



How I Treat

How I Approach Hematologic Abnormalities in Hospitalized Patients with Infectious Diseases

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Abstract. Patients hospitalized with infectious diseases often develop cytopenias, coagulopathy, hyperinflammation, or tissue abnormalities that may reflect infection, treatment toxicity, organ failure, immune dysregulation, or occult hematologic disease. Drawing on 20 years of daily consultation at the National Institute for Infectious Diseases “Lazzaro Spallanzani” IRCCS, I organize my approach around six recurring scenarios: fever with thrombocytopenia or schistocytes; persistent cytopenia during anti-infective therapy; fever, cytopenias, and hyperferritinemia; pancytopenia prompting marrow assessment; severe anemia or hemolysis; and persistent lymphadenopathy, effusion, or unexplained inflammation, particularly in an immunocompromised patient. Across scenarios, I first identify diagnoses in which delay changes outcome, then integrate tempo, the peripheral blood smear, reticulocyte response, medication, heparin, and transfusion exposure, organ dysfunction, and immune status. Guidelines define diagnostic and therapeutic standards; experience determines how those standards are ordered, combined, and revisited when evidence is incomplete. The approach prioritizes immediate treatment of suspected thrombotic thrombocytopenic purpura, clinically significant disseminated intravascular coagulation, heparin-induced thrombocytopenia or severe drug-induced immune thrombocytopenia, acute promyelocytic leukemia, severe hemolysis, and rapidly progressive secondary hemophagocytic lymphohistiocytosis; disciplined attribution of drug toxicity; physiology-based transfusion and anticoagulation; and timely marrow or tissue diagnosis when infection no longer explains the trajectory. The goal is a reproducible, stewardship-aware bedside method.

Keywords: Consultative hematology; Hospitalized patients; Infectious diseases; How I Treat; Clinical reasoning; Cytopenias; Thrombotic microangiopathy; Hemophagocytic lymphohistiocytosis; HIV; Lymphoma; Antimicrobial toxicity; Diagnostic stewardship.

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Article Highlights.

- Six recurrent inpatient scenarios organize an experience-informed method developed during 20 years

of daily consultation at a national infectious diseases referral center.

- The first decisions are driven by urgency, blood-film morphology, tempo, medication, heparin, and transfusion exposure, organ function, and immune status.
- Guideline-based standards are distinguished from the judgment required in gray areas such as marrow timing, antimicrobial withdrawal, anticoagulation, and tissue diagnosis.
- Secondary HLH is separated from severe infection-associated hyperinflammation; macrophage activation syndrome is reserved for the rheumatologic or autoinflammatory context.
- A documented infection does not close the diagnostic process when the trajectory suggests lymphoma, PTLT, acute leukemia, or another marrow or tissue-based disorder.

Introduction. For the past 20 years, daily consultative hematology at the National Institute for Infectious Diseases “Lazzaro Spallanzani” IRCCS has required a form of reasoning that differs from a conventional organ-based consultation. The referral may be for thrombocytopenia, anemia, an abnormal coagulation profile, hyperferritinemia, lymphadenopathy, or an effusion. The more important question is usually different: which mechanism is at work, how urgent is it, and which next step can change the patient’s course? Modern practice generates extensive hematologic, coagulation, inflammatory, and molecular data; however, they become useful only when placed in context with timing, morphology, medication exposure, immune status, and the infection’s trajectory.¹⁻⁴ In hospitalized patients with infectious diseases, inflammation, prolonged antimicrobial exposure, organ dysfunction, immune compromise, unusual pathogens, and neoplasia often coexist. The same abnormality may therefore be

reactive, iatrogenic, immune-mediated, consumptive, infiltrative, or clonal. Repeated exposure to this overlap has led to a stable sequence in my practice: triage first; then morphology and chronology; then mechanism, targeted testing, and an explicit contingency plan.

This article is not a case series, an institutional audit, or a description of local custom. The term referral-center approach identifies the clinical environment in which the method was refined; it does not imply that institutional volumes or outcomes are being reported. The framework is personally constructed but evidence-based in its boundaries. I identified supporting evidence through targeted PubMed/MEDLINE searches and current ASH, AABB, ISTH, WHO, CDC, and disease-specific guidance from January 2000 through August 2026, supplemented by hand-searching key references and updates. Where evidence is robust, guideline recommendations govern practice. Where evidence is incomplete, I identify the operational choice as judgment rather than presenting it as a formal recommendation.

The decision sequence before naming the diagnosis.

The opening sequence is deliberately repetitive. I first decide whether delay could change outcome. Only after that decision do I classify the abnormality by lineage and tempo, review the blood film, reconstruct infection and treatment exposure, and decide whether the dominant mechanism is destruction or consumption, reduced production, sequestration or dilution, or clonal/infiltrative disease. This sequence is summarized in **Figure 1**, which provides the operational decision pathway used before a disease label is accepted. Six clinical scenarios account for most of the difficult consultations and make the method easier to reproduce. **Table 1** defines the key question in each scenario; the following sections explain where the evidence is clear and where judgment comes in.

Table 1. Six archetypal clinical scenarios and the decisions that structure my practice.

Clinical scenario	What I look at first	Cannot-miss decision	Threshold for immediate treatment or invasive diagnosis
Fever with thrombocytopenia, schistocytes, or coagulopathy	Repeat count and smear; PT/aPTT, fibrinogen, D-dimer; hemolysis; heparin and transfusion exposure; bleeding and thrombosis phenotype	TTP/TMA versus DIC/SIC; HIT or DITP when the timeline fits	Treat suspected TTP before ADAMTS13 returns; stop heparin and start non-heparin anticoagulation when 4Ts probability is intermediate/high; support bleeding DIC
Persistent cytopenia during anti-infective treatment	Affected lineage, reticulocyte response, start date and cumulative dose, renal/hepatic function, concurrent marrow-toxic agents, infection control	Drug toxicity versus uncontrolled infection, marrow infection, hypersplenism, or primary hematologic disease	Modify an essential anti-infective only when severity and causal coherence justify it; perform marrow evaluation when the trajectory or morphology is discordant
Fever, cytopenias, hyperferritinemia, and organ dysfunction	Trajectory of counts, ferritin, fibrinogen, triglycerides, liver injury, spleen size, organ failure, response to antimicrobial therapy	Secondary HLH versus severe infection-associated hyperinflammation; occult lymphoma or marrow infection	Start syndrome-directed therapy when organ failure is progressing while infectious and malignant triggers are investigated in parallel
Pancytopenia with or without splenomegaly	Reticulocytes, smear, B symptoms, immune status, exposure history, organomegaly, virology and marrow-toxic drugs	Marrow infection, leukemia/lymphoma/MDS, aplasia, HLH, or reversible suppression	Obtain marrow when cytopenia persists, reticulocytopenia is severe, morphology is abnormal, or fever/organomegaly remains unexplained

Severe anemia or hemolysis	Reticulocytes, LDH, bilirubin, haptoglobin, DAT, smear, travel history, oxidant exposure, recent transfusion	MAHA/TTP/DIC; immune or drug hemolysis; malaria/babesiosis; transfusion reaction	Do not delay red-cell support for physiologic instability or treatment of TMA/severe malaria while confirmation proceeds
Persistent lymphadenopathy, effusion, or unexplained inflammation, particularly in an immunocompromised patient	Distribution and tempo, LDH/uric acid, HIV/EBV/HHV-8 context, cytopenias, abnormal cells, and the best tissue target	Lymphoma, PTL, HHV-8/KSHV disease, acute leukemia, or plasma-cell disorder coexisting with infection	Accelerate core/excisional, effusion, marrow, or other tissue diagnosis; avoid corticosteroids before biopsy when feasible

Legend: The table summarizes the six recurrent clinical scenarios and the immediate diagnostic and therapeutic decisions that structure the initial hematology consultation. ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; DAT = direct antiglobulin test; DIC = disseminated intravascular coagulation; DITP = drug-induced immune thrombocytopenia; EBV = Epstein-Barr virus; HHV-8 = human herpesvirus 8; HIT = heparin-induced thrombocytopenia; HIV = human immunodeficiency virus; HLH = hemophagocytic lymphohistiocytosis; KSHV = Kaposi sarcoma-associated herpesvirus; LDH = lactate dehydrogenase; MAHA = microangiopathic hemolytic anemia; MDS = myelodysplastic syndrome; PT/aPTT = prothrombin time/activated partial thromboplastin time; PTL = post-transplant lymphoproliferative disorder; SIC = sepsis-induced coagulopathy; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura; 4Ts = clinical pretest probability score for HIT based on thrombocytopenia, timing of platelet-count fall, thrombosis, and other causes of thrombocytopenia.

