Sepsis and the Immunocompromised Host

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KEYWORDS

• Sepsis • Immunocompromised • Malignancy • Transplant • Neutropenia • Immunomodulation • ICU triage

KEY POINTS

- Immunocompromised patients are increasing, and *delayed intensive care unit admission worsens outcomes*.
- Sepsis in this group is *biologically distinct*—not just *sepsis with comorbidities*.
- *No single consensus definition/stratification* exists; immune-defect-based frameworks may be better than disease labels.
- *Diagnosis can be challenging*: fever and white blood cells (WBC) signals may be absent; midregional proadrenomedullin and computed tomography (CT)/advanced tests can help, but polymerase chain reaction positives may reflect colonization.
- Management is complex: use *early*, *risk-adapted antimicrobials* but also screen for *sepsis-mimicking immune syndromes*.

INTRODUCTION

Immunosuppression is a critical risk factor for infection and sepsis,[1] and as the global burden of acquired immunosuppression continues to grow,[2] optimizing care for this vulnerable population represents an urgent public health priority. The prevalence of immunosuppression within the general population is increasing, with up to one-third of all critically ill patients being immunocompromised at baseline. Three converging trends necessitate renewed focus. First, survival among patients with immunocompromising conditions has improved dramatically.[3] Contemporary data demonstrate that intensive care unit (ICU) survival in selected patients with cancer approaches that of immunocompetent patients when adjusted for organ failure severity.[4] Yet triage

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Crit Care Clin 42 (2026) 821–837
https://doi.org/10.1016/j.ccc.2026.05.007 **criticalcare.theclinics.com**
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Abbreviations	
APCs	antigen-presenting cells
CAR	chimeric antigen receptor
CRP	C-reactive protein
CRS	cytokine release syndrome
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HSCT	hematopoietic stem cell transplantation
ICANS	immune effector cell-associated neurotoxicity syndrome
ICU	intensive care unit
IL	interleukin
MR-proADM	midregional proadrenomedullin
PCR	polymerase chain reaction
PJP	pneumocystis jirovecii
SOT	solid organ transplantation

thresholds remain inconsistent, and delayed ICU transfer is associated with excess mortality.[5,6] Second, the therapeutic landscape has fundamentally altered immune function by introducing unique infectious risks and inflammatory syndromes that may mimic sepsis. Third, immunocompromised patients are underrepresented in sepsis trials. The Surviving Sepsis Campaign recommendations are derived largely from immunocompetent populations.[7] Whether fluid strategies, vasopressor thresholds, steroid responsiveness, and antimicrobial duration should differ remains uncertain. Importantly, sepsis in the immunocompromised host is not simply sepsis plus comorbidity.

Understanding the relationship between immunity and infection risk is crucial in developing personalized approaches to patient care and improving clinical outcomes. However, with prolonged survival among those with varying immunosuppressive conditions, compounded by an aging and increasingly comorbid population, this relationship is more complex than ever before. The recent seismic expansion in immunomodulating therapies, including biologics and T-cell-engaging therapies, has required physicians to recognize a new repertoire of immune toxicities, including novel infections and immune syndromes masquerading as sepsis. With clear evidence supporting an association between immune dysfunction and adverse clinical outcomes among critically ill patients, early sepsis identification, awareness of sepsis-mimickers, and tailored management strategies are of paramount importance for optimizing patient care and long-term outcomes.

