Chapter e125: Drug-Induced Hematologic Disorders

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Appendix 5, Drug-Induced Hematologic Disorders.

KEY CONCEPTS

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1. The most common drug-induced hematologic disorders are aplastic anemia, agranulocytosis, megaloblastic anemia, hemolytic anemia, and thrombocytopenia.
2. Drug-induced hematologic disorders are rare adverse drug reactions (ADRs) associated with drug therapy.
3. The incidence of rare ADRs is usually established by postmarketing surveillance and reporting.
4. Rechallenging a patient with an agent suspected of inducing a blood disorder is not generally recommended.
5. Drug-induced hematologic disorders can occur by two mechanisms: direct drug or metabolite toxicity or an immune reaction.
6. The primary treatment of drug-induced hematologic disorders is the removal of the drug in question and symptomatic support of the patient.

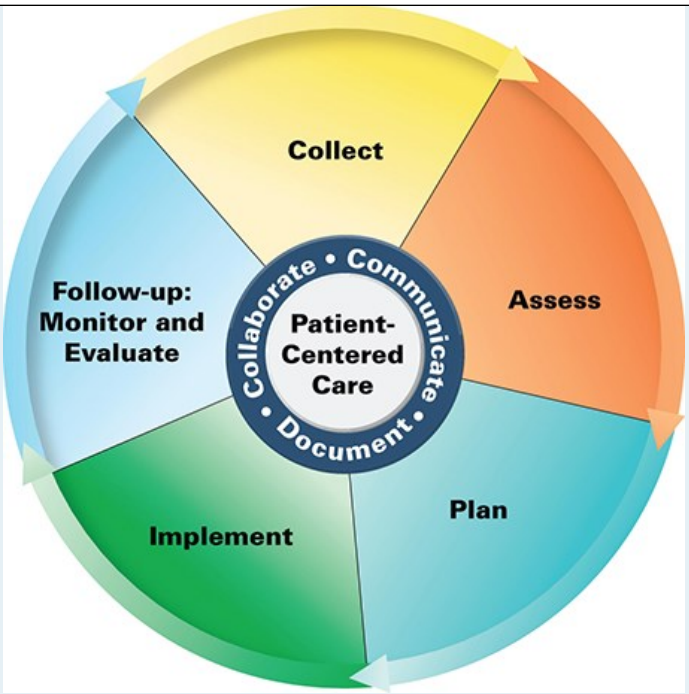
BEYOND THE BOOK

BEYOND THE BOOK

Watch the video entitled "Part 1: Anemia: Pathophysiology and Diagnostic Approach" (https://accessmedicine.mhmedical.com/MultimediaPlayer.aspx?MultimediaID=16442308) in AccessMedicine by Scott Stern, MD. This can be found by clicking on Multimedia, Lectures, Diagnostic Reasoning, then Part 1: Anemia (https://accessmedicine.mhmedical.com/MultimediaPlayer.aspx?MultimediaID=16442308). This 21-minute video provides an overview of the foundational knowledge of anemia, the approach to evaluate a patient with anemia, common causes of anemias, and differential diagnosis for different types of anemias. This video increases student understanding regarding the COLLECT and ASSESS steps in the patient care process.

PATIENT CARE PROCESS

Patient Care Process for Drug-Induced Hematologic Disorders



Collect

- Medication history
- ADR probability scale data
- Laboratory data (eg, CBC, antibody tests)
- Medication history (eg, has the patient taken heparin? What is the timing?)

Assess

- Determine probable cause and severity of illness based on information above (eg, how likely is heparin-induced thrombocytopenia based on the Naranjo Algorithm? Have bleeding or thrombotic complications arisen?)

Plan*

- Determine alternate and additional therapy if indicated (eg, which alternative anticoagulant should be chosen? Is there a preference for IV, SQ, or PO therapy? Is there a contraindication to argatroban? If severe bleeding is present, should corticosteroids, IVIG, or blood transfusions be considered?)

Implement

- Remove suspected causative agent and replace as needed (eg, stop heparin, start argatroban)

Follow-up: Monitor and Evaluate

- Reassess clinical and laboratory data (eg, CBC to ensure that platelet counts recover appropriately)
- Consider appropriateness of transition to SQ or PO anticoagulation
- Continue to follow pertinent parameters to ensure resolution (eg, daily CBCs while patient is hospitalized with goal of platelet recovery within 1 week)

- Continue anticoagulation at least 2 to 3 weeks to minimize ongoing risk of thrombosis
- Evaluate over time (eg, has the situation been resolved satisfactorily? Is additional therapy or action needed? In the future, what could be changed to provide better care in similar situations?)

See Introduction and Drug-Induced Thrombocytopenia (Clinical Presentation and Management of Toxicity) sections for more information related to the patient care process.

Collaborate with patient, caregivers, and other healthcare professionals.

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 (eg, antineoplastics), but others induce idiosyncratic reactions not directly related to the drugs' pharmacology. The most common drug-induced hematologic disorders are 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 are 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 disorder, with reports suggesting that between 0.1% and 5% of patients who receive heparin develop heparin-induced thrombocytopenia (HIT).[2,3] The Berlin Case-Control Surveillance Study was conducted from 2000 to 2009 to assess the incidence and risks of drug-induced hematologic disorders and found that almost 30% of all cases of blood dyscrasias were "possibly" attributable to drug therapy.[4]

Although drug-induced hematologic disorders are less common than other types of adverse reactions, they are associated with significant morbidity and mortality. Aplastic anemia is the leading cause of death followed by thrombocytopenia, agranulocytosis, and hemolytic anemia.[5] Similar to most other adverse drug reactions (ADRs), drug-induced hematologic disorders are more common in older individuals than in the young; the risk of death is also greater with increasing age.

3 The MedWatch program supported by the Food and Drug Administration (FDA)[6] is the most common avenue for postmarketing surveillance to establish the incidence of ADRs. The FDA's Adverse Event Reporting System (FAERS) is the database that contains the reports submitted to the FDA and supports the post-marketing safety and surveillance program for both drug and therapeutic biologic products. It has a dashboard that allows the public to search for human adverse events that have been reported by the pharmaceutical industry, healthcare providers, and consumers. Many facilities have similar drug-reporting programs to follow ADR trends and to determine whether an association between a drug and an ADR is causal or coincidental. These programs enable practitioners to confirm that an adverse event is the result of drug therapy rather than one of many other potential causes; general guidelines are readily available.[7,8]

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.[9] These methods are often expensive, however, and require facilities and expertise that are not generally available. Although the diagnosis of HIT requires laboratory testing,[10] laboratory confirmation of drug causation is not always necessary to warrant interruption or discontinuation of therapy. Therefore, it is extremely important that clinicians be able to clinically evaluate suspect drugs quickly and to interrupt therapy when necessary.

Through the use of surveillance programs, lists of drugs that may be associated with adverse events have been published. These lists include a large number of commonly used drugs. Although these lists may help clinicians identify specific drug causes of adverse events, the large number of agents implicated may make this a difficult process. The absence of a drug from such a list should not discourage the investigation and reporting of a suspected 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 obtained from the patient in order to best determine any potential for drug causation.

A common tool used to rate the likelihood of causality in ADR investigations is the ADR probability scale (algorithm). One such scale was developed and tested by Naranjo et al.[11] This tool provides a series of scored questions that lead 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. Greater weight should be assigned to prospective study designs such as clinical trials or cohort studies than to case reports or expert opinion.

Evaluating drug-induced hematologic disorders requires a basic understanding of hematopoiesis (see Chapter e106, “Function and Evaluation of the Immune System”). The pluripotent hematopoietic stem cells in the bone marrow self-reproduce in order to maintain the blood. These cells further differentiate into 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. 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 drug-induced anemias, including immune hemolytic anemia, oxidative hemolytic anemia, or megaloblastic anemia (see Chapter 122, “Anemias”). 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 characterized by pancytopenia (anemia, neutropenia, and thrombocytopenia),[12] hypocellular bone marrow and no gross evidence of increased peripheral blood cell destruction.[13] Bone marrow examination shows an absence or marked reduction of hematopoietic stem cells and an increase in fat cells.

