Thrombocytopenia in the Intensive Care Unit and After Solid Organ Transplantation

8

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Abbreviations

CMV	Cytomegalovirus
CPB	Cardiopulmonary bypass
DIC	Disseminated intravascular coagulation
DITP	Drug-induced immune thrombocytopenia
EBV	Epstein–Barr virus
ECMO	Extracorporeal membrane oxygenation
GVHD	Graft-versus-host disease
HHV	Human herpes virus
HIT	Heparin-induced thrombocytopenia
HPA	Human platelet antigen
HPS	Hemophagocytic syndrome
ICU	Intensive care unit
IL	Interleukin
ITP	Immune thrombocytopenia
PCR	Polymerase chain reaction
PTLD	Post-transplant lymphoproliferative disorder
PTP	Posttransfusion purpura
SOT	Solid organ transplantation
TMA	Thrombotic microangiopathy
VAD	Ventricular assist device
VZV	Varicella zoster virus

Introduction

Thrombocytopenia may arise from a diversity of mechanisms and etiologies (Table 8.1). In this chapter, we review the causes of, diagnostic approach to, and management of thrombocytopenia in two special populations: patients with critical illness and those who have undergone solid organ transplantation (SOT). Although such patients may be subject to any of the causes of thrombocytopenia that afflict individuals in other settings, herein we focus on etiologies of particularly high prevalence and/or clinical importance in the intensive care unit (ICU) and post-transplant settings.

Thrombocytopenia in the Intensive Care Unit

You are asked to urgently evaluate a 77-year-old woman with end-stage renal disease for the acute onset of severe thrombocytopenia and gastrointestinal bleeding. She was admitted to the hospital 10 days ago for methicillin-resistant *Staphylococcus aureus* bacteremia associated with her tunneled dialysis catheter. The catheter was replaced,

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Table 8.1 Selected mechanisms and etiologies of thrombocytopenia

Pseudothrombocytopenia
Dilutional thrombocytopenia
Disorders of decreased platelet production
Congenital thrombocytopenias
Myelosuppressive therapy (e.g., radiation, chemotherapy)
Ethanol toxicity
Folate or vitamin B12 deficiency
Primary bone marrow disorders (e.g., myelofibrosis, myelodysplasia, leukemia)
Infiltrative diseases of the bone marrow
Certain viral infections (e.g., HIV, Epstein–Barr virus)
Hepatic insufficiency
Splenic sequestration
Portal hypertension
Infiltrative diseases of the spleen
Disorders of decreased platelet survival
Immune thrombocytopenia
Certain drugs (e.g., heparin, quinine)
Alloimmune thrombocytopenias (e.g., posttransfusion purpura)
Disseminated intravascular coagulation
Infection/sepsis
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
Extracorporeal circuits and intravascular devices (e.g., cardiopulmonary bypass, intra-aortic balloon pump, ventricular assist device)

and she was initiated on vancomycin with clinical improvement and clearance of blood cultures. During this interval, her platelet count rose from 112×10^9/L on admission to 247×10^9/L when it was last checked 2 days ago. A red blood cell transfusion was administered 1 week ago. This morning, while awaiting discharge, the patient developed new-onset rectal bleeding and epistaxis. A repeat complete blood count showed a platelet count of 2×10^9/L. The prothrombin time and activated partial thromboplastin time were normal. You recommend immediate platelet transfusion and discontinuation of vancomycin and request a peripheral blood smear and testing for anti-human platelet antigen 1a antibodies.

Thrombocytopenia in the outpatient setting is discussed in Chap. 7. Thrombocytopenia in pregnancy is addressed in Chap. 17.

Epidemiology

Thrombocytopenia is traditionally defined as a platelet count less than 150×10^9/L, though some ICU studies have used lower cutoffs. Irrespective of definition, thrombocytopenia is common among patients with critical illness. In a systematic review of 24 studies, thrombocytopenia was present in 8.3–67.6 % of patients on admission to the ICU. Of those with a normal or a supranormal platelet count at admission, an additional 13.0–44.1 % of patients acquired thrombocytopenia during their ICU course (Hui et al. 2011). The large variation in the prevalence and incidence of thrombocytopenia among these studies is likely attributable to differences in patient population and definitions of thrombocytopenia.

Thrombocytopenia is more common in surgical than in medical ICU patients (Greinacher and Selleng 2010). Other independent risk factors for the development of thrombocytopenia include sepsis, organ dysfunction, and a high severity of illness (Hui et al. 2011; Greinacher and Selleng 2010) as measured by a variety of scales including the Acute Physiology and Chronic Health Evaluation (APACHE) score, Simplified Acute Physiology Score (SAPS), and Multiple Organ Dysfunction Score (MODS) (Vanderschueren et al. 2000; Strauss et al. 2002).

Clinical Manifestations

Bleeding

The most common clinical concern in patients with thrombocytopenia is bleeding. Among patients with immune thrombocytopenia (ITP), spontaneous bleeding is rare when the platelet count exceeds $20–30\times10^9$/L (Lacey and Penner 1977). An early study in patients with leukemia also suggested a relationship between bleeding risk and degree of thrombocytopenia (Gaydos et al. 1962). In a Cochrane review of studies

evaluating different platelet transfusion triggers in patients with hematologic malignancies, bleeding rates were similar with thresholds of 10×10^9/L or 20×10^9/L (Estcourt et al. 2012). A recent randomized controlled trial of different platelet doses in patients with chemotherapy-induced thrombocytopenia showed that major bleeding was primarily restricted to individuals with a platelet count of 5×10^9/L or less (Slichter et al. 2010). Therefore, in cancer patients, only severe thrombocytopenia (less than $5–10 \times 10^9$/L) is associated with a clear increased risk of bleeding (Arnold and Lim 2011).

