recombinant human IL-10 in HIV failed to demonstrate a beneficial effect on plasma viral load or $CD4^+$ T-cell counts.[146]

Interleukin-11

IL-11 has been classified as a primarily antiinflammatory cytokine and therefore has been studied as a mediator of the excessive immune response in sepsis. In a case-control study of patients with severe sepsis and thrombocytopenia, those who received recombinant human IL-11 demonstrated lower APACHE II scores from experimental day 3 to day 14, and a significantly lower 28-day mortality rate.[147] IL-11 has also been studied in a small randomized, placebo-controlled trial of 40 patients with hematologic malignancies in which IL-11 reduced the incidence of bacteremia and polymicrobial bacteremia when administered for at least 21 days and until resolution of neutropenia.[148] It should be noted, however, that serious adverse events have been reported. In a small RCT of 13 patients undergoing allogeneic HSCT in whom IL-11 was administered for 21 days from the conditioning regimen, 5 of the 10 recipients of IL-11 died with multiorgan failure and severe, diuretic-resistant fluid retention.[149]

Interleukin-12

IL-12 is produced primarily by macrophages, dendritic cells, and B lymphocytes and regulates activation, IFN-γ production, and cytotoxicity of T cells and NK cells.[150] IL-12 appears to play a critical role in defense against intracellular pathogens, particularly *Mycobacterium* species, and has been studied for the treatment of nontuberculous mycobacterial infection, although the findings have yet to be published. In chronic hepatitis B virus (HBV) and HCV infections, IL-12 has proved clinically ineffective, and in HCV-infected patients may be associated with serious toxicity, including fulminant liver failure.[151,152] Although phase I trials of IL-12 as therapy for HIV infection did not demonstrate clinical benefit, some, but not all, studies that have used IL-12 as an adjuvant for HIV therapeutic vaccines have reported improved $CD4^+$ T-cell cytokine production in response to subsequent HIV-specific antigen stimulation ex vivo.[153–157]

THYMIC HORMONES

Although not currently approved for clinical use in North America or Europe, thymosin-α_1, produced by the thymus and capable of inducing expression of IL-1, IL-2, IFN-α, and IFN-γ, has been proposed as immunomodulatory therapy for sepsis. In a multicenter, randomized, single-blind, placebo-controlled trial of 361 critically ill patients with severe sepsis, those who received a 5-day course of thymosin-α_1 had a significantly lower rate of in-hospital, but not 28-day, mortality.[158] A phase III trial of thymosin-α_1 is currently recruiting participants and is expected to complete data collection in 2019 (ClinicalTrials.gov identifier: NCT02867267).

Based on the cytokine profile stimulated by thymosin-α_1, it has also been proposed as monotherapy or combination therapy for the treatment of chronic hepatitis B. In an early meta-analysis, patients who received 6 to 12 months of thymosin-α_1 therapy were more likely to become HBV DNA and hepatitis B e-antigen (HBeAg) negative (if positive at baseline) than were those who received placebo, but this effect was not seen until 12 months after the completion of therapy.[159] No difference was seen in normalization of liver enzymes between the groups. A more recent meta-analysis included eight studies that enrolled a total of 583 patients and compared thymosin-α_1 plus lamivudine versus lamivudine alone in patients who were HBeAg positive.[160] Patients who received thymosin-α_1 for 6 to 12 months in combination with lamivudine for 1 year were significantly more likely to normalize their liver enzymes and become HBV DNA and HBeAg negative than were those who received lamivudine alone. Consistent with the earlier meta-analysis, the virologic response was sustained for up to a year after treatment. It should be noted, however, that there are as yet no published studies of thymosin-α_1 in combination with newer antiviral agents.

IMMUNOGLOBULINS

Immunoglobulin (pooled immune globulin) therapy has existed in many forms for decades. There are preparations available for intravenous (intravenous immune globulin [IVIG]), subcutaneous, and/or intramuscular use. Pooled products are nonspecific in their composition, whereas hyperimmune products have an augmented concentration of antigen-specific antibodies. Pooled IVIG products are prepared from plasma obtained from thousands of donors per lot, and although the various preparations are thought to be therapeutically equivalent for clinical indications, the individual protocols used to isolate immunoglobulin G (IgG) and the excipients used for stabilization may render certain preparations preferable over others for an individual patient.[161] For instance, sucrose-containing products should be avoided in patients with renal dysfunction, and hyperosmolar products may be avoided in those with cardiac disease. IgA content may play a role in product selection for those with IgA deficiency (see later). With multiple variations in product processing, the composition of the particular product chosen should be matched with the particular risk factor profile for each individual patient.

One of the oldest uses of pooled, nonspecific immunoglobulin therapy is in the treatment of a variety of primary immunodeficiency disorders, including X-linked agammaglobulinemia, severe combined immunodeficiency, hyper-IgM syndrome, Wiskott-Aldrich syndrome, and common variable immunodeficiencies (CVIDs), in which pneumonia and other invasive bacterial infections are significantly reduced by immunoglobulin replacement therapy.[162] Pooled IVIG has also been studied for use in a variety of conditions in which individuals have normal immunoglobulin levels. For instance, infants and young children with HIV infection often have depressed antibody responses and an associated increased incidence of bacterial and viral infections. Infants and children with advanced HIV disease were shown to benefit from IVIG alone (in the pre-antiretroviral era) or in combination with zidovudine.[163] Since that time, however, a double-blind, crossover study of children with HIV disease well controlled with combination ART found that discontinuation of IVIG prophylaxis was safe in the short term.[164] In addition, a retrospective cohort study reported no benefit for IVIG use in the treatment of acute bacterial infections in the same patient population.[165] An HIV hyperimmune globulin product has been studied as adjunctive therapy administered with, and compared with, single-dose nevirapine in HIV-infected pregnant women and their newborns in Uganda. However, the addition of HIV hyperimmune globulin to standard nevirapine therapy was associated with an increased rate of HIV infection in neonates that was statistically significant at 2 weeks but not at 6 months. This study confirmed the negative results of a much earlier study of HIV hyperimmune globulin in a non–breast-feeding American cohort.[166,167]

In preterm or low-birth-weight infants, prophylaxis with IVIG yielded only a small reduction in the occurrence of sepsis and other serious infections, but did not affect mortality.[168] Polyclonal antistaphylococcal immunoglobulin, when administered to very-low-birth-weight infants, failed to reduce the incidence of staphylococcal or other infections.[169] When used for treatment, rather than prophylaxis, of infections in neonates, IVIG has also not been shown to improve outcome. In a landmark multicenter, placebo-controlled, randomized trial (International Neonatal Immunotherapy Study [INIS]) enrolling 3493 neonates with suspected or proven infection, the majority of whom had low birth weight, two weight-based infusions of IVIG failed to affect the incidence of sepsis (secondary outcome) or death/major disability at 2 years (primary outcome).[170] A subsequent meta-analysis of nine studies, albeit dominated by the INIS trial, also concluded that IVIG administration did not reduce in-hospital mortality or death/major disability at 2 years in infants with either proven or suspected infection, and in addition found that IgM-enriched IVIG was also ineffective in reducing in-hospital mortality in neonates with suspected infection.[171]

In adults with established sepsis, both polyclonal IVIG and IgM-enriched IVIG have been proposed as immunomodulatory adjuncts to standard care. A meta-analysis of 10 trials, enrolling 1430 adults with sepsis, found a significant reduction in mortality in those who received polyclonal IVIG when compared with those who received placebo.[172] A reduction in mortality was also seen in a pooled analysis of 7 trials that compared IgM-enriched IVIG and placebo in this patient population. However, when only those studies judged to be at low risk of bias (3 using polyclonal IVIG and 2 using IgM-enriched IVIG) were included in the analysis, the mortality benefit disappeared. Since publication of

the meta-analysis, several other studies have explored immunoglobulins for use in sepsis. A large retrospective study identified mechanically ventilated adult patients with pneumonia and septic shock from a nationwide database in Japan and found no significant difference in 28-day mortality between those who received polyclonal IVIG and those who did not, when analyzed via either the large unmatched cohorts or via 1045 propensity-matched pairs.[173] Using the same methodology, no mortality benefit was associated with IVIG use in propensity-matched pairs of mechanically ventilated patients with septic shock after emergency laparotomy for colonic perforation.[174] Given the lack of proven benefit, current guidelines recommend against the use of immunoglobulins in patients with sepsis and septic shock.[175]

In toxic shock syndromes, exotoxins such as streptococcal pyrogenic exotoxin A and toxic shock syndrome toxin 1 play key pathophysiologic roles as superantigens. In vitro studies demonstrating the ability of pooled immunoglobulin to rapidly neutralize these exotoxins suggest a potential role for IVIG therapy in clinical management, and several observational studies have reported reduced mortality with IVIG (often in combination with clindamycin) in patients with streptococcal toxic shock and/or necrotizing fasciitis (see Chapters 194 and 197).[176,177,178] However, a randomized, double-blind, placebo-controlled trial investigating IVIG therapy in adults with streptococcal toxic shock syndrome was prematurely terminated because of poor patient enrollment and failed to demonstrate a statistically significant benefit of IVIG therapy.[179] A retrospective cohort study of children with streptococcal toxic shock syndrome found no survival benefit in those patients who received IVIG, but both overall numbers and mortality were low.[180] As a result of conflicting evidence, use of IVIG in the setting of streptococcal toxic shock varies widely and is influenced by individual institutional practices.

IVIG has also been studied for host antibody replacement and immunomodulation after immunosuppression, although it is not currently used for these indications. A large systematic review and meta-analysis found no impact of IVIG on infection or mortality after HSCT.[181] Similarly, an open-label phase II study, published after the meta-analysis, of IVIG for the prevention of cytomegalovirus (CMV) infection at day 100 after allogeneic HSCT found no benefit of regular IVIG prophylaxis.[182] In a small randomized, blinded, placebo-controlled crossover trial of lung transplant recipients with hypogammaglobulinemia, monthly infusions of IVIG had no impact on bacterial or other infections during the 3-month trial period.[183]

Finally, polyvalent IVIG has been proposed as therapy for flavivirus infection. There are case reports of therapeutic IVIG use in West Nile virus (WNV) infection in immunosuppressed patients, and a double-blind, placebo-controlled randomized trial of 22 children in Nepal with suspected Japanese encephalitis found an increase in antibodies specific to the Japanese encephalitis virus, but no significant difference in mortality or neurologic recovery among the small number of participants.[184,185] It should be noted that the IVIG selected for use in the trial was obtained from blood donors in a region endemic for Japanese encephalitis virus and therefore known to have high seropositivity.

Adverse effects of IVIG are common and include headache, myalgias, arthralgias, fatigue, and malaise, all or some of which may be alleviated by slowing the infusion rate.[186] Transient acute renal insufficiency and aseptic meningitis can occur, and arterial and venous thrombotic events are being recognized with increasing frequency.[187] In individuals with complete IgA deficiency, anti-IgA antibodies have been implicated in anaphylaxis on receipt of IVIG. However, a review highlighted the lack of a definitive causal role (anaphylaxis can occur in the absence of these antibodies), and the successful receipt of IVIG by some individuals with IgA deficiency and anti-IgA antibodies.[188] In the past, IVIG has been a source of transmitted HCV infection, however, the risk is lower with viral inactivation procedures now required in the production of all IVIG products, and input plasma screening by minipool nucleic acid testing for HBV, HCV, and HIV.[189,190]

In contrast to the pooled, nonspecific IVIG, hyperimmune globulin therapy is designed to provide or replace pathogen-specific antibodies that are lacking in the recipient. Hyperimmune (high specific titer) IgG preparations are routinely available for passive prophylaxis, treatment, or prevention of vertical transmission of a number of viral and toxin-mediated infectious diseases, including CMV, hepatitis B, varicella, rabies, botulism, anthrax, and tetanus (see Chapters 316, 145, 136, 163, 245, 207, and 244). Pathogen-specific hyperimmune globulin was also found to lower both viral load and mortality in a small double-blind RCT in a subgroup of critically ill patients with 2009 pandemic influenza A (H1N1) infection who received the hyperimmune globulin within 5 days of symptom onset.[191] At the time of publication, at least two further studies were recruiting participants: a phase III RCT of antiinfluenza hyperimmune globulin for the treatment of patients hospitalized with influenza A or B (ClinicalTrials.gov identifier: NCT02287467), and a phase II RCT of antiinfluenza immune globulin for the treatment of patients hospitalized with serious influenza A (H3N2) or (H1N1) infection (ClinicalTrials.gov identifier: NCT03315104).

MONOCLONAL ANTIBODIES

Pathogen-specific MAbs are an attractive alternative to nonspecific IVIG and even hyperimmune globulin preparations, although their clinical usefulness has been somewhat hampered by cost and time required for development. Nonetheless, MAbs have been approved for use for both primary and secondary prophylaxis, and treatment, of several viral and toxin-mediated infectious diseases.

Best established among the antiinfective MAbs is palivizumab, a humanized mouse monoclonal IgG1 that binds to a conserved protein in the respiratory syncytial virus (RSV) to prevent both viral fusion with respiratory epithelial cells and cell-to-cell fusion of infected epithelial cells.[192] Palivizumab is administered as a maximum of five monthly intramuscular doses (15 mg/kg) during RSV season (typically November through March in the Northern Hemisphere) to selected high-risk infants with the goal of reducing both the severity of infection and the resulting need for hospitalization (primary data summarized in both a Cochrane Library systematic review and the technical report accompanying the American Academy of Pediatrics [AAP] guidelines).[193,194] There are some data to suggest that palivizumab prophylaxis reduces recurrent wheezing (as per parental report or recall) during the first 1 to 2 years of life depending on the population studied, but none to suggest that it affects mortality or long-term pulmonary outcome.[193,195,196] As a result, the AAP has revised its guidelines on palivizumab use several times in an attempt to better define the pediatric populations at highest risk of RSV-related morbidity. According to those guidelines, palivizumab may be considered for RSV prophylaxis during RSV season in the following high-risk pediatric populations: (1) infants born before 29 weeks, 0 days gestational age and who will be younger than 12 months at the start of RSV season; (2) preterm infants in the first year of life with chronic lung disease of prematurity, and those in the second year of life for whom medical treatment for chronic lung disease of prematurity is required in the 6 months preceding RSV season; (3) infants in the first year of life who have hemodynamically significant congenital heart disease, particularly those with acyanotic heart disease being treated for congestive heart failure (CHF) and awaiting surgery, and those with moderate-to-severe pulmonary hypertension; (4) heart transplant recipients younger than 2 years whose transplantation was performed during RSV season; (5) infants in the first year of life who have pulmonary or neuromuscular abnormalities that impair clearance of secretions; (6) children younger than 2 years who are significantly immunocompromised during RSV season; and (7) infants with cystic fibrosis and chronic lung disease or nutritional compromise in the first year of life, and those with severe lung disease or weight for length less than the 10th percentile in the second year of life. Most significantly, the use of palivizumab in otherwise healthy preterm infants born at or after 29 weeks' gestation is no longer recommended. A large retrospective nonrandomized study published after the AAP guidelines found that, among infants born between 29 and 32 weeks of gestational age, receipt of palivizumab was associated with a small but statistically significant decrease in hospitalization for RSV but a reciprocal increase (of similar magnitude) in hospitalization for bronchiolitis without RSV.[197] Palivizumab had no impact on hospitalization for preterm infants born after 32 weeks. There are insufficient data to support the use of palivizumab for the treatment of active RSV disease in either adults or children, for the prophylaxis of RSV infection in adults, or

for the prevention and control of nosocomial RSV outbreaks. Used in pediatric populations, palivizumab is well tolerated, with idiosyncratic hypersensitivity reactions being the most common serious adverse event.[198]

Bezlotoxumab is an MAb directed against TcdB, the pathogenic exotoxin B of *Clostridioides difficile* (formerly *Clostridium difficile*), and prevents binding of the toxin to host cells.[199] Endogenous anti–toxin B antibodies have been shown to be protective against recurrent *C. difficile* infection, and a single infusion of bezlotoxumab was found to reduce recurrence at 12 weeks in two large double-blind, placebo-controlled, randomized trials (MODIFY I and II) of adults with primary or recurrent *C. difficile* receiving concurrent treatment with metronidazole, vancomycin, or fidaxomicin (4% of patients).[200,201] Patients received bezlotoxumab within a median of 3 days of starting therapy for *C. difficile* infection. Of note, there was a numeric but not statistically significant reduction in recurrent infection in the prespecified subgroups of patients who received bezlotoxumab and who were infected with *C. difficile* strains associated with worse outcome, including those infected with 027 and a composite subgroup of those infected with 027, 078, or 244. However, there was a statistically significant reduction in recurrent infection in these subgroups when bezlotoxumab was administered with actoxumab, an MAb directed against *C. difficile* toxin A. Important to note, participants infected with these strains represented only a small proportion of the total study population, and actoxumab was not found to affect recurrence rates, whether used alone or in addition to bezlotoxumab, in the trial population as a whole. Bezlotoxumab was approved by the FDA in 2016 as adjunctive therapy for the prevention of recurrent *C. difficile* infection in adult patients who are already receiving antibacterial therapy against *C. difficile* and are at high risk of recurrence.[202] A caution regarding the use of bezlotoxumab in patients with CHF was included in the labeling, based on the observation that administration of bezlotoxumab was associated with increased risk of heart failure exacerbation in patients with a prior history of CHF. Because the approval for bezlotoxumab came after the completion of the most recent guidelines for the treatment of *C. difficile* infection by the IDSA and Society for Healthcare Epidemiology of America (SHEA), no recommendations regarding its role in the treatment algorithm were made.[203]

Eculizumab is a humanized MAb that binds C5 of the complement system and prevents its cleavage by C5 convertases into C5a, a potent anaphylatoxin that can mediate degranulation and phagocytosis by neutrophils, and C5b, a terminal complement component and part of the membrane attack complex responsible for cytolysis.[204] Eculizumab is currently approved in the United States and Europe for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical (without *Shiga* toxin–producing *E. coli* [STEC] infection) hemolytic-uremic syndrome (aHUS), and refractory generalized myasthenia gravis in those patients who are anti–acetylcholine receptor antibody positive (see Table 49.3). During the 2011 outbreak of STEC O104:H4 infection in Europe, eculizumab therapy was used for the first time in the treatment of typical, diarrhea-positive, STEC-associated hemolytic-uremic syndrome (HUS).[205] Although administration of eculizumab was not randomized, several matched and unmatched observational studies found no reduction in dialysis, seizures, or death among those who received eculizumab versus those who received best supportive care.[206] Longer-term follow-up of children from the same outbreak (median follow-up time of 3 years) demonstrated no difference in renal outcome parameters between those who received eculizumab and those who did not.[207] Therefore eculizumab is not indicated for the treatment of STEC-induced HUS.

Raxibacumab is a human MAb directed against the protective antigen of *Bacillus anthracis* and approved by the FDA for use in adults and children for treatment of inhalational anthrax, in combination with antibacterial therapy, and for prophylaxis of inhalational anthrax in the absence of other appropriate therapy. Given the near impossibility of studies of inhalational anthrax in humans, raxibacumab was approved on the basis of preclinical animal studies and evaluation of its pharmacokinetics and safety in healthy volunteers.[208] Rabbits treated with prophylactic raxibacumab had a dose-dependent improvement in 14-day survival as compared with placebo, and cynomolgus monkeys given prophylactic raxibacumab demonstrated improvement in 28-day survival and in outcome after rechallenge 1 year later in those animals that survived the initial insult.[209] When administered for treatment, raxibacumab improved survival in both rabbits and cynomolgus macaques as compared with placebo. In a relatively large study of 76 rabbits that survived to 84 hours after receiving 200 times the median lethal dose of *B. anthracis* spores, treatment with raxibacumab in addition to levofloxacin resulted in a numerically but not statistically significant improvement in survival rate when compared with treatment with levofloxacin alone.[210] As a result, raxibacumab has been included as part of anthrax preparedness guidelines from both the Centers for Disease Control and Prevention and the AAP as adjunctive treatment to antimicrobial therapy for systemic anthrax.[211,212] A second anthrax antitoxin MAb, obiltoxaximab, has been approved by the FDA for the same indication. In a rabbit model of inhalational anthrax, use of obiltoxaximab in combination with doxycycline resulted in a numerically but not statistically significant increase in survival at 30 days.[213] Important to note, neither raxibacumab nor obiltoxaximab is expected to cross the blood-brain barrier, and therefore these agents are not expected to be effective for the treatment of meningitis in this setting.

ZMapp is a combination of three humanized chimeric MAbs that reduced mortality in nonhuman primate models of Ebola virus disease (EVD).[214] In a randomized, controlled trial of 72 patients with EVD, three weight-based intravenous infusions of ZMapp every 3 days in addition to standard of care did not meet the a priori established target for superior reduction in 28-day mortality when compared with the standard of care alone.[215] It should be noted that the trial was closed early, before the planned enrollment of 200 individuals, when the EVD outbreak in West Africa was declared over. At the time of publication, ZMapp was not approved for use in either the United States or Europe. Convalescent blood products have also been studied in EVD. A nonrandomized observational study of two infusions of ABO-compatible convalescent plasma in patients with EVD in Guinea found no significant difference in 14-day mortality as compared with usual standard of care.[216] However, levels of neutralizing antibodies in the convalescent plasma were not known before administration.

Finally, several anti-HIV MAbs have been identified and target either epitopes on the HIV envelope or on the T cell itself. Included in the first group are broadly neutralizing antibodies such as the anti-CD4 binding site antibodies VRC01 and 3BNC117, and the anti-V3 glycan supersite antibody 10-1074. In phase I and/or IIa studies, these antibodies appear to be well tolerated and capable of reducing viremia in antiretroviral naïve patients and delaying reemergence of viremia after analytic treatment interruption of ART in previously treated patients.[217–219] However, they were also associated with varying degrees of rebound viremia with antibody-resistant virus when used as monotherapy. As a result, current studies are focused on using the broadly neutralizing antibodies (1) in combination with each other—for example, several phase I studies combining 3BNC117 and 10-1074 in patients with HIV infection (ClinicalTrials.gov identifiers: NCT03526848, NCT02825797, and NCT02824536); (2) as adjuncts to antiviral therapy—for example, a phase I/II study of VRC01 in combination with ART in HIV-infected infants at 12 weeks of age or younger (ClinicalTrials.gov identifier: NCT03208231) and a phase I study of VRC01 with or without ART in adults with acute HIV infection (ClinicalTrials.gov identifier: NCT02591420); and (3) as a means of HIV prevention in at-risk individuals—for example, two phase IIb studies using VRC01 for immunoprophylaxis of HIV infection (ClinicalTrials.gov identifiers: NCT02568215 and NCT02716675).

Monoclonal antibodies that target the T cell include PRO 140, which binds to the CCR5 coreceptor, and ibalizumab-uiyk, which binds to the CD4 receptor. Both prevent entry of HIV-1 into $CD4^+$ T cells. Weekly administration of PRO 140 monotherapy was shown in a phase IIb study to prevent viral rebound at 12 weeks after analytic treatment interruption in 56.1% of patients with CCR5-tropic virus whose viral load was suppressed on their current oral antiretroviral regimen.[220] Phase III trials of PRO 140 are ongoing in virologically suppressed patients and in treatment-experienced patients with detectable viral loads despite oral ART (ClinicalTrials.gov identifiers: NCT02859961 and NCT02483078). Ibalizumab-uiyk received FDA approval in May 2018 for use, in combination with other antiretroviral medications, in the treatment of heavily treatment-experienced adults with

multidrug-resistant HIV-1 infection in whom current therapy is failing.[221] Approval was granted on the basis of a phase III open-label clinical trial (TMB-301; ClinicalTrials.gov identifier: NCT02475629) that enrolled 40 patients who received a loading dose of ibalizumab-uiyk in combination with their failing antiretroviral regimen and were then transitioned to maintenance doses of ibalizumab-uiyk every 2 weeks in combination with an optimized background antiretroviral regimen that included at least one medication to which the virus was susceptible. Virologic suppression was achieved in 83% of patients 1 week after the loading dose was administered, and remained suppressed at <50 copies/mL in 43% of patients 24 weeks later. Immune reconstitution inflammatory syndrome (IRIS) was noted in 1 patient who received ibalizumab-uiyk in combination with other ART.

GLUCOCORTICOSTEROIDS

Glucocorticosteroids have prominent antiinflammatory effects and are used to restrain an overactive host immune response contributing to the pathology of an infection. Glucocorticosteroids have proved beneficial to overall clinical outcome when combined with effective antimicrobial therapy in *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia (PJP) in HIV-infected individuals, some forms of extrapulmonary TB, and bacterial meningitis. They are recommended for selected patients with sepsis and have been studied with varying effect in other infectious disease syndromes.

In HIV-infected individuals with PJP and moderate-to-severe hypoxia (arterial Po_2 <70 mm Hg), clinical studies have conclusively demonstrated that initiation of glucocorticosteroid therapy within 72 hours after initiation of antibiotics significantly increases arterial oxygenation and decreases the incidence of respiratory failure and mortality (see Chapters 129 and 269).[222]

Adjunctive glucocorticosteroid therapy has also been used to dampen the damaging host inflammatory response in extrapulmonary TB and in paradoxical reactions to appropriate antimycobacterial therapy (see Chapters 129 and 249). A landmark RCT of adjunctive steroids for the management of tuberculous meningitis in individuals older than 14 years demonstrated that patients who received steroids in combination with antituberculous therapy had a reduced risk of death versus those who received antituberculous therapy alone.[223] A subsequent systematic review of nine RCTs enrolling a total of 1337 participants confirmed a significant survival benefit at 3 to 18 months of follow-up in those who received adjunctive steroid therapy, although no impact on disabling neurologic deficit was detected.[224] Five-year follow-up of patients enrolled in one of the included RCTs demonstrated no long-term benefit on either mortality or severe disability in those who had received steroid therapy.[225] Although only one trial in the systematic review included patients with HIV disease, results did not appear to differ between patients with and without HIV infection, and current guidelines suggest that adjunctive steroid therapy be considered in HIV-infected individuals with TB involving either the central nervous system (CNS) or the pericardium.[226] In HIV-negative individuals, steroids likely reduce the risk of death from pericarditis, whereas in HIV-infected individuals, the majority of whom were not receiving ART, steroids may reduce the risk of constrictive pericardial disease.[227] In the largest trial to explore corticosteroids for the treatment of tuberculous pericarditis, in which two-thirds of the patients had HIV disease, the reduction in constrictive pericardial disease in prednisolone-treated individuals was associated with a reduction in hospitalization.[228] However, prednisolone therapy was also associated with an increased risk of HIV-associated malignancy. Unlike in CNS or pericardial TB, adjunctive corticosteroid use in pulmonary TB has not been shown to reduce mortality.[229]

Corticosteroid therapy has been shown to benefit patients living with HIV who have experienced a paradoxical TB-associated IRIS in the setting of ART initiation. In a randomized, double-blind, placebo-controlled trial of prednisone for the treatment of non–life-threatening TB-IRIS, steroid therapy reduced the combined end point of days of hospitalization and outpatient procedures.[230] Steroid therapy, with a gradual taper, is recommended in patients with HIV and TB-associated paradoxical IRIS with significant symptoms or involving the CNS, except when concurrent Kaposi sarcoma is present or when the diagnosis of IRIS is not clear.[223] Steroid therapy is also recommended in patients with HIV and life-threatening unmasking TB-IRIS, owing to preexisting TB unrecognized at the time of initiation of ART, with the caveat that there are no objective data in this patient population. A similar caveat exists regarding the use of corticosteroids in the treatment of IRIS associated with cryptococcal meningitis in patients living with HIV. Although brief courses of steroids might be recommended by some, there are no data to support this practice, and steroids are not recommended for the treatment of cryptococcal meningitis not complicated by IRIS.[223] In a double-blind, placebo-controlled RCT of 451 patients with HIV-associated cryptococcal meningitis in Asia and Africa, those who received dexamethasone in addition to antifungal therapy (amphotericin and fluconazole) experienced a higher rate of mortality at 10 weeks and 6 months and disability at 10 weeks than did those who received antifungal therapy alone.[231] Adverse events were also more common, and fungal clearance of the CSF slower, in those who received dexamethasone, and the trial was concluded early on the basis of safety. Furthermore, no benefit to dexamethasone was detected even in a subgroup analysis of the 86 patients who had initiated ART within the 3 months before enrollment and were presumed to have unmasking IRIS.