The incidence is estimated to be about two per million per year in Europe and North America, and four to six per million per year in Asia, which suggests a relationship between the environment and risk.[14] Fifty percent of aplastic anemia cases are acquired in nature, but a definitive causative agent cannot be identified in most cases.[15,16] Men and women are affected equally, but there is a bimodal risk distribution when it comes to age, with peak incidences in those aged 10 to 25 years and again in those older than 60 years.[16]

Diagnosis and Classification

The diagnosis of aplastic anemia requires 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; 6.21 mmol/L) or less with a reticulocyte count of 30,000 cells/mm^3 (30×10^9/L) or less.[17] Depending on the blood counts, aplastic anemia can be categorized as moderate, severe, and very severe aplastic anemia.[17,18]

- 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 (100 g/L; 6.21 mmol/L).
- 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), and reticulocytes less than 1%.

- 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.[17] The patient must not have had previous exposure to cytotoxic chemotherapy or intensive radiation.

Mechanism

Aplastic anemia can be divided into two broad categories, inherited and acquired. Inherited aplastic anemias, such as Fanconi's and Blackfan Diamond, result in bone marrow failure, fatty infiltration of the marrow, and loss of circulating blood cells. 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.

5 Three major mechanisms of acquired aplastic anemia have been identified: direct toxicity, metabolite-driven toxicity, and immune-mediated mechanisms.[18] 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.[19] When intermediate metabolites of drugs bind to proteins and DNA on hematopoietic cells, bone marrow failure can occur. Genetic variation leads to variability in the presence of these reactive metabolites and explains the idiosyncratic nature of these drug reactions. The most common cause of drug-induced aplastic anemia is the development of an immune reaction. The exposure to an inciting antigen (ie, drug) activates the immune system, leading to the death of stem cells.[18] The immune mechanism of aplastic anemia explains the responsiveness of the disease to immunosuppressive therapy.[18]

Genetic predisposition can also influence the development of drug-induced aplastic anemia.[20] Pharmacogenetic research to identify patients who are abnormal metabolizers of drugs can increase the clinician's ability to predict the development of aplastic anemia. 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.[20]

Causative Agents

Table e125-1 shows a list of medications that have been associated with drug-induced aplastic anemia. Cytotoxic chemotherapy and radiation therapy can 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 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.

TABLE e125-1

Drugs Associated with Aplastic Anemia

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
Temozolomide
Ticlopidine
MedWatch postmarketing reports 2009-2020
Adalimumab
Aliskirin
Amlodipine
Carvedilol
Dantrolene
Etanercept
Infliximab
Oxcarbazepine
Pembrolizumab
Posaconazole
Valsartan

NSAIDs, nonsteroidal anti-inflammatory drugs.

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, but the overall prevalence has declined with decreased use of this agent.[19] The dose-dependent and idiosyncratic reactions seen with chloramphenicol are not related. Other drugs thought to induce aplastic anemia through toxic metabolites include phenytoin and carbamazepine. The metabolites of these medications 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.[21]

Management of Toxicity

Rapid diagnosis and immediate therapy initiation are important because of the high mortality rate associated with SAA and VSAA. 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 (G-CSF) does not improve outcomes and is not recommended for the management of aplastic anemia except when life-threatening infections are present.[12] Current treatment guidelines for aplastic anemia recommend the use of prophylactic antibiotics and antifungal agents when neutrophil counts are below 500 cells/mm^3 (0.5×10^9/L). If patients experience febrile neutropenia, broad-spectrum intravenous 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 major treatment options for patients with drug-induced aplastic anemia are allogeneic hematopoietic stem cell transplantation (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 donor. For healthy patients younger than 50 years, the treatment of choice is allogeneic HSCT from an HLA-matched sibling donor. This is associated with potential cure and results in a 5-year survival rate of 77% in adults and up to 90% in children.[12,22,23] Unfortunately, most patients do not have a matched sibling donor and so allogeneic HSCT from an HLA-matched unrelated donor may be considered, but it is usually reserved for those who fail prior 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.[24,25] For patients older than 50 years and for those who are not candidates for transplant due to comorbidities or no available match, the preferred first-line therapy is immunosuppressive therapy.[12] 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 standard immunosuppressive regimen for the treatment of MAA that does not respond to supportive care is combination therapy with antithymocyte globulin (often referred to as ATG) and cyclosporine. This combination has been reported to achieve 5-year survival rates between 75% and 85%, but the response rate in older individuals is lower.[26] Although cyclosporine monotherapy has been used to treat MAA, the combination of these agents increase response rate, improve failure-free survival, and reduce the number of immunosuppressive courses needed.[27,28] Cyclosporine inhibits interleukin-2 production and release and subsequent activation of resting T cells. Cyclosporine dosing has varied from 4 to 6 mg/kg/day to 10 to 12 mg/kg/day, with the most frequently reported initial dose of 5 mg/kg/day in two divided doses. Cyclosporine doses are titrated to a target blood concentration that can be patient- and institution-specific but is usually in the range of 150 to 250 µg/L (125-208 nmol/L) for adult patients. Cyclosporine should be continued for at least 12 months after response and then tapered slowly, as increased relapse rates have been observed when tapering rapidly.[26] Antithymocyte globulin is composed of polyclonal immunoglobulin G (IgG) against human T lymphocytes derived from either horses or rabbits and has been a standard component of immunosuppressive therapy for aplastic anemia for many years. In one study comparing the horse versus rabbit product, both given in combination with cyclosporine, treatment with the horse-derived antithymocyte globulin 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 antithymocyte globulin as compared with horse antithymocyte globulin may be associated with adverse outcomes. However, other studies found no difference between formulations.[12,29] Based on these results, treatment with the horse-derived antithymocyte globulin product may be preferred for treatment when available. Because response to immunosuppressive therapy is often delayed (3-4 months), patients require continued supportive care until recovery. Patients should be monitored for ADRs, including serum sickness, which can occur about 1 week after antithymocyte globulin begins.[26]

Corticosteroids are added to antithymocyte globulin-based immunosuppression because of their ability to reduce adverse reactions associated with antithymocyte globulin 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.[22] However, they have not been shown to be superior to the combination of antithymocyte globulin and cyclosporine, and their place in therapy is not clearly defined. In the case of refractory or relapsed disease, a second cycle or an alternative agent, such as alemtuzumab or high-dose

cyclophosphamide, may be able to achieve a remission rate of 50%.[12]

The addition of G-CSF to the combination of antithymocyte globulin and cyclosporine results in high response rates but does not prolong survival as compared with antithymocyte globulin and cyclosporine.[28,30-32] However, one study indicated that in patients receiving this combination, the neutrophil count on day +30 predicted response and survival.[32] This may allow for early recognition of those patients who are not likely to respond to therapy and lead to earlier transplants in those affected.[33] Eltrombopag, a thrombopoietin nonpeptide agonist, is used as first-line therapy in the treatment of SAA in combination with antithymocyte globulin and cyclosporine. In one study in 88 patients, the response rate at 6 months was 85% and survival approached 90%.[34] Another trial showed similar response rates at 6 months, and at a median follow-up of 2 years, had a survival rate of 97%.[35] Initial dose is 50 mg orally once daily and is titrated based on platelet response. Initially, the dose is 150 mg orally once daily and is titrated based on platelet response; however, patients of Asian ethnicity should be initiated at a dose of 75 mg once daily. This is due to an increased plasma exposure seen in trials. A review of use in 22 Japanese patients with AA refractory to immunosuppressive therapy found a significant improvement in 47.6% of patients at 6 months. Patients were initiated on a dose of 25 mg once daily, then titrated every 2 weeks to a maximum of 100 mg daily.[36]

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. The incidence ranges from 1.6 to 9.2 cases per million in Europe and 2.4 to 15.4 cases per million in the United States.[37,38] Older patients are thought to be at greater risk for drug-induced agranulocytosis, most likely due to increased medication use.[38,39] Drug-induced agranulocytosis also occurs more frequently in women than in men.