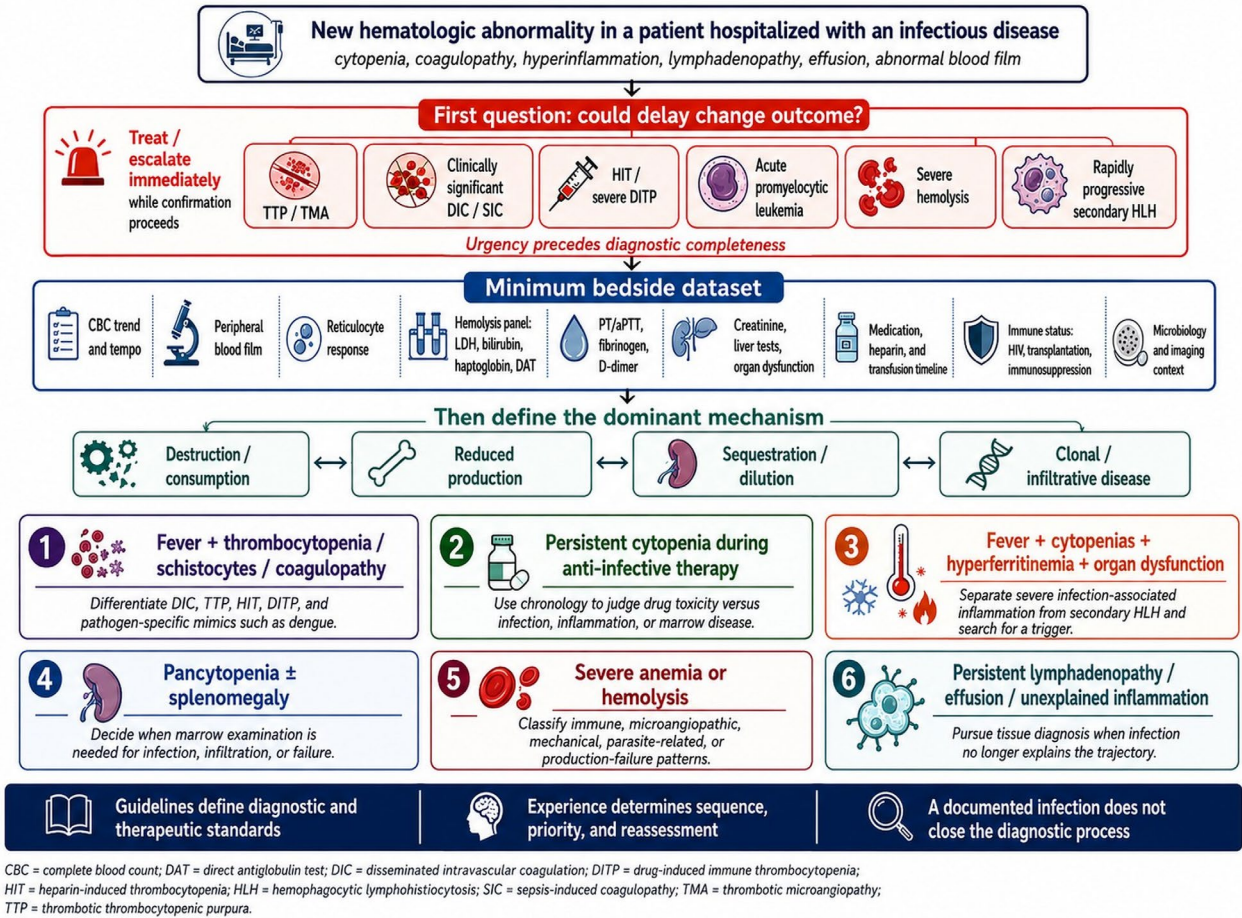


Figure 1. Integrated decision pathway for a new hematologic abnormality in a patient hospitalized with an infectious disease. Abbreviations: aPTT = activated partial thromboplastin time; CBC = complete blood count; DAT = direct antiglobulin test; DIC = disseminated intravascular coagulation; DITP = drug-induced immune thrombocytopenia; HIT = heparin-induced thrombocytopenia; HIV = human immunodeficiency virus; HLH = hemophagocytic lymphohistiocytosis; LDH = lactate dehydrogenase; PT = prothrombin time; SIC = sepsis-induced coagulopathy; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.

Box 1. Six non-negotiable rules in my initial hematology consultation.

- Identify diagnoses in which delay changes outcome: TTP/TMA, clinically significant DIC/SIC, HIT or severe DITP, APL, severe hemolysis, rapidly progressive secondary HLH, and catastrophic multiorgan thrombosis such as CAPS.
- Review the peripheral blood film early; automated counts do not replace morphology when schistocytes, blasts, parasites, platelet clumps, dysplasia, or leukoerythroblastosis are possible.
- Reconstruct the timeline: prior counts, infection onset, antimicrobial and heparin exposure, transfusion, immune reconstitution, renal/hepatic change, and clinical response.

• Obtain time-sensitive diagnostic samples before treatment when feasible (for example, ADAMTS13 before plasma exchange), but never delay emergency therapy to complete the work-up.
• Order a test only if its result changes a defined management branch; low pretest probability is a reason not to test.
• Write the contingency plan at the first review: what will be reassessed, when, and which new finding will trigger escalation, tissue diagnosis, or treatment.

The blood film and the minimum data set. How I begin. I review the blood film early, not after a broad laboratory cascade. In infectious diseases, it can reveal pseudothrombocytopenia, platelet-size abnormalities, schistocytes, toxic granulation, left shift, blasts, dysplasia, malaria parasites, Babesia, spherocytes, agglutination, Howell-Jolly bodies, target cells, teardrop cells, nucleated red cells, and leukoerythroblastosis. These findings frequently change both urgency and test selection.⁵⁻⁶ The minimum data set is deliberately small. For cytopenia, it includes a CBC with differential, reticulocyte count, smear, renal and liver function, inflammatory trajectory, a medication list with dates, hemolysis testing, and context-directed nutritional and

viral studies. For coagulopathy, it includes serial platelets, PT, aPTT, fibrinogen, D-dimer, smear, lactate, organ dysfunction, and bleeding or thrombosis phenotype. Expanded testing is reserved for a question that can change management; low pretest probability is a reason not to test.²

Scenario 1: Fever with Thrombocytopenia, Schistocytes, or Coagulopathy.

Typical referral. A hospitalized patient with sepsis develops a rapid platelet fall, anemia, renal or neurologic change, an abnormal coagulation profile, or new thrombosis.

My first task is to separate platelet count from

Table 2. Minimum diagnostic data set used in my practice for common hematology consultations.

Consult scenario	Minimum data in the first assessment	Tests to reserve for selected cases	Common diagnostic error
Anemia in infection	CBC with indices, prior Hb trend, reticulocyte count, smear, creatinine, liver tests, ferritin, transferrin saturation, CRP/ESR, LDH, bilirubin, haptoglobin, DAT when hemolysis suspected	EPO level, soluble transferrin receptor, B12/folate/copper, marrow biopsy, parvovirus B19 PCR, CT for occult infection or malignancy	Calling anemia iron deficiency solely because transferrin saturation is low during inflammation.
Thrombocytopenia	Repeat CBC if clumping suspected, citrate tube if needed, smear, PT/aPTT/ fibrinogen/D-dimer, medication timeline, heparin exposure, transfusion history, HIV/HCV/HBV when unexplained	HIT immunoassay/functional assay, ADAMTS13, antiphospholipid antibodies, marrow biopsy, platelet antibody testing, inherited thrombocytopenia sequencing	Ordering HIT tests in low 4Ts probability or ignoring pseudothrombocytopenia.
Neutropenia/leukopenia	Prior counts, differential with ANC/ALC, smear, medication exposure, HIV testing when appropriate, B12/folate/copper if chronic, spleen size, fever or mucosal infection	Bone marrow biopsy, flow cytometry, autoimmune work-up, viral PCRs, G-CSF only for selected severe cases	Stopping essential antimicrobials without assessing infection severity and substitute options.
Pancytopenia	CBC trend, reticulocytes, smear, LDH/bilirubin/haptoglobin, coagulation tests, ferritin, liver/spleen evaluation, HIV/EBV/HCV, EBV/CMV/parvovirus as appropriate	Bone marrow aspirate/biopsy with cultures, AFB/fungal stains, flow cytometry, cytogenetics, NGS, HLH work-up	Assuming all pancytopenia is sepsis-related when blasts, leukoerythroblastosis, or persistent reticulocytopenia are present.
Coagulopathy in sepsis	Serial platelet count, PT/INR, aPTT, fibrinogen, D-dimer, smear, lactate, organ dysfunction, bleeding/thrombosis assessment	Factor levels, thromboelastography/rotational thromboelastometry, protein C/antithrombin, antiphospholipid antibodies	Treating laboratory DIC without treating source control and shock, or transfusing plasma solely for abnormal PT in nonbleeding patients.
Suspected HLH	Fever curve, CBC trend, ferritin trajectory, triglycerides, fibrinogen, AST/ALT, LDH, bilirubin, spleen size, immunosuppression, infection and malignancy search	sIL-2R (soluble CD25), NK-cell function, marrow biopsy, PET/CT, HScore, and genetic testing in selected cases	Starting prolonged immunosuppression before excluding treatable infection triggers when clinical stability permits.