Similar evidence of a relationship between platelet count and bleeding risk in the ICU is scant. Four studies have shown a significantly increased incidence of major bleeding in thrombocytopenic (27.1–39.0 %) compared to non-thrombocytopenic ICU patients (4.1–11.0 %) by univariate analysis (Vanderschueren et al. 2000; Strauss et al. 2002; Chakraverty et al. 1996; Ben Hamida et al. 2003). However, difference in risk between the two groups was no longer statistically significant after adjustment for confounders in the one study that applied multivariate analysis (Ben Hamida et al. 2003).

Based on the recognized importance of platelets in hemostasis, it is probable that thrombocytopenia below a certain threshold is associated with increased bleeding risk in ICU patients. What that threshold is and the magnitude of its contribution to bleeding risk require further study. Additional factors including the etiology of thrombocytopenia; the presence of congenital or acquired platelet dysfunction; coagulopathy due to liver disease, vitamin K deficiency, or hyperfibrinolysis; invasive procedures; acid–base disturbances; and hypothermia also contribute to an individual patient's bleeding risk (Greinacher and Selleng 2010).

Thrombosis

Thrombocytopenia is often used as a justification to withhold pharmacologic thromboprophylaxis in critically ill patients. However, thrombocytopenia cannot be presumed to be protective against thrombosis without an understanding of its etiology. Indeed, several relatively prevalent causes of thrombocytopenia in the ICU such as disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT), and postoperative state are associated with a *heightened* risk of thromboembolism. In an analysis of 408 patients with acute HIT, severity of thrombocytopenia was positively correlated with thrombotic risk (Greinacher et al. 2005).

Mortality

Whatever its cause, thrombocytopenia portends an ominous prognosis in patients with critical illness. At least six studies have shown an increased risk of in-ICU or in-hospital mortality in thrombocytopenic patients by multivariate analysis (OR 2.1–26.2) (Vanderschueren et al. 2000; Stephan et al. 1999b; Brogly et al. 2007; Martin et al. 2009; Vandijck et al. 2010; Caruso et al. 2010).

Select Causes

While critically ill patients are vulnerable to any of the multiplicitous acute and chronic causes of thrombocytopenia that afflict patients in other settings (Table 8.1), most cases of thrombocytopenia in the ICU are acute and arise around the time of or during admission to the ICU. In general, acute thrombocytopenic disorders affecting critically ill patients can be divided into two categories: those arising as a complication of the illness for which the patient is admitted (illness related) and those arising as a complication of management (iatrogenic) (Table 8.2). A brief description of each of these disorders is provided below.

Sepsis

Sepsis is an independent risk factor for thrombocytopenia in the ICU, and thrombocytopenia complicates 14.5–59.5 % of cases of sepsis (Martin et al. 2009; Vandijck et al. 2010; Charoo

Table 8.2 Common and clinically important causes of thrombocytopenia in the ICU

Illness-related causes	Iatrogenic causes
Sepsis	Dilutional thrombocytopenia
Disseminated intravascular coagulation	Drug-induced immune thrombocytopenia
	Heparin-induced thrombocytopenia
	Posttransfusion purpura
	Extracorporeal circuitry/ intravascular devices
	Surgery

ICU intensive care unit

et al. 2009; Lee et al. 1993; Sharma et al. 2007). Although the pathophysiology of sepsis-induced thrombocytopenia is not fully understood, platelet activation and consumption, peripheral immune destruction, marrow suppression, and hemodilution have been postulated (Hui et al. 2011; Kelton et al. 1979). Thrombocytopenia is usually mild or moderate unless a concomitant etiology such as DIC is present. The platelet count is lower in patients with severe sepsis and septic shock than in patients with sepsis without organ dysfunction or hypotension (Mavrommatis et al. 2000). Treatment involves supportive care and antimicrobial therapy.

Disseminated Intravascular Coagulation

DIC is a systemic consumptive thrombocytopenia and coagulopathy. It occurs not in isolation but as a sequela of an underlying disorder, the most common of which include sepsis, trauma and tissue injury, malignancy, and obstetrical complications. DIC complicates approximately 1 % of hospital admissions and a greater proportion of admissions to the ICU (Matsuda 1996). Clinical features include a propensity for both thrombosis due to activation of coagulation and hemorrhage due to depletion of platelets and clotting factors. Laboratory abnormalities of acute DIC include decreased fibrinogen and elevated fibrin degradation products (including D-dimers). Thrombocytopenia is characteristically moderate to severe and may be accompanied by microangiopathic changes on the peripheral blood smear. A platelet count of less than 100×10^9/L is observed in 50–60 % of patients with DIC, whereas 10–15 % of patients have a platelet count less than 50×10^9/L (Stephan et al. 1999a; Hanes et al. 1997). Treatment is aimed at the underlying disorder. Transfusion of platelets and coagulation factors is justified in patients who have major bleeding, have a high risk for bleeding, or require invasive procedures. Cautious use of heparin may be appropriate in select patients with thrombosis or refractory bleeding (Hook and Abrams 2012).

Dilutional Thrombocytopenia

Patients who receive large-volume resuscitation with packed red blood cells and/or intravenous fluids without concomitant platelet administration are at risk for dilutional thrombocytopenia. The degree of thrombocytopenia is related to the volume of fluid administered (Leslie and Toy 1991). In studies of massively transfused subjects, the platelet count ranged from 47 to 100×10^9/L and 25 to 61×10^9/L in patients receiving 15 and 20 units of red cells within a 24-h period, respectively (Leslie and Toy 1991; Counts et al. 1979).