Clinical Presentation

Agranulocytosis is a rare reaction that typically presents with fever. Symptoms arise from the increased infection risk associated with the lack of WBCs and include sore throat, fever, malaise, weakness, and chills. Agranulocytosis may develop 19 to 60 days after exposure of the offending drugs but typical time of onset is at least 1 month after drug initiation. Symptoms may appear either immediately or insidiously, depending on the time course of neutropenia development.[40]

Mechanism

5 The cause of drug-induced agranulocytosis is not fully understood, but two mechanisms—direct toxicity and immune-mediated toxicity—have been proposed. Direct toxicity may be due to either the parent drug or a toxic metabolite or byproduct. Agranulocytosis associated with direct toxicity is usually associated with a slower decline in neutrophils, with a more insidious presentation of symptoms.[41,42] With immune-mediated mechanisms, agranulocytosis occurs within days to a few weeks after drug exposure, with rapid appearance of symptoms.[42] Within the immune-mediated subset of agranulocytosis, three mechanisms of toxicity have been proposed. 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.

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. 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. In all mechanisms, cell destruction occurs via antibody-mediated cell toxicity, complement activation, and phagocytic elimination through the mononuclear phagocytic system.

Causative Agents

A list of medications that have been associated with drug-induced agranulocytosis can be seen in Table e125-2. Antipsychotics, antibiotics, and antithyroid medications are commonly implicated.[43] Nearly all classes of drugs have been associated with some incidence of acute neutropenia or agranulocytosis, but the risk is exceedingly small. The risk may be higher for some drugs, such as antithyroid medications (propylthiouracil and methimazole), ticlopidine, clozapine, sulfasalazine, trimethoprim–sulfamethoxazole, deferapirone, and β-lactam antibiotics. Mechanisms associated with selected agents can be seen in Table e125-3.

TABLE e125-2

Drugs Associated with Agranulocytosis

Observational Study Evidence	Case Report Evidence (*Probable* or *Definite* Causality Rating)		MedWatch Postmarketing Reports 2009-2020
β-Lactam antibiotics	Acetaminophen	Levodopa	Amlodipine
Carbamazepine	Acetazolamide	Meprobamate	Bocepravir
Carbimazole	Ampicillin	Methazolamide	Clozapine
Clomipramine	Aripiprazole	Methyldopa	Defarasirox
Digoxin	Captopril	Metronidazole	Fluoxetine
Dipyridamole	Carbenicillin	Nafcillin	Haloperidol
Ganciclovir	Cefepime	NSAIDs	Hydrochlorothiazide
Glyburide	Cefotaxime	Octreotide	Iacosamide
Gold salts	Ceftriaxone	Olanzapine	Ibrutinib
Imipenem–cilastatin	Cefuroxime	Oxacillin	Leflunomide
Indomethacin	Chloramphenicol	Penicillamine	Levitiracetam
Macrolide antibiotics	Chlorpromazine	Penicillin G	Linezolid
Methimazole	Chlorpropamide	Pentazocine	Memantine
Mirtazapine	Chlorpheniramine	Phenytoin	Metformin
Phenobarbital	Clindamycin	Primidone	Molindone
Phenothiazines	Clozapine	Procainamide	Olanzapine
Prednisone	Colchicine	Propylthiouracil	Oseltamivir
Propranolol	Doxepin	Pyrimethamine	Oxcarbazepine
Spironolactone	Dapsone	Quinidine	Paliperidone
Sulfonamides	Desipramine	Quinine	Pantoprazole
Sulfonylureas	Ethacrynic acid	Rifampin	Pimozide
Ticlopidine	Ethosuximide	Streptomycin	Propafenone
Valproic acid	Flucytosine	Terbinafine	Quetiapine

Zidovudine	Gentamicin	Ticarcillin	Rifabutin
	Griseofulvin	Tocainide	Risperidone
	Hydralazine	Tolbutamide	Rituximab
	Hydroxychloroquine	Valganciclovir	Sulfasalazide
	Imipenem–cilastatin	Vancomycin	Thiothixene
	Imipramine		Tocilizumab
	Lamotrigine		Trandolapril
			Ustekinumab
			Ziprasidone

NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE e125-3

Mechanisms of Drug-Induced Agranulocytosis

Direct Toxicity to Myeloid Cells	Hapten Mechanism	Immune Complex Mechanism	Autoimmune Mechanism
Chlorpromazine	Aminopyrine	Quinine	Levisamole
Procainamide	Penicillin	Quinidine	
Clozapine	Gold compounds		
Dapsone			
Sulfonamides			
Carbamazepine			
Phenytoin			
Indomethacin			
Diclofenac			

The mechanism by which antithyroid agents cause agranulocytosis is unknown, but antineutrophil cytoplasmic antibodies have been identified.[44] Agranulocytosis occurs more frequently in patients older than 40 years and within 2 months after the initiation of therapy. Although a possible dose-response relationship has been reported,[45] agranulocytosis has been associated with long-term low doses of propylthiouracil and methimazole treatment.[46] Recent studies have identified genetic variants associated with the development of antithyroid drug-induced agranulocytosis in several different ethnic groups.[47] Genome-wide association studies have shown an association between agranulocytosis induced by antithyroid drugs and the HLA alleles *HLA-B*38:02* and *HLA-DRB1*08:03* in ethnic Chinese.[48] In a study in white European adults, agranulocytosis associated with antithyroid drug

use was associated with *HLA-B*27:05*.[49] Additional investigations have associated agranulocytosis with these drugs in Taiwanese (*HLA-B*38:02* and *HLA-DRBI*0803*) and Vietnamese (*HLA-B*38:02*) populations.[50,51] These findings may help clinicians in the future to better monitor and manage therapy in those requiring antithyroid medications.

Ticlopidine produces neutropenia in about 2.4% and agranulocytosis in 0.8% of patients, possibly by inhibiting hematopoietic progenitor stem cells.[52] Agranulocytosis associated with ticlopidine most commonly occurs within 1 to 3 months from the initiation of the drug.

Clozapine is associated with a significantly higher risk of agranulocytosis compared with other antipsychotic medications.[53] Because of the frequency and seriousness of this effect and its reversible nature if detected early, clozapine is only available through a limited distribution program that requires strict monitoring of WBC count.[54]

The phenothiazine class of drugs is known to cause drug-induced agranulocytosis by the immune-complex mechanism. When the bone marrow from a patient with phenothiazine-induced agranulocytosis is examined, it initially has no cellularity (aplastic), but it eventually becomes hyperplastic. It is believed that the 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.[55] 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.[56]

Penicillin derivatives may suppress WBCs by several mechanisms. Although the hapten mechanism is suspected to be the cause of penicillin-induced agranulocytosis because of the rapid onset of symptoms and the dose-related phenomenon, a second mechanism could possibly be involved. 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.[57]

Management of Toxicity

6 Removal of the drug is the best treatment option, with blood cell counts usually returning to normal within 2 to 4 weeks. Sargramostim (granulocyte-macrophage colony-stimulating factor, or GM-CSF) and filgrastim (G-CSF) shorten the duration of neutropenia, length of antibiotic therapy, and hospital length of stay.[58] Although the use of both agents has been reported in the literature, a commonly used regimen is G-CSF 300 µg/day via subcutaneous injection. 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.