In bacterial meningitis, the beneficial effects of adjunctive steroid therapy were first identified in 1988, in a study in which dexamethasone significantly decreased sensorineural hearing loss in infants and children with *Haemophilus influenzae* meningitis.[232] In 2002, a prospective, randomized, double-blind, multicenter trial showed that early treatment with dexamethasone (10 mg administered 15–20 minutes before or with the first dose of antibiotics, followed by 10 mg every 6 hours for 4 days) reduced mortality and improved overall clinical outcome in adults with acute bacterial meningitis, particularly pneumococcal meningitis.[233] Long-term follow-up of patients in this study demonstrated a mortality benefit in those who had received dexamethasone that persisted for a median duration of at least 13 years.[234] A subsequent systematic review, including 25 studies enrolling a total of 4121 adults and children, found that corticosteroid use reduced hearing loss and short-term neurologic sequelae, but not death, among the total mixed population of patients, but not among the subgroup of patients treated in resource-limited settings.[235] Mortality was reduced only in those with meningitis due to *Streptococcus pneumoniae*. Based on the overall evidence, adjunctive dexamethasone administered with the first dose of empirical antimicrobial therapy has become the standard of care in adults with suspected bacterial meningitis in non–resource-constrained settings.

Glucocorticosteroids were also the first immunomodulatory agents studied in patients with sepsis. A regimen of low-dose hydrocortisone and fludrocortisone reduced 28-day mortality when used in patients with adrenal insufficiency by cosyntropin test.[236] However, a second RCT in 499 patients with septic shock, 47% of whom did not have a response to the cosyntropin test, found no impact on 28-day mortality overall or in the predefined subgroup with adrenal insufficiency among patients who received hydrocortisone (50 mg intravenously every 6 hours for 5 days followed by a 6-day tapering dose).[237] A subsequent review of 27 trials enrolling a total of 3176 critically ill patients with sepsis found that steroid therapy reduced 28-day mortality, albeit with a caveat regarding the low quality of the evidence, partly based on the variety of dosing regimens trialed.[238] Subgroup analysis found a survival benefit with long-course (≥3 days), low-dose (≤400 mg/day of hydrocortisone or its equivalent) steroid therapy, but not with short-course, high-dose therapy. Important to note, reversal of shock at both day 7 and day 28 was significantly more likely in those who received steroid therapy. A second, more inclusive meta-analysis assessed trials that enrolled patients with less severe illness, anywhere along the sepsis spectrum from SIRS to septic shock, and found no impact of high- or low-dose corticosteroids on mortality.[239] Similarly, a randomized, double-blind trial of critically ill patients with sepsis found no benefit to low-dose steroid therapy for the prevention of shock within 14 days.[240] Current international consensus guidelines, therefore, recommend adjunctive low-dose hydrocortisone (200 mg/day) only in patients in whom adequate fluid resuscitation and vasopressor therapy have failed to resolve hemodynamic instability.[175] An exception to the rule against high-dose steroid therapy may be typhoid fever, in which mortality was

reduced approximately 50% by chloramphenicol plus high-dose dexamethasone (3 mg/kg followed by 1 mg/kg every 6 hours for eight doses) in a randomized, double-blind, placebo-controlled trial.[241] No trials have been conducted in the era of modern antimicrobial therapy. Glucocorticosteroid use in the treatment of patients hospitalized with community-acquired pneumonia has been an area of recent research interest. In a small RCT, patients who received dexamethasone (5 mg intravenously for 4 days) had no difference in outcome compared with those who received placebo.[242] Dexamethasone did appear to shorten the median duration of hospitalization by 1 day, but also significantly increased the incidence of hyperglycemia. Similarly, a double-blind, placebo-controlled RCT of 785 adults hospitalized for less than 24 hours with community-acquired pneumonia found that prednisone (50 mg/day for 7 days) shortened time to clinical stability and duration of hospitalization by approximately 1 day but resulted in more hyperglycemic episodes requiring insulin than did placebo.[243] A meta-analysis confirmed the reduced length of stay and increased incidence of hyperglycemia that were found in the individual trials, but also reported no reduction in all-cause mortality and an increase in readmission to hospital within 30 days due to community-acquired pneumonia.[244] Without more definitive benefit to clinical outcomes, adjunctive corticosteroid therapy is not considered current standard of care in patients hospitalized with community-acquired pneumonia.

Finally, glucocorticosteroid therapy has been used to reduce the inflammatory sequelae of a variety of other infections. A systematic review and meta-analysis of RCTs in patients aged 5 years and older who presented to either the emergency department or a primary care setting with acute tonsillitis, pharyngitis, or sore throat found that those who were treated with a single low dose of corticosteroid experienced faster pain relief and resolution than did those who received placebo.[245] Adverse events in this patient population were infrequent and similar in both the treatment and placebo groups. Glucocorticosteroids are also often administered in severe type 1 (reversal) and type 2 (erythema nodosum leprosum) reactions to prevent nerve damage in patients with leprosy, although evidence for their use in this context is limited.[246] In addition, glucocorticosteroids are recommended for the treatment of severe inflammatory syndromes, including pericarditis, rheumatologic disease, and mediastinal lymphadenitis associated with histoplasmosis.[247]

SYNTHETIC COMPOUNDS WITH IMMUNOMODULATORY ACTIVITY

The lipid-lowering HMG-CoA reductase inhibitors (statins) have been shown to modulate the immune response through a variety of mechanisms, including alteration of intracellular signaling pathways, decreased cytokine production, and changes in leukocyte trafficking and function.[248] Multiple observational studies have been published that document an association between the use of statin and risk for infection. In a large meta-analysis of published RCTs up to 2011, however, statin therapy had no demonstrable impact on the incidence of infection or infection-related mortality.[249] Nonetheless, multiple studies have been undertaken in the interim in an attempt to better define a specific population in whom statin therapy might improve outcome. Best studied are hospitalized patients with sepsis, in whom several meta-analyses have likewise documented no impact of statin therapy on mortality.[250,251] Critically ill patients with ARDS, most or all of whom have had ARDS on the basis of sepsis, have also shown no improvement in clinical outcomes including 28-day or 60-day in-hospital mortality.[252,253] The latter study followed the patient cohort for a year after enrollment, and likewise found no long-term survival benefit among those who received statins versus those who did not.[254] A retrospective cohort study of 2139 bacteremic patients reported no impact of prehospital statin use on survival after a propensity-matched analysis was performed to account for differences in clinical characteristics between the groups at baseline.[255] At the current time, therefore, there is no evidence to support the initiation of statin therapy to either prevent or treat sepsis or sepsis-associated ARDS.

Observational studies that have found an inverse relationship between statin use and pneumonia have provided the rationale for subsequent RCTs in this patient population. In a small trial of 34 patients who were hospitalized for community-acquired pneumonia, those randomized to receive statins experienced the same time to clinical stability as did patients randomized to receive placebo.[256] In a crossover randomized trial of statins in patients with severe bronchiectasis and chronic *Pseudomonas aeruginosa* colonization, patients randomized to receive statins had no change in the primary end point of cough.[257] Statins have been studied for their preventive impact on infections after stroke or transient ischemic attack (TIA), with similarly negative results.[258]

Imiquimod is a Toll-like receptor 7 agonist that upregulates IFN-α, IFN-γ, TNF, and IL-12. It is available as a cream in multiple strengths and is approved for topical treatment of external genital and perianal condylomata acuminata in patients age 12 and older (see Chapter 48). Imiquimod has not been shown to be effective for the treatment of molluscum contagiosum in children ages 2 to 12, and therefore should not be used for this indication. For the treatment of anogenital warts, topical imiquimod has been shown to be more effective than placebo, and not inferior to other patient- or provider-administered treatments. However, the authors of one systematic review considered the evidence to be of low or very low quality, with a high risk of bias in the included trials.[259,260] Topical imiquimod has also been shown to induce a clinical response in patients with high-grade human papillomavirus–induced vaginal intraepithelial neoplasia, and has also been used successfully in acyclovir-resistant anogenital herpes simplex virus infections in immunocompromised individuals.[261–263] Although not approved for this indication, topical imiquimod has also been demonstrated to enhance the serologic response to the intradermal seasonal influenza vaccine, and in a trial of older adults with a median age of 73 years was also associated with fewer hospitalizations for either influenza or pneumonia.[264]

Pentoxifylline is a methylxanthine derivative that has been shown to inhibit the production and effects of TNF. Pentoxifylline has been studied as an adjunct to antimicrobial therapy in neonates with sepsis, in whom it was found to reduce all-cause in-hospital mortality and length of hospitalization in a systematic review of several small trials.[265] Nonetheless, at least one double-blind RCT published after the systematic review found no survival benefit when pentoxifylline was added to standard therapy in preterm neonates with late-onset sepsis.[266] Pentoxifylline also continues to be studied as an adjunct to pentavalent antimony in adults with cutaneous leishmaniasis, with variable success.[267,268] At this time, pentoxifylline remains an investigational agent for the treatment of infectious diseases.

Thalidomide functions as an immunomodulator via selective inhibition of TNF production by monocytes-macrophages and is well established as an effective treatment for erythema nodosum leprosum.[269] Peripheral neuropathy is a relatively common adverse effect associated with long-term use, whereas arterial thromboembolic events and second primary malignancies are less common but more severe. The teratogenicity of thalidomide is well known, and in the United States it is available only to prescribers registered with the Risk Evaluation and Mitigation Strategies (REMS) program.

CELL-BASED IMMUNOMODULATORY THERAPY

MSC therapy is a promising candidate approach for immunomodulation in sepsis. MSCs are immune-privileged progenitor cells that can differentiate into multiple stromal or supporting cell types, produce a wide variety of cytokines and chemokines that influence immune cell maturation and function, and respond in vivo to proinflammatory stimuli.[270,271] In animal models of sepsis, intravenous administration of MSCs reduces mortality and increases bacterial clearance through enhanced phagocytic activity.[272] A systematic review and meta-analysis of all preclinical animal studies of MSCs in sepsis reported a significant reduction in mortality despite different models of sepsis and outcome measures, albeit with a substantial suspected overestimate of effect due to publication bias.[273] MSCs have already been studied for the treatment of a variety of cardiovascular diseases, and for GVHD, and have been found to be safe for intravascular administration to humans.[274] MSC therapy has been studied in phase I clinical trials for the treatment of sepsis and ARDS, much of which is sepsis-related. In a phase I

safety and dose escalation trial of nine patients with refractory septic shock and median APACHE II scores of 25, enrolled within 30 hours of admission to the intensive care unit, single intravenous infusions of varying doses of allogeneic single-donor bone marrow–derived MSCs were well tolerated, without infusion-related or serious and unexpected adverse events even in patients followed for a year after MSC infusion.[275] Sepsis-related serious and expected adverse events did occur and included bacterial and fungal infections, clinically important bleeding, arrhythmias, and pulmonary embolism. Similarly, in a phase I clinical trial of nine patients with moderate-to-severe ARDS, enrolled within 96 hours of meeting the Berlin definition for ARDS, receipt of a single intravenous infusion of allogeneic bone marrow–derived MSCs was well tolerated without demonstrable infusion-related events or serious treatment-related adverse events, although serious adverse events thought to be unrelated to treatment did occur.[276] Future studies will need to define not only the optimal dose of MSCs to deliver, but also the optimal timing of administration needed to produce a clinically significant benefit.

MSCs have also been studied in other infectious syndromes as well. In a small prospective study, that included 13 patients with HIV and $CD4^+$ T-cell counts <250 cells/mm^3 despite virologic suppression on ART, half of the patients were assigned to receive three monthly transfusions of MSCs and the other half to receive saline. MSCs were well tolerated, and were associated with increased $CD4^+$ T-cell counts.[277] Other cell products have also been explored in HIV disease. In a phase IIB, multicenter, double-blind trial of 54 patients with HIV, $CD4^+$ T-cell counts >450 cells/mm^3, and viral loads <50 copies/mL participants were randomized to receive engineered autologous dendritic cell injections or placebo every 4 weeks for 16 weeks. Monocytes were collected via leukapheresis, transformed into dendritic cells ex vivo, and engineered to express HIV viral proteins based on HIV RNA isolated from each patient's pre-ART plasma. Patients who received the engineered dendritic cells had enhanced $CD8^+$ effector/memory T-cell responses, but no change in viral load, when compared with patients who received placebo.[278] Although still in preclinical stages, an HIV-specific chimeric antigen receptor (CAR) $CD4^+$ T-cell product was able to control viral replication better than infusions of nonengineered T cells in a humanized mouse model of HIV.[279]

IMMUNOMODULATORY THERAPY AND INFECTIOUS RISKS

Immunomodulatory therapy is being used increasingly frequently by physicians in a variety of specialties for the treatment of immune-mediated diseases in rheumatology, gastroenterology, dermatology, neurology, and pulmonary medicine, and to enhance the immune-mediated antitumor response in solid tumors or target a malignant lineage of cells in hematopoietic malignancies. As a result, the population of immunosuppressed patients, and the specific iatrogenic immune deficits those patients may now possess, has grown considerably. This section of the chapter focuses on the infectious risks associated with immunomodulatory therapies that are currently approved for use in humans to treat noninfectious diseases. Conventional chemotherapeutic agents, novel agents whose primary risk relates to the infectious complications of neutropenia, and agents most commonly used in solid organ transplant or HSCT are not addressed here (see Chapters 306, 307, and 308). Instead, this chapter focuses on novel therapeutic agents that manipulate one or more aspects of the immune system to limit the impact of a noninfectious disease, and in doing so allow latent, opportunistic, or even common infections to manifest.

TNF inhibitors were one of the first groups of immunomodulatory agents to be recognized for their significant infectious risk. Anti-TNF therapy can be used for the treatment of a diverse array of noninfectious inflammatory diseases including rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, hidradenitis suppurativa, noninfectious uveitis, ulcerative colitis, and Crohn disease, depending on the particular TNF inhibitor chosen (e.g., adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab). In all cases, however, US labeling carries an FDA boxed warning about the risk of serious infections including TB, bacterial sepsis, invasive fungal infections such as histoplasmosis, and other opportunistic infections. TNF is an important proinflammatory cytokine and is crucial for the formation and activation of macrophages, phagosomes, and granulomas. Its inhibition, therefore, predisposes to infection by intracellular pathogens and pathogens that are controlled by the immune system via sequestration into granulomas.

Data for the association of TNF inhibitors and TB come largely from registries and long-term extensions of RCTs, and indicate lesser risk with screening and prophylaxis for latent tuberculosis infection (LTBI).[280,281,282] Therefore, several specialty societies have issued guidelines to minimize infectious risk with the use of TNF inhibitors. The American College of Rheumatology (ACR) currently recommends screening all patients for active or latent TB before therapy, and that immunosuppressed patients with risk factors for TB with an initial negative test result undergo repeated testing after 1 to 3 weeks.[283–285] Active TB should be treated appropriately before initiation of an anti-TNF agent, and at least 1 month of treatment for latent TB should be completed before initiation of anti-TNF therapy.[283–285] A high index of suspicion for reactivated or de novo TB should be maintained for the entire duration of anti-TNF therapy, regardless of initial screening test results. The ACR currently recommends that screening be repeated intermittently (if the initial test result is negative) if risk factors for TB infection persist.[283–285]

In addition to TB, the ACR identifies other risks with TNF inhibitor use and recommends that TNF inhibitors not be initiated or resumed in the setting of serious bacterial infection requiring antibiotics, febrile and presumed viral upper respiratory tract infection, infected skin ulcer, active and life-threatening invasive fungal infection, active herpes zoster infection, acute hepatitis B or C infection, and chronic hepatitis B or C infection with significant liver injury.[283–285] The 2015 ACR recommendations reference guidelines from the American Association for the Study of Liver Diseases (AASLD) with regard to screening for hepatitis B.[286] The AASLD recommends screening all individual who are preparing to undergo immunosuppression, whether associated with cancer chemotherapy, transplantation, or biologic or corticosteroid therapy (especially at high doses of >20 mg of prednisone or its equivalent per day) for autoimmune or inflammatory diseases, with measurement of hepatitis B surface antigen and hepatitis B core antibody. Risk stratification to guide prophylactic or preemptive therapy can then be undertaken on the basis of each individual patient's serologic profile and planned immunosuppressive regimen.

Highlighted in the AASLD recommendations is the high risk of HBV reactivation, particularly in those who are HBV surface antigen positive, with the anti-CD20 MAb rituximab (see also Table 49.3). Because of the substantial risk of reactivation, prophylactic antiviral therapy is recommended for patients who are surface antigen positive, and for those who are surface antigen negative but core antibody positive.[286] Randomized trials have demonstrated the effectiveness of prophylaxis in both groups of patients.[287,288] Important to note, the risk of HBV reactivation may extend well beyond rituximab use; HBV reactivation has been reported more than 24 months after rituximab was discontinued.[289] Rituximab carries an FDA boxed warning regarding the risk of fulminant hepatitis, hepatic failure, and death in the setting of HBV reactivation associated with therapy, and of progressive multifocal leukoencephalopathy (PML), also potentially fatal.

Other immunomodulators are outlined in Tables 49.2 and 49.3. The infectious risk associated with each immunomodulator depends on its unique target within the immune system.

For instance, the group of immunomodulators collectively referred to as checkpoint inhibitors includes anti-PD-1 antibodies and anti-CTLA-4 antibodies. These molecules differ significantly from traditional chemotherapy, which, either purposefully or as an unintended consequence, reduces the number and function of immune cells. Checkpoint inhibitors, on the other hand, exert their antitumor effects by blocking inhibitory ligands from binding with receptors, thereby releasing target cells from inhibition, and stimulating rather than inhibiting the immune response with the goal of inducing an antitumor immune response. As a result, their direct infectious risks are relatively minimal. However, by releasing immune cells from inhibitory stimuli, these agents often precipitate immune-mediated adverse reactions that in

Text continued on p. 654

TABLE 49.2 Infectious Risks Associated With Selected Immunomodulatory Therapies Used in the Treatment of Malignancy

AGENT	MODE OF ACTION	IMMUNE DEFICIT	INFECTIOUS RISKS, MIMICKERS, AND PREVENTION	FDA-APPROVED CLINICAL INDICATIONS	REFERENCES
Immunomodulators Targeting Solid Tumors					
Atezolizumab (Tecentriq) Avelumab (Bavencio) Durvalumab (Imfinzi)	Monoclonal Abs directed against PD-L1, which may be found on tumor cells or tumor-infiltrating immune cells	Block the interaction between PD-L1 and PD-1 and B7.1 receptors on T cells and APCs, thereby increasing T-cell proliferation, cytokine production, and cytotoxic T-cell function in the tumor microenvironment	UTI is the most common infection in patients with urothelial cell carcinoma with all three agents Neutropenia and febrile neutropenia are rare Immune-mediated pneumonitis, hepatitis, colitis, nephritis, endocrinopathies and other immune-mediated phenomena may occur with all three agents *Atezolizumab:* 38.4% of patients developed infection Pneumonia most common in those with lung cancer Sepsis, herpes encephalitis, and mycobacterial infection have all been reported *Durvalumab:* Sepsis, necrotizing fasciitis, and osteomyelitis have all been reported In a study of durvalumab for use in NSCLC, for which it is not currently approved, pneumonia was the most frequent grade 3 or 4 adverse event, but was not increased with durvalumab over placebo	Locally advanced or metastatic urothelial carcinoma in patients who are not eligible for cisplatin chemotherapy (atezolizumab only) or who have had disease progression during or after platinum-containing chemotherapy or within 12 mo of adjuvant/ neoadjuvant chemotherapy[a] Metastatic NSCLC in patients with disease progression during or after platinum-containing chemotherapy and EGFR or ALK-specific therapies if applicable (atezolizumab only) Metastatic Merkel cell carcinoma in patients older than 12 yr (avelumab only)[a]	290–294
Ipilimumab (Yervoy)	Monoclonal Ab against CTLA-4	Binds and blocks CTLA-4, an inhibitor of T-cell function (checkpoint blockade), leading to T-cell activation and proliferation, and reduced Treg function	Fever in >5% Immune-mediated enterocolitis (with or without bowel perforation), hepatitis, dermatitis, neuropathy, and endocrinopathy can all occur, and in many cases, infectious causes will need to be ruled out[b] High-dose corticosteroids or TNF inhibitors (in the case of colitis) may be required for treatment of immune-mediated adverse reactions, may need to be continued for months, and may predispose to other opportunistic infections such as invasive fungal infections or PJP	Unresectable metastatic melanoma in patients aged >12 yr Cutaneous melanoma with >1 mm involvement of regional lymph nodes, as an adjuvant to complete resection and total lymphadenectomy	295–298
Pembrolizumab (Keytruda) Nivolumab (Opdivo)	Monoclonal Abs against PD-1	Bind and block the PD-1 receptor, which inhibits T-cell proliferation and cytokine production (checkpoint blockade), thereby allowing for enhanced T-cell function and surveillance	Immune-mediated adverse reactions may include pneumonitis, colitis, hepatitis, endocrinopathies, dermatologic disorders (including SJS or TEN), encephalitis, or nephritis High-dose corticosteroids may be required for immune-related adverse reactions Fever reported in ≥20% with anti-PD-1 therapy Active tuberculosis has been reported during both pembrolizumab and nivolumab therapy Allogeneic HSCT after anti-PD-1 therapy may be complicated by severe acute or hyperacute graft-versus-host disease, hepatic veno-occlusive disease, or a steroid-requiring febrile syndrome Postmarketing studies have reported an association of pembrolizumab with rejection of solid organ transplants	*Pembrolizumab:* Unresectable or metastatic melanoma Metastatic NSCLC: Single-agent first-line therapy for tumors with high PD-L1 expression and no EGFR or ALK mutations, or for tumors that express PD-L1 and have progressed on or after platinum-containing chemotherapy or therapy directed against EGFR or ALK mutations In combination with pemetrexed and carboplatin for nonsquamous NSCLC[a] Recurrent or metastatic head and neck squamous cell cancer with disease progression on or after platinum-containing chemotherapy[a] Refractory Hodgkin lymphoma or relapse after three or more lines of therapy[a] Locally advanced or metastatic urothelial carcinoma if not eligible for cisplatin-containing chemotherapy[a] or in patients with disease progression during or after platinum-containing chemotherapy (and within 12 mo if adjuvant or neoadjuvant) Unresectable or metastatic microsatellite instability–high cancer (but not in pediatric patients with CNS tumors), mismatch repair deficient solid tumors that have progressed and have no alternative therapies, and mismatch repair deficient colorectal cancer that has progressed after receipt of a regimen of fluoropyrimidine, oxaliplatin, and irinotecan[a] Recurrent, locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma expressing PD-L1, with progression on two or more lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and HER2/neu-targeted therapy (where applicable)[a]	299–307

Continued

TABLE 49.2 Infectious Risks Associated With Selected Immunomodulatory Therapies Used in the Treatment of Malignancy—cont'd

AGENT	MODE OF ACTION	IMMUNE DEFICIT	INFECTIOUS RISKS, MIMICKERS, AND PREVENTION	FDA-APPROVED CLINICAL INDICATIONS	REFERENCES
				Nivolumab: Unresectable or metastatic melanoma: single agent for BRAF V600 wild-type (or BRAF V600 mutation-positive[a]) disease, or in combination with ipilimumab[a] Metastatic NSCLC with progression on or after platinum-containing chemotherapy or EGFR- or ALK-specific therapy, if applicable Advanced renal cell carcinoma, after antiangiogenic therapy Hodgkin lymphoma with relapse or progression after autologous HSCT and posttransplantation brentuximab[a]	
Talimogene laherparepvec (Imlygic)	Oncolytic virus for local, intralesional injection	HSV-1 induces lysis of tumor cells, release of antigens, and overexpression of human GM-CSF, thereby increasing $CD8^+$ T cells and reducing inhibitory Tregs	Fever and influenza-like illness reported in ≥25% Herpetic infections (mucocutaneous and keratitis) have been documented. Acyclovir or other antiviral agents may interfere with antitumor activity Necrosis of the local injection site may occur, with secondary cellulitis or systemic bacterial infection reported Live-attenuated HSV may result in disseminated infection in immunocompromised patients and should not be administered to those with primary, acquired, or iatrogenic immunodeficiency or to those who are pregnant Effective contraception is recommended for recipients of childbearing potential owing to possible risk to fetus or neonate during therapy Immunocompromised or pregnant HCWs should not prepare or administer the virus, nor contact dressings, injection sites, or body fluids of recipients Any HCW, close contact, pregnant contact, or newborn should avoid direct contact with injection sites, dressings, and body fluids of the recipient Instructions for infection control and accident exposure precautions are included in the product monograph	Melanoma with unresectable cutaneous, subcutaneous, and nodal lesions that recur after surgery, with the caveat that talimogene laherparepvec has not been shown to affect survival or visceral metastases	308, 309
Immunomodulators Targeting Hematologic Malignancies					
Axicabtagene ciloleucel (Yescarta) Tisagenlecleucel (Kymriah)	CAR T-cell therapy	Autologous $CD8^+$ T cells directed against CD19 (B-lymphocyte antigen) after genetic modification with a transgene-carrying viral vector ex vivo Results in B-cell depletion or aplasia Preceded by lymphodepletion chemotherapy Corticosteroids or tocilizumab may be used to treat CRS	CRS may occur and may be fatal[b] Infections in ≥20% with either agent Bacterial, viral, and fungal pathogens all implicated Neutropenia, hypogammaglobulinemia, or agammaglobulinemia occur and may be prolonged Febrile neutropenia is common HBV reactivation is possible given B-cell target, so screening for HBV, HCV, HIV recommended before cell collection No live virus vaccines from 2 wk (tisagenlecleucel) to 6 wk (axicabtagene) before lymphodepleting therapy and until immune recovery after CAR T-cell infusion For tisagenlecleucel, myeloid growth factors, especially GM-CSF, are not recommended within 3 wk of infusion and until CRS has resolved Sample prophylactic regimen used in a phase I/II single institution study of tisagenlecleucel: Levofloxacin and fluconazole during neutropenia, acyclovir or valacyclovir from lymphodepletion until at least 3 mo after infusion, trimethoprim-sulfamethoxazole from neutrophil recovery until at least 3 mo after infusion, and IVIG for hypogammaglobulinemia when serum IgG levels measured monthly	*Axicabtagene:* Treatment of adults with relapsed or refractory large B-cell lymphoma (but not primary CNS lymphoma) after receipt of at least two lines of systemic therapy. *Tisagenlecleucel:* Treatment of B-cell ALL, refractory or in second or later relapse, in patients up to 25 yr old	310–312

