous studies have shown that authors commonly make claims not justified by the results. A review of trials in obstetrics and pediatrics journals concluded that in only 10% of the trials were the conclusions justified by the results.[139] In another study, the authors found doubtful or invalid

statements in 76% of 196 trials.[140] Authors may tend to highlight statistically significant results over less impressive findings, whether or not those results represent the primary hypothesis of the study or post hoc subgroup analyses.[141]

Some common pitfalls readers should look for in examining the discussion section of clinical trials (Table 52.1) include the following:

1. Conclusions from studies with an unclear objective: Because the results of a study are evaluated based on the research questions chosen before study initiation, it is impossible to evaluate study results without clearly stated objectives or hypotheses. For clinical trials, this should include explanation of the types of error and the sample size. Understanding the chosen objective of the study also ensures that investigators chose the hypotheses before examining the results, rather than examining the results and deciding what the hypotheses "should have been." For instance, clinical trials of monoclonal antibodies in sepsis failed to show decreases in mortality compared with placebo, but post hoc analyses claimed benefits in patients with bacteremia, as if the hypothesis "should have been" related to only participants with bacteremia. Subsequent studies did not support this hypothesis.[142] Readers should also evaluate single-trial results in the context of other similarly designed trials. A single "positive" trial in the context of other trials that do not confirm that result is more likely to represent a false-positive finding.
2. Drawing conclusions about treatment effects of interventions from studies wherein control groups lack baseline comparability: Many types of nonexperimental studies do not evaluate comparability between the test and control groups or make comparisons between groups that are known to differ in important baseline characteristics. For instance, comparing unadjusted outcomes in patients with disease caused by resistant pathogens with outcomes in patients with susceptible pathogens compares people with inherently different baseline characteristics that independently affect outcomes.
3. Concluding noninferiority from a trial designed to demonstrate superiority: Conclusions of superiority or noninferiority of the study drug should relate to the initial hypothesis. A noninferiority trial may show a superior result for one of the drugs when the results show a lower bound of the CI around the difference in the point estimates that is greater than zero. However, it is difficult to claim noninferiority from a superiority trial. In most cases, investigators do not select a noninferiority margin before initiation of a superiority trial or evaluate whether the design of the current study conforms to prior studies that demonstrated the effect of the control intervention. This results in difficulties in interpretation of the results because noninferiority is based on comparison of the lower bound of the CI to the prespecified noninferiority margin. In addition, the sample size of a noninferiority trial is often larger than in a superiority trial; therefore the trial may not have an adequate sample size to conclude noninferiority when designed for superiority. Studies have demonstrated that the reporting of noninferiority trials is often poor, and investigators often have reported failed superiority trials as showing noninferior results.[143,144]
4. Extrapolation of results to types of patients not studied in the trial and who differ substantially from patients in the trial: The results of the trial are most applicable to patients who fit the definition and stage of the disease and the population in the study. It is more difficult to extrapolate results to other populations, especially those that may differ in host immune function, age, and pathophysiology or severity of underlying disease. For instance, demonstration of noninferiority of interventions in populations with disease caused by susceptible pathogens does not justify conclusions of superiority of the test intervention in patients with disease caused by resistant pathogens, given differences in patient characteristics between those with disease caused by susceptible or resistant pathogens.
5. Extrapolating results of explanatory trials broadly to clinical practice when interventions are used under different conditions in practice: Data from explanatory trials may not describe the effectiveness of interventions in the real-world setting. Conversely, pragmatic trials do not rule out effects of interventions in other populations or when used under other conditions. Using evidence from explanatory trials to justify noninferiority trials using pragmatic designs is similarly problematic because it extrapolates effects from one setting to another without evidence.
6. Presenting the results in a way to make them appear more favorable: The presentation of results may influence clinicians' interpretations of trials and their application in clinical practice.[94] A meta-analysis of studies showed that clinicians were more impressed and indicated a higher likelihood of prescribing an intervention to patients when investigators presented the results of trials as a relative difference in outcomes rather than as an absolute difference.[94] One should examine both the relative and absolute differences in outcomes when interpreting the results of trials. Small absolute differences may translate into large relative differences that may be clinically insignificant.
7. Conclusions based on results that do not achieve statistical significance: Authors may describe results that do not achieve statistical significance as a "trend" toward successful outcomes. Readers should interpret such claims with care. A trend assumes that further study of a larger sample size with similar patients would yield similar results. However, the likelihood of confirmatory results in a second trial when the *P* value of the first trial is 0.10 is 37%.[125] Similarly, readers should be wary of conclusions that rely on statements related to the trial being "underpowered" after the trial is complete. Power analyses are a measure of pretrial probability, and are not appropriate when a trial is over. Rather, an examination of CIs related to trial results is more appropriate.
8. Conclusions based on subgroup analyses when results were not significant for the primary end point: The results of the trial are most relevant for the specified primary end point. The most problematic types of subgroups are those based on factors chosen after randomization, such as adherence, drug exposure, or success or failure, because these subgroups select patients with different baseline characteristics.[135] As described earlier, results from subgroup analyses may be biased because of several issues. Subgroup analyses are most useful in confirming the overall results rather than drawing difference conclusions from the primary analysis and for generating hypotheses for study in future clinical trials.
9. Conclusions regarding direct patient-centered outcomes on symptoms, patient function, or survival based on nonvalidated surrogate end points: The relationship between treatment effects

TABLE 52.1 Points to Examine in Interpreting Clinical Trials

- Define goals of study
  - Type of research study—descriptive or analytical
  - Explanatory or pragmatic study
  - Define random error and sample size
  - Type of hypothesis—superiority or noninferiority
- Select control groups
- Select participants by appropriate inclusion and exclusion criteria
- Baseline comparability of participants
  - Randomization
  - Blinding
  - Stratification
- Minimizing bias
  - Selection bias—randomization
  - Observer bias—blinding
  - Confounding—randomization
  - Minimize missing data
- Selection of appropriate end points with direct benefit to patients or valid surrogate end points
- Appropriate analysis of results
- Appropriate conclusions based on data presented in trial

on direct outcomes and indirect outcomes, including biomarkers, should be clearly demonstrated. A correlation between direct and indirect outcomes is not sufficient to evaluate this relationship. For instance, studies that use decrease in organism colonization as the primary end point in a prophylaxis trial or negative cultures in a treatment trial can claim a decrease in direct patient-centered outcomes only if results of the current trial or previous trials show that a treatment effect on colonization reflects a treatment effect on decreasing disease in similar patient populations tested under similar conditions. A correlation between patients who are decolonized or who have negative cultures and direct outcomes does not provide such information. Validation of surrogate end points applies only to the population, disease definition, end–time point timing and definitions, and types of interventions used in the validation studies.

10. Ignoring the impact of bias on study outcomes: Various types of bias can influence the validity of study results and thereby impact clinical practice and patient outcomes through the promotion of ineffective or unsafe interventions. The problem is that the effect of bias is not directly measurable. Demonstration of statistical significance does not measure bias, and studies with larger sample sizes are more influenced by bias. Different scoring systems are available to evaluate the various biases that may occur in randomized trials and may help readers to systematically evaluate the presence and impact of bias.[145] The impact of bias is different in the setting of superiority and noninferiority trials, with many types of bias resulting in false-positive conclusions of noninferiority. The evaluation of study design and results is not solely an academic exercise but one that directly affects patient care. Scientific validity is the basis for ethical testing of interventions involving humans, so minimizing bias is an ethical in addition to a scientific concern.[5]

There can be significant variation in trial results based on differing definitions of disease, outcomes, and patient populations. When making treatment decisions in clinical practice, clinicians should examine a range of trials on a given disease. Reproducible or related confirmatory results in several trials of adequate design are the strongest evidence of a true effect.[12] Also, clinicians should examine all the evidence, including studies that show positive, negative, and neutral results, the potential sources of bias, and the variability and precision in those results. However, investigators are more likely to publish trials with positive results.[146] This publication bias can, in turn, affect meta-analyses and reviews. One study showed that review articles tend to omit trials with negative or neutral results.[3]

Ultimately, clinicians must decide the relevance of a study to particular patients. The distinction between clinical significance and statistical significance is an important one. Statistical significance indicates that the results of the trial are unlikely to occur by chance and that the results likely reflect the outcomes in a population similar to those studied in the trial, as long as the results are not influenced by bias. However, statistics do not reflect the clinical importance of the outcomes of the trial. Clinical significance reflects the value of the outcomes for patients and reflects a balance of both benefits and harms.[48] A trial with a very large sample size may show that small differences in outcomes are statistically significant, but such small differences may be clinically meaningless.

Clinical studies examine average effect on a population of patients. When making individual treatment decisions, however, clinicians should examine the risks and benefits of administering the drug for a particular patient. This entails an evaluation of such factors as the patient's comorbid illnesses, drug allergies and intolerance, concomitant medications, and the severity of the disease under treatment. Whereas a careful consideration of the design, analysis, and results of clinical trials helps guide clinical decision making, there is no substitute for sound clinical judgment based on applying the evidence from appropriately designed studies. Conversely, individual experience is not a substitute for sound evidence.

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The complete reference list is available online at Expert Consult.

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53 Outpatient Parenteral Antimicrobial Therapy

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Outpatient parenteral antibiotic therapy (OPAT) refers to the practice of administering intravenous (IV) antibiotic therapy in a non-inpatient hospital setting. The non-inpatient setting may include a variety of sites, such as home-based therapy, a physician's office or hospital-based ambulatory practice, infusion center, hemodialysis center, emergency department, skilled nursing facility (SNF), or long-term acute care facility. The goal of OPAT programs is to provide the required infrastructure for optimal patient selection, monitoring, and treatment, and to enable patients to complete IV therapy safely and effectively in one of these outpatient settings. Ongoing quality assurance efforts are essential to an effective OPAT enterprise. When successful, these programs shorten hospital stays, thereby lowering health care expenses, reducing the risk for hospital-acquired complication, and increasing patient satisfaction.[1–3]

THE HISTORY AND GROWTH OF OPAT

The practice of providing OPAT in the home was first described in the early 1970s for the treatment of pulmonary infections in children with cystic fibrosis.[4] Over the following years, multiple additional studies demonstrated the use of OPAT for a broad range of conditions in adults, including soft tissue infection, infective endocarditis, osteomyelitis, septic arthritis, pyelonephritis, and pulmonary infection.[5–9] Major advances in vascular access devices and the development of relatively nontoxic antibiotics that may be administered once daily during this time significantly contributed to the ability to deliver antibiotic infusions in the non-inpatient setting.[10–14]

In addition to clinical advancements, health care reform played a major role in the spread of OPAT programs by establishing financial incentives for innovations that reduce inpatient length of stay. The first of such major health care reforms occurred in 1983 with the adoption of diagnostic-related group (DRG) models for payment of clinical services by the United States Healthcare Financing Administration (now Centers for Medicare and Medicaid Services [CMS]). This payment structure transitioned from fee-for-service billing to lump-sum payments based on a weighted estimate of cost for specific diagnoses multiplied by a fixed average inpatient length of stay.[15] In this new payment structure, facilitating earlier discharge for patients requiring prolonged IV therapy offered significant potential for cost savings[8,16] and further promoted spread of the OPAT model. The passage of the Affordable Care Act in 2010 further promoted the trend for payers to transition from fee-for-service to bundled payment models based on the development of a readmission reduction program and value-based purchasing models. These programs have contributed to the development of accountable care organizations, with a focus on creating novel care delivery models that provide health care in a more efficient and cost-effective way.

One major limitation to the continued expansion of OPAT to all patients remains the lack of coverage for home infusion provided by Medicare services. Despite the coverage of OPAT services by most commercial payers, Medicare covers OPAT services as a Part D benefit, meaning that only coverage for the medication is provided and not the required equipment or supplies. Despite these limitations, OPAT represents a significant opportunity for an innovative approach to improve population health and to reduce the per-capita costs of health care.[17,18]

It has previously been estimated that more than 250,000 Americans are treated by OPAT annually,[21] although it is likely this figure now underestimates current practices. The extensive use of OPAT has been characterized by recent surveys of infectious diseases (ID) consultants performed through the Emerging Infections Network. In 2006[19] 94% of 454 respondents (54% response rate) indicated that they "frequently" discharged patients on OPAT, and use was reported throughout North America. An additional survey published in 2014[20] found that the use of OPAT was common among ID physicians, with greater than 80% of respondents discharging one or more patients on OPAT in an average month. However, with the use of OPAT becoming the standard of care for patients requiring prolonged IV antibiotic therapy, continued attention is required to ensure proper patient selection is performed and the adequate programmatic structure is available to provide optimal care.

Despite the continued growth of OPAT in the United States and internationally, there remain limited prospective study and registry data to guide best practices. Available practice guidelines focus on the key elements of a program, appropriate patient selection, and recommended clinical and laboratory monitoring.[1–3]

PATIENT SELECTION FOR OPAT

It is important that all programs develop a standard approach for the assessment of patients before discharge and OPAT program enrollment. Patient selection criteria will vary depending on the model for OPAT care chosen; often this means the focus is on proper selection of the best discharge location (e.g., SNF, infusion center, or home infusion) rather than maintaining an inpatient status for the full duration of IV therapy. The key components of patient selection include an assessment of pertinent medical and patient factors.[1,3,21]

Medical factors include ensuring adequate source control of infection, necessity of IV antibiotic therapy, and readiness for discharge.[1,3,21] Success with OPAT has been demonstrated for a multitude of different infections, including soft tissue infection, bone and joint infection, endocarditis, and pneumonia. OPAT may be optimally used when a clear diagnosis has been made, culture data with antibiotic microbial susceptibility information is available, and a response to treatment can be monitored. If a patient requires source control via drain placement or surgery (e.g., percutaneous drainage of a liver abscess or surgical débridement of devitalized tissue in a diabetic foot infection), this should occur before discharge. Patients with bloodstream infection should have demonstrated clearance of blood cultures and a full assessment for metastatic foci of infection. Those with initial sepsis physiology must have demonstrated clear hemodynamic stability before discharge.

Patient factors to consider before OPAT enrollment include an assessment of the likelihood of adherence to therapy and follow-up, social support, and insurance coverage. The lattermost often determines options for discharge location.[1,3] If a patient is planned to be discharged home for OPAT, he or she or their caregivers must be able to adhere to the required care of vascular access and administration of antibiotic infusions. This additionally includes being able to recognize clinical changes, including new fever, rash, redness or swelling at the vascular access site, and to communicate effectively to ensure timely notification of changes to care providers. Patients should be willing and able to return to an outpatient clinic during regular intervals or if new symptoms develop, and to comply with recommended safety laboratory monitoring and vascular access care. In addition, patients must be fully informed of the economic aspects of OPAT, including their individual insurance coverage before initiation of treatment. It is important that patients be informed of any potential out-of-pocket costs for medication treatment,

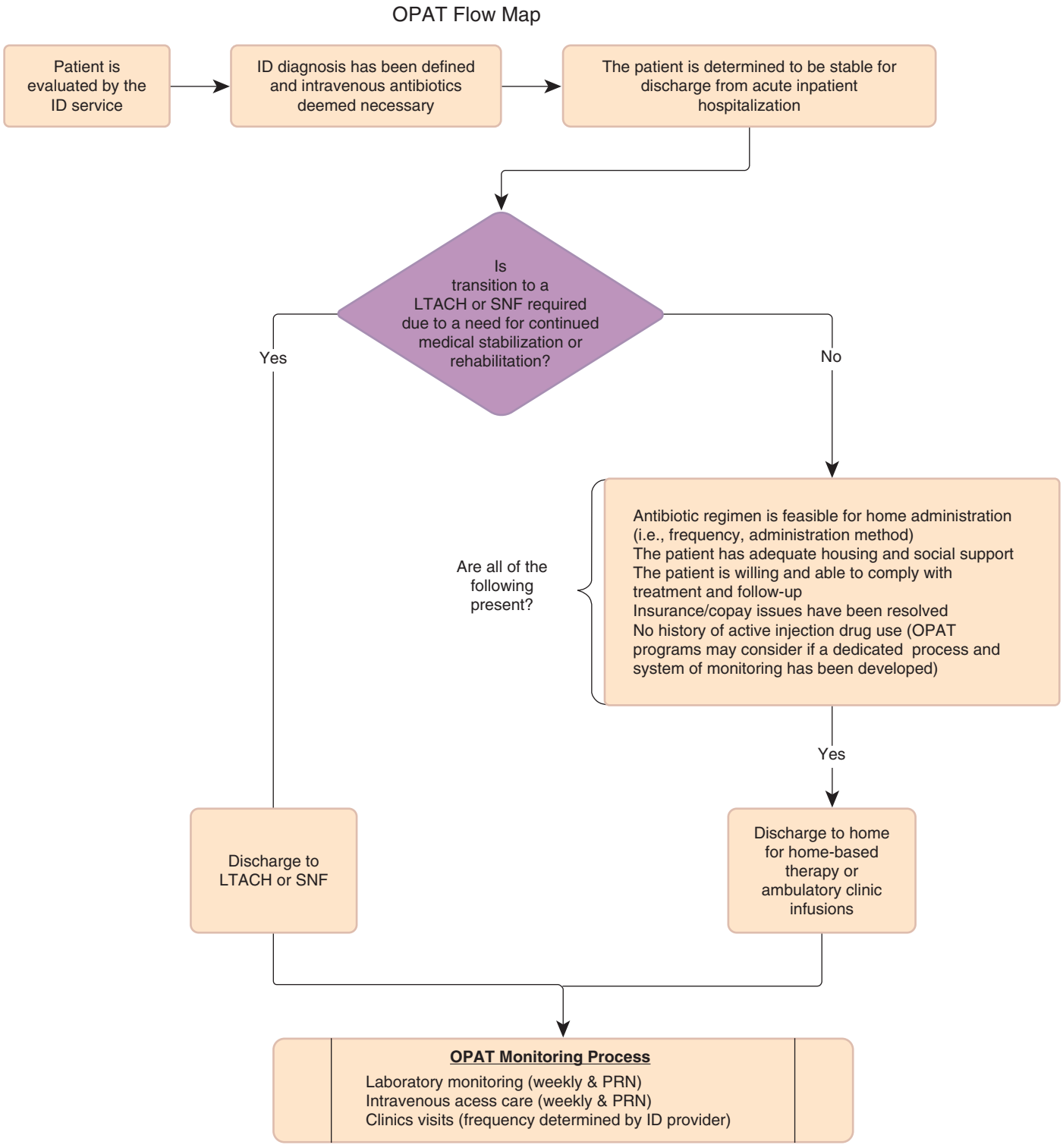

FIG. 53.1 Outpatient parenteral antibiotic therapy enrollment process. *ID,* Infectious diseases; *LTACH,* long-term acute-care hospital; *OPAT,* outpatient parenteral antibiotic therapy; *PRN,* as needed; *SNF,* skilled nursing facility. *(Modified from Tice AD, Rehm SJ, Dalovisio JR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines.* Clin Infect Dis. *2004;38:1651–1672; Muldoon EG, Snydman DR, Penland EC, Allison GM. Are we ready for an outpatient parenteral antimicrobial therapy bundle? A critical appraisal of the evidence.* Clin Infect Dis. *2013;57:419–424.)*

vascular access care, office visits, and laboratory monitoring. If a patient incurs unexpected out-of-pocket costs, it may lead to unexpected treatment interruption or early discontinuation of IV therapy.