The overall mortality rate of agranulocytosis has fallen dramatically over the past 20 years largely because of improvements in infection prophylaxis and supportive care.[37,40] The mortality rate is highest among older individuals and patients with renal failure, bacteremia, or shock at the time of diagnosis.[37,39-41] 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.[40] Restarting the drug is not usually recommended. 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 recurrence of drug-induced agranulocytosis.[59]

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 in the spleen and liver. The process of premature red blood cell (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 the exact incidence has been difficult to ascertain because of difficulty in establishing a clear diagnosis and relationship to a specific agent.[60]

Clinical Presentation

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. Patients may present with abdominal pain, lumbar pain, or red urine as a result of hemolysis.[61]

Diagnosis

The best means to diagnose drug-induced immune hemolytic anemia is with the direct Coombs test (or direct antiglobulin test [DAT]), which identifies foreign immunoglobulins either in the patient's serum or on the RBCs themselves. The direct Coombs test involves combining the patient's RBCs with antiglobulin serum. This serum is created by injecting rabbits with preparations of human complement, crystallizable fragment (of immunoglobulin [Fc]), or immunoglobulins. The rabbits then produce antibodies against human immunoglobulins and complement, which becomes the antiglobulin serum. In a drug-induced process, the patient's RBCs are coated with antibody or complement and the antibodies in the antiglobulin serum attach to the separate RBCs, creating a lattice formation called agglutination.[62] This agglutination is considered positive for the presence of IgG or complement on the cell surfaces.

An indirect Coombs test can identify the presence of 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. This process is important in blood bank procedures.

Mechanism

5 The mechanism of drug-induced hemolytic anemia can be divided into two categories, immune or metabolic (ie, oxidative).

Immune

In immune hemolytic anemia, IgG, immunoglobulin M (IgM), or both bind to antigens on the surface of RBCs and initiate their destruction through the complement and mononuclear phagocytic systems.[63] Immunologic mechanisms can be either drug dependent or independent.[64]

Drug Dependent

The drug-dependent mechanism is most common and involves the formation of antibodies directed against RBCs. In this scenario, antibodies are only present when the drug itself is present.[64]

Four mechanisms have been proposed to explain how drugs can induce immune hemolytic anemia; these are similar to those proposed for drug-induced agranulocytosis.[65]

The first mechanism is the "hapten mechanism" or "drug adsorption" mechanism. Haptens are drugs or molecules that cause an immune response when they bind to a protein in the body. 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.[65] 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 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.[65] 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 mechanism is associated with acute intravascular hemolysis that can be severe, sometimes leading to hemoglobinuria and renal failure. After clearance of the drug from the circulation, the direct Coombs test result will become negative.

The third mechanism involves the production of true RBC autoantibodies. The mechanism for autoantibody production is poorly understood, although two hypotheses have been proposed.[66] The first suggests that the medication 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. Methyldopa is the prototype drug for this mechanism. About 10% to 20% of patients receiving methyldopa will develop a positive

Coombs test, usually within 6 to 12 months of initiating therapy.[67] However, less 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.[67] Because of the autoantibodies produced, methyldopa is often considered to cause autoimmune hemolytic anemia.[68] It is not known why only some patients develop autoantibodies and why only some of the patients who have autoantibodies develop hemolytic disease.

The fourth mechanism of drug-induced immune hemolytic anemia is through nonimmunologic protein adsorption to RBC membranes.[65] 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.

Drug Independent

Drug-independent mechanisms are also referred to as *in vitro* reactions. With this mechanism, antibodies are present even in the absence of the drug.[65] These are true RBC antibodies and can be the cause of 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.

Metabolic

Metabolic mechanisms of hemolytic anemia are considered to be oxidative. These most often occur in the presence of a glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency). A G6PD deficiency is a disorder of the hexose monophosphate shunt, which is responsible for producing nicotinamide adenine dinucleotide phosphate hydrogen, or 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.[69] Without reduced glutathione, oxidative drugs can oxidize the sulfhydryl groups of hemoglobin, removing them prematurely from the circulation (ie, causing hemolysis).

Causative Agents

Over 130 drugs have indisputable evidence of causing hemolytic anemia. Since 2008, piperacillin is the most commonly reported agent.[60,63] A list of drugs associated with drug-induced immune hemolytic anemia is provided in Table e125-4. Of note, diclofenac, fludarabine, oxaliplatin, and cephalosporins are some of the most frequent offenders.[70] Of these, diclofenac is the most common, but can be especially prone to misdiagnosis.[68] Certain drugs and their responsible mechanisms are listed in Table e125-5. A list of agents associated with drug-induced metabolic hemolytic anemia is presented in Table e125-6.

TABLE e125-4

Drugs Associated with Immune 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
Dabigatran
Dimethyl fumarate

Efavirenz
Erythromycin
Etoricoxib
Hydrochlorothiazide
Indinavir
Interferon alfa
Iomeprol
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
Vancomycin

MedWatch Postmarketing reports 2009-2020

Amlodipine
Bevacizumab
Chlorpropamide
Deferasirox
Fludarabine
Pegademase
Pioglitazone
Rosiglitazone

NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE e125-5

Mechanisms of Drug-Induced Hemolytic Anemia

Hapten Mechanism	Innocent Bystander (Immune Complex) Mechanism	Red Blood Cell Autoantibodies Mechanism	Nonimmunologic Protein Adsorption Mechanism
Cefotetan	Ceftriaxone	Methyldopa	Beta-lactamase inhibitors
Piperacillin		Fludarabine	Cisplatin
Minocycline		Cladribine	Oxaliplatin
Tolbutamide			
Streptomycin			

TABLE e125-6

Drugs Associated with Metabolic 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

Management of Toxicity

The treatment of drug-induced immune hemolytic anemia includes the immediate removal of the offending agent and supportive care. The severity of the reaction depends on the rate of hemolysis.

Immune

Immune 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) can have a sudden onset, lead to severe hemolysis, and result in renal failure. In the metabolic mechanism, 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 the prescribed quantities of the suspected drug.[69] Although severe hemolysis is rare, any drug that places oxidative stress on RBCs can cause drug-induced metabolic hemolytic anemia.

Glucocorticoids can be helpful in severe cases, but their use outside of autoimmune hemolytic anemia is not supported by strong evidence.[71] Other agents such as rituximab and IgG treatments have been used, but their role is yet to be clearly defined.[72-74] Patients experiencing hemolytic anemia from cephalosporins should be advised to avoid all agents in the class. Cross-reactivity may occur, and the second episode is likely to be worse than the first.[65]

Metabolic

6 Removal of the offending drug is the primary treatment for drug-induced metabolic hemolytic anemia. No other therapy is usually necessary because most cases are mild in severity. Patients with known G6PD enzyme deficiencies should be advised to avoid medications capable of inducing 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. However, megaloblastosis can result from any interference with the synthesis of purines, pyrimidines, or protein.[75]

Diagnosis

Examination of peripheral blood shows an increase in the mean corpuscular hemoglobin concentration. Some patients can have a normal-appearing cell line, and the diagnosis must be made by measurement of vitamin B_{12} and folate concentrations. These megaloblastic changes are caused by the direct or indirect effects of the drug on DNA synthesis. The abnormality can be seen in any portion of the replication process, including DNA assembly, base precursor metabolism, or RNA synthesis.[75]

Causative Agents

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.[76] Other drugs, such as cotrimoxazole, phenytoin, and barbiturates, have also been implicated in megaloblastic anemia. Cotrimoxazole, at both low and high doses, can cause drug-induced megaloblastic anemia,[77,78] particularly in patients with a partial vitamin B_{12} or folate deficiency. 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 either by inhibiting folate absorption or by increasing folate catabolism. In both instances, the patient develops a relative folate deficiency. A list of drugs that have been implicated as causative factors in drug-induced megaloblastic anemia is given in Table e125-7.

TABLE e125-7

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
MedWatch Postmarketing reports 2009-2020
Adalimumab
Aripiprazole
Carbamazepine
Esomeprazole
Metformin
Risperidone
Rivaroxaban
Telaprevir

Management of Toxicity

When drug-induced megaloblastic anemia occurs following chemotherapy, the anemia occurs rapidly, is considered an accepted ADR of therapy, and will resolve after removing the causative agent. If drug-induced megaloblastic anemia results from impairment of cellular availability or use of folic acid or vitamin B_{12}, supplementation with adequate amounts of these agents is indicated.[75] In cases of cotrimoxazole-induced megaloblastic anemia, a trial course of folinic acid, 5 to 10 mg up to four times a day, can correct the anemia.[77,78] Folic acid supplementation of 1 mg daily 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 these medications.[79]

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.

