Drug-Induced Hematologic Disorders

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e|CHAPTER 24

KEY CONCEPTS

1. The most common drug-induced hematologic disorders include aplastic anemia, agranulocytosis, megaloblastic anemia, hemolytic anemia, and thrombocytopenia.
2. Drug-induced hematologic disorders are generally rare adverse effects associated with drug therapy.
3. Reporting during postmarketing surveillance of a drug is usually the method by which the incidence of rare adverse drug reactions is established.
4. Because drug-induced blood disorders are potentially dangerous, rechallenging a patient with a suspected agent in an attempt to confirm a diagnosis is not generally recommended.
5. The mechanisms of drug-induced hematologic disorders can be the result of either direct drug or metabolite toxicity or an immune reaction.
6. The primary treatment of drug-induced hematologic disorders is removal of the drug in question and symptomatic support of the patient.

INTRODUCTION

1 Hematologic disorders have long been a potential risk of modern pharmacotherapy. Granulocytopenia (agranulocytosis) was reported in association with one of medicine's early therapeutic agents, sulfanilamide, in 1938.[1] Some agents cause predictable hematologic disease (e.g., antineoplastics), but others induce idiosyncratic reactions not directly related to the drugs' pharmacology. The most common drug-induced hematologic disorders include aplastic anemia, agranulocytosis, megaloblastic anemia, hemolytic anemia, and thrombocytopenia.

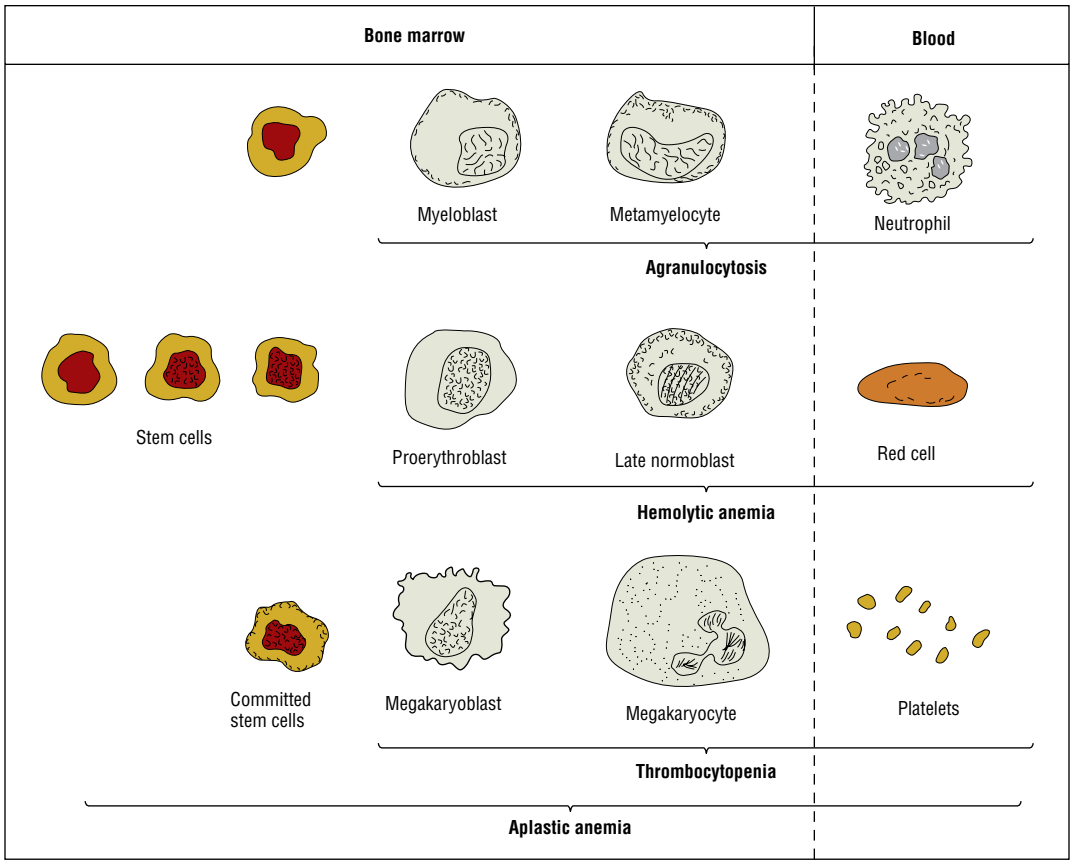
2 The incidence of idiosyncratic drug-induced hematologic disorders varies depending on the condition and the associated drug. Few epidemiologic studies have evaluated the actual incidence of these adverse reactions, but these reactions appear to be rare. Women are generally more susceptible than men to the hematologic effects of drugs. The incidence varies based on geography, which suggests that genetic differences may be important determinants of susceptibility. Drug-induced thrombocytopenia is the most common drug-induced hematologic disorders, with some reports suggesting that as many as 5% of patients who receive heparin develop heparin-induced thrombocytopenia.[2] The Berlin Case-Control Surveillance Study was conducted from 2000 to 2009 to assess the incidence and risks of drug-induced hematologic disorders. This evaluation found that almost 30% of all cases of blood dyscrasias were "possibly" attributable to drug therapy.[3]

Although drug-induced hematologic disorders are less common than other types of adverse reactions, they are associated with significant morbidity and mortality. An epidemiologic study conducted in the United States estimated that 4,490 deaths in 1984 were attributable to blood dyscrasias from all causes. Aplastic anemia was the leading cause of death followed by thrombocytopenia, agranulocytosis, and hemolytic anemia.[4] Similar to most other adverse drug reactions, drug-induced hematologic disorders are more common in elderly adults than in the young; the risk of death also appears to be greater with increasing age.

3 Because of the seriousness of drug-induced hematologic disorders, it is necessary to track the development of these disorders to predict their occurrence and to estimate their incidence. Reporting during postmarketing surveillance of a drug is the most common method of establishing the incidence of adverse drug reactions. The MedWatch program supported by the Food and Drug Administration is one such program.[5] Many facilities have similar drug-reporting programs to follow adverse drug reaction trends and to determine whether an association between a drug and an adverse drug reaction is causal or coincidental. In the case of drug-induced hematologic disorders, these programs can enable practitioners to confirm that an adverse event is indeed the result of drug therapy rather than one of many other potential causes; general guidelines are readily available.[6,7]

4 Because drug-induced blood disorders are potentially dangerous, rechallenging a patient with a suspected agent in an attempt to confirm a diagnosis is not recommended. In vitro studies with the offending agent and cells or plasma from the patient's blood can be performed to determine causality.[8] These methods are often expensive, however, and require facilities and expertise that are not generally available. Laboratory confirmation of drug causation is not always necessary to warrant interruption or discontinuation of therapy. Therefore, it is extremely important that practitioners be able to clinically evaluate suspect drugs quickly and to interrupt therapy when necessary.

Throughout the past decades, lists of drugs that have been associated with adverse events have been developed to help clinicians identify possible causes. Unfortunately, these lists are extremely extensive, including a large number of very commonly used drugs, making it difficult to determine the cause of any abnormality. Furthermore, the absence of a drug from such a list should not discourage the investigation and reporting of an agent associated with an adverse event. It is imperative that clinicians use a rational approach to determine causality and identify the agents associated with a reaction. The clinician should focus on the issue, perform a rigorous investigation, develop appropriate criteria, use objective criteria to grade the response, and complete a quantitative summary. A complete, thorough, and detailed drug and exposure history must be



eFIGURE 24-1 Differentiation of the stem cell into committed cell lines, illustrating the origins of various drug-induced hematologic disorders.

obtained from the patient in order to best determine any potential for drug causation. A systematic approach to evaluate the information available in the literature also helps the clinician focus and intervene in the cause of the disorder.

A common tool used by clinicians to rate the likelihood of causality in adverse drug reaction (ADR) investigations is an ADR probability scale (algorithm). One such scale was developed and tested by Naranjo and colleagues.[9] This tool provides a series of scored questions that leads an investigator to the likelihood that an ADR was caused by the suspected medication. Depending on the aggregate score, the causality is rated as *doubtful, possible, probable, or definite*. The scale gives the most weight to the temporal relationship of the reaction with relation to administration of the drug, observations after a rechallenge of the suspected medication, and alternate explanations for the ADR. As mentioned earlier, it is often unethical to rechallenge patients who experience severe hematologic toxicities. Thus, without a rechallenge, it is difficult to achieve a causality rating of *definite* with such an algorithm.

In determining the likelihood that an observed reaction is caused by a particular medication, clinicians should review the medical literature for past reports supporting the observation. Using an evidence-based approach such as that proposed by Sackett,[10] the investigator assigns greater weight to prospective study designs such as clinical trials or cohort studies than to case reports or expert opinion. This provides a framework for the investigator's confidence in published literature describing ADRs.

The pathophysiology of drug-induced hematologic disorders requires a basic understanding of hematopoiesis. The pluripotential hematopoietic stem cells in the bone marrow, which have the ability to self-reproduce, maintain the blood. These pluripotential hematopoietic stem cells further differentiate to intermediate precursor cells, which are also called *progenitor cells or colony-forming cells*. Committed to a particular cell line, these intermediate stem cells differentiate into colonies of each type of blood cell in response to specific colony-stimulating factors (eFig. 24-1).