Drug-Induced Immune Thrombocytopenia

The primary mechanism of drug-induced immune thrombocytopenia (DITP) is accelerated platelet destruction caused by drug- or drug metabolite-dependent antibodies (Aster et al. 2009). Antibodies may also target megakaryocytes, resulting in reduced platelet production (Perdomo et al. 2011). An extensive list of drugs has been implicated in DITP (Nguyen et al. 2011). An updated, evidence-based catalog of these agents is available at http://www.ouhsc.edu/platelets. Frequently reported drugs associated with DITP

Table 8.3 Frequently reported drugs associated with DITP

Class	Specific agents
Antibiotics	Beta-lactam antibiotics (especially piperacillin)
	Linezolid
	Rifampin
	Sulfonamides (especially trimethoprim–sulfamethoxazole)
	Vancomycin
Antiepileptics	Carbamazepine
	Phenytoin
	Valproic acid
Glycoprotein IIb/IIIa antagonists	Abciximab
	Eptifibatide
	Tirofiban
Miscellaneous	Gold compounds
	Heparin
	Quinidine
	Quinine

are shown in Table 8.3. Classically, the onset of thrombocytopenia occurs approximately 1–3 weeks after initial exposure to the offending agent (George et al. 1998; Pedersen-Bjergaard et al. 1997), though it may arise rapidly in patients with prior exposure and preformed antibodies. An exception to this rule is thrombocytopenia induced by glycoprotein IIb/IIIa antagonists, which may arise shortly after initial exposure due to the existence of naturally occurring antibodies (Bougie et al. 2002; Berkowitz et al. 1997). Thrombocytopenia in DITP is characteristically severe (median nadir platelet count 11×10^9/L) and is associated with major bleeding and fatal hemorrhage in 9 % and 1–4 % of cases, respectively. The median time to platelet recovery after withdrawal of the offending drug is 5–8 days (George et al. 1998; Pedersen-Bjergaard et al. 1997). Most patients require no specific therapy other than discontinuation of the offending agent. Although high-level evidence of efficacy is lacking, bleeding patients may also be treated with platelet transfusion, intravenous immune globulin, or corticosteroids (Pedersen-Bjergaard et al. 1997; Ray et al. 1990). Laboratory assays demonstrating drug-dependent antibodies may be useful for confirmation of the diagnosis (Aster et al. 2009) but are available only at select reference laboratories and do not yield results in a time frame necessary to inform initial clinical decision making.

Heparin-Induced Thrombocytopenia

HIT is a unique DITP caused by platelet-, endothelial-, and monocyte-activating antibodies against complexes of platelet factor 4 and heparin (Amiral et al. 1992). In contrast to most other forms of DITP, thrombocytopenia is relatively mild in HIT (median nadir platelet count $60–70 \times 10^9$/L), and the major clinical complication is thrombosis (venous and arterial) rather than hemorrhage (Warkentin 1998). Thromboembolism is present in approximately half of patients at the time of diagnosis (Greinacher et al. 1999), and an increased thrombotic risk persists for up to 30 days following discontinuation of heparin (Warkentin and Kelton 1996). In heparin-naïve patients, the platelet count begins to fall 5–14 days after initial heparin exposure. In patients with recent heparin exposure (usually within the last 30 days) and preformed HIT antibodies, the platelet count may fall immediately upon re-exposure (i.e., rapid-onset HIT) (Warkentin and Kelton 2001). Treatment requires cessation of heparin, initiation of an alternative anticoagulant, and avoidance or postponement of warfarin until platelet count recovery (Linkins et al. 2012; Cuker and Cines 2012). Laboratory testing is used to confirm the diagnosis. Immunoassays are highly sensitive but have poor positive predictive value due to detection of both platelet-activating and non-activating antibodies (Pouplard et al. 1999). Functional assays are more specific, but technical requirements preclude their use in all but a small number of reference laboratories (Sheridan et al. 1986). Owing to the prevalence of thrombocytopenia and thrombosis in the ICU, the limited specificity of widely available immunoassays, and the limited availability of more specific functional assays, HIT is frequently considered in patients with critical illness (Cuker and Cines 2012). Nevertheless, HIT is uncommon in the

ICU with an incidence of approximately 0.4 % (Selleng et al. 2008; Crowther et al. 2005; Crowther et al. 2010). Also see Chap. 14.

Posttransfusion Purpura

Posttransfusion purpura (PTP) is a rare transfusion reaction in which severe thrombocytopenia (typically less than 10×10^9/L), often lasting days to weeks, develops 5–10 days after transfusion of a platelet-containing product such as red cells or platelets (Mueller-Eckhardt, 1986). Patients with PTP have been sensitized to a foreign platelet antigen by pregnancy or prior transfusion. The antigen most commonly implicated is human platelet antigen-1a (HPA-1a) (Vogelsang et al. 1986). Antibody binding results in rapid clearance of antigen-positive transfused platelets. By a poorly understood mechanism, the recipient's antigen-negative autologous platelets are also destroyed. The diagnosis is confirmed by demonstration of a circulating alloantibody to a common platelet antigen (usually HPA-1a) in patient serum that is absent from the patient's platelets. First-line treatment is with intravenous immune globulin.