Blinatumomab (Blincyto)	Bispecific T-cell engager (BiTE) monoclonal Ab	Ab binds to CD19 on B cells, both malignant and nonmalignant, and CD3 on T cells, thereby connecting the two and upregulating cell surface adhesion molecules, proinflammatory cytokines, and cytolytic proteins, resulting in lysis of $CD19^+$ B cells	CRS may occur and may be life-threatening or fatal[b] CRS is often accompanied by fever and elevated liver enzymes, and may be accompanied by DIC, CLS, and hemophagocytic histiocytosis/macrophage activation syndrome Serious, life-threatening, or fatal infections including sepsis, pneumonia, bacteremia, and opportunistic and catheter site infections were reported in 25% Neutropenia and febrile neutropenia have been reported Live vaccine should not be administered within 2 wk of therapy or until after immune recovery following final dose	Relapsed or refractory B-cell precursor ALL in adults and children	313–315
Brentuximab vedotin (Adcetris)	CD30-directed Ab-drug conjugate, consisting of a chimeric IgG1 anti-CD30 Ab, a microtubule disrupting agent (MMAE), and a linkage molecule	Binding of brentuximab to CD30 on Reed-Sternberg cells in Hodgkin lymphoma leads to internalization of the Ab-drug conjugate, intracellular release of MMAE, disruption of the microtubule network, and ultimately, cell-cycle arrest and apoptosis CD30 is also expressed by activated T and B cells	PML has been reported, may occur as early as 3 mo after initiation of therapy, and may be fatal; further doses should be held while PML is being investigated and discontinued once diagnosed[b] Neutropenia is common, may be prolonged or severe, and may require dose delays or reductions, discontinuation, or subsequent secondary G-CSF prophylaxis Bacterial, fungal, and viral infections can occur; clinical syndromes including pneumonia, bacteremia, sepsis, and septic shock have been reported CMV reactivation and viremia have been reported In a trial of brentuximab for Hodgkin lymphoma, primary prophylaxis with trimethoprim-sulfamethoxazole, ciprofloxacin, and G-CSF was used In the trial of brentuximab for post-HSCT consolidation, prophylaxis against HSV and VZV was administered for a median duration of 11.1 mo, and prophylaxis against PJP was administered for a median of 6.5 mo MMAE is a substrate of CYP3A4/5, and therefore administration with CYP3A4 inhibitors such as ketoconazole increases MMAE exposure, and administration with CYP3A4 inducers such as rifampin reduces MMAE exposure MMAE is also a substrate for the P-glycoprotein efflux transporter	Hodgkin lymphoma in adults after failure of either autologous HSCT or two or more multidrug chemotherapeutic regimens if HSCT cannot be used Hodgkin lymphoma in adults after autologous HSCT for consolidation therapy in patients at high risk of relapse or progression Primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides, in adults, after receipt of prior systemic therapy Systemic anaplastic large cell lymphoma in adults after failure of one or more multidrug chemotherapeutic regimens[a]	316–319
Copanlisib (Aliqopa) Idelalisib (Zydelig)	Small molecular inhibitors of phosphatidylinositol 3-kinase (PI3K) isoforms, which regulate signals from B-cell, integrin, cytokine, and chemokine receptors	Blockade of PI3Kα and PI3Kδ (copanlisib) or PI3Kδ (idelalisib) leads to disrupted intracellular signaling and B-cell apoptosis	Severe or fatal infections (including CMV and PJP),[b] hepatoxicity,[b] diarrhea/colitis,[b] pneumonitis,[b] and intestinal perforation[b] have all been documented in patients receiving idelalisib; serial monitoring of liver enzymes and blood counts is recommended Idelalisib-related noninfectious pneumonitis and/or colitis may necessitate treatment with corticosteroids Noninfectious pneumonitis may also occur with copanlisib Severe cutaneous reactions, neutropenia, and pneumonia may occur with either agent SJS and TEN have been seen with idelalisib CMV infection and viremia have been reported with idelalisib In those with a history of CMV infection or with positive serology, serial clinical and laboratory monitoring is required If infection or viremia occurs, idelalisib should be held until resolution, and if reintroduced, should be accompanied by monthly CMV PCR monitoring PJP has been reported with both agents, and documented PJP is a contraindication to resumption of idelalisib therapy, even after complete treatment of infection	*Copanlisib:* Relapsed follicular lymphoma despite at least two prior therapies[a] *Idelalisib:* With rituximab for relapsed chronic lymphocytic leukemia in patients for whom rituximab alone would also be indicated Relapsed follicular lymphoma or relapsed small lymphocytic lymphoma, despite receipt of at least two prior therapies[a] Not for use as first-line therapy in any patient or in combination with bendamustine or rituximab in follicular lymphoma	320–325

Continued

TABLE 49.2 Infectious Risks Associated With Selected Immunomodulatory Therapies Used in the Treatment of Malignancy—cont'd

AGENT	MODE OF ACTION	IMMUNE DEFICIT	INFECTIOUS RISKS, MIMICKERS, AND PREVENTION	FDA-APPROVED CLINICAL INDICATIONS	REFERENCES
			Primary prophylaxis for PJP should be given with idelalisib therapy and may be considered with copanlisib Copanlisib should be held during PJP treatment and resumed only after PJP treatment and if secondary PJP prophylaxis is provided Avoid use of either agent with strong CYP3A4 inducers such as rifampin, and monitor or dose adjust (see product monographs) if concomitant administration with strong CYP3A4 inhibitors cannot be avoided		
Elotuzumab (Empliciti)	Monoclonal Ab directed against SLAMF7	Binding of the monoclonal Ab to SLAMF7 leads to NK cell activation and destruction of SLAMF7-expressing cells	Fever, pneumonia, upper respiratory tract infection, and nasopharyngitis reported in ≥20% Opportunistic infections including fungal infections and herpes zoster have also been reported Lymphopenia is common	Multiple myeloma, in combination with lenalidomide and dexamethasone, after receipt of 1–3 prior treatment regimens	326–328
Ibrutinib (Imbruvica)	Covalent inhibitor of Bruton tyrosine kinase	Inhibition of Bruton tyrosine kinase interferes with signaling from B-cell and chemokine receptors, impairing B-cell migration and adhesion	Bacterial, viral and fungal infections may occur HBV reactivation, PML, PJP, and disseminated cryptococcosis have been documented Invasive aspergillosis, particularly of early onset and affecting the central nervous system, has also been identified in patients receiving ibrutinib Neutropenia is common and blood counts should be monitored at least monthly Coadministration with strong CYP3A inducers and inhibitors should be avoided Dose modifications according to indication are provided in the product monograph for concomitant use with azoles	Mantle cell lymphoma after one or more prior therapies[a] CLL or small lymphocytic lymphoma, including those with 17p deletion Waldenström macroglobulinemia Marginal zone lymphoma in patients who are candidates for systemic therapy and have received one or more prior anti-CD20 therapies[a] Chronic graft-versus-host disease after failure of at least one line of systemic therapy	329–332
Inotuzumab ozogamicin (Besponsa)	Anti-CD22 Ab-drug conjugate	Binding of the Ab component of inotuzumab to CD22 leads to internalization and then release of drug which subsequently induces breaks in the DNA, cell-cycle arrest, and apoptosis	Higher day 100 post-HSCT mortality, not related to relapse, hepatotoxicity, and fatal or life-threatening hepatic veno-occlusive disease have been reported[b] Neutropenia, fever, and febrile neutropenia reported in ≥20%	Relapsed or refractory B-cell precursor ALL	333, 334
Obinutuzumab (Gazyva) Ofatumumab (Arzerra) Rituximab (Rituxan) is discussed in greater detail in the body of the text	Monoclonal Ab targeting CD20 on pre-B and mature B cells Each of the three molecules binds to a unique epitope on CD20	B-cell lysis and depletion	Hepatitis B reactivation can occur in both HBsAg- and HBcAb/HBsAb-positive patients, and may be fatal[b] All patients should be tested for HBsAg and HBcAb before initiation of therapy, and those who are positive should be considered for antiviral therapy and monitored during and for several months after therapy Ofatumumab has been associated with HBV reactivation 12 mos after therapy Anti-CD20 therapy should be discontinued in the event of HBV reactivation, and treatment for HBV should be initiated There are no data to indicate whether anti-CD20 therapy can be reinstated after HBV reactivation Fatal new infection with HBV has been reported with ofatumumab PML can occur and has been fatal[b] Anti-CD20 therapy should be discontinued if PML occurs Neutropenia is common, and antimicrobial prophylaxis is recommended for severe neutropenia lasting more than 1 wk Neutropenia may be prolonged (lasting >28 days) or delayed (occurring >28 days after therapy)	*Obinutuzumab:* Previously untreated CLL in adults, in combination with chlorambucil Follicular lymphoma (relapsed or refractory to rituximab-containing therapy), in combination with bendamustine and then as monotherapy Previously untreated follicular lymphoma, stages II bulky, III, or IV, in combination with chemotherapy and followed by obinutuzumab monotherapy in those achieving at least partial remission *Ofatumumab:* Previously untreated CLL, in combination with chlorambucil, if fludarabine cannot be used Relapsed CLL, in combination with fludarabine and cyclophosphamide Extended treatment of recurrent or progressive CLL in complete or partial remission after two or more lines of therapy CLL refractory to fludarabine and alemtuzumab	335, 336, 337–342

			Bacterial, fungal, and viral infections (new and reactivated) can occur and may be serious or fatal, and anti-CD20 therapy should not be administered to those with active infection Serious adverse events, and those graded 3–5 in severity, were more common with obinutuzumab than rituximab when used for follicular lymphoma, although progression-free survival was better with obinutuzumab Trials in RA have screened for latent TB infections as per local guidelines, and excluded those with LTBI, and trials in follicular lymphoma excluded HBsAg-positive patients and included HBcAb-positive patients provided they were willing to undergo monthly HBV testing. HBsAb-positive patients were included. Live vaccines are not recommended during treatment and until B-cell recovery; at least one trial of obinutuzumab excluded patients who had received a live vaccine in the preceding 28 days Immunogenicity of any vaccine after ofatumumab is unknown		
Ruxolitinib (Jakafi) See also: Tofacitinib (Xeljanz)	Inhibitor of Janus kinase (JAK) 1 and 2	Inhibition of JAKs 1 and 2 disrupts cytokine and growth factor signaling, thereby altering immune function, in particular that of dendritic cells Proinflammatory cytokines may also be reduced	Serious bacterial, viral (PML, herpes zoster), mycobacterial, and fungal infections have been reported Therapy should not be initiated until serious infections have resolved Localized and disseminated tuberculosis has been reported with ruxolitinib Prior to therapy, patients should be assessed for risk of active or latent tuberculosis, and testing for LTBI should be performed in those at higher risk HBV DNA titers can increase during therapy with or without concomitant increases in liver enzymes; clinical guidelines for monitoring and treatment of patients with chronic HBV should be observed Neutropenia, including severe neutropenia, may occur Dose modifications are required if coadministered with strong CYP3A4 inhibitors or fluconazole ≤200 mg/day (see product monograph); use with fluconazole >200 mg/day should be avoided	Myelofibrosis, intermediate or high risk, and including primary, post–polycythemia vera, and post–essential thrombocythemia myelofibrosis Polycythemia vera with inadequate response or intolerance to hydroxyurea	343–346

[a]Accelerated approval; confirmatory clinical trials may be required to maintain this indication.
[b]FDA boxed warning.
Ab, Antibody; *ALL,* acute lymphoblastic leukemia; *APCs,* antigen-presenting cells; *ALK,* anaplastic lymphoma kinase; *CAR,* chimeric antigen receptor; *CLL,* chronic lymphocytic leukemia; *CLS,* capillary leak syndrome; *CMV,* cytomegalovirus; *CNS,* central nervous system; *CRS,* cytokine release syndrome; *CTLA-4,* cytotoxic T-lymphocyte antigen 4; *DIC,* disseminated intravascular coagulation; *EGFR,* epidermal growth factor receptor; *FDA,* US Food and Drug Administration; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *G-CSF,* granulocyte colony-stimulating factor; *HBcAb,* hepatitis B virus core antibody; *HBsAb,* hepatitis B virus surface antibody; *HBsAg,* hepatitis B virus surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HCW,* health care worker; *HSCT,* hematopoietic stem cell transplant; *HSV,* herpes simplex virus; *IgG,* immunoglobulin G; *IVIG,* intravenous immune globulin; *LTBI,* latent tuberculosis infection; *MMAE,* monomethyl auristatin E; *NSCLC,* non–small cell lung cancer; *PCR,* polymerase chain reaction; *PD-1,* programmed death receptor 1; *PD-L1,* programmed death ligand 1; *PJP, Pneumocystis jirovecii* pneumonia; *PML,* progressive multifocal leukoencephalopathy; *SJS,* Stevens-Johnson syndrome; *SLAMF7,* signaling lymphocytic activation molecule family member 7; *TB,* tuberculosis; *TEN,* toxic epidermal necrolysis; *TNF,* tumor necrosis factor; *Treg,* regulatory T cell; *UTI,* urinary tract infection; *VZV,* varicella zoster virus.

TABLE 49.3 Infectious Risks Associated With Selected Immunomodulatory Therapies in the Treatment of Nonmalignant Diseases

AGENT	MODE OF ACTION	IMMUNE DEFICIT	INFECTIOUS RISKS, MIMICKERS, AND PREVENTION	FDA APPROVED CLINICAL INDICATIONS	REFERENCES
Immunomodulators Targeting Autoimmune or Connective Tissue Diseases					
Abatacept (Orencia)	Fusion protein composed of the hinge, CH2, and CH3 domains of IgG1 and the extracellular domain of CTLA-4	By binding to costimulatory molecules (CD80 and CD86) on antigen-presenting dendritic cells, abatacept prevents T-cell activation and proinflammatory cytokine release	In clinical trials, the most commonly reported infections have been upper respiratory tract infections, nasopharyngitis, sinusitis, UTIs, cellulitis, and bronchitis, among others Pneumonia and sepsis, including fatal cases, have been observed in patients receiving abatacept Abatacept should not be initiated in the setting of active infection, and should be discontinued if a serious infection develops on therapy Patients should be screened for LTBI, and if positive, anti-TB therapy should be initiated, prior to beginning therapy with abatacept; at least one open-label clinical trial used this protocol and found no cases of active TB at 6 mo Although reactivation of TB with abatacept therapy has been reported, it appears to be rare Screening for HBV should be done before abatacept therapy, because reactivation, even in patients who are isolated HBcAb positive, has been reported; important to note, those who screened positive for HBV were excluded from initial clinical trials Abatacept should not be administered concurrently with TNF inhibitors owing to the increased risk of infection Live vaccines should not be administered during, or within 3 mo after, abatacept therapy Inactivated vaccines may be less effective during abatacept therapy; therefore vaccinations should be up-to-date prior to beginning therapy, in accordance with local guidelines	Moderate-severe active RA in adults Moderately to severely active polyarticular juvenile idiopathic arthritis in children ≥2 yr old Active psoriatic arthritis in adults	280, 347, 348, 349, 350
Anakinra (Kineret)	IL-1 receptor antagonist	By binding to the IL-1 receptor, anakinra competitively inhibits both IL-1α and IL-1β and prevents the resulting proinflammatory cascade	If serious infection occurs during therapy, anakinra should be discontinued for patients with RA; patients with NOMID may be at risk of a flare of their underlying disease and therefore a risk-benefit analysis applies Anakinra should not be initiated in patients with active infections Cellulitis, pneumonia, and bone and joint infections were reported most frequently in clinical trials of anakinra in RA; fungal (including histoplasmosis and *Candida* esophagitis), mycobacterial, and bacterial opportunistic infections have been reported in postmarketing experience Upper respiratory tract infection, sinusitis, otitis media, and nasopharyngitis were the infections most often observed in clinical trials in patients with NOMID Reactivation of TB has been reported, including after negative screening for LTBI prior to anakinra initiation; however, TB reactivation in this setting (with appropriate screening and treatment for LTBI before therapy) appears to be rare HBV reactivation with anakinra use has not been studied Neutropenia can occur and therefore blood counts should be assessed at baseline, monthly for 3 mo, and then every 3 mo for 1 yr Combination use with TNF inhibitors is not recommended owing to increased risk of infection Live vaccines should not be administered during anakinra therapy; no difference in serologic response to Td vaccine was detected between patients receiving anakinra and those receiving placebo	Moderate-to-severe active RA in adults without response to one or more prior DMARDs CAPS, specifically NOMID	280, 351–353
Belimumab (Benlysta)	Monoclonal Ab against B-lymphocyte stimulator (BLyS), previously known as BAFF	By binding to BLyS, required for B-cell survival and maturation, belimumab inhibits autoreactive B cells and B-cell differentiation into plasma cells	Serious infections reported, including at least one episode of fatal CMV pneumonia PML has been reported in patients receiving belimumab, and in some cases has been fatal; belimumab should be discontinued if PML is confirmed Live vaccines should not be administered for 30 days before, or during, belimumab therapy Upper respiratory tract infections are most commonly reported; pneumonia, cellulitis, and UTIs are among the most common serious infections reported Severe hypogammaglobulinemia occurs infrequently	Adult patients with active SLE and positive autoantibodies (ANA or dsDNA) despite standard therapy Belimumab should not be used in CNS lupus, active lupus nephritis, or in individuals receiving other biologics or intravenous cyclophosphamide, as it has not been studied in these patient populations	336, 354, 355

Brodalumab (Siliq) Ixekizumab (Taltz) Secukinumab (Cosentyx)	Monoclonal Abs directed against IL-17 or IL-17 receptor A	By binding either IL-17 or its receptor, these therapies prevent cytokine signaling and subsequent release of other proinflammatory cytokines	In clinical trials, patients receiving anti-IL-17 therapy had a higher rate of infections overall than did those receiving placebo The most commonly reported infections include upper respiratory tract infections, pharyngitis, UTIs, and oral candidiasis One instance of cryptococcal meningitis has been reported with brodalumab Perform a risk-benefit evaluation before initiating anti-IL-17 therapy in patients with chronic or recurrent infections, and suspend anti-IL-17 therapy until infection resolves if serious infection develops on therapy Patients should be screened for LTBI before initiation of therapy with anti-IL-17 agents, and if positive, treatment for LTBI should be started before anti-IL-17 therapy is administered Active TB is a contraindication to anti-IL-17 therapy, and patients should be monitored for active TB during and after therapy With ixekizumab or secukinumab, empirical anti-TB therapy may be considered for those with a past history of TB or LTBI but without clear documentation of adequate treatment Neutropenia can occur with anti-IL-17 therapy Live vaccines should not be administered to patients receiving anti-IL-17 therapy; response rates to inactivated vaccines administered during anti-IL-17 therapy may be reduced, so all age-appropriate recommended, inactivated vaccinations should be completed before therapy as per current guidelines	Moderate-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy (ixekizumab and secukinumab) and have not responded adequately to other systemic therapy (brodalumab) Active psoriatic arthritis in adults (secukinumab only) Active ankylosing spondylitis in adults (secukinumab only)	356–361
Canakinumab (Ilaris)	See later				
Guselkumab (Tremfya)	Monoclonal Ab directed against IL-23	Guselkumab prevents binding of IL-23 to its receptor and limits the proinflammatory immune response that would otherwise result	Upper respiratory tract infections, gastroenteritis, tinea infections, and HSV infections have been reported in ≥1% and more commonly than placebo Guselkumab should be discontinued in the event of serious infection Patients should be evaluated for TB before beginning therapy; active TB is a contraindication to guselkumab, and treatment for LTBI should be initiated before beginning therapy Anti-TB therapy may be considered in those with a history of LTBI or active TB in whom an adequate treatment course cannot be confirmed Use of live vaccines should be avoided during therapy; there are no data on the immunogenicity of inactivated vaccines during treatment with guselkumab	Moderate-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	362
Sarilumab (Kevzara)	Monoclonal Ab directed against the IL-6 receptor	Sarilumab binds to soluble and membrane-bound IL-6 receptors, thereby inhibiting the effect of proinflammatory IL-6 on immune effector cells	Serious, life-threatening, or fatal bacterial, viral, fungal and other opportunistic infections have been reported, often during coadministration with corticosteroids, methotrexate, or other immunosuppressive medications; sarilumab should be interrupted if these occur[a] Sarilumab should not be used with other biologic DMARDs owing to risk of additive immunosuppression Invasive candidiasis and PJP have been reported; fungal infections may be disseminated[a] Sarilumab should not be started in patients with an active infection Testing (and initiation of treatment) for LTBI should occur before therapy; pulmonary or extrapulmonary TB has been reported during therapy[a] Treatment for LTBI should be considered if there is a past history of latent or active TB for which adequate treatment cannot be confirmed, or in those with risk factors for TB despite a negative result of testing for LTBI Retest for LTBI during therapy[a] (frequency not specified) Cellulitis and pneumonia are among the most common serious infections Herpes zoster has been reported during therapy with sarilumab Patients at risk for HBV reactivation were excluded from clinical trials, so risk remains unknown Neutropenia may occur; neutrophils should be monitored prior to therapy, 4–8 wk after initiation, and every 3 mo thereafter GI perforation has been reported Live vaccines should not be administered to patients receiving sarilumab Interaction with CYP enzymes is possible, requiring monitoring of coadministered CYP substrates	Moderate-severe active rheumatoid arthritis in which one or more DMARDs have been ineffective or intolerable	363–365

Continued

TABLE 49.3 Infectious Risks Associated With Selected Immunomodulatory Therapies in the Treatment of Nonmalignant Diseases—cont'd

AGENT	MODE OF ACTION	IMMUNE DEFICIT	INFECTIOUS RISKS, MIMICKERS, AND PREVENTION	FDA APPROVED CLINICAL INDICATIONS	REFERENCES
Tocilizumab (Actemra)	Monoclonal Ab directed against IL-6	Tocilizumab binds to both soluble and membrane-bound IL-6, thereby inhibiting its various proinflammatory functions	Life-threatening or fatal infections with mycobacteria (pulmonary or extrapulmonary TB), bacteria, fungi, and viruses have occurred, as have other opportunistic infections, in patients receiving tocilizumab[a] Fungal infections may be disseminated rather than localized, and have included candidiasis, aspergillosis, cryptococcosis, and PJP Tocilizumab should be suspended if an infection develops during therapy, at least until the infection is controlled[a] Tocilizumab should not be started during active infection, even if the infection is localized Patients should be screened for LTBI before therapy, and if result is positive, anti-TB treatment should be initiated before tocilizumab is administered[a] Consider empirical anti-TB treatment in patients with a past history of latent or active TB in whom adequate therapy cannot be confirmed All patients should be monitored for active TB throughout therapy, even in the setting of prior negative test for LTBI[a]; active pulmonary TB after negative screening at the onset of therapy has been reported with tocilizumab Per the product monograph, consider the risk-benefit profile when proposing tocilizumab for use in patients who have chronic or recurring infection, prior severe or opportunistic infection, prior exposure to TB or risk factors for TB or endemic mycoses, or coexisting conditions that increase risk of infection The most common infections observed during tocilizumab therapy are upper respiratory tract infection or nasopharyngitis; the most common serious infections include pneumonia, UTIs, cellulitis, and herpes zoster GI perforation has been reported after diverticulitis Neutropenia may occur, although it has not commonly been associated with infection in patients receiving tocilizumab Patients with HBV and HCV were excluded from clinical trials, so impact on these infections is unknown; tocilizumab is not recommended in those with active hepatic disease or impairment Live vaccines are contraindicated with tocilizumab; patients who received live vaccines within 4 wk of planned study entry were excluded from clinical trials Tocilizumab is presumed, but has not been shown, to reduce the efficacy of other, inactivated vaccines	Moderate-severe active RA in adults without sufficient response to one or more DMARDs Giant cell arteritis in adults Active polyarticular or active systemic juvenile idiopathic arthritis in children >2 yr old	366–370, 371, 372
Tofacitinib (Xeljanz) See also: Ruxolitinib (Jakafi)	Inhibitor of Janus kinases (JAKs), specifically JAK1 and JAK3, and to a lesser extent JAK2	By inhibiting JAKs, which are associated with intracellular signaling of receptors for IL-2, IL-6, IL-7, and IL-12, tofacitinib prevents cytokine signaling and limits lymphocyte activation, differentiation, and function	Tuberculosis (pulmonary, extrapulmonary, or disseminated), bacterial, fungal, viral, and other opportunistic infections, some life-threatening or fatal, have occurred during therapy with tofacitinib; therapy should be interrupted until the infection is controlled[a] Therapy should be interrupted for any active, serious infection, even if localized All patients should be screened for LTBI before starting tofacitinib; if result is positive, treatment for LTBI should be initiated before tofacitinib is started[a] Patient who have had LTBI or TB with unclear treatment or who have risk factors for TB despite a negative test for LTBI may also be considered for empirical anti-TB therapy All patients should be monitored for TB throughout therapy, regardless of initial LTBI screening results[a] Median time to diagnosis of active TB from start of tofacitinib therapy was 10 mo Per the product monograph, consider the risk-benefit profile when proposing tofacitinib for use in patients who have chronic or recurring infection, prior severe or opportunistic infection, prior exposure to TB or risk factors for TB or endemic mycoses, or coexisting conditions that increase risk of infection, including chronic or interstitial lung disease or lymphopenia Fungal infections have included PJP and cryptococcosis, and disseminated disease is possible Other reported opportunistic infections have included esophageal candidiasis, CMV, BK virus infection, and listeriosis Patients with HBV or HCV were excluded from clinical trials; however, HBV reactivation has been reported	Moderate-severe active RA in adult patients for whom methotrexate cannot be tolerated or has not been sufficiently effective	373–378