Drug-induced hematologic disorders can affect any cell line, including white blood cells (WBCs), red blood cells (RBCs), and platelets. When a drug causes decreases in all three cell lines accompanied by a hypoplastic bone marrow, the result is drug-induced aplastic anemia. The decrease in WBC count alone by a medication is drug-induced agranulocytosis. Drugs can affect RBCs by causing a number of different anemias, including drug-induced immune hemolytic anemia, drug-induced oxidative hemolytic anemia, or drug-induced megaloblastic anemia. A drug-induced decrease in platelet count is drug-induced thrombocytopenia.

DRUG-INDUCED APLASTIC ANEMIA

Aplastic anemia is a rare, serious disease of unclear etiology. It was first described by Ehrlich in 1888 after an episode of failed hematopoiesis identified during the autopsy of a pregnant woman.[11] Since that first report, numerous cases of aplastic anemia have been described, but the true incidence of the disease remains uncertain. Drug-induced aplastic anemia was initially reported in the 1930s, associated with arsenicals and aminopyrines.[12] Reports in the literature describe an incidence of two per million in Europe and North America. The incidence in Asian countries is two or three times greater, pointing to a relationship between environment and risk.[13,14] There are no greater risks for women or men, but there is a bimodal risk distribution when it comes to age, with peak

incidences in those ages 10 to 25 years and again in those older than 60 years of age.[15]

Aplastic anemia can be divided into two broad categories, inherited and acquired. Inherited aplastic anemias are a set of inherited diseases that result in bone marrow failure, fatty infiltration of the marrow, and loss of circulating blood cells. The most common of these disorders are Fanconi's anemia, dyskeratosis congenita, and Blackfan Diamond anemia. Acquired aplastic anemia is the focus of this section because it is the type of aplastic anemia that results from drugs, radiation, viruses, or chemical exposure, and it accounts for most cases of aplastic anemia. Acquired, drug-induced aplastic anemia is an idiosyncratic reaction, with unpredictable severity and time to recovery. It has been estimated that 50% of aplastic anemia cases are acquired in nature, but a definitive causative agent cannot be identified in most cases.[16,17]

Acquired aplastic anemia is characterized by pancytopenia (anemia, neutropenia, and thrombocytopenia) with a hypocellular bone marrow and no gross evidence of increased peripheral blood cell destruction.[18] Bone marrow examination shows an absence or marked reduction of hematopoietic stem cells and an increase in fat cells. The diagnosis of aplastic anemia can be made by the presence of two of the following criteria: a WBC count of 3,500 cells/mm^3 (3.5×10^9/L) or less, a platelet count of 55,000 cells/mm^3 (55×10^9/L) or less, or a hemoglobin value of 10 g/dL (100 g/L; 6.2 mmol/L) or less with a reticulocyte count of 30,000 cells/mm^3 (30×10^9/L) or less.[19] Depending on the blood counts, aplastic anemia can be categorized as moderate, severe, and very severe aplastic anemia[20–22]:

1. Moderate aplastic anemia (MAA): Two of the following three criteria—neutrophils less than 1,500 cells/mm^3 (1.5×10^9/L), platelets less than 50,000 cells/mm^3 (50×10^9/L), and hemoglobin less than 10 g/dL (6.2 mmol/L)
2. Severe aplastic anemia (SAA): Two of the following three criteria—neutrophils less than 500 cells/mm^3 (0.5×10^9/L), platelets less than 20,000 cells/mm^3 (20×10^9/L), reticulocytes less than 1%
3. Very severe aplastic anemia (VSAA): SAA with a neutrophil count less than 200 cells/mm^3 (0.2×10^9/L)

The diagnosis of aplastic anemia requires a bone marrow aspirate and biopsy to exclude other causes of pancytopenia.[23] The patient must not have previous iatrogenic exposure to cytotoxic chemotherapy or intensive radiation.

Aplastic anemia is considered the most serious drug-induced blood dyscrasia because of its associated high mortality rate compared with other blood dyscrasias. The mortality rate associated with acquired aplastic anemia varies by series but averages about 50%.[20,24] The onset of drug-induced aplastic anemia is variable and insidious. Symptoms have been reported to appear from days to months after initiation of the offending drug, with the average being about 6.5 weeks.[25] In some instances, symptoms appear after the drug has been discontinued. Neutropenia typically presents first followed by thrombocytopenia. Anemia develops slowly because of the longer life span of RBCs.[26] Clinical features of drug-induced aplastic anemia depend on the degree to which each cell line is suppressed. Symptoms of anemia include pallor, fatigue, and weakness; fever, chills, pharyngitis, or other signs of infection can characterize neutropenia. Thrombocytopenia, often the initial clue to diagnosis, is manifested by easy bruisability, petechiae, and bleeding.

5 The cause of drug-induced aplastic anemia is damage to the pluripotential hematopoietic stem cells before their differentiation to committed stem cells. This damage effectively reduces the normal levels of circulating erythrocytes, neutrophils, and platelets. There are three major etiologies of acquired aplastic anemia: direct toxicity, metabolite-driven toxicity, and immune-mediated mechanisms.[21]

Cytotoxic chemotherapy and radiation therapy are known to induce varying degrees of bone marrow suppression or failure. The antineoplastic agents exemplify the dose-dependent mechanism for the development of aplastic anemia. Many of these agents have the ability to suppress one or more cell lines in a reversible manner. The degree of suppression and the cell line involved depend on the nature of the particular drug and its potential for inhibiting marrow proliferation. Certain chemicals or agents may also induce direct injury to hematopoietic cells. Chloramphenicol, an antimicrobial agent, is such an agent, causing bone marrow suppression that is dose dependent and reversible.[26]

Drug toxicity on hematopoietic cells is usually mediated through intermediate metabolites that bind to proteins and DNA to cause bone marrow failure. Genetic variation leads to variability in the presence of these reactive metabolites and explains the idiosyncratic nature of these sorts of drug reactions. Idiosyncratic drug-induced aplastic anemia secondary to direct toxicity can be characterized by dose independence, a latent period before the onset of anemia, and continued marrow injury after drug discontinuation.[27] Chloramphenicol, already known to cause a dose-dependent reaction, is the prototype drug for the idiosyncratic mechanism. The estimated incidence of chloramphenicol-induced aplastic anemia is one case per 20,000 patients treated,[28] but the overall prevalence has declined with decreased use of this agent.[27] The idiosyncratic mechanism is believed to result from abnormal metabolism of chloramphenicol. The nitrobenzene ring on chloramphenicol is thought to be reduced to form a nitroso group on the chloramphenicol molecule.[26] The nitroso group may then interact with DNA in the stem cell, causing chromosomal damage and eventually cell death. Other investigators have hypothesized that bacteria from the gastrointestinal tract may metabolize chloramphenicol to marrow-toxic metabolites.[29] The dose-dependent and idiosyncratic reactions seen with chloramphenicol do not appear to be related. Other drugs thought to induce aplastic anemia through toxic metabolites include phenytoin and carbamazepine. Investigators have theorized that metabolites of phenytoin and carbamazepine bind covalently to macromolecules in the cell and then cause cell death either by exerting a direct toxic effect on the stem cell or by causing the death of lymphocytes involved in regulating hematopoiesis.[30]

Of the three potential mechanisms, the most common cause of drug-induced aplastic anemia is the development of an immune reaction. It is proposed that exposure to an inciting antigen (drug) activates cells and cytokines of the immune system, leading to the death of stem cells.[21] **eTable 24-1** lists drugs that have been associated with drug-induced aplastic anemia.

Early laboratory studies showed that removal of T lymphocytes from patients with aplastic anemia improved in vitro colony formation, and their addition to normal marrow inhibited hematopoiesis in vitro.[31] The observation of improved hematopoiesis in aplastic anemia patients who receive a conditioning regimen with antithymocyte globulin and cyclophosphamide before allogeneic hematopoietic stem cell transplantation (HSCT) supports this hypothesis.[32] After the initiation of immunosuppressive therapy, bone marrow concentrations of interferon-γ decreased, and all cell lines improved.[33] The immune mechanism of aplastic anemia is most strongly supported by the responsiveness of the disease to immunosuppressive therapy.[21]

Additional support for an immunologic basis as a mechanism of aplastic anemia comes from a prospective, randomized, placebo-controlled trial evaluating the efficacy of antilymphocyte globulin and methylprednisolone, with or without cyclosporine, in patients with severe aplastic anemia.[34] The primary response variable was an improvement in blood counts (i.e., platelets, RBCs, and WBCs) at 3 months. Patients receiving therapy with antilymphocyte globulin, methylprednisolone, and cyclosporine had a response rate of 65% versus a response rate of 39% in the group not receiving

eTABLE 24-1 Drugs Associated with Aplastic Anemias

Observational study evidence
Carbamazepine
Furosemide
Gold salts
Mebendazole
Methimazole
NSAIDs
Oxyphenbutazone
Penicillamine
Phenobarbital
Phenothiazines
Phenytoin
Propylthiouracil
Sulfonamides
Thiazides
Tocainide
Case report evidence (*probable* or *definite* causality rating)
Acetazolamide
Aspirin
Captopril
Chloramphenicol
Chloroquine
Chlorothiazide
Chlorpromazine
Dapsone
Felbamate
Interferon alfa
Lisinopril
Lithium
Nizatidine
Pentoxifylline
Quinidine
Sulindac
Ticlopidine

NSAID, nonsteroidal antiinflammatory drug.

cyclosporine. The favorable response rate with immunosuppressive drugs supports the overall hypothesis of an immune-based mechanism for aplastic anemia. One can also conclude that the degree of immunosuppression is related to a better response rate.