Extracorporeal Circuitry/ Intravascular Devices

Extracorporeal circuits such as cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO) frequently result in thrombocytopenia due to platelet activation and consumption on artificial surfaces. In a study of 581 patients who underwent surgery on CPB, 56.3 and 2.9 % developed thrombocytopenia (less than 150×10^9/L) and severe thrombocytopenia (less than 50×10^9/L), respectively (Selleng et al. 2010). The platelet count falls by a mean of 40 % from preoperative levels after CPB (Nader et al. 1999), typically nadirs within 24–72 h after surgery, and begins to recover by postoperative day 4. ECMO induces a 40–50 % fall in platelet count within 1 h of initiation (Robinson et al. 1993; Cheung et al. 2000). Thrombocytopenia requiring platelet transfusion is nearly universal and persists until circulatory support is discontinued (Robinson et al. 1993). In addition to thrombocytopenia, CPB and ECMO are associated with acquired platelet dysfunction, which may exacerbate bleeding risk (Konkle 2011). Continuous renal replacement therapy, unlike CPB and ECMO, typically effects only minor, clinically insignificant reductions in platelet count (Mulder et al. 2003).

Indwelling intravascular devices may also reduce platelet counts. In a prospective study of 58 patients with acute coronary syndrome and insertion of an intra-aortic balloon pump, the platelet count decreased to a mean nadir of 63 % of the pre-insertion count by day 4, remained stable thereafter, and rose rapidly after pump removal (Vonderheide et al. 1998). Although thrombocytopenia is common among patients with ventricular assist devices (VADs) (Warkentin and Crowther 2007), the presence of a VAD was not associated with a significant reduction in platelet count in a controlled study (Steinlechner et al. 2009). VADs may predispose to bleeding through other mechanisms including platelet dysfunction and acquired von Willebrand disease (Steinlechner et al. 2009; Uriel et al. 2010). At least two studies have shown pulmonary artery catheters to be associated with thrombocytopenia in ICU patients (Bonfiglio et al. 1995; Vicente Rull et al. 1984), though a causative relationship has not been established.

Surgery

Major surgery, even in the absence of CBP, lowers platelet counts due to consumption, blood loss, and dilution. In a study of 1,415 admissions to a surgical ICU, the median nadir platelet count was 113×10^9/L on postoperative day 2 and typically recovered to preoperative levels by days 3–5 (Nijsten et al. 2000). The fall in circulating platelet count after surgery leads to an increase in thrombopoietin levels with consequent stimulation of megakaryopoiesis, resulting in a postoperative thrombocytosis that is often two- to threefold greater than the preoperative baseline and peaks

approximately 2 weeks after surgery (Warkentin et al. 2003; Kaushansky 2009). A blunted or an absent rise in platelet count beyond postoperative days 3–5 suggests the presence of another etiology of thrombocytopenia (e.g., sepsis) (Greinacher and Selleng 2010) and is associated with increased mortality (Nijsten et al. 2000).

Diagnostic Approach

Our approach to thrombocytopenia in the ICU is shown in Fig. 8.1. We make every effort to obtain prior platelet counts to confirm that the thrombocytopenia is acute and not reflective of a chronic thrombocytopenic disorder. In addition, we use information from the history including a detailed chronicle of exposure to drugs and transfusions; the physical examination and radiographic studies for evidence of bleeding or thrombosis; the severity and timing of onset of thrombocytopenia and the pace of fall in the platelet count over the patient's hospital course; and the peripheral blood smear to form our initial differential diagnosis. On the basis of this assessment, specialized laboratory testing is requested for specific entities that we suspect.

Several patterns of clinical presentation are worth highlighting. Immune-mediated thrombocytopenic disorders such as DITP, HIT, and PTP typically present with an abrupt fall in the platelet count 5–14 days after exposure to the offending drug or blood product. Whereas DITP and PTP are typified by severe thrombocytopenia and bleeding, HIT is characterized by moderate thrombocytopenia and predisposition to thromboembolism. Platelet counts that fall within 48 h of large-volume resuscitation, surgery, CPB, or insertion of a balloon pump are often due to the intervention, itself. Sepsis, DIC, and disorders of impaired platelet production characteristically manifest as more gradual declines in platelet count over 5–7 days. In practice, thrombocytopenia in the ICU is often multifactorial, and patients may not fit a single stereotypical pattern. Nevertheless, we find the algorithm shown in Fig. 8.1 to be a useful guide for the evaluation of these complex patients.

Management

Appropriate management is highly dependent on the etiology of thrombocytopenia. For instance, whereas platelet transfusion and suspension of anticoagulant prophylaxis may be indicated in a patient with severe DITP, HIT requires prompt initiation of an alternative anticoagulant in lieu of heparin and constitutes a relative contraindication to platelet transfusion. Treatment must therefore be individualized to the underlying cause of thrombocytopenia as well as any concomitant thrombotic or hemorrhagic risk factors the patient may harbor.

As noted, high-quality evidence linking a platelet count threshold with bleeding risk in ICU patients is lacking. If a patient with platelet dysfunction (congenital or acquired) has major bleeding, platelet transfusion is indicated irrespective of the platelet count. Published guidelines recommend a platelet count trigger of 50×10^9/L for prophylactic platelet administration in patients with DIC or massive transfusion and platelet counts of $50–100 \times 10^9$/L for invasive interventions, depending on the nature of the procedure (Samama et al. 2005; British Committee 2003; Practice Guidelines 1996; Practice Parameter 1994). These recommendations are based largely on expert opinion and experience rather than data. Higher quality evidence supports the practice of prophylactic platelet transfusion to maintain a platelet count of at least 10×10^9/L in non-bleeding oncology patients, whether in the ICU or on the wards.

