Chapter 2
Passive Immunization

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Introduction

Following certain high-risk exposures, coadministration of both passive and active immunization is required to optimize protection. Under these circumstances, the passive immunization (antibody) and the first (or missing) dose of active immunization needed for the primary series are given as soon as the exposure is recognized. Additional doses of active immunization are then scheduled to complete the primary series according to recommended dosing intervals.

Short-term protection against certain infections can be achieved by passive immunization by the administration of antibodies. The antibodies present in the injection or infusion bind to and neutralize the pathogen, thereby preventing infection, or neutralize a toxin, thereby treating an ongoing toxin-mediated process. The main benefit of using this strategy to prevent infection is that the protection conferred is immediate. Passive immunization, therefore, is ideal for individuals who are exposed to a preventable infection, but have not been previously vaccinated. Despite the benefit of providing immediate protection, passive immunization suffers from two major shortcomings. First, the protection afforded is brief. Most antibodies have a circulating half-life of ~20 days. As the concentration of the antibody provided by the injection declines over time, the protective effect wanes. Ongoing, or re-exposure to the same pathogen would require repeated dosing to maintain protection if active immunization is not or cannot be provided. Second, when passive immunization is successful in preventing infection, the individual's immune system does not engage, so adaptive immunity does not develop.

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Passive Immunity and Newborns

During the 3rd trimester of pregnancy, maternal immunoglobulin G (IgG) is actively transported across the placenta from the mother to the fetus. The process begins at approximately 28 weeks gestational age (GA), slowly becoming more efficient as the pregnancy progresses. By 36 weeks GA, fetal IgG levels approximate those of the mother. Transplacental active transport of IgG continues until birth explaining why term infants, born at 40 weeks GA, typically have umbilical cord blood IgG concentrations that exceed maternal IgG levels by 20%.

Healthy adults have a mean total serum IgG concentration of ~1000 mg/dL. Mean cord blood IgG levels are dependent on the newborn's GA. Premature infants born at or before 28 weeks are endowed with little or no maternal IgG, those born between 29 and 35 weeks GA have mean cord blood IgG concentrations well below maternal levels, and those born at 36 weeks GA or later have cord blood IgG concentrations that meet or exceed maternal levels.

Maternal IgG contains high-quality (affinity-matured) antibodies directed against a repertoire of pathogens and vaccines to which the mother has been exposed. Maternally derived, transplacental antibodies provide term infants with a broad range of passive humoral immune protection during the first several months of life as they begin to mount their own active immune responses to the vaccines and pathogens they encounter.

Passive Immunity Administered Therapeutically

Beyond the newborn period, passive humoral immunity can be provided medically, when necessary, using various antibody preparations. Passive immunization formulations are available for the prevention of an array of infections and for the treatment of envenomation following certain bites and stings. Available products can be grouped into three main categories:(1) pooled human immunoglobulin (IgG), (2) hyperimmune globulin, and (3) monoclonal antibodies. Indications for their use depend on the specific target for neutralization, the timing of or potential for an exposure, and a variety of host specific details such as immune competence, age, prior active immunization history, and underlying risk factors for severe illness, among others.

Pooled Human Immunoglobulin (IgG)

Pooled human IgG, derived from plasma, was first used in the early 1950s as an intramuscular injection for the treatment of X-linked agammaglobulinemia (Bruton disease). Patients with this condition lack B lymphocytes, so they do not produce

immunoglobulins. The deficiency in circulating antibody places these individuals at high risk for the development of severe sinopulmonary and gastrointestinal infections. Infections caused by encapsulated bacteria (e.g., *Streptococcus pneumoniae, Haemophilus influenzae, Salmonella spp.*) are especially problematic. Other inherited humoral (antibody) immune deficiencies that are associated with hypogammaglobulinemia (low serum IgG) or the production of normal amounts, but poor-quality, IgG share clinical characteristics with Bruton disease. Immunoglobulin treatment for this group of primary immunodeficiencies is now administered by intravenous or subcutaneous infusion. Regular treatment with replacement IgG infusions reduces the frequency and severity of bacterial infections in these patients by conferring transient passive immunity reflective of the infection and active immunization status of the general population (or more accurately, of the donor group). Since the half-life of human IgG is less than 3 weeks, the protective effect of each infusion wanes quickly. Ongoing protection requires life-long replacement at monthly (or more frequent) intervals.