Legend: The table defines the information required before expanding the work-up. AFB = acid-fast bacilli; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; CBC = complete blood count; CRP = C-reactive protein; DAT = direct antiglobulin test; EBV = Epstein-Barr virus; ESR = erythrocyte sedimentation rate; G-CSF = granulocyte colony-stimulating factor; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; NGS = next-generation sequencing; PCR = polymerase chain reaction; PT/aPTT = prothrombin time/activated partial thromboplastin time.

pathophysiology. Thrombocytopenia in the ICU is often multifactorial: consumption, immune destruction, marrow suppression, splenic sequestration, dilution, extracorporeal circuits, liver disease, invasive infection, and microangiopathy may coexist.² The count alone does not define bleeding risk. I repeat the count when clumping is plausible, review the smear, assess hemolysis and coagulation, and reconstruct heparin, drug, and transfusion exposure. Severe ITP with bleeding and post-transfusion purpura remain in the differential, but ITP treatment is individualized according to bleeding, platelet count, comorbidity, and procedure need.⁷⁻⁸

DIC versus TTP. Sepsis-induced coagulopathy is a continuum; platelet decline and D-dimer elevation may precede overt DIC. Overt DIC reflects systemic coagulation activation, dysregulated fibrinolysis, endothelial injury, microthrombosis, factor and platelet consumption, bleeding, thrombosis, and organ failure.⁹⁻

¹¹ I treat the infection, source, shock, and organ failure first.¹²⁻¹⁴ Plasma, platelets, cryoprecipitate, or fibrinogen concentrate are used for bleeding, high-risk procedures, or severe contextual deficits rather than to normalize laboratory values.¹⁵ Serial fibrinogen is often more informative than a single value because it may rise early as an acute-phase reactant and later fall with consumption.

I accept the least delay in diagnosing TTP. A classic pentad is not required; thrombocytopenia and microangiopathic hemolytic anemia without a better explanation are sufficient to activate the pathway.¹⁶⁻¹⁷ ADAMTS13 is drawn before plasma when feasible, but treatment does not wait when suspicion is high. Current ISTH guidance retains plasma exchange and corticosteroids as the acute immune TTP backbone, with caplacizumab and rituximab incorporated according to guideline recommendations and availability. In congenital TTP, recombinant ADAMTS13 is preferred over plasma for prophylaxis where available.¹⁸⁻²⁰ The broader TMA differential includes Shiga toxin-associated HUS, complement-mediated HUS, pneumococcal HUS, transplant-associated TMA, malignant hypertension, drug-associated TMA, HIV-associated TMA, and severe sepsis-associated microangiopathy.

HIT and DITP. For suspected HIT, the first test is clinical. I calculate the 4Ts score before ordering an assay because low-probability testing creates false-positive diagnoses and unnecessary anticoagulation.²¹⁻²² With an intermediate or high probability, all heparin is stopped and a non-heparin anticoagulant is started if bleeding risk permits; immunoassay results are interpreted with functional confirmation when needed. Drug-induced immune thrombocytopenia is different: it is often abrupt and bleeding predominant. Vancomycin, selected beta-

lactams, rifampicin, trimethoprim-sulfamethoxazole, quinine-containing exposures, and glycoprotein IIb/IIIa inhibitors are relevant causes. Causality requires a coherent timeline and exclusion of sepsis, DIC, and TMA; platelet transfusion is reserved for life-threatening bleeding while drug-dependent antibodies persist.²³⁻²⁴

Thrombosis and testing. Infection increases venous thromboembolism risk through inflammation, endothelial and platelet activation, tissue factor expression, neutrophil extracellular traps, catheters, immobilization, cancer, and critical illness. SARS-CoV-2, HIV, tuberculosis, HCV, and CMV are relevant settings,²⁵ and HIV-specific literature supports a clinically important prothrombotic phenotype, particularly with advanced disease and low CD4 counts.²⁶ Pharmacologic thromboprophylaxis is generally used in acutely ill medical patients with increased VTE risk and acceptable bleeding risk; critical illness, thrombocytopenia, renal or hepatic dysfunction, and active cancer require individualization.²⁷⁻²⁸ COVID-19 anticoagulation is severity-specific rather than D-dimer-driven.²⁹⁻³² I do not order broad inherited thrombophilia panels during acute, clearly provoked infection-associated VTE. APS testing is reserved for situations in which it may change long-term management, and infection-associated antiphospholipid antibodies require confirmation after at least 12 weeks when classification matters.³³⁻³⁵

A pathogen-specific exception is dengue. Here, the platelet count can distract from the dominant physiology of plasma leakage and bleeding. Prophylactic platelet transfusion is not recommended; blood products are reserved for clinically significant bleeding, hemodynamic instability, or a falling hematocrit despite adequate fluids.³⁶⁻³⁸

Scenario 2: Persistent Cytopenia During Anti-Infective Treatment.

Typical referral. Counts fall after several days or weeks of therapy, but the anti-infective regimen remains important and the infection is not yet fully controlled.

The timeline is the diagnostic instrument. I define which lineage is affected, whether the process is isolated or pancytopenic, the reticulocyte response, the start date and cumulative dose of each drug, renal and hepatic function, concurrent marrow-toxic agents, and the response of the infection. A drug should not be blamed simply because it is capable of causing a cytopenia; the pattern must fit better than uncontrolled infection, DIC, viral suppression, marrow infection, hypersplenism, nutritional deficiency, or primary hematologic disease.

Anemia of inflammation is common and is mediated by hepcidin, impaired ferroportin-dependent iron export, reduced erythropoietin responsiveness, shortened red-cell survival, and suppressed marrow proliferation. Iron

Table 3. Immediate differentiation of overlapping thrombocytopenic, thrombotic, and hyperinflammatory syndromes.

Syndrome	Dominant clinical problem	Typical laboratory pattern	Immediate management principle
Sepsis-induced coagulopathy / overt DIC	Bleeding, thrombosis, purpura fulminans, organ failure; often both bleeding and clotting risk	Falling platelets, high D-dimer, prolonged PT/aPTT, falling fibrinogen in overt consumption, schistocytes variable	Treat infection and shock; transfuse platelets/plasma/fibrinogen for bleeding or high-risk procedures; serial monitoring.
Immune TTP	Microvascular thrombosis; neurologic symptoms may occur; bleeding usually not dominant	Thrombocytopenia, MAHA, schistocytes, high LDH, low haptoglobin, ADAMTS13 usually <10%; PT/aPTT often not markedly prolonged	Do not wait for ADAMTS13 if suspicion high; start plasma exchange and corticosteroids; add caplacizumab/rituximab per guidance and availability.
HIT	Thrombosis despite thrombocytopenia	Platelet fall >50%, nadir often $\geq 20 \times 10^9/L$, onset 5-10 days after heparin; PT/aPTT not diagnostic	Calculate 4Ts; if intermediate/high, stop heparin and start non-heparin anticoagulation; confirm with immunoassay and functional assay as needed.
DITP	Bleeding from severe immune platelet destruction	Abrupt severe thrombocytopenia, often $< 20 \times 10^9/L$; coagulation tests usually normal unless concomitant illness	Stop culprit drug; supportive care; IVIG or steroids in severe bleeding; platelet transfusion only for major bleeding.
CAPS	Rapid multiorgan thrombosis, often infection-triggered	Thrombocytopenia, hemolysis or DIC-like abnormalities may occur; antiphospholipid antibodies; biopsy microthrombosis when feasible	Combination therapy: anticoagulation, corticosteroids, plasma exchange and/or IVIG; treat trigger; multidisciplinary ICU care.
Secondary HLH	Hyperinflammation and organ failure; not primarily a coagulation disorder	Fever, cytopenias, high ferritin, hepatitis, hypertriglyceridemia, low fibrinogen, high sIL-2R; hemophagocytosis is neither required nor specific	Treat the trigger; obtain early expert input for corticosteroids, anakinra, IVIG, etoposide, or targeted therapy; do not delay in rapidly progressive disease
Dengue thrombocytopenia	Plasma leakage and bleeding risk in severe dengue; low platelets alone often not the problem	Leukopenia, thrombocytopenia, hemoconcentration; coagulation variable	No prophylactic platelet transfusion; fluids and monitoring; transfuse blood products for clinically significant bleeding or shock.