This article aims to summarize the current understanding of sepsis in the immunocompromised host, highlighting diagnostic challenges and management controversies while raising awareness of important parallel immune syndromes and future research opportunities. Immunosuppression may result from primary immunodeficiencies that is, caused by genetic or congenital abnormalities, or secondary immunodeficiencies, which are acquired throughout the lifespan owing to underlying disease, comorbidities, and immunosuppressive agents. This article focuses on the latter; however, the general approaches and considerations outlined here may be applicable to the broader population. Importantly, sepsis-induced immunosuppression in critical illness is an increasingly recognized entity, underscoring the importance of viewing the immune system as a dynamic rather than static state, the kinetics of which evolve over the course of a hospital admission. Integrating temporal patterns of immune dysfunction into the care of critically ill patients represents an important area of ongoing research that, while beyond the scope of this article, has been described elsewhere.[8]

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DEFINITION OF IMMUNOCOMPROMISED HOST

One of the greatest challenges facing the field is the variability in how immunocompromised patients are defined, described, and stratified. Without consistent definitions, clinical and trial populations will remain detrimentally heterogeneous, limiting the application and generalizability of findings. Unfortunately, there is no consensus definition that currently exists. Traditional disease-based categories include: hematologic malignancy, solid tumor receiving active therapy, hematopoietic stem cell transplantation (HSCT), solid organ transplantation (SOT), autoimmune or vasculitic disease, advanced human immunodeficiency virus (HIV) infection, and chronic corticosteroid exposure.

While a useful starting point, this approach is limited by a lack of granularity and obscures heterogeneity. With the rising complexity of the modern immunocompromised host, many patients carry multiple diagnoses with overlapping or competing immune defects, making it difficult to identify a single dominant immune pathology resulting in intervention uncertainty. The number of diseases and exposures that may result in an immunocompromised state are also very broad and therefore creating a comprehensive list of possible conditions may be cumbersome. For example, patients with HIV, sick cell disease or history of splenectomy, may not fit into any of the abovementioned categories. Furthermore, these conditions are not static and may evolve and differ within the same disease state over time (eg, a patient's immunocompromised state at the time of HIV diagnosis verses at the time of follow-up after years of appropriate antiviral therapy). Importantly, immunosuppression may affect the immune system in terms of both quantity—as seen in neutropenia or lymphopenia—and quality—as seen in functional asplenia, chronic steroid use, or uremia, where cell counts may appear normal despite profound functional impairment. These important considerations remain agnostic to the disease-based classification system.

Immune Defect Classification

An alternative framework stratifies patients according to predicted baseline immune defects, categorized as[1] barrier disruption,[2] innate immune dysfunction,[3] adaptive immune suppression, and[4] immune reprogramming (**Fig. 1**, **Table 1**). This approach offers a more precise and flexible alternative to disease-based classification, compelling clinicians to consider multiple simultaneous forms of immune compromise and their associated infection risks.

Barrier disruption

The outermost layer of the host's defense system is the anatomic barrier that is, the patient's physical *envelope*, which provides both mechanical and chemical protection against pathogen entry. Barrier defense encompasses skin integrity, mucosal membrane function, mucociliary clearance, and the absence of foreign bodies breaching sterile compartments. Barrier disruption is particularly prevalent in patients with hematological malignancy or those undergoing cytotoxic chemotherapy, in whom mucositis, chemotherapy-induced colitis, and indwelling central venous catheters are common. Another important patient population that cannot be overlooked in this category are burn patients, whose mortality due to nosocomial infection are significant. These disruptions facilitate translocation of cutaneous and gastrointestinal flora into the bloodstream, where even organisms of low intrinsic virulence, such as coagulase-negative staphylococci, can cause life-threatening sepsis.

Innate immune dysfunction

The innate immune system constitutes the first cellular line of defense, providing rapid, nonspecific responses to invading pathogens. Its principal functions include

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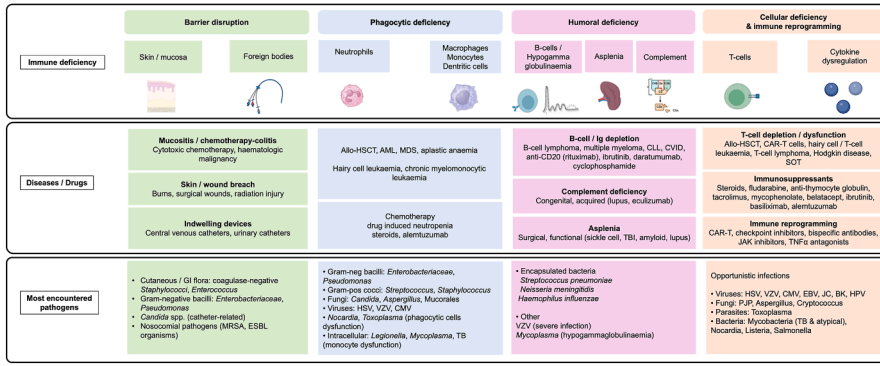