Genetic predisposition can also influence the development of drug-induced aplastic anemia. Studies in animals and a case report of chloramphenicol-induced aplastic anemia in identical twins suggest a genetic predisposition to the development of drug-induced aplastic anemia.[26,28] Furthermore, pharmacogenetic research to identify patients who may be slow or normal metabolizers of drugs can increase the clinician's ability to predict the development of aplastic anemia. Initial observational studies have not demonstrated a significant difference between control participants and cases, but continued research may establish the role of altered metabolism in patients with aplastic anemia.[35]

TREATMENT
Drug-Induced Aplastic Anemia

Because of the high mortality rate associated with severe and very severe aplastic anemia, it is imperative that drug-induced aplastic anemia be diagnosed quickly and therapy initiated immediately. Treatment should be based on the severity of disease, with the goal of therapy being to improve peripheral blood counts, limit the requirement for transfusions, and minimize the risk for infections.

6 As with all cases of drug-induced hematologic disorders, the first step is to remove the suspected offending agent. Early withdrawal of the drug can allow for reversal of the aplastic anemia. Appropriate supportive care is also essential because the major causes of mortality in patients with aplastic anemia are infections (bacterial and fungal) and bleeding. Patients must receive transfusion support with erythrocytes and platelets, as well as appropriate antimicrobial prophylaxis or treatment during neutropenic periods. Routine use of growth factors such as recombinant human erythropoietin and granulocyte colony-stimulating factor has not been shown to improve outcome and are not recommended for the management of aplastic anemia. Current treatment guidelines for aplastic anemia recommend the use of prophylactic antibiotic and antifungal agents when neutrophil counts are below 500 cells/mm^3 (0.5×10^9/L). If patients experience febrile neutropenia, broad-spectrum IV antibiotics should be started immediately. Current guidelines do not recommend the use of prophylaxis for viruses or *Pneumocystis jiroveci*. For patients who have been heavily transfused, iron chelation therapy with agents such as deferoxamine or deferasirox may be necessary to avoid the serious consequences of iron overload.

The clinical course of aplastic anemia is variable. The condition can progress to severe or very severe disease in some patients, although it can remain relatively stable or even resolve in others.[36] The treatment of moderate disease ranges from no clinical intervention to immunosuppressive regimens, and treatment should be based on the degree of cytopenias.[36]

For patients with disease requiring treatment, the two major treatment options for patients with drug-induced aplastic anemia are allogeneic HSCT and immunosuppressive therapy. Factors that determine which therapy would be preferred include age, disease severity, and availability of a human leukocyte antigen– (HLA-) matched sibling donor. For patients younger than the age of 40 years, the treatment of choice is allogeneic HSCT from an HLA-matched sibling donor. This treatment modality is associated with potential cure and results in a 5-year survival rate of 77% in adults and up to 90% in children.[36,37] Unfortunately, most patients do not have a matched sibling donor. For young patients who do not have an available HLA-matched sibling, allogeneic HSCT from an unrelated donor may be considered but is usually reserved for those who fail to respond to upfront immunosuppressive therapy. When used in this setting, the 5-year overall survival rate in these patients has improved to over 50%, primarily because of improvements in HLA typing and unrelated donor selection.[38,39]

For patients older than the age of 40 years and for those who are not candidates for allogeneic HSCT, the preferred first-line therapy is immunosuppressive therapy. Allogeneic HSCT in older patients is associated with significantly higher transplant-related morbidity and mortality. The highest mortality rate was seen in older patients and those with poorer clinical status at the time of transplantation. Complications of allogeneic HSCT, such as graft-versus-host disease and graft rejection, require all patients to be closely monitored for an extended period of time.

The current standard immunosuppressive regimen for the treatment of acquired aplastic anemia is combination therapy with antithymocyte globulin (ATG) and cyclosporine. This combination has been reported to achieve 5-year survival rates between 75% and 85%, but the response rates in older patients are lower.[40]

Antithymocyte globulin is composed of polyclonal immunoglobulin G (IgG) against human T lymphocytes derived from either horses or rabbits, and it has been a standard component of immunosuppressive therapy for aplastic anemia for many years. In a study comparing the horse versus rabbit product, both given in combination with cyclosporine, treatment with the horse-derived ATG product resulted in significantly higher response rates (68% vs. 37%) and 3-year overall survival rates (96% vs. 76%). Although the mechanism for this difference is not completely understood, the greater depletion of CD4$^+$ cells associated with the rabbit ATG as compared with horse ATG may be associated with adverse outcomes.[41] Based on these results, treatment with the horse-derived ATG product is preferred for

treatment. Because response to immunosuppressive therapy is often delayed (3–4 months), patients require continued supportive care until recovery. Patients should be monitored for adverse effects, including serum sickness, which can occur about 1 week after ATG begins.[40]

Cyclosporine plays an important role in immunosuppressive therapy for aplastic anemia. Although cyclosporine monotherapy has been used to treat moderate aplastic anemia, it is more often used in combination with ATG. The addition of cyclosporine to ATG therapy has been shown to increase response rate, improve failure-free survival, and reduce the number of immunosuppressive courses needed.[42,43] Cyclosporine inhibits interleukin-2 production and release and subsequent activation of resting T cells. Cyclosporine dosing has varied from 4 to 6 mg/kg per day to 10 to 12 mg/kg per day, with the most frequently reported initial dose of 5 mg/kg per day in two divided doses. Cyclosporine doses are titrated to a target blood concentration that can be patient and institution specific but are usually in the range of 150 to 250 mcg/L (125–208 nmol/L) for adult patients. Increased relapse rates have been observed when tapering cyclosporine rapidly, and it is recommended that cyclosporine be continued for at least 12 months after response and then tapered slowly.[40] Corticosteroids are added to ATG-based immunosuppression because of their ability to reduce adverse reactions associated with ATG administration. In an effort to improve outcomes, several other agents have also been investigated in the treatment of aplastic anemia. The additive benefits of other immunosuppressive agents such as mycophenolate, cyclophosphamide, and sirolimus have been evaluated.[36] However, they have not been shown to be superior to the combination of ATG and cyclosporine, and their place in therapy is not defined.

Clinical **Controversy. . .**

Allogeneic HSCT has long been the established treatment of drug-induced aplastic anemia. Although current practices in allogeneic stem cell procurement generally favors the use of peripheral blood stem cell harvesting, recent experiences have suggested that for patients with aplastic anemia, stem cells sourced from bone marrow may be associated with better outcomes because of the relative lack of T cells in a bone marrow product, which is thought to confer a decreased risk of graft-versus-host disease. Data to support this theory are largely from single-center experiences, and the benefit of one source has not been proven in well-designed trials. Until it is clearer whether one stem cell source is better than another, the choice of stem cell source should be largely based on donor availability and preference.

DRUG-INDUCED AGRANULOCYTOSIS

Agranulocytosis is defined as a reduction in the number of mature myeloid cells in the blood (granulocytes and immature granulocytes [bands]) to a total count of 500 cells/mm^3 (0.5×10^9/L) or less. In Europe, the incidence rate is reported to range from 1.6 to 9.2 cases per million population. In the United States, reported rates are slightly higher, ranging from 2.4 to 15.4 cases per million population.[44–46] Geographic variability in incidence is related to both differences in reporting and medication usage but could also suggest genetic differences in susceptibility.[47] Older patients are thought to be at greater risk for to drug-induced agranulocytosis, probably because of increased medication use.[45,48] Drug-induced agranulocytosis also occurs more frequently in women than in men. The overall mortality rate of agranulocytosis has fallen dramatically over the past 20 years from 10% to 20% to 5%, largely because of improvements in infection prophylaxis and supportive care.[44,49] The mortality rate is highest among elderly adults and patients with renal failure, bacteremia, or shock at the time of diagnosis.[50,51]

Symptoms of agranulocytosis arise from the increased infection risk associated with the lack of WBCs and include sore throat, fever, malaise, weakness, and chills. Symptoms may appear either immediately or insidiously, depending on the time course of neutropenia development. The median duration of exposure before the development of agranulocytosis ranges from 19 to 60 days for most drugs associated with this adverse event, but the time to onset is greater than 1 month for most of these agents.[52] Drug-induced agranulocytosis usually resolves over time with supportive care and management of infection. The time to neutrophil recovery has typically been reported to range from 4 to 24 days.[52] eTable 24-2 provides a list of medications that have been associated with drug-induced agranulocytosis.