Legend: These syndromes can share thrombocytopenia, hemolysis, organ dysfunction, or abnormal coagulation but require different immediate actions. ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; APS = antiphospholipid syndrome; CAPS = catastrophic antiphospholipid syndrome; DIC = disseminated intravascular coagulation; DITP = drug-induced immune thrombocytopenia; HIT = heparin-induced thrombocytopenia; HLH = hemophagocytic lymphohistiocytosis; HUS = hemolytic uremic syndrome; IVIG = intravenous immunoglobulin; MAHA = microangiopathic hemolytic anemia; TTP = thrombotic thrombocytopenic purpura.

and transferrin saturation are low, transferrin is low or normal, and ferritin is normal or increased. Treatment of the infection and inflammation usually takes priority over reflex iron or erythropoiesis-stimulating therapy.^{2,39}

A normal MCV does not exclude iron deficiency, while a low transferrin saturation in sepsis does not prove it. Gastrointestinal blood loss, renal disease, malnutrition, and phlebotomy loss often coexist.

Leukocyte abnormalities require the same discipline. Neutrophilia can reflect infection, inflammation, corticosteroids, stress, smoking, obesity, asplenia, or a myeloproliferative neoplasm. Neutropenia may arise from overwhelming infection, viral disease, autoimmune disease, nutritional deficiency, hypersplenism, advanced HIV, marrow infiltration, or therapy. When ANC is below $0.5 \times 10^9/L$, fever, mucosal infection, and the possibility of an alternative antimicrobial regimen become immediate considerations. Basophilia, circulating blasts, persistent monocytosis, leukoerythroblastosis, dysplasia, splenomegaly, or associated cytopenias move the assessment away from simple drug toxicity. The common drug patterns are

consolidated in **Table 4**. Beta-lactam neutropenia is most typical after at least two weeks of intravenous treatment, including OPAT courses.⁴⁰⁻⁴¹ Linezolid toxicity is exposure-related and may appear earlier with renal impairment; prolonged treatment can produce thrombocytopenia, anemia, leukopenia, lactic acidosis, and sideroblastic change, so baseline and at least weekly CBC monitoring and selected exposure-guided TDM are useful.⁴²⁻⁴³

Trimethoprim-sulfamethoxazole, ganciclovir/valganciclovir, dapsone, rifampicin, isoniazid, flucytosine, amphotericin, and zidovudine create distinct patterns.⁴⁰⁻⁴⁴ In gray areas, I involve pharmacy early and change an essential anti-infective only after balancing the severity and causal coherence of the cytopenia against the cost of losing infection control.

Scenario 3: Fever, Cytopenias, Hyperferritinemia, and Organ Dysfunction.

Typical referral. Persistent fever, falling counts, hepatitis, rising ferritin, splenomegaly, or progressive organ failure continues despite treatment of a presumed infection.

Table 4. Anti-infective agents and clinically important hematologic toxicities.

Agent or class	Main hematologic toxicity	Typical timing/risk factors	Consultative management
Linezolid	Thrombocytopenia, anemia, leukopenia; prolonged use may cause mitochondrial toxicity, lactic acidosis, and sideroblastic anemia	Often within 7-14 days; may occur earlier with renal impairment or high exposure; older age, low baseline platelets, and prolonged therapy increase risk	Baseline and at least weekly CBC; review renal function; consider exposure-guided TDM or an alternative agent in high-risk patients; investigate persistent macrocytosis or suspected sideroblasts.
Beta-lactams, especially prolonged IV courses	Neutropenia; occasionally immune hemolysis or thrombocytopenia	Usually after ≥ 2 weeks; high cumulative dose; OPAT/endocarditis/osteomyelitis courses	CBC monitoring during prolonged therapy; stop or switch the implicated agent for severe neutropenia, particularly if febrile or infected; G-CSF only in selected severe cases.
Vancomycin	Immune thrombocytopenia; less commonly neutropenia	Variable; may be abrupt and severe; prior exposure can accelerate onset	Stop drug when suspected; avoid re-exposure; IVIG/steroids for severe immune thrombocytopenia with bleeding.
Trimethoprim-sulfamethoxazole	Neutropenia, thrombocytopenia, megaloblastic changes, hemolysis in susceptible patients	Higher risk with renal impairment, high dose, folate deficiency, prolonged therapy, immunocompromise	Check folate/B12 if macrocytosis is present; ensure renal dose adjustment; stop or replace the drug when cytopenia is severe; correct documented nutritional deficiency.
Ganciclovir / valganciclovir	Neutropenia, anemia, thrombocytopenia	Dose and renal function related; transplant and CMV treatment populations	Renal dosing, CBC monitoring, balance CMV control with marrow toxicity; consider growth factor or alternative antiviral in selected cases.
Dapsone	Oxidant hemolysis, methemoglobinemia; risk higher in G6PD deficiency but not limited to it	Dose related; G6PD deficiency, renal disease, high dose, anemia	Check G6PD before use when feasible; investigate cyanosis or a saturation gap with co-oximetry; stop dapsone. If clinically significant methemoglobinemia requires antidotal therapy, obtain urgent specialist input; methylene blue should be avoided in known G6PD deficiency because it may be ineffective and can worsen hemolysis.
Rifampicin	Immune thrombocytopenia, hemolysis, DIC-like reactions rarely	Intermittent or re-exposure patterns increase risk	Stop immediately if severe immune thrombocytopenia; avoid rechallenge; manage bleeding supportively.
Isoniazid	Rare pyridoxine-responsive sideroblastic anemia; peripheral neuropathy from pyridoxine antagonism	Malnutrition, pregnancy, alcoholism, renal disease, prolonged therapy	Provide pyridoxine according to risk and treatment guidance; investigate microcytic or dimorphic anemia with elevated iron indices or suspected sideroblasts.
Antiretroviral therapy (particularly zidovudine)	Zidovudine: macrocytic anemia and neutropenia; other effects are drug specific	Advanced HIV, marrow infection, renal/hepatic dysfunction, interacting drugs	Do not attribute cytopenias to ART alone; assess HIV control, opportunistic infections, lymphoma, nutrition, and marrow disease.
Antifungals and adjuncts	Flucytosine can cause marrow suppression; amphotericin contributes to anemia via renal injury and inflammation	Renal impairment, high levels, prolonged treatment	Monitor CBC and drug levels where relevant; renal dosing; differentiate drug effect from fungal marrow infiltration.

Legend: The examples are clinically important but not exhaustive. ART = antiretroviral therapy; CBC = complete blood count; CMV = cytomegalovirus; G6PD = glucose-6-phosphate dehydrogenase; G-CSF = granulocyte colony-stimulating factor; IV = intravenous; OPAT = outpatient parenteral antimicrobial therapy; TDM = therapeutic drug monitoring.

Ferritin is a warning signal, not a diagnosis. Sepsis can generate an HLH-like laboratory profile, and secondary HLH can initially look indistinguishable from severe infection. I therefore follow the trajectory of fever, counts, fibrinogen, triglycerides, liver injury, ferritin, organomegaly, and response to adequate antimicrobial therapy. HLH-2004 criteria and the HScore support the assessment but do not replace clinical judgment.⁴⁵⁻⁴⁷

Macrophage activation syndrome is not used here as a generic synonym for infection-associated secondary

HLH. I reserve MAS for the rheumatologic or autoinflammatory context in which that term has clinical meaning. In an infectious-diseases ward, the operative differential is secondary HLH versus severe infection-associated hyperinflammation, with occult lymphoma and marrow infection kept active until excluded.