It is the combination of the assessment of medical factors and patient factors that inform the decision regarding the optimal modality of OPAT at the time of hospital discharge (Fig. 53.1). If a patient has not yet demonstrated adequate clinical improvement for discharge home but no longer meets criteria for inpatient hospitalization, or is unlikely to comply with home- or office-based therapy due to patient or social factors, a transition of care to a long-term acute-care facility or SNF for continued treatment with ongoing daily monitoring is the most reasonable initial option. If a patient is medically ready for discharge

home, daily treatment in a physician's office or infusion center may be optimal for patients who have a preference for this approach. This may be because of discomfort with home infusion or a lack of caregiver support to assist with medication administration, and the patient may live close to the ambulatory practice or lacks of insurance coverage for treatment at home. If the patient does not live near an available ambulatory practice or infusion center, at times use of a local emergency department is required. For those patients meeting criteria for home infusion, a clear communication plan with an infusion company and/or visiting nurse service is required to ensure continuity of care at the time of discharge. Due to the frequent occurrence and spotty nature of antimicrobial drug shortages, which particularly effect generic injectable antibiotics,[22,23] the OPAT team should confirm that the infusion company has access to sufficient supplies of the recommended agent (or a suitable alternative) to complete the planned course of treatment.

OPAT IN PEOPLE WHO INJECT DRUGS

The current epidemic of opioid abuse has been marked by a rapid increase in the number of people who inject drugs (PWIDs). This, in turn, has been associated with an alarming increase in infectious diseases associated with injection drug use (IDU) from hepatitis C virus and human immunodeficiency virus, along with morbid and life-threatening bacterial infections, such as endocarditis; spinal epidural abscess; and bone, joint, and soft tissue infections.[24] As a result, most ID clinicians are faced with the potentially increasingly consequential consideration of OPAT in PWIDs.[24] The current, somewhat dated, Infectious Diseases Society of America (IDSA) Practice Guidelines for Outpatient Parenteral Antimicrobial Therapy give little practical guidance in this area, suggesting consideration of alternatives to home-based OPAT, such as SNF placement, intramuscular injection, or daily infusion with IV catheter removal for patients likely to manipulate an IV catheter.[1] A more recent OPAT guideline from the United Kingdom does not appear to directly address the issue.[3] High-quality evidence is still sparse; however, some preliminary observations can be made. First, this is a common scenario faced by many ID clinicians.[24] Second, compared with other patients receiving OPAT, PWIDs tend to have more severe infections, although they tend to be younger and have fewer medical comorbidities, as observed by Buerhle and colleagues,[25] who compared their PWIDs OPAT population with an unselected Department of Veterans Affairs (VA) health care facility OPAT population.[26] Third, more recent IDU is associated with an increased risk for OPAT failure.[25] Finally, several reports suggest that careful selection of lower-risk patients and/or use of well-structured and comprehensive OPAT programs designed for this population can produce outcomes that are similar to non-IDU populations.[25,27–29] Elements of successful programs for the provision of OPAT to PWIDs include careful patient selection, contracts of care requiring adherence to follow-up appointments and laboratory testing, prohibition of manipulation of the IV devices, and attention to the substance abuse diagnosis with available medically assisted treatment and harm reduction strategies for ongoing IDU.[27–30] Successful examples include the experience of Ho and colleagues,[27] who reported approximately 97% of the 29 PWIDs (defined as IDU in the past 12 months) they studied were compliant with OPAT, and about 21% required readmission during the study period. Their OPAT program included a contract of care, prohibition of illicit drug use enforced with as-needed urine testing, daily clinic visits for infusions, and the application of decals to prevent manipulation of peripherally inserted central catheter (PICC) lines. Beieler and colleagues[28] reported another successful OPAT program embedded in a residential "respite care center" associated with an urban hospital that also included a care contract and antimanipulation decals for catheters. Harm reduction strategies included allowance of safer injection practices and opiate replacement therapy, but precluded illicit use of the IV catheter. Camsari and colleagues[29] took a potentially more generalizable approach to this problem by using an addiction specialist and a psychiatrist to carefully risk stratify PWIDs, then used that risk assessment to make recommendations regarding the conditions for OPAT. They were able to achieve uniformly successful OPAT in low-risk populations, a 90% success in a moderate-risk population (including prior IDU no less than 12 months ago), and reasonable success (80%) even in the highest-risk population, although most of those went to a SNF. A more cautionary note was provided by a study of OPAT in population of IDUs, lacking some of the structural elements outlined earlier, wherein 61% of patients failed to complete their treatment successfully. Failure was associated with more recent IDU (3 vs. 8 weeks), although patients who had a more remote history of IDU (>5 years) had a relatively low failure rate (21%).[25] The alternative to successful execution of an OPAT strategy for PWIDs is prolonged hospital stays for inpatient treatment. It is clear that we must move past an overly simplistic approach to this population, acknowledging that the data are not robust, and the risk of failure is probably somewhat higher than a general OPAT population; however, that risk can be mitigated using proactive strategies of risk stratification and harm reduction in well-structured OPAT programs.

ALTERNATE OPTIONS FOR OPAT

OPAT is not the preferred approach for all patients, particularly those with a lack of ability to self-administer IV therapy or for those without adequate social support or stable housing to complete the required treatment. Factors such as substance abuse, most prominently active opioid use disorder, may render a patient unsuitable for vascular access device placement in the outpatient setting. In addition, not all patients who fail to meet criteria for home-based therapy may be able to be placed in a SNF due to insurance coverage or patient preference against facility placement.

USE OF ORAL ANTIBIOTIC THERAPY

There are times when use of parenteral antibiotic therapy would be preferable. However, it may not be determined to be a safe approach by the ID service due to concern for challenges with adherence to therapy, active IDU, or needed follow-up. In these instances, offering an alternative of oral therapy may be an acceptable, although a suboptimal, approach. When used, agents with excellent oral bioavailability, such as the fluoroquinolones, metronidazole, trimethoprim-sulfamethoxazole, clindamycin, and linezolid, should be chosen when possible.

Although the role of oral antibiotic therapy for serious infections, such as endocarditis and osteomyelitis, has not been well established, there are limited data that demonstrate the efficacy of this approach.[31–36] For example, there are few studies of oral antibiotic treatment of endocarditis. Limited data suggest that oral ciprofloxacin in combination with rifampin was active against right-sided *Staphylococcus aureus* endocarditis in a small randomized trial.[37] There are a handful of small retrospective and observational studies suggesting that oral penicillins, sometimes combined with probenecid, may be effective for primarily streptococcal endocarditis.[32] Even more limited data suggest that linezolid may be effective treatment for endocarditis.[38] In addition, if initial parenteral therapy has been used to treat endocarditis, a recent large randomized multicenter trial suggested that providers can consider an early transition to oral therapy in some patients without loss of efficacy.[34] When considering use of an oral regimen for osteomyelitis, this is ideally done after any needed surgical débridement has been performed, and the causative pathogens have been identified and are susceptible to a highly bioavailable oral agent. If this approach is taken, typically more prolonged courses of therapy are used.[35,36]

USE OF LONG-ACTING PARENTERAL AGENTS

Although currently only approved for use in skin and soft tissue infection, the long-acting parenteral lipoglycopeptides dalbavancin and oritavancin present an additional option for outpatient antibiotic therapy.[39,40] Their long half-lives obviate the need for placement of long-term IV access, which may be a particularly attractive option in the setting of PWIDs. Available data suggests that these agents may be active in the treatment of bloodstream infections,[41] and excellent penetration in bone and articular tissues has been reported.[42] However, additional clinical studies are required before recommending the use of these agents as a standard practice. The risk of emergence of resistance to these drugs in prolonged courses also requires further study.[43,44] Acquisition costs for these agents are high, and cost-effective implementation of their use requires careful economic analysis.

PROGRAMMATIC REQUIREMENTS

OPAT should be provided through a team approach, led by an ID clinician with experience in managing all of the common modalities of outpatient IV antibiotic therapy. The OPAT multidisciplinary team should optimally also include a pharmacist with ID training, a nurse with expertise in parenteral medication administration and venous access devices, and administrative support to facilitate timely office visits and communication with patients, infusion companies, and care facilities.

INFECTIOUS DISEASES PROVIDER

The physician responsible for oversight of OPAT should have ample knowledge and experience in the diagnosis of infectious diseases and the unique challenges of the management of antimicrobials in the outpatient setting.[1,3] Specific experience is required to allow timely identification of poor clinical responses or complications of therapy, such as adverse drug reaction (ADR) and complications of venous access devices. Experience in performing an assessment of patient factors to help guide optimal selection of OPAT modality or deferral of this approach is needed. In addition, provider oversight of an OPAT program should include a focus on optimization of team management and continuous quality improvement work, including an assessment of complications of therapy and outcomes.

ID consultation has been shown to provide significant benefit in performance of salient medical and patient factors assessment. A major beneficial impact may be deferred IV therapy, if not required. Shrestha and colleagues[45] assessed 263 ID consultations for the purpose of OPAT and found that 84% of patients had an optimization of their antibiotic regimen, 52% had a significant change in assessment, and additional medical care contribution was provided in 71%. In addition, OPAT was found to be unnecessary in 27% of patients. Conant and colleagues[46] retrospectively reviewed 577 requests for OPAT by the ID consult service and found a 10.4% denial rate. Of the 56 patients available for evaluation, the cure rate was 87.5%, with 6 of 7 failures attributed to nonadherence with oral antibiotic therapy or deemed to have an incurable infection.

Once the decision has been made that OPAT is the preferred approach, the OPAT clinician should be responsible for approving all changes in medication orders and final interpretation of safety laboratory values to ensure that change in medication or treatment is not needed.

OPAT PHARMACIST

The role of a pharmacist on the OPAT team serves multiple purposes, including working with the ID provider to determine the most effective, safe, and narrowest spectrum of therapy with the least likelihood of adverse reaction. This includes screening for unrecognized drug interactions and ensuring optimal antibiotic dosing based on changing patient factors, such as fluctuating renal function. In addition, pharmacists have been used to implement IV switch programs to oral therapy, with the goal of shortening the required OPAT duration.[1,3,47,48]

After patient discharge the role of the pharmacist and interactions with the OPAT team often varies because of the site of care chosen and the OPAT program structure. For example, if a patient is discharged to a facility, the OPAT team will often interact with the pharmacists responsible for medication administration at that site. However, if a patient is receiving IV therapy at home via an infusion company, the interaction will be with a pharmacist responsible for acquisition, storage, compounding, and dispensing of antibiotics to the home.

INFUSION NURSE SUPPORT

The role of nursing services varies with the OPAT model chosen and site of care. At the time enrollment in OPAT occurs, nursing services are required to provide patient education regarding IV access devices and medication administration. When home therapy is performed, nursing provides regular home assessments to ensure oversight of medication administration and IV access care by the patient or caregiver, as well as providing notification to the responsible clinician regarding any clinical changes. Regardless of the modality of OPAT chosen, nursing plays a significant role in the coordination of care and ongoing patient education and monitoring.[1]

ANTIMICROBIAL STEWARDSHIP

A policy statement from the Society for Healthcare Epidemiology of America, IDSA, and Pediatric Infectious Diseases Society proclaimed "antimicrobial stewardship must be a fiduciary responsibility for all healthcare institutions across the continuum of care."[49] There is a growing focus on the importance of antimicrobial stewardship programs expanding to the non-inpatient setting, of which OPAT represents a significant opportunity. There is a substantial need for ID consultants and OPAT pharmacists to determine the necessity for OPAT and to balance providing narrow-spectrum therapy with facilitating the convenience of once-daily home infusion when feasible.[46,47]

SYSTEM FOR DATA MANAGEMENT AND COMMUNICATION

For OPAT programs to meet their goals to provide IV therapy safely and effectively in the outpatient setting, a reliable system of communication among the patient, clinician, pharmacy, and nursing staff is required. Programs should have established policies and procedures to detail the responsibility of each team member, as well as to define standards for patient selection criteria, laboratory monitoring, responses to critical or urgent values, and complications of vascular access. All patients should be informed and demonstrate knowledge of the program's emergency access numbers and know which conditions should prompt a telephone call or urgent visit. Programs need to have a system for rapid communication between the patient and care providers, documentation of this communication, and ability to accommodate urgent clinic visits to assess concerns.[1,3,21]

ANTIMICROBIAL CONSIDERATIONS

In addition to the usual considerations regarding antimicrobial activity, pharmacokinetics-pharmacodynamics, drug toxicity, drug interactions, selection for drug resistance, and overgrowth syndromes such as *Clostridioides difficile* (formerly *Clostridium difficile*) infection (CDI), the choice of antimicrobial drugs for OPAT requires consideration of certain logistical issues that are unique to this care setting. Therapeutic drug monitoring (TDM) can be challenging in the OPAT setting as the timing of phlebotomy versus the drug infusion may be logistically difficult. Although the need for TDM does not preclude use of drugs monitored in OPAT, it does make OPAT more complex for those drugs that need to have timely phlebotomy performed (sometimes repeatedly), along with the ability to acquire, record, interpret, and act upon results with new drug orders as necessary. The number of infusions per day and the duration of those infusions must be taken into account when considering a drug regimen for OPAT use. For some drugs, such as vancomycin, infusion time is prolonged in an effort to prevent infusion-relative toxicity, whereas for β-lactams and other drugs with activity related to time above minimum inhibitory concentration (MIC), a prolonged infusion may be used to improve predicted activity.[50] For this reason, prolonged infusion is recommended in the package insert for some newer β-lactam drugs, such as ceftazidime-avibactam (2 hours) and meropenem-vaborbactam (3 hours).[51,52] Drugs administered by a visiting nurse should generally be limited to once- or, at most, twice-daily infusions of a limited duration. If the patient and/or a family member or friend can be trained to administer the IV drug and care for the line before and after, there can be a bit more flexibility, but numerous and/or prolonged infusions may be expected to have a negative impact on the patient's quality of life. Venous access device compatibility is yet another consideration. Certain drugs are thought to be sufficiently caustic to veins (phlebitogenic) that they should be administered through central lines, although there is some debate about which drugs require central access.[53,54] For example, the safety of provision of vancomycin via midline has been debated, and most recent data suggest that this may be a safe practice.[55] Drug stability at room temperature is another factor that must be considered for OPAT. More stable drugs can potentially be administered by a programmable IV pump at more frequent intervals (e.g., penicillin every 4 hours) or as an extended infusion over 24 hours (potentially requiring periodic bag changes). Drug shortages, particularly common among generic injectable antibiotics, are yet another consideration.[23] Because hospitals and infusion companies may have different supply chains, providers should be certain that infusion companies

have adequate supplies of drugs in shortage before discharge on OPAT. Last, but certainly not least, the cost of the drug may be a determinative factor, depending on the patient's insurance coverage, and this should be considered in the context of stewardship of health care financial resources.