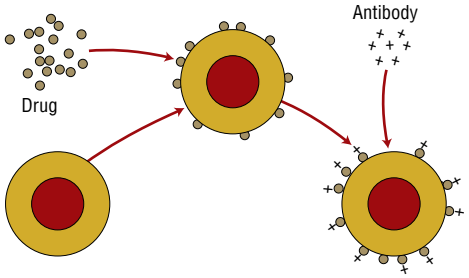
The cause of drug-induced agranulocytosis is not fully understood, but two mechanisms—direct toxicity and immune-mediated toxicity—have been proposed. Direct toxicity to myeloid cells, particularly neutrophils, has been shown with medications such as chlorpromazine, procainamide, clozapine, dapsone, sulfonamides, carbamazepine, phenytoin, indomethacin, and diclofenac. The toxicity may be due to either the parent drug or a toxic metabolite or byproduct. The severity of neutropenia associated with these drugs is often dose dependent, but the occurrence of reactions is still idiosyncratic. Agranulocytosis associated with direct toxicity is usually associated with a slower decline in neutrophils, with a more insidious presentation of symptoms.[53–55]

Within the immune-mediated subset of agranulocytosis, there are three proposed mechanisms of toxicity. The *hapten mechanism* involves the drug or its metabolite binding to the membrane of neutrophils or myeloid precursors. After binding, antibodies are induced that destroy the cell. This is thought to be the mechanism of agranulocytosis induced by aminopyrine, penicillin, and gold

eTABLE 24-2 Drugs Associated with Agranulocytosis

Observational study evidence	Case report evidence (*probable* or *definite* causality rating)	
β-Lactam antibiotics	Acetaminophen	Levodopa
Carbamazepine	Acetazolamide	Meprobamate
Carbimazole	Ampicillin	Methazolamide
Clomipramine	Captopril	Methyldopa
Digoxin	Carbenicillin	Metronidazole
Dipyridamole	Cefotaxime	Nafcillin
Ganciclovir	Cefuroxime	NSAIDs
Glyburide	Chloramphenicol	Olanzapine
Gold salts	Chlorpromazine	Oxacillin
Imipenem–cilastatin	Chlorpropamide	Penicillamine
Indomethacin	Chlorpheniramine	Penicillin G
Macrolide antibiotics	Clindamycin	Pentazocine
Methimazole	Clozapine	Phenytoin
Mirtazapine	Colchicine	Primidone
Phenobarbital	Doxepin	Procainamide
Phenothiazines	Dapsone	Propylthiouracil
Prednisone	Desipramine	Pyrimethamine
Propranolol	Ethacrynic acid	Quinidine
Spironolactone	Ethosuximide	Quinine
Sulfonamides	Flucytosine	Rifampin
Sulfonylureas	Gentamicin	Streptomycin
Ticlopidine	Griseofulvin	Terbinafine
Valproic acid	Hydralazine	Ticarcillin
Zidovudine	Hydroxychloroquine	Tocainide
	Imipenem–cilastatin	Tolbutamide
	Imipramine	Vancomycin
	Lamotrigine	

NSAID, nonsteroidal antiinflammatory drug.



eFIGURE 24-2 Drug adsorption mechanism. The drug binds to the membrane of the blood cell. Antibodies are formed to the drug–membrane complex (hapten). The antibodies then attach to the complex, and cell toxicity occurs. *(This article was published in Transfus Med Rev, Vol 7(Oct), Petz LD, Drug-induced autoimmune hemolytic anaemia, pages 242–254, Copyright © Elsevier 1993.)*

compounds (eFig. 24-2).[55,56] In the *immune-complex mechanism*, antibodies form complexes with the causative drug, and the immune complex adheres to the target cell, leading to cell destruction. This is the proposed mechanism of agranulocytosis induced by quinidine and quinine (eFig. 24-3).[55,56] Finally, in the *autoimmune mechanism*, the drug triggers the production of autoantibodies that react with neutrophils. In this reaction, the causative drug is not directly involved with the serologic reaction. This is the mechanism of toxicity associated with levamisole (eFig. 24-4).[55,57] In all mechanisms, cell destruction occurs via antibody-mediated cell toxicity, complement activation, and phagocytic elimination through the mononuclear phagocyte system. Typically, in immune-mediated mechanisms, agranulocytosis occurs within days to a few weeks after drug exposure, with rapid appearance of symptoms.[55]

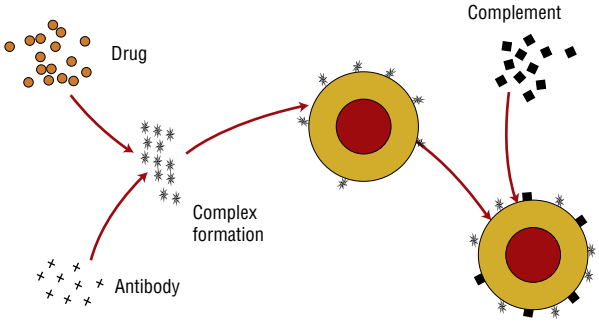
Nearly all classes of drugs have been associated with some incidence of acute neutropenia or agranulocytosis, although the risk is exceedingly small. For some drugs, though, the risk may be higher. These agents include antithyroid medications, ticlopidine, clozapine, sulfasalazine, trimethoprim–sulfamethoxazole, and β-lactam antibiotics.

In the case of penicillin-induced agranulocytosis, the patient can often begin taking penicillin again, at a lower dosage, after the neutropenia has resolved without any relapse of drug-induced agranulocytosis.[58] Because of the rapid onset of symptoms and the dose-related phenomenon, a second mechanism could possibly be involved with penicillin-induced agranulocytosis. That mechanism involves an accumulation of drug to toxic concentrations in hypersensitive individuals. Researchers have shown with in vitro cell cultures that penicillin derivatives in high concentrations inhibit the growth of myeloid colony-forming units (CFUs) in patients recovering from drug-induced agranulocytosis.[59] Penicillin derivatives, therefore, may suppress WBCs by several mechanisms.

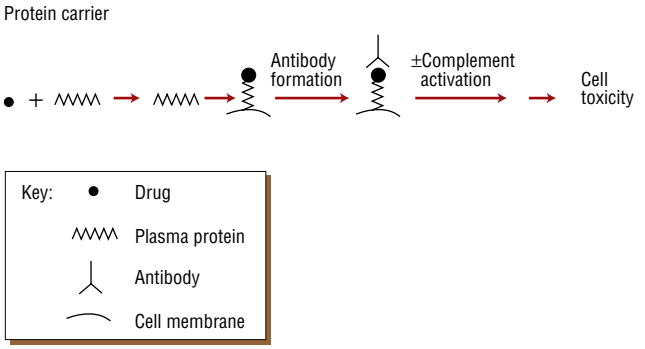
Antithyroid medications, such as propylthiouracil and methimazole, have been reported to cause agranulocytosis. The current incidence of this adverse effect is unknown, but early publications report agranulocytosis in about three per 10,000 users.[60] The mechanism by which antithyroid agents cause agranulocytosis is unknown, but antineutrophil cytoplasmic antibodies have been identified.[61] In a study by Cooper and coworkers, agranulocytosis occurred more frequently in older patients (>40 years old) and appeared within 2 months after the initiation of therapy; a possible dose–response relationship was also observed.[62] More recently, Takata and colleagues found the prevalence of neutropenia to be significantly greater in patients receiving methimazole 30 mg/day compared with those receiving 15 mg/day.[63] No dose–response relationship has been observed with conventional doses of propylthiouracil. However, another study demonstrated no relationship between age or dose and the incidence of thionamide-induced agranulocytosis.[64]

Ticlopidine is an antiplatelet agent indicated for the treatment of cerebrovascular disease and the prevention of reocclusion associated with stent placement. It produces neutropenia in about 2.4% of patients and agranulocytosis in 0.8%, possibly by inhibiting hematopoietic progenitor stem cells.[65] Patient factors that can be associated with the development of agranulocytosis include poor bone marrow reserve and age. Agranulocytosis most commonly occurs within 1 to 3 months from the initiation of ticlopidine. Removal of the drug is the best treatment option, with counts usually returning to normal within 2 to 4 weeks.

The phenothiazine class of drugs is known to cause drug-induced agranulocytosis by the innocent bystander mechanism. The onset of phenothiazine-induced agranulocytosis is about 2 to 15 weeks after the initiation of therapy, with a peak onset between 3 and 4 weeks.[66,67] The mechanism by which phenothiazines cause drug-induced agranulocytosis has been studied primarily with chlorpromazine,[62] which is thought to affect cells in the cell cycle phase that manufactures enzymes needed for DNA synthesis (G_1 phase) or the phase in which cells are resting and not committed to cell division (G_0 phase).[68] The antipsychotic agents are known to precipitate proteins and may co-precipitate polynucleotides so they can no longer participate in nucleic acid synthesis. Chlorpromazine also increases



eFIGURE 24-3 Innocent bystander mechanism. The drug induces antibody formation. The antibodies and drug form a complex in the serum, and the complex nonspecifically binds to the cell membrane. Complement is activated, and the cell is lysed. *(This article was published in Ballieres Clin Haematol, Vol 91, Petz LD, Drug-induced haemolytic anaemia, pages 455–482, Copyright © Elsevier 1980.)*



eFIGURE 24-4 Protein carrier mechanism. The drug combines with a plasma protein. The complex then attaches to the cell membrane, and antibody formation is stimulated. Antibodies later attach to the complex and activate complement. The cell is then lysed by the complement. *(This article was published in Clin Haematol, Vol 9(Oct), Young GA, Vincent PC, Drug-induced agranulocytosis, pages 483–504, Copyright © Elsevier 1980.)*

the loss of macromolecules from the intracellular pools that are essential for cellular replication.[68] When the bone marrow from a patient with phenothiazine-induced agranulocytosis is examined, it initially appears to have no cellularity (aplastic), but over time, it becomes hyperplastic. It is believed that toxic effects of the phenothiazines are not seen in all patients taking the medications because most patients have enough bone marrow reserve to overcome the toxic effects.[68]