My approach runs on three tracks at the same time: stabilize organ failure and start syndrome-directed therapy when delay is dangerous; search immediately for treatable infectious triggers; and pursue marrow or tissue

when malignancy or invasive infection remains plausible. EBV-HLH, lymphoma-associated HLH, disseminated histoplasmosis, visceral leishmaniasis, tuberculosis, rickettsial disease, and COVID-19-associated hyperinflammation do not justify identical immunosuppression. In a stable patient, prolonged immunosuppression should wait until major treatable infections have been investigated. In rapidly progressive organ failure, completion of the work-up must not delay treatment.

Scenario 4: Pancytopenia with or Without Splenomegaly: When Marrow Becomes Necessary.

Typical referral. Cytopenias persist, involve several lineages, or are accompanied by reticulocytopenia, splenomegaly, fever, B symptoms, or abnormal blood-film morphology.

Pancytopenia is a high-information syndrome. Transient viral marrow suppression may resolve, but severe reticulocytopenia, teardrop cells, blasts, monocytopenia with splenomegaly, leukoerythroblastosis, or a discordant clinical course should not be dismissed as sepsis. The differential includes HIV, EBV, CMV, viral hepatitis, parvovirus B19, disseminated tuberculosis, nontuberculous mycobacteria, histoplasmosis, leishmaniasis, brucellosis, rickettsial disease, malaria, secondary HLH, aplastic anemia, MDS, acute leukemia, lymphoma, hairy cell leukemia, hypersplenism, and drug toxicity.

When I request marrow. The procedure is justified when the result can change management: persistent unexplained cytopenias, suspected marrow infection, fever of unknown origin in an immunocompromised patient, severe reticulocytopenia, abnormal smear findings, or suspected leukemia, lymphoma, or MDS. The request must specify the problem. Aspirate and core biopsy may need morphology, flow cytometry, cytogenetics, molecular testing, bacterial/AFB/fungal cultures, special stains, and pathogen PCR. A marrow sent only for morphology can miss the diagnosis.

HIV and transplantation magnify diagnostic overlap. In advanced HIV, fever with cytopenia may reflect disseminated tuberculosis, MAC, histoplasmosis, cryptococcosis, leishmaniasis, EBV-driven lymphoma, Kaposi sarcoma-associated inflammatory syndromes, parvovirus B19 pure red-cell aplasia, secondary HLH, or treatment toxicity. Hematologic abnormalities are usually multifactorial, and marrow examination is most useful when cytopenias are persistent, unexplained, febrile, morphologically abnormal, or associated with organomegaly.⁴⁸⁻⁴⁹ In transplant recipients, valganciclovir/ganciclovir, trimethoprim-sulfamethoxazole, mycophenolate, azathioprine, calcineurin inhibitors, CMV, HHV-6, EBV/PTLD,

parvovirus B19, and drug-associated TMA must be assessed in parallel.⁵⁰⁻⁵²

A separate host-safety issue is asplenia or functional hyposplenism. Vaccination and antimicrobial-prevention strategies vary by age and jurisdiction, but any febrile illness still requires urgent assessment and empiric antibiotics per local protocols; vaccination does not eliminate risk.⁵³⁻⁵⁴

Scenario 5: Severe Anemia or Hemolysis.

Typical referral. Hemoglobin falls rapidly, reticulocytes or hemolysis markers change, the DAT becomes positive, hemoglobinuria appears, or transfusion compatibility becomes difficult.

The first step is classification rather than treatment by label: immune-mediated, microangiopathic, mechanical, drug-induced, parasite-related, enzyme-related, or transfusion-associated. Warm autoimmune hemolytic anemia may accompany viral infection, lymphoproliferation, immune dysregulation, or drugs. Cold agglutinin-mediated hemolysis can accompany *Mycoplasma pneumoniae* or EBV infection, but persistent cold agglutinin disease usually points to a clonal B-cell disorder. Microangiopathic hemolysis returns immediately to Scenario 1 because DIC, TTP, HUS, malignant hypertension, drug-associated TMA, transplant-associated TMA, and severe infection-associated endothelial injury cannot be separated by hemoglobin alone.

Reticulocyte response is decisive. Profound reticulocytopenia suggests reduced production rather than peripheral destruction; parvovirus B19 pure red-cell aplasia is particularly important in transplant recipients, advanced HIV, and other immunocompromised patients. PCR is generally more useful than serology in this setting, and IVIG is often effective.⁵⁵⁻⁵⁶ Recent transfusion adds delayed or acute hemolytic transfusion reactions to the differential.⁵⁷ When anemia is physiologically dangerous, red-cell support should not be delayed solely because complete serologic compatibility cannot be achieved; transfusion medicine involvement is essential.

Travel and exposure history can change the entire pathway. Malaria requires thick and thin smears, a rapid diagnostic test where appropriate, and parasite quantification; babesiosis is assessed by smear and, when necessary, PCR. Severe malaria can produce anemia, thrombocytopenia, DIC, and multiorgan failure.⁵⁸⁻⁵⁹ After intravenous artesunate, hemoglobin and hemolysis markers should be monitored weekly for four weeks because delayed hemolysis usually appears after one to three weeks but can occur in the fourth.⁶⁰⁻⁶¹ Severe non-malaria febrile illness in travelers and migrants remains an epidemiologic diagnosis as much as a laboratory one.⁶²

Table 5. Cross-scenario pathogen- and host-linked hematologic patterns.

Infection or syndrome	Common hematologic manifestations	Hematology consult pitfalls	High-yield actions
HIV infection	Anemia, neutropenia, thrombocytopenia, lymphopenia, marrow dysplasia-like changes, lymphoma, TTP, opportunistic infection-related cytopenias	Attributing cytopenia to HIV alone while missing lymphoma, marrow TB/MAC/fungal disease, drug toxicity, or immune thrombocytopenia	Assess ART status, CD4 count, viral load, drugs, opportunistic infection, smear, reticulocytes; consider marrow biopsy for unexplained cytopenia plus fever, B symptoms, splenomegaly, or abnormal smear.
Sepsis and septic shock	Thrombocytopenia, leukocytosis or leukopenia, anemia of inflammation, DIC/SIC, elevated D-dimer, low fibrinogen in overt DIC, microangiopathic features	Misclassifying DIC as TTP or correcting coagulation tests without bleeding or procedures	Serial hemostasis panel; source control and antimicrobial therapy; transfusion only when clinically indicated; evaluate schistocytes and organ pattern.
Endocarditis	Anemia of inflammation, hematuria, immune phenomena, thrombocytopenia, splenomegaly, sometimes DIC or embolic infarcts	Confusing anemia of inflammation with isolated iron deficiency; missing hemolysis from prosthetic valves	Blood cultures, echocardiography, iron studies with inflammation context, smear, hemolysis labs when prosthetic valves present.
Tuberculosis and disseminated mycobacteria	Anemia of inflammation, pancytopenia, marrow granulomas, HLH, splenomegaly, drug-induced cytopenias from therapy	Starting HLH immunosuppression without parallel mycobacterial investigation in compatible cases	Marrow biopsy/culture when pancytopenia or fever persists; monitor CBC during anti-TB therapy.
Viral hepatitis and chronic liver disease	Thrombocytopenia, hypersplenism, anemia, coagulopathy, immune cytopenias, HCC-associated thrombosis	Overcorrecting INR as if it measured bleeding risk accurately in cirrhosis	Assess portal hypertension, fibrinogen, platelet count, procedures, varices, antiviral treatment status.
EBV/CMV	Atypical lymphocytosis, lymphadenopathy, splenomegaly, hepatitis, ITP, AIHA, HLH, marrow suppression in immunocompromised hosts	Giving corticosteroids for cytopenia without assessing HLH, lymphoma, or transplant context	Quantitative PCR when immunocompromised; DAT and hemolysis labs; HLH screen if fever plus falling counts and ferritin.
Parvovirus B19	Reticulocytopenic anemia, aplastic crisis in hemolytic disorders, pure red cell aplasia in immunocompromised patients	Relying on serology in immunocompromised hosts	Reticulocyte count; parvovirus PCR; IVIG in chronic PRCA; adjust immunosuppression if feasible.
Malaria	Thrombocytopenia, hemolysis, anemia, splenomegaly, DIC in severe disease, post-artesunate delayed hemolysis	Missing malaria in febrile thrombocytopenia; failing to follow hemolysis after artesunate	Thick/thin smear and rapid test; parasite density; severe malaria criteria; monitor Hb, LDH, bilirubin, and haptoglobin weekly for 4 weeks after IV artesunate.
Dengue and arboviruses	Leukopenia, thrombocytopenia, hemoconcentration, plasma leakage, bleeding in severe disease	Prophylactic platelet transfusion for low count alone	Monitor warning signs, hemodynamics, hematocrit; avoid NSAIDs; transfuse red cells/blood only for significant bleeding or shock; no routine steroids.
Leishmaniasis, histoplasmosis, brucellosis, rickettsioses	Fever, splenomegaly, pancytopenia, HLH-like inflammation	Diagnosing idiopathic HLH or lymphoma before adequate infection testing	Exposure/travel history; marrow aspirate/biopsy with cultures/stains/PCR; targeted therapy.
COVID-19	Inflammation, thrombocytopenia, lymphopenia, high D-dimer, VTE/PE, microvascular injury; rare ITP/TTP/AIHA	Assuming D-dimer alone mandates therapeutic anticoagulation in all patients	Use severity-specific anticoagulation guidance; evaluate true thrombosis and bleeding risk; consider alternative diagnoses when cytopenias are severe.