It is also crucial to consider adjunctive measures for control of bleeding. These include replacement of deficient clotting factors (including fibrinogen); maintenance of a hemoglobin of 10 g/dL or more to optimize rheology for hemostasis (Valeri et al. 2001); use of antifibrinolytic agents (except in DIC); surgical, endoscopic, or interventional radiologic procedures to stop bleeding; and correction of uremia, acid/base disturbances, and hypothermia.

Observational data suggest that platelet transfusion is overused in the ICU (Blood Observational Study 2010). In a retrospective study of 76 platelet transfusions administered to

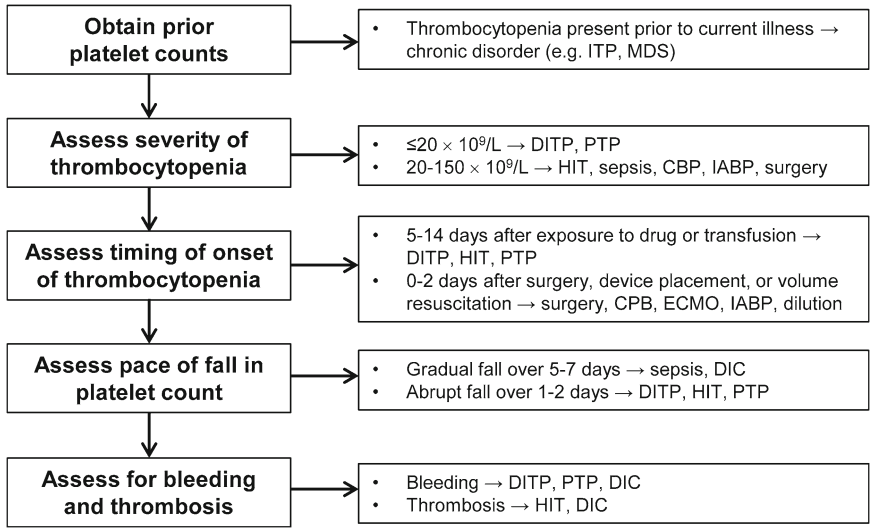

Fig. 8.1 An approach to the diagnosis of thrombocytopenia in the ICU. *ITP* immune thrombocytopenia, *MDS* myelodysplastic syndrome, *DITP* drug-induced immune thrombocytopenia, *PTP* posttransfusion purpura, *HIT* heparin-induced thrombocytopenia, *CPB* cardiopulmonary bypass, *IABP* intra-aortic balloon pump, *ECMO* extracorporeal membrane oxygenation, *DIC* disseminated intravascular coagulation

27 patients, the threshold platelet count for prophylactic transfusion was 33×10^9/L (Arnold et al. 2006). The same study indicated that use of liberal transfusion may be associated with an increased risk of infection, length of stay in the ICU, and mortality, though these observations remain to be validated in a controlled trial.

Thrombocytopenia among ICU patients may lead not only to platelet transfusion but also to delay of invasive procedures and withholding of anticoagulant thromboprophylaxis. Although high-quality evidence is not available, it has been proposed that prophylactic dose anticoagulation is likely to be safe in most patients with platelet counts of 30×10^9/L or greater. Higher platelet counts may be necessary for individuals with other risk factors for bleeding or those who require therapeutic dose anticoagulation (Arnold and Lim 2011). Randomized controlled trials are needed to guide platelet transfusion and anticoagulant thromboprophylaxis practice in thrombocytopenic patients in the ICU.

The peripheral blood smear shows severe thrombocytopenia without clumping, schistocytes, or other abnormalities. The patient's serum tests negative for HPA-1a antibodies. HPA-1a typing of her own platelets cannot be performed due to the severity of her thrombocytopenia. The patient receives intravenous immune globulin and platelet transfusions for suspected vancomycin-induced thrombocytopenia. She also undergoes hemodialysis with a high permeability filter to maximize drug removal (Castellano et al. 2008). Her platelet count normalizes 1 week after discontinuation of vancomycin. Vancomycin-dependent antiplatelet antibody testing is sent to a reference laboratory and is positive, confirming the diagnosis of DITP due to vancomycin. Vancomycin is added to the patient's list of allergies, and she is advised to obtain a Medic-alert bracelet.

Thrombocytopenia After Solid Organ Transplantation

You are asked to see a 36-year-old woman for pancytopenia. She underwent renal transplant 6 weeks ago for end-stage diabetic nephropathy. Over the last week, she has developed a rash and fever. Her laboratory

(continued)

studies demonstrate a white blood cell count of 2.0×10^9/L, a hemoglobin of 7.2 g/dL, and a platelet count of 38×10^9/L. She is taking azathioprine, prednisone, and tacrolimus. There have been no signs of graft rejection or dysfunction. Blood cultures are negative. The patient was cytomegalovirus (CMV) seronegative and received a cadaveric allograft from a CMV-seropositive donor. You recommend CMV nucleic acid testing, peripheral blood lymphocyte chimerism studies, and bone marrow aspirate and biopsy. You also recommend discontinuation of azathioprine.

Select Causes

Thrombocytopenia, either in isolation or in combination with other cytopenias, is a common finding among SOT patients and may be an early sign of a serious or a life-threatening disorder (Smith 2010). Although SOT patients are subject to any of the myriad causes of thrombocytopenia that affect other populations (Table 8.1), the discussion that follows is limited to etiologies of particular clinical relevance to the post-transplant setting. These etiologies include drug-, infection-, and immune-mediated complications of SOT (Table 8.4).