Epidemiology

The annual incidence of drug-induced thrombocytopenia is about 10 cases per 1,000,000 population (excluding cases associated with heparin).[80] An increased incidence has been reported in older individuals, critically ill, and those exposed to sulfamethoxazole–trimethoprim, quinine, and GPIIb/IIIa inhibitors.[81] 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; however, a retrospective cohort analysis found that increased severity of thrombocytopenia was more likely in patients with sickle cell disease, malnutrition, infection, and tobacco, antibiotic, diuretic, or proton-pump inhibitor use.[82]

Heparin-induced thrombocytopenia has garnered much attention. Certain patient populations have a higher risk of developing HIT than others; patients older than 50 years and those who have had recent major cardiac or vascular surgery are the highest risk groups.[2,83] A lower risk is seen in patients receiving low-molecular-weight heparin (LMWH) (5/1,000) instead of unfractionated heparin (UFH) ((22/1,000).[83] Case-control and cohort analyses have found an increased burden of autoimmune disease and low albumin, respectively, among patients who develop HIT suggesting a possible link to increased risk in these populations. The most recent practice guidelines by the American Society of Hematology recommend varying degrees of platelet monitoring based on the relative risk of developing HIT.[84]

In 2020, the SARS-CoV2 epidemic revealed a HIT-like syndrome associated with both natural infection and immunization against the virus.[85,86] Positive platelet factor 4 (PF-4) antibodies were found in 6% to 12% of patients positive for SARS-CoV2 compared to 3% in the general population.[85,86] Vaccine-induced immune thrombotic thrombocytopenia (VITT) was established as a cause of cerebral venous thrombosis and other unusual thrombotic complications following vaccination against SARS-CoV2 and has a mechanism similar to HIT.[87] VITT is characterized by thrombosis, thrombocytopenia, and positive PF-4-heparin enzyme-linked immunoassay, or ELISA, and platelet activation assays.[87] Few patients with VITT have known risk factors for thrombosis. It is most frequently reported in women younger than 55 years within the first 16 days following vaccination with AZD1222 or Ad26.COV2.S vaccines, but has also rarely been reported in men, older individuals, up to 4 weeks after vaccination or following receipt of mRNA vaccines.[88]

Clinical Presentation

Drug-induced thrombocytopenia typically presents 1 to 2 weeks after a new drug is initiated, but may present immediately after a dose when an agent has been used intermittently in the past.[89] Rapid onset may also occur with the GPIIb/IIIa inhibitor class of drugs.[90] Development of thrombocytopenia may be associated with the systemic drug concentration, as is the case with linezolid.[91] This condition may be overlooked or misdiagnosed as idiopathic thrombocytopenic purpura (ITP); clinicians may distinguish between the two by the severity of thrombocytopenia (platelets <20,000 cells/mm^3 [20 ×10^9/L]), timing in relation to medication administration, and the presence of bleeding which almost always accompanies drug-induced thrombocytopenia.[90,92]

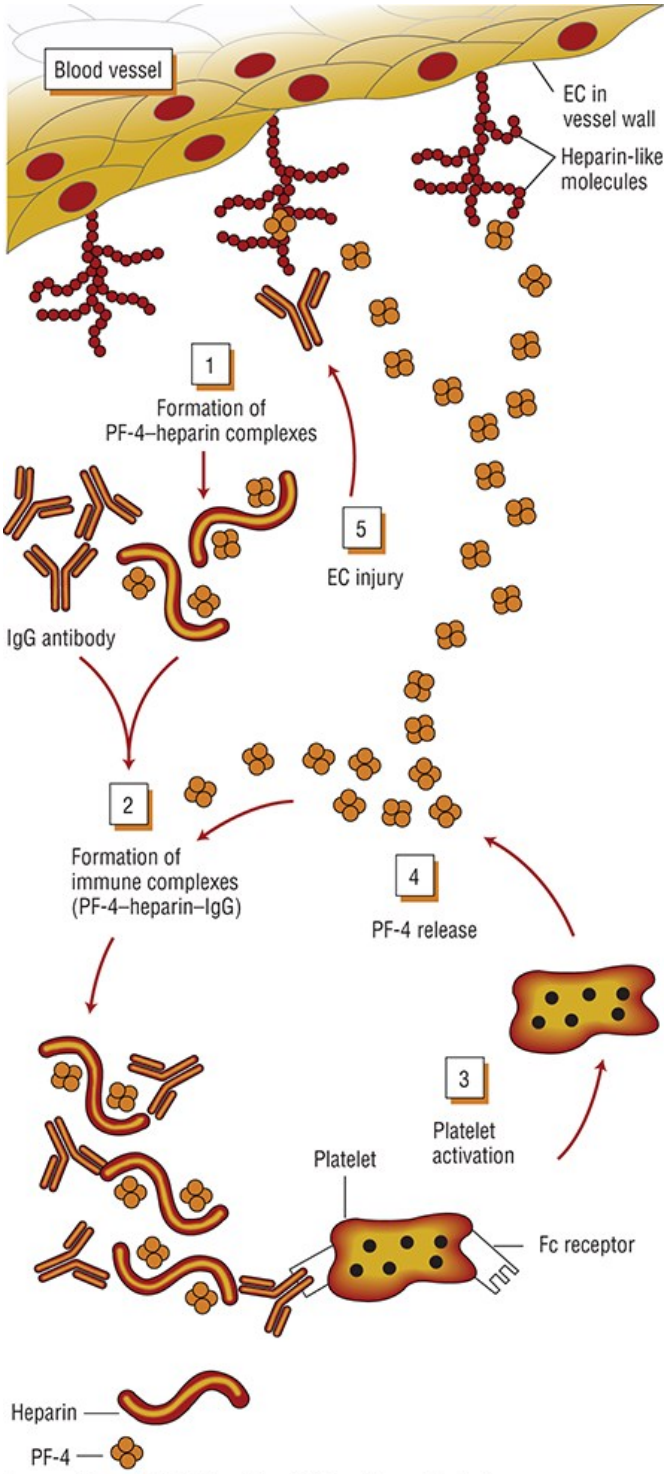
Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia causes paradoxical increases in thrombotic rather than bleeding complications, with about 50% of patients with confirmed HIT developing thromboembolic complications.[93] It is caused by the development of antibodies against PF-4 and heparin complexes (Fig. e125-1).[93] Low-molecular-weight heparin binds 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.[83] 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.[83]

FIGURE e125-1

Heparin-induced thrombocytopenia. Pathogenesis of HIT. IgG is the autoantibody against the heparin–PF4 complex. Platelets can bind to each other and become activated via the IgG–Fc receptor interaction, the PF4–PF4 receptor interaction, or both. Aggregation and thrombus formation may thus occur. Furthermore, IgG may bind to the endothelial cell–bound heparin–PF4 construct and cause vascular damage, which may also provoke thrombus

formation. *(Reproduced, with permission, from Hammer GD, McPhee SJ. Pathophysiology of Disease: An Introduction to Clinical Medicine. 8th ed. New York: McGraw Hill; 2019.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

At least two types of HIT have been identified, spontaneous and delayed onset, but the true incidence has not been well established.[83] Patients with HIT type II usually present with a low platelet count (eg, below 150,000 cells/mm^3 [150 × 10^9/L]) or a 50% or more decrease in platelet count from the

highest platelet count value after initiation of heparin, and thrombosis may be present at diagnosis.[93] 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 received heparin (ie, within 100 days).[93] Major surgery can function as a reset for the window of developing HIT, and HIT may occur within 5 to 10 days after surgery despite previous exposures.[93] Thrombocytopenia and thrombosis can develop with low-dose heparin, heparin-coated catheters, or even heparin flushes.[93]