Legend: The patterns should be interpreted together with epidemiology, travel history, immune status, treatment exposure, and blood-film morphology. AIHA = autoimmune hemolytic anemia; ART = antiretroviral therapy; CMV = cytomegalovirus; COVID-19 = coronavirus disease 2019; DAT = direct antiglobulin test; EBV = Epstein-Barr virus; Hb = hemoglobin; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HLH = hemophagocytic lymphohistiocytosis; MAC = Mycobacterium avium complex; PRCA = pure red-cell aplasia; TB = tuberculosis.

Scenario 6: Persistent Lymphadenopathy, Effusion, or Unexplained Inflammation.

Typical referral. Fever, cytopenias, high LDH, lymphadenopathy, an extranodal mass, recurrent effusion, or an inflammatory syndrome persists despite microbiologically adequate treatment.

This is where premature closure causes the most harm. A positive blood culture, viral PCR, or radiologic pneumonia does not exclude lymphoma, acute leukemia, plasma-cell disease, or PTLT. Conversely, EBV DNAemia, a monoclonal protein, or reactive lymphadenopathy does not prove cancer. I keep one

uncomfortable question active: what malignant process would explain the whole syndrome better than the infection currently being treated? The question is especially important in advanced HIV, transplantation, iatrogenic immunosuppression, chronic viral hepatitis, HTLV-1 exposure, and persistent EBV- or HHV-8/KSHV-driven inflammation.⁶³⁻⁷⁰

Lymphoma is the neoplastic process most likely to masquerade as infection. HIV-associated disease includes DLBCL, Burkitt lymphoma, primary CNS lymphoma, plasmablastic lymphoma, primary effusion lymphoma, and Hodgkin lymphoma.^{63-66,71} Prediagnostic polyclonal serum free light chains are associated with later HIV-associated lymphoma, but they mark B-cell activation and risk rather than serving as stand-alone diagnostic tests.⁷² Plasmablastic lymphoma is a useful model of the diagnostic problem because immunodeficiency, plasmacytic differentiation, and frequent CD20 negativity create overlap with aggressive lymphoid and plasma-cell neoplasms.⁷³ HIV alone is not a reason to withhold effective lymphoma therapy; ART, opportunistic-infection prophylaxis, drug interactions, hepatitis screening, CNS assessment, and treatment toxicity must be coordinated.⁶⁵

Primary CNS lymphoma highlights the need for reassessment. In advanced HIV, toxoplasmosis, tuberculosis, cryptococcosis, progressive multifocal leukoencephalopathy, and other focal infections compete with malignancy. Empiric anti-toxoplasma therapy may be appropriate, but lack of clinical or radiologic response should prompt rapid reconsideration. CSF EBV DNA is supportive, not a tissue substitute when uncertainty persists and biopsy is feasible.⁶⁶

EBV and HHV-8/KSHV sit directly at the infection-neoplasia boundary. EBV DNAemia is a warning signal rather than a diagnosis of PTL; architecture, clonality, EBER status, clinical context, burden, organ involvement, and allograft constraints determine urgency and treatment.^{52,67-68} HHV-8/KSHV is linked to Kaposi sarcoma, multicentric Castleman disease, primary effusion lymphoma, HHV-8-positive DLBCL, and KSHV inflammatory cytokine syndrome.⁶⁹⁻⁷⁰ Fever, edema, effusions, cytopenias, hypoalbuminemia, high CRP, hypergammaglobulinemia, splenomegaly, and an HLH-like phenotype should not be labelled as nonspecific sepsis without node-, effusion-, skin-, or marrow-directed diagnosis.

Other viral links require different decisions. In selected untreated HCV-positive indolent lymphomas without criteria for immediate conventional therapy, prospective phase II data support direct-acting antivirals as first-line treatment, with universal sustained virologic response and a 45% lymphoma response rate.⁷⁴ HBV is primarily a treatment-safety issue because anti-CD20 therapy, high-dose corticosteroids, anthracyclines, and several lymphoma regimens can reactivate infection;

screening and prophylaxis or monitoring must precede treatment.⁷⁵ HTLV-1 testing is required in compatible epidemiologic settings or unexplained mature T-cell neoplasia.⁷⁶

Acute leukemia and plasma-cell disease are different forms of the same diagnostic trap. Blasts, Auer rods, severe unexplained pancytopenia, leukoerythroblastosis, marked monocytosis with dysplasia, or persistent abnormal neutropenia should lead to urgent flow cytometry and marrow assessment rather than repeated antimicrobial escalation. Suspected APL is an emergency: all-trans retinoic acid is started while molecular confirmation is obtained.⁷⁷ With monoclonal gammopathy, acute inflammation can generate polyclonal hypergammaglobulinemia and rouleaux, while a true monoclonal component may be incidental or may indicate myeloma, lymphoplasmacytic lymphoma, AL amyloidosis, cryoglobulinemia, cold agglutinin disease, or MGCS. HIV-related polyclonal free light-chain elevation reflects B-cell activation,⁷⁸ and MGUS can be present even in younger adults at HIV diagnosis.⁷⁹

When I insist on tissues. Tissues become the shortest path out of ambiguity when fever and inflammatory markers persist despite adequate antimicrobial therapy; lymphadenopathy is bulky, progressive, asymmetric, extranodal, or PET-avid in a malignant pattern; cytopenias persist with splenomegaly, leukoerythroblastosis, or abnormal lymphoid/plasmacytoid cells; an effusion recurs; EBV/HHV-8 disease is suspected; or secondary HLH lacks a convincing infectious trigger. Fine-needle aspiration is usually insufficient as the sole procedure for lymphoma. Allocate core or excisional tissue, effusion, marrow, or another accessible site prospectively for histology, immunohistochemistry, EBER, HHV-8 LANA, flow cytometry, cytogenetics/FISH, molecular testing, and microbiology when infection remains in the differential.

Cross-Cutting Support Decisions: Transfusion and Hemostasis. Transfusion decisions recur across all six scenarios and should follow physiology rather than laboratory reflex (**Table 7**). For most hemodynamically stable adult inpatients, a restrictive red-cell strategy is appropriate, with transfusion generally considered below 7 g/dL; higher thresholds may be selected for cardiac surgery, orthopedic surgery, or pre-existing cardiovascular disease.⁸⁰ Randomized septic-shock data show no survival advantage for a 9 g/dL threshold over 7 g/dL.⁸¹ The number is not applied mechanically in active hemorrhage, myocardial ischemia, profound hypoxemia, ongoing hemolysis, or shock.

Platelet thresholds are indication-specific. The 2025 AABB/ICTMG guideline recommends or suggests lower thresholds than many historical practices: $<10 \times 10^9/L$ in

Table 6. Neoplastic hematology at the infectious-diseases interface: red flags, diagnostic traps, and first actions.