			Screening for HBV and HCV should occur before tofacitinib treatment The most commonly observed serious infections in patients receiving tofacitinib included pneumonia, cellulitis, herpes zoster, and UTIs; one large retrospective study found a higher incidence of herpes zoster with tofacitinib than with other biologic DMARDs in patients with RA Lymphopenia may occur and may be associated with increasing risk of infection in a dose-dependent manner; tofacitinib should not be started or continued in severe lymphopenia Neutropenia may also occur Blood counts should be monitored at baseline, at weeks 4–8, and every 3 mo thereafter EBV-associated PTLD has been reported more frequently in renal transplant recipients who receive tofacitinib in combination with other immunosuppressive medications[a] Tofacitinib should not be used in combination with biologic DMARDs or other potent immunosuppressive medications, such as azathioprine or cyclosporine Live vaccines should not be administered to patients receiving tofacitinib; dissemination of vaccine strain varicella occurred in a varicella-naïve patient 16 days after vaccination with the live-attenuated zoster vaccine and 2 days after first receipt of tofacitinib Tofacitinib has several drug-drug interactions, including with antiinfective agents such as rifampin, fluconazole, or ketoconazole, for which dose modification may be required in the setting of concomitant therapy		
Ustekinumab (Stelara)	Monoclonal Ab directed against a shared subunit of both IL-12 and IL-23	By inhibiting IL-12 and IL-23, ustekinumab interferes with NK cell activation and $CD4^+$ T-cell differentiation, thereby limiting the immune response	Serious bacterial, fungal and viral infections have been reported with ustekinumab; listeria meningitis and ophthalmic HSV occurred in one patient each in the trials of Crohn disease Ustekinumab should not be started in the presence of significant active infection; if infection develops during treatment, consideration should be given to holding ustekinumab until resolution Genetic deficiencies in IL-12/IL-23 have been associated with infections due to mycobacteria, BCG (vaccinations), and salmonella; the risk of these infections in association with ustekinumab use is unknown Patients should be evaluated for LTBI, and if positive, should begin treatment for LTBI before starting therapy with ustekinumab; anti-TB therapy may be considered empirically in patients with a history of LTBI or active TB in whom prior treatment is unconfirmed In clinical trials, one trial required LTBI therapy to start 3 wk before ustekinumab; the remainder allowed LTBI therapy to begin at or before the first dose of ustekinumab LBTI therapy with isoniazid was well tolerated among patients receiving ustekinumab in the context of clinical trials for psoriasis Patients receiving ustekinumab should be monitored closely for active TB regardless of treatment; reactivation of LTBI in the setting of ustekinumab use despite negative TB skin testing and interferon-γ release assay prior to start of ustekinumab has been reported Patients with HBV, HCV, HIV, or prior nontuberculous mycobacterial or other opportunistic infection were excluded from clinical trials, so impact of ustekinumab in these situations is unknown; a small study documented HBV reactivation in two of seven HBsAg positive patients not receiving antiviral therapy Live vaccines are contraindicated with ustekinumab use, and clinical trials excluded patients with receipt of live vaccine within 12 wk of the planned initiation of ustekinumab therapy, and in at least one trial it was stipulated that live vaccines could not be used in the year following last administration of ustekinumab Also in keeping with clinical trial protocols, BCG vaccines are contraindicated for 1 yr before and 1 yr after therapy with ustekinumab Concern exists about the potential risk of shedding of live vaccines from close household contacts All recommended vaccines should be up-to-date before beginning therapy with ustekinumab as serologic response to vaccination during therapy may not be protective	Moderate-severe plaque psoriasis in patients ≥12 yr old who are candidates for phototherapy or systemic therapy Active psoriatic arthritis in adults ± methotrexate Moderate-severe active Crohn disease in adults who fail to respond to or tolerate one or more immunomodulators, corticosteroids, or TNF inhibitors	379–384

Continued

TABLE 49.3 Infectious Risks Associated With Selected Immunomodulatory Therapies in the Treatment of Nonmalignant Diseases—cont'd

AGENT	MODE OF ACTION	IMMUNE DEFICIT	INFECTIOUS RISKS, MIMICKERS, AND PREVENTION	FDA APPROVED CLINICAL INDICATIONS	REFERENCES
Immunomodulators Targeting Inflammatory Bowel Diseases					
Natalizumab (Tysabri)	See later				
Ustekinumab (Stelara)	See earlier				
Vedolizumab (Entyvio)	Monoclonal Ab directed against the α4β7 integrin	Vedolizumab binds to the α4β7 integrin to prevent its interaction with MAdCAM-1, thereby blocking the migration of a subset of memory T cells into the GI tract	Vedolizumab should not be started in patients with active, severe infections until those infections are controlled, caution should be used before initiating vedolizumab in patients with severe and recurring infections, and vedolizumab should be held if severe infections develop during therapy PML, including fatal episodes, have occurred during treatment with natalizumab, another integrin antagonist; although PML has not been observed in patients treated with vedolizumab and followed for up to 5 yr, PML remains a theoretical risk Upper respiratory tract infections and nasopharyngitis are the most commonly reported infections with vedolizumab; however, serious infections have included anal abscess, sepsis (at times fatal), salmonellosis, *Listeria* meningitis, tuberculosis (all considered primary infections), giardiasis, and CMV colitis Vedolizumab product monograph advises to consider screening for tuberculosis; all patients in clinical trials were screened Live vaccines should be administered concurrently with vedolizumab only if the benefit outweighs the risk; vaccination before therapy is preferred Owing to additive infectious risk, vedolizumab should not be administered with natalizumab or anti-TNF therapy	Moderate-severe active ulcerative colitis or Crohn disease in adults who have not responded adequately or cannot tolerate a TNF inhibitor, other immunomodulatories, or corticosteroids, or who are dependent on corticosteroid therapy	385, 386
Immunomodulators Targeting Multiple Sclerosis					
Daclizumab (Zinbryta)	Monoclonal Ab directed against the IL-2 receptor	Daclizumab binds to CD25, a subunit of the Il-2 receptor, and is presumed to mediate IL-2-induced activation of lymphocytes	Severe liver injury, including autoimmune hepatitis and hepatic failure can occur[a]; daclizumab is therefore contraindicated in those with preexisting hepatic disease or impairment (AST or ALT >2× ULN) Use other hepatotoxic medications with caution Immune-mediated dermatologic disorders, colitis, hemolytic anemia, and lymphadenopathy may occur and may require corticosteroid or other immunosuppressive therapy[a] Infections and serious infections are increased over placebo Upper respiratory tract infections and pharyngitis among most commonly reported adverse events CMV hepatitis, CMV pneumonia, and TB have occurred in patients receiving daclizumab Screening for TB, HBV, and HCV recommended before therapy, and daclizumab should not be administered in those with active, severe infection Live vaccines should not be administered during and up to 4 mo after therapy	Relapsing MS in adults, usually after lack of response to two or more other medications	387–389
Fingolimod (Gilenya)	Sphingosine 1-phosphate receptor modulator	Binding of fingolimod-phosphate (after metabolism by sphingosine kinase) to sphingosine 1-phosphate receptors blocks lymphocytes from exiting lymph nodes and reduces peripheral blood lymphocyte counts	Infection can occur up to 2 mo after discontinuation of fingolimod, and fingolimod should not be initiated in the setting of active infection PML may occur, usually in patients receiving fingolimod for ≥2 yr, although the relationship between treatment duration and risk of PML is not known; fingolimod should be discontinued during evaluation, diagnosis, and management of PML Influenza was reported in ≥10% of patients receiving fingolimod, and at higher rates than in those receiving placebo; bronchitis, sinusitis, pneumonia and herpes zoster were also observed more commonly with fingolimod than with placebo Response to influenza vaccine is reduced in those receiving fingolimod as opposed to those receiving placebo JCV, disseminated HSV and VZV with multiorgan failure, cryptococcosis, atypical mycobacteria, and HHV-8–associated KS have all been reported VZV serology should be done before initiation of fingolimod in anyone without a clear prior episode of VZV (confirmed by a health care professional) or documented complete vaccination series; Ab-negative individuals should be vaccinated and fingolimod postponed until at least 1 mo after last vaccination In clinical trials, fatal disseminated primary HSV and fatal HSV encephalitis were each diagnosed in one patient, both of whom were receiving higher-than-recommended doses of fingolimod	Relapsing MS to reduce exacerbations and delay physical disability	390, 391, 392, 393, 394

			Cryptococcal infections may include cryptococcal meningitis and disseminated cryptococcosis Because fingolimod can result in a dose-dependent decrease in lymphocyte count, a CBC within 6 mo should be available before initiation of therapy Live vaccines should not be administered during or for 2 mo after discontinuation of fingolimod; all vaccines may be less effective during this period Coadministration of fingolimod with ketoconazole raises blood levels of fingolimod and increases risk of adverse events; multiple other drug-drug interactions have been reported		
Natalizumab (Tysabri)	Monoclonal Ab directed against the α4-integrin subunit	Natalizumab binds to the α4 subunit of α4β1 and α4β7 integrins, located on the cell surface of leukocytes (except neutrophils), and blocks integrin binding (and therefore leukocyte adhesion) to cognate receptors such as VCAM-1 and MAdCAM-1; ultimately this prevents leukocyte migration into tissue	Increased risk of PML, with high risk of subsequent morbidity and mortality; duration of therapy (especially >2 yr), prior immunosuppression, and anti-JCV antibodies are all associated with the development of PML[a] Risk of PML in the United States varies from <1/1000 in patients who are anti-JCV Ab negative, or anti-JCV Ab positive with <2 yr natalizumab use and no prior immunosuppression, to 13/1000 for those who are anti-JCV Ab positive, with 4–6 yr of natalizumab use and prior immunosuppression In risk assessment, a single positive anti-JCV Ab is considered a positive result regardless of previous or subsequent testing Testing should be done 2 wk after plasma exchange and ≥6 mo after IVIG Retesting for anti-JCV Ab should be done periodically for the purposes of risk stratification, not for diagnosis of PML or other JCV-related syndrome In one study of patients with MS receiving natalizumab, the anti-JCV Ab seroconversion rate was 7.1% per year Natalizumab product monograph suggests consideration of periodic monitoring for MRI evidence of PML even in asymptomatic patients, and a baseline MRI in patients with MS prior to natalizumab Monitoring for PML should be continued for ≥6 mo after discontinuation of natalizumab, because PML has occurred after discontinuation of therapy Prior PML is a contraindication to natalizumab JCV granule cell neuronopathy can cause cerebellar dysfunction with or without concurrent PML, but is diagnosed and managed similarly IRIS can complicate PML in patients who discontinue natalizumab and often undergo plasma exchange to further remove natalizumab HSV and VZV meningitis, encephalitis, and acute retinal necrosis have been observed with natalizumab, and in some patients have resulted in blindness, life-threatening illness, or death Hepatic failure requiring transplant has occurred Urinary tract and lower respiratory tract infections are reported in ≥10% of patients receiving natalizumab for MS Opportunistic infections such as cryptosporidiosis, PJP, aspergillosis, and others do occur with natalizumab, although infrequently Natalizumab should not be combined with other immunosuppressive medications, including anti-TNF medications, for the treatment of Crohn disease; if corticosteroid therapy cannot be withdrawn within 6 mo of beginning natalizumab, natalizumab should be discontinued	Relapsing MS Moderate-severe active Crohn disease, with evidence of inflammation, in adults who have not responded to or tolerated usual therapy and TNF inhibitors	395, 396, 397, 398, 399
Ocrelizumab (Ocrevus)	Monoclonal antibody directed against CD20	Ocrelizumab binds to CD20 and facilitates lysis of pre-B, mature B, and memory B cells	Screening for HBV is required prior to initiation of therapy; HBsAg positivity is a contraindication to therapy Reactivation in the setting of isolated HBcAb positivity with negative HBV DNA has been reported with ocrelizumab use for rheumatoid arthritis Ocrelizumab should not be initiated in patients with an active infection Live virus vaccines are contraindicated during and after ocrelizumab therapy, until B-cell repletion has occurred; all vaccines should be initiated ≥6 wk before start of ocrelizumab therapy Upper and lower respiratory tract infections and skin infections are among the most common infections reported, depending on the population studied Herpesvirus infections have also been reported more frequently	Relapsing or primary progressive MS	400–403

Continued

TABLE 49.3 Infectious Risks Associated With Selected Immunomodulatory Therapies in the Treatment of Nonmalignant Diseases—cont'd

AGENT	MODE OF ACTION	IMMUNE DEFICIT	INFECTIOUS RISKS, MIMICKERS, AND PREVENTION	FDA APPROVED CLINICAL INDICATIONS	REFERENCES
			Immunoglobulin levels decrease with therapy, but in the clinical trial population studied, no association was found with risk of infection Neutropenia was also observed, but was largely nonsevere in magnitude PML has not been reported with ocrelizumab but has been identified in other patients receiving anti-CD20 therapy Although not mentioned in the product monograph, some trials in rheumatoid arthritis (for which ocrelizumab is not currently approved) required screening for TB before entry, and others in MS excluded patients with known TB or a history thereof		
Immunomodulators Targeting Asthma					
Benralizumab (Fasenra)	Monoclonal Ab directed against IL-5 receptor subunit α	Benralizumab binds to the IL-5 receptor on eosinophils and basophils, and to FcγRIII receptors on NK cells, leading to apoptosis of eosinophils and basophils via antibody-dependent cell-mediated cytotoxicity	Known parasitic infection was an exclusion criteria for clinical trials, and therefore the impact of benralizumab on parasitic infections is not known Helminthic infections should be treated before receipt of benralizumab, and new infections may require discontinuation of benralizumab until infection resolves	Severe asthma in patients >12 yr old with an eosinophilic phenotype, when used for add-on maintenance therapy	404, 405
Mepolizumab (Nucala) Reslizumab (Cinqair)	Monoclonal Abs directed against IL-5	Mepolizumab and reslizumab bind IL-5 and prevent binding to the IL-5 receptor on eosinophils, reducing eosinophil differentiation, activation, and survival	Herpes zoster infections have been reported with mepolizumab; vaccination against VZV may be considered (if appropriate) prior to therapy Known parasitic infection was an exclusion criteria for clinical trials, and therefore the impact of anti-IL-5 therapy on parasitic infections is not known Helminthic infections should be treated before anti-IL-5 therapy, and new infections may require discontinuation of anti-IL-5 therapy until infection resolves Anaphylaxis can occur with reslizumab, and therefore it should be administered only in a health care setting with the means to address anaphylaxis, if required[a]	Severe asthma in patients >12 yr old (mepolizumab) or ≥18 yr old (reslizumab) with an eosinophilic phenotype, when used for add-on maintenance therapy	406–409
Omalizumab (Xolair)	Monoclonal Ab directed against IgE	Omalizumab binds to IgE, lowers free IgE levels, and prevents IgE binding to its cell surface receptor on mast cells and basophils, thereby reducing release of soluble mediators	Viral infections, upper respiratory tract infections, sinusitis, and pharyngitis were among the most common adverse events reported, but were similar between patients with asthma ≥12 yr old receiving omalizumab and placebo Anaphylaxis can occur after the first dose, or longer than 1 yr into a course of therapy[a] Fever, arthralgias, and rash can occur In an RCT of patients at risk for geohelminth infection who received prestudy antihelminthic treatment, more patients receiving omalizumab developed a new intestinal geohelminth infection than did those receiving placebo	Moderate-to-severe persistent asthma despite inhaled corticosteroids in patients ≥6 yr old with a positive skin test result or in vitro reactivity to a perennial allergen Chronic idiopathic urticaria despite H_1 antihistamine therapy in patients ≥12 yr old	410, 411
Immunomodulators Targeting Miscellaneous Conditions					
Canakinumab (Ilaris)	Monoclonal Ab directed against IL-1β	By binding IL-1β and blocking its downstream effector functions, canakinumab reduces the proinflammatory immune response	Increased risk of serious infections with canakinumab therapy; caution should be used when considering canakinumab for those with recurrent infections or conditions that predispose to infections Canakinumab should not be administered during active infections and should be discontinued if a serious infection develops during therapy Opportunistic infections including aspergillosis, mycobacterial infections, herpes zoster, and CMV infections have been reported during therapy with canakinumab Nasopharyngitis, upper respiratory tract infections, and influenza are among the most commonly reported infections Canakinumab has not been studied in patients with LTBI, including those receiving anti-TB therapy; screening for active and latent TB before therapy, and treatment if positive, is recommended, although safety in this population is unknown In a recent trial, patients with HBV and HCV were excluded, as were those with evidence of, risk factors for, or currently treated, active TB Coadministration with TNF inhibitors is not recommended owing to the increased risk of infection Live vaccinations are contraindicated during therapy with canakinumab	Periodic fever syndromes such as CAPS (including FCAS and Muckle-Wells syndrome), in patients ≥4 yr old TNF receptor–associated periodic syndrome (TRAPS) in adults and children Hyperimmunoglobulin D syndrome/mevalonate kinase deficiency in adults and children Familial Mediterranean fever in adults and children Active systemic juvenile idiopathic arthritis in patients ≥2 yr old	412–415

Eculizumab (Soliris)	Binds to C5, preventing conversion into C5a and C5b	Eculizumab reduces terminal complement components and inhibits formation of the membrane attack complex (MAC; C5b-9) required for cytolysis	Life-threatening and fatal meningococcal infections can occur[a] Follow current recommendations with respect to meningococcal vaccination (and revaccination depending on the duration of therapy) for patients with terminal complement deficiencies[a] Meningococcal vaccination should be given at least 2 wk before beginning eculizumab, unless the risks of a meningococcal infection are outweighed by the risks of delayed eculizumab[a] Meningococcal infection has been documented in previously vaccinated patients with both aHUS and PNH, so a high index of suspicion is required throughout therapy; 14 of 16 eculizumab recipients with meningococcal disease in the United States from 2008–2016 had received at least one dose of vaccine Antimicrobial prophylaxis, either temporarily (2 wk after vaccination in those who were not vaccinated 2 wk prior to eculizumab) or lifelong (with penicillin or a macrolide if penicillin allergic), has been proposed for risk reduction, although the risks and benefits of either practice have not been fully studied Eculizumab therapy may predispose children to infection with *Streptococcus pneumoniae* or *Haemophilus influenzae* type b, and therefore vaccination against these organisms should occur as per current guidelines Upper respiratory tract and urinary tract infections were among the commonly reported infections in studies of patients with aHUS	PNH to reduce hemolysis Atypical (but not Shiga toxin–induced) hemolytic-uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy Generalized myasthenia gravis in adults with positive anti–acetylcholine receptor antibodies	416–419
Rilonacept (Arcalyst)	Monoclonal Ab directed against IL-1	Rilonacept binds Il-1 and prevents interaction with the receptor	Upper respiratory tract infection was the most commonly reported infection Serious infections can occur Combination therapy with an anti-TNF agent is not recommended owing to additive immunosuppression Treatment should not be initiated in the setting of active or chronic infection, and should be discontinued if a serious infection develops on therapy Reactivation of LTBI may occur, so screening and treatment as per current guidelines should occur before therapy Vaccinations should be given before therapy is initiated, and live vaccines are contraindicated during therapy	CAPS including FCAS and Muckle-Wells syndrome, in patients ≥12 yr old	420
Dupilumab (Dupixent)	Monoclonal Ab directed against the IL-4 receptor subunit α	Dupilumab binds to the shared IL-4 receptor subunit α and inhibits IL-4 and IL-13 signaling, ultimately reducing proinflammatory cytokines and IgE	Conjunctivitis (including allergic, bacterial, viral, and other), keratitis (including due to HSV), and blepharitis were observed in clinical trials HSV infections have been reported with therapy Known helminthic infection was a trial exclusion, and therefore the impact of dupilumab on helminth infections is unknown Patients with HBV, HCV, HIV, or other immunosuppression were also excluded from trials Use of live vaccines is not recommended for patients receiving dupilumab; immune responses 4 wk postvaccination to tetanus toxoid and serogroup C meningococcal polysaccharide were not different in patients treated with dupilumab for 12 wk and then vaccinated with Tdap and a meningococcal polysaccharide vaccine	Moderate-to-severe atopic dermatitis in adults, when topical therapies are ineffective or cannot be used	421, 422

[a]FDA boxed warning.

aHUS, Atypical hemolytic-uremic syndrome; *ALT,* alanine aminotransferase; *ANA,* antinuclear antibody; *AST,* aspartate aminotransferase; *BCG,* bacillus Calmette-Guérin; *CAPS,* cryopyrin-associated periodic syndrome; *CBC,* complete blood count; *CMV,* cytomegalovirus; *CNS,* central nervous system; *CTLA-4,* cytotoxic T-lymphocyte antigen 4; *CYP,* cytochrome P450; *DMARD,* disease-modifying antirheumatic drug; *dsDNA,* double-stranded DNA; *EBV,* Epstein-Barr virus; *FCAS,* familial cold autoinflammatory syndrome; *GI,* gastrointestinal; *HBcAb,* hepatitis B virus core antibody; *HBsAg,* hepatitis B virus surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HHV-8,* human herpesvirus 8; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *Ig,* immunoglobulin; *IL,* interleukin; *IRIS,* immune reconstitution inflammatory syndrome; *IVIG,* intravenous immune globulin; *JCV,* John Cunningham (JC) virus; *KS,* Kaposi sarcoma; *LTBI,* latent tuberculosis infection; *MAdCAM-1,* mucosal addressin cell adhesion molecule 1; *MRI,* magnetic resonance imaging; *MS,* multiple sclerosis; *NOMID,* neonatal-onset multisystem inflammatory disease; *PJP, Pneumocystic jirovecii* pneumonia; *PML,* progressive multifocal leukoencephalopathy; *PNH,* paroxysmal nocturnal hemoglobinuria; *PTLD,* posttransplant lymphoproliferative disorder; *RA,* rheumatoid arthritis; *RCT,* randomized controlled trial; *SLE,* systemic lupus erythematosus; *TB,* tuberculosis; *Td,* tetanus and diphtheria (vaccine); *Tdap,* tetanus, diphtheria, and acellular pertussis (vaccine); *TNF,* tumor necrosis factor; *ULN,* upper limit of normal; *UTI,* urinary tract infection; *VCAM-1,* vascular cell adhesion molecule-1; *VZV,* varicella zoster virus.

turn require immunosuppressive medications, leading to secondary risk of infection.

Better characterization of the infectious risks associated with immunomodulatory therapy will be an important area of research in future. Identifying high-risk patients, the best method and algorithm for screening, the ideal means and duration of prophylaxis or monitoring, and the impact of immunomodulators on geographically restricted infections all represent key areas for future investigation.

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The complete reference list is available online at Expert Consult.

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50 Hyperbaric Oxygen

Juan Carlos Sarria and Norbert J. Roberts, Jr.

SHORT VIEW SUMMARY

Physiologic Effects
- Modulation of inflammation and immune function (cytokine downregulation).
- Angiogenesis and improved wound healing (growth factor upregulation).
- Direct antibacterial properties and increased activity of antimicrobial agents.

Administration
- Monoplace chambers are used more commonly owing to their portability.
- Chamber pressures are usually 2 to 3 atmospheres absolute. Most sessions last 90 to 120 minutes.
- Acute therapy may require one to two sessions, whereas a typical wound-healing protocol may involve more than 40.

Indications
- Diabetic foot ulcers (Wagner grade III or higher without signs of healing after 30 days) are the most common indication for hyperbaric oxygen treatment (HBOT). An accumulating body of clinical evidence (with variable methodologic design) suggests improved healing rates. However, HBOT has not been proven to contribute to resolution of infection. Questions remain regarding patient selection and cost-effectiveness. Routine use is not recommended.
- Necrotizing soft tissue infections and clostridial myonecrosis (gas gangrene) have also been treated with HBOT. Recent studies have reported variable impact on mortality and amputation rates. The role of HBOT in these infections remains uncertain.
- HBOT has been used for refractory osteomyelitis, bacterial intracranial abscess, and mucormycosis, but there is insufficient clinical evidence to support routine use for these indications.

Side Effects and Complications
- HBOT has a good safety record. Prolonged treatment may result in higher rates of adverse events.
- Complications can result from barotrauma due to expansion of gases in enclosed anatomic compartments (including middle ear, paranasal sinuses, lung) or oxygen toxicity (to central nervous system, eye, lung).
- Untreated pneumothorax is the only absolute contraindication for HBOT.
- Seizure incidence has been markedly reduced with routine use of "air breaks."
- Myopia is characteristically mild. Cataract formation may complicate prolonged treatment.
- Careful patient selection and baseline evaluation for underlying conditions (e.g., cataracts, upper respiratory or cardiopulmonary disease, seizures) may reduce the risk for complications.

Conclusions
- The role of HBOT in infectious diseases remains controversial, primarily because advocates have not generated adequate controlled data to define conclusively its appropriate uses.
- Selection of treatment candidates is difficult and should be individualized for each patient and each clinical situation. It is critical to weigh the risks of transport, lack of access to the patient, potential complications, and cost against any potential benefit that the treatment may provide.

Hyperbaric oxygen treatment (HBOT) has been proposed for a wide range of indications. In fact, it has been described as a treatment in search of indications. The indications for its use vary between professional organizations and countries. Most accepted uses are based on experimental models and observational clinical experience. The role of HBOT in infectious diseases remains a contentious issue. In this chapter we review aspects of HBO relevant to the infectious disease field, including physiologic effects, methods of administration, clinical evidence supporting approved indications, side effects and complications, patient selection and evaluation, cost, and certification in hyperbaric medicine. Strengths, weaknesses, and controversial aspects of this treatment are also discussed.

PHYSIOLOGIC EFFECTS IN EXPERIMENTAL MODELS

Individuals breathing ambient air (21% oxygen) at sea level pressure (1 atmosphere absolute [1 ATA]) normally achieve an arterial oxygen pressure (Pao_2) of 90 mm Hg and a tissue oxygen pressure (Pto_2) of 55 mm Hg. HBOT, in which patients breathe 100% oxygen inside a chamber at a pressure higher than sea level (>1 ATA), results in a Pao_2 of up to 2000 mm Hg and a Pto_2 of up to 500 mm Hg.[1] These high oxygen concentrations have been associated with several physiologic effects in experimental models. Those pertaining to infectious diseases are discussed in Table 50.1.