Intramuscular, intravenous, and subcutaneous immunoglobulin products all contain IgG that is collected, purified, and pooled from blood donated by thousands of individuals. The final products are >90% IgG, with trace amounts of immunoglobulin A (IgA) and/or immunoglobulin M (IgM). Several different intramuscular, intravenous, and subcutaneous preparations are approved by the Food and Drug Administration (FDA) for the prevention of infections in patients with primary humoral immunodeficiencies. Immunoglobulin intravenous (IgIV) infusions can also be considered for HIV-infected children who are experiencing recurrent bacterial infections. Excellent reviews on the medical indications for immunoglobulin infusions other than for passive protection from infectious diseases can be found in the suggested readings.

Adverse Reactions to IgIV

As many as 25% of individuals will experience one or more adverse reactions during an infusion with IgIV. Patients may develop fever, headache, chills, cough, or muscle aches. Most reactions are mild, transient, and self-limiting. Slowing the infusion rate helps in most situations. Relief can also be achieved by administering diphenhydramine and acetaminophen or ibuprofen. Some patients respond better to the use of glucocorticoids. Premedication with one or more of these drugs may help to reduce or eliminate reactions during subsequent infusions. Rarely, an anaphylactic reaction occurs. In such instances, the infusion should be stopped. Appropriate resuscitative measures should be implemented immediately including the administration of epinephrine, isotonic fluid support, diphenhydramine, and glucocorticoids.

Some patients experience adverse reactions 1–2 days following the infusions. Headache is common, resulting from IgIV-associated aseptic meningitis. This chemical irritation can usually be managed easily with nonsteroidal

anti-inflammatory drugs (NSAIDs) such as ibuprofen. Some patients respond best to migraine rescue medications in the triptan group (e.g., sumatriptan). Others benefit from treatment with glucocorticoids. Systemic complaints of malaise with or without myalgia are also reported fairly regularly. NSAIDs are generally effective. Since many of these infusion and postinfusion adverse reactions are product-specific, switching to an alternate for subsequent dosing may offer relief. Trial and error are typically necessary to determine which product(s) and which premedication regimens work best for individuals.

Immunoglobulin Subcutaneous (IgSC)

Pooled immunoglobulin products have also been formulated to be administered via subcutaneous infusion. Rates of systemic adverse reactions are generally much lower than seen with IgIV preparations. Patients do not require placement of an intravenous catheter. Subcutaneous placement of the small gauge catheters is not technically difficult, so most patients self-administer the infusions at home. The volume administered per site is limited, so multiple sites on the abdomen and legs are used, and rotated with subsequent doses. Dosing intervals vary from daily to once every 2 weeks.

Immunoglobulin Intramuscular (IgIM)

Immunoglobulin intramuscular (IgIM) preparations are no longer used as a treatment for primary humoral immune deficiency because the volume that can be injected into the muscle limits dosing. The current role for the use of IgIM is limited to specific circumstances where passive prophylaxis is desired for susceptible individuals following exposure to hepatitis A, measles, or rubella (Table 2.1).