Entity or interface	Consultative clues	Diagnostic traps	First actions and minimum work-up
HIV-associated aggressive lymphoma: DLBCL, Burkitt lymphoma, plasmablastic lymphoma, PCNSL	B symptoms, rapidly enlarging nodes or extranodal masses, oral/GI/CNS disease, high LDH, cytopenias, marrow involvement, TLS risk.	Attributing fever and cytopenias to infection or HIV alone; giving corticosteroids before diagnostic tissue when avoidable; confusing PCNSL with toxoplasmosis without reassessment.	Core/excisional biopsy; PET/CT; LDH/uric acid; HIV viral load/CD4; HBV/HCV serology; histology/IHC, EBER, MYC testing when indicated; CSF evaluation in CNS-risk settings; TLS prevention and ART/chemotherapy interaction review.
Hodgkin lymphoma in people living with HIV	Fever, night sweats, weight loss, lymphadenopathy, splenomegaly, marrow symptoms; EBV association is common.	Assuming tuberculosis or immune reconstitution alone; relying on imaging without tissue.	Excisional/core biopsy with CD30, CD15, PAX5 and EBER; PET/CT staging; evaluate opportunistic infections; coordinate ART, chemotherapy, and antimicrobial prophylaxis.
EBV-driven LPD and PTLD	Transplant or iatrogenic immunosuppression, EBV DNAemia, fever, adenopathy, extranodal disease, cytopenias, organ involvement.	Treating EBV viral load as equivalent to PTLD diagnosis; reducing immunosuppression without tissue or organ-risk planning.	Biopsy with architecture, clonality, EBER, flow/IHC; EBV viral-load trend; assess graft risk; coordinate transplant team, pathology, oncology, and infectious diseases.
HHV-8/KSHV spectrum: KS, MCD, KICS, PEL, HHV-8-positive DLBCL	Fever, edema, effusions, pleural/peritoneal/pericardial disease, cytopenias, high CRP, hypoalbuminemia, splenomegaly, Kaposi lesions.	Calling the syndrome sepsis, idiopathic HLH, or tuberculosis effusion without HHV-8-directed studies.	Skin/node/effusion diagnosis; HHV-8 LANA IHC; EBER; effusion cytology and flow; plasma HHV-8 DNA when available; HIV testing/status; early oncology input.
HCV-associated indolent B-cell LPD/MZL and cryoglobulinemia	Splenomegaly, cytopenias, monoclonal or oligoclonal IgM, mixed cryoglobulinemia, purpura, neuropathy, renal disease.	Treating as autoimmune cytopenia or vasculitis without HCV RNA and clonal B-cell assessment.	HCV RNA, cryoglobulins, C4, rheumatoid factor, SPEP/IFE, and marrow or node evaluation as indicated; in untreated HCV-positive indolent lymphoma without criteria for immediate conventional therapy, prioritize direct-acting antiviral treatment.
HTLV-1-associated adult T-cell leukemia/lymphoma	Origin or exposure from endemic regions, mature T-cell process, skin lesions, generalized nodes, hypercalcemia, eosinophilia, opportunistic infection, atypical lymphoid cells.	Misclassifying as cutaneous T-cell lymphoma, sepsis, or nonspecific T-cell lymphoma without HTLV-1 testing.	HTLV-1 serology/proviral confirmation, flow cytometry, calcium/LDH, tissue biopsy, staging, strongyloidiasis assessment before immunosuppression where epidemiologically relevant.
Acute leukemia, MDS/CMML, marrow-infiltrating lymphoma	Persistent fever plus blasts, severe pancytopenia, monocytosis, dysplasia, leukoerythroblastosis, DIC, oral ulcers, recurrent infection.	Prolonged antimicrobial escalation while smear or marrow clues are present.	Urgent smear review; flow cytometry; marrow aspirate/biopsy with cytogenetics/molecular testing; cultures/stains if infection remains possible; if APL is suspected, initiate the APL emergency pathway and all-trans retinoic acid without waiting for molecular confirmation.
Plasma cell dyscrasia and monoclonal gammopathy	Rouleaux, high globulin, anemia, renal dysfunction, hypercalcemia, bone pain/lytic lesions, neuropathy, cold agglutinin disease, cryoglobulins.	Overcalling MGUS during acute inflammation or ignoring myeloma/AL amyloidosis/MGCS when organ damage is present.	SPEP/IFE, serum free light chains interpreted with renal function, urine studies, calcium/renal evaluation, imaging and marrow biopsy when CRAB/amyloid/MGCS features are present.

Legend: This is a consultative triage table, not a treatment algorithm. APL = acute promyelocytic leukemia; ART = antiretroviral therapy; CRAB = hypercalcemia, renal impairment, anemia, bone lesions; DLBCL = diffuse large B-cell lymphoma; EBER = Epstein-Barr virus-encoded small RNA; GI = gastrointestinal; HHV-8/KSHV = human herpesvirus 8/Kaposi sarcoma-associated herpesvirus; IFE = immunofixation electrophoresis; IHC = immunohistochemistry; KICS = KSHV inflammatory cytokine syndrome; KS = Kaposi sarcoma; LANA = latency-associated nuclear antigen; LDH = lactate dehydrogenase; LPD = lymphoproliferative disorder; MCD = multicentric Castlemann disease; MGCS = monoclonal gammopathy of clinical significance; MZL = marginal zone lymphoma; PCNSL = primary central nervous system lymphoma; PEL = primary effusion lymphoma; PTLD = post-transplant lymphoproliferative disorder; SPEP = serum protein electrophoresis; TLS = tumor lysis syndrome.

common hypoproliferative prophylactic settings and for central venous catheter placement at compressible sites, $<20 \times 10^9/L$ before lumbar puncture and for low-risk interventional radiology, and $<50 \times 10^9/L$ for high-risk interventional radiology and major nonneuraxial surgery.⁸² In DIC, support is driven by bleeding, procedure risk, and the specific deficit. In TTP and HIT, prophylactic platelet transfusion is avoided unless major bleeding or an emergent procedure requires it. Dengue remains the clearest example of why a low count alone is not a transfusion indication.³⁶⁻³⁸

Making the Consultation Reproducible

The consult note as a safety instrument. The consultation note should be shorter than a textbook chapter but more explicit than an impression list. I state the exact clinical question, acuity, leading diagnosis, dangerous alternatives, immediate actions, samples that should precede therapy, tests intentionally deferred, transfusion and anticoagulation thresholds, the contingency plan, and the timing of reassessment. Time-sensitive recommendations, including suspected TTP, bleeding DIC, HIT, secondary HLH, acute leukemia, severe hemolysis, unexpected parasites, or a nonstandard transfusion decision, are also communicated verbally. Communication is part of the intervention.

Table 7. Transfusion, hemostatic support, and selected safety rules.

Situation	Preferred approach	Rationale	Caveat
Stable nonbleeding medical inpatient anemia	Restrictive red-cell transfusion; often consider transfusion when Hb <7 g/dL	Reduces exposure without worse outcomes in most stable adult inpatients	Individualize for myocardial ischemia, severe hypoxemia, active bleeding, shock, chronic transfusion programs.
Dengue thrombocytopenia without bleeding	No prophylactic platelet transfusion	Platelets do not prevent severe bleeding and may worsen fluid overload or prolong care	Transfuse blood products for clinically significant bleeding, hemodynamic instability, or falling hematocrit despite fluids.
DIC with bleeding	Treat trigger; platelets, plasma, cryoprecipitate/fibrinogen based on deficit and bleeding/procedure risk	Consumption coagulopathy requires source control plus targeted replacement	Do not chase mild lab abnormalities in nonbleeding patients.
Suspected TTP	Avoid platelet transfusion unless life-threatening bleeding; start plasma exchange urgently	Problem is microvascular thrombosis, not simple platelet shortage	Draw ADAMTS13 before plasma if feasible, but do not delay treatment.
HIT	Avoid platelet transfusion unless major bleeding or urgent invasive procedure; anticoagulate with non-heparin agent	Thrombosis is the dominant risk	Anticoagulant intensity must account for bleeding risk and renal/hepatic function.
Lumbar puncture in thrombocytopenia	Consider platelet transfusion when the platelet count is <20 × 10 ⁹ /L; individualize for additional bleeding risks	The 2025 AABB/ICTMG guideline supports a lower, indication-specific threshold	This threshold does not define safety for neuraxial anesthesia, which requires separate specialist and institutional guidance.
Major nonneuraxial surgery in thrombocytopenia	Consider platelet transfusion when the platelet count is <50 × 10 ⁹ /L	Recognizes the bleeding consequences of major surgery while avoiding unnecessary liberal transfusion	Individualize for active bleeding, platelet dysfunction, procedure type, and local policy.
Asplenia or planned splenectomy	Apply current age- and jurisdiction-specific vaccination and antimicrobial-prevention guidance; provide written fever and emergency-antibiotic instructions	Reduces the risk of overwhelming infection with encapsulated organisms	Any febrile illness requires urgent assessment and empiric antibiotics according to local protocols; vaccination does not eliminate risk.

Legend: Thresholds are decision aids and must be individualized according to bleeding, procedure type, hemodynamics, myocardial ischemia, hypoxemia, renal or hepatic failure, and local policy. Lumbar puncture and major nonneuraxial surgery require distinct platelet thresholds; these recommendations do not apply to neuraxial anesthesia. Asplenia-related care should follow current national guidance and local resistance patterns.⁵³⁻⁵⁴ ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; DIC = disseminated intravascular coagulation; Hb = hemoglobin; HIT = heparin-induced thrombocytopenia; TTP = thrombotic thrombocytopenic purpura.