DRUG CHARACTERISTICS AND REGIMENS

The ideal OPAT drug is highly active against the target organism(s), has a high barrier to selection for resistance, is sufficiently narrow in spectrum to confer limited selective pressure for CDI, and is inexpensive, stable, and can be infused rapidly and infrequently. Few drugs meet all of these criteria, so compromises are required. Properties of commonly used OPAT antibiotics are detailed in Table 53.1. Common parenteral regimens for methicillin-susceptible *S. aureus* (MSSA) include cefazolin and ceftriaxone, although some providers shy away from once-daily ceftriaxone for the most serious MSSA infections.[56] Antistaphylococcal penicillins (nafcillin and oxacillin) have historically been perceived to be the most active agents for the most serious MSSA infections, but these drugs require frequent infusion, and a number of recent retrospective studies suggest similar clinical outcomes can be achieved with cefazolin with reduced drug toxicity (see "Adverse Drug Reaction") and lower mortality in some studies.[56–58] However, in the absence of randomized controlled clinical data, some experts continue to favor antistaphylococcal penicillins for the most difficult-to-treat MSSA infections.[59] Cefazolin may be used in patients exhibiting non–immunoglobulin E–mediated reactions to antistaphylococcal penicillins. Vancomycin should not be used for MSSA infection in the absence of severe β-lactam allergy, including for patients on dialysis, as clinical outcomes are inferior to β-lactam treatment.[60,61] For methicillin-resistant *S. aureus* (MRSA), vancomycin remains a work-horse agent, although vancomycin treatment is laden with the use of TDM and increased toxicity versus some comparators, as well as concerns about efficacy, resulting in the increased use of daptomycin. Daptomycin has been shown to be a safe and effective OPAT drug for MRSA compared with vancomycin,[62] although some studies suggest both drugs have higher rates of ADRs in OPAT versus comparators.[63] For a variety of reasons, including multiple allergies and drug resistance, there is some OPAT uptake for IV and oral (PO) linezolid and ceftaroline, although both drugs have risk of ADRs, including hematologic toxicity, particularly linezolid.[64–66] Vancomycin and daptomycin are also options for MSSA infection in the setting of a serious β-lactam allergy (see Chapter 194). Once-daily ceftriaxone is an ideal option for most streptococcal infections, and in the setting of serious β-lactam allergies, vancomycin or daptomycin may be considered. For serious enterococcal infections, such as endocarditis due to ampicillin-susceptible enterococci, ampicillin is still a favored agent, despite the need for frequent infusions, whereas vancomycin and daptomycin are also used for allergies or resistance to β-lactams[67] and potentially for logistical reasons in less serious infections. The use of gentamicin for synergistic treatment of ampicillin-susceptible enterococcal endocarditis is covered elsewhere (see also Chapter 80), but it would be worth noting in this section that use of thrice-daily aminoglycosides would be challenging in most OPAT settings, and high-dose ceftriaxone combined with ampicillin or alternatives to ampicillin should be considered for endocarditis treatment. A variety of agents may be chosen for gram-negative rod (GNR) infections, including extended-spectrum cephalosporins—for instance, ceftriaxone, ceftazidime, and cefepime. For patients with some types of antibiotic resistance and some mixed infections, the β-lactam plus β-lactamase inhibitor combination of piperacillin-tazobactam is heavily used for inpatients and sees some use in OPAT, but this requires 3 to 4 daily infusions in patients with normal renal function and makes it a less-than-optimal drug in that setting. The carbapenem ertapenem,

TABLE 53.1 Properties of Commonly Used OPAT Antibiotics

DRUG	HALF-LIFE (H)	STABILITY AT 5°C/25°C	PHLEBITIS RISK	ISSUES OF CONCERN DURING OPAT
Cefazolin	1–2	10 days/1 day	1	
Ceftazidime	1.4–2	21 days/2 days	1	
Ceftriaxone	5.4–10.9	10 days/3 days	1	LFTs should be checked weekly.
Daptomycin	8.1	12 h/48 h	1	Occasional myopathy; CPK should be checked weekly. Eosinophilic pneumonitis is an unusual adverse effect. Can falsely prolong INR without changing anticoagulation; INR should be checked at least 24 h after daptomycin dosing
Ertapenem	4	24 h/6 h	2	LFTs should be checked weekly.
Gentamicin	2–3	30 days/30 days	1	Ototoxicity and nephrotoxicity common, so hearing and vestibular function must be clinically assessed regularly. Drug levels (typically trough concentrations) should be tested weekly, and kidney function must be checked twice weekly.
Meropenem	1.5	24 h/4 h	1	LFTs should be checked weekly.
Nafcillin	0.5–1.5	3 days/1 day	3	Occasional hepatotoxicity; LFTs should be checked weekly. Also risk of allergic nephritis. Frequent dosing generally requires programmable IV infusion device.
Oxacillin	0.3–0.8	7 days/1 day	2	Higher risk of thrombophlebitis and DVTs. Also risk of allergic nephritis. Frequent dosing generally requires programmable IV infusion device.
Penicillin G	0.4–0.9	14 days/2 days	2	Frequent dosing generally requires programmable IV infusion device.
Tobramycin	2–3	4 days/2 days	1	Ototoxicity and nephrotoxicity common, so hearing and vestibular function must be clinically assessed regularly. Drug levels (typically trough concentrations) should be tested weekly, and kidney function must be checked twice weekly.
Vancomycin	4–6	63 days/7 days	2	Occasional nephrotoxicity; kidney function should be checked weekly. Therapeutic drug monitoring (weekly trough concentration) recommended. Avoid rapid infusion to reduce the risk of "red man" syndrome (histamine release reaction).

CPK, Creatine phosphokinase; *DVTs,* deep vein thromboses; *INR,* international normalized ratio; *IV,* intravenous; *LFTs,* liver function tests; *OPAT,* outpatient parenteral antibiotic therapy.

Modified from Tice AD, Rehm SJ, Dalovisio JR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. Clin Infect Dis. *2004;38:1651–1672.*

which can be given once daily, is a favored agent for OPAT for mixed infections[68,69] and mild–to–moderately severe infections caused by extended-spectrum β-lactamase–producing GNRs. However, unlike the more frequently dosed carbapenems (meropenem, imipenem, doripenem), it lacks activity against *Pseudomonas* spp. For coverage of *Pseudomonas* spp., favored drugs include cefepime, ceftazidime, piperacillin-tazobactam, carbapenems exclusive of ertapenem, and IV/PO levofloxacin and ciprofloxacin. For coverage of anaerobic infections, metronidazole IV/PO can be used, often added to a regimen with activity against gram-negative and gram-positive aerobes for mixed infections. The drug has caused neuropathy in prolonged use, but recent data would suggest that this is uncommon, and ADRs occur typically after more than 4 weeks of treatment.[70,71]

METHODS OF INFUSION AND DRUG DELIVERY

The logistics of home infusion of antibiotics will vary depending on a number of factors, including the duration of treatment, the nature of the drug, patient and caregiver capacity to perform infusions, type of insurance, and the home infusion company.[14] First doses of an OPAT regimen are often given in the hospital before discharge but may be given in an infusion center or, increasingly, at home by home infusion companies staffed by health care personnel "trained and equipped to manage anaphylaxis."[3] Vascular access devices used for OPAT range from peripherally inserted devices, such as peripheral venous catheters for very short-term use (days), to midlines, which typically extend from the antecubital fossa to the axilla, to what is probably the most common type of access for OPAT, the PICC. Most often, when patients requiring prolonged IV treatment are unable to receive a PICC line, a surgically implanted direct central access is used, typically via a cuffed implanted central venous catheter (CVC; brand names include Hickman, Groshong, and Broviac) or totally implanted CVCs with a subcutaneous reservoir accessed by percutaneous needle (e.g., Port-a-Cath).[72] Noncuffed central lines are not favored for home infusion because of a risk of dislodgement and infection. Formats that may be used to prepare drugs for IV infusion will depend on the drug, its stability, dilution requirements, and so forth.[14] Drugs may be prepared in syringes for relatively rapid infusion by a nurse or may be given by a syringe pump, in bags of IV fluid that may be gravity dripped (when the rate of infusion is not critical) or infused by rate-controlled devices, for instance, an elastomeric pump (nonelectronic pump) or an electronic pump. Programmable electronic pumps allow frequent or continuous infusions, although drug stability at room temperature must be taken into account. Some elastomeric devices and electronic pumps are sufficiently portable to allow full patient mobility.

LABORATORY MONITORING OF ANTIBIOTIC THERAPY

Laboratory monitoring of OPAT serves several important purposes: to assess for evidence of progressive resolution of the infection, to assess for changes in the patient's capacity to clear drugs, and to test for possible drug toxicity.[1] In addition to white blood cell count and differential, it may be helpful to regularly (e.g., weekly) track inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, over time to provide evidence for progressive resolution of some infections, for instance, endovascular and osteoarticular infections.[73,74] Changes in kidney function, and liver function for some drugs, independent of drug toxicity may alter the patient's ability to clear the drug and warrant dose adjustments. For instance, resolution of kidney injury after hospital discharge may warrant a dose increase, or a decline in creatinine clearance due to treatment of heart failure may warrant a reduction. The routine monitoring of a set of laboratory parameters to assess for drug toxicity is required for the safe administration of OPAT. Blood is typically obtained at least weekly for patients receiving OPAT, and the menu of tests are determined by the more common toxicities and route of clearance of the OPAT regimen components (Table 53.2). For most regimens (with drugs subject to renal clearance), weekly renal function (creatinine and blood urea nitrogen) and a complete blood count with differential to test for hematologic toxicity is appropriate. The differential is important to detect eosinophilia, suggesting hypersensitivity, as well as neutropenia related to direct bone marrow suppression or immune-mediated phenomena. Twice-weekly testing of renal function is appropriate for nephrotoxic agents, such as aminoglycosides. Drugs with significant hepatic toxicity and/or hepatic metabolism (e.g., nafcillin, oxacillin, ceftriaxone, meropenem, and ertapenem) should have a weekly liver panel (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin). Other chemistries may be relevant for particular agents, for instance, electrolytes for drugs with high electrolyte content (typically penicillins such as nafcillin) and creatinine phosphokinase (CPK) for daptomycin due to the muscle toxicity of that drug. Weekly TDM should be performed for vancomycin (trough level), and twice-weekly testing should be performed for aminoglycosides, with troughs for all indications and the addition of peak concentrations for enterococcal and staphylococcal synergy dosing. It is a considerable logistical challenge for OPAT programs to obtain timely blood draws and acquire, document, and communicate laboratory results on numerous OPAT patients, who are often cared for by a variety of home infusion vendors, visiting nurse organizations, and SNFs. The challenge is even greater for TDM, as blood draws have to be timed properly for doses of drugs. Optimally, documentation of test results should be in a cumulative format to reveal trends before more overt toxicity occurs.

TABLE 53.2 Suggested Laboratory Monitoring for Commonly Prescribed OPAT Antibiotics

DRUG	CBC/ DIFFERENTIAL	RENAL FUNCTION (BUN, CREATININE)	LIVER ENZYMES/LIVER FUNCTION TESTS	THERAPEUTIC DRUG MONITORING	OTHER
Vancomycin	Weekly	Weekly		Weekly trough	
Daptomycin	Weekly	Weekly			Weekly CPK
Linezolid	Weekly				
Antistaphylococcal penicillins	Weekly	Weekly	Weekly		
Ceftriaxone	Weekly	Weekly	Weekly		
Carbapenems	Weekly	Weekly	Weekly		
Other β-lactams	Weekly	Weekly			
Fluoroquinolones			Weekly		
Aminoglycosides	Weekly	Twice weekly		Weekly trough	Clinical monitoring for hearing and vestibular function at each visit

BUN, Blood urea nitrogen; *CBC,* complete blood count; *CPK,* creatine phosphokinase; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate; *OPAT,* outpatient parenteral antibiotic therapy.
Consider weekly ESR/CRP for patients with bone/joint infections and endocarditis or endovascular infections.
Modified from Tice AD, Rehm SJ, Dalovisio JR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. Clin Infect Dis. *2004;38:1651–1672.*

OPAT PROGRAM OUTCOME MEASUREMENT

The measurement of outcomes is an integral part of an OPAT program's responsibility to assess the safety and efficacy of care and to inform continuous process improvement efforts. At a minimum an assessment should include clinical outcome, response to treatment, and adverse events related to the OPAT course. This should include the course of antibiotic therapy, vascular access device, and need for readmission. The IDSA guidelines have recommended metrics used to assess the safety and efficacy of OPAT, including an assessment of clinical status, infection status, program outcome, antibiotic use, and vascular access complications.[1] The ability of OPAT programs to share data and allow comparison is limited by a lack of standard timing of outcome measurement and lack of a national database for benchmarking. The most robust studies of outcomes of OPAT include an assessment of cost savings and of financial analyses, which can be used to advocate for the programmatic support required for OPAT services. Additional studies assessing patient reported outcomes and experience are needed.

READMISSIONS

One of the major benefits of OPAT programs are a reduction in inpatient length of stay through facilitating ongoing IV antibiotic treatment in the non-inpatient setting. A principal balancing measure of increasing OPAT program use is unplanned hospitalization related to preventable complications of therapy. Unplanned readmissions are common; however, rates are widely variable across studies and range between 3% and 26%.[75–79] Common causes of readmission include worsening infection, ADR, and CVC-related complications. However, in published studies readmissions were frequently non-OPAT related (27%–57%), and thus a significant portion may be less likely to be preventable through enhanced OPAT services. This emphasizes the complex medical illnesses that many OPAT patients suffer.[75,76,80] Several studies have attempted to elucidate the predictors of unplanned hospitalization after OPAT initiation at the time of hospital discharge, to better tailor patient selection and needed patient and programmatic support. Common identified predictors include age and prior hospitalization in the previous 12 months. In addition, drug-resistant organisms, aminoglycoside use, increased planned OPAT duration, and lack of available laboratory monitoring have also been observed as risk factors.[75–78] The incidence of ADR varies widely based on the definition used[62,81] but accounts for up to 25% of readmission in the OPAT population.[76,82] OPAT-related ADRs often occur within the first 2 weeks of discharge from the hospital and frequently lead to need for dosing change, alteration in treatment, or early discontinuation of therapy.[63] The risk of ADRs stresses the importance of frequent safety laboratory monitoring, and guidelines based on expert opinion recommend weekly monitoring.[1] Nonavailability of recommended tests has been associated with an increased risk of readmission during OPAT.[78] Timely antibiotic changes based on responses to the development of ADRs may reduce the need for readmission.[83] Additional multicenter studies are required to elucidate the risk factors associated with readmission—related to patient factors as well as to the site of delivery of therapy—to inform optimal patient selection and future interventions for programmatic improvement.

COMPLICATIONS OF VASCULAR ACCESS DEVICES

The presence of a vascular device for delivery of outpatient IV antibiotics confers risk to the patient of complications that include occlusion, dislodgement, thrombosis, bleeding, and infection. The most common type of catheter used for OPAT is a PICC. However, some patients already have long-term venous access for existing comorbidities, such as malignancy, which require treatment with chemotherapy or for gastrointestinal tract malabsorption requiring total parenteral nutrition, for which a tunneled cuffed catheter (e.g., Hickman) or totally implanted catheter (e.g., Port-a-Cath) may be used. The incidence of complications related to vascular access devices range from 0.4 to 5 complications per 1000 OPAT days.[77,84,85] A recent retrospective cohort study from a large academic medical center found a rate of 4.29 complications per 1000 OPAT days, and catheter occlusion accounted for 53% of complications. In this cohort catheter-related thrombosis and infection were seen in less than 1% of OPAT courses. Complications were more common in PICCs compared with Hickman catheters or Port-a-Caths. Patients with a history of IDU had three times as many complications than those without this history. Of note, vascular access device-related complications were not associated with an increased risk of readmission.[84] A recent study found that midline catheters, commonly used for shorter courses (<4 weeks) of antibiotic therapy, were an independent risk factor for catheter-related complications. However, additional studies are needed to further investigate the impact of catheter type on complications.[54]

Given the risk of vascular access device-related complication, education regarding the signs and symptoms of this complication, such as redness, pain, swelling, drainage, or catheter migration, as well as regular assessment in the outpatient setting, is required. In addition, a structured approach to assessment and management of catheter occlusion is needed as an integral component of an OPAT program, to avoid emergency department visits or readmission.

FINANCIAL ANALYSIS OF OPAT PROGRAMS

The assessment of the full economic impact of OPAT requires estimates of both direct and indirect medical costs. Direct medical costs assessed for OPAT typically include expenses for inpatient care, physician visits, ancillary services, and medical supplies. Indirect costs include absenteeism from work, caregiver labor provided by family members or friends, and limited activity. However, indirect costs are challenging to ascertain for OPAT therapy because of a lack of validated quality-of-life instruments specific for infectious diseases and antibiotic therapy.[16]

The early OPAT literature focused largely on direct costs of health care, demonstrating significant reductions in cost, mainly driven by a reduction in inpatient bed-days.[5,7,16,86,87] However, this approach is limited as it does not take into account differences in incentive for reimbursement across the health care system. Additional factors to consider are the cost savings of the risk reduction of hospital-acquired infection by reducing length of stay,[88] as well as the costs of OPAT-related adverse events, such as readmission or ADRs.

PATIENT SATISFACTION

Available studies assessing patient satisfaction with OPAT therapy demonstrated that nearly all patients reported being satisfied overall with the program and had a willingness to participate in OPAT again, should the need arise.[89–94] Much of the benefit of enhanced patient satisfaction from OPAT stems from the patient's ability to self-administer antibiotic treatment, allowing increased responsibility for treatment and for autonomy with return home. It was common for patients to express fear about outpatient treatment, particularly the need for a vascular access device.[93] Thus adequate patient education and training, as well as visiting nursing support, are necessary components to enhance patient comfort with the process. Additional studies to assess patient satisfaction in OPAT and to benchmark programs would significantly benefit from use of a standard and validated questionnaire.

FUTURE OF OPAT

Current trends in health care that focus on cost-effective high-quality care, are associated with high rates of patient satisfaction, and focus on the aging population are likely to contribute to further growth in OPAT. The burgeoning opioid epidemic will continue to challenge OPAT to provide effective approaches to the care of to these complex patients.

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The complete reference list is available online at Expert Consult.

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54 Tables of Antiinfective Agent Pharmacology

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This chapter serves as a centralized source of pharmacologic information on antiinfective agents. The first table provides an index of all the tables that are included in this chapter (Table 54.1). Tables detailing generic and trade names for antiinfective agents are provided in an alphabetized sequence (Tables 54.2 and 54.3). Tables describing existing dosage formulations also are categorized by chemical or pharmacologic class (Tables 54.4 through 54.16). Available information regarding the usual doses in adults and children, pharmacokinetic (PK) information, and dose adjustment in renal impairment is provided according to chemical or pharmacologic class (Tables 54.17 through 54.30). Several antiinfective agents are substrates, inducers, and/or inhibitors of drug metabolism enzymes and transporters. Tables categorizing these potential mechanisms for drug-drug interactions as either the victim or the perpetrator drug are included (Tables 54.31 through 54.36).

DOSAGE GUIDELINES

The selection of an appropriate dose of an antiinfective agent is based on the site of infection, identity and known or presumed antibiotic susceptibility of the infecting organism, dose-related drug toxicity, and patient's ability to eliminate the drug (see Chapter 19). In general, dose selections from the higher end of the dosage range are recommended for severe, life-threatening infections (e.g., sepsis, meningitis). Known organisms with intermediate susceptibility (i.e., high minimal inhibitory concentration [MIC]) also should prompt the use of higher doses. More recent data with various types of antiinfectives suggest that higher doses or use of extended infusions of certain agents may increase the probability of response against some resistant organisms. This may be true with agents that concentrate at the infection site and that concentrate in the phagocytes that clear the organisms, such as quinolones and macrolides or azalides.