Fig. 1. Classification of immunocompromised state based upon immune deficiencies. Allo-HSCT, Allogeneic hematopoietic stem cell transplant; AML, Acute myeloid leukemia; CLL, Chronic lymphocytic leukemia; CMV, Cytomegalovirus; CVID, Common variable immune deficiency; EBV, Epstein-barr virus; ESBL, Extended spectrum beta-lactamase; HPV, Human papilloma virus; HSV, Herpes simplex virus; JAK, Janus kinase; JC, John Cunningham virus (human polyomavirus 2); MDS, Myelodysplastic syndrome; MRSA- Methicillin-resistant staphylococcus aureus; PJP, Pneumocystis jirovecii pneumonia; SOT, Solid organ transplant; TB, Tuberculosis; TNF, Tumor necrosis factor; VZV, Varicella zoster virus. (*Created in* MS Power Point and pictograms were taken from SERVIER MEDICAL ART. Servier Medical Art is licensed under CC BY 4.0.)

pathogen recognition, opsonization via complement activation, and phagocytic clearance, with neutrophils and monocytes serving as the primary effector cells. Neutrophils eliminate pathogens through phagocytosis, degranulation, and oxidative killing mechanisms. Monocytes differentiate into macrophages and dendritic cells, which not only perform phagocytosis but also serve as critical antigen-presenting cells (APCs), bridging innate and adaptive immunity by initiating downstream lymphocyte responses. Derangements may be seen in the early phase following chemotherapy, allogeneic hematopoietic stem cell transplantation, acute myeloid leukemia and aplastic anemia. Impairment of innate immune function, whether through quantitative depletion or qualitative dysfunction, increases susceptibility to both gram-positive and gram-negative bacterial infections, fungal infections including candidemia, and molds including invasive aspergillosis.

Adaptive immune suppression

Adaptive immunity comprises 2 principal arms: (1) cellular immunity, mediated by antigen-specific T lymphocytes activated through interactions with APCs; and (2) humoral immunity, mediated by B lymphocytes that differentiate into plasma cells or memory B cells and produce antigen-specific antibodies. T lymphocyte subsets, principally $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells, are activated following major histocompatibility complex-dependent antigen presentation by dendritic cells and macrophages. These subsequently proliferate to mount pathogen-specific effector responses. Cytotoxic T cells induce apoptosis of cells displaying foreign peptides on their surface, while helper T cells augment this response through macrophage activation and cytokine secretion including interferon-γ. Collectively, cellular immunity is directed primarily against intracellular pathogens-including mycobacteria, Listeria, Leishmania, and Histoplasma—and against virus-infected cells that cannot be targeted by circulating antibodies alone. The clinical consequences of cellular immune deficiency are well illustrated by HIV infection, in which progressive $CD4^+$ T cell depletion produces

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Table 1
Immune defect driven risk stratification

Immune Defect	Common Causes	Infection Risk	Sepsis Phenotype	Management Implications
Barrier disruption	Chemotherapy, mucositis, lines	Gram-positive, gut translocation	Rapid bacteremia	Broad early antibiotics
Innate dysfunction	Neutropenia, steroids	Bacterial + fungal (Candida, Aspergillus)	Blunted inflammation	Consider antifungals early
Adaptive (T-cell)	HIV, calcineurin inhibitors	Viral, intracellular (TB, PJP)	Atypical presentations	Broaden to viral/opportunistic
Adaptive (B-cell)	Rituximab, myeloma	Encapsulated organisms	Recurrent infections	IVIG ± targeted antibiotics
Immune reprogramming	CAR-T, checkpoint inhibitors	Mixed (CRS vs infection)	Hyperinflammatory mimic	Immunomodulation vs antibiotics
Mixed defects	Most ICU patients	Broad spectrum	Heterogeneous	Individualized approach

Abbreviation: IVIG, intravenous immunoglobulin.