The iron chelator deferapirone has been associated with a significant risk of neutropenia (8.5%) and agranulocytosis (0.5%).[69] The incidence of neutropenia was significantly higher in patients who had intact spleens. The mechanism of toxicity is largely unknown. Suggested mechanisms have included inhibition of granulocyte-macrophage colony-forming unit (CFU-GM) colonies in the bone marrow, maturation arrest of the granulocytic lineage at the stage of the CFU, or interactions with other essential metal atoms such as copper.[69]

Clozapine, an antipsychotic agent, is associated with a significantly higher risk of agranulocytosis compared with other antipsychotic medications and has received much attention over recent years.[70] The annual incidence of clozapine-induced agranulocytosis in the United States is reported to be 1.3% and can occur at any time during treatment, although the risk is highest at around 3 months after initiation.[71] Because of the frequency and seriousness of clozapine-induced agranulocytosis and because of its reversible nature if detected early in therapy, clozapine is currently only available through a limited distribution program that requires strict monitoring of WBC count.[71] In vitro studies have suggested that the formation of a nitrenium ion unstable metabolite may be responsible for clozapine-induced agranulocytosis.[56] The resulting oxidative stress caused by this metabolite may cause cytotoxicity or an immune reaction.[72]

TREATMENT
Drug-Induced Agranulocytosis

The primary treatment of drug-induced agranulocytosis is the removal of the offending drug. After discontinuation of the drug, most cases of neutropenia resolve over time, and only symptomatic treatment (e.g., antimicrobials for infection treatment and prophylaxis) and appropriate vigilant hygiene practices are necessary. Sargramostim (granulocyte-macrophage colony-stimulating factor [GM-CSF]) and filgrastim (granulocyte colony-stimulating factor [G-CSF]) have been shown to shorten the duration of neutropenia, length of antibiotic therapy, and hospital length of stay.[51] Although the use of both agents has been reported in the literature, a commonly reported regimen is G-CSF 300 mcg/day via subcutaneous injection. The only prospective, randomized trial to date did not confirm the benefit of these growth factors.[73] However, some experts have questioned the validity of these results based on the small sample size ($n = 24$) and the lower than standard dose of filgrastim used (i.e., 100–200 mcg/day). One systematic review found that patients with a neutrophil nadir less than 100 cells/mm^3 (0.1×10^9/L) had a higher rate of infections and fatal complications than those with a higher nadir.[52] Therefore, most clinicians recommend the use of growth factors in patients with a neutrophil nadir less than 100 cells/mm^3 (0.1×10^9/L), regardless of the presence of infection.

DRUG-INDUCED HEMOLYTIC ANEMIA

After their release from the bone marrow, normal RBCs survive for about 120 days before they are removed by phagocytic cells of the spleen and liver. The process of premature RBC destruction is referred to as hemolysis, which can occur because of either defective RBCs or abnormal changes in the intravascular environment. Drugs can promote hemolysis by both processes. The incidence of drug induced hemolytic anemia is estimated to be about one in 1 to 2 million individuals, although a clear incidence has been difficult to ascertain because of difficulty in establishing a clear diagnosis and relationship to a specific agent.[74]

The causes of drug-induced hemolytic anemia can be divided into two categories, immune or metabolic. Those in the first category may operate much like the process that leads to immune-mediated agranulocytosis, or they can suppress regulator cells, which can lead to the production of autoantibodies. The second category involves the induction of hemolysis by metabolic abnormalities in the RBCs. Patients with drug-induced hemolytic anemia can present with signs of intravascular or extravascular hemolysis. Intravascular hemolysis, the lysis of RBCs in the circulation, can result from trauma, complement fixation to the RBC, or exogenous toxic factors. Extravascular hemolysis refers to the ingestion of RBCs by macrophages in the spleen and liver, a process that requires the presence of surface abnormalities on RBCs, such as bound immunoglobulin.[75]

The onset of drug-induced hemolytic anemia is variable and depends on the drug and mechanism of the hemolysis. Symptoms of hemolytic anemia can include fatigue, malaise, pallor, and shortness of breath. eTable 24-3 provides a list of drugs that have been associated with drug-induced immune hemolytic anemia.

eTABLE 24-3 Drugs Associated with Hemolytic Anemia

Observational study evidence
Phenobarbital
Phenytoin
Ribavirin
Case report evidence (*probable* or *definite* causality rating)
Acetaminophen
Angiotensin-converting enzyme inhibitors
β-Lactam antibiotics
Cephalosporins
Ciprofloxacin
Clavulanate
Erythromycin
Hydrochlorothiazide
Indinavir
Interferon alfa
Ketoconazole
Lansoprazole
Levodopa
Levofloxacin
Methyldopa
Minocycline
NSAIDs
Omeprazole
p-Aminosalicylic acid
Phenazopyridine
Probenecid
Procainamide
Quinidine
Rifabutin
Rifampin
Streptomycin
Sulbactam
Sulfonamides
Sulfonylureas
Tacrolimus
Tazobactam
Teicoplanin
Tolbutamide
Tolmetin
Triamterene

NSAID, nonsteroidal antiinflammatory drug.

Drug-Induced Immune Hemolytic Anemia

In immune hemolytic anemia, IgG or immunoglobulin M (IgM) (or both) binds to antigens on the surface of RBCs and initiates their destruction through the complement and mononuclear phagocytic systems.[68] Drug-induced immune hemolytic anemias involve the formation of antibodies directed against RBCs. Antibodies associated with drug-induced immune hemolytic anemia are of two main types. Drug-independent antibodies are those that are found even in the absence of the drug. These are true RBC antibodies and can be the cause of true autoimmune hemolytic anemia. The laboratory and clinical findings may be indistinguishable from those found with idiopathic autoimmune hemolytic anemia. It is thought that drugs evoke the formation of these antibodies by having a direct effect on the immune system in a mechanism similar to microbial or viral infections. Drug-dependent antibodies are those that will only react in the presence of drug, and are the more common form of antibodies causing drug-induced immune hemolytic anemia.[76]

A laboratory test called the direct Coombs test (or direct antiglobulin test [DAT]), which identifies foreign immunoglobulins either in the patient's serum or on the RBCs themselves, is the best means to diagnose drug-induced immune hemolytic anemia. The Coombs test begins with the antiglobulin serum, which is produced by injecting rabbits with preparations of human complement, crystallizable fragment (of immunoglobulin) (Fc), or immunoglobulins. The rabbits produce antibodies against human immunoglobulins and complement. The direct Coombs test involves combining the patient's RBCs with the antiglobulin serum. If the patient's RBCs are coated with antibody or complement (as a result of a drug-induced process), the antibodies in the serum (produced by the rabbit) will attach to the Fc regions of the autoimmune globulins on separate RBCs, creating a lattice formation called agglutination.[77] This agglutination is considered positive for the presence of IgG or complement on the cell surfaces.

An indirect Coombs test can identify antibodies in a patient's serum. This test is performed by combining the patient's serum with normal RBCs and then subjecting them to the direct Coombs test. Antibodies that have attached to the normal RBCs will be identified. This process is important in blood bank procedures.

Four mechanisms have been proposed to explain how drugs can induce immune hemolytic anemia; these are similar to those proposed for drug-induced agranulocytosis.[78]

The first mechanism is the "hapten mechanism" or "drug adsorption" mechanism. In this mechanism, patients make an antibody against a stable complex of the drug with some soluble noncellular molecule or protein. When the drug is administered again, an immune complex of drug–antidrug forms and attaches nonspecifically to RBCs, activating complement and leading to cell destruction.[78,79] The anemia usually develops gradually over 7 to 10 days and reverses over a couple of weeks after the offending drug is discontinued. The direct Coombs test result may remain positive for several weeks. The penicillin and cephalosporin derivatives, when given in high doses, are primarily associated with this type of immune reaction. Of the cephalosporins, cefotetan and ceftriaxone are the agents most commonly associated with drug-induced immune hemolytic anemia.[76] Other drugs that have been reported to cause drug-induced immune hemolytic anemia by this process include minocycline tolbutamide and streptomycin.[80,81]

The second mechanism is the immune complex or "innocent bystander" mechanism. In this mechanism, drugs bind to an antibody, usually IgM, to form an immune complex. This immune complex then attaches to the RBC membrane, activating complement and leading to intravascular hemolysis.[78] As soon as complement is activated, the complex can detach and move on to other RBCs. Because of this low affinity, only a small amount of drug is needed to cause the reaction, and the direct Coombs test result is positive for complement only. RBCs are essentially victims, or "innocent bystanders," of the immunologic reaction. This type of mechanism is associated with acute intravascular hemolysis that can be severe, sometimes leading to hemoglobinuria and renal failure. After discontinuation and clearance of the drug from the circulation, the direct Coombs test result will become negative.[78]

The third mechanism involves the production of true RBC autoantibodies. The first drug associated with this type of reaction was methyldopa.[79,82,83] About 10% to 20% of patients receiving methyldopa will develop a positive Coombs test result, usually within 6 to 12 months of initiating therapy.[84] However, fewer than 1% of these patients experience hemolysis, and hemolysis can develop from 4 to 6 months to more than 2 years after the start of therapy. After the withdrawal of the drug, results of the Coombs test can remain positive for many months.[81] The mechanism by which methyldopa induces antibody production is not completely known, but two hypotheses have been proposed.[82] The first suggests that methyldopa or its metabolites act on the immune system and impair immune tolerance. An alternative hypothesis is that the offending drug may bind to immature RBCs, altering the membrane antigens and inducing autoantibodies. Other drugs associated with the production of true autoantibodies include fludarabine and cladribine.