Modulation of Inflammation and Immune Function

Accumulating experimental evidence is shedding light on the effects of HBO at the cellular and molecular levels. Increases in nitric oxide generation triggered by HBO have been associated with decreased neutrophil adhesion and sequestration.[2] These changes reduce reactive oxygen species formation,[3] which in turn decreases production of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α.[4] HBO showed a protective effect on mortality in a murine sepsis model that appeared to be linked to enhanced IL-10 expression[5] and demonstrated a protective effect in an ischemia-reperfusion injury model (in which restoration of blood flow produces a "second hit" phenomenon that may be more damaging than the initial event) by ameliorating neutrophil infiltration to the affected tissues.[2] In addition, HBO has been shown to reduce thrombosis, tissue edema, and compartmental pressures.[6]

Angiogenesis and Improved Wound Healing

Animal models have demonstrated that HBO creates the necessary oxygen gradients between the blood and injured tissues to promote angiogenesis via vascular endothelial growth factor upregulation.[7] A proposed mechanism for improved wound healing is the maintenance of a critical level of hyperoxia required for increased production of

TABLE 50.1 Physiologic Effects of Hyperbaric Oxygen Shown in Experimental Models

Modulation of Inflammation and Immune Function
Decreased neutrophil adhesion and sequestration[2]
Decreased production of reactive oxygen species in neutrophils[3]
Decreased production of proinflammatory cytokines (interleukin [IL]-1, IL-6, tumor necrosis factor-α)[4]
Enhanced IL-10 expression[5]
Protective effect in ischemia-reperfusion injury model[2]
Reduced thrombosis, edema, and compartmental pressures[6]
Improved Wound Healing
Promote angiogenesis via vascular endothelial growth factor upregulation[7]
Increased fibroblast proliferation and collagen synthesis[8]
Increased extracellular matrix synthesis in cartilage[10]
Enhanced osteogenesis and bone mineralization[12]
Antibacterial Properties
Formation of bactericidal toxic oxygen radicals[13]
Decreased α-toxin production by *Clostridium*[14]
Restoration of neutrophil-mediated killing of bacteria by oxidative mechanisms[15]
Activity of Antimicrobial Agents
Potentiated effect of tobramycin, linezolid, vancomycin, tigecycline, cefazolin, penicillin, imipenem, and ciprofloxacin[16–22]
No effect when added to daptomycin plus rifampin in a model of *Staphylococcus aureus* implant-associated osteomyelitis[23]

TABLE 50.2 Indications Approved by the Undersea and Hyperbaric Medicine Society for Hyperbaric Oxygen Treatment

INFECTIOUS DISEASES	NONINFECTIOUS DISEASES
Clostridial myonecrosis (gas gangrene)	Air or gas embolism
Intracranial abscess	Carbon monoxide poisoning
Necrotizing soft tissue infections	Crush injury, compartment syndrome, and other acute traumatic ischemia
Refractory osteomyelitis	Decompression sickness
	Arterial insufficiencies
	Central retinal artery occlusion
	Enhancement of healing in selected problem wounds
	Severe anemia
	Delayed radiation injury (soft tissue and bony necrosis)
	Compromised grafts and flaps
	Thermal burns
	Idiopathic sudden sensorineural hearing loss

growth factors necessary for fibroblast proliferation.[8] It has been shown that when the environment of the fibroblast has a low oxygen tension, the cell can divide but can no longer synthesize collagen, nor can it migrate to where it is needed for healing. When the oxygen tension is increased, the fibroblast can regain these wound-healing functions. Increased expression, deposition, and maturation of collagen have been demonstrated.[9] In murine and rabbit models, positive effects in cartilage were observed, including hydroxyapatite formation, decreased chondrocyte apoptosis, and increased extracellular matrix synthesis.[10,11] There is evidence that HBO may enhance osteogenesis. Increased serum osteoprotegerin levels and improved bone mineralization were observed in a group of patients with femoral head necrosis exposed to HBO.[12]

Antibacterial Properties

The antimicrobial action of oxygen occurs when reduced nicotinamide adenine dinucleotide phosphate–linked oxygenase acts as a catalyst for the production of toxic oxygen radicals, particularly a superoxide ion that kills bacteria. Anaerobic organisms are extremely sensitive to these radicals because most lack the superoxide-degrading enzyme superoxide dismutase.[13] HBO also can affect the production of bacterial toxins. At a Pto_2 of 250 mm Hg, α-toxin production by *Clostridium perfringens* completely ceases.[14] This toxin is a virulence factor that degrades cell membranes and produces liquefactive necrosis. Moreover, neutrophil-mediated killing of *Staphylococcus aureus* is restored when a low Pto_2 in osteomyelitic bone is increased to physiologic or supraphysiologic levels.[15]

Activity of Antimicrobial Agents

Increased tobramycin efficacy was observed in an experimental murine model of *S. aureus* endocarditis.[16] This was likely the result of enhanced transport of aminoglycosides across bacterial cell walls, an oxygen-dependent mechanism. In another murine model of *S. aureus* endocarditis, linezolid plus HBO was found to be more effective in reducing the number of bacterial colonies in aortic valve vegetations than either treatment alone.[17] In a murine model of *S. aureus* mediastinitis, bacterial counts in tissue were significantly lower when vancomycin or tigecycline were combined with HBO ($P < .05$).[18] A positive effect has also been shown for certain cephalosporins. The combination of cefazolin and HBO produced a 100-fold greater reduction in bacterial counts than cefazolin or HBO alone.[19] The combined treatment of penicillin and HBO exerted additive effects in decreasing bacterial counts and increasing survival in a murine model of streptococcal myositis.[20] With in vitro models of *Pseudomonas aeruginosa* infection, HBO enhanced the effect of imipenem[21] and ciprofloxacin in biofilms.[22] These effects are believed to be mediated by stimulation of aerobic respiration and enhanced bactericidal activity by oxidative mechanisms. Conversely, HBO was ineffective when combined with daptomycin plus rifampin in a murine model of *S. aureus* implant-associated osteomyelitis suggesting a lack of effect in device-associated infections.[23]

ADMINISTRATION

HBOT can be carried out in either monoplace (single person) or multiplace (typically 2–14 patients) chambers. In monoplace chambers the entire atmosphere is pressurized (typically 2–3 ATA) with 100% oxygen, and the patient breathes the ambient chamber oxygen directly. Modern monoplace chambers have transparent acrylic walls offering a clear view of the patient and a less secluded feeling. Monoplace chambers are used more commonly because of their portability. In multiplace chambers the pressurized ambient oxygen contains normal room air, and patients breathe 100% oxygen from hoods or masks. Modern multiplace chambers are integrated into hospital architecture to appear and function as ordinary treatment rooms. They incorporate patient monitoring equipment, control panels to regulate air flow, intercom systems, automatic fire suppression, entertainment systems, and other technologic advancements to enhance clinical support, safety, and patient comfort.

Most HBOT sessions are administered over 90 to 120 minutes. Acute therapy may require only one or two treatments, whereas chronic medical conditions, such as those addressed by wound-healing protocols, may warrant more than 40 sessions. In the United States HBOT facilities are relatively widely available and can be found in every state. They vary widely from storefront clinics in strip malls to advanced wound care units in major academic medical centers. Multiplace chambers are typically operated by hospitals, navies, professional diving organizations, and dedicated recompression facilities. The slang term, at some facilities, for a cycle of pressurization inside the HBOT chamber is "a dive."

Directories of clinics and centers listing contact information, type of facility, and chamber types are available.[24] Similarly, directories of HBOT practitioners can be found covering the full range of training and education, from nonphysician wellness entrepreneurs to board-certified specialists. HBOT should not be self-administered in the home or administered by noncertified providers. Critical care monitoring and treatment, including mechanical ventilation, should be readily available during treatments.

INDICATIONS

The Undersea and Hyperbaric Medicine Society (UHMS) publishes a list of approved indications (Table 50.2).[25] Among the infectious diseases listed, treatments for necrotizing soft tissue infections (NSTIs), clostridial myonecrosis, and refractory osteomyelitis are reimbursable by the Centers for Medicare and Medicaid Services and third-party payers. High-grade diabetic ulcers of the lower extremities without signs of healing after

30 days of standard treatment are also reimbursable indications. The American College of Hyperbaric Medicine (ACHM) supports treatment of patients with nonapproved indications in a research setting.[26]

Diabetic Foot Ulcers

Even though HBOT has long been used for diabetic foot ulcers (DFUs), its effectiveness is debated. A number of randomized controlled trials (RCTs) and systematic reviews have been published in the last decade. Most, but not all, suggest a benefit. Significant variability in methodologic design is evident. Results of these reviews are summarized as follows.

A Cochrane Database systematic review of 10 RCTs ($n = 531$ patients) compared wound healing in patients treated with adjuvant HBO versus standard treatment.[27] Even though an increase in the rate of ulcer healing (risk ratio [RR], 2.35) with HBOT at 6 weeks was observed, this benefit was not evident at 1 year. There was no statistically significant difference in major amputation rates. Another pooled analysis that included observational trials and RCTs found that HBOT was associated with reduced risk for amputation (odds ratio [OR], 0.2; 7 studies) and improved healing rates (OR, 9.9; 6 studies).[28] A review of 13 studies ($n = 624$) that included 7 RCTs showed that adjuvant HBOT resulted in a higher proportion of healed ulcers (RR, 2.33) and a significant risk reduction for major amputations (RR, 0.29), compared with standard treatment; however, the rate of minor amputations was not affected ($P = .37$).[29] A recent review of 7 RCTs compared standard care plus HBOT with standard care alone and found a significant difference in favor of standard care plus HBOT in relation to ulcers healed, mixed results for major amputation rates, and no difference in adverse events.[30] Improved mortality (35% vs. 47%) and lower cost of care ($33,100 vs. $66,300) were observed in a cohort of 106 patients with high-grade ulcers treated with a limb salvage protocol that included HBOT, compared with a historical cohort of 53 patients treated primarily with amputation without HBOT.[31]

Other investigators have reported less encouraging results. HBOT was associated with reduced rates of wound healing (hazard ratio [HR], 0.68) and an increased risk of requiring amputation (HR, 2.37) in an observational cohort of 6259 patients (HBOT group = 793 vs. non-HBOT group = 5466) from a US national wound care company.[32] Similarly, in a recent prospective RCT of 103 patients (HBOT = 49 vs. non-HBOT = 54), HBOT did not offer an additional advantage to comprehensive wound care in facilitating wound healing or reducing the indication for amputation.[33]

Professional organizations have issued position statements regarding the role of HBOT in DFUs. The American Diabetes Association Professional Practice Committee reviewed the available data on the use of HBOT in 2016 and did not identify sufficient supporting data on the efficacy of this treatment to recommend its use.[34] The 2015 UHMS practice guidelines stated that HBOT was recommended for patients with Wagner grade III or higher ulcers that have just undergone surgical débridement or ulcers that have shown no significant improvement after 30 days of treatment.[35] The 2012 Infectious Diseases Society of America diabetic foot infection practice guideline stated that a limited number of RCTs are available to support the use of HBOT for wound healing and concluded that no adjunctive therapy, including HBO, has been proven to improve resolution of infection, but for selected wounds that are slow to heal, clinicians might consider using HBOT (strong recommendation, moderate-quality evidence).[36]

Despite the increased number of published studies and systematic reviews, the available evidence remains conflicting and makes it difficult to draw any definitive conclusions regarding the role of HBOT in DFUs. Questions remain regarding patient selection, timing of treatment, optimal protocols, and cost. The impact on morbidity and mortality is unclear. Therefore routine use is not recommended.

Necrotizing Soft Tissue Infections

In a retrospective analysis of 45,913 patients diagnosed with NSTIs in the US Nationwide Inpatient Sample, 405 patients received HBOT (0.9%).[37] These patients had a lower mortality rate (4.5 vs. 9.4%, $P = .001$). This advantage persisted after controlling for other predictors of mortality and possible confounders (OR, 0.49). Higher hospitalization costs ($52,205 vs. $45,464) and longer length of stay (14.3 days vs. 10.7 days) were also observed in the HBOT group. Another systematic review conducted by German investigators found 250 related articles (993 patients treated with HBO).[38] There were only 10 comparative studies. Fifty percent of articles were case series or reports. In this review the authors identified nine chambers enabling intensive care in the country and reported an average cost of €8000 to €25,000/patient. They concluded that the published studies lacked the quality to confirm a therapeutic benefit of HBOT in NSTIs, and the limited resources available and high costs involved did not allow comprehensive clinical care with HBOT in Germany. In a case-controlled study from Australia of necrotizing fasciitis conducted over a 13-year period, mortality was 12% in the HBOT group ($n = 275$) vs. 24.3% in the non-HBOT group ($n = 66$).[39]

Other retrospective studies have not demonstrated a statistically significant impact on mortality, need for amputations, or length of hospital stay in patients with NSTIs treated with HBO.[40–42] In a recent retrospective cohort of 43 patients with necrotizing fasciitis of the head and neck, more complications (63% vs. 25%) and sequelae (77% vs. 40%) were observed in the HBOT group ($n = 30$) compared with the non-HBOT group ($n = 13$).[43] Adjunctive HBO decreased mortality and limited the extent of débridement in an observational study of 70 patients with Fournier gangrene.[44] However, another study of 42 patients with this infection showed increased mortality, morbidity, and cost of care among patients treated with HBO.[45]

HBOT has been recommended as adjuvant to surgical débridement and antimicrobial treatment for NSTIs in many body locations, particularly perineal gangrene. The role of this treatment remains uncertain primarily because published clinical studies are observational and continue to report conflicting results (e.g., variable impact on mortality and amputation rates). Higher costs of care and longer hospital stays have also been observed.

Clostridial Myonecrosis (Gas Gangrene)

Although there has never been an RCT evaluating the role of HBOT in clostridial myonecrosis, experimental animal data and clinical experience suggest a beneficial effect. Evidence has shown that HBO may help define necrotic tissue, facilitating more precise surgical débridement. In a review of 20 clinical series, including more than 1200 patients with clostridial myonecrosis treated with HBO, a cumulative mortality of 23% was reported.[46] Historical controls had a mortality of 45% without HBOT. A Medline review analyzed 650 patients with clostridial myonecrosis treated with HBO from four comparative studies and 13 case series.[47] Most investigators stated that adjunctive HBO was beneficial. However, because of the noncomparative nature of the case series, it is impossible to reliably assess the therapeutic effects of HBO. The reported mortality rates in these studies ranged from 11% to 52%.

Some HBO practitioners recommend aggressive treatment protocols for clostridial myonecrosis (and other anaerobic or mixed bacterial infections), such as two to three daily 90- to 120-minute sessions at 2.8 to 3 ATA started early in the course of treating the infection. These pressures maintain tissue oxygen tension above thresholds needed to inhibit clostridial spore and exotoxin production. As is the case for other NSTIs, the role of HBOT in clostridial myonecrosis is controversial due to the observational nature of the available evidence because no RCTs have been performed.

Refractory Osteomyelitis

Few controlled studies have been performed to confirm the efficacy of HBOT in refractory osteomyelitis. More rapid resolution of infection and prevention of recurrences, when compared with standard treatment, have been reported in patients with sternal, skull, and spinal infections.[48–50] This clinical experience should be viewed with caution. Patient selection and optimal assessment of treatment response remain unsolved questions. HBOT is not routinely recommended as an adjuvant to standard treatment in patients with refractory osteomyelitis.

Bacterial Intracranial Abscess

In a cohort study of 40 patients (HBOT = 20 vs. non-HBOT = 20) with bacterial intracranial abscess, the HBOT group had fewer recurrences (14% vs. 58%, $P < .01$), decreased need for reoperation (10% vs. 45%, $P = .03$), and improved long-term outcomes (higher Glasgow scores in

80% vs. 45%, $P = .04$) compared with the non-HBOT group.[51] In another series of 13 patients, decreased need for reoperations and decreased duration of antimicrobial therapy were reported.[52] Infection was controlled in all patients, and there were no recurrences. A cumulative review of 48 patients treated with HBO reported a 2% mortality.[53]

Adjunctive HBOT has been suggested in selected cases (i.e., multiple or deep abscesses, underlying immunosuppression, suboptimal response to standard treatment, and poor surgical candidates). This recommendation is based primarily on expert opinion.[54] The available clinical evidence is insufficient to support routine use of adjuvant HBOT in bacterial intracranial abscess.

Mucormycosis

A review of 28 published cases indicated that adjunctive HBOT may be beneficial in patients with mucormycosis and underlying diabetes (94% survival), whereas its benefit in patients with underlying hematologic malignancies or bone marrow transplantation is doubtful (33% survival).[55] This experience suggests that it was the underlying immunosuppression, and not HBOT, that ultimately impacted outcomes. A retrospective study examined 14 patients with invasive fungal infections caused by *Mucor* or *Aspergillus* over a 12-year period.[56] Most had rhinocerebral or pulmonary involvement. These patients had a 50% survival with a treatment regimen consisting of surgery, antimicrobial therapy, and HBOT.

There are no controlled studies evaluating the role of HBOT in mucormycosis. Mortality rates for this infection remain high despite treatment. The role of HBOT in mucormycosis remains uncertain.

SIDE EFFECTS AND COMPLICATIONS

Concerns about the safety aspects of HBO have been raised due to the unique atmospheric conditions to which patients are exposed. In a recent database evaluation that contained information on 1.5 million HBO treatments, the overall rate of adverse events per session was 0.68%. Severe events were extremely uncommon, with fewer than 0.05 instances per 1000 treatments.[57] In a retrospective analysis of 2334 patients from Israel, 406 (17.4%) experienced adverse events, but the event-per-session rate was 0.72%.[58] These data support the notion that single-session or short-term HBOT is generally safe. In the elective setting serious complications are rare when patients are properly prepared and monitored and treatment adheres to standard protocols (duration <120 minutes, pressure <3 ATA, and <40 sessions). Complications can result from barotrauma due to expansion of gases in enclosed anatomic compartments (middle ear, paranasal sinuses, lung) or oxygen toxicity (central nervous system, eye, lung) (Table 50.3). Oxygen has been shown to be harmful to tissues via the formation of oxygen free radicals. The higher partial pressures of oxygen used during HBOT are believed to saturate protective enzymes and unfavorably shift oxidative stress reactions in the direction of cellular damage.

The incidence of middle ear barotrauma varies between treatment centers. Most episodes are self-limited, but continued high pressure may cause middle ear hemorrhage and tympanic membrane bulging, resulting in severe pain. In a report of 1115 patients otalgia was described in 157 patients (14%).[59] Ear fullness, hearing loss, tinnitus, and vertigo were uncommon (≤1%). Age older than 60 years and female sex were independent risk factors for otologic symptoms. Half of the patients experienced symptoms at the first treatment session in this study. Among 58 symptomatic patients evaluated, abnormal otoscopic findings were recognized in 58 (50%)/116 ears. Twenty-seven ears required myringotomy or tube insertion, and HBOT had to be stopped in 4 patients. To prevent injury to the tympanic membrane, alert patients need to be appropriately coached to equalize by swallowing to facilitate eustachian tube clearance during decompression, as one does during descent in an aircraft. In the obtunded or mechanically ventilated patient it is recommended to perform a myringotomy before compression. Prophylactic myringotomy is performed at variable rates in the United States.

Paranasal sinus barotrauma has been reported mainly in patients with upper respiratory tract infections or allergic rhinitis. These patients experience difficulty equalizing their sinuses, which can result in sinus congestion or "sinus squeeze" and epistaxis.[58] This problem may be alleviated by pretreatment with nasal decongestants, steroids, or antihistamines. Impaired nasal mucociliary clearance, as measured by a saccharin clearance test, was reported in a cohort of 47 patients receiving long-term exposure to HBOT.[60]

A more serious complication is pulmonary barotrauma causing pneumothorax during decompression.[57] Gas trapped in air spaces not in communication with the diminishing pressure in the chamber (lung cysts or bullae) will expand rapidly. Bronchospasm, which may cause localized air trapping, should be corrected before institution of HBOT. Patients with a history of spontaneous pneumothorax must be evaluated for occult pneumothorax. Untreated pneumothorax is the only absolute contraindication for HBOT. A history of chest surgery is usually not considered a contraindication. However, there is concern that air may be trapped in lesions that were created by surgical scarring. Pulmonary barotrauma is more problematic in monoplace chambers, where the clinician cannot reach the patient until the chamber is decompressed, which may take several minutes even in an emergency.

Pulmonary oxygen toxicity, manifested by chest tightness, cough, dyspnea, or a reversible decline of pulmonary function, occurs most commonly in patients receiving multiple treatments.[58] Cardiovascular responses to HBOT include reduction in cardiac output and systemic vasoconstriction with increased peripheral vascular resistance. Although these effects are well tolerated by normal individuals, cardiogenic pulmonary edema was reported in three patients with underlying cardiac disease, including one fatality.[61]

Breathing oxygen at sufficiently elevated pressures can trigger seizures. Seizures due to oxygen toxicity, however, do not typically result in permanent structural brain damage. In a survey from Israel of 62,614 HBOT therapies administered to 2334 patients, the incidence of seizures was 0.01% per therapy occurring in 0.3% of patients.[62] Seizure incidence has been markedly reduced with the routine use of "air breaks." Should a seizure occur in the chamber, it is important to wait until the seizure has ceased before beginning emergent decompression; rapid decompression with a closed glottis may result in tension pneumothorax. Underlying seizures unrelated to oxygen therapy are not a contraindication to HBOT.

Myopic shift on examination, reported in up to 81% of patients receiving HBOT,[63] may be due to direct oxygen toxicity or deformity of the lens as a result of repeated compressions and decompressions. It is characteristically mild and reversible within few days to 4 weeks after cessation of treatment. Other ocular effects include eyelid twitching, blurry vision, and visual field defects. Cataract formation rarely occurs during commonly used treatment protocols, but it has been described in patients who received intense treatment for extended periods. Cataracts are not reversible after cessation of treatment. Cataract formation may occur due to an excess of reactive oxygen species or a deficiency in antioxidant activity in ocular tissues.[64] Similar mechanisms may contribute to other ocular pathologies, including keratoconus, macular edema, and macular degeneration.[65]

Claustrophobia may occur even in multiplace chambers.[58] Occasionally, anxiolytics are required to facilitate treatment. Decompression sickness with formation of gas bubbles in soft tissues may occur in patients breathing compressed air that contains nitrogen. This complication has also been described among clinical staff in multiplace chambers. The

TABLE 50.3 Side Effects and Complications of Hyperbaric Oxygen Treatment

Otalgia, 14%[59]
Middle ear hemorrhage, tympanic membrane bulging[59]
Ear fullness, hearing loss, tinnitus, vertigo ≤ 1%[59]
Paranasal sinus congestion or "sinus squeeze," epistaxis[58]
Impaired nasal mucociliary clearance[60]
Pneumothorax[57]
Chest tightness, cough, dyspnea, reversible decline of pulmonary function[58]
Cardiogenic pulmonary edema, death (case reports)[61]
Seizures, 0.3%[62]
Myopic shift on examination in up to 81%[63]
Eye twitching, blurred vision, visual field defects
Cataract formation with prolonged treatment, may be irreversible[64]
Dizziness and/or weakness, 1.5%[58]
Claustrophobia[58]
Decompression sickness

likelihood of decompression sickness is reduced by administration of 100% oxygen toward the end of the treatment and by recompression or gradual decompression.

PATIENT SELECTION AND EVALUATION

HBOT providers need to be aware of the potential complications associated with HBOT. Selection of patients mandates a careful risk-benefit analysis. Risk for complications may outweigh benefits in situations where treatment effectiveness is considered uncertain. Patients should be provided with complete information about potential risks as part of their informed consent. A baseline ophthalmology examination is suggested in patients at increased risk for cataract development (age older than 50 years, diabetes, radiation therapy of the head, and systemic corticosteroids). Similarly, evaluation for underlying upper respiratory or cardiopulmonary disease, and seizures may be warranted depending upon the patient's history. Any history of brain, ear, or thoracic surgery should be elicited. HBOT in small children poses particular challenges. Pregnancy is not considered a contraindication for HBOT. Mechanical ventilation is generally considered safe during HBOT, but sedation needs to be optimized to avoid patient-ventilator asynchrony.[66] Hemodynamically unstable patients should not be treated with HBO. Multiplace chambers allow closer monitoring of critically ill patients, whereas monoplace chambers are most appropriate for the treatment of chronic medical conditions in stable patients. The risks associated with transportation of patients for HBOT are acceptable with meticulous monitoring performed by well-trained personnel.[67] It is always important to consider the potential impact of reduced access to the patient during HBOT, which should be balanced against any potential differential benefit over standard care that the treatment may provide.

COST

Cost of an HBOT session in the United States can range from $150 in outpatient clinics to $1000 or more in hospitals. Physician consultation fees, technical supervision, type of insurance carrier, and geographic location all impact costs. A full course of treatment for a conventional diabetic wound healing protocol typically costs $50,000 (Medicare) to $200,000 (private payer).[68] Despite these figures, some economic analyses suggest that HBOT may be cost-effective.[31,69] These analyses, however, rely primarily on outcome data reported from uncontrolled studies. An in-depth analysis of broad implementation of HBOT for DFUs in the United States concluded that the resources consumed by this treatment modality could be better spent on other aspects of management and prevention.[70] HBOT is less expensive in other countries. A 40-session course was reported to cost €6916 in the Netherlands.[71] In the United Kingdom most chambers are financed by the National Health Service, and others are nonprofit. China and Russia treat more than 80 conditions with HBO because their costs are low compared with those in the United States.

CONTROVERSY

Although HBOT has been proposed for many decades, a sense of controversy continues to pervade the field (Table 50.4). Advocates typically quote its beneficial physiologic effects, effectiveness shown by a growing body of clinical experience, indications recognized by professional organizations and third-party payers, and its safety record. Opponents point at the lack of well-designed RCTs for the proposed indications as the main weakness of HBOT. For DFUs in particular, it is important to recognize that numerous parameters affect wound healing. Wounds that exhibit normal tissue oxygenation usually fail to heal only when not appropriately off-loaded or when not properly débrided. Failure to recognize correctable arterial insufficiency will result in a poor response to HBOT. In addition, it is difficult to assess the value of HBOT in patients already receiving multidisciplinary treatment (local wound care, off-loading, antimicrobials, surgical débridement, and revascularization). In addition, there are challenges associated with HBOT administration. Using HBOT in critically ill or unstable patients is difficult. Other standard treatments should never be delayed, access to the patient should never be compromised, and only a patient whose condition is stable should be considered for transfer to a facility with HBOT capability. Last, HBOT consumes substantial resources. How it should be used in practice alongside other treatment modalities in a real world with finite resources is unclear.