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a predictable hierarchy of opportunistic infections that forms the basis of well-established prophylactic guidelines. In non-HIV immunocompromised patients however, $CD4^+$ dysfunction induced by corticosteroids, calcineurin inhibitors, and purine analogs are responsible for the mechanisms of cellular immunosuppression.

Unlike T cells, B cells recognize antigens directly via surface-expressed immunoglobulins. Upon activation, B cells differentiate into plasma cells that secrete antigen-specific antibodies, which mediate pathogen elimination through complement activation, promotion of opsonization and phagocytosis, and recruitment of innate immune effectors. While a detailed review of immunoglobulin class structure and function is beyond the scope of this article, 2 clinically important causes of functional verses depletion hypogammaglobulinemia warrant specific consideration in the context of the immunocompromised host. In multiple myeloma, overproduction of a nonfunctional monoclonal paraprotein paradoxically suppresses normal antibody production, rendering patients functionally hypogammaglobulinemic despite elevated total protein levels. The use of a common biologic, Rituximab, an anti-CD20 monoclonal antibody, depletes mature B cells while sparing CD20-negative plasma cells; hypogammaglobulinemia therefore develops in a delayed fashion as the existing plasma cell pool turns over in the periphery and cannot be replenished from the depleted B cell compartment. Patients with humoral deficiency from either qualitative or quantitative mechanism are at heightened risk of infection with encapsulated bacteria, including Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis, which exploit their polysaccharide capsule to resist phagocytosis in the absence of the targeted opsonizing antibodies. Recognition of this specific vulnerability should inform prophylactic vaccination strategies and empiric antimicrobial selection in this population.

Immune reprogramming

The advent of immune effector cell therapy has created a unique category of immune dysregulation that may include cytokine excess, immune exhaustion via PD-1 axis activation and a mixed hyper and hypoinflammatory state. Of note, chimeric antigen receptor (CAR)-T cell therapy exploits the same cytotoxic mechanisms described earlier to eliminate tumor cells; however, T cell activation may simultaneously trigger pathologic cytokine release, producing sepsis-mimicking syndromes including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which add to the diagnostic complexity and ambiguity at the bedside.

Current Framework Limitations

Categorization of immunosuppression according to disease categorization versus immune dysfunction has limitations. Disease-based classification frameworks lack the mechanistic specificity required to individualize treatment decisions or inform targeted drug development. Immune defect-based frameworks aim to address this granularity, but the coexistence of multiple parallel mechanisms of immunosuppression means that the dominant immune defect precipitating infection at the time of clinical presentation currently cannot be determined. Validated biomarkers to stratify patients according to immune defect for patient enrollment in clinical trials are currently not available. Efforts to quantify immune dysfunction—monocyte human leukocyte antigen-DR isotype (HLA-DR) expression, ex vivo endotoxin challenge, cytokine profiling, programmed cell death 1/programmed cell death 1 ligand 1 (PD-1/PD-L1) expression—currently remain investigational.[9] Many immune-paralysis constructs are derived from small studies and lack longitudinal validation in immunocompromised cohorts. In addition, the fluidity of immune phenotypes with class switching observed in immunocompetent populations has not been rigorously studied in

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immunocompromised patients; however likely also exists.[10] An additional complexity is survivorship. When does a patient cured of lymphoma cease to be immunocompromised? These questions remain unanswered.