The lowest doses are typically used for urinary tract infections or when the isolated pathogen is extremely susceptible to the antiinfective. A sizable range in dosage intervals exists for some antiinfective agents, with longer durations between doses appropriate for less severe infections in which a critical threshold level in serum or other site of infection (e.g., central nervous system) is not mandatory, or the drug concentrates significantly at the site of infection (e.g., urine, bile). Lower doses may be appropriate when the patient has impairment in the function of eliminating organs (but not in all instances).

In the past, knowledge regarding the optimal dosage of an antiinfective agent was limited at the time that the drug was approved by regulatory bodies. However, with use of modern PK and pharmacodynamic (PD) principles, this has changed in many instances. Limited optimal dosing information may still be true in "special populations" including pediatric, geriatric, or pregnant patients; those with liver and kidney disease; and those who are obese. Patients treated with antiinfectives may also concurrently be receiving other medications, minerals, herbal supplements, and foods that may be associated with drug-drug or drug-food interactions. These interactions and resultant untoward effects may not be apparent during drug development. In addition, the pharmacokinetics of some drugs that are metabolized by drug metabolizing enzymes (DMEs) or acted on by transporters, or both, may change as the burden of the infectious agent decreases, with resultant decreases in cytokine production and the downregulation of DMEs and transporters. Hence, dosage recommendations for all agents will change as research into them evolves. To prevent dosage errors, the recommendations discussed in this chapter should be compared with the most recent scientific literature, package labeling, and other current reference sources.

DOSAGE ADJUSTMENT FOR RENAL IMPAIRMENT

Drug half-lives in adults with impaired renal function and changes related to dialysis procedures (hemodialysis, peritoneal dialysis) are summarized for the user. However, renal replacement therapy now encompasses multiple potential modalities, such as (1) high-flux hemodialysis; (2) nocturnal hemodialysis; (3) slow–low-efficiency hemodialysis; and (4) continuous renal replacement therapy, among others. Specific dosage guidance may not be available for these various dialysis modalities, and determination of dosage will require an educated decision based on the pharmacology of the antiinfective. To date, even learned nephrology groups cannot provide useful guidelines for drug dosages in patients receiving renal replacement therapy. Our recommendation is to consider the toxicity of an agent compared with the ability to treat the infection. In many situations the risk-benefit ratio is low, and therefore more aggressive administration often should be used. An alternative to the elongation of the interval between doses is a reduction of the daily dose given at the usual dosing interval. Antiinfective serum concentrations should be determined and patient-specific dosage adjustments made on the basis of these determinations, when appropriate and available. In the absence of therapeutic drug monitoring, a surrogate biomarker of this impaired drug clearance mechanism is used. Serum creatinine is the most commonly used clinical biomarker for estimation of renal function and drug dosage adjustment in patients with chronic kidney disease. The production of creatinine is regulated by numerous factors, such as diet composition and amount, patient muscle mass, liver function, age, and sex, which can bias the value of this biomarker. The elimination of creatinine is regulated by renal function and involves both glomerular filtration and tubular secretion. Creatinine clearance (CrCl) equates to an estimate of both elimination processes when serum creatinine is used. The Cockcroft-Gault equation is the most common equation that has been used to define CrCl and to inform the dose adjustments in the drug labels approved by regulatory bodies. Newer equations to estimate the glomerular filtration rate (GFR) have been developed to estimate kidney function in patients with chronic kidney disease (<60 mL/min/1.73 m^2). Specific estimates of GFR may be automatically reported with the measurement of serum creatinine in the clinical setting by using the Modification of Diet in Renal Disease (MDRD) equation.

The estimated CrCl and GFR calculations derived from these equations may yield comparable results, but it is important to remember that these values may not be interchangeable. Accordingly, this is a source of major controversy when applied to drug dosage calculation. A fundamental point of consideration is that patients with serious infections are likely to be in a dynamic physiologic state that can influence both the production and the elimination of serum creatinine. Calculation of GFR and CrCl with the aforementioned equations serves only as a point estimate for a patient under conditions of physiologic stability. These equations are not reliable in patients with changing renal function (increase or decrease), those with malnutrition (overestimation), elderly patients (overestimation), those with low serum creatinine (overestimation), and those with moderate-to-severe liver disease (overestimation).

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TABLE 54.1 Index of Tables Included in This Chapter

TABLE 54.2 Generic and Trade Names

GENERIC NAME	TRADE NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Abacavir	Epzicom,[a] Triumeq,[a] Trizivir,[a] Ziagen	Antiretroviral	NRTI
Acyclovir	Zovirax	Antiviral	Nucleoside analogue
Adefovir dipivoxil	Hepsera	Antiviral	Nucleotide reverse-transcriptase inhibitor
Albendazole	Albenza	Anthelmintic	Benzimidazole
Amantadine hydrochloride	Symmetrel	Antiviral	Adamantane
Amikacin sulfate	Amikin	Antibacterial	Aminoglycoside
Aminosalicylic acid	Paser	Antimycobacterial	Aminosalicylic acid
Amoxicillin	Amoxil, Prevpac[a]	Antibacterial	Penicillin
Amoxicillin-clavulanate potassium	Augmentin[a]	Antibacterial	Penicillin–β-lactamase inhibitor
Amphotericin B deoxycholate	Fungizone	Antifungal	Polyene
Amphotericin B lipid complex	Abelcet	Antifungal	Polyene
Amphotericin B liposomal	AmBisome	Antifungal	Polyene
Ampicillin sodium	Polycillin-N	Antibacterial	Penicillin
Ampicillin trihydrate	Polycillin	Antibacterial	Penicillin
Ampicillin-sulbactam	Unasyn[a]	Antibacterial	Penicillin–β-lactamase inhibitor
Anidulafungin	Eraxis	Antifungal	Echinocandin
Artemether-lumefantrine	Coartem[a]	Antimalarial	Artemisinin-aryl aminoalcohol
Artesunate	Plasmotrim (CDC[b])	Antimalarial	Artemisinin
Atazanavir	Evotaz,[a] Reyataz	Antiretroviral	Protease inhibitor
Atovaquone	Mepron, Malarone[a]	Antiprotozoal	Naphthoquinone
Atovaquone-proguanil	Malarone[a]	Antimalarial	Naphthoquinone-antifolate
Azithromycin	Zithromax	Antibacterial	Azalide
Aztreonam	Azactam	Antibacterial	Monobactam
Bacitracin	Baci-IM	Antibacterial	Polypeptide
Bedaquiline	Sirturo	Antimycobacterial	Diarylquinoline
Benznidazole	—	Antiprotozoal	Nitroimidazole
Besifloxacin	Besivance	Antibacterial	Fluoroquinolone
Butoconazole nitrate	Femstat 3	Antifungal	Azole
Capreomycin sulfate	Capastat Sulfate	Antimycobacterial	Aminoglycoside
Caspofungin	Cancidas	Antifungal	Echinocandin
Cefaclor	Ceclor	Antibacterial	Cephalosporin
Cefadroxil	Duricef	Antibacterial	Cephalosporin
Cefazolin sodium	Ancef	Antibacterial	Cephalosporin
Cefdinir	Omnicef	Antibacterial	Cephalosporin
Cefditoren pivoxil	Spectracef	Antibacterial	Cephalosporin
Cefepime	Maxipime	Antibacterial	Cephalosporin
Cefixime	Suprax	Antibacterial	Cephalosporin
Cefotaxime sodium	Claforan	Antibacterial	Cephalosporin
Cefotetan disodium	Cefotan	Antibacterial	Cephalosporin
Cefoxitin sodium	Mefoxitin	Antibacterial	Cephalosporin
Cefpodoxime proxetil	Vantin	Antibacterial	Cephalosporin
Cefprozil	Cefzil	Antibacterial	Cephalosporin
Ceftaroline	Teflaro	Antibacterial	Cephalosporin
Ceftazidime	Fortaz	Antibacterial	Cephalosporin
Ceftazidime-avibactam	Avycaz[a]	Antibacterial	Cephalosporin–β-lactamase inhibitor
Ceftibuten	Cedax	Antibacterial	Cephalosporin
Ceftolozane-tazobactam	Zerbaxa[a]	Antibacterial	Cephalosporin–β-lactamase inhibitor
Ceftriaxone sodium	Rocephin	Antibacterial	Cephalosporin

Continued

TABLE 54.2 Generic and Trade Names—cont'd

GENERIC NAME	TRADE NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Cefuroxime axetil	Ceftin	Antibacterial	Cephalosporin
Cefuroxime sodium	Zinacef	Antibacterial	Cephalosporin
Cephalexin	Keflex	Antibacterial	Cephalosporin
Chloramphenicol sodium succinate	Chloromycetin	Antibacterial	Chloramphenicol
Chloroquine phosphate	Aralen	Antimalarial	Quinoline
Ciclopirox	Loprox	Antifungal	Miscellaneous antifungals
Cidofovir	Vistide	Antiviral	Nucleotide analogue
Ciprofloxacin hydrochloride	Cipro	Antibacterial	Fluoroquinolone
Ciprofloxacin lactate	Cipro	Antibacterial	Fluoroquinolone
Clarithromycin	Biaxin, Prevpac[a]	Antibacterial	Macrolide
Clindamycin hydrochloride	Cleocin HCl	Antibacterial	Lincosamide
Clindamycin palmitate hydrochloride	Cleocin	Antibacterial	Lincosamide
Clindamycin phosphate	Cleocin Phosphate	Antibacterial	Lincosamide
Clioquinol-hydrocortisone	Ala-Quin	Antifungal	Miscellaneous antifungal-corticosteroid
Clofazimine	Lamprene	Antimycobacterial	Miscellaneous antimycobacterial
Clotrimazole	Lotrimin	Antifungal	Azole
Cobicistat	Evotaz,[a] Genvoya,[a] Prezcobix,[a] Stribild,[a] Tybost	Antiretroviral	CYP3A inhibitor
Colistimethate sodium	Coly-Mycin M	Antibacterial	Polymyxin
Cycloserine	Seromycin	Antimycobacterial	Miscellaneous antimycobacterial
Daclatasvir	Daklinza	Antiviral (HCV)	NS5A inhibitor
Dalbavancin	Dalvance	Antibacterial	Lipoglycopeptide
Dapsone	—	Antibacterial	Sulfone
Daptomycin	Cubicin	Antibacterial	Lipopeptide
Darunavir	Prezcobix,[a] Prezista	Antiretroviral	Protease inhibitor
Delafloxacin	Baxdela	Antibacterial	Fluoroquinolone
Delavirdine	Rescriptor	Antiretroviral	NNRTI
Demeclocycline hydrochloride	Declomycin	Antibacterial	Tetracycline
Dicloxacillin sodium	Pathocil	Antibacterial	Penicillin
Didanosine	Videx	Antiretroviral	NRTI
Diethylcarbamazine	Hetrazan, DEC (CDC[b])	Anthelmintic	Miscellaneous anthelmintic
Dolutegravir	Tivicay, Triumeq[a]	Antiretroviral	INSTI
Doripenem	Doribax	Antibacterial	Carbapenem
Doxycycline calcium	Vibramycin Calcium	Antibacterial	Tetracycline
Doxycycline hyclate	Vibramycin Hyclate	Antibacterial	Tetracycline
Doxycycline monohydrate	Monodox, Vibramycin Monohydrate	Antibacterial	Tetracycline
Econazole nitrate	Ecoza, Spectazole	Antifungal	Azole
Efavirenz	Atripla,[a] Sustiva	Antiretroviral	NNRTI
Efinaconazole	Jublia	Antifungal	Azole
Eflornithine	Ornidyl, DFMO (CDC[b])	Antiprotozoal	Miscellaneous antiprotozoal
Elbasvir-grazoprevir	Zepatier[a]	Antiviral (HCV)	NS5A inhibitor-NS3/4A inhibitor
Elvitegravir	Genvoya,[a] Stribild[a]	Antiretroviral	INSTI
Emtricitabine	Atripla,[a] Complera,[a] Descovy,[a] Emtriva, Genvoya,[a] Odefsey,[a] Stribild,[a] Truvada[a]	Antiretroviral	NRTI
Enfuvirtide	Fuzeon	Antiretroviral	Fusion inhibitor
Entecavir	Baraclude	Antiviral	NRTI
Ertapenem	Invanz	Antibacterial	Carbapenem
Erythromycin	ERYC, PCE	Antibacterial	Macrolide
Erythromycin ethylsuccinate	E.E.S., EryPed	Antibacterial	Macrolide
Erythromycin lactobionate	Erythrocin	Antibacterial	Macrolide

TABLE 54.2 Generic and Trade Names—cont'd

GENERIC NAME	TRADE NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Erythromycin stearate	Erythrocin Stearate	Antibacterial	Macrolide
Ethambutol hydrochloride	Myambutol	Antimycobacterial	Miscellaneous antimycobacterial
Ethionamide	Trecator	Antimycobacterial	Miscellaneous antimycobacterial
Etravirine	Intelence	Antiretroviral	NNRTI
Famciclovir	Famvir	Antiviral	Nucleoside analogue
Fidaxomicin	Dificid	Antibacterial	Macrolide
Finafloxacin	Xtoro	Antibacterial	Fluoroquinolone
Fluconazole	Diflucan	Antifungal	Azole
Flucytosine	Ancobon	Antifungal	Miscellaneous antifungal
Fosamprenavir	Lexiva	Antiretroviral	Protease inhibitor
Foscarnet sodium	Foscavir	Antiviral	Miscellaneous antiviral
Fosfomycin tromethamine	Monurol	Antibacterial	Phosphonic acid derivative
Ganciclovir sodium	Cytovene	Antiviral	Nucleoside analogue
Gatifloxacin	Zymar	Antibacterial	Fluoroquinolone
Gemifloxacin	Factive	Antibacterial	Fluoroquinolone
Gentamicin sulfate	Garamycin	Antibacterial	Aminoglycoside
Glecaprevir-pibrentasvir	Mavyret[a]	Antiviral (HCV)	NS3/4A inhibitor–NS5A inhibitor
Gentian violet	—	Antifungal	Miscellaneous antifungal
Griseofulvin	Grisactin, Gris-PEG	Antifungal	Miscellaneous antifungal
Hydroxychloroquine sulfate	Plaquenil	Antimalarial	Quinoline
Imipenem-cilastatin	Primaxin[a]	Antibacterial	Carbapenem–dihydropeptidase inhibitor
Indinavir	Crixivan	Antiretroviral	Protease inhibitor
Iodoquinol	Aloquin	Antiprotozoal	Hydroxyquinoline
Isavuconazonium sulfate	Cresemba	Antifungal	Azole
Isoniazid	Rimifon, Rifamate,[a] Rifater[a]	Antimycobacterial	Miscellaneous antimycobacterial
Itraconazole	Sporanox	Antifungal	Azole
Ivermectin	Sklice, Soolantra, Stromectol	Anthelmintic	Avermectin
Kanamycin sulfate	Kantrex	Antibacterial	Aminoglycoside
Ketoconazole	Nizoral	Antifungal	Azole
Lamivudine	Combivir,[a] Epivir, Epivir-HBV, Epzicom,[a] Triumeq,[a] Trizivir[a]	Antiretroviral	NRTI
Levofloxacin	Levaquin	Antibacterial	Fluoroquinolone
Lincomycin hydrochloride	Lincocin	Antibacterial	Lincosamide
Linezolid	Zyvox	Antibacterial	Oxazolidinone
Lopinavir-ritonavir	Kaletra[a]	Antiretroviral	Protease inhibitor, CYP3A inhibitor
Luliconazole	Luzu	Antifungal	Azole
Mafenide	Sulfamylon	Antibacterial	Sulfonamide
Maraviroc	Selzentry	Antiretroviral	CCR5 receptor antagonist
Mebendazole	Vermox	Anthelmintic	Benzimidazole
Mefloquine	Lariam	Antimalarial	Miscellaneous antimalarial
Melarsoprol	Arsobal (CDC[b])	Antiprotozoal	Arsenical
Meropenem	Merrem	Antibacterial	Carbapenem
Meropenem-vaborbactam	Vabomere	Antibacterial	Carbapenem–β-lactamase inhibitor
Methenamine hippurate	Hiprex, Urex	Antibacterial	Urinary antiinfective
Methenamine mandelate	—	Antibacterial	Urinary antiinfective
Metronidazole	Flagyl, Pylera[a]	Antibacterial	Nitroimidazole
Micafungin	Mycamine	Antifungal	Echinocandin