TABLE 50.4 Strengths and Weaknesses of Hyperbaric Oxygen Treatment

STRENGTHS	WEAKNESSES
Positive physiologic effects in experimental models	Lack of randomized controlled trials
Effectiveness shown by accumulating clinical experience (mostly uncontrolled)	Cumulative toxicities
Indications approved and recognized by professional organizations and third-party payers	Difficult selection of treatment candidates
Good safety record	Risks of transport and lack of access to the patient
	Delay of standard treatments
	Availability
	Cost

CERTIFICATION IN HYPERBARIC MEDICINE

Physicians with a current certification from one of the member boards of the American Board of Medical Specialties (ABMS) can obtain board certification through the undersea and hyperbaric medicine unit of the American Board of Preventive Medicine (ABPM).[25] Board eligibility requires successful completion of a minimum of 12 months in an accredited hyperbaric medicine fellowship program, and certification requires successful completion of the UHMS examination.

An alternative pathway that certifies added qualification in hyperbaric medicine includes a 40-hour course approved by the ACHM, the US Department of Defense, or the UHMS. Applicants must also submit documentation of supervision of at least 300 hyperbaric treatments for approved indications as noted by either the UHMS or the Centers for Medicare and Medicaid Services, and pass a final examination. This pathway does not replace fellowship training or board certification, which is considered the gold standard for training in undersea and hyperbaric medicine.

The UHMS also provides a program of facility accreditation based on adherence to recognized treatment protocols, facility safety, and operational methodology. Table 50.5 lists professional organizations and other Internet resources on hyperbaric medicine.

CONCLUSIONS

HBOT has been both lauded and questioned, primarily because advocates have not generated adequate controlled data to define conclusively its appropriate uses. It is difficult to assess the efficacy of HBOT in infectious diseases, even those for which use is endorsed by the UHMS and reimbursed by third-party payers. In clinical practice nonhealing wounds,

TABLE 50.5 Internet Resources on Hyperbaric Medicine

RESOURCE	WEBSITE	COMMENT
American College of Hyperbaric Medicine (ACHM)	www.achm.org	Specialty society, education, training
HBO Evidence	http://hboevidence.unsw.wikispaces.net/	Database of clinical trials (non-infectious disease indications, nonhealing wounds)
HyperbaricLink	www.hyperbariclink.com	Independent guide, general information, directory of treatment centers, links
Undersea and Hyperbaric Medical Society (UHMS)	www.uhms.org	Primary professional body, education, training, credentialing, certification, list of approved indications, publications, employment opportunities

HBO, Hyperbaric oxygen.

including complicated DFUs, have become the most common indications for HBOT. Use of HBOT in clinical practice has increased considerably in the last decade and will likely continue to rise if current modes and extent of reimbursement continue. It is not entirely clear which patients with infections, if any, truly stand to benefit from HBOT, and how they should be selected. Prospective RCTs are needed to provide definitive answers regarding efficacy of HBOT in infectious diseases. Until convincing controlled data appear, each patient and each clinical situation must be evaluated individually. Most important, it is critical to weigh the risks of transport, lack of access to the patient, potential complications, and cost against any potential differential benefit over standard care that the treatment may provide.

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51 Antimicrobial Stewardship

Conan MacDougall and Sara E. Cosgrove

SHORT VIEW SUMMARY

ANTIMICROBIAL STEWARDSHIP

- Systematic approaches to improve antimicrobial use across the health care spectrum are termed *antimicrobial stewardship.*
- The desired outcomes of antimicrobial stewardship are to ensure that patients receive optimal antimicrobial therapy when it is indicated and to limit adverse events associated with antimicrobial use including *Clostridioides difficile* (formerly *Clostridium difficile*) infection and emergence of resistance at the patient and population levels.

PHILOSOPHY AND SOCIOLOGY OF ANTIMICROBIAL USE

- Antimicrobial use is a key driver of antimicrobial resistance. Most clinicians consider antimicrobial resistance to be an important public health threat but do not view their own prescribing as being a significant driver of resistance.
- Perceived patient expectations, fear of providing inadequate therapy, lack of knowledge, inadequate diagnostics, and local prescribing etiquette contribute to suboptimal antimicrobial prescribing.

ANTIMICROBIAL STEWARDSHIP STRATEGIES

- Educational strategies aim to bring clinicians to a common understanding of principles of antimicrobial use, institutional best practices and processes, and recommended disease management approaches.
- Development of institutional guidelines for antibiotic use to ensure standard prescribing practice is a cornerstone of antimicrobial stewardship program building.
- Antimicrobial restriction strategies limit the prescribing scope of clinicians, either through exclusive use of certain agents at the institution or through requirements for prior authorization by phone call to a stewardship team member or completion of an order set or form before the pharmacy dispenses the agent.
- Postprescription review and feedback strategies involve targeted review of courses of antimicrobials after their initiation. In cases in which antimicrobial use could be optimized, prescribers are contacted with patient-specific suggestions for modifying the current antimicrobial regimen.
- Computer-assisted strategies involve use of information technology tools to make other stewardship processes, such as restriction or postprescription review, both more effective and efficient.

MEASURING OUTCOMES FROM ANTIMICROBIAL STEWARDSHIP PROGRAMS

- Analysis of the impact of antimicrobial stewardship programs on clinical and microbiologic outcomes is complex, but most studies suggest a beneficial or at least a neutral impact. Economic analyses strongly favor antimicrobial stewardship programs, especially when accounting for the entire spectrum of cost savings associated with improving suboptimal antimicrobial use.
- Antimicrobial stewardship programs should determine approaches to track their success, including monitoring antibiotic use and resistance and results of specific interventions designed to improve antibiotic use.

ANTIMICROBIAL STEWARDSHIP PROGRAM STRUCTURE AND IMPLEMENTATION

- Early involvement of administrators and key opinion leaders, dedicated funding, involvement of a range of specialties, extensive use of longitudinal and benchmarking data, development of institution-tailored guidelines for therapy, and constant quality assessment are key strategies for implementing and maintaining a successful stewardship program.

THE FUTURE OF ANTIMICROBIAL STEWARDSHIP

- Governmental and accrediting agencies are instituting requirements for antimicrobial stewardship in hospitals and long-term care facilities. Antimicrobial stewardship in outpatient settings is an emerging area, with the need for different strategies to be tailored to this care environment.

Issues associated with use of antibiotics were recognized shortly after their introduction into clinical medicine in the early 1940s, including a warning from Alexander Fleming about risks of emergence of resistance to penicillin during his Nobel Prize acceptance speech. In his review of the subject in 1956, Jawetz[1] was one of the first to recognize the problems caused by the attractiveness of new antibiotics to physicians, the exaggerated claims by the pharmaceutical industry, and the enormous impact that promotion by the drug companies had on medical practice. The problem has only worsened. In 2011, 262 million courses of antibiotics were prescribed to outpatients in the United States, a rate of 842 per 1000 population.[2] More than half of all hospitalized patients in the United States receive at least one dose of an antibacterial drug during hospitalization.[3] Studies estimate that 30% to 60% of antibacterial use is unnecessary or otherwise inappropriate.[4-6] Among the unwanted consequences of antimicrobial therapy are adverse reactions, *Clostridioides difficile* (formerly *Clostridium difficile*) infection, increased length of stay, increased cost of hospitalization, predisposition to secondary infections, and the emergence of drug-resistant microorganisms.[7] Antimicrobial drug use is a contributor to the rising incidence of serious infections caused by methicillin- and glycopeptide-resistant *Staphylococcus aureus,* vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase–producing Enterobacteriaceae, multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* spp., and *Klebsiella* spp. expressing *Klebsiella pneumoniae* carbapenemases, and the proliferation of more virulent strains of *C. difficile.*[8,9] Despite recent initiatives to incentivize antimicrobial development, introduction of novel antimicrobial agents active against these resistant organisms has not kept pace with their proliferation; therefore, more effective use of current agents is essential to preserve the value that antimicrobials provide to modern medicine.[10,11]

ANTIMICROBIAL STEWARDSHIP

Programs designed to increase the appropriateness of antimicrobial use in hospitals appeared initially in the 1970s; most had cost reduction as a primary goal because antibiotic expenditures can account for 30% to 50% of a hospital's drug budget.[12] Aside from cost, antimicrobials differ from other drug classes in that their use in one person can lead to selection for resistant organisms that can then be spread to others. In addition, when resistance to a particular antibiotic reaches a certain threshold at the population level, that agent is no longer reliable for use as empirical therapy, driving use toward broader-spectrum agents. Thus, the focus of antimicrobial stewardship programs (ASPs) has shifted

away from cost savings to improvement in the quality of patient care, with the primary goals of improving clinical outcomes, reducing adverse events associated with antibiotic use, and stabilizing or reducing rates of resistance.[13,14]

The last decade has seen widespread support for the implementation of ASPs across all health care settings with publication of updated stewardship guidelines from the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA), recommendations for Core Elements for Stewardship Programs from the Centers for Disease Control and Prevention (CDC), incorporation into the National Action Plan to Combat Antibiotic-Resistant Bacteria, a Standard from The Joint Commission requiring hospitals to have ASPs for accreditation, and requirements for ASPs in long-term care setting from the Centers for Medicare and Medicaid Services (CMS).[15–21] This chapter reviews antimicrobial stewardship strategies that have been reported in the literature, summarizes their goals and the clinical and institutional outcomes of these efforts, and ends with recommendations for the development, implementation, and funding of a successful ASP.

PHILOSOPHY AND SOCIOLOGY OF ANTIMICROBIAL USE

To address the problem of inappropriate antimicrobial usage, we must understand the constraints under which physicians work and the pressures exerted on them to prescribe drugs. The prescription of antibiotics has become as much a psychological or philosophical endeavor as a scientific exercise.[22,23] Physicians must balance the risks of not treating or inadequately treating a patient with antimicrobials against the risks of antimicrobial use in terms of adverse effects, drug costs, and contribution to antimicrobial resistance. Because emergence of antimicrobial resistance and even other adverse consequences such as development of *C. difficile* infection typically are removed in time and place from the original prescribing decision, they often receive little weight. Indeed, a study by Metlay and colleagues found that "risk of contributing to antimicrobial resistance" ranked last among seven factors that physicians were asked to weigh when deciding which antimicrobial to prescribe for a hypothetical patient.[24] In the same study, perceived patient expectations around antimicrobial prescribing was identified as a key factor in overprescribing of antimicrobials. Although studies have demonstrated that patients can be dissuaded from demanding unnecessary antimicrobials without adverse effects on satisfaction with their physician, these interventions may be more time consuming and require more training relative to simply prescribing an antimicrobial.[25] Diagnostic tests for infections may be perceived as overly expensive, invasive, or time consuming relative to simply prescribing an antimicrobial for a suspected infection. When diagnostic tests for infections are ordered, they are often slow to turn around and limited in their sensitivity. Prescribers may be unwilling to take the risks of not prescribing an antimicrobial or prescribing a narrower-spectrum antimicrobial because of malpractice and litigation concerns if a patient truly has an infection. Clinicians may lack knowledge regarding infectious disease diagnostics and management, especially in the face of a growing population of immunocompromised patients (human immunodeficiency virus, stem cell and solid-organ transplantation).[26] Local "prescribing etiquette" may dictate that junior physicians follow the prescribing practices of senior physicians and may dissuade any clinician from modifying antimicrobial (or other) therapy started by another, regardless of its appropriateness.[27] All these factors may lead physicians to fall back on the relative "comfort" of broad-spectrum antimicrobial use.[25,28]

In this environment, some physicians believe that ASPs impose unnecessary or even deleterious constraints on the practice of medicine.[29] Prescribers may fail to appreciate that antimicrobial use has significant ecologic consequences that extend beyond the individual patient under their care and can affect their entire practice population. Their skepticism may arise from the perception that there is a lack of documented efficacy of ASPs across varied health care settings, a paucity of direct evidence demonstrating an improvement in clinical outcomes, limited physician time or incentive to pursue such efforts, and a weak causal link between the emergence of resistance and antibiotic use patterns. Although there are few large multicenter, randomized controlled trials to address all of these questions, there is a growing evidence base that on balance supports the implementation of antimicrobial stewardship efforts.[30]

TABLE 51.1 Antimicrobial Stewardship Strategies for Health Care Institutions Rated by the Infectious Diseases Society of America

STRATEGY	STRENGTH OF RECOMMENDATION AND QUALITY OF EVIDENCE
Recommended Strategies to Implement	
Prior authorization, prospective audit and feedback, or both	Strong recommendation, moderate-quality evidence
Targeting antibiotics associated with a high risk of *Clostridioides difficile* (formerly *Clostridium difficile*) disease	Strong recommendation, moderate-quality evidence
Programs to increase appropriate use of oral antibiotics and intravenous-to-oral switch	Strong recommendation, moderate-quality evidence
Promotion of shortest effective durations of antibiotic therapies	Strong recommendation, moderate-quality evidence
Pharmacokinetic monitoring and adjustment programs for aminoglycosides	Strong recommendation, moderate-quality evidence
Suggested Strategies to Implement	
Facility-specific clinical practice guidelines	Weak recommendation, low-quality evidence
Syndrome-specific interventions	Weak recommendation, low-quality evidence
Regular prescriber self-review of antibiotic appropriateness (e.g., antibiotic time-outs)	Weak recommendation, low-quality evidence
Computerized clinical decision support at point of prescribing	Weak recommendation, moderate-quality evidence
Pharmacokinetic monitoring and adjustment programs for vancomycin	Weak recommendation, low-quality evidence
Pharmacokinetic-pharmacodynamic-based dosage strategies for β-lactams	Weak recommendation, low-quality evidence
Allergy assessment including penicillin skin testing as appropriate	Weak recommendation, low-quality evidence
Stratified antibiograms to supplement traditional antibiograms	Weak recommendation, low-quality evidence
Selective reporting of antibiotic susceptibilities	Weak recommendation, low-quality evidence
Rapid viral testing for respiratory pathogens	Weak recommendation, low-quality evidence
Rapid diagnostic testing for bacterial pathogens in blood cultures	Weak recommendation, moderate-quality evidence
Serial procalcitonin measurements in critically ill patients with suspected infection	Weak recommendation, moderate-quality evidence
Suggested Strategies to Avoid	
Antibiotic cycling	Weak recommendation, low-quality evidence
Reliance on didactic education as sole strategy	Weak recommendation, low-quality evidence

From Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. *2016;62:e51–e77.*

ANTIMICROBIAL STEWARDSHIP STRATEGIES

Table 51.1 lists the stewardship strategies evaluated by the IDSA and SHEA guidelines on implementing an ASP in the acute-care setting.[16] A 2015 survey of 4569 US hospitals found that 63% of teaching hospitals and 42% of nonteaching hospitals had all seven of the CDC's Core Elements in place.[31] The most common strategies used among the institutions represented were facility-specific treatment guidelines (77%), prospective audit and feedback (74%), antimicrobial preauthorization

programs (63%), requirements to document an antibiotic indication (26%), and antibiotic time-outs (23%). In addition, 62% reported providing education about resistance to clinicians and other staff.

In the following sections, we provide examples of data supporting major strategies. The reader is referred to many excellent reviews of stewardship programs for a more comprehensive review.[32,33,34-36]

Educational Strategies

Education is a common approach in medicine to impart information with the goal of changing practice. Current undergraduate and postgraduate training in antimicrobial management may be inadequate, because there are significant ongoing deficiencies in clinicians' knowledge base concerning antimicrobial pharmacology, spectrum, and correct use.[29,37-39] A variety of approaches have been used for education regarding appropriate antimicrobial use, including staff conferences, grand rounds, newsletters, and continuing education programs.

Educational programs are difficult to assess because of the complex nature of educational variables, the diversity of efforts, the lack of standardized feedback, and the intricacy of the infectious diseases decision-making process. Nonetheless, several generalizations can be culled from the existing literature. Individual instruction by an antibiotic-utilization expert appears to be the most successful educational strategy, whereas more passive methods such as printed materials and large group instruction are less useful.[40,41] Contemporaneous interventions have a greater impact than those removed from the original antibiotic order by space and time. The development of guidelines and clinical pathways can also be considered a form of education; these are a critical component of all ASPs because they require the relevant institutional stakeholders to gather together and agree on recommendations and approaches. For guidelines and clinical pathways to modify antimicrobial prescribing, however, they must be accompanied with an implementation strategy to ensure their continued adoption by frontline providers.[42,43] Therefore, although education and locally developed guidelines should be cornerstones of any ASP, these approaches should not be used as the sole strategy.[15,16]

Antimicrobial Formulary Restriction Strategies

Limiting the availability of agents on formulary is the most direct method to influence antimicrobial use. The purpose of a limited formulary may be to discourage use of newer, more expensive antimicrobials in favor of older, equally effective drugs or to take advantage of similarities between drugs within a class to obtain preferential manufacturer pricing by exclusively using one agent.[44,45] Beyond the issue of cost, exercising control over which antimicrobials are available for physicians to prescribe also may strongly influence the development of antimicrobial resistance in a health care institution. There is debate as to whether certain antibiotic classes or agents have a lower intrinsic risk of selecting for antimicrobial-resistant pathogens. A national antimicrobial stewardship intervention in Scotland restricted the use of fluoroquinolones, amoxicillin-clavulanate, clindamycin, and cephalosporins.[46] Although the total use of antimicrobials did not change, significant reductions in the prevalence of *C. difficile* infection were found in hospitals and the community. Other studies, however, have found that restriction of certain antimicrobial classes may lead to emergence of resistance to agents that become more commonly used, a phenomenon termed "squeezing the balloon."[47] Design of an antimicrobial formulary should also pay careful attention to an institution's recommended doses, because resistance may be associated with inadequate drug dosing.[48]

Preauthorization Strategies

At a level below institution-wide decisions about which antimicrobials are available are strategies that require physicians to justify their use of antimicrobials in individual patients in some way. These stretch across a spectrum from less restrictive (e.g., requiring use of antimicrobial order forms, mandating that an indication accompany every antimicrobial order) to more restrictive (e.g., requiring physicians to obtain approval from an infectious diseases clinician before restricted antimicrobial release—also known as "preprescription approval" [PPA], mandating formal infectious diseases consultation for use of specific agents). Published studies suggest that these policies are effective at reducing the use of the targeted agents, although sometimes with an increase in use of nontargeted agents. Because agents are frequently targeted based on cost, net cost avoidance for the institution may be observed.[49] The impact on antimicrobial resistance patterns is variable, sometimes resulting in favorable reductions in the prevalence of pathogens such as *C. difficile* or multidrug-resistant gram-negative rods.[50,51,52] For example, in a study at a county hospital in which PPA from an infectious diseases attending physician was required before empirical prescription of broad-spectrum antimicrobials, a 32% reduction in antimicrobial expenditures was associated with increase in *P. aeruginosa* susceptibilities to imipenem from 65% to 83% in the intensive care unit (ICU) and 83% to 95% on the floor. No adverse events such as an increase in mortality or longer hospitalization were observed.[53] Enforcement of more restrictive types of prior-approval programs can be difficult, and the process may be viewed as a punitive exercise. In a survey of residents in a teaching hospital, a majority agreed that a restrictive antimicrobial program was a "good idea" and that such a program "improved individual patient care," but a majority also agreed that the requirement for call approval led to delays in patient receipt of antimicrobial agents and that calling for approval was frustrating.[54] Some studies have found delays in receipt of antimicrobial therapy for agents requiring PPA, although online or electronic medical record (EMR)–integrated approval approaches may reduce some of these issues.[55,56] In private practices, infectious diseases physicians are not enthusiastic about restricting antibiotics because of concerns that the policies will place them in a policing role and thereby damage their traditional referral patterns.[57] Preauthorization strategies offer direct control over antimicrobial use but may be best used in well-staffed programs targeting agents with high cost, particularly niches of use requiring expertise in identification, risk of contributing to resistance, or toxicity. In addition, temporary use of preauthorization strategies may be valuable in the setting of antimicrobial shortages or in response to outbreaks of resistant bacteria.[58,59]

Postprescription Review With Feedback

Postprescription review with feedback (PPRF; also known as prospective audit and feedback) consists of review of prescriptions of targeted antimicrobials (usually at least 2 or 3 days per week) coupled with feedback to physicians to improve antimicrobial use specific to that patient, and is an important stewardship strategy. Feedback should be educational and evidence based, with the goal of appropriate individualized therapy. Interventions occurring as part of a PPRF strategy include switching patients from intravenous to oral therapy, from broad-spectrum and combination therapy to narrower-spectrum therapy (also called *streamlining*), stopping antibiotic therapy if an alternative, noninfectious diagnosis has been identified, determining the optimal duration of therapy, and modifying doses. Prescribers tend to view PPRF strategies as less onerous than prior-approval programs. PPRF has been identified as a core stewardship strategy, and most effective stewardship programs will have at least some form of this strategy, which has been supported by a variety of studies including randomized trials.[60,61]

As an illustrative example, Elligsen and colleagues used an interrupted time-series design to study the impact of a PPRF program implemented at 72 hours on streamlining broad-spectrum antimicrobial use in three ICUs.[62] Review of antimicrobials was performed by a pharmacist with backup from an infectious diseases physician. During the intervention period, suggestions for drug optimization were given for 34% of broad-spectrum antimicrobial orders, and 82% were accepted. Compared with the prior 12 months before the intervention, the mean monthly use of targeted antimicrobials decreased by 22% during the intervention period. Use of nontargeted antimicrobials did not increase during the intervention, leading to an overall reduction in antimicrobial use. The percentage of drug-resistant isolates was similar between the two periods, except for a reduction in meropenem resistance among gram-negative organisms. The monthly rate of *C. difficile* infections was decreased by 31% during the intervention period. Hospital and ICU length of stay and mortality were similar between the two study periods. The authors subsequently expanded their intervention outside of the ICU in the context of a stepped-wedge randomized trial, with a reduction in targeted antimicrobial use of approximately 20% among patients qualifying for audit and feedback.[63] However, targeted antimicrobial use did not significantly

decrease among all patients, a finding that the authors attributed to the shorter length of stay of floor patients. Another approach to PPRF might be termed "self-stewardship." Using approaches adapted from surgical quality improvement, these interventions include use of prescribing checklists or an "antibiotic time-out" to enforce monitoring at a team or prescriber level instead of by ASP personnel. Although intuitively attractive and resource efficient, data on the effectiveness of these approaches are currently limited.[64-67]

Some limitations of PPRF strategies include that in most programs the treating clinician has the option to accept or reject the recommendations made by the ASP. Therefore it is important that ASPs develop collegial relationships with providers and use evidence-based approaches supported by local or national guidelines that are likely to be acted on by clinicians when making recommendations. ASPs must also develop a mechanism to identify patients who have been started on targeted antimicrobials, which can be difficult in the absence of support for information technology. Finally, PPRF strategies do not ensure appropriateness of initial selection of empirical therapy in an individual patient, which can put patients at risk for overtreatment or undertreatment (although an effective PPRF intervention may improve the future empirical prescribing of the receiving clinician).

Some studies have attempted to compare the two major strategies for ASPs. Mehta and colleagues performed a before-and-after quasiexperimental study assessing the impact on use of antibiotics before and after prior approval restrictions (PPA) were lifted and PPRF was instituted for cefepime, piperacillin-tazobactam, and vancomycin.[68] They found that use of cefepime and piperacillin-tazobactam increased significantly after the change ($P = .03$), as did hospital length of stay after antibiotic initiation ($P = .004$), suggesting that a restrictive approach may have been associated with less antibiotic use. Tamma and colleagues conducted a crossover quasiexperimental study among four medicine units in which control units used PPA only and intervention units had PPA removed and PPRF implemented. Overall antibiotic use decreased by approximately 1 day in the PPRF group; however, empirical therapy was more appropriate in the PPA group.[69] Of note, a Cochrane review published in 2013 reported that restrictive strategies such as PPA were more effective in making short-term change than persuasive approaches such as PPRF, but the 2017 update of this review found that nonrestrictive approaches were also effective in reducing antibiotic use.[70,71]

ASPs must determine what are the most effective strategies for improving antibiotic use locally and may elect to use a combination of PPA and PPRF based on program and institutional resources and needs.

Computer-Assisted Antimicrobial Stewardship

Information systems have the potential to be effective adjuncts for antibiotic stewardship and education strategies. Computer order entry affords a unique opportunity for instantaneous feedback, education, and alteration in prescription patterns.[72] A report of an Internet-based ASP developed and studied at the Johns Hopkins Children's Medical and Surgical Center demonstrated improved communication, more timely antimicrobial administration, increased user satisfaction, and significant cost savings over prior stewardship methods.[56] Effective information technology support can also be very effective on the "back end" by helping to target audit and feedback to the highest-yield interventions. These programs have been associated with an increased number of stewardship interventions and reductions in targeted antimicrobial use, "drug-bug" mismatches, and resistant infections.[73-75] Other examples of integration of information technology include sharing of institutional guidelines on intranet or Internet sites or through mobile applications.[76,77]

A few computer-assisted programs offer sophisticated point-of-care decision support incorporating institution- and patient-specific data from the EMR and other systems and applying algorithms to suggest appropriate therapy and provide alerts. Studies of these systems have demonstrated improvements in appropriateness of therapy and patient outcomes; however, they are more complex and require significant investment to integrate into hospital systems.[78,79,80] Nevertheless, with advances in computer systems and artificial intelligence, there is clear potential for growth in this area over time.

MEASURING OUTCOMES FROM ANTIMICROBIAL STEWARDSHIP PROGRAMS

Implementation of programmatic antimicrobial stewardship strategies should be accompanied by well-considered plans to measure the outcomes of these strategies. Indeed, regulatory bodies are beginning to mandate that institutions track stewardship metrics internally, and required external reporting (including the possibility of public reporting) is on the horizon.[81] We briefly examine some of the key considerations for assessing the outcomes of ASPs.

Clinical Outcomes

Most studies of the impact of ASPs have had as their primary outcome the amount of aggregate antimicrobial use, antimicrobial costs, or rates of antimicrobial resistance.[32,33,34-36,71] When clinical outcomes such as clinical cure rate, length of hospital stay, or mortality have been examined, there has frequently been no difference between the stewardship group and the control group, although many of these studies are underpowered to detect these differences. A Cochrane Collaboration meta-analysis found no difference in mortality across 28 randomized controlled trials and an average reduction of 1 day in mean length of stay between stewardship and control arms across 15 randomized controlled trials in hospitalized patients.[71] Given the small average effect sizes, detecting significant improvements in clinical outcomes may not be realistic for most ASPs. Exceptions might be programs specifically targeting transitions of care (e.g., intravenous to oral administration conversion programs) or patients at highest risk of death (e.g., sepsis protocols or ICU-targeted interventions).