EPIDEMIOLOGY OF SEPSIS IN THE IMMUNOCOMPROMISED HOST

The epidemiology of sepsis is evolving in parallel with transformative advances in cancer therapeutics, transplantation, and immune-modifying agents. Current estimates indicate that 6.6% of adults in the United States were immunocompromised in 2021 based on reported health conditions, prescription medications, and medical treatments, representing a substantial increase from 2.7% in 2013.[2] Up to 15% of ICU patients in European registries carry a cancer diagnosis.[11,12] This expanding demographic is driven, in part, by the increasing use of immunosuppressive medications.

Notably, cancer-specific mortality has declined substantially, with a 33% reduction since 1991 attributable to advances in preventive strategies, alongside the development of novel therapeutics. Despite these gains, patients with cancer face a nearly ten-fold greater risk of developing sepsis compared with the general population, constituting a vulnerable and growing subpopulation with substantial health care resource needs. A large epidemiologic study by Yang and colleagues, examining emergency department utilization in the United States from 2006 to 2012, identified approximately 4 million annual adult emergency visits involving patients with active cancer diagnoses, of whom 60% were admitted primarily for severe infections and associated complications.[13]

Resource utilization and clinical outcomes are not uniform across malignancy types however, with considerable heterogeneity even within the hematological malignancy population. Among patients with solid organ tumors, sepsis-related mortality accounts for approximately 9% of all deaths, with the highest mortality rates (5%–13%) observed in the context of severe infections complicating postchemotherapy neutropenia. In contrast, 12% to 27% of patients with hematological malignancies develop sepsis within the first year of diagnosis, with an associated in-hospital mortality rate of 14%.[14,15] The incidence of severe sepsis is approximately 5 times higher among recipients of hematopoietic stem cell transplantation compared with hospitalized patients without a history of hematopoietic stem cell or solid organ transplantation.[16] Collectively, these data underscore the growing public health significance of immunosuppression.

UNDERSTANDING THE PATHOPHYSIOLOGY OF SEPSIS IN IMMUNOCOMPROMISED PATIENTS

The pathophysiology of sepsis is characterized by a dysregulated immune response to infection, involving the synchronized activation and cross-talk between the innate and adaptive immune systems. The rapid, nonspecific effector functions of innate immunity followed by the sophisticated and targeting adaptive immune response, are both amplified by proinflammatory cascades mediated by cytokines, coagulation factors, and markers of endothelial and epithelial injury. This inflammatory cascade underlies the immune dysregulation hypothesis central to sepsis pathobiology and has been implicated in driving deleterious vasodilation, microvascular leak, microthrombotic formation, and acute organ injury. A concurrent anti-inflammatory response also exists, which may, when persistently dysregulated, contribute to subacute adaptive immune exhaustion and heightened susceptibility to secondary infections.

The determinants of the host immune response to infection are numerous and likely encompass a broad range of endogenous and exogenous factors, including genetic

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composition, age, biological sex, comorbidities, metabolic state, prior microbial exposure, and concurrent medications. The interplay of these variables gives rise to profound interindividual heterogeneity in immune response. Over the past decade, significant progress has been made in characterizing this heterogeneity through the discovery of molecular phenotypes of sepsis. Approaches leveraging plasma protein biomarkers, transcriptomics, and metabolomics combined with unsupervised clustering techniques have identified biologically distinct patient subgroups with differential risks of adverse outcomes and heterogeneity in treatment effects with supportive and targeted therapies. Collaborative efforts, such as the Subtyping in Sepsis and Critical Illness Consortium, aim to harmonize findings across independent research groups to define generalizable patient cohorts characterized by distinct molecular pathways and immune cell-specific dysregulation.[17] These initiatives hold promise for a biology-driven classification framework that may inform future prospective targeted trials to test novel and supportive interventions. However, phenotypic frameworks have been derived in immunocompetent patient cohorts shaped by carefully curated inclusion criteria and therefore may not be generalizable immunocompromised patients.