Table 2.1 Recommendations for the use of pooled human immunoglobulin intramuscular (IgIM)

Exposed to	Timing	Indication	Comments
Hepatitis A	Within 14 days of exposure	Immunocompromised Chronic liver disease Less than 12 months or more than 40 years of age	Healthy individuals 12 months through 40 years of age who are not previously immunized should receive hepatitis A vaccine, not IgIM
Measles	Within 6 days of exposure	Not previously immunized Immunocompromised	Vaccine eligible individuals 12 months and older should receive MMR vaccine, not IgIM if within 72 hours of initial exposure
Rubella	ASAP[a]	Rubella-susceptible pregnant women	Should only be offered for those who decline a therapeutic abortion

[a]Congenital rubella syndrome has occurred even when IgIM is administered soon after exposure

Adverse Reactions to IgIM

Injection site discomfort is expected, and can be reduced by administering the dose at room temperature. Some recipients experience transient flushing, headache, or nausea. Allergic reactions are uncommon. Anaphylaxis is rare. Those who have received IgIM doses for other reasons in the past are more likely to experience fever and chills. IgIM should not be administered to individuals known to have selective IgA deficiency because of the risk for developing anti-IgA antibodies. Such individuals are at risk for developing an anaphylaxis reaction from subsequent infusions of blood products containing IgA.

Hyperimmune Globulins

Hyperimmune globulins are pooled immunoglobulin products prepared from the plasma of donors known to have high concentrations of antibody directed against a specific target. These products are administered to susceptible individuals following a suspected or known exposure to a specific pathogen or toxin. Administration of hyperimmune globulin delivers short-term, but immediate, neutralizing antibody. The more commonly used, and most familiar, hyperimmune globulins are used to target tetanus toxin and hepatitis B, rabies, and varicella viruses. These products are derived from pooled plasma collected from human donors and are easily recognized by their product descriptions, tetanus immune globulin (TIG), hepatitis B immune globulin (HBIG), rabies immune globulin (RIG), and varicella zoster immune globulin (VariZIG).

Unlike IgIV, IgIM, and IgSC, not all hyperimmune globulin products are derived from human blood donors. The origins and targets for available hyperimmune globulins are summarized in Table 2.2. For example, hyperimmune globulins used for the treatment of foodborne and wound botulism, and those used for the treatment of diphtheria, are derived from horses that have been hyperimmunized (i.e., given multiple doses of diphtheria toxoid) for the purpose of harvesting and purifying the

Table 2.2 Source and targets of available hyperimmune globulins

	Human origin		Animal origin: commonly called antitoxins
Target of the high-titer antibody	Hepatitis B surface antigen	Botulinum toxins A + B	Diphtheria toxin
	rabies virus	cytomegalovirus	botulinum toxins A thru G
	tetanus toxin	vaccinia virus	toxins associated with various envenomations[a]
	varicella virus		

[a]Bites from black widow spiders, rattlesnakes, coral snakes, and stings from scorpions; most administered intravenously. Black widow antitoxin is given intramuscularly

desired product. Similarly, the "antivenins" and "antitoxins" used for the treatment of some poisonous snake and spider bites and scorpion stings are hyperimmune globulins derived from horses or sheep.

As noted, some hyperimmune globulins are used therapeutically, while others are used for prevention of illness following a known or suspected exposure. Products that are specifically designed to bind to and neutralize toxin, such as botulism antitoxin, work best when administered early in the toxin-mediated disease process. Most, but not all, hyperimmune globulins that are administered to prevent transmission of an infection, following an exposure, are used in combination with active vaccination (Table 2.3). The hyperimmune globulin provides immediate, passive, and transient protection for the 2–3 week period needed for the active vaccination to initiate durable immunity.