Economic Outcomes

Institutional cost avoidance with regard to antimicrobial expenditures is among the most frequently reported outcomes of ASPs.[82,83] However, if savings are calculated as a function of pharmacy expenditures, they tend to plateau over time, probably because of improved antimicrobial-utilization practices and sustained benefits of the program.[84] Thus, comparison of drug expenditure savings relative to projected cost growth in the absence of stewardship is a more relevant comparison than ongoing year-over-year savings.[84,85] Expenditures beyond drug acquisition costs should also be considered in evaluating the impact of ASPs. Gross and colleagues developed a probability pathway model to calculate both the direct and the indirect cost savings of a stewardship program.[86] In this model, total cost was defined as the sum of drug expenditures, microbiology costs, bed costs, and the costs of infectious diseases consultations; additional costs accrued if the initial antibiotic regimen failed. The median drug costs per recommendation were $50 lower for the ASP compared with usual practice, and total costs were $379 lower per recommendation. Based on the probability pathway model, the annualized savings were $363,000 in antibiotic expenditures and $2.7 million in total costs. Thus, institutions implementing ASPs should consider the broad range of expenditures that antimicrobial stewardship activities can affect, and should develop business proposals that provide sustainable support for antimicrobial stewardship program costs.[82] Failing to account for the entire spectrum of antimicrobial stewardship–related costs and savings risks providing an inaccurate economic foundation for a stewardship program's operation.

Microbiologic Outcomes

Studies using robust methodologies, including sophisticated mathematical modeling, have demonstrated convincing relationships between reductions in antimicrobial use and resistance on an aggregate level, including for *C. difficile,* multidrug-resistant gram-negative organisms, and methicillin-resistant *S. aureus* (MRSA).[46,87,88] However, the relationship between antibiotic use in the hospital and rates of antimicrobial resistance is complex. Further work is needed to evaluate the relative impact of infection control interventions to limit transmission and importation of resistant organisms from the community, long-term care facilities, and other health care settings, and the nature of antimicrobial changes within the acute-care institution.[89] Many investigators have reported the impact of antimicrobial stewardship interventions on antimicrobial resistance in terms of the metrics measured by hospital antibiograms—percentage

of clinical testing susceptible over a given time period. However, such measures may not be reflective of the absolute burden of resistance, which is better measured by the rate of resistant isolates in the population.[90,91] In addition, many studies use a "before-and-after" design without following trends in antibiotic use or resistance for sufficiently long periods before and after the intervention in order to establish a causal relationship or adequately controlling for confounding variables.[91] Finally, the relationship between antimicrobial use and resistance may be multifactorial (i.e., use of one antimicrobial may select for resistance to an unrelated antimicrobial if they are carried on the same genetic element) and nonsymmetrical (i.e., the relationship between increasing antimicrobial use and resistance may be different from that observed with decreasing use).[89,92,93] Guidelines for investigators that recommend standards for the conduct and analysis of quasiexperimental interventions to reduce nosocomial infections have been published and may be useful in designing and reporting the impact of antimicrobial stewardship interventions on resistance in an institution.[94]

ANTIMICROBIAL STEWARDSHIP PROGRAM STRUCTURE AND IMPLEMENTATION

Acute-Care Hospitals and Long-Term Care Facilities

As discussed earlier, the CDC has published its Core Elements for acute-care hospital ASPs, which largely agree with the published evidence-based guidelines released by IDSA and SHEA and are reflected in the standards implemented by the CMS and The Joint Commission.[15-17] The CDC has also published Core Elements for long-term care facilities such as nursing homes, which adapt the acute-care hospital Core Elements for the long-term care environment.[18] These Core Elements are summarized in Table 51.2. Among the acute-care hospitals surveyed by the National Healthcare Safety Network (NHSN) in 2014, 48% reported implementing all seven Core Elements.[31] Notably, the single lowest category for which implementation was reported was "hospital leadership commitment," with only 60% reporting having secured this; this is a crucial point. Following are recommendations for the design and implementation of a successful ASP in acute-care and long-term care facilities. Although resources for stewardship implementation (both financial and from the standpoint of having access to infectious diseases physician and pharmacist expertise) in the long-term care settings at this time are generally not as robust as in acute-care settings, the steps listed should be considered and modified based on local resources.[95]

1. Define the philosophy of the program. This may seem to be a trivial step, but the initial approach defined at this early time is likely to form the foundation for the success or failure of the program. Although surveys suggest that prescribers agree that antibiotic resistance is increasing in scope, costly, and related to antibiotic resistance, they tend to view their own antibiotic prescribing as appropriate.[23] Therefore, prescribers are more likely to respond to a program designed to "improve" antibiotic use or patient care rather than as efforts to "restrict" or "control" antimicrobials. Most prescribers will alter their behavior to improve the quality of patient care. Tying program objectives to specific patient care outcomes, such as reducing the incidence of *C. difficile* infection or carbapenem-resistant organisms, may engender more support than programs to generically "reduce antibiotic resistance." Identify key "influencers" of antimicrobial prescribing (e.g., senior or influential physicians) and open a dialogue with them early in the process of program implementation.
2. Involve hospital and long-term care administrators early in the design and implementation process. Provide evidence of the broad effects of suboptimal antimicrobial use beyond antimicrobial costs, and the spectrum of potential benefits to be realized. The support of key officials is critical to the success of the program. Prescribers are more likely to comply with a health system effort rather than with an infectious diseases or pharmacy program that may be perceived to have predominantly financial motives. Maintain an open dialogue with chief administrative personnel, and update them frequently concerning the progress of the program.
3. Develop a budget for all official positions and operating costs, including reasonable compensation for stewardship activities. Almost 500 infectious diseases physicians who participated in the Emerging Infections Network of the IDSA responded to a questionnaire that assessed their roles in ASPs.[57] Overall, half indicated that the hospitals in which they worked required approval of an infectious diseases physician before restricted antimicrobials could be dispensed, but payment for such services was rare (18%). Agree on a formula to calculate cost savings, ideally including savings beyond just antimicrobial costs, from stewardship activities. It may be prudent to involve managed-care organizations in these discussions if they are at risk for pharmacy costs.
4. Define the structure for accountability, reporting, and participation for the ASP. A program lead ultimately accountable for success needs to be identified, along with a core group of personnel, each of whose responsibilities should be defined. A reporting structure to facility administration should be created and a schedule for regular reporting implemented.

TABLE 51.2 Centers for Disease Control and Prevention Core Elements for Acute-Care Hospital and Long-Term Care Facility Antimicrobial Stewardship Programs

Leadership Commitment
Formal statements of support from administration
Dedication of staff time for stewardship activities
Supporting stewardship education and training
Ensuring and empowering participation from groups that can support stewardship activities (e.g., microbiology, infection control, nursing, information systems) *(Nursing commitment may be especially important in long-term care facilities.)*
Accountability
Identification of a single accountable leader for the program (e.g., infectious diseases physician, nursing home medical director)
Drug Expertise
Identification of a pharmacy leader who will colead the program *(For long-term care facilities, engage the facility consultant pharmacist in stewardship or recruit a trained infectious diseases pharmacist to consult with the program.)*
Active Stewardship Strategies
Broad interventions (prior authorization, prospective audit and feedback, antibiotic time-outs)
Pharmacy-driven interventions (e.g., intravenous-to-oral transition, dose optimization, automatic stop orders)
Infection- and syndrome-specific interventions (e.g., pneumonia pathway, asymptomatic bacteriuria policy)
Tracking
Process (e.g., adherence to guidelines) and outcome measures (e.g., *Clostridioides difficile* (formerly *Clostridium difficile*) rate)
Aggregate antibiotic use and facility-wide antimicrobial resistance
Reporting
Regular feedback of tracking metrics to facility personnel and reporting to agencies as required
Education
Education of clinicians about appropriate antimicrobial use, resistance, and infection management

Considerations specific to long-term care facilities are in *italics*.
From Pollack LA, Srinivasan A. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. Clin Infect Dis. *2014;59(suppl 3):S97–S100.*

5. Gather baseline data concerning antimicrobial expenditures, antimicrobial-utilization patterns, and susceptibilities of nosocomial and community pathogens. Benchmark the antimicrobial budget and antimicrobial use to similar institutions, if possible. Participation in the NHSN's Antimicrobial Use and Resistance Module allows measurement of aggregate antimicrobial use in days of therapy per 1000 patient-days present and enables benchmarking against other participating institutions. Access to antibiotic use data can be challenging in the long-term care setting, but sites should work with consulting pharmacists to identify potential sources of data.
6. Evaluate the antimicrobial formulary for redundancy and seek competitive bidding between therapeutically equivalent antimicrobials as a cost-saving measure when feasible.
7. Develop and publish guidelines for antibiotic use and empirical antimicrobial therapy. Recommendations should be based on local susceptibility profiles. In addition, establish appropriate dosing and dosage intervals based on disease-state and pharmacokinetic principles. This step is critical to the success of the program. Involve key personnel from relevant departments when designing the guidelines in order to build consensus for the recommendations. Be willing to compromise on certain issues, but demand that all recommendations be evidence based. It is also worthwhile to consider multimedia formats. Creation of an institutional website for sharing ASP information and guidelines is recommended; a number of examples are available.[76] The website can include institutional antimicrobial susceptibility, dosing recommendations, and price lists along with the clinical guidelines.
8. Define the strategies that the program will use. Interventions must be tailored to the character of the institution. For example, telephone-approval mechanisms are less likely to be successful at a community hospital staffed by busy private practitioners. Begin with a focus on targeted agents based on frequency of use, cost, toxicity, and contribution to resistance. Consider whether inappropriate laboratory and microbiology testing (e.g., testing for *C. difficile* or urinary tract infection in the absence of signs and symptoms of infection) is leading to overuse of antibiotics, and address these issues with appropriate interventions. In the long-term care setting, consideration should be given to obtaining infectious disease expertise for implementation of stewardship activities through consulting agreements with infectious diseases physicians, pharmacists at local acute-care hospitals, or both or via telemedicine, because involvement of infectious disease expertise has been associated with improved uptake of stewardship activities in this setting.[96,97]
9. Develop mechanisms to arbitrate disagreements. A discussion between the prescriber and the director of the program is usually sufficient if the director has administrative time to handle these issues. A mandatory infectious diseases consultation is another option.
10. Develop innovative educational methods. The Internet can be a useful tool in this regard. Information systems personnel may be helpful in incorporating guidelines, recommendations, or reminders into the hospital computer network. Ensuring that guidance on testing and treatment is available at the point of care is likely to increase their adoption. Especially focus on education of health profession trainees who are eager to improve their knowledge of antimicrobial use.
11. Develop and maintain a database to monitor clinical and institutional outcomes, publish and present results, and share best practices.
12. Continually reevaluate the program, paying particular attention to changes in susceptibility profiles and patterns of use. Drug-utilization evaluations should be a part of this process. Reformulate the program as indicated to address problems as they arise. This should be a dynamic process that is responsive to the needs of prescribers and their patients.

Outpatient and Ambulatory Care

The vast majority of studies of antimicrobial stewardship focus on acute-care hospital settings (and especially academic medical centers), despite the fact that most antimicrobial consumption occurs outside of the hospital.[98] A number of recent studies have demonstrated the feasibility and effectiveness of ASPs at improving antimicrobial use in these settings.[99,100,101] CDC guidelines provide Core Elements for antimicrobial stewardship in ambulatory and outpatient care (Table 51.3).[19] These guidelines recognize the need to adapt traditional antimicrobial stewardship approaches to this different care environment. Examples of comprehensive outpatient stewardship programs are currently uncommon, but studies from the literature suggest certain strategies to consider when implementing a stewardship program in the outpatient setting.

1. Form partnerships with patients and parents. Prescriber perceptions of real or assumed patient or caregiver demands for antimicrobial treatment are a key driver of antimicrobial prescribing in the outpatient setting.[102] Training for providers in communication and shared decision making can reduce inappropriate antimicrobial use while maintaining patient satisfaction.[103,104] Provide a balanced view of the risks and benefits of antibiotic use on patients' health and the health of those around them.
2. Provide aggregated feedback. Traditional patient-level audit-and-feedback approaches are not feasible in the outpatient

TABLE 51.3 Centers for Disease Control and Prevention Core Elements for Outpatient Antimicrobial Stewardship

ELEMENT	CLINICIAN EFFORTS	ORGANIZATIONAL EFFORTS
Demonstrate commitment to appropriate antimicrobial use	Publicly attest to commitment to appropriate antimicrobial use (e.g., signed poster in clinic)	Appoint and hold accountable a single leader for stewardship at the facility Incorporate stewardship-related duties in job functions and descriptions Ensure all clinic staff communicate and demonstrate antimicrobial stewardship messages to patients
Act to improve antimicrobial prescribing	Adhere to evidence-based diagnostic and prescribing standards Incorporate delayed prescribing or watchful waiting into care plans when appropriate	Provide communications skills training for clinicians Require explicit justification for nonrecommended antimicrobial prescribing Provide decision support to facilitate best-practice prescribing Reduce unnecessary clinic visits for low-acuity conditions by using call centers, hotlines, or pharmacist consultation
Tracking and reporting	Self-evaluate antimicrobial prescribing practices Participate in quality improvement activities to track and improve antimicrobial prescribing	Implement an antimicrobial tracking and reporting system Assess and share performance on quality measures
Education and expertise	Use effective strategies to communicate with patients around the need for antimicrobials Educate patients about potential harms of antimicrobial use Provide patient education materials, refer patients to reputable sources of information on appropriate antimicrobial use, or both	Provide face-to-face academic detailing for clinicians Provide continuing education programs for clinicians Ensure timely access to persons with expertise

From Sanchez GV, Fleming-Dutra KE, Roberts RM, et al. Core elements of outpatient antibiotic stewardship. MMWR Recomm Rep. *2016;65:1–12.*

environment, given the greater volume of patient visits, the lower degree of objective data (e.g., microbiologic cultures), and the "one-off" nature of most outpatient encounters. However, providing periodic feedback to prescribers on their aggregate antimicrobial prescribing for targeted conditions, especially if performed with peer benchmarking data or in the context of an in-person academic detailing visit, can be effective in improving prescribing.[105,106,107]

3. Set expectations for prescribing at the practice level and develop approaches for prescribers to follow them. Posting commitment pledges to prescribe antibiotics only when indicated, which are personalized to the practice and provider, have been shown to be effective in improving antibiotic use. Providing clear and easily accessible guidelines for prescribers around common outpatient disease states may help to improve appropriate prescribing, although the impact may wane without reinforcement.[40,109] Designing electronic order entry systems to prioritize or default to guideline-concordant therapies and to require written justification for nonconcordant therapies at the time of prescribing can further encourage appropriate antimicrobial use.[108,110,111]

THE FUTURE

The rising prevalence of antimicrobial resistance and its clinical and economic impacts are being recognized as critical by clinicians, administrators, and health care regulatory bodies.[15-21] Comprehensive ASPs decrease costs while improving both patient and institutional outcomes.[70,71,83] However, further work is needed to clearly identify the relationship between antimicrobial use and the emergence of resistance in a way that colleagues will appreciate and accept. Relevant studies will require sufficient statistical power to characterize baseline resistance, to deal with random variation, and to control for a multitude of confounding variables. The explosion of electronically collected data provides the opportunity to programs to continually monitor their performance and to use benchmarks from other institutions. However, further work needs to be done to identify key metrics, provide risk adjustments, and create estimates of appropriateness of antimicrobial use from aggregate data.

The pace of new antimicrobial development has increased recently from its long nadir, in response to investment from the pharmaceutical industry and changes to government regulations and incentives.[112] However, it is far from clear whether this increased development will keep pace with the growth in antimicrobial resistance. Moreover, indiscriminate use of new agents will compromise their efficacy, too. The focus on antimicrobial stewardship strategies must continue to shift from cost containment to efforts to limit resistance and improve patient safety. It is likely that the increasingly sophisticated information systems being deployed in all hospitals will play a more prominent role in antimicrobial stewardship. Several companies currently market products that can either assist in monitoring antimicrobial therapy and evaluating interventions or actually offer computer decision support for antimicrobial selection and dosing. Advances in the development of rapid diagnostics and biomarkers will likely improve the precision of determining the need for and optimal selection and duration of antimicrobial therapy, and ASPs will be critical in ensuring that providers integrate these new technologies into practice. The development of improved infection diagnostics is at least as essential to the control of antimicrobial resistance as new antimicrobials and should be similarly incentivized. The current crisis of antimicrobial resistance and the paucity of viable therapeutic options mandates that antimicrobial stewardship will become an increasingly important responsibility of all clinicians.

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52 Designing and Interpreting Clinical Studies in Infectious Diseases

John H. Powers III

LEXICON OF TERMS IN CLINICAL STUDY DESIGN AND ANALYSIS

Types of Studies

Exploratory studies: Studies that provide preliminary evidence used as the basis for designing further studies to confirm the effects of a test intervention compared with a control intervention; sometimes called "pilot studies," to evaluate operational characteristics of a study (e.g., ability to enroll participants or enrollment processes); often provide erroneous results, given the small study size or outcomes based on biologic activity that does not reflect patient outcomes. Results are sometimes erroneously presented as confirmatory evidence after the conclusion of study. May use descriptive or inferential statistical methods.

Confirmatory studies: Studies intended to provide firm evidence in support of causal relationships between an exposure or intervention and outcomes between a test and a control group; include statement of hypothesis, adherence to protocols, and standard operating procedures. Use inferential statistical methods to analyze results.

Controls in Clinical Studies

Control group: A group in which an intervention is administered for which the effects of the intervention are already known from prior evidence; outcomes in the group that receives the test intervention are compared with the outcomes of this control group. The purpose of a control group is to evaluate whether the effects of the intervention are due to the intervention or to the conditions of the experiment or other factors through *counterfactual evidence*—what would happen to a group that did not receive the test intervention. Control groups are unnecessary only in rare situations. Examples would be diseases in which an unbiased outcome is well known, such as all-cause mortality, or even rarer situations in which patient factors or other factors have limited or no effects on outcomes.

No-treatment concurrent control: No specific treatment prescribed to control group (does not exclude supportive care); cannot be blinded; uses superiority hypotheses.

Placebo concurrent control: Control group receives placebo that appears similar to test intervention; can be blinded; uses superiority hypotheses.

Dose-comparison concurrent control: A higher dose or exposure to the test intervention is compared with a lower dose or exposure of the test intervention; uses superiority hypotheses.

Active concurrent control: Control group receives biologically active intervention known to be effective from prior studies; may or may not be blinded; can be superiority or noninferiority hypotheses; placebo can be used to blind study in add-on trials testing older standard of care plus placebo compared with older standard of care plus new intervention.

External concurrent control or historical control: Study that compares a group receiving the test intervention with a control group external to the study, rather than to an internal control group from the same population assigned to a different treatment. The external control can be a group evaluated at an earlier time (historical control) or a group evaluated during the same time period but in another setting (external control); design is more susceptible to bias in terms of selection of participants (control groups in historical controls, on average, have worse outcomes than concurrent controls) and changes in medical care over time.

Trial Hypotheses

Hypothesis: The investigator's proposed explanation for the relationship between the exposure or intervention (e.g., a drug) and the outcomes of the study (e.g., mortality, symptoms) that is tested in the study; based on prior accrued evidence. The results of a study are compared to the prestated hypothesis of the study to allow valid interpretation of the results. Studies without hypothesis provide exploratory and not confirmatory evidence.

Null hypothesis: The starting point of all trials in which the assumption is that the investigators' hypothesis is *not* true and the study cannot exclude the possibility that the intervention or drug has no effect on outcome; based on the "theory of falsification," in which hypotheses must be rigorously tested to show that they are not false.

Alternative hypothesis: If evidence from the study shows the null hypothesis is unlikely to be true, then investigators can accept (not prove) the alternative hypothesis that the relationship between the exposure or intervention and the outcome is likely to be true.

Noninferiority hypothesis: A hypothesis in an active controlled trial that evaluates whether the test intervention is no worse than the control intervention by a predefined difference. The predetermined difference is selected because it is considered clinically insignificant to patients. The difference must be greater than the known effect of the control intervention compared with placebo or no specific therapy. This hypothesis is misnamed in that the test intervention can be inferior to the control intervention, just by an amount smaller than a predefined amount. The predefined amount of difference in end points between the test and control groups, called the noninferiority margin, or "delta," is the difference for which the test intervention may be permitted to be worse than the control, using 95% confidence limits. If the difference is less than the delta, one may accept the alternative hypothesis that the treatment being compared is not worse than the other treatment by the prespecified amount.

Equivalence hypothesis: A hypothesis in an active controlled trial that evaluates whether the test intervention is no worse *and* no better than the control intervention by a predefined amount. Unlike in noninferiority studies, there is an upper limit of the difference in addition to a lower limit on the difference between the end points in the test and control groups. A classic example is bioequivalence studies, in which a generic drug must have concentrations that are no lower and no higher than some prespecified amount.

Superiority hypothesis: A hypothesis in a no-treatment, placebo, dose-response, or active controlled study that evaluates whether the test group has better outcomes than the control group by some prespecified amount; often designed to rule out no effect (zero absolute difference) but can be designed to rule out some clinically meaningful effect other than zero (e.g., confidence interval (CI) around difference between test and control groups should rule out some nonzero amount for intervention to be clinically useful);

asks that one treatment is at least a certain percentage better than the other treatment.

Types of Error in Clinical Trials

Random error: Error due to chance alone or random sampling error; statistics are used in the study planning to decrease random error through techniques such as selecting a sufficient number of participants for a study (sample size) and to evaluate the results of a study for potential effects of random chance; can be decreased by increasing sample size.

Alpha or type 1 error: The prespecified false-positive error rate or probability (i.e., concluding that the evidence is sufficient to accept that the intervention is effective when in truth it is not) for a study conventionally set at 0.05 or 5%, meaning that for every 100 studies performed, 5 would show results as great as those observed by chance alone in the absence of other biases; relates to the *P* value and hypothesis testing after the study is over because the *P* value should be smaller than the type 1 error chosen.

Beta or type 2 error: The prespecified false-negative error rate (i.e., concluding that the evidence is insufficient to accept that the intervention is effective when in truth it is effective); conventionally set at 0.10 or 0.20 (10% or 20%).

Power: The ability of a study to detect a difference if in truth a difference exists; determined *before* initiation of a study; defined as 1 minus the type 2 error; type 2 error of 10% or 20% corresponds to power of 90% or 80%, respectively. It is inappropriate to perform power calculations on observed results after a study is complete.

Delta, or effect size: The predetermined amount of difference between the test and control groups expected in the study; in superiority hypotheses, the delta equals the expected amount of superiority of the test group compared with the control group; in noninferiority hypotheses, the delta equals the amount of inferiority of the test group compared with the control group that would be the limit one would accept as not being clinically important; in equivalence hypotheses, the delta is the largest difference one would accept as showing equivalence to the comparator.

Sample size: The number of participants or groups planned to be enrolled in a study; based on calculation using the type 1 error, type 2 error, effect size, and standard deviation (spread of values in the data).

Systematic error: Errors that do not occur by chance in the course of designing, conducting, or analyzing studies and can cause the observed results of a study to deviate from true results; addressed by design of study and not by statistical methodologies after study is complete; increasing sample size increases effects of systematic bias, so a larger study is more incorrect.

Selection bias: Systematic differences between participants in test and control groups with regard to factors that independently affect outcomes; can result from lack of randomization or exclusion of participants from randomized studies.

Observer or assessment bias: Bias that is present when persons assessing outcome are influenced by knowledge of treatment assignment that influences assessment of outcomes.

Misclassification bias: Bias that is present when a given measurement is defined in error (e.g., *cure* is called *failure*); occurs when insufficient instructions or training is given to make assessments (e.g., clinician judgment when clinicians are not clearly instructed regarding what to assess in making judgments).

Instrument bias: When instrument (scoring system or laboratory test or clinician judgment) does not make accurate measurements compared with true value.

Confounding: Factors that can affect study independent of test and control intervention such that outcomes are not causally related to interventions tested (e.g., prescribing of concomitant effective medications in the setting of a noninferiority trials obviates assessments of both test and control drug); addressed by randomization in superiority trials; can still occur in randomized noninferiority trials because of factors such as effective therapy prescribed before randomization. This therapy biases the study toward showing no difference. Confounding occurs more often in nonrandomized studies.

Methods to Control Bias in Clinical Trials

Randomization: Nonsystematic method (e.g., flipping a coin or random table of numbers) used to assign participants to test and control groups to decrease selection bias and balance groups by baseline factors that affect outcomes; randomization gives best chance of avoiding confounding differences between the groups and of incorrectly assigning causality of the outcomes to the interventions tested; effective randomization minimizes baseline differences between test and control groups; does not control for sources of bias that occur after randomization, such as misclassification of outcomes; excluding participants from the analysis decreases protection of randomization against selection bias.

Individual randomization: Unit of randomization is the individual participant; used where effects of the intervention have direct effects on individuals but no indirect effects on the group.

Cluster or group randomization: Unit of randomization is a group such as a hospital, institution, neighborhood, or geographic area; used where indirect effects of the intervention may carry over to others in the group (e.g., herd immunity in vaccination studies).

Allocation concealment: Lack of knowledge of the randomization code so that investigators cannot affect who is enrolled in the study groups and who is not (selection bias).

Blinding: Lack of knowledge of the assigned intervention by any or all of these three groups: participants in the study, investigators implementing the study, and those who assess the outcomes of the study; "double-blind" studies usually are those in which there is lack of knowledge of the treatment intervention by both participants and investigators, and in which investigators both implement the study and assess outcomes.

Types of Nonrandomized Studies

Prospective study: Study in which hypotheses precede data collection.

Retrospective study: Study in which hypotheses are formed after data have already been collected.

Case-control study: Retrospective study in which investigator selects outcomes of interest and then looks backward in time to compare exposures between the test and control groups (e.g., examine survivors of disease, then look back in time to see proportion of survivors who did or did not receive a drug).

Cohort study: Prospective or retrospective longitudinal study in which investigator selects exposure of interest and then compares outcomes between test and control groups (e.g., comparing sexual activity of teenagers who did or did not receive the human papillomavirus vaccine).

Methods to Attempt to Control Selection Bias in Nonrandomized Studies

Matched control: The test and control groups are matched for the baseline variables thought to be most likely to influence the outcome being evaluated by using methods such as logistic regression. Unrecognized confounding differences between the two groups that influence outcome are the major limitation of this method of analysis.