Continued

TABLE 54.2 Generic and Trade Names—cont'd

GENERIC NAME	TRADE NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Miconazole	Monistat	Antifungal	Azole
Miltefosine	Impavido	Antiprotozoal	Alkylphosphocholine
Minocycline hydrochloride	Minocin	Antibacterial	Tetracycline
Moxifloxacin	Avelox	Antibacterial	Fluoroquinolone
Mupirocin	Bactroban	Antibacterial	Pseudomonic acid
Nafcillin sodium	Unipen	Antibacterial	Penicillin
Naftifine	Naftin	Antifungal	Allyamine
Natamycin	Natacyn	Antifungal	Polyene
Nelfinavir	Viracept	Antiretroviral	Protease inhibitor
Neomycin sulfate	Mycifradin, Neosporin[a]	Antibacterial	Aminoglycoside
Nevirapine	Viramune	Antiretroviral	NNRTI
Nifurtimox	Lampit (CDC[b])	Antiprotozoal	Nitrofuran
Nitazoxanide	Alinia	Antiprotozoal	Thiazolide
Nitrofurantoin	Furadantin, Macrobid, Macrodantin	Antibacterial	Nitrofuran
Nystatin	Mycostatin, Nilstat	Antifungal	Polyene
Ofloxacin	Floxin	Antibacterial	Fluoroquinolone
Ombitasvir-paritaprevir-ritonavir	Technivie[a]	Antiviral (HCV)	NS5A inhibitor–NS3/4A inhibitor–CYP3A inhibitor
Ombitasvir-paritaprevir-ritonavir-dasabuvir sodium	Viekira Pak,[a] Viekira XR[a]	Antiviral (HCV)	NS5A inhibitor–NS3/4A inhibitor–CYP3A inhibitor–NS5B inihibitor
Oritavancin diphosphate	Orbactiv	Antibacterial	Lipoglycopeptide
Oseltamivir phosphate	Tamiflu	Antiviral	Neuraminidase inhibitor
Oxacillin sodium	Bactocill	Antibacterial	Penicillin
Oxiconazole nitrate	Oxistat	Antifungal	Azole
Oxytetracycline hydrochloride	Terramycin	Antibacterial	Tetracycline
Paromomycin sulfate	Humatin	Antiprotozoal	Aminoglycoside
Penciclovir	Denavir	Antiviral	Nucleoside analogue
Penicillin G benzathine	Bicillin, Bicillin C-R,[a] Bicillin L-A	Antibacterial	Penicillin
Penicillin G potassium	Pfizerpen	Antibacterial	Penicillin
Penicillin G procaine	Bicillin C-R,[a] Pfizerpen-AS	Antibacterial	Penicillin
Penicillin G sodium	—	Antibacterial	Penicillin
Penicillin V potassium	Pfizerpen VK	Antibacterial	Penicillin
Pentamidine isethionate	NebuPent, Pentam	Antiprotozoal	Miscellaneous antiprotozoal
Peramivir	Rapivab	Antiviral	Neuraminidase inhibitor
Piperacillin-tazobactam	Zosyn[a]	Antibacterial	Penicillin–β-lactamase inhibitor
Pivmecillinam[c]	Selexid	Antibacterial	Penicillin
Polymyxin B sulfate	Aerosporin, Neosporin[a]	Antibacterial	Polymyxin
Posaconazole	Noxafil	Antifungal	Azole
Praziquantel	Biltricide	Anthelmintic	Miscellaneous antihelmintic
Primaquine phosphate	—	Antimalarial	Quinoline
Pyrantel pamoate	Pin-X, Reese's Pinworm Medicine	Anthelmintic	Miscellaneous anthelmintic
Pyrazinamide	Rifater[a]	Antimycobacterial	Miscellaneous antimycobacterial
Pyrimethamine	Daraprim	Antiprotozoal	Miscellaneous antiprotozoal
Quinine sulfate	Qualaquin	Antimalarial	Quinoline
Quinupristin-dalfopristin	Synercid[a]	Antibacterial	Streptogramins
Raltegravir	Isentress	Antiretroviral	INSTI
Retapamulin	Altabax	Antibacterial	Pleuromutilin
Ribavirin	Copegus, Rebetol, Virazole	Antiviral	Nucleoside analogue

TABLE 54.2 Generic and Trade Names—cont'd

GENERIC NAME	TRADE NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Rifabutin	Mycobutin	Antimycobacterial	Rifamycin
Rifampin	Rifadin, Rifamate,[a] Rifater[a]	Antimycobacterial	Rifamycin
Rifapentine	Priftin	Antimycobacterial	Rifamycin
Rifaximin	Xifaxan	Antibacterial	Rifamycin
Rilpivirine	Complera,[a] Edurant, Odefsey[a]	Antiretroviral	NNRTI
Rimantadine	Flumadine	Antiviral	Adamantane
Ritonavir	Kaletra,[a] Norvir, Technivie,[a] Viekira Pak,[a] Viekira XR[a]	Antiretroviral	Protease inhibitor–CYP3A inhibitor
Saquinavir	Invirase	Antiretroviral	Protease inhibitor
Secnidazole	Solosec	Antibacterial	Nitroimidazole
Sertaconazole	Ertaczo	Antifungal	Azole
Silver sulfadiazine	Silvadene	Antibacterial	Sulfonamide
Simeprevir	Olysio	Antiviral (HCV)	NS3/4A inhibitor
Sodium stibogluconate	Pentostam (CDC[b])	Antiprotozoal	Antimonial
Sodium thiosulfate	Versiclear	Antifungal	Miscellaneous antifungal
Sofosbuvir	Sovaldi	Antiviral (HCV)	NS5B inhibitor
Sofosbuvir-ledipasvir	Harvoni	Antiviral (HCV)	NS5B inhibitor–NS5A inhibitor
Sofosbuvir-velpatasvir	Epclusa[a]	Antiviral (HCV)	NS5B inhibitor–NS5A inhibitor
Sofosbuvir-velpatasvir-voxilaprevir	Vosevi	Antiviral (HCV)	NS5B inhibitor–NS5A inhibitor–NS3/4A inhibitor
Stavudine	Zerit	Antiretroviral	NRTI
Streptomycin sulfate	—	Antibacterial	Aminoglycoside
Sulconazole	Exelderm	Antifungal	Azole
Sulfacetamide	—	Antibacterial	Sulfonamide
Sulfadiazine	—	Antibacterial	Sulfonamide
Sulfanilamide	AVC	Antibacterial	Sulfonamide
Suramin	Germanin (CDC[b])	Antiprotozoal	Miscellaneous antiprotozoal
Tavaborole	Kerydin	Antifungal	Oxaborole
Tedizolid	Sivextro	Antibacterial	Oxazolidinone
Telavancin	Vibativ	Antibacterial	Lipoglycopeptide
Telbivudine	Tyzeka	Antiviral	Nucleoside analogue
Tenofovir alafenamide fumarate	Descovy,[a] Genvoya,[a] Odefsey,[a] Vemlidy	Antiretroviral	NRTI
Tenofovir disoproxil fumarate	Atripla,[a] Complera,[a] Stribild,[a] Truvada,[a] Viread	Antiretroviral	NRTI
Terbinafine	Lamisil	Antifungal	Allylamine
Terconazole	Terazol	Antifungal	Azole
Tetracycline hydrochloride	Achromycin, Pylera[a]	Antibacterial	Tetracycline
Tigecycline	Tygacil	Antibacterial	Glycylcycline
Tinidazole	Tindamax	Antiprotozoal	Nitroimidazole
Tioconazole	Vagistat-1	Antifungal	Azole
Tipranavir	Aptivus	Antiretroviral	Protease inhibitor
Tobramycin sulfate	Nebcin	Antibacterial	Aminoglycoside
Tobramycin inhalation solution	Tobi	Antibacterial	Aminoglycoside
Tolnaftate	Tinactin	Antifungal	Miscellaneous antifungal
Trifluridine	Viroptic	Antiviral	Nucleoside analogue
Trimethoprim	Bactrim,[a] Primsol, Septra[a]	Antibacterial	Antifolate
Trimethoprim-sulfamethoxazole	Bactrim,[a] Septra[a]	Antibacterial	Antifolate-sulfonamide
Undecylenic acid	Fungi-Nail	Antifungal	Miscellaneous antifungal
Valacyclovir	Valtrex	Antiviral	Nucleoside analogue

Continued

TABLE 54.2 Generic and Trade Names—cont'd

GENERIC NAME	TRADE NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Valganciclovir	Valcyte	Antiviral	Nucleoside analogue
Vancomycin hydrochloride	Vancocin	Antibacterial	Glycopeptide
Voriconazole	Vfend	Antifungal	Azole
Zanamivir	Relenza	Antiviral	Neuraminidase inhibitor
Zidovudine	Combivir,[a] Retrovir, Trizivir[a]	Antiretroviral	NRTI

[a]A combination product.
[b]US Centers for Disease Control and Prevention (CDC) Drug Service for distribution to US clinicians.
[c]Not available in the United States.
HBV, Hepatitis B virus; *HCV,* hepatitis C virus; *INSTI,* integrase strand transfer inhibitor; *NNRTI,* nonnucleoside reverse-transcriptase inhibitor; *NRTI,* nucleoside reverse-transcriptase inhibitor.

TABLE 54.3 Trade and Generic Names

TRADE NAME	GENERIC NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Abelcet	Amphotericin B lipid complex	Antifungal	Antifungal
Aerosporin	Polymyxin B sulfate	Antibacterial	Polymyxin
Ala-Quin[a]	Clioquinol-hydrocortisone	Antifungal	Miscellaneous antifungal-corticosteroid
Albenza	Albendazole	Anthelmintic	Benzimidazole
Alinia	Nitazoxanide	Antiprotozoal	Thiazolide
Aloquin	Iodoquinol	Antiprotozoal	Hydroxyquinoline
Altabax	Retapamulin	Antibacterial	Pleuromutilin
AmBisome	Amphotericin B liposomal	Antifungal	Polyene
Amikin	Amikacin sulfate	Antibacterial	Aminoglycoside
Amoxil	Amoxicillin	Antibacterial	Penicillin
Ancef	Cefazolin sodium	Antibacterial	Cephalosporin
Ancobon	Flucytosine	Antifungal	Miscellaneous antifungal
Aptivus	Tipranavir	Antiretroviral	Protease inhibitor
Aralen	Chloroquine phosphate	Antimalarial	Quinoline
Arsobal (CDC[b])	Melarsoprol	Antiprotozoal	Arsenical
Atripla[a]	Efavirenz–tenofovir disoproxil fumarate–emtricitabine	Antiretroviral	NNRT-NRTI-NRTI
Augmentin[a]	Amoxicillin-clavulanate potassium	Antibacterial	Penicillin–β-lactamase inhibitor
AVC	Sulfanilamide	Antibacterial	Sulfonamide
Avelox	Moxifloxacin	Antibacterial	Fluoroquinolone
Avycaz[a]	Ceftazidime-avibactam	Antibacterial	Cephalosporin–β-lactamase inhibitor
Azactam	Aztreonam	Antibacterial	Monobactam
Baci-IM	Bacitracin	Antibacterial	Polypeptide
Bactocill	Oxacillin sodium	Antibacterial	Penicillin
Bactrim[a]	Trimethoprim-sulfamethoxazole	Antibacterial	Antifolate-sulfonamide
Bactroban	Mupirocin	Antibacterial	Pseudomonic acid
Baraclude	Entecavir	Antiviral	NRTI
Baxdela	Delafloxacin	Antibacterial	Fluoroquinolone
Biaxin	Clarithromycin	Antibacterial	Macrolide
Bicillin C-R[a]	Penicillin G procaine–penicillin G benzathine	Antibacterial	Penicillin
Bicillin L-A	Penicillin G benzathine	Antibacterial	Penicillin
Biltricide	Praziquantel	Anthelmintic	Miscellaneous anthelmintic
Cancidas	Caspofungin	Antifungal	Echinocandin
Capastat Sulfate	Capreomycin sulfate	Antimycobacterial	Aminoglycoside
Ceclor	Cefaclor	Antibacterial	Cephalosporin

TABLE 54.3 Trade and Generic Names—cont'd

TRADE NAME	GENERIC NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Cedax	Ceftibuten	Antibacterial	Cephalosporin
Cefotan	Cefotetan disodium	Antibacterial	Cephalosporin
Ceftin	Cefuroxime axetil	Antibacterial	Cephalosporin
Cefzil	Cefprozil	Antibacterial	Cephalosporin
Chloromycetin	Chloramphenicol sodium succinate	Antibacterial	Chloramphenicol
Cipro	Ciprofloxacin hydrochloride (oral formulation), Ciprofloxacin lactate (IV formulation)	Antibacterial	Fluoroquinolone
Claforan	Cefotaxime sodium	Antibacterial	Cephalosporin
Cleocin	Clindamycin palmitate hydrochloride (pediatric formulation)	Antibacterial	Lincosamide
Cleocin HCl	Clindamycin hydrochloride	Antibacterial	Lincosamide
Cleocin Phosphate	Clindamycin phosphate	Antibacterial	Lincosamide
Coartem[a]	Artemether-lumefantrine	Antimalarial	Artemisinin-aryl aminoalcohol
Coly-Mycin M	Colistimethate sodium	Antibacterial	Polymyxin
Combivir[a]	Lamivudine-zidovudine	Antiretroviral	NRTI-NRTI
Complera[a]	Rilpivirine–tenofovir disoproxil fumarate–emtricitabine	Antiretroviral	NNRTI-NRTI-NRTI
Copegus	Ribavirin	Antiviral	Nucleoside analogue
Cresemba	Isavuconazonium sulfate	Antifungal	Azole
Crixivan	Indinavir	Antiretroviral	Protease inhibitor
Cubicin	Daptomycin	Antibacterial	Lipopeptide
Cytovene	Ganciclovir sodium	Antiviral	Nucleoside analogue
Daklinza	Daclatasvir	Antiviral (HCV)	NS5A inhibitor
Dalvance	Dalbavancin	Antibacterial	Lipoglycopeptide
Daraprim	Pyrimethamine	Antiprotozoal	Miscellaneous antiprotozoal
DEC (CDC[b])	Diethylcarbamazine	Anthelmintic	Miscellaneous anthelmintic
Declomycin	Demeclocycline hydrochloride	Antibacterial	Tetracycline
Denavir	Penciclovir	Antiviral	Nucleoside analogue
Denvar	Cefixime	Antibacterial	Cephalosporin
Descovy	Tenofovir alafenamide fumarate	Antiretroviral	NRTI
DFMO (CDC[b])	Eflornithine	Antiprotozoal	Miscellaneous antiprotozoal
Dificid	Fidaxomycin	Antibacterial	Macrolide
Diflucan	Fluconazole	Antifungal	Azole
Doribax	Doripenem	Antibacterial	Carbapenem
Duricef	Cefadroxil	Antibacterial	Cephalosporin
Ecoza	Econazole nitrate	Antifungal	Azole
Edurant	Rilpivirine	Antiretroviral	NNRTI
E.E.S.	Erythromycin ethylsuccinate	Antibacterial	Macrolide
Emtriva	Emtricitabine	Antiretroviral	NRTI
Epclusa[a]	Sofosbuvir-velpatasvir	Antiviral (HCV)	NS5B inhibitor–NS5A inhibitor
Epivir, Epivir-HBV	Lamivudine	Antiretroviral	NRTI
Epzicom[a]	Abacavir-lamivudine	Antiretroviral	NRTI-NRTI
Eraxis	Anidulafungin	Antifungal	Echinocandin
Ertaczo	Sertaconazole	Antifungal	Azole
ERYC	Erythromycin	Antibacterial	Macrolide
EryPed	Erythromycin ethylsuccinate	Antibacterial	Macrolide
Erythrocin	Erythromycin lactobionate	Antibacterial	Macrolide
Erythrocin Stearate	Erythromycin stearate	Antibacterial	Macrolide
Evotaz[a]	Atazanavir-cobicistat	Antiretroviral	Protease inhibitor–CYP3A inhibitor

Continued

TABLE 54.3 Trade and Generic Names—cont'd

TRADE NAME	GENERIC NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Exelderm	Sulconazole	Antifungal	Azole
Factive	Gemifloxacin	Antibacterial	Fluoroquinolone
Famvir	Famciclovir	Antiviral	Nucleoside analogue
Femstat 3	Butoconazole nitrate	Antifungal	Azole
Flagyl	Metronidazole	Antibacterial	Nitroimidazole
Floxin	Ofloxacin	Antibacterial	Fluoroquinolone
Flumadine	Rimantadine	Antiviral	Adamantane
Fortaz	Ceftazidime	Antibacterial	Cephalosporin
Foscavir	Foscarnet sodium	Antiviral	Miscellaneous antiviral
Fungi-Nail	Undecylenic acid	Antifungal	Miscellaneous antifungal
Fungizone	Amphotericin B	Antifungal	Polyene
Furadantin	Nitrofurantoin	Antibacterial	Nitrofuran
Fuzeon	Enfuvirtide	Antiretroviral	Fusion inhibitor
Garamycin	Gentamicin	Antibacterial	Aminoglycoside
Genvoya[a]	Elvitegravir–cobicistat–tenofovir alafenamide fumarate–emtricitabine	Antiretroviral	INSTI–CYP3A inhibitor–NRTI–NRTI
Germanin (CDC[b])	Suramin	Antiprotozoal	Miscellaneous antiprotozoal
Grisactin	Griseofulvin	Antifungal	Miscellaneous antifungal
Gris-PEG	Griseofulvin	Antifungal	Miscellaneous antifungal
Harvoni[a]	Sofosbuvir-ledipasvir	Antiviral (HCV)	HS5A inhibitor–NS5A inhibitor
Hepsera	Adefovir dipivoxil	Antiviral	Nucleotide reverse-transcriptase inhibitor
Hetrazan (CDC[b])	Diethylcarbamazine	Anthelmintic	Miscellaneous anthelmintic
Hiprex	Methenamine hippurate	Antibacterial	Urinary antiinfective
Humatin	Paromomycin sulfate	Antiprotozoal	Aminoglycoside
Impavido	Miltefosine	Antiprotozoal	Alkylphosphocholine
Intelence	Etravirine	Antiretroviral	NNRTI
Invanz	Ertapenem	Antibacterial	Carbapenem
Invirase	Saquinavir	Antiretroviral	Protease inhibitor
Isentress	Raltegravir	Antiretroviral	INSTI
Jublia	Efinaconazole	Antifungal	Azole
Kaletra[a]	Lopinavir-ritonavir	Antiretroviral	Protease inhibitor–CYP3A inhibitor
Kantrex	Kanamycin sulfate	Antibacterial	Aminoglycoside
Keflex	Cephalexin	Antibacterial	Cephalosporin
Kerydin	Tavaborole	Antifungal	Oxaborole
Lamisil	Terbinafine	Antifungal	Allylamine
Lampit (CDC[b])	Nifurtimox	Antiprotozoal	Nitrofuran
Lamprene	Clofazimine	Antimycobacterial	Miscellaneous antimycobacterial
Lariam	Mefloquine	Antimalarial	Miscellaneous antimalarial
Levaquin	Levofloxacin	Antibacterial	Fluoroquinolone
Lexiva	Fosamprenavir	Antiretroviral	Protease inhibitor
Lincocin	Lincomycin hydrochloride	Antibacterial	Lincosamide
Loprox	Ciclopirox	Antifungal	Miscellaneous antifungal
Lotrimin	Clotrimazole	Antifungal	Azole
Luzu	Luliconazole	Antifungal	Azole
Macrobid	Nitrofurantoin	Antibacterial	Nitrofuran
Macrodantin	Nitrofurantoin	Antibacterial	Nitrofuran
Malarone[a]	Atovaquone-proguanil	Antimalarial	Naphthoquinone-antifolate
Mavyret[a]	Glecaprevir-pibrentasvir	Antiviral (HCV)	NS3/4A inhibitor–NS5A inhibitor
Maxipime	Cefepime	Antibacterial	Cephalosporin