Table 8.4 Etiologies of thrombocytopenia after solid organ transplant

Category	Etiologies
Drug mediated	Drug-induced thrombocytopenia
	Calcineurin inhibitor-induced thrombotic microangiopathy
Infection mediated	Viral infection (e.g., CMV, EBV, VZV, HHV6)
	Infection-induced hemophagocytic syndrome
	Post-transplant lymphoproliferative disorder
Immune-mediated	Graft-versus-host disease
	Immune thrombocytopenia (ITP)

CMV cytomegalovirus, *EBV* Epstein–Barr virus, *VZV* Varicella zoster virus, *HHV6* human herpes virus-6

Drug-Induced Thrombocytopenia

SOT patients are routinely exposed to a variety of drugs that can cause cytopenias. Immunosuppressive and antimicrobial agents are frequent culprits. The mechanisms of drug-induced thrombocytopenia are varied and include marrow suppression and immune destruction (i.e., DITP). A third mechanism, thrombotic microangiopathy (TMA) due to calcineurin inhibitors, is discussed separately (see "Thrombotic Microangiopathy" below).

Perhaps the most common culprit in the SOT setting is the purine analog, azathioprine, which causes dose-related marrow suppression that may present as single or multilineage cytopenias. In a series of 739 inflammatory bowel disease patients treated with azathioprine, 37 (5 %) and 15 (2 %) developed clinically significant cytopenias and thrombocytopenia, respectively. Most cases arose during the first 4 weeks of treatment, but late presentations also occur (Connell et al. 1993). Because azathioprine and its principal metabolite are predominantly cleared in the kidneys, toxicity may occur in the setting of worsening renal function (e.g., in a renal transplant patient with allograft rejection). Thiopurine methyltransferase deficiency and concomitant use of several drugs commonly prescribed in the post-transplant setting such as angiotensin-converting enzyme inhibitors, allopurinol, and trimethoprim/sulfamethoxazole also increase drug levels and predispose to hematologic toxicity.

Other commonly employed immunosuppressive agents such as mycophenolate mofetil, tacrolimus, cyclosporine, and sirolimus may also cause cytopenias through suppression of hematopoiesis. Anti-thymocyte globulin is associated with the frequent occurrence of a mild, immune-mediated fall in the platelet count that typically resolves within a week of initiation of therapy (Rostaing et al. 2010). Alemtuzumab, a humanized anti-CD52 antibody that depletes T- and B-lymphocytes, is associated with a high incidence of thrombocytopenia within the first few weeks of therapy. An increased rate of ITP occurring months after exposure has also been reported (Cuker et al. 2011).

Ganciclovir and valganciclovir, which are used for prevention and treatment of CMV disease after SOT, cause marrow suppression and cytopenias. Cytopenias including thrombocytopenia are a common complication of treatment with trimethoprim–sulfamethoxazole and may result from DITP or interference with folic acid metabolism (Asmar et al. 1981).

Thrombotic Microangiopathy

TMA is characterized by intravascular platelet aggregation and thrombosis in the microcirculation, leading to microangiopathic hemolytic anemia, thrombocytopenia, and end-organ ischemic injury. Clinical and laboratory features include anemia, elevated lactate dehydrogenase, reticulocytosis, fragmented and nucleated erythrocytes in the peripheral blood smear, variable renal dysfunction, and multiorgan dysfunction in severe cases.

TMA in SOT patients most commonly arises as a complication of calcineurin inhibitor therapy. The disease occurs more frequently with cyclosporine but has also been reported with tacrolimus (Trimarchi et al. 1999). The addition of sirolimus to either drug appears to increase the risk (Hachem et al. 2006). The proposed mechanism is drug-induced direct endothelial injury (Myers 1986). In vitro studies suggest that cyclosporine may also enhance platelet aggregation (Grace et al. 1987). Histologic evidence of TMA is generally restricted to the kidneys (Zarifian et al. 1999). In a series of 950 kidney recipients, the incidence of calcineurin-induced TMA was 1.3 % and median onset was 7 days after transplant (Said et al. 2010). In most patients, the disease resolves with discontinuation of the offending agent. Although high-quality evidence to support its use in this setting is lacking, plasma exchange is often used in severe cases and those that do not resolve quickly after drug cessation. In renal transplant recipients, two other entities may cause a TMA-like picture and must be differentiated from calcineurin inhibitor-induced disease: hyperacute humoral rejection and administration of muromonab-CD3 (OKT3), an anti-CD3 monoclonal antibody given for prevention of acute rejection (Abramowicz et al. 1992).

TMA may also arise as a complication of the transplant, itself. This phenomenon, known as post-transplant TMA, is well documented following allogeneic hematopoietic stem cell transplantation, but reports following SOT in the absence of calcineurin inhibitor use are scant (Lipshutz et al. 2008). The pathogenesis of this disorder is not well understood. Proposed mechanisms include direct endothelial injury by immunosuppressive drugs, allograft rejection, post-transplant lymphoproliferative disorder (PTLD), and infection. In rare cases, severe acquired ADAMTS13 deficiency due to an inhibitor has been reported (Pham et al. 2002; Mal et al. 2006). Management involves withdrawal of any suspected immunosuppressive agents, evaluation for CMV and other viral infections, and supportive care. Plasma exchange may be attempted in severe cases but is probably of limited utility (George et al. 2004).