The diagnosis of HIT is made using a combination of clinical and laboratory assessments. Clinicians should use a scoring system, such as the 4T scoring system, to evaluate the probability of HIT.[93] Such a system should evaluate timing and magnitude of platelet drop, thrombosis, and other potential causes of thrombocytopenia.[93] If the scoring system indicates that HIT is possible or likely, the clinician should order laboratory tests, as HIT is difficult to exclude or confirm with only clinical information. Tests such as platelet activation assays, platelet aggregation studies, and enzyme-linked immunosorbent assay methods each have varying sensitivities and specificities and assist in the diagnosis of HIT.[7,10] Overall, these tests have a high negative predictive value.[93]

Protamine is an agent often used to neutralize heparin's anticoagulant action. Protamine-induced thrombocytopenia may be confused with HIT, since patients may have exposure to both agents. In protamine-induced thrombocytopenia, antibodies activate platelets similar to those in HIT, but it often occurs after cardiovascular surgery and is associated with earlier onset of thrombocytopenia and thrombosis, compared with the 5 to 10 day delay usually seen with HIT.[94]

Vaccine-Induced Thrombotic Thrombocytopenia

Vaccine-induced thrombotic thrombocytopenia (VITT) may also be confused with HIT. It may present with thrombotic complications or symptoms including headache, abdominal pain, nausea and vomiting, vision changes, shortness of breath, and/or leg swelling and pain.[88] It typically occurs within 4 to 20 days following vaccination, and patients may be critically ill before thrombocytopenia is discovered. Although the presentation may be confused with HIT, patients with VITT have not had prior exposure to heparin. If VITT is suspected, clinicians should use laboratory and imaging assessments to confirm the diagnosis. CBC with platelet count, D-dimer and fibrinogen assays, PF-4 antibody testing and imaging such as ultrasounds as needed to diagnosis thrombosis should be gathered for the initial work up. Patients with confirmed thrombosis or severe symptoms accompanied by thrombocytopenia and high D-dimers may be treated presumptively while awaiting confirmatory testing for PF-4 antibodies.

Mechanism

5 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 dose dependent and often takes weeks to manifest.[90] Several mechanisms have been proposed for the development of immune-mediated drug-induced thrombocytopenia. These include hapten-type reactions, drug-dependent antibody mechanism, platelet-specific autoantibody, immune complex-induced thrombocytopenia, and drug-specific autoantibody type reaction. 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.

Hapten-Type Reactions

In hapten-type reactions, the offending drug binds covalently to certain platelet glycoproteins (GP). 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.[95,96] Platelets are destroyed by the autoantibodies.[90] 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.

Drug-Dependent Antibody

This mechanism is slightly different from the hapten-type mechanism. In this type of reaction, platelet-reactive antibodies bind platelets when the drug is present. The antibodies may occur naturally, but there is an increased affinity if the drug is present. Reactions typically occur after 5 to 10 days of therapy.[90] 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 between the antibody and the platelet surface, with the drug "trapped" in-between, resulting in antibody binding of platelet.[95]

Eptifibatide and tirofiban are platelet GPIIb/IIIa receptor antagonists that prevent platelet activation and binding of fibrinogen, thereby inhibiting platelet thrombus formation. Competitive inhibition of fibrinogen binding causes platelet clearance and activation, so concomitant thrombosis may occur.[90] In clinical trials and postmarketing studies, about 0.1% to 2% of patients treated with these medications experience acute profound thrombocytopenia within several hours of their first exposure to the drug.[95-97] 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 (ie, a ligand-induced binding site). In contrast to the two previously discussed immune-mediated mechanisms, 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.[96]

Abciximab, a GPIIb/IIIa receptor antagonist like tirofiban and eptifibatide, is also associated with thrombocytopenia. Abciximab-induced thrombocytopenia occurs through a different drug-specific antibody mechanism as opposed to a ligand-induced binding site mechanism with eptifibatide and tirofiban.[95-97] Abciximab is a chimeric monoclonal antibody. Therefore, it is not surprising that this molecule may exhibit some immunogenic properties. The murine component binds platelets' surface proteins and attracts antibodies that then destroy the platelet.[90] It has been demonstrated that patients who experience thrombocytopenia after the administration of abciximab have circulating antibodies that directly recognize the drug.[95,96] 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.[98] 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.[99] Since all three GPIIb/IIIa receptor antagonists are coadministered with heparin, it is important to distinguish between GPIIb/IIIa receptor antagonist-induced thrombocytopenia and HIT. A heparin-induced platelet aggregation study can help the clinician 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.[100] This type of reaction may also occur with rituximab, and may be complicated by infusion reactions and disseminated intravascular coagulopathy (DIC).[90]

Platelet-Specific Autoantibody

In this type of reaction, a drug, such as gold or procainamide, 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. These autoantibodies can persist after discontinuation of the agent. Reports of thrombocytopenia up to 39 months after exposure have been published.[90] In contrast, the drug-dependent antibody reaction requires the presence of the drug to allow antibody binding.

Immune Complex

The final type of immune-mediated thrombocytopenia has been categorized as immune complex-induced thrombocytopenia.[95,96] This describes the mechanism of the most serious type of HIT, type II. HIT type II is less common but more severe than HIT type I and can be associated with more complications. In this type of reaction, heparin binds the platelet and forms an antigenic structure, which is then bound by antibodies. This complex activates the platelets.[93] HIT has been reported to occur in 1 of every 5,000 hospitalized patients and in 1% to 3% of patients after cardiac surgery. The risk is higher following major surgery than minor surgical procedures or medical treatment, and may be up to 10 times higher for those receiving UFH as compared to LMWH.[93]

A similar mechanism is seen in VITT, where vaccination leads to endogenous production of antibodies which cross-react to bind to PF-4 in the same

manner as heparin.[88]

Causative Agents

The first systematic review of the literature and case reports associated with drug-induced thrombocytopenia were published in 1998.[101] At that time, 98 drugs were reported to be associated with thrombocytopenia. The Oklahoma group has continued to update this systematic review nearly every 2 years since 1998.[102] As of 2018, 339 drugs had been implicated in thousands of reports through 2014.[103] It has also been reported with foods, such as walnuts, cranberries, milk, and sesame seed.[104] The FAERS Public Dashboard reveals that reports of drug-induced thrombocytopenia have been increasing over the past 2 decades with 4,725 cases and 802 associated deaths in 2021.[105] One study found that only about 40% of implicated agents had a positive laboratory test, and only 10% should be considered definite causes.[90] This condition is more common in adults than children but may not be recognized in children. Thirty-one medications have been noted as definite or probable causes of thrombocytopenia in children.[92]

According to one analysis, carbamazepine, eptifibatide, ibuprofen, quinine, quinidine, oxaliplatin, rifampin, vancomycin, and sulfamethoxazole–trimethoprim are the agents most frequently associated with drug-induced thrombocytopenia.[81] The agents most commonly implicated in immune-mediated thrombocytopenia are quinine, quinidine, gold salts, sulfonamide antibiotics, rifampin, GPIIb/IIIa receptor antagonists, vancomycin, and heparin.[90,96] A list of medications (excluding cancer chemotherapeutic agents) associated with drug-induced thrombocytopenia is provided in Table e125-8.