TABLE 54.3 Trade and Generic Names—cont'd

TRADE NAME	GENERIC NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Mefoxitin	Cefoxitin	Antibacterial	Cephalosporin
Mepron	Atovaquone	Antiprotozoal	Naphthoquinone
Merrem	Meropenem	Antibacterial	Carbapenem
Minocin	Minocycline hydrochloride	Antibacterial	Tetracycline
Monistat	Miconazole	Antifungal	Azole
Monodox	Doxycycline monohydrate	Antibacterial	Tetracycline
Monurol	Fosfomycin tromethamine	Antibacterial	Phosphonic acid derivative
Myambutol	Ethambutol hydrochloride	Antimycobacterial	Miscellaneous antimycobacterial
Mycamine	Micafungin	Antifungal	Echinocandin
Mycifradin	Neomycin sulfate	Antibacterial	Aminoglycoside
Mycobutin	Rifabutin	Antimycobacterial	Rifamycin
Mycostatin	Nystatin	Antifungal	Polyene
Naftin	Naftifine	Antifungal	Allyamine
Natacyn	Natamycin	Antifungal	Polyene
Nebcin	Tobramycin sulfate	Antibacterial	Aminoglycoside
NebuPent	Pentamidine isethionate	Antiprotozoal	Miscellaneous antiprotozoal
Neosporin[a]	Neomycin–polymyxin B		Aminoglycoside-polymyxin
Nilstat	Nystatin	Antifungal	Polyene
Nizoral	Ketoconazole	Antifungal	Azole
Norvir	Ritonavir	Antiretroviral	Protease inhibitor–CYP3A inhibitor
Noxafil	Posaconazole	Antifungal	Azole
Odefsey[a]	Rilpivirine–tenofovir alafenamide fumarate–emtricitabine	Antiretroviral	NNRTI-NRTI-NRTI
Olysio	Simeprevir	Antiviral (HCV)	NS3/4A inhibitor
Omnicef	Cefdinir	Antibacterial	Cephalosporin
Orbactiv	Oritavancin diphosphate	Antibacterial	Lipoglycopeptide
Ornidyl (CDC[b])	Eflornithine	Antiprotozoal	Miscellaneous antiprotozoal
Oxistat	Oxiconazole nitrate	Antifungal	Azole
Paser	Aminosalicylic acid	Antimycobacterial	Aminosalicylic acid
Pathocil	Dicloxacillin sodium	Antibacterial	Penicillin
PCE	Erythromycin	Antibacterial	Macrolide
Pentam	Pentamidine isethionate	Antiprotozoal	Miscellaneous antiprotozoal
Pentostam (CDC[b])	Sodium stibogluconate	Antiprotozoal	Antimonial
Pfizerpen	Penicillin G potassium	Antibacterial	Penicillin
Pfizerpen VK	Penicillin V potassium	Antibacterial	Penicillin
Pfizerpen-AS	Penicillin G procaine	Antibacterial	Penicillin
Pin-X	Pyrantel pamoate	Anthelmintic	Miscellaneous anthelmintic
Plaquenil	Hydroxychloroquine sulfate	Antimalarial	Quinoline
Plasmotrim (CDC[b])	Artesunate	Antimalarial	Artemisinin
Polycillin	Ampicillin trihydrate	Antibacterial	Penicillin
Polycillin-N	Ampicillin sodium	Antibacterial	Penicillin
Prevpac[a]	Amoxicillin-clarithromycin-lansoprazole	Antibacterial (*Helicobacter pylori*)	Penicillin–macrolide–proton pump inhibitor
Prezcobix[a]	Darunavir-cobicistat	Antiretroviral	Protease inhibitor–CYP3A inhibitor
Prezista	Darunavir	Antiretroviral	Protease inhibitor
Priftin	Rifapentine	Antimycobacterial	Rifamycin
Primaxin[a]	Imipenem-cilastatin	Antibacterial	Carbapenem–dihydropeptidase inhibitor
Primsol	Trimethoprim	Antibacterial	Antifolate
Pylera[a]	Bismuth subcitrate–metronidazole–tetracycline	Antibacterial (*H. pylori*)	Antidiarrheal-nitroimidazole-tetracycline
Qualaquin	Quinine sulfate	Antimalarial	Quinoline

Continued

TABLE 54.3 Trade and Generic Names—cont'd

TRADE NAME	GENERIC NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Rapivab	Peramivir	Antiviral	Neuraminidase inhibitor
Rebetol	Ribavirin	Antiviral	Nucleoside analogue
Reese's Pinworm Medicine	Pyrantel pamoate	Anthelmintic	Miscellaneous anthelmintic
Relenza	Zanamivir	Antiviral	Neuraminidase inhibitor
Rescriptor	Delavirdine	Antiretroviral	NNRTI
Retrovir	Zidovudine	Antiretroviral	NRTI
Reyataz	Atazanavir	Antiretroviral	Protease inhibitor
Rifadin	Rifampin	Antimycobacterial	Rifamycin
Rifamate[a]	Rifampin-isoniazid	Antimycobacterial	Rifamycin–miscellaneous antimycobacterial
Rifater[a]	Rifampin-isoniazid-pyrazinamide	Antimycobacterial	Rifamycin–miscellaneous antimycobacterial
Rimifon	Isoniazid	Antimycobacterial	Miscellaneous antimycobacterial
Rocephin	Ceftriaxone sodium	Antibacterial	Cephalosporin
Selexid[c]	Pivmecillinam	Antibacterial	Penicillin
Selzentry	Maraviroc	Antiretroviral	CCR5 receptor antagonist
Septra[a]	Trimethoprim-sulfamethoxazole	Antibacterial	Antifolate-sulfonamide
Seromycin	Cycloserine	Antimycobacterial	Miscellaneous antimycobacterial
Silvadene	Silver sulfadiazine	Antibacterial	Sulfonamide
Sirturo	Bedaquiline	Antimycobacterial	Diarylquinoline
Sivextro	Tedizolid	Antibacterial	Oxazolidinone
Sklice	Ivermectin	Anthelmintic	Avermectin
Solosec	Secnidazole	Antibacterial	Nitroimidazole
Soolantra	Ivermectin	Anthelmintic	Avermectin
Sovaldi	Sofosbuvir	Antiviral (HCV)	NS5B inhibitor
Spectazole	Econazole nitrate	Antifungal	Azole
Spectracef	Cefditoren pivoxil	Antibacterial	Cephalosporin
Sporanox	Itraconazole	Antifungal	Azole
Stribild[a]	Elvitegravir–cobicistat–emtricitabine–tenofovir disoproxil fumarate	Antiretroviral	INSTI–CYP3A inhibitor–NRTI-NRTI
Stromectol	Ivermectin	Anthelmintic	Avermectin
Sulfamylon	Mafenide	Antibacterial	Sulfonamide
Suprax	Cefixime	Antibacterial	Cephalosporin
Sustiva	Efavirenz	Antiretroviral	NNRTI
Symmetrel	Amantadine hydrochloride	Antiviral	Adamantane
Synercid[a]	Quinupristin-dalfopristin	Antibacterial	Streptogramins
Tamiflu	Oseltamivir	Antiviral	Neuraminidase inhibitor
Technivie[a]	Ombitasvir-paritaprevir-ritonavir	Antiviral (HCV)	NS5A inhibitor–NS3/4A inhibitor–CYP3A inhibitor
Teflaro	Ceftaroline	Antibacterial	Cephalosporin
Terazol	Terconazole	Antifungal	Azole
Tindamax	Tinidazole	Antiprotozoal	Nitroimidazole
Tivicay	Dolutegravir	Antiretroviral	INSTI
Tobi	Tobramycin inhalation solution	Antibacterial	Aminoglycoside
Trecator	Ethionamide	Antimycobacterial	Miscellaneous antimycobacterial
Triumeq[a]	Dolutegravir-abacavir-lamivudine	Antiretroviral	INST-NRTI-NRTI
Trizivir[a]	Abacavir-lamivudine-zidovudine	Antiretroviral	NRTI-NRTI-NRTI
Truvada[a]	Emtricitabine–tenofovir disoproxil fumarate	Antiretroviral	NRTI
Tybost	Cobicistat	Antiretroviral	CYP3A inhibitor
Tygacil	Tigecycline	Antibacterial	Glycylcycline
Tyzeka	Telbivudine	Antiviral	Nucleoside analogue
Unasyn[a]	Ampicillin-sulbactam	Antibacterial	Penicillin–β-lactamase inhibitor

TABLE 54.3 Trade and Generic Names—cont'd

TRADE NAME	GENERIC NAME	PATHOGEN CLASS	PHARMACOLOGIC CLASS
Unipen	Nafcillin sodium	Antibacterial	Penicillin
Urex	Methenamine hippurate	Antibacterial	Urinary antiinfective
Vabomere[a]	Meropenem-vaborbactam	Antibacterial	Carbapenem–β-lactamase inhibitor
Valcyte	Valganciclovir	Antiviral	Nucleoside analogue
Valtrex	Valacyclovir	Antiviral	Nucleoside analogue
Vancocin	Vancomycin hydrochloride	Antibacterial	Glycopeptide
Vantin	Cefpodoxime proxetil	Antibacterial	Cephalosporin
Vemlidy	Tenofovir alafenamide fumarate	Antiretroviral	NRTI
Vermox	Mebendazole	Anthelmintic	Benzimidazole
Versiclear	Sodium thiosulfate	Antifungal	Miscellaneous antifungal
Vfend	Voriconazole	Antifungal	Azole
Vibativ	Televancin	Antibacterial	Lipoglycopeptide
Vibramycin Calcium	Doxycycline calcium	Antibacterial	Tetracycline
Vibramycin Hyclate	Doxycycline hyclate	Antibacterial	Tetracycline
Vibramycin Monohydrate	Doxycycline monohydrate	Antibacterial	Tetracycline
Videx	Didanosine	Antiretroviral	NRTI
Viekira Pak,[a] Viekira XR[a]	Ombitasvir–paritaprevir-ritonavir–dasabuvir sodium	Antiviral (HCV)	NS5A inhibitor–NS3/4A inhibitor–NS5B inhibitor–CYP3A inhibitor
Viracept	Nelfinavir	Antiretroviral	Protease inhibitor
Viramune	Nevirapine	Antiretroviral	NNRTI
Virazole	Ribavirin (inhalation)	Antiviral	Nucleoside analogue
Viread	Tenofovir disoproxil fumarate	Antiretroviral	NRTI
Viroptic	Trifluridine	Antiviral	Nucleoside analogue
Vistide	Cidofovir	Antiviral	Nuceoside analogue
Vosevi[a]	Sofosbuvir-velpatasvir-voxilaprevir	Antiviral (HCV)	NS5B inhibitor–NS5A inhibitor–NS3/4A inhibitor
Xifaxan	Rifaximin	Antibacterial	Rifamycin
Xtoro	Finafloxacin	Antibacterial	Fluoroquinolone
Zepatier[a]	Elbasvir-grazoprevir	Antiviral (HCV)	NS5A inhibitor–NS3/4A inhibitor
Zerbaxa[a]	Ceftolozane-tazobactam	Antibacterial	Cephalosporin–β-lactamase inhibitor
Zerit	Stavudine	Antiretroviral	NRTI
Ziagen	Abacavir	Antiretroviral	NRTI
Zinacef	Cefuroxime sodium	Antibacterial	Cephalosporin
Zithromax	Azithromycin	Antibacterial	Azalide
Zosyn[a]	Piperacillin-tazobactam	Antibacterial	Penicillin–β-lactamase inhibitor
Zovirax	Acyclovir	Antiviral	Nucleoside analogue
Zymar	Gatifloxacin	Antibacterial	Fluoroquinolone
Zyvox	Linezolid	Antibacterial	Oxazolidinone

[a]A combination product.
[b]US Centers for Disease Control and Prevention (CDC) Drug Service for distribution to US clinicians.
[c]Not available in the United States.
HBV, Hepatitis B virus; *HCV,* hepatitis C virus; *INSTI,* integrase strand transfer inhibitor; *NNRTI,* nonnucleoside reverse-transcriptase inhibitor; *NRTI,* nucleoside reverse-transcriptase inhibitor.

TABLE 54.4 Penicillin Dosage Forms

	FORMULATIONS		
	ORAL		
GENERIC NAME	Tablets/Capsules (mg)	Liquid (mg/mL)	PARENTERAL (g)
Amoxicillin	125,[a] 250,[a] 250, 500, 775,[b] 875	125/5, 200/5, 250/5, 400/5	0.25[c], 0.5[c], 1[c]
Amoxicillin-clavulanate	200-28.5,[a] 400-57,[a] 250-125, 500-125, 875-125, 1000-62.5[b]	125-31.25/5, 200-28.5/5, 250-62.5/5, 400-57/5, 600-42.9/5	0.5–0.1[c], 1–0.2[c]
Ampicillin	250, 500	125/5, 250/5	0.125, 0.25, 0.5, 1, 2, 10
Ampicillin-sulbactam[d]			1.5, 3, 15
Dicloxacillin	250, 500		
Nafcillin			1, 2, 10
Oxacillin			1, 2, 10
Penicillin G sodium[e]			1 MU, 2 MU, 3 MU, 5 MU, 20 MU
Penicillin G potassium[e]			1 MU, 2 MU, 3 MU, 5 MU, 20 MU
Penicillin G benzathine			0.6 MU, 1.2 MU, 2.4 MU
Penicillin G procaine			0.6 MU
Penicillin G benzathine–penicillin G procaine			0.6 MU–0.6 MU, 0.9 MU–0.3 MU
Penicillin V potassium	250, 500	125/5, 250/5	
Piperacillin-tazobactam[d]			2.25, 3.375, 4.5, 13.5, 40.5
Pivmecillinam[c]	200		

[a]Chewable.
[b]Extended release.
[c]Not available in the United States.
[d]Dose expressed as the sum of the penicillin and β-lactamase inhibitor
[e]400,000 IU = 0.4 MU = 250 mg.

TABLE 54.5 Cephalosporin Dosage Forms

	FORMULATIONS		
	ORAL		
GENERIC NAME	Tablets/Capsules (mg)	Liquid (mg/mL)	PARENTERAL (g)
First Generation			
Cefadroxil	500, 1000	250/5, 500/5	
Cefazolin			0.5, 1, 2, 10, 20, 100, 300
Cephalexin	250, 333, 500, 750	125/5, 250/5	
Second Generation			
Cefaclor	250, 500, 500[a]	125/5, 250/5, 375/5	
Cefotetan			1, 2, 10
Cefoxitin			1, 2, 10
Cefprozil	250, 500	125/5, 250/5	
Cefuroxime	250, 500	125/5, 250/5	0.75, 1.5, 7.5
Third Generation			
Cefdinir	300	125/5, 250/5	
Cefditoren pivoxil	200, 400		
Cefixime	100,[b] 200,[b] 400	100/5, 200/5, 500/5	
Cefotaxime			0.5, 1, 2, 10
Cefpodoxime proxetil	100, 200	50/5, 100/5	
Ceftazidime			0.5, 1, 2, 6, 100
Ceftibuten	400	180/5	
Ceftriaxone			0.25, 0.5, 1, 2, 10, 100
Fourth Generation			
Cefepime			1, 2
Fifth Generation			
Ceftaroline fosamil			0.4, 0.6
Cephalosporin, β-Lactamase Inhibitor Combinations			
Ceftazidime-avibactam			2-0.5
Ceftolozane-tazobactam			1.5[c]

[a]Extended release.
[b]Chewable.
[c]Dose expressed as the sum of the cephalosporin and β-lactamase inhibitor.

TABLE 54.6 Carbapenem, Monobactam, and Polymyxin Dosage Forms

GENERIC NAME	FORMULATIONS		
	ORAL		
	Tablets/Capsules (mg)	Liquid (mg/mL)	PARENTERAL (g)
Monobactams			
Aztreonam		75/1[a]	1, 2
Carbapenems			
Doripenem			0.25, 0.5
Ertapenem			1
Imipenem-cilastatin			0.25-0.25, 0.5-0.5
Meropenem			0.5, 1
Meropenem-vaborbactam			2[b]
Polymyxins			
Colistimethate			0.15[c]
Polymyxin B			500,000 IU[d]

[a]For inhalation.
[b]Dose expressed as the sum of the carbapenem and β-lactamase inhibitor.
[c]Dose expressed in units of colistin base activity.
[d]500,000 IU = 0.5 MIU = 50 mg.

TABLE 54.7 Aminoglycoside Dosage Forms

GENERIC NAME	FORMULATIONS		
	ORAL		
	Tablets/Capsules (mg)	Liquid (mg/mL)	PARENTERAL (g)
Amikacin			0.5, 1
Gentamicin			0.02, 0.06, 0.08, 0.1, 0.12, 0.8
Kanamycin			0.5, 1
Neomycin	500		
Streptomycin			1
Tobramycin	28[a]	300[a]	0.02, 0.08, 1.2, 2

[a]For inhalation.