Viral Infections

Immunosuppressed SOT recipients are vulnerable to a multitude of opportunistic infections, a number of which may be associated with cytopenias. The most prevalent of these is CMV. Older literature cites an incidence of symptomatic CMV infection of 8, 29, 25, and 39 % in renal, liver, heart, and lung transplant patients, respectively (Patel et al. 1996). These rates have likely been reduced by modern prevention strategies (Andrews et al. 2011), but CMV disease remains common. Risk factors include type of transplant, intensity of immunosuppression, and CMV serologic status of the donor and recipient (with highest risk when a CMV-seronegative patient receives an organ from a CMV-seropositive donor). The characteristic clinical presentation consists of fever, arthralgias, myalgias, and cytopenias. Invasive tissue disease affecting the gut, lungs, retina, central nervous system, or allograft may also occur. In a series of 100 renal transplant patients with CMV disease, the incidence of thrombocytopenia was 43 % (Pour-Reza-Gholi et al. 2005). Proposed mechanisms of CMV-induced thrombocytopenia include direct infection of megakaryocytes or other hematopoietic

progenitors (Crapnell et al. 2000), immune destruction (Sahud and Bachelor 1978), or splenic sequestration (Sola-Visner et al. 2009). Current guidelines recommend quantitative polymerase chain reaction (PCR) viral load or antigenemia testing for diagnosis of CMV infection (Kotton et al. 2010). First-line agents for prevention and treatment of CMV disease are ganciclovir and valganciclovir (Andrews et al. 2011), which themselves may cause thrombocytopenia through myelosuppression.

Varicella zoster virus (VZV) and Epstein–Barr virus (EBV) are other herpes viruses that may cause thrombocytopenia in both immunocompetent and immunocompromised hosts (Carter 1965). Mechanisms include immune destruction (Steeper et al. 1989) and splenic sequestration. EBV viremia after SOT may also be associated with PTLD (discussed separately, see "Post-transplant Lymphoproliferative Disorder"). Human herpes virus-6 (HHV6) may present with cytopenias, fever, pneumonitis, hepatitis, and/or encephalitis after SOT (Dockrell and Paya 2001). Reactivation of HHV6 from latency is common in this setting, but clinical disease is probably infrequent (Hentrich et al. 2005) and may be difficult to distinguish from disease caused by other viruses such as CMV. The preferred method for diagnosing viral reactivation is quantitative PCR. First-line therapy is ganciclovir or foscarnet.

Infection-Induced Hemophagocytic Syndrome

Infection may also induce hemophagocytic syndrome (HPS), a life-threatening systemic inflammatory disease in which there is hemophagocytosis by activated, nonneoplastic macrophages in the bone marrow, lymph nodes, liver, and spleen. The disorder results from aberrant T-cell activation in response to a precipitating infection, leading to elaboration of macrophage-activating cytokines such as interleukin-2 (IL-2) and gamma-interferon. The activated macrophages, in turn, secrete the T-cell-activating cytokines IL-1, IL-6, IL-12, and tumor necrosis factor-α, producing a vicious cycle of T-cell and macrophage activation (Smith, 2010). Clinical and laboratory features include fever, hepatosplenomegaly, lymphadenopathy, rash, jaundice, neurologic dysfunction, cytopenias, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, elevated levels of the soluble IL-2 receptor (CD25), and diminished natural killer cell activity (Henter et al. 2007).

A recent literature review identified 69 reports of HPS after SOT: 60 in kidney (or kidney–pancreas), 5 in liver, 2 in heart, and 2 in lung transplant recipients. The mortality rate was 52 %. A precipitating viral infection was identified in approximately half of the cases (CMV in 20, EBV in 8, and other herpes viruses in 7 patients) (Diaz-Guzman et al. 2011). The largest published case series reported 17 cases of HPS after cadaveric renal transplant out of a total of 4,230 transplants for an overall incidence of 0.4 %. The median time to onset in this series was 52 days after transplant, and an infectious etiology was indentified in 14 of the patients (Karras et al. 2004). Management of HPS involves an aggressive search for and treatment of precipitating infection and supportive care.

Post-transplant Lymphoproliferative Disorder

PTLD refers to a family of predominantly EBV-driven, B-cell lymphoproliferative disorders that arise following hematopoietic stem cell or solid organ transplant. The disorder is caused by systemic immunosuppression, which impairs EBV-specific cytotoxic T-cell function, permitting expansion of B-cells latently infected with EBV. The EBV-infected B-cells that give rise to PTLD can originate in the recipient or the donor. PTLD following SOT is most commonly recipient derived. The clinical spectrum of PTLD after SOT ranges from an infectious mononucleosis-like polyclonal lymphoproliferation to aggressive non-Hodgkin's lymphoma (Smith 2010). The overall incidence at 10 years after SOT is approximately 1–2 %, with most cases occurring within the first year (Caillard et al. 2006; Andreone et al. 2003). Risk factors for the development of PTLD include the type of transplant (small bowel > heart

or lung > liver or kidney) (Cockfield 2001), the intensity of immunosuppression (Opelz and Henderson 1993), and the EBV serologic status of the donor and recipient (with the highest risk when an EBV-seronegative patient receives an organ from an EBV-seropositive donor) (Walker et al. 1995).