Propensity score control group: Assigns a score based on several baseline factors to individual study participants that represents the probability that the person had a given exposure (e.g., received a particular drug), then compares outcomes between test and control group participants with similar propensity scores. Several methods exist for comparing propensity scores (e.g., matching patients with identical scores, matching patients with similar scores, matching patients with scores similar within some range); cannot compensate for large differences in choice of treatment or clustering in choice of treatment or unmeasured confounders. For example, if one treatment was largely confined to intensive care patients, or inpatients, and the other treatment was not, propensity scoring cannot compensate for the differences in outcome.

Outcomes of Clinical Studies

Outcome assessment: The actual measurements performed in clinical trials that are used to define end point(s). Outcome assessments can include survival, biomarkers, patient-reported outcomes (PROs), clinician-reported outcomes (ClinROs), observer-reported outcomes (ObsROs), and performance outcomes (PerfOs).

Clinical outcomes assessments: Direct or indirect measures of how patients feel (symptoms) or function in their daily lives that are based on judgments or efforts of the observers or patients. Include PROs, ClinROs, and PerfOs but not biomarkers or survival.

Patient-reported outcomes (PROs): Direct measures of how patients feel or function obtained directly from patients without interpretation by anyone else.

Clinician-reported outcomes (ClinROs): Indirect measures of patient benefit involving evaluation of physical signs or other observations captured by clinicians based on clinician judgments.

Surrogate outcome assessments: Indirect measures of patient's health status, which are physical signs or biologic parameters, including laboratory measurements used as substitutes for how patients feel (symptoms), function, or survive.

End points: End points of a study include the following: (1) outcome and how it is defined (e.g., survival, cure) or (2) timing when the outcome is to be assessed (single or multiple fixed times, time to event). End points can be composed of a single measurement (e.g., all-cause survival), multiple independent measurements (coprimary), or multiple measurements combined into a single evaluation (composite end points; e.g., all-cause survival plus symptoms plus patient function).

Primary end point: The single specified outcome compared between the test and control groups. The sample size of the study is usually chosen based on this outcome.

Secondary end points: Multiple outcomes that may help explain the primary end point but are not appropriate for statistical analysis unless the study is designed with secondary hypotheses and appropriate sample size, and increase in false-positive rate resulting from multiple testing is controlled for. For example, a new drug may be better than an old drug in terms of the primary end point, and a secondary end point may indicate that this is particularly true for one subset of patients. Secondary outcomes are particularly problematic when used to claim outcomes different from the primary outcome—for instance, finding noninferiority in one group but claiming superiority on secondary end points that were not designed appropriately at study inception.

Analysis Populations

Analysis population: The types of participants in the study who are included in the analysis.

Intention-to-treat (intent-to-treat) analysis (ITT): Includes all randomized participants regardless of intervention actually received in the analysis; maintains protection of randomization from selection bias.

Modified intention-to-treat analysis (mITT): Includes patients in analysis based on information obtained before randomization (such as a particular diagnosis); maintains protection of randomization from selection bias as long as numbers of exclusions compared with ITT analysis are few.

Per-protocol/as-treated/clinically evaluable analysis (PP): Includes patients in the analysis who follow the protocol as specified; based on excluding patients from analysis based on events that occur after randomization. Exclusions can bias study results and decrease randomization's protection from selection bias.

Analysis of Study Results

Number needed to treat: The number of patients needed to treat in order to benefit one patient is defined as the inverse of the absolute difference in outcomes between the test and control groups; can evaluate number needed to treat to benefit one person and number needed to treat to harm one person.

95% confidence interval (CI): A measure of *estimation* used to estimate the difference in a population from the observed results in a sample; based on the theory that, on average, if 100 identical studies were performed, 95 of the studies would include the true difference and 5 studies would not contain the true difference between the test and control groups; any value within the 95% CI is equally likely to be the true mean (it is not a probability), but often the 95% CI is misinterpreted as the upper and lower boundaries around a difference. Results are in the units of the study outcome and so can be readily interpreted in terms of clinical meaning. The range of values useful in interpreting both "positive" and "negative" studies—for instance, a "negative" study with wide 95% CI that does not exclude clinically meaningful differences is inconclusive, but a study with narrow CIs that does exclude clinically meaningful differences can provide stronger evidence.

***P* value:** A measure of *hypothesis testing*; interpreted as the probability that results as extreme as those seen in the study could occur by chance; statistical significance is defined conventionally as *P* values less than .05 (<5% or 1 in 20 probability of results occurring by chance alone); not a measure of bias, so biased studies can show "statistically significant" results; not a measure of clinical meaningfulness because not measured in terms of study outcomes. Studies with larger sample size can show "statistically significant" results that are not clinically meaningful. It is not a measure of the likelihood that intervention is or is not effective—for instance, a *P* value of .01 does not mean that there is only a 1% chance the intervention is ineffective, but it is often misinterpreted as such. False-positive error in *P* values increases with greater number of comparisons between test and control groups (called *multiplicity*).

Inferential statistics: Statistical methods using the results from the sample of patients studied to draw conclusions about the results in the population from which the study patients were drawn. Includes hypothesis testing (*P* values) and CIs around the difference between the test and control groups**.** Used to evaluate effects of medical interventions in the larger population based on the sample of patients studied in a clinical trial.

Descriptive statistics: Statistical methods used to report the results in the sample studied without comparison to another group or inference to a larger population—for example, describing the number of patients in an institution who develop pneumonia in 1 year without comparison to another year or another institution. Not appropriate for evaluating the effect of medical interventions in clinical trials or for making inferences about effects in larger populations based on a single sample.

OVERVIEW

The volume of information available to caregivers and patients increases exponentially with each passing year. The availability of information in textbooks, in journals, and through the Internet requires an ability to sift through data efficiently to determine what is valuable in clinical decision making versus what is hypothetical, hype, or harmful. A comparison of the time necessary to review medical journals compared with the time available for general practitioners showed that clinicians would need to read 19 journal articles per day for 365 days a year to stay current.[1] However, in this same study, clinicians indicated by self-reports that they had well less than an hour a week to review new medical information. The half-life of scientific information is quite short, and therefore there is a continual need to reevaluate as new information emerges. Inappropriately designed studies may be accurate measures of prevailing biases rather than informative for clinical practice.[2,3] In addition, authors have pointed to an increasing inability to confirm the results of clinical research, which may in part be due to the design and analysis of those studies.[4] These issues make the knowledge to critically evaluate evidence a necessity rather than a luxury.

Clinical practice and clinical research continuously interact. Observations in clinical practice form the basis for research questions that are then evaluated to determine the probability of their truthfulness, their generalizability, and their reliability. The results of research are then

applied in practice, leading to a new set of questions. However, clinical practice and clinical research differ in important aspects. Clinical practice refers to interventions designed solely to enhance the well-being of an individual patient and that have reasonable expectations of success. The purpose of clinical practice is to provide diagnosis, preventive treatment, or therapy to particular individuals. By contrast, clinical research designates an activity designed to test hypotheses in groups of research participants, to permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge expressed in theories, principles, and statements of relationships.[5] Research is described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. Because interventions are used in clinical practice does not necessarily make them more beneficial than harmful. In addition, although in vitro data and pharmacokinetic and animal studies form the building blocks for proofs of principles and generation of important hypotheses concerning effectiveness and harms of medical interventions, these hypotheses require adequate testing in humans to ascertain the benefits and harms of medical interventions, including drugs, biologics (e.g., vaccines, antibodies), diagnostics, and devices. A study showed that 28.1% of investigational new drug (IND) applications for antimicrobials submitted to the US Food and Drug Administration (FDA) were subsequently approved, a higher percentage than in any other therapeutic area.[6] However, all of the 71.9% of drugs that were not approved had promising in vitro data and animal studies, showing the importance of appropriately designed trials in humans to test hypotheses. More than half the recommendations in treatment guidelines are based on opinions or case series, demonstrating the need for appropriate testing of much of what is recommended in the absence of substantial evidence.[7] Clinical research performs the systematic evaluations that allow clinicians, caregivers, patients, payers, and policy makers to understand that interventions truly are helping more than hurting.

HISTORY

Before the 1930s, fields in science based conclusions on personal experience and observations that were then extrapolated widely. This *observationalist-inductivist* view led to incorrect and harmful theories, such as bloodletting for various infections, a practice that lasted for thousands of years.[8] Since the 1930s, however, science has been based on *falsifiability*—that is, testing hypotheses to ascertain whether they might be false.[9] For example, one might conclude by observing a lake full of white swans that all swans are white. Further testing of this hypothesis and finding a single black swan "falsifies" this conclusion. To test the percentage of swans that are white, one would have to make enough observations to draw valid conclusions. This relates to the statistical principle of the "null" hypothesis—starting with the hypothesis that the intervention is not effective, then gathering evidence to show with sufficient probability that the null hypothesis is unlikely to be correct. In this regard, hypotheses are not "proven" but are shown likely to be correct based on the evidence. Inherent in this view is that hypotheses must be appropriately tested in a fair and unbiased manner.[10]

The field of infectious diseases has a distinguished history in advancing the methodology to elucidate descriptions of disease and testing hypotheses by making fair comparisons among medical interventions. The first studies to use control groups, placebos, double-blinding, and randomization were all performed to study various infections.[11] The investigators of these studies were well aware of how the play of chance and bias could affect the validity and clinical usefulness of their results. Although drugs such as penicillin, used in the treatment of various infections, had large treatment effects on decreasing mortality, even penicillin was studied in thousands of patients in order to understand its effects in different infections.[12] The promotion of ineffective and harmful antibiotics in the 1950s prompted infectious disease physician-scientists to lead the way in establishing "adequate and well-controlled trials" as the regulatory standard in law for determining the effectiveness of new drugs, including antibiotics.[13]

DEFINING TERMS

A common language is necessary to communicate about both the design and the results of clinical research studies. Research and science, in general, entail making measurements and applying those measurements to study natural phenomena. Some terms are commonly used in the description of measures. One of the most common is the term *validity*. Validity refers to the extent to which measures actually reflect what they purport to measure. Although all measures have some associated error, validity implies that the amount of error does not appreciably affect the truthfulness and the usefulness of the results.[14] Therefore, even though measures are not "perfect," the goal is to minimize error as much as possible. Validity is not an all-or-none quality but rather is contextual, affected by factors such as the use to which the measure is put (diagnosis vs. prognosis vs. outcome) or the population from which the measures are obtained. A measurement that is valid in one situation may lack validity in another setting. *Internal validity* refers to the validity of the results of an individual study in that the study is capable of providing adequate evidence for the primary research question. *External validity* refers to the generalizability of the results to patients or clinical settings outside the study. Internal validity is a prerequisite for external validity. If the results are not valid for the study itself, it is not possible to extrapolate those results to other settings. *Reliability* is the ability to obtain similar data that are reproducible on repeated measurements. Validity must precede consideration of reliability. If a measure lacks validity, it may be reliable but just reliably wrong. *Responsiveness* is the ability of measurements to detect change over time.

Association, correlation, and causality are terms used to describe the relationships between measures.[15] *Association* implies a general relationship, whereas correlation is a means of quantifying that relationship. *Correlation* is a subset of association and implies that as the value of a measure changes, the value of a related measure also changes, either in the same or the opposite direction. For instance, as the human immunodeficiency virus (HIV) load increases, mortality from HIV/acquired immunodeficiency syndrome (AIDS) increases (a positive correlation), whereas, as CD4 count decreases, mortality increases (an inverse correlation). Neither association nor correlation implies causality. *Causality* means that one measure precedes the other and that the first measure is necessary and sufficient to cause the second measure. Correlation is often sufficient when evaluating questions related to risk factors and prognosis of disease, but correlation alone is insufficient when evaluating effects of interventions on outcomes, wherein assessment of causality is needed.

Treatment effects are measures of the causal impacts of interventions on outcomes, measured by differences in outcomes between baseline comparable test and control groups. Treatment effects are not measured by correlation alone. For instance, there is a correlation between patients with disease caused by organisms with higher minimal inhibitory concentrations (MICs) to a specific drug and increased mortality.[16,17] However, this relationship may not be a measure of treatment effects if patients infected with higher MIC organisms differ from patients with organisms with lower MICs on important factors that influence mortality.[18,19] Therefore, higher MICs are not a measure of treatment effects of the chosen drug because other factors such as age, severity of disease, and comorbidities also affect outcomes. Factors that affect outcomes independent of the chosen factors because of imbalances between study groups are called confounders. *Confounding* can occur when there are baseline imbalances between study groups, most often in nonrandomized, observational studies. For instance, in an observational study comparing interventions, if there are more patients with higher Acute Physiology and Chronic Health Evaluation (APACHE) scores in the test group than in the control group, then an imbalance in severity of disease may be causally related to outcomes rather than the interventions tested. Confounding differs from effect modification. *Effect modification* refers to treatment effects that differ in specific groups of patients that are baseline comparable with regard to other factors. For instance, in a randomized trial, if the treatment effect on mortality (the difference between the test and control groups) of a new drug is greater in an appropriately designed subgroup analysis of patients with lower baseline APACHE scores, but smaller or nonexistent in an appropriately designed subgroup of patients with higher APACHE scores, then the severity of illness as measured with APACHE is a causal effect modifier, not a confounder, because randomization balances other factors between the groups besides the interventions received.

CHOOSING A RESEARCH QUESTION AND DEFINING GOALS OF A STUDY

Before discussing other aspects of a clinical research study, one must first decide on the research question that will be evaluated. Many types of questions form the basis for clinical research, including questions related to biologic, behavioral, cognitive, environmental, and sociologic and cultural aspects of disease. This chapter focuses mainly on biologic questions. Biologic questions include those related to natural history, diagnosis, risk factors for acquisition of disease or outcomes, and prognosis, in addition to testing of interventions to influence the outcomes of disease.[20]

A common error in clinical research is lack of clarity on the end points, the specific question or questions asked by the study, or asking too many questions, resulting in a study that cannot answer any question validly or reliably. Because the type of research question directly affects the choice of the study design, greater specificity about the research question allows better choice of study design.

There are two main categories of research studies. *Descriptive research* makes observations and describes the results of those findings, providing an accounting and delineating components of a problem (such as the number of persons in a hospital with a particular disease) without making inferences regarding causality. There are usually no specific hypotheses in this type of study, and the sample size is defined based on the setting (e.g., all patients in a hospital) or on obtaining a certain degree of precision around the estimate of the described data. Examples of descriptive research include single case reports and case series. An "open-label, noncomparative, single-arm trial" is in fact not a trial but a case series. *Qualitative research,* such as patient interviews, is a form of descriptive research. These types of studies are useful in providing observations that form hypotheses for future testing.

Analytical research studies attempt to make comparisons between groups. Analytical research entails specific hypotheses stated by investigators that are evaluated during the course of the study. Hypotheses are investigators' statements of belief, but they are not decided on haphazardly because they are based on prior studies that have informed both the research question and design of the planned study. However, multiple prior hypothesis-generating studies do not obviate the need to test specific hypotheses.[21]

TYPES OF ANALYTICAL STUDY DESIGNS

Analytical research is divided into *experimental* and *nonexperimental (observational)* research designs.[16] The primary difference is that in nonexperimental designs the investigator does not assign research participants to the study groups. Rather, participants are assigned according to usual practice, such as the drug they would ordinarily be given, which may result in differences in both measured and unmeasured factors between study groups, affecting the comparability of those groups. Nonexperimental research designs include cohort, case-control, and cross-sectional study designs. *Case-control studies* choose participants based on outcomes and then look back in time to evaluate differences in exposures between the groups. Case-control studies are inherently retrospective, meaning data collection occurs before hypotheses are formed. Case-control studies are useful when the outcomes evaluated are uncommon.[22] *Cohort studies* begin with exposures and then evaluate differences in outcomes between the groups. Cohort studies can be prospective, meaning that hypotheses precede collection of the data, or retrospective. Cohort studies can also contain nested case-control studies. Cohort studies are useful when exposures are uncommon. *Cross-sectional studies* evaluate exposures and outcomes at a particular point in time.

In experimental studies, also called *clinical trials,* investigators choose the groups to which participants are assigned, as discussed in more detail later. There are two basic approaches to clinical trials that differ in design characteristics. The first type is called an *explanatory trial,* in which an intervention is evaluated under "optimal" conditions wherein the intervention is expected to have an effect, such as in a narrow population in which the intervention is administered by specialists in the field. These trials test for a causal effect on outcomes but often do not ask the more generalizable question of outcomes with the intervention as used in practice. The other approach is a *pragmatic trial,* which evaluates strategies or approaches under usual care conditions, with the goal of helping to select options for care as interventions as used in practice.[23] In reality, trials often extend along a continuum between explanatory and pragmatic, but investigators should be clear about the particular approach and the reason for choosing elements of trial design for that approach. Explanatory and pragmatic trials differ in their selection criteria for participants, flexibility in application of the interventions, intensity of follow-up and measurement of adherence, and other design factors.

There has been increasing interest in designing studies to acquire "real-world evidence" regarding therapeutics. An exact definition of real-world evidence is not clear, and may mean different things to different stakeholders, However the basic principle is evaluating the effects of interventions under the conditions in which they are used in practice.[24] Real-world evidence may be acquired both from observational studies and from randomized trials designed to be more pragmatic and reflective of real-world practice.[25] Randomization is not inconsistent with real-world evidence, and more pragmatic trials often have broader inclusion and exclusion criteria and patient-centered end points, measuring patient function and symptoms rather than biomarkers.[26]

When testing interventions, investigators should clearly explain if they plan to evaluate whether those interventions will be used for *diagnosis,* to *prevent* disease, or to *treat* patients with existing disease. The design characteristics differ for each of these types of studies.

COMPARISON WITH A CONTROL GROUP

The purpose of control groups is to distinguish the effect of some chosen factor in the test group on outcomes from effects caused by other factors, such as the natural history of disease, placebo effects, or observer or patient expectations.[27,28] A control group demonstrates what would happen to patients who are not in the test group. A control group is necessary except in rare circumstances in which the course of disease is uniform for any given patient or group of patients and outcomes are predictable based on patient characteristics. In most situations, variability exists in patient outcome such that a control group is necessary. Even when diseases are claimed to be "universally fatal," collection of such information for a historical control group, to validate that assumption, usually is necessary. The selection of control groups depends on the goals of the study. For instance, in evaluating a diagnostic test. the test and control groups consist of those with and without a disease diagnosed by some reference standard.

The choice of comparison groups is based on selecting participants who are like those in the test group except for the factor that is analyzed. Some types of control groups, such as patients who refuse a particular therapy or those who receive "inappropriate" therapy, are inherently different from the test group of patients who agree to therapy or receive "appropriate" therapy.[21] Also, for a group to function as a control, the outcomes in that group should be known or expected based on prior evidence. Experimental studies make comparisons between test outcomes that are unknown and control groups in which the outcomes are known or expected. Experimental studies assign participants by using the process of randomization (explained later in this chapter) or nonrandom methods to assign participants to study groups. Control groups can be *concurrent* or *historical.* In concurrent studies, participants in the test and control groups are evaluated over a similar time frame. In historical studies, a current test group is compared with a control group from which the data were collected sometime in the past and therefore are always nonrandomized. Patient characteristics between the historical control and current patients often differ because of changes in medical practice over time or differences in selection criteria for current versus past patients.[28] Historical studies, on average, show lower success rates for their control groups than do concurrent control groups, biasing the studies toward showing a difference that may not exist or toward a larger treatment effect than truly exists.[29]

In concurrent studies, investigators can choose several types of control groups. *No specific treatment* concurrent controls and *placebo* concurrent controls both compare the test group with groups that receive no specific

active interventions. The placebo intervention does not contain the active test intervention but appears similar in all aspects to it. The main difference is that assignment to study groups can be blinded in placebo-controlled studies but not in trials in which treatment of the comparison group is not specified and/or based on current standards of care. The fact that a trial is placebo controlled does not mean that patients receive no treatment at all. In *add-on studies,* patients receive current standard of care plus placebo in the control group, whereas the test group receives current standard of care plus the new intervention. Dose-response trials compare higher and lower exposure of the test intervention. Active controlled trials compare the test intervention and another active intervention.

Types of Hypotheses

Because an investigator often cannot directly test interventions in the entire population of interest, the investigator starts off with the hypothesis that the intervention does *not* have an effect and then gathers evidence to show that this hypothesis of lack of effect is unlikely to be correct. This is consistent with the principles of falsification expounded in the 1930s.[9] An analogous situation is assuming a defendant in a court case is innocent until shown guilty by examining evidence showing beyond a reasonable doubt that the defendant is not innocent. The hypothesis that the intervention does not have the proposed effect is called the *null hypothesis,* termed *null* because the assumption is that there is no proposed effect of the intervention being studied. If there is sufficient evidence from the study, then the null hypothesis is said be "rejected," and the investigators can "accept" the alternative hypothesis that the intervention does have the observed effect. Note that the alternative hypothesis is not "proven" but rather is accepted based on available evidence. The result is the somewhat confusing double-negative terminology of not showing that the intervention is not effective.[30]

No-therapy, placebo-controlled, and dose-response trials are usually designed as *superiority* trials. The null hypothesis in a superiority trial is that the intervention is not more effective than the control regimen, whereas the alternative hypothesis states that there exists a difference between the test and control groups. This difference must be at least greater than zero in absolute terms or different from one in relative terms.[31]

Active controlled trials can be designed to test *superiority, equivalence,* or *noninferiority* hypotheses.[31] Equivalence and noninferiority trials attempt to rule out absolute differences, other than zero, or relative differences between two groups. The null hypothesis is that the intervention is less effective than the control regimen by some amount. In other words, these trials allow that the outcomes in the test group might be slightly inferior to those in the control group, as long as that amount of inferiority is judged not to be clinically meaningful—making them really "not too much inferior" trials. Neither type of hypothesis can show that two interventions are equal or "just as good as" each other because this would require an infinite sample size to rule out any difference at all.[32] Rather, these trials attempt to rule out some amount of inferiority and/or superiority of a chosen magnitude between the groups. Equivalence trials attempt to rule out that the test intervention is both not worse than a chosen amount and no better than a chosen amount when compared with the control group. The classic examples are bioequivalence trials, where a new formulation of a drug is compared with an older formulation with the goal of showing that concentrations with the new formulation are not much lower or higher with the test formulation compared with the control formulation. Equivalence trials entail a choice of an upper boundary and a lower boundary for superiority and inferiority.[33] In most cases, however, investigators would be happy and it would be clinically relevant to show that a test intervention was more effective than the active intervention in the control group. In these situations, investigators wish only to rule out that the test group is not too much inferior to the control group. These types of trials carry the unfortunate name of "noninferiority" trials.[34] This name is misleading because the test group can show frank inferiority or superiority to the control group, yet still be termed "noninferior," as long as the amount of inferiority of the test drug demonstrated in the trial compared with the control drug does not exceed a prechosen magnitude of inferiority.[35,36]

The reason to perform a noninferiority trial is not just the existence of an older intervention that has been shown to be effective or that placebo cannot ethically be used, but that the test intervention is hypothesized to have benefits other than improved effectiveness, such as fewer harms or greater convenience, while preserving most of the effectiveness seen with the control intervention.[37] It is ethically questionable to expose research participants to more toxic and somewhat less effective interventions in serious and life-threatening diseases for which effective therapy exists and when patients may experience irreversible harm, remembering that noninferiority trials cannot demonstrate that a new intervention is "as good as" the control.[38] A noninferiority hypothesis is not appropriate if the hypothesized benefits of the new intervention are superior effectiveness in a population other than the one studied, which should be tested by superiority hypotheses. If the intervention is hypothesized to have advantages in a specific population (those intolerant to other interventions or in whom other interventions fail), it is more logical and ethical to test the intervention in the target group of patients, to avoid exposing the nontarget population to less effective or more toxic interventions.[37] For instance, in the setting in which there is no effective therapy, as in patients infected with pan-resistant organisms, there is no effective control regimen; therefore, interventions should be tested in superiority hypotheses against current standards of care. Showing noninferiority in patients with susceptible organisms does not provide evidence for effectiveness in patients with no options, because the study does not test the hypothesis of superior treatment effects in patients with resistant organisms. Given differences in characteristics between the patient groups, benefit cannot be extrapolated from one type of patient to different patients. It also exposes patients who have other effective options to potentially less effective drugs.[39] For instance, tigecycline was shown to be "noninferior" to control drugs on an outcome of "clinical response," yet it had higher mortality in all patient groups, and excess mortality, compared with the control drugs, was highest in those with resistant pathogens.[40]

Noninferiority trials are justifiable when placebo-controlled trials cannot be used because the demonstrated effect of the control intervention has important benefits for patients on morbidity and mortality and the new intervention is hypothesized to have non-efficacy benefits in a setting where patients are not exposed to irreversible harm. Placebo-controlled trials are still ethical if the benefits of the control intervention are improvements in non–life-threatening symptoms. Placebo-controlled superiority trials are also ethical in the setting of add-on trials, in which all participants receive current standard of care, such as recent clinical trials in multidrug-resistant tuberculosis.[41]

Conclusions from superiority and noninferiority trials have different implications in that demonstration of superiority is direct evidence that an intervention has some effect (whether that effect is clinically meaningful is a different question). Demonstration of noninferiority is indirect evidence of an effect and could mean that the two interventions are either similarly effective within the range of the noninferiority margin or similarly ineffective if a noninferiority trial is not designed properly.[28] This is because noninferiority trials have no "negative control" group, and the evidence that the control intervention is superior to a putative placebo usually is external to the study itself, unless the study has a third placebo group in addition to the two active intervention groups. In this sense, noninferiority trials are like historically controlled trials in that the evidence of the effect in the control group could have changed over time. Patients could receive cointerventions currently that were not prescribed in the past, which could attenuate the effects of the control intervention—for instance, patients may have received prior effective antimicrobial before enrollment in a noninferiority trial.[42]

The risk-benefit assessment for patients differs in noninferiority compared with superiority trials. In superiority trials, patients may be willing to accept increased toxicity if there is superior effectiveness on outcomes such as all-cause mortality. Noninferiority trials are based on the hypothesis of a trade-off of some amount of lesser effectiveness in exchange for some nonefficacy benefit such as fewer adverse effects. Patients may be willing to accept some small amount of lesser effectiveness in non–life-threatening illness in exchange for fewer adverse effects.[43]

Last, bias in trials affects superiority and noninferiority trials differently. Many types of bias that tend to skew results toward no difference between groups tend to move superiority trials toward a negative result, whereas those same biases result in false-positive conclusions for a noninferiority trial.[44] For instance, enrolling participants who have the