TABLE 54.8 Tetracycline, Glycylcycline, and Folate Antagonist Dosage Forms

GENERIC NAME	FORMULATIONS		
	ORAL		
	Tablets/Capsules (mg)	Liquid (mg/mL)	PARENTERAL (g)
Tetracyclines and Glycylcyclines			
Demeclocycline	150, 300		
Doxycycline	20, 40,[a] 50, 50,[a] 75, 75,[a] 100, 100,[a] 120,[a] 150, 150,[a] 200[a]	25/5, 50/5	0.1
Minocycline	45,[b] 50, 55,[b] 65,[b] 75, 80,[b] 90,[b] 100, 105,[b] 115,[b] 135[b]		0.1
Tetracycline	250, 500		
Glycylcyclines			
Tigecycline			0.05
Folate Antagonists			
Trimethoprim-sulfamethoxazole	80-400, 160-800	40-200/5	0.080-0.400, 0.160-0.800, 0.480-2.400
Trimethoprim	100	50/5	
Sulfadiazine	500		
Dapsone	25, 100		

[a]Delayed release.
[b]Extended release.

TABLE 54.9 Macrolide, Azalide, Lincosamide, and Miscellaneous Antibacterial Agent Dosage Forms

GENERIC NAME	FORMULATIONS: ORAL Tablets/Capsules (mg)	ORAL Liquid (mg/mL)	PARENTERAL (g)
Macrolides and Azalides			
Azithromycin	250, 500, 600, 1000	100/5, 200/5, 2000/60[a]	0.5
Clarithromycin	250, 500, 500[a]	125/5, 250/5	
Erythromycin base	250, 250,[b] 500, 500[b]		
Erythromycin stearate	250		
Erythromycin ethylsuccinate	400	200/5, 400/5	
Erythromycin lactobionate			0.5
Fidaxomicin	200		
Lincosamides			
Clindamycin	75, 100,[c] 150, 300	75/5	0.3, 0.6, 0.9, 9
Lincomycin			0.6, 3
Miscellaneous Antibacterial Agents			
Chloramphenicol			1
Metronidazole	250, 375, 500, 750[a]	250/5, 500/5	0.5
Rifaximin	200, 550		
Secnidazole	2000[d]		

[a]Extended release.
[b]Delayed release.
[c]Vaginal suppository.
[d]Oral granules.

TABLE 54.10 Glycopeptide, Lipopeptide, Lipoglycopeptide, Polypeptide, Oxazolidinone, and Streptogramin Dosage Forms

GENERIC NAME	FORMULATIONS: ORAL Tablets/Capsules (mg)	ORAL Liquid (mg/mL)	PARENTERAL (g)
Bacitracin			50,000 IU[a]
Dalbavancin			0.5
Daptomycin			0.5
Linezolid	600	100/5	0.2, 0.6
Oritavancin			0.4
Quinupristin-dalfopristin			0.15-0.35
Tedizolid	200		0.2
Telavancin			0.75
Vancomycin	125, 250	125/5, 250/5	0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 5, 10

[a]For intramuscular injection.

TABLE 54.11 Fluoroquinolone and Urinary Antiinfective Dosage Forms

GENERIC NAME	FORMULATIONS: ORAL Tablets/Capsules (mg)	ORAL Liquid (mg/mL)	PARENTERAL (g)
Fluoroquinolones			
Ciprofloxacin	100, 250, 500, 500,[a] 750, 1000[a]	250/5, 500/5	0.2, 0.4
Delafloxacin	450		0.3
Gemifloxacin	320		
Levofloxacin	250, 500, 750	250/5	0.25, 0.5, 0.75, 2.5, 5
Moxifloxacin	400		0.4
Ofloxacin	300, 400		
Urinary Antiinfectives			
Fosfomycin	3000		2,[b] 4,[b] 8[b]
Methenamine[c]	500, 1000		
Nitrofurantoin	25, 50, 100	25/5	

[a]Extended release.
[b]Not available in the United States.
[c]Available as both mandelate and hippurate salt forms.

TABLE 54.12 Antimycobacterial Dosage Forms

GENERIC NAME	FORMULATIONS: ORAL Tablets/Capsules (mg)	ORAL Liquid (mg/mL)	PARENTERAL (g)
Aminosalicylic acid	4000		
Bedaquiline	100		
Capreomycin			1
Clofazimine	50, 100		
Cycloserine	250		
Ethambutol	100, 400		
Ethionamide	250		
Isoniazid	100, 300	50/5	0.1
Pyrazinamide	500		
Rifabutin	150		
Rifampin	150, 300	125/5	0.6
Rifapentine	150		
Streptomycin			1

TABLE 54.13 Antifungal Dosage Forms

GENERIC NAME	FORMULATIONS: ORAL Tablets/Capsules (mg)	FORMULATIONS: ORAL Liquid (mg/mL)	FORMULATIONS: PARENTERAL (g)
Polyenes			
Amphotericin B deoxycholate			0.05
Amphotericin B lipid complex			0.1
Amphotericin B liposomal			0.05
Nystatin	100,000 IU,[a] 500,000 IU, 1,000,000 IU	500,000 IU/5	
Echinocandins			
Anidulafungin			0.05, 0.1
Caspofungin			0.05, 0.07
Micafungin			0.05, 0.1
Azoles			
Clotrimazole	10[b]		
Fluconazole	50, 100, 150, 200	50/5, 200/5	0.1, 0.2, 0.4
Isavuconazonium	186		372
Itraconazole	100, 200	50/5	
Ketoconazole	200		
Miconazole	50,[b] 100,[a] 200[a]		0.01
Posaconazole	100	200/5	0.3
Terconazole	80[a]		
Voriconazole	50, 200	200/5	0.2
Allylamines			
Terbinafine	250		
Miscellaneous Antifungals			
Flucytosine	200, 250, 500		2.5
Griseofulvin	125, 250, 500	125/5	

[a]Vaginal tablet, ovule, suppository form.
[b]Oral lozenge, troche or buccal tablet.

TABLE 54.14 Antiparasitic Dosage Forms

GENERIC NAME	FORMULATIONS: ORAL Tablets/Capsules (mg)	FORMULATIONS: ORAL Liquid (mg/mL)	FORMULATIONS: PARENTERAL (g)
Anthelmintics			
Albendazole	200		
Diethylcarbamazine[b]	100		
Ivermectin	3		
Mebendazole	100[a]		
Praziquantel	600		
Pyrantel pamoate	62.5	250/5	
Antimalarials			
Artemether-lumefantrine	20-120		
Artesunate[b]			0.11
Atovaquone-proguanil	62.5-25, 250-100		
Chloroquine phosphate[c]	150, 300		

Continued

TABLE 54.14 Antiparasitic Dosage Forms—cont'd

GENERIC NAME	FORMULATIONS		
	ORAL		
	Tablets/Capsules (mg)	Liquid (mg/mL)	PARENTERAL (g)
Hydroxychloroquine sulfate	200		
Mefloquine	250		
Primaquine phosphate	26.3		
Proguanil	100		
Quinine sulfate	324		
Antiprotozoals			
Atovaquone		750/5	
Benznidazole	12.5,[d] 100		
Eflornithine[b]			20
Iodoquinol	210, 650		
Melarsoprol[b]			0.180
Miltefosine	50		
Nifurtimox[b]	120		
Nitazoxanide	500	100/5	
Paromomycin sulfate	250		
Pentamidine isethionate		300/1[e]	0.3
Pyrimethamine	25		
Sodium stibogluconate[b]			10[f]
Suramin[b]			1
Tinidazole	250, 500		

[a]Chewable.
[b]Must be obtained from the Centers for Disease Control and Prevention in the United States.
[c]Dose expressed as chloroquine base.
[d]Dispersible tablet for pediatric use.
[e]For inhalation.
[f]Dose expressed as grams of pentavalent antimony per bottle.

TABLE 54.15 Antiviral Dosage Forms

GENERIC NAME	FORMULATIONS		
	ORAL		
	Tablets/Capsules (mg)	Liquid (mg/mL)	PARENTERAL (g)
Acyclovir	200, 400, 800	200/5	0.5, 1
Adefovir	10		
Amantadine	100	50/5	
Cidofovir			0.375
Entecavir	0.5, 1	0.25/5	
Famciclovir	125, 250, 500		
Foscarnet			6
Ganciclovir			0.5
Oseltamivir	30, 45, 75	30/5, 60/5	
Peramivir			0.2
Ribavirin	200, 400, 600	200/5, 6000/1[b]	
Rimantadine	100		
Telbivudine	600		
Valacyclovir	500, 1000		
Valganciclovir	450	250/5	
Zanamivir	5[b]		

[a]Not including antivirals active against hepatitis C virus or antiretrovirals. For information on available dosage forms for these antivirals, refer to Tables 54.16 and 54.17.
[b]For inhalation.

TABLE 54.16 Hepatitis C Direct-Acting Antiviral Dosage Forms

GENERIC NAME	FORMULATIONS		
	ORAL		
	Tablets/Capsules (mg)	Liquid (mg/mL)	PARENTERAL (g)
Daclatasvir	30, 60, 90		
Elbasvir-grazoprevir	50-100		
Glecaprevir-pibrentasvir	100-40		
Ombitasvir-paritaprevir-ritonavir	12.5-75-50		
Ombitasvir-paritaprevir-ritonavir-dasabuvir	8.33-50-33.33-200,[a] 12.5-75-50-250[b]		
Simeprevir	150		
Sofosbuvir	400		
Sofosbuvir-ledipasvir	400-90		
Sofosbuvir-velpatasvir	400-100		
Sofosbuvir-velpatasvir-voxilaprevir	400-100-100		

[a]Extended release.
[b]Tablet therapy pack.

TABLE 54.17 Antiretroviral Dosage Forms

GENERIC NAME	FORMULATIONS		
	ORAL		
	Tablets/Capsules (mg)	Liquid (mg/mL)	PARENTERAL (g)
Abacavir	300	20/1	
Abacavir-lamivudine	600-300		
Abacavir-lamivudine-zidovudine	300-150-300		
Atazanavir	50,[a] 150, 200, 300		
Atazanavir-cobicistat	300-150		
Cobicistat	150		
Darunavir	75, 150, 600, 800	100/1	
Darunavir-cobicistat	800-150		
Delavirdine	100, 200		
Didanosine	125,[b] 200,[b] 250,[b] 400[b]	2000, 4000	
Dolutegravir	50, 25, 50		
Dolutegravir-abacavir-lamivudine	50-600-300		
Efavirenz	50, 200, 600		
Efavirenz–emtricitabine–tenofovir disoproxil fumarate	600-200-300		
Elvitegravir–cobicistat–emtricitabine–tenofovir alafenamide fumarate	150-150-200-10		
Elvitegravir–cobicistat–emtricitabine–tenofovir disoproxil fumarate	150-150-200-300		
Emtricitabine	200	10/1	
Emtricitabine–tenofovir alafenamide fumarate	200-25		
Emtricitabine-tenofovir disoproxil fumarate	100-150, 133-200, 167-250, 200-300		
Enfuvirtide			0.09
Etravirine	25, 100, 200		
Fosamprenavir	700	50/1	
Indinavir	200, 400		
Lamivudine	100, 150, 300	5/1, 10/1	
Lamivudine-zidovudine	150-300		
Lopinavir-ritonavir	100-25, 200-50	80-20/1	
Maraviroc	25, 75, 150, 300	20/1	
Nelfinavir	250, 625		
Nevirapine	100,[c] 200, 400[c]	50/5	
Raltegravir	25,[d] 100,[d] 100,[a] 400, 600		
Rilpivirine	25		
Rilpivirine-emtricitabine-tenofovir alafenamide fumarate	25-200-25		
Rilpivirine-emtricitabine-tenofovir disoproxil fumarate	25-200-300		
Ritonavir	100	80/1	
Saquinavir	200, 500		
Stavudine	15, 20, 30, 40	1/1	
Tenofovir alafenamide fumarate	25		
Tenofovir disoproxil fumarate	40,[a] 150, 200, 250, 300		
Tipranavir	250	100/1	
Zidovudine	100, 300	50/5	0.2

[a]Oral powder.
[b]Delayed release.
[c]Extended release.
[d]Chewable.

TABLE 54.18 Antiinfective Agent Pharmacology: Penicillins

Drug (Oral Absorption, %)	Serum and Urine Concentration: Selected Doses			DOSAGE RECOMMENDATIONS							SERUM HALF-LIFE (h)	
				Adults			Children: Dose/Interval		Newborn (Parenteral): Dose/Interval		With Normal and Anuric CrCl Values (mL/min)	
	Dose (g)	Peak Serum (μg/mL)	Peak or Range, Urine (μg/mL)	Dose (g)/Interval Oral	Dose (g)/Interval Parenteral	Serious Infection Daily Dose (g)	Oral[p]	Parenteral[p]	Up to 1 wk	1–4 wk	>80	<10
Amoxicillin[b] (74–92)	0.25 PO[c]	3.5–5		0.25–2 q8–12h		4	20–90 mg/kg/day in 3 doses				0.7–1.4	7.4–21
	0.5 PO[c]	5.5–11										
Amoxicillin-clavulanate[f]	0.25 PO	3.7–4.8[g]	381[g]	0.25–2 q8–12h		4	20–90 mg/kg/day in 3 doses[h]				1.1–1.3	7.5
	0.5 PO 0.875 PO	6–9.7 11.6										
Ampicillin[b] (30–55)	0.25 PO[c]	1.8–2.9		0.25–1 q6h	0.5–2 q4–6h	4 PO, 12 IV	50–100 mg/kg/day in 3–4 doses	100–300 mg/kg/day in 3–4 doses[j]	100–300 mg/kg/day in 2–3 doses	100–300 mg/kg/day in 3–4 doses	0.7–1.4	7.4–21
	0.5 PO[c] 2 IV	3–6 47.6										
Ampicillin-sulbactam	1.5 IV	40–71[g]			1.5–3 q6h	12		100–200 mg/kg/day in 3–4 doses[f,p]			1	9
	3 IV	109–150[g]										
Dicloxacillin[b] (35–76)	0.5 PO	10–18		0.125–0.5 q6h		2	12.5–50 mg/kg/day in 4 doses				0.6–0.8	1–2.2
Nafcillin[b,l] (36)	1 IM	7.6			0.5–2 q4–6h	12 IV		100–200 mg/kg/day in 4 doses	50–75 mg/kg/day in 2–3 doses[m]	75–150 mg/kg/day in 3–4 doses[n]	0.5–1.5	1.8–2.8
	0.5 IV[e]	30										
Oxacillin[b,l] (30–35)	0.25 PO	1.65			0.5–2 q4–6h	12 IV		100–200 mg/kg/day in 4 doses	50–75 mg/kg/day in 2–3 doses[m]	75–150 mg/kg/day in 3–4 doses[n]	0.3–0.8	0.5–2
	0.5 PO 0.5 IV q6h[i]	2.6–3.9 52–63										
Penicillin G[b,l] (15–30)	1 MU	25			1–4 MU q4–6h	24 MU IV		50,000-500,000 U/kg/day in 4–6h doses[p]	50,000–450,000 U/kg/day q8–12h[m]	75,000–500,000 U/kg/day q6–8h[n]	0.4–0.9	6–20
	5 MU	400										
Penicillin G benzathine	1.2 MU IM	0.15 U/mL			0.6–2.4 MU IM × 1	2.4 MU		0.6 MU IM × 1		50,000 U/kg IM × 1	Days	
Penicillin G procaine	0.6 MU IM	1.6			0.6–1.2 MU IM	4.8 MU		50,000 MU/kg/day IM in 1 dose		50,000 U/kg/day IM in 1 dose	24	
	1.2 MU IM	1.95										
Penicillin V potassium[b] (60–73)	0.25 PO	2.3–2.7		0.25-0.5 q6h		2	25–75 mg/kg/day in 3–4 doses				0.5	7–10
	0.5 PO	4.9–6.3										
Piperacillin-tazobactam[l]	3.375 IV[q]	209[g]			3.375–4.5 q6–8h	18		200 mg/kg/day in 3–4 doses[f,p]	100 mg/kg q12h[f]	100 mg/kg q8h[f]	0.7–1.1	1.9–3.5
	4.5 IV[q]	224[g]										

[a]Inflamed meninges.
[b]Decreased rate and/or extent of absorption when given with food.
[c]Fasting.
[e]Specified dose should be administered in addition to scheduled dosing after a dialysis session to supplement drug clearance during dialysis.
[f]Dose based on penicillin component only.
[g]Penicillin component only.
[h]Children <40 kg should not receive the 250-mg film-coated tablet.
[i]Children <40–50 kg.
[j]16.7–33.3 mg/kg q4h for meningitis.
[l]Administration by extended (3–4 h) or continuous infusion (23–24 h) should be strongly considered to optimize efficacy. This is especially important in patients who are critically ill, immunosuppressed, or with deep-seated infections due to resistant organisms.
[m]q8h if >2 kg; q12h if <2 kg.
[n]q6h if >2 kg; q8h if <2 kg.
[q]IV push (over 2–10 min).
[p]Dosage should not exceed adult dosage.
[q]Infusion over 15–30 min.
CrCl, Creatinine clearance; *CSF,* cerebrospinal fluid; *HD,* hemodialysis; *PD,* peritoneal dialysis.