Table 2.3 Use of hyperimmune globulins for the prevention and treatment of infectious diseases

Product	Nickname	Route[a]	Indications	Co-administer active vaccine?
Botulinum antitoxin bivalent A + B	Baby-BIG, BIG-IV	IV	Infant botulism	N/A, no vaccine available
Botulinum antitoxin heptavalent A − G	BAT	IV	Foodborne, wound, and other noninfant forms of botulism	N/A, no vaccine available
Cytomegalovirus immune globulin	CMV-Ig	IV	Prevention of CMV in seronegative organ transplant recipients from a seropositive donor	N/A, no vaccine available
Diphtheria antitoxin	none	IV	Treatment for diphtheria, in combination with antibiotics	YES, but later during convalescence
Hepatitis B immune globulin	HBIG	IM	Prevention of hepatitis B transmission following exposure, if not previously immunized	YES
Rabies immune globulin	RIG	IM[b]	Prevention of rabies transmission following exposure, if not previously immunized	YES
Tetanus immune globulin	TIG	IM	Prevention of tetanus following a tetanus-prone injury for anyone who has received fewer than 3 doses of tetanus vaccine	YES
Vaccinia immune globulin	VIG	IV	Complications following smallpox vaccination	NO
Varicella zoster immune globulin	VariZIG	IV	Prevention of varicella in susceptible, high-risk individuals within 10 days of exposure	NO

[a]*IV* intravenous, *IM* intramuscular

[b]As much of the dose as possible should be infiltrated directly into the wound. Any remaining volume should be given IM

Monoclonal Antibodies

When the immune system is challenged with an antigen, such as a vaccine, a number of different B-cell clones are activated. Each of the activated B-cell clones produces antibodies directed against different epitopes of the antigen. This results in a polyclonal antibody response, defined as the collection of different antibodies that recognize different binding sites on the same antigen. In the laboratory, it is possible to identify and isolate each of those B-cell clones. Each individual B-cell clone produces antibody with a single affinity directed against a specific epitope of the antigen. Antibodies produced by a single B-cell clone are referred to as monoclonal. A B-cell clone that is found to produce an antibody with desired characteristics can be immortalized using special laboratory techniques, and then used as a cellular "factory" to produce large quantities of the monoclonal antibody for therapeutic indications.

More than 80 different therapeutic monoclonal antibodies have been approved for use by the US FDA for use in humans, with hundreds of others currently under evaluation in various phases of human clinical trials. The vast majority of these specialized products are used or being developed to treat malignancies, autoimmune diseases, and metabolic disorders. At the time of this writing, only ~6% of approved monoclonal antibody products target the prevention or treatment of infectious diseases (Table 2.4). Of those listed, palivizumab is the only one that is widely used.

Respiratory Syncytial Virus: RSV

Palivizumab was the first monoclonal antibody to gain FDA licensure (1998) for the prevention of an infection. Infections caused by its target pathogen, respiratory syncytial virus (RSV), are severe enough to require hospitalization in 1–2% of the US birth cohort each winter. Hospitalization rates among some high-risk infant populations exceed 12%. Like other antibody-based prophylaxis, the protection conferred by palivizumab is passive and short-lived. As such, high-risk infants, such as those born prematurely, are recommended to receive monthly intramuscular dosing of palivizumab during "RSV season" (see http://bit.ly/2kwhSpF). This strategy reduces RSV-associated hospitalizations by ~54%. A safe and effective active vaccine for the prevention of infant RSV infection has remained elusive; therefore, monthly intramuscular injections of palivizumab have remained the standard of care for high-risk infants for more than 20 years. In an effort to improve on the modest success of palivizumab, new-generation, investigational monoclonal RSV antibodies have been developed. Nirsevimab is a fully human monoclonal RSV antibody that was strategically modified during development to offer several advantages. First, amino acids were modified in the Fab region to optimize its capacity to neutralize RSV. Next, 3 amino acids were modified in the Fc region to extend its half-life such that one dose could offer protection for an entire season. Phase 2b clinical