The fourth mechanism of drug-induce immune hemolytic anemia is through nonimmunologic protein adsorption (NIPA) to RBC membranes.[78,85] In this "membrane modification mechanism," drugs can change the RBC membrane so that proteins attach to the cell, leading to a positive antiglobulin test result. This phenomenon was originally thought to be important only because of laboratory test interference, but then, β-lactamase inhibitors were shown to induce drug-induced immune hemolytic anemia through NIPA.[86] Other drugs that may cause immune hemolytic anemia through NIPA are cisplatin and oxaliplatin.[87]

It is not known why only some patients develop autoantibodies and why only some of the patients who have autoantibodies develop hemolytic disease. In an effort to explain why patients have a positive result from a Coombs test and no hemolysis, Kelton et al. showed that methyldopa impairs the ability of these patients to remove antibody-sensitized cells.[88] In Coombs-positive patients receiving methyldopa, patients with impairment of the mononuclear phagocytic system could not clear the RBCs coated with autoantibodies from their bloodstream, and therefore hemolysis did not occur. Patients with hemolysis had no impairment of the mononuclear phagocytic system. Procainamide has also been reported to cause a positive result on the indirect Coombs test and hemolytic anemia.[89] Other drugs that have been reported to cause autoimmune hemolytic anemia include levodopa, mefenamic acid, and diclofenac.[90]

Drug-Induced Oxidative Hemolytic Anemia

A hereditary condition, drug-induced oxidative hemolytic anemia, most often accompanies a glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency, but it can occur because of other enzyme defects (reduced nicotinamide adenine dinucleotide phosphate [NADPH] methemoglobin reductase or reduced glutathione peroxidase). A G6PD deficiency is a disorder of the hexose monophosphate shunt, which is responsible for producing NADPH in RBCs, which in turn keeps glutathione in a reduced state. Reduced glutathione is a substrate for glutathione peroxidase, an enzyme that removes peroxide from RBCs, thus protecting them from oxidative stress.[91] Without reduced glutathione, oxidative drugs can oxidize the sulfhydryl groups of hemoglobin, removing them prematurely from the circulation (i.e., causing hemolysis).

eTABLE 24-4 Drugs Associated with Oxidative Hemolytic Anemia

Observational study evidence
Dapsone
Rasburicase
Case report evidence (*probable* or *definite* causality rating)
Ascorbic acid
Metformin
Methylene blue
Nalidixic acid
Nitrofurantoin
Phenazopyridine
Primaquine
Sulfacetamide
Sulfamethoxazole
Sulfanilamide

A G6PD deficiency is the most common of all enzyme defects, affecting millions of people. Because the G6PD gene is located on the X chromosome, the disorder is therefore inherited through a sex-linked mode. Both homozygotes and heterozygotes can be symptomatic, but homozygotes tend to have the most severe cases.[92] There are many G6PD variants, but the most common types occur in American and African blacks (~10%), people from Mediterranean areas (e.g., Greeks, Sardinians, and Khurdic and Sephardic Jews), and Asians.[92]

The degree of hemolysis depends on the severity of the enzyme deficiency and the amount of oxidative stress. However, the dose required for hemolysis to occur is often less than prescribed quantities of the suspected drug.[81,91] Although severe hemolysis is rare, any drug that places oxidative stress on RBCs can cause drug-induced oxidative hemolytic anemia. One case of drug-induced oxidative hemolytic anemia has been reported in a nursing child when dapsone (an oxidizing agent) was transferred from the breast milk of the mother.[93] For a list of agents associated with drug-induced oxidative hemolytic anemia, refer to eTable 24-4.

TREATMENT
Drug-Induced Hemolytic Anemia

Drug-Induced Immune Hemolytic Anemia

The severity of drug-induced immune hemolytic anemia depends on the rate of hemolysis. Hemolytic anemia caused by drugs through the hapten or adsorption and autoimmune mechanisms tends to be slower in onset and mild to moderate in severity. Conversely, hemolysis prompted through the immune complex mechanism (innocent bystander) phenomenon can have a sudden onset, lead to severe hemolysis, and result in renal failure. The treatment of drug-induced immune hemolytic anemia includes the immediate removal of the offending agent and supportive care. In severe cases, glucocorticoids can be helpful, but their use outside of autoimmune hemolytic anemia is not supported by strong evidence.[94] Other agents such as the chimeric anti-CD20 monoclonal antibody rituximab and IgG treatments have been used, but their role is yet to be clearly defined.[95,96]

Drug-Induced Oxidative Hemolytic Anemia

Removal of the offending drug is the primary treatment for drug-induced oxidative hemolytic anemia. No other therapy is usually necessary because most cases of drug-induced oxidative hemolytic anemia are mild in severity. Patients with these enzyme deficiencies should be advised to avoid medications capable of inducing the hemolysis.

DRUG-INDUCED MEGALOBLASTIC ANEMIA

In drug-induced megaloblastic anemia, the development of RBC precursors called megaloblasts in the bone marrow is abnormal.

Deficiencies in either vitamin B_{12} or folate are responsible for the impaired proliferation and maturation of hematopoietic cells, resulting in cell arrest and subsequent sequestration. Examination of peripheral blood shows an increase in the mean corpuscular hemoglobin concentration. These megaloblastic changes are caused by the direct or indirect effects of the drug on DNA synthesis. Some patients can have a normal-appearing cell line, and the diagnosis must be made by measurement of vitamin B_{12} and folate concentrations. The abnormality can be seen in any portion of the replication process, including DNA assembly, base precursor metabolism, or RNA synthesis.[97]

Because of their pharmacologic action on DNA replication, the antimetabolite class of chemotherapeutic agents is most frequently associated with drug-induced megaloblastic anemia. Methotrexate, an irreversible inhibitor of dihydrofolate reductase, causes megaloblastic anemia in 3% to 9% of patients.[98] Dihydrofolate reductase is an enzyme responsible for generating tetrahydrofolate, an essential factor in making deoxythymidine triphosphate, which is necessary for DNA synthesis. Other drugs, such as cotrimoxazole, phenytoin, and the barbiturates, have also been implicated in megaloblastic anemia. Cotrimoxazole, for example, has been reported to cause drug-induced megaloblastic anemia with both low and high doses,[99,100] particularly in patients with a partial vitamin B_{12} or folate deficiency.[83] Because the drug's affinity for human dihydrofolate reductase is low, patients with adequate stores of these vitamins are at low risk of developing drug-induced megaloblastic anemia. It has been postulated that phenytoin, primidone, and phenobarbital cause drug-induced megaloblastic anemia by either inhibiting folate absorption or by increasing folate catabolism. In both instances, the patient develops a relative deficiency of folate. eTable 24-5 provides a list of drugs that have been suggested as causative factors in drug-induced megaloblastic anemia.

eTABLE 24-5 Drugs Associated with Megaloblastic Anemia

Case report evidence (*probable* or *definite* causality rating)
Azathioprine
Chloramphenicol
Colchicine
Cotrimoxazole
Cyclophosphamide
Cytarabine
5-Fluorodeoxyuridine
5-Fluorouracil
Hydroxyurea
6-Mercaptopurine
Methotrexate
Oral contraceptives
p-Aminosalicylate
Phenobarbital
Phenytoin
Primidone
Pyrimethamine
Sulfasalazine
Tetracycline
Vinblastine

TREATMENT
Drug-Induced Megaloblastic Anemia

When drug-induced megaloblastic anemia is related to chemotherapy, no real therapeutic option is available, and the anemia becomes an accepted side effect of therapy. If drug-induced megaloblastic anemia results from cotrimoxazole, a trial course of folinic acid, 5 to 10 mg up to four times a day, can correct the anemia.[99,100] Folic acid supplementation of 1 mg every day often corrects the drug-induced megaloblastic anemia produced by either phenytoin or phenobarbital, but some clinicians suggest that folic acid supplementation can decrease the effectiveness of the antiepileptic medications.[101]

DRUG-INDUCED THROMBOCYTOPENIA

Thrombocytopenia is usually defined as a platelet count below 100,000 cells/mm^3 (100×10^9/L) or greater than 50% reduction from baseline values. The annual incidence of drug-induced thrombocytopenia is about 10 cases per 1,000,000 population (excluding cases associated with heparin).[102,103] Although numerous epidemiologic studies have been reported, none of them have identified patient-specific risk factors that are associated with an increased risk for the development of drug-induced thrombocytopenia.[102] In 1998, George et al. from the University of Oklahoma undertook the first attempt at a systematic review of the literature and case reports associated with drug-induced thrombocytopenia.[104] At that time, there were 98 drugs identified that had reports associated with thrombocytopenia. The Oklahoma group has continued to update this systematic review nearly every 2 years since 1998.[105]

The agents most commonly implicated in immune-mediated thrombocytopenia are quinine, quinidine, gold salts, sulfonamide antibiotics, rifampin, glycoprotein (GP) IIb/IIIa (GPIIb/IIIa) receptor antagonists, and heparin.[106] A list of medications (excluding cancer chemotherapeutic agents) associated with drug-induced thrombocytopenia is provided in eTable 24-6.