TABLE e125-8

Drugs Associated with Thrombocytopenia

Observational study evidence	Isotretinoin	Ado-trastuzumab
Carbamazepine	Itraconazole	Alfuzosin
Oxaliplatin	Levamisole	Aliskirin
Phenobarbital	Levetiracetam	Amlodipine
Phenytoin	Levofloxacin	Benazapril
Valproic acid	Linezolid	Bocepravir
Case report evidence (*probable* or *definite* causality rating)	Lithium	Bortezomib
	Intravenous immunoglobulin-weight heparins	Chlorambucil
Abciximab	Lurasidone	Cladribine
Acetaminophen	Measles, mumps, and rubella vaccine	Cotrimoxazole
Acyclovir	Meclofenamate	Dalteparin
Albendazole	Mesalamine	Dantrolene
Aminoglutethimide	Methyldopa	Deferasirox
Aminosalicylic acid	Minoxidil	Didanosine
Amiodarone	Morphine	Drotecogin alfa
Amphotericin B	Moxifloxacin	Efalizumab
Ampicillin	Nalidixic acid	Eltrombopag
Aspirin	Naphazoline	Enoxaparin
Atezolizumab	Naproxen	Epirubicin
Atorvastatin	Nitroglycerin	Epoprostenol
Bevacizumab	Octreotide	Eptifibatide
Bisoprolol	Olanzapine	Ethionamid
Capecitabine	Olmesartan	Filgrastim
Captopril	Oseltamivir	Fondaparinux
Chlorothiazide	Oxacillin	Glimepiride
Chlorpromazine	*p*-Aminosalicylic acid	Heparin
Chlorpropamide	Pantoprazole	Hydrochlorothiazide

Cimetidine	Penicillamine	Indomethacin
Ciprofloxacin	Pentamidine	Iloprost
Clarithromycin	Pentoxifylline	Interferon beta 1a
Clopidogrel	Piperacillin	Leflunomide
Dabigatran	Primidone	Losartan
Danazol	Procainamide	Montelukast
Deferoxamine	Pyrazinamide	Obinutuzumab
Diazepam	Quinidine	Octreotide
Diazoxide	Quinine	Oxcarbazepine
Diclofenac	Ranitidine	Palivizumab
Diethylstilbestrol	Recombinant hepatitis B vaccine	Pamidronate
Digoxin	Red Bush Tea (Rooibos)	Pemetrexed
Ethambutol	Rifampin	Pioglitazone
Enzalutamide	Rivaroxaban	Pomalidomide
Felbamate	Sevoflurane	Propylthiouracil
Fenofibrate	Simvastatin	Quinine
Fluconazole	Sirolimus	Raltegravir
Fondaparinux	Sulfasalazine	Rosiglitazone
Gabapentin	Sulfonamides	Rosuvastatin
Gold salts	Sulindac	Spironolactone
Haloperidol	Tacrolimus	Sunitinib
Heparin	Tamoxifen	Telmisartan
Hydrochlorothiazide	Tolmetin	Torsemide
Ibuprofen	Trastuzumab	Trepostinil
Inamrinone	Trimethoprim	Ursodiol
Indinavir	Vancomycin	
Indomethacin	**MedWatch postmarketing reports 2009-2020**	
Interferon alfa-2b	Acarbose	
Isoniazid	Adalimumab	

Management of Toxicity

The primary treatment of drug-induced thrombocytopenia is immediate 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 experts recommend it in severe cases.[106] Corticosteroids are sometimes helpful when clinicians are initially trying to distinguish between drug-induced thrombocytopenia and ITP. Clinicians may also consider the use of intravenous immunoglobulin, especially in severe illness, although data is limited.[90] Platelet transfusions may be used if severe bleeding is present.[90]

Heparin-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.[93] Direct thrombin inhibitors are the traditional alternative; however, newer data increasingly supports use of fondaparinux and direct oral anticoagulants (DOACs) as viable options. A 2021 comprehensive systemic review and meta-analysis of 4,698 patients' data found similar safety and efficacy among multiple alternative agents, including argatroban, bivalidrudin, fondaparinux, DOACs, and danaparoid (not available in the United States).[107] The newest of the treatments, DOACs, are gaining popularity due to ease of oral administration strong safety and efficacy data and risk of

rare fondaparinux cross-reactivity.[108]

Direct thrombin inhibitors are the alternative anticoagulants traditionally used in current practice. Four direct thrombin inhibitors are available in the United States: argatroban, bivalirudin, desirudin, and dabigatran, but only argatroban and bivalirudin are approved by the FDA for this indication.[93] Argatroban and bivalirudin are IV thrombin inhibitors. Argatroban is preferred for use in renal insufficiency,[83] 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. Bivalirudin is renally metabolized and requires dosage adjustments for patients with renal impairment. Because of this, it may be preferred in those with hepatic impairment. Both agents affect the partial thromboplastin time (PTT) and international normalized ratio (INR), so clinicians should follow labeled dosing protocols when transitioning patients to warfarin.[83,93] Time to therapeutic anticoagulation is faster with argatroban versus bivalirudin.[109] Safe and effective use of direct thrombin inhibitors may be limited by infrequent use, leading to their inappropriate dosing and monitoring, as well as misinterpretations of PTT due to the confounding effect of these agents.[10] Fondaparinux, an anticoagulant pentasaccharide that inhibits factor Xa, d, is not FDA-approved for treatment of HIT but is increasingly considered a primary treatment option.

The most recent guidelines by the American Society of Hematology include fondaparinux with argatroban, bivalirudin, danaparoid, and DOACs as possible treatment options with little evidence to suggest one over another.[84] Fondaparinux may also be considered when the patient is not in the intensive care unit due to ease of subcutaneous administration.[93] 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. Subcutaneous dosage form may not result in cost savings as compared to DOACs. Although DOACs are not FDA-approved for treatment of HIT, they are increasingly being used in clinical practice. DOACs such as apixaban, dabigatran, edoxaban, and rivaroxaban do not react with PF4 or elicit recognition from HIT antibodies, which provides in vitro rationale for their use. Benefits of these agents include the oral dosage forms, rapid onset of action, and the ability to avoid long-term vitamin K antagonist therapy. Published case reports, case series, and prospective studies have evaluated DOAC use in HIT for over 4,500 person-days, and reported an incidence of recurrent thrombosis of 0.43/1,000 person-days. Most of the published data is for rivaroxaban. A 2021 review found that DOACs prevented thrombosis in 98%, while bleeding complications were only found in 3% of patients treated with them.[108] Although data is limited, preliminary evidence supports use of DOACs in the management of HIT. However, additional study is needed to determine their place in therapy and optimal duration of therapy.[10]

Thrombosis can occur in up to 50% of patients with HIT[83] and is often the precipitating factor that leads to the diagnosis. Because the high risk of thrombosis continues for days to weeks after heparin discontinuation and platelet recovery, continued anticoagulation with an alternative agent is essential during this time period.[93] Recovery begins within 1 to 2 days of discontinuation of the offending agent and is complete at 1 week. Antibodies to that agent may persist for years, so patients should be advised to avoid the drug indefinitely.[89] In cases where platelet recovery has not occurred after 5 days, some clinicians recommend considering intravenous immunoglobulin under the hypothesis that it may interrupt platelet activation and lead to more rapid recovery.[110,111] One analysis found similar outcomes between patients treated with intravenous immunoglobulin and therapeutic plasma exchanges, another immunomodulatory therapy posited to work by removing the antibody complexes.[112]

Vaccine-Induced Thrombotic Thrombocytopenia

Similar to that of severe HIT, treatment for VITT consists of non-heparin anticoagulation and may have more of a role for intravenous immunoglobulin. Platelet transfusion should be avoided in VITT in the absence of bleeding due to theoretical risk of thrombosis.[88] Steroids may be considered when platelet count is below 50,000/mm^3 [50 × 10^9/L].[113] Low fibrinogen levels are often associated with this condition and should not preclude use of anticoagulation.[88]

CONCLUSION

Drug-induced hematologic disorders are a heterogenous group of conditions which may cause mild to life-threatening illness. Numerous agents have been implicated as likely causing drug-induced hematologic disorders. Reports of these reactions have been increasing with many newly approved biologic and chemotherapeutic agents in use.