Recipient-derived PTLD is typically a multisystem disease characterized by constitutional symptoms, lymphadenopathy, and cytopenias if bone marrow involvement is present. Extranodal disease is also frequent, most commonly involving the gastrointestinal tract, lungs, skin, liver, and central nervous system. Donor-derived PTLD, in contrast, is often limited to the allograft tissue (Petit et al. 2002). The diagnosis of PTLD is suggested by an elevated EBV viral load in the peripheral blood (Stevens et al. 2001) and is confirmed by tissue biopsy. Management involves immediate reduction in immunosuppression to the minimal level required for preservation of the allograft. Rituximab monotherapy is added to treat disease that does not respond to reduced immunosuppression alone. Rituximab in combination with anthracycline-based chemotherapy is used for relapsed or refractory disease as well as in the initial treatment of cases associated with high-grade histology and a clinically aggressive course (Smith 2010).

Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) is a rare and frequently fatal complication of SOT in which donor-derived T-cells in the transplanted organ engraft, proliferate, and attack tissues of donor origin. Transplantation of organs with a large quantity of lymphoid tissue (e.g., small bowel, liver) carries a greater risk of GVHD than organs with a lesser amount. Other reported risk factors include age greater than 65 and a greater degree of HLA match between donor and recipient (Kato et al. 2009).

The reported incidence rate of GVHD after orthotopic liver transplantation is 0.1–2 % (Smith et al. 2003) and less than 0.05 % after lung transplant (Worel et al. 2008). Clinical manifestations include fever, rash, diarrhea, and cytopenias and generally present within 2–8 weeks after transplant (Assi et al. 2007), though late occurrences have been reported (Pollack et al. 2005). The diagnosis is based on confirmation of lymphocyte chimerism in the peripheral blood, marrow, or affected tissues and tissue biopsy. Given the rarity of the disease, no evidence-based guidelines on treatment are available. Initial therapy is often with high-dose corticosteroids. Cases of successful treatment with antagonists of tumor necrosis factor-α have been reported (Piton et al. 2009; Thin et al. 2009). Consideration may be given to reducing immunosuppression to facilitate rejection of the allografted donor T-cells by the recipient immune system. Despite these efforts, mortality remains well in excess of 50 % in most reports (Pavenski et al. 2008).

Post-transplant Immune Thrombocytopenia

ITP, either alone or in combination with autoimmune hemolytic anemia (Evans syndrome), has been rarely reported as a complication of SOT, possibly as a result of a central tolerance defect induced by systemic immunosuppression (Cines et al. 2009). In a pediatric series of 158 liver transplants, the incidence of ITP was 1.9 % (Miloh et al. 2011). Substantial clinical heterogeneity has been observed in reported cases. ITP may arise in the immediate post-transplant period or months later and may be self-limited and responsive to conventional ITP therapies or assume a chronic, refractory course (Cines et al. 2009). In one report, ITP was transferred from a donor to a recipient after orthotopic liver transplant (Friend et al. 1990). ITP is a diagnosis of exclusion. Treatment is discussed elsewhere (see Chap. 7).

Diagnostic Approach

Determination of the etiology of thrombocytopenia in SOT patients is often challenging. We consider the time of onset of thrombocytopenia in relation to transplant in developing our differential

Table 8.5 An approach to the diagnosis of thrombocytopenia after SOT. Our initial differential diagnosis is formulated, in part, on the time of onset of thrombocytopenia after SOT. Specific laboratory and pathologic testing, when available, is used to confirm the diagnosis

Etiology	Typical time of onset after SOT	Diagnostic testing
TMA	Median 7 days	Microangiopathic changes on smear
GVHD	2–8 weeks	Lymphocyte chimerism
		Tissue biopsy
Viral infection	1–6 months	Varies depending on virus
Infection-induced HPS	1–6 months	See consensus criteria (Henter et al. 2007)
		Hemophagocytosis on biopsy
PTLD	Within 1 year	EBV PCR Tissue biopsy
Drug induced	Any time, often within several weeks of starting a new medication	–
ITP	Any time	–

SOT solid organ transplant, *TMA* thrombotic microangiopathy, *GVHD* graft-versus-host disease, *HPS* hemophagocytic syndrome, *PTLD* post-transplant lymphoproliferative disorder, *EBV* Epstein–Barr virus, *PCR* polymerase chain reaction, *ITP* immune thrombocytopenia

diagnosis and request definitive testing, when available, to confirm the diagnosis (Table 8.5). TMA generally occurs in the early post-transplant period with a median onset at day 7 (Said et al. 2010). Identification of microangiopathic changes on the peripheral blood smear is critical for verifying the diagnosis. GVHD generally arises 2–8 weeks after transplantation and is confirmed with lymphocyte chimerism studies and biopsy of affected tissue. Viral infections may occur at any time during the post-transplant course but are most common between 1 and 6 months when patients suffer the greatest impact of immunosuppression. Confirmatory testing for CMV, the most common infection in this setting, involves quantitative PCR or an antigen assay. Infection-induced HPS tends to occur in the same time frame as the infections that drive it. Diagnostic criteria for this condition have been published (Henter et al. 2007), among them evidence of hemophagocytosis on biopsy of the bone marrow or the lymphoid tissue. Most cases of PTLD occur in the first year. The diagnosis is suggested by EBV quantitative PCR and confirmed by biopsy of affected tissue. Drug-induced thrombocytopenia may occur at any time after transplant but is most likely to arise within several weeks of initiation of a new medication. ITP may occur at any time after SOT and remains a diagnosis of exclusion from other causes.

Quantitative PCR is consistent with CMV viremia. Bone marrow biopsy demonstrates hypocellularity (20 %) but otherwise normal trilineage hematopoiesis. Lymphocyte chimerism studies are negative for the presence of donor lymphocytes. CMV disease is suspected, and ganciclovir is initiated with resolution of the patient's rash and fever and rapid improvement in blood counts.

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