Drug-induced thrombocytopenia can result from immune-mediated mechanisms or through a nonimmune-mediated mechanism. Nonimmune-mediated mechanisms, such as direct-toxicity-type reactions, are associated with medications that cause bone marrow suppression. This results in suppressed thrombopoiesis and a decreased number of megakaryocytes. This type of reaction is commonly associated with chemotherapeutic agents.

Several mechanisms have been proposed for the development of immune-mediated drug-induced thrombocytopenia. In hapten-type reactions, the offending drug binds covalently to certain platelet GPs. Antibodies are generated that bind to these drug-bound GP epitopes. After the binding of antibodies to the platelet surface, lysis occurs through complement activation or through clearance from the circulation by macrophages.[103,106,107] Hapten-mediated immune thrombocytopenia usually occurs at least 7 days after the initiation of the drug, although it can occur much sooner if the exposure is actually a reexposure to a previously administered drug. The recovery period, after the suspected drug is discontinued, is often short in duration with a median recovery time within 1 week.[105] Although relatively rare, penicillins and cephalosporins can cause thrombocytopenia through this mechanism.[102]

Quinine, anticonvulsants, and nonsteroidal antiinflammatory medications are thought to induce thrombocytopenia through the drug-dependent antibody mechanism.[103,106] This mechanism is slightly different from the hapten-type mechanism. In this type of reaction, it is thought that antibodies exist within the patient's circulation that recognize an epitope on the platelet GP, but this recognition is too weak to result in antibody binding to the platelet surface. However, the drug contains structural elements that are noncovalently complementary to regions of the antibody and the GPs on the platelet surface. This causes an improved fit or increased K_A between the antibody and the platelet surface, with the drug "trapped" in between, resulting in antibody binding of platelet.[103,106] A recently published study suggests that vancomycin-induced thrombocytopenia is related to drug-dependent antibodies.[108,109]

Eptifibatide and tirofiban are platelet GPIIb/IIIa receptor antagonists that prevent platelet activation and binding of fibrinogen,

eTABLE 24-6 Drugs Associated with Thrombocytopenia

Observational study evidence
Carbamazepine
Phenobarbital
Phenytoin
Valproic acid

Case report evidence (*probable* or *definite* causality rating)
Abciximab
Acetaminophen
Acyclovir
Albendazole
Aminoglutethimide
Aminosalicylic acid
Amiodarone
Amphotericin B
Ampicillin
Aspirin
Atorvastatin
Captopril
Chlorothiazide
Chlorpromazine
Chlorpropamide
Cimetidine
Ciprofloxacin
Clarithromycin
Clopidogrel
Danazol
Deferoxamine
Diazepam
Diazoxide
Diclofenac
Diethylstilbestrol
Digoxin
Ethambutol
Felbamate
Fluconazole
Gold salts
Haloperidol
Heparin
Hydrochlorothiazide
Ibuprofen
Inamrinone
Indinavir
Indomethacin
Interferon-α
Isoniazid
Isotretinoin
Itraconazole
Levamisole
Linezolid
Lithium
Low-molecular-weight heparins
Measles, mumps, and rubella vaccine
Meclofenamate
Mesalamine
Methyldopa
Minoxidil
Morphine
Nalidixic acid
Naphazoline
Naproxen
Nitroglycerin
Octreotide
Oxacillin
p-Aminosalicylic acid
Penicillamine
Pentamidine
Pentoxifylline
Piperacillin
Primidone
Procainamide
Pyrazinamide
Quinidine
Quinine
Ranitidine
Recombinant hepatitis B vaccine
Rifampin
Simvastatin
Sirolimus
Sulfasalazine
Sulfonamides
Sulindac
Tamoxifen
Tolmetin
Trimethoprim
Vancomycin

thereby inhibiting platelet thrombus formation. In clinical trials and postmarketing studies, it was found that about 0.1% to 2% of patients treated with these medications experienced acute profound thrombocytopenia within several hours of their first exposure to the drug.[103,106,109,113] This acute drop in platelets without prior drug exposure suggested initially that this reaction was mediated by a nonimmune mechanism. However, a plausible immune-mediated mechanism has since been proposed. After binding to the GPIIb/IIIa receptor, these medications cause a conformational change in the receptor that allows it to be recognized by naturally occurring antibodies already in the patient's blood (i.e., a ligand-induced binding site). In contrast to the two previously discussed immune-mediated mechanisms (hapten type and drug dependent), the drug is not present within the binding between the antibody and the platelet surface. The drug has been removed from the platelet surface before the antibody binds, but the conformational change in the GPIIb/IIIa receptor remains.[106]

Abciximab, a GPIIb/IIIa receptor antagonist like tirofiban and eptifibatide, is also associated with thrombocytopenia. Abciximab-induced thrombocytopenia appears to occur through a different drug-specific antibody mechanism as opposed to a ligand-induced binding site mechanism with eptifibatide and tirofiban.[103,106,113] Unlike tirofiban and eptifibatide, abciximab is a chimeric (human–mouse) monoclonal antibody. Therefore, it is not surprising that this molecule may exhibit some immunogenic properties. It has been demonstrated that patients who experience thrombocytopenia after the administration of abciximab have circulating antibodies that directly recognize the drug.[103,106] Because the drug is bound to platelets, thrombocytopenia results. About 2% of patients experience thrombocytopenia with the first administration and 10% to 12% with subsequent administrations.[109,110] Furthermore, in patients who experience the reaction with the first administration, some experience immediate thrombocytopenia, but a few patients develop delayed thrombocytopenia about 1 week after drug administration. In patients who experience immediate thrombocytopenia, drug-specific antibodies are naturally occurring and present at the time of drug administration. For those with a delayed response (6–8 days later), drug-specific antibodies are produced during this time, and because abciximab remains bound to platelets for up to 2 weeks, the reaction can still occur.[111] Because all three GPIIb/IIIa receptor antagonists are coadministered with heparin, it is important to distinguish between GPIIb/IIIa receptor antagonist-induced and heparin-induced thrombocytopenia. A heparin-induced platelet aggregation study can help to determine the offending agent. Pseudothrombocytopenia, defined as in vitro platelet aggregation in blood anticoagulated with ethylenediamine tetraacetic acid (EDTA), is clinically insignificant, but it must also be differentiated from thrombocytopenia induced by GPIIb/IIIa receptor antagonists.[112]

Gold compounds and procainamide appear to induce thrombocytopenia through the platelet-specific autoantibody-type reaction.[102,103] In this type of reaction, a drug induces the production of autoantibodies that bind to platelet membranes and cause destruction, but the causative drug does not have to be present for the reaction to occur. In contrast, the drug-dependent antibody reaction requires the presence of the drug to allow antibody binding. Although several mechanisms of drug-induced thrombocytopenia have been proposed, it is often not possible to determine the mechanism for an individual drug or patient, and more than one mechanism can be responsible for the condition.

The final type of immune-mediated thrombocytopenia has been categorized as immune complex–induced thrombocytopenia.[103,106] This describes the mechanism of the most serious type of heparin-induced thrombocytopenia (HIT) type II.

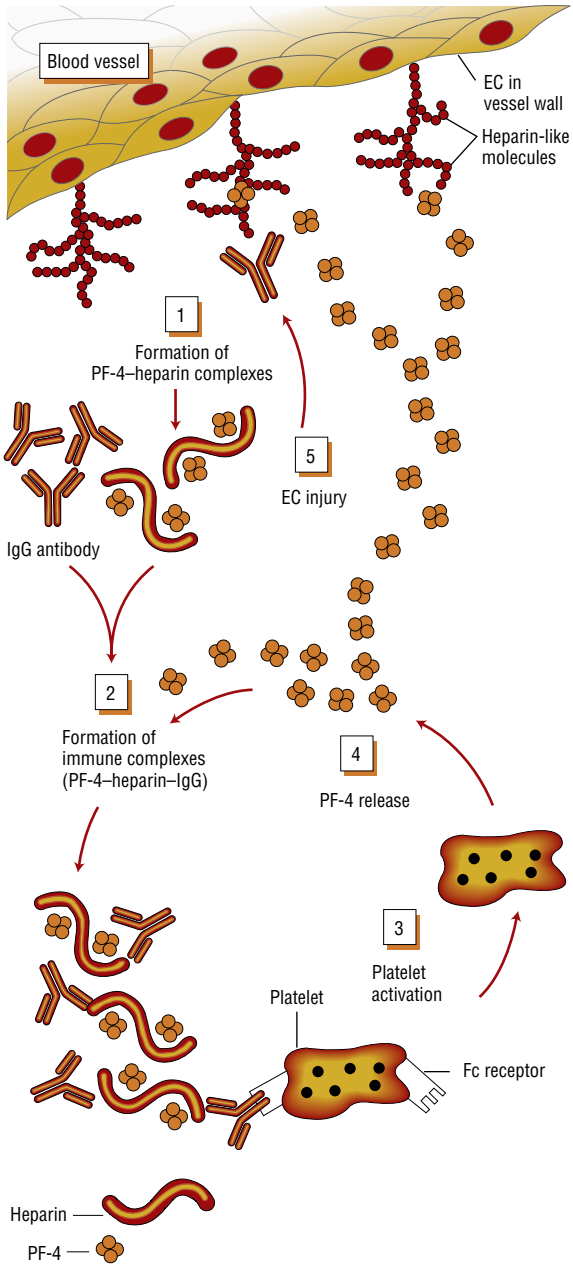
At least two types of HIT have been identified. The most common, type I, occurs in about 10% to 20% of patients treated with heparin.[114] It is a mild, reversible, nonimmune-mediated reaction that usually occurs within the first 2 days of therapy. The platelet count slowly returns to baseline after an initial decline despite continued heparin therapy. HIT type I is usually an asymptomatic condition and is thought to be related to platelet aggregation.[2]