STANDARD DOSE WITH DOSING INTERVALS IN RENAL IMPAIRMENT													
With Dialysis			For CrCl Ranges (mL/min)				Dosage With Dialysis		Body Fluid Concentrations				
HD	PD	Usual Adult Dose (g)	>80	80–50	50–10	<10 (Anuric)	HD	PD	CSF/ Serum (%)[a]	Newborn Serum/ Maternal Serum (%)	Breast Milk/ Maternal Serum (%)	Bile/ Serum (%)	Aqueous Humor/ Serum (%)
		0.25–2	8–12	8–12	0.25–0.5 q12h	0.25–0.5 q24h	0.25–0.5 q24h, with 0.25–0.5[e] after HD	0.25 q12h	5–10	25–33	5	100–3000	Negligible
		0.25–2	8–12	8–12	0.25–0.5 q12h	0.25–0.5 q24h	0.25–0.5 q24h, with 0.25–0.5[e] after HD	0.25 q12h	6		Low	1100	
		0.5–2 IV	4–6	4–6	8–12	12–24	0.5–2 q12–24h, with 0.5–2[e] after HD	0.5–2 q12h		100	11	100–3000	2–8
		1.5–3.0	6–8	6–8	8–12	12–24	1.5–3 q12–24h	1.5–3 q12h					
1–2.2	1–2.2	0.125–0.5	6	6	6	6	0.125–0.5 q6h	0.125–0.5 q6h	Minimal	0–10		5–8	
1.8–2.8	1.8–2.8	0.5–2	4–6	4–6	4–6	4–6	0.5–2 q4–6h	0.5–2 q4–6h	9–20	10–15		≥100	Negligible
0.5–2	0.5–2	0.5–2	4–6	4–6	4–6	4–6	0.5–2 q4–6h	0.5–2 q4–6h		10–15	≤3.5	20–30	0
	6–20	1–4 MU	4–6	4–6	4–6	0.5–2 MU q4–6h	0.5-2 MU q4–6h, with 0.5 MU[e] after HD		0–10	100	6	200–800	
		0.6–1.2 MU	× 1	× 1	75% dose × 1	20%–50% dose × 1							
		0.6–1.2 MU	12–24	12–24	75% dose q12–24h	20%–50% dose q12–24h			Minimal				
		0.25–0.5	6	6	6	8	0.25–0.5 q8h, with 0.25[e] after HD						
		3.375–4.5	6–8	6–8	6–8	2.25 q8h	2.25 q8h					>100	

TABLE 54.19 Antiinfective Agent Pharmacology: Cephalosporins

Drug (Oral Absorption, %)	Serum and Urine Concentration: Selected Doses			DOSAGE RECOMMENDATIONS							SERUM HALF-LIFE (h)	
				Adults			Children: Dose/Interval[a]		Newborn (Parenteral): Dose/Interval		With Normal and Anuric CrCl Values (mL/min)	
	Dose (g)	Peak Serum (μg/mL)	Peak or Range, Urine (μg/mL)	Dose (g)/Interval Oral	Dose (g)/Interval Parenteral	Serious Infection Daily Dose (g)	Oral	Parenteral	Up to 1 wk	1–4 wk	>80	<10
First Generation												
Cefadroxil (100)	0.5 PO 1 PO	10–18 24–35	1800	0.5–1 q12–24h		2	30 mg/kg/day in 2 doses				1.1–2	20–25
Cefazolin	1 IV 1 IM	188 64–76	4000		0.5–2 q8h	6		25–150 mg/kg/day in 3–4 doses	25 mg/kg q12h[d]	25 mg/kg q8–12h[d]	1.2–2.2	18–36
Cephalexin (100)	0.25 PO 0.5 PO	9 15–18	2000	0.25–1 q6h		4	25–100 mg/kg/day in 3–4 doses				0.5–1.2	5–30
Second Generation												
Cefaclor[e] (>52)	0.25 PO 0.5 PO	5–7 13–15	600 900	0.25–0.5 q8h		1.5	20–40 mg/kg/day in 2–3 doses[f]				0.5–1	2.8
Cefotetan	1 IV[g] 2 IV[g]	142–179.6 237	1400–2000 3500–4000		1–2 q12h	4		30–50 mg/kg/day in 2 doses[h]			2.8–4.6	12–30
Cefoxitin	1 IM 1 IV[g] 2 IV[g]	22–24 110–125 221	3000		1–2 q6–8h	8		80–160 mg/kg/day in 3–4 doses[i]	35 mg/kg q8–12h[d]	35 mg/kg q6–8h[d]	0.7–1.1	13–22
Cefprozil (95)	0.25 PO 0.5 PO 1 PO	5.6–6.8 8.2–10.4 15.5–19.9	250 1000 2900	0.25–0.5 q12–24h		1	15 mg/kg q12h				0.9–1.5	5.9
Cefuroxime (37–52)[j]	0.5 PO 0.75 IV[j]	7 51.1	1150	0.25–0.5 q12h	0.75–1.5 q8h	1 PO 4.5 IV	50 mg/kg q12h	50 mg/kg q8–12h[d,k]			1–2	20
Third Generation												
Cefdinir[e] (36)	0.2 PO 0.6 PO	0.7–1.7 2.4		0.6/day in 1–2 doses		0.6	14 mg/kg/day in 1–2 doses				1.1–4.4	
Cefditoren pivoxil (14–16)	0.2 0.4	2.5–3 4.4–4.6		0.2–0.4 q12h		0.8	3–6 mg/kg q8h[h]				1.3–2	4.7
Cefixime[e] (30–50)	0.4 PO tabs 0.4 PO susp	3.7 4.6	15.7–305 15.7–305	0.4/day in 1–2 doses		0.4	8 mg/kg/day in 1–2 doses				2.4–4	11.5
Cefotaxime	0.5 IM 1 IV[g] 2 IV[g]	11.7–11.9 102.4 214.1	90–3261		1–2 q6–12h	12		50–200 mg/kg/day in 4–6 doses	50 mg/kg q12h	50 mg/kg q8–12h[d]	0.9–1.7	
Cefpodoxime proxetil[m] (50)	0.1 PO 0.2 PO 0.4 PO	1.4 2.3 3.9	60	0.1–0.4 q12h		0.8	5 mg/kg q12h[n]				1.9–3.2	9.8
Ceftazidime[o,p]	0.5 IV[l] 1 IV[l] 2 IV[l]	42 69 159–185.5			1–2 q8–12h	6		90–150 mg/kg/day in 3 doses	50 mg/kg q12h	50 mg/kg q8–12h[d]	1.4–2	11.9–35
Ceftibuten (80)	0.4 PO	15		0.4 q24h		0.4	9 mg/kg/day in 1 dose				1.5–2.9	18–29

STANDARD DOSE WITH DOSING INTERVALS IN RENAL IMPAIRMENT													
With Dialysis			For CrCl Ranges (mL/min)				Dosage With Dialysis		Body Fluid Concentrations				
HD	PD	Usual Adult Dose (g)	>80	80–50	50–10	<10 (Anuric)	HD (g)	PD (g)	CSF/ Serum (%)[b]	Newborn Serum/ Maternal Serum (%)	Breast Milk/ Maternal Serum (%)	Bile/Serum (%)	Aqueous Humor/ Serum (%)
		0.5–1	12–24	12–24	0.5 q12–24h	0.5 q36h	1 q72h, 1[c] after HD			50	0.9–1.9	22	
		0.5–2	8	8	0.5–1 q8–12h	0.5–1 q18–24h	0.5–1 q24h	0.5 q12h	1–4	35–69	3	29–300	<1.7
		0.25–1	6	6	8–12	24–48	0.25–0.5 q12–24h	0.25–0.5 q12–24h	Minimal	60	2	216	11
		0.25–0.5	8	8	8	8	0.25–0.5 q8–12h, 0.25[c] after HD	0.25 q8–12h			2	≥60	1–3
		1–2	12	12	24	48	25% dose nondialysis days, 50% dose dialysis days				2.3	2–21	
		1–2	6–8	8–12	12–24	0.5–1 q12–48h	0.5–2 q24h, 1–2[c] after HD		2.8	100	≤3	280	4–7
		0.25–0.5	12–24	12–24	50% dose q12–24h	50% dose q12–24h	50% dose q12–24h, 0.25[c] after HD	50% dose q12–24h					
		0.25–0.5 PO 0.75–1.5 IV	12 8	12 8	12–24 8–12	48 24	0.25–0.5 q24–48h, 0.25–0.5[c] after HD 0.75–1.5 q24h, 0.75–1.5[c] after HD	 0.75–1.5 q24h	17–88	20–33	≤3	35–80	10–14
		0.3 0.6	12 24	12 24	0.3 q12–24h	0.3 q24h	0.3 q48h, 0.3[c] after HD						
		0.2–0.4	12	12	0.2 q12–24h								
7												>100	
		1–2	6–8	6–8	8–12	24	1–2 g q24h	1g q24h	1.8–3.1	20–50	≤ 1.5	800–1200	1–6
		0.1–0.4	12	12	12–24	24	0.1–0.4 thrice weekly after HD						
		1–2	8–12	8–12	12–24	24	0.5–1 q24h		27		Up to 3–8	15–7510	0.5–4
	16	0.4	24	24	0.2–0.4 q24h	0.1 q24h	0.4 thrice weekly after HD						

Continued

TABLE 54.19 Antiinfective Agent Pharmacology: Cephalosporins—cont'd

Drug (Oral Absorption, %)	Serum and Urine Concentration: Selected Doses			DOSAGE RECOMMENDATIONS							SERUM HALF-LIFE (h)	
				Adults			Children: Dose/Interval[a]		Newborn (Parenteral): Dose/Interval		With Normal and Anuric CrCl Values (mL/min)	
	Dose (g)	Peak Serum (μg/mL)	Peak or Range, Urine (μg/mL)	Dose (g)/Interval Oral	Dose (g)/Interval Parenteral	Serious Infection Daily Dose (g)	Oral	Parenteral	Up to 1 wk	1–4 wk	>80	<10
Ceftriaxone	1 IV[f]	123.2–150.7	504–995		1–2 q12–24h	4		50–100 mg/kg/day in 1–2 doses	50 mg/kg q24h	50 mg/kg q24h	5.4–10.9	12.2–18.2
	2 IV[f]	223–276										
	2 IV[q]	216–281										
Fourth Generation												
Cefepime[p]	1 IV	81.7			0.5–2 q8–12h	6		100–150 mg/kg/day in 2–3 doses	30–50 mg/kg q12h	30–50 mg/kg q12h	2	13.5
	2 IV	163.9										
Fifth Generation												
Ceftaroline fosamil	0.6	21.3			0.6 q8–12h	1.8		8 mg/kg q8h			1.6–2.7	6
Cephalosporin/β-Lactamase Inhibitor Combinations												
Ceftazidime-avibactam[r]	2-0.5	88.1-15.2			2.5 q8h	7.5					2.76[s]	7.7[s]
Ceftolozane-tazobactam[t]	1-0.5 q8h	74.4-18			1.5 q8h	4.5					3.12/1.10	11.1/2.15

[a]Dosage should not exceed adult dosage.
[b]Inflamed meninges.
[c]Specified dose should be administered in addition to scheduled dosing after a dialysis session to supplement drug clearance during dialysis.
[d]Lower end of dosing range if weight <2 kg and higher end if >2 kg.
[e]Decreased rate and/or extent of absorption when given with food.
[f]Should not exceed 1 g.
[g]IV push (over 2–10 min).
[h]Not FDA approved for use in this population.
[i]Should not exceed 12 g.
[j]52% after food.
[k]Doses up to 200–240 mg/kg/day q6–8h are used for meningitis.
[l]Infusion over 15–30 min.
[m]Should be given with food to increase absorption.
[n]No more than 400 mg/day for otitis or 100 mg/day for pharyngitis, tonsillitis.
[o]Arginine component not approved for children <12 yr.
[p]Administration by extended (2–4 h) or continuous infusion (23–24 h) should be strongly considered to optimize efficacy. This is especially important in patients who are critically ill, are immunosuppressed, or have deep-seated infections due to resistant organisms.
[q]2g q24h at steady state.
[r]Labeled infusion time is 2 h.
[s]Cephalosporin component only.
[t]Labeled infusion time is 1 h.
CrCl, Creatinine clearance; *CSF,* cerebrospinal fluid; *HD,* hemodialysis; *PD,* peritoneal dialysis.

TABLE 54.20 Antiinfective Agent Pharmacology: Monobactams, Carbapenems, and Polymyxins

Drug (Oral Absorption, %)	Serum and Urine Concentration: Selected Doses			DOSAGE RECOMMENDATIONS							SERUM HALF-LIFE (h)	
				Adults			Children: Dose/Interval[n]		Newborn (Parenteral): Dose/Interval		With Normal and Anuric CrCl Values (mL/min)	
	Dose (g)	Peak Serum (μg/mL)	Peak or Range, Urine (μg/mL)	Dose (g)/Interval Oral	Dose (g)/Interval Parenteral	Serious Infection Daily Dose (g)	Oral	Parenteral	Up to 1 wk	1–4 wk	>80	<10
Monobactams												
Aztreonam[b]	1 IV[c]	90–164	3000–3500		1–2 q6–8h	8		90–120 mg/kg/day in 3–4 doses	30–50 mg/kg q8–12h[d]	30–50 mg/kg q6–12h[d]	1.3–2.2	6–9
	2 IV[c]	204–255	5600–6600									
Carbapenems												
Doripenem[b]	0.5 IV	23	601		0.5 q8h	1.5		60 mg/kg/day in 3 doses			1	
Ertapenem (90 IM)	1 IV[c]	155			1 q24h	1		30 mg/kg/day in 2 doses			4	14

STANDARD DOSE WITH DOSING INTERVALS IN RENAL IMPAIRMENT													
With Dialysis			For CrCl Ranges (mL/min)				Dosage With Dialysis		Body Fluid Concentrations				
HD	PD	Usual Adult Dose (g)	>80	80–50	50–10	<10 (Anuric)	HD (g)	PD (g)	CSF/Serum (%)[b]	Newborn Serum/Maternal Serum (%)	Breast Milk/Maternal Serum (%)	Bile/Serum (%)	Aqueous Humor/Serum (%)
12.2–18.2	12.2–18.2	1–2	12–24	12–24	12–24	12–24	1–2 q12–24h	1–2 q12–24h	16–32	18–25	3–4	200–500	
13.5	19	0.5–2	8–12	8–12	12–24	0.25–1 q24h	0.5–1 q24h	1–2 q48h			0.5 mg/L		
		0.6	12	12	0.3–0.4 q12h	0.2 q12h	0.2 q12h						
		2.5	8	8	0.94 q12 to 1.25 q8h	0.94 q24–48h	0.94 q24–48h						
		1.5	8	8	0.375–0.75 q8h		0.15 q8h						

STANDARD DOSE WITH DOSING INTERVALS IN RENAL IMPAIRMENT													
With Dialysis			For CrCl Ranges (mL/min)				Dosage With Dialysis		Body Fluid Concentrations				
HD	PD	Usual Adult Dose (g)	>80	80–50	50–10	<10 (Anuric)	HD (g)	PD (g)	CSF/Serum (%)[a]	Newborn Serum/Maternal Serum (%)	Breast Milk/Maternal Serum (%)	Bile/Serum (%)	Aqueous Humor/Serum (%)
2.7		1–2	6–8	6–8	8–12	0.5–1 q12h	0.5–1 q12h	0.5–1 q12h	3–52		0.1–0.6	115–405	5–14
		0.5	8	8	0.25 q8–12h							117	
		1	24	24	0.5–1 q24h	0.5 q24h	0.5 q24h, 0.15[e] after HD[f]				Minimal		

Continued

TABLE 54.20 Antiinfective Agent Pharmacology: Monobactams, Carbapenems, and Polymyxins—cont'd

Drug (Oral Absorption, %)	Serum and Urine Concentration: Selected Doses			DOSAGE RECOMMENDATIONS							SERUM HALF-LIFE (h)	
				Adults			Children: Dose/Interval[n]		Newborn (Parenteral): Dose/Interval		With Normal and Anuric CrCl Values (mL/min)	
	Dose (g)	Peak Serum (μg/mL)	Peak or Range, Urine (μg/mL)	Dose (g)/Interval: Oral	Dose (g)/Interval: Parenteral	Serious Infection Daily Dose (g)	Oral	Parenteral	Up to 1 wk	1–4 wk	>80	<10
Imipenem–cilastatin[b]	0.25 IV[c] 0.5 IV[c] 1 IV[c]	14–24 21–58 41–83	50 100 > 100		0.5–1 q6h	4		15–25 mg/kg q6h	20–25 mg/kg q12h[d]	25 mg/kg q8–12h[d]	0.8–1	3.5
Meropenem[b]	0.5 IV[c] 1 IV[c]	26 55–62			0.5–2 q8–12h	6		20–40 mg/kg q8h			0.8–1	6–20
Meropenem/vaborbactam[h,i]	2/2 IV[i]	46.0/50.7			4 q8h	12					1.22/1.33	5.71/11.7
Polymyxins												
Colistimethate[k]	0.15 IM	5–7.5	200–270		2.5–5 mg/kg/day in 2–4 doses	5 mg/kg		2.5–5 mg/kg/day in 2–4 doses	Not recommended	Not recommended	1.5–8	48–72
Polymyxin B[l]	0.5 mg/kg q48–1.25 mg/kg q12h	2.38–13.9			1.25 mg/kg q12h	2.5 mg/kg/days		1.5–2.5 mg/kg/day in 2 doses	Not recommended	Not recommended	4.3–6	48–72

[a]Inflamed meninges.
[b]Administration by extended (2–4 h) or continuous infusion (23–24 h) should be strongly considered to optimize efficacy. This is especially important in patients who are critically ill, are immunosuppressed, or have deep-seated infections due to resistant organisms.
[c]IV infusion over 15–30 min.
[d]Lower end of dosing range if weight <2 kg and higher end if >2 kg.
[e]Specified dose should be administered in addition to scheduled dosing after a dialysis session to supplement drug clearance during dialysis.
[f]A supplemental dose after dialysis is recommended if the maintenance ertapenem dose is administered within 6 h before a dialysis session.
[g]Imipenem-cilastatin is not recommended with CrCl <15 mL/min unless hemodialysis will be initiated within 48 h.
[h]Dose expressed as the sum of both components.
[i]Manufacturer labeling recommends infusion time of 3 h.
[j]IV infusion over 3 h.
[k]Colistimethate is the sulfamethyl derivative of colistin, and the doses are based in milligrams of colistin base activity. Although 300 mg/day is considered to be the maximum daily dose, doses up to 480 mg/day may be necessary but are likely to also increase the risk for toxicity.
[l]Manufacturer labeling expresses doses in units; however, milligrams are more commonly used in clinical practice. For conversion, 10,000 units = 1 mg of polymyxin B.
[m]Manufacturer labeling recommends reducing the dose to <1.5 mg/kg/day in patients with renal impairment; however, recent data suggest that polymyxin B doses should not be adjusted for renal dysfunction.
[n]Dosage should not exceed adult dosage.
CrCl, Creatinine clearance; *CSF,* cerebrospinal fluid; *HD,* hemodialysis; *PD,* peritoneal dialysis.