Table 2.4 Monoclonal antibodies used for the prevention of infectious diseases

	Palivizumab	Nirsevimab	Raxibacumab	Obiltoxaximab	Bezlotoxumab	Ibalizumab
Year approved	1998	BTD	2012	2016	2016	2018
Source	Humanized	Human with strategic modifications[a]	Human	Chimeric Mouse/ human	Human	humanized
Route of administration	IM	IM	IV	IV	IV	IV
Target	RSV F protein	RSV F protein	Anthrax toxin	Anthrax toxin	*Clostridioides difficile* toxin B	HIV-1
Indication	Prevents severe RSV disease	Prevents severe RSV disease	Treatment of inhalation anthrax[b]	Treatment of inhalation anthrax[b]	Prevents recurrence of *C. difficile* diarrhea	Treatment of HIV-1 infection[b]

BTD Breakthrough therapy designation by the US FDA, *IM* intramuscular, *IV* intravenous, *RSV* respiratory syncytial virus, *HIV* human immunodeficiency virus

[a]Modifications made to Fab fragment to enhance and broaden neutralizing activity; modifications of Fc fragment prolong serum half-life. Ongoing phase 3 trials due to complete enrollment in 2021

[b]In combination with anti-infective medications

trial results showing an 80% reduction in severe RSV infection and an excellent safety profile following a single intramuscular injection just prior to the start of RSV season have earned the product "breakthrough therapy designation" status by the US FDA. The designation expedites investigational drug development under Section 902 of the Food and Drug Administration Safety and Innovation Act when early clinical trial data suggest a substantial therapeutic advantage over existing options for serious or life-threatening diseases.

Anthrax

In the fall of 2001, letters containing anthrax spores were mailed to news media offices and to 2 US Senators. As a result, at least 22 people were infected; 5 died. The nefarious nature of the bioterrorism, and the scientific expertise needed to produce the highly purified spores, led to speculation that the bacteria could also be genetically modified to be resistant to penicillin and other antibiotics. Interest in developing therapeutic interventions for use in combination with antibiotics ultimately led to the development of monoclonal antibodies targeting anthrax toxin. Two different products, raxibacumab (2012) and obiltoxaximab (2016), have now been approved for the treatment of inhalation anthrax, but only in combination with antibiotics.

Clostridioides difficile

Bezlotoxumab, a monoclonal antibody directed against toxin B of *Clostridioides difficile*, was approved in 2016 as an intravenous infusion to prevent recurrent *C. difficile* diarrhea. During clinical trials, the coadministration of a second investigational monoclonal antibody directed against *C. difficile* toxin A offered no added benefit compared with the administration of bezlotoxumab alone.

Human Immunodeficiency Virus, HIV

Highly effective, well-tolerated, combination antiretroviral treatment regimens are available for the majority of patients who are infected with human immunodeficiency virus (HIV). Drug-resistant HIV strains are unlikely to emerge in those patients with good adherence to an effective regimen. A number of factors can lead to intermittent or prolonged interruptions in medication adherence. Patients who struggle with consistency in their medication regimen are at risk for developing multidrug resistance. Despite the growing armamentarium of available medications, identifying effective drug combinations can become challenging for those patients

infected with multidrug resistant strains. Ibalizumab is a monoclonal antibody approved for the treatment of multidrug resistant HIV type-1 when used in combination with other antiretroviral drugs. The antibody functions as an entry inhibitor by binding to CD4, the primary HIV receptor, and blocking virus from access to the CCR5 and CXCR4 coreceptors.

Conclusions

Passive immunity is a state of temporary protection against infection that occurs among individuals who receive antibodies from another source. Full-term infants are born with passive immunity from maternal IgG that is actively transported across the placenta during the 3rd trimester of pregnancy. Available pharmaceutical products used to provide passive immune protection are formulated with antibodies derived from humans or animals. Indications for their use depend on the specific pathogen(s) being targeted, the timing of or potential for an exposure, and various host factors such as immune competence, age, prior active immunization history, and underlying risk factors for severe illness, among others. Passive immune protection occurs immediately upon receipt of the antibody, but is temporary, waning over time. Ongoing protection requires repeat dosing at regular intervals (usually monthly), or, if appropriate and available, the administration of an active immunization series.

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Pooled Human Immunoglobulin

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