Heparin-induced thrombocytopenia type II is less common but more severe and can be associated with more complications. About 1% to 5% of patients receiving unfractionated heparin (UFH) and up to 0.8% of patients receiving low-molecular-weight heparin (LMWH) can develop HIT.[2,114] Patients typically present with a low platelet count (e.g., below 150,000 cells/mm^3 [150 × 10^9/L]) or a 50% or more decrease in platelet count from baseline, and thrombosis can occur.[115] The platelet count generally begins to decline 5 to 10 days after the start of heparin therapy. However, this decline can occur within hours of receiving heparin if the patient has recently received heparin (i.e., within 100 days).[115] Thrombocytopenia and thrombosis can develop with low-dose heparin,[116] heparin-coated catheters,[117] or even heparin flushes. Certain patient populations have a higher risk for developing HIT than others; patients who have had recent, major surgery are one of the highest risk groups.[114] The next highest risk groups include patients receiving heparin for thrombosis prophylaxis after peripheral vascular surgery, cardiac surgery, and orthopedic surgery.[118] A lower incidence is seen in medical, obstetric, and pediatric patients, especially those receiving LMWH instead of UFH.[114] The most recent practice guidelines by the American College of Chest Physicians recommend varying degrees of platelet monitoring based on the relative risk of developing HIT.[119]

HIT is caused by the development of antibodies against platelet factor-4 (PF-4) and heparin complexes[115] (**eFig. 24-5**). MWH bind less well to PF-4 than UFH, and therefore antibody formation is less common. However, antibodies developed by patients receiving UFH react against LMWH; thus, LMWH should not be used in patients with HIT.[114] After the antibodies bind to the complexes, platelet activation and aggregation occur, with subsequent release of more circulating PF-4 to interact with heparin. In addition, procoagulant microparticles are also released that increase the risk of thrombosis.[114] Thrombosis is one of the major complications of HIT and can occur in up to 20% to 50% of patients with HIT.[115] Thrombosis is the precipitating factor that leads the clinician to diagnose HIT in many patients. This high risk of thrombosis continues for days to weeks after heparin discontinuation and platelet recovery, and continued anticoagulation with an alternative agent is essential during this time period.[115] Other less-frequent manifestations of HIT include heparin-induced skin necrosis and venous gangrene of the limbs.[114,115] The diagnosis of HIT is frequently a clinical one, supported by laboratory testing. Several types of assays are available to aid in the diagnosis of HIT, including platelet activation assays, platelet aggregation studies, and enzyme-linked immunosorbent assay methods, each with varying sensitivities and specificities.[6]

TREATMENT
Drug-Induced Thrombocytopenia

The primary treatment of drug-induced thrombocytopenia is removal of the offending drug and symptomatic treatment of the patient. The use of corticosteroid therapy in the treatment of drug-induced thrombocytopenia is controversial, although some authors recommend it in severe symptomatic cases.[120] Corticosteroids are sometimes helpful when clinicians are initially trying to distinguish between drug-induced thrombocytopenia and idiopathic thrombocytopenic purpura (ITP).



eFIGURE 24-5 Proposed explanation for the presence of both thrombocytopenia and thrombosis in heparin-sensitive patients who are treated with heparin. Injected heparin reacts with platelet factor-4 (PF-4), which is normally present on the surface of endothelial cells (ECs) or released in small quantities from circulating platelets, to form PF-4–heparin complexes *(1)*. Specific immunoglobulin G (IgG) antibodies react with these conjugates to form immune complexes *(2)* that bind to crystallizable fragment (Fc) receptors on circulating platelets. Fc-mediated platelet activation *(3)* releases PF-4 from α-granules in platelets *(4)*. Newly released PF-4 binds to additional heparin, and the antibody forms more immune complexes, establishing a cycle of platelet activation. PF-4 released in excess of the amount that can be neutralized by available heparin binds to heparin-like molecules (glycosaminoglycans) on the surface of ECs to provide targets for antibody binding. This process leads to immune-mediated EC injury *(5)* and heightens the risk of thrombosis and disseminated intravascular coagulation. *(From Aster RH. Heparin-induced thrombocytopenia and thrombosis. N Engl J Med 1995;332:1374–1376. Copyright © 1995 Massachusetts Medical Society. All rights reserved.)*

Clinical **Controversy. . .**

Drug induced thrombocytopenia, in most cases, resolves quickly after removal of the offending agent. In some cases, however, thrombocytopenia can persist for weeks or months, especially in the case of chemotherapy-induced thrombocytopenia or thrombocytopenia caused by immune mechanisms. In this setting, limited options are available to maintain platelets in a safe range while awaiting count recovery. Historically, transfusions were used to maintain platelet counts until bone marrow recovery. The emergence of thrombopoietin analogs such as eltrombopag and romiplostim has raised the question of using drug therapy to treat drug-induced thrombocytopenia. Current indications for these agents are limited to ITP, but preliminary data suggest a potential benefit in patients with prolonged drug-induced thrombocytopenia. Currently, this treatment cannot be recommended routinely, but future studies can help to elucidate if there is a role for these agents in the management if drug-induced thrombocytopenia.

In the case of HIT, the main goal of management is to reduce the risk of thrombosis or thrombosis-associated complications in patients who have already developed a clot. All forms of heparin must be discontinued, including heparin flushes, and alternative anticoagulation must begin immediately.[121] The direct thrombin inhibitors are the alternative anticoagulants most commonly used in current practice. Three direct thrombin inhibitors are currently available: lepirudin, argatroban, and bivalirudin. Lepirudin, the first drug that was approved for the treatment of HIT, is a recombinant analogue of hirudin, a natural anticoagulant found in leeches. Lepirudin is renally eliminated and requires dosage adjustment in those patients with kidney dysfunction. It is also important to note that antibodies to lepirudin develop in about 30% of patients who receive this agent for the first time, and it is therefore recommended that patients receive only one course of lepirudin.[115] Argatroban is another IV thrombin inhibitor indicated for the management of HIT. But unlike lepirudin, argatroban is metabolized in the liver and can be used in patients with end-stage renal disease. However, dosage adjustment is needed for patients with significant hepatic impairment. The most recently approved direct thrombin inhibitor is bivalirudin. It is similar to lepirudin in that is a parenteral bivalent analogue of hirudin. It requires dosage adjustment only in severe renal failure. Fondaparinux, an anticoagulant pentasaccharide that inhibits factor Xa, has been proposed by some as a potential treatment for HIT because it does not appear to cause in vitro cross-reactivity with HIT antibodies.[122,123] Clinical data, however, to support the use of fondaparinux in the treatment of HIT-induced thrombosis are lacking. The most recent guidelines by the American College of Chest Physicians suggest that fondaparinux is most appropriately used in patients at relatively low risk of having HIT but for whom the use of either UFH or LMWH is not desired.[119] These agents should also be considered for the treatment of patients who have acute HIT without thrombosis because of the increased risk of thrombosis occurring in these patients. Because of the increased risk of venous limb gangrene, warfarin should not be used alone to treat acute HIT complicated by deep vein thrombosis.[119]

ABBREVIATIONS

ADR	adverse drug reaction
ATG	antithymocyte globulin
CFU	colony-forming unit

CFU-GM	granulocyte-macrophage colony-forming unit
DAT	direct antiglobulin test
EDTA	ethylenediamine tetraacetic acid
Fc	crystallizable fragment (of immunoglobulin)
G6PD	glucose-6-phosphate dehydrogenase
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GPIIb/IIIa	glycoprotein IIb/IIIa
HIT	heparin-induced thrombocytopenia
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
IgG	immunoglobulin G
IgM	immunoglobulin M
ITP	idiopathic thrombocytopenic purpura
LMWH	low-molecular-weight heparin
MAA	moderate aplastic anemia
NADPH	reduced nicotinamide adenine dinucleotide phosphate
PF-4	platelet factor-4
RBC	red blood cell
SAA	severe aplastic anemia
UFH	unfractionated heparin
WBC	white blood cell
VSAA	very severe aplastic anemia

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