ABBREVIATIONS

ADR	adverse drug reaction
CFU	colony-forming unit
DAT	direct antiglobulin test
DIC	disseminated intravascular coagulopathy
DOAC	direct oral anticoagulant
ELISA	enzyme-linked immunoassay
FAERS	FDA Adverse Event Reporting System
Fc	crystalizable fragment (of immunoglobulin)
FDA	US Food and Drug Administration
G6PD	glucose-6-phosphate dehydrogenase
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GP	glycoproteins
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	intravenous immunoglobulin-weight heparin
MAA	moderate aplastic anemia
PF-4	platelet factor-4
RBC	red blood cell
SAA	severe aplastic anemia

UFH	unfractionated heparin
WBC	white blood cell
VITT	vaccine-induced thrombotic thrombocytopenia
VSAA	very severe aplastic anemia

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SELF-ASSESSMENT QUESTIONS

1. The incidence of drug-induced hematologic diseases is best established by use of which method?
   A. Meta-analyses
   B. Phase II trials
   C. Postmarketing surveillance
   D. Randomized controlled trials
2. Initial management of suspected drug-induced thrombocytopenia should include which one as the first step?
   A. Removal of the offending agent
   B. Initiation of argatroban
   C. Order for a stat CBC
   D. Preparation for blood transfusion
3. When is it appropriate to rechallenge a patient with an agent suspected to cause drug-induced hematologic disease in order to confirm the diagnosis?
   A. In stable patients
   B. At the patient's request
   C. When antibiotics are implicated
   D. Rechallenges should be avoided
4. When evaluating drugs as a possible cause of drug-induced hematological disease, clinicians should use which approach?
   A. Employ an ADR probability scale
   B. Expect a definite diagnosis
   C. Rely on laboratory data for confirmation
   D. Rule out agents started in the distant past

5. Which is considered the *most* severe drug-induced hematologic disease?

   A. Agranulocytosis

   B. Aplastic anemia

   C. Hemolytic anemia

   D. Thrombocytopenia

6. When evaluating a patient for possible aplastic anemia, which of the following is the *most likely* cause?

   A. Acetaminophen

   B. Metformin

   C. Phenytoin

   D. Simvastatin

7. In patients with acquired aplastic anemia who are not candidates for HSCT, initial standard treatment includes:

   A. Cyclosporine monotherapy

   B. Cyclosporine and antithymocyte globulin

   C. Cyclosporine, antithymocyte globulin, and eltrombopag

   D. Eltrombopag monotherapy

8. The *most* commonly reported cause of drug-induced hemolytic anemia is

   A. Propylthiouracil.

   B. Phenytoin.

   C. Penicillin.

   D. Piperacillin.

9. HIT can be differentiated from VITT by

   A. Presence of bleeding.

   B. Presence of thrombosis.

   C. Prior heparin exposure.

   D. Presence of PF-4 antibodies.

10. Which of the following drugs is *most likely* to cause megaloblastic anemia?

    A. Methotrexate

    B. Metformin

    C. Clozapine

    D. Doxycycline

11. A patient with recent HIT presents with deep vein thrombosis in the left lower extremity. Initial outpatient treatment should include

    A. Argatroban.

    B. Apixiban.

    C. Enoxaparin.

    D. Warfarin.

12. Which of the following medications are most likely to be associated with direct toxicity on neutrophils, resulting in agranulocytosis?

    A. Penicillin

    B. Quinidine

    C. Sulfonamides

    D. Minocycline

13. Granulocyte colony-stimulating factor should be considered for use if a patient's neutrophil count, due to drug-induced agranulocytosis, falls below

    A. 5,000 cells/mm^3 (5×10^9/L)

    B. 500 cells/mm^3 (0.5×10^9/L)

    C. 1,000 cells/mm^3 (1×10^9/L)

    D. 100 cells/mm^3 (0.1×10^9/L)

14. Which test is *best* used to diagnose drug-induced hemolytic anemia?

    A. Hemoglobin

    B. Direct Coombs

    C. Reticulocyte count

    D. Red blood cell count

15. Treatment of drug-induced megaloblastic anemia should start with which of the following?

    A. Initiation of folinic acid

    B. Removal of the causative drug

    C. Initiation of vitamin B_{12}

    D. RBC transfusion

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Because the incidence of drug-induced hematologic disease is relatively rare, the use of postmarketing surveillance systems such as the FDA MedWatch program is necessary to establish credible reports from practice. (See the "Introduction" section and Key Concept 3 for more information on this concept.)

2. **A.** As with any drug-induced disease, the initial management includes removal of the suspected agent. Blood transfusion is not always necessary. Argatroban is only appropriate in heparin-induced thrombocytopenia (HIT). CBC may be rechecked, but should wait until after withdrawal of suspected agent. (See the Management of Toxicity portion of the "Heparin-Induced Thrombocytopenia" section and Key Concept 6 for more information on this concept.)

3. **D.** Rechallenging is not recommended due to the potential for life-threatening and/or dangerous complications. In vitro studies are often available to help determine causality. (See the "Introduction" section and Key Concept 4 for more information on this concept.)

4. **A.** Definitive diagnosis is difficult without a rechallenge. In the absence of a rechallenge, algorithms are useful to help determine the likelihood of an individual medication having caused the reaction. Laboratory data may be helpful but cannot always confirm diagnosis. (See the "Introduction" section for more information on this concept.)

5. **B.** Aplastic anemia is considered most severe, due to complications that can arise from the depletion of all blood cell lines. Rapid diagnosis and immediate treatment is crucial because of the high mortality rate. (See the "Drug-Induced Aplastic Anemia" section for more information on this concept.)

6. **C.** Cytotoxic agents such as antineoplastic therapy are well-known common causes; however, other agents such as phenytoin induce aplastic anemia through the production of a toxic metabolite. (See the Causative Agents portion of section "Drug-Induced Aplastic Anemia" for more information on this concept.)

7. **C.** The triple combination of cyclosporine, antithymocyte globulin, and eltrombopag has been more effective in achieving the best balance of outcomes and toxicity in adults with severe aplastic anemia, compared to other immunotherapy options. (See the Management of Toxicity portion of section "Drug-Induced Aplastic Anemia" for more information on this concept.)

8. **D.** While over 100 different medications have been linked to causing hemolytic anemia, the most commonly reported drug is piperacillin. (See the Causative Agents portion of section "Drug-Induced Hemolytic Anemia" for more information on this concept.)

9. **C.** Bleeding, thrombosis, and PF-4 antibodies may be present in both HIT and VITT. The syndromes are similar in presentation and distinguished only by prior exposure to heparin in HIT. (See the Epidemiology and Clinical Presentation portion of section "Drug-Induced Thrombocytopenia" for more information on this concept.)

10. **A.** The antimetabolite class is the most common cause of megaloblastic anemia due to their action on DNA replication. Methotrexate is associated with the development of megaloblastic anemia in up to 9% of patients. (See the Causative Agents portion of section "Drug-Induced Megaloblastic Anemia" for more information on this concept.)

11. **B.** DOACs, including apixaban, are a first-line option in patients with HIT who are not in the ICU setting. Argatroban would not be used in the outpatient setting due to its IV formulation. Enoxaparin should not be used in patients with HIT and warfarin should not be used in the initial treatment because it could worsen thrombosis. (See the Management of Toxicity portion of section "Heparin-Induced Thrombocytopenia" for more information on this concept.)

12. **C.** Sulfonamides are known to have direct toxicity to myeloid cells. Penicillin acts through the Hapten mechanism, quinidine through an immune-complex mechanism, and minocycline is not associated with agranulocytosis. (See Table e125-4 for more information on this concept.)

13. **D.** The use of growth-factors in the management of agranulocytosis is appropriate when the patient's neutrophils are less than 100 cells/mm^3 (0.1×10^9/L). This is considered standard of care among most clinicians. (See the Management of Toxicity portion of section "Drug-Induced Agranulocytosis" for more information on this concept.)

14. **B.** The Direct Coombs test identifies foreign immunoglobulins by combining a patients' RBCs with antiglobulin serum. It is the standard of practice for the diagnosis of drug-induced hemolytic anemia. The other choices here are not specific enough for a definitive diagnosis. (See the Diagnosis portion of section "Drug-Induced Hemolytic Anemia" for more information on this concept.)

15. **B.** As with all drug-induced hematologic diseases, removal of the causative agent is the first essential step, central to initial treatment. In addition,

for drug-induced megaloblastic anemia, the addition of folinic acid or vitamin B_{12} may be helpful to correct the anemia. (See the Management of Toxicity portion of section "Drug-Induced Megaloblastic Anemia" for more information on this concept.)