Box 2. The hematology consult note used as a safety instrument.

Section	What to include	Example phrasing
Clinical question and acuity	State the exact question and time sensitivity	"Urgent consult for platelets 24 × 10 ⁹ /L and schistocytes in septic shock: exclude TTP versus DIC."
Syndrome definition	Lineage(s), severity, trajectory, symptoms	"New severe thrombocytopenia with MAHA and renal injury; PT/aPTT only mildly abnormal."
Most likely diagnosis	One leading explanation integrating infection, drugs, and morphology	"Findings fit sepsis-induced coagulopathy more than TTP because fibrinogen is falling, PT is prolonged, cultures are positive, and ADAMTS13 sample has been sent."
Dangerous alternatives	List what must not be missed	"TTP remains a dangerous alternative; if neurologic changes or worsening MAHA occur, start plasma exchange while awaiting ADAMTS13."
Immediate recommendations	Actionable management, not vague suggestions	"Stop all heparin; initiate a non-heparin anticoagulant if bleeding risk permits; send a PF4/heparin immunoassay and obtain functional confirmation according to the immunoassay result and local assay availability because the 4Ts score is 6."
Diagnostic stewardship	State tests deferred or not indicated	"No inherited thrombophilia testing during acute infection; results would not change acute management and may be misleading."
Transfusion/anticoagulation thresholds	Explicit thresholds and exceptions	"No platelet transfusion unless active bleeding or procedure; target fibrinogen >150 mg/dL if bleeding continues."
Follow-up and contingency	Who will check what and when	"Hematology will review the smear and fibrinogen trend in 6 hours; call immediately for bleeding, neurologic symptoms, or platelet count <10 × 10 ⁹ /L."

Legend: The note should define acuity, syndrome, dangerous alternatives, immediate actions, explicit thresholds, and follow-up responsibility. ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; HIT = heparin-induced thrombocytopenia; MAHA = microangiopathic hemolytic anemia; PF4 = platelet factor 4; TTP = thrombotic thrombocytopenic purpura.

Box 3. High-value negative recommendations in my infectious-diseases hematology practice.

• Do not test for HIT when the 4Ts score is low.
• Do not transfuse platelets prophylactically in dengue solely because the platelet count is low.
• Do not order inherited thrombophilia testing during acute, clearly provoked infection-associated VTE.
• Do not diagnose ITP without smear review and exclusion of pseudothrombocytopenia, HIV, HCV, drug causes, DIC, and TMA.
• Do not diagnose HLH from ferritin alone; use the complete clinical trajectory and syndrome criteria.
• Do not start prolonged corticosteroid or immunosuppressive treatment for unexplained fever and cytopenia without actively considering tuberculosis, invasive fungal disease, leishmaniasis, EBV-driven lymphoma, and other treatable infections when clinical stability permits.
• Do not manage progressive lymphadenopathy, recurrent malignant effusion, persistent leukoerythroblastosis, or PET-avid extranodal disease as infection alone when the clinical course is discordant.
• Do not perform marrow biopsy for transient mild cytopenia that is improving with infection control unless morphology or the clinical trajectory suggests another process.

Table 8. Quality indicators derived from the consultative model.

Domain	Process indicator	Outcome or balancing measure
TTP/TMA pathway	Median time from MAHA recognition to hematology review; ADAMTS13 sample before plasma when feasible; time to plasma exchange	Mortality, ICU length of stay, relapse planning, line complications.
HIT stewardship	Percentage of HIT tests with documented 4Ts score; percentage low 4Ts tested	Bleeding from unnecessary alternative anticoagulation; missed HIT thrombosis.
DIC/SIC	Serial fibrinogen/platelet/PT/D-dimer monitoring in septic shock with coagulopathy; documentation of bleeding/procedure indication for transfusion	Blood product use, bleeding, thrombosis, source-control timing.
Dengue	Percentage of thrombocytopenic nonbleeding dengue patients receiving prophylactic platelets	Fluid overload, bleeding, ICU transfer, transfusion reactions.
Antimicrobial cytopenia	CBC monitoring in linezolid or prolonged beta-lactam therapy; medication timeline in consult note	Severe neutropenic infection, antimicrobial interruption without alternative, cytopenia recovery.
Transfusion medicine	Documentation of the physiologic indication when RBC transfusion occurs above the context-specific guideline threshold	Transfusion reactions, volume overload, blood utilization.
HLH	Ferritin plus cytopenia escalation pathway; HScore or HLH criteria documented when suspected	Time to trigger diagnosis, inappropriate immunosuppression, survival.
Marrow biopsy stewardship	Indication, planned cultures/stains/flow/cytogenetics documented before procedure	Diagnostic yield, repeat biopsy rate, time to pathogen or malignancy diagnosis.
Neoplastic interface	Documentation of tissue-diagnosis plan for persistent lymphadenopathy, malignant effusion, suspected PTLN/HHV-8 disease, or unexplained cytopenia with malignant smear features	Time to biopsy, diagnostic yield, avoidable corticosteroid exposure before tissue, time to oncologic referral.

Legend: The indicators are proposed for implementation studies and local audit and should be adapted to case-mix, laboratory access, transfusion services, and referral structure. DIC = disseminated intravascular coagulation; Hb = hemoglobin; HIT = heparin-induced thrombocytopenia; HLH = hemophagocytic lymphohistiocytosis; SIC = sepsis-induced coagulopathy; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.

Diagnostic stewardship: what I deliberately do not do. A useful method defines restraint as clearly as escalation. Unselected molecular panels, inherited thrombophilia tests, autoimmune panels, marrow biopsies, and non-directed imaging create false-positive results, cost, and delay. Each test should answer a question that opens a management branch. The same rule applies to EBV or HHV-8 testing, PET/CT, and marrow studies: a vague concern is not an indication.

From individual method to service quality. A personal approach becomes useful to a service only when it can be reproduced and audited. The model described here relies on rapid morphology review, defined pathways for

TMA, DIC/SIC, HIT, secondary HLH, antimicrobial cytopenia, transfusion decisions, and suspected neoplasia, and early partnership with infectious diseases, intensive care, pharmacy, transfusion medicine, microbiology, pathology, nephrology, and oncology. The most informative measures are process measures: time from TTP suspicion to plasma exchange, low-4Ts testing rates, inappropriate prophylactic platelet transfusion in dengue, time from severe neutropenia to a medication plan, documentation of transfusion rationale, marrow diagnostic yield, and time to tissue diagnosis.

Boundaries and Research Priorities. This is an experience-informed expert paper, not evidence

generated by an institutional cohort. It does not provide consultation volumes, case frequencies, audited outcomes, or comparative effectiveness data. Its value lies in making a mature decision sequence explicit and showing how guideline-based standards are applied when infection, treatment toxicity, organ failure, immune dysfunction, and malignancy overlap. The approach must be adapted to physiology, comorbidity, local epidemiology, diagnostic access, and institutional policy.

The next step is prospective evaluation rather than further expansion of the differential diagnosis. Multicenter registries and implementation studies should test whether structured consultation pathways shorten time to TTP therapy or tissue diagnosis, improve transfusion and anticoagulation safety, increase marrow diagnostic yield, and reduce low-value testing. That research agenda is narrower than a general biomarker program, but it directly tests the contribution claimed by this How I Treat model.

Conclusions. New hematologic abnormalities in patients hospitalized with infectious diseases should be approached as time-dependent syndromes rather than isolated laboratory deviations. The sequence developed during two decades of daily consultation at Spallanzani is to identify conditions in which delay changes outcome, use morphology and chronology to define the dominant mechanism, and order only tests that open a management branch. Treatment may need to precede confirmation in TTP, clinically significant DIC/SIC, HIT, APL, severe hemolysis, or rapidly progressive secondary HLH; conversely, low-value testing, reflex transfusion, and premature attribution to infection should be actively avoided. Marrow or tissue diagnosis becomes necessary when the clinical trajectory is discordant with the presumed infection. Guidelines define the standards, but

complex inpatients require those standards to be sequenced, combined, and repeatedly reassessed. The practical value of this framework now requires prospective evaluation through process measures such as time to definitive therapy or tissue diagnosis, transfusion and anticoagulation safety, and diagnostic yield. Its governing rule remains simple: identify the finding that can change outcome, act at the correct level of urgency, and define in advance when the diagnosis must be reopened.

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