Efforts to address this gap are nonetheless emerging. Notably, studies by Ronner and colleagues and Weingart and colleagues have investigated how baseline perturbations in host immune function may influence molecular phenotype assignment and its generalizability.[18,19] Both studies examined the performance of the inflammatory subphenotypes of sepsis, developed by Calfee and colleagues. Weingart and colleagues examined the relationship between immunocompromised status and subphenotype assignment, demonstrating that patients with hematological malignancies were disproportionately classified as hyperinflammatory and that this phenotype was significantly associated with impaired survival. Interestingly, elevated cytokine levels of interleukin (IL)-8, a powerful neutrophil chemoattractant, emerged as a key determinant of phenotype assignment in this population, highlighting retained mechanistic relevance even in patients who are often plagued by neutropenia. Ronner and colleagues found that unlike in immunocompetent cohorts, parsimonious models incorporating IL-6 and IL-8 inconsistently predicted hospital mortality and discordantly classified patients by inflammatory phenotype, particularly among those with leukemia. Collectively, these studies suggest that immunocompromised patients may not easily mirror existing sepsis phenotypes. Simply put, the assumption that immunocompromised patients are uniformly hypoinflammatory is overly simplistic. In reality, what may exist is a phenotypic spectrum that spans various categories including hyperinflammatory, hypoinflammatory, mixed hyper–hypo and immunoparalysis. Temporal evolution likely occurs, but longitudinal data in immunocompromised cohorts are sparse.

DIAGNOSTICS AND CHALLENGES

Early recognition of sepsis in immunocompromised patients is fraught with challenges. Clinical presentations may differ substantially from that of immunocompetent patients leading to delays in diagnosis and initiation of time-sensitive interventions. Immune-modulating medications can further distort or mask the cardinal features of infection. Classic findings such as fever and leukocytosis become unreliable diagnostic markers in this context: corticosteroids may suppress fever, while lymphoproliferative disorders can produce noninfectious pyrexia. Similarly, the hallmark local inflammatory signs of erythema, pain, warmth, and swelling may be attenuated due to an impaired inflammatory response. Neutropenia may both minimize the clinical

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manifestations of infection and paradoxically worsen during the recovery phase—a phenomenon most prominently described in patients with hematological malignancy with acute respiratory failure.[20]

Conventional biomarkers, including C-reactive protein (CRP), procalcitonin, and leukocyte count, although lacking robust evidence even in the immune competent patient, may be even less sensitive and specific for signaling infection in immunocompromised patients. Alternative biomarkers, such as midregional proadrenomedullin (MR-proADM) however may represent a potentially valuable emerging biomarker in this population. Adrenomedullin is a potent vasodilator and endothelial barrier stabilizer that regulates vascular tone, reduces vascular permeability, and modulates inflammation. During sepsis, circulating levels rise dramatically within hours, reflecting a compensatory response to endothelial dysfunction, vascular leak, and vasodilation. MR-proADM has demonstrated superior performance compared with CRP for the prediction of bloodstream infection and sepsis in immunocompromised patients with cancer,[21] and has also shown prognostic utility in predicting clinical outcomes and treatment response.[22]

Pulmonary infections are the most common source of sepsis in immunocompromised patients and carry significant implications for morbidity and mortality. Accordingly, diagnostic strategies aimed at early identification of pulmonary infection and causative pathogen should be prioritized in this population. Radiographical assessment using chest X-ray imaging has limited sensitivity and specificity for detecting pulmonary infiltrates and may be difficult to distinguish from competing diagnosis that is, drug-related toxicity or radiation injury; therefore, low-dose computed tomography has demonstrated superior diagnostic performance.[23] Evidence behind the utility of lung ultrasound in this population is currently lack. The diagnostic yield of noninvasive testing has improved substantially with the introduction of more sensitive molecular diagnostics, including polymerase chain reaction (PCR)-based assays. However, these tests are characterized by high sensitivity at the expense of specificity, and the clinical significance of a positive result is thus not always certain. This is well illustrated by PCR detection of pneumocystis jirovecii (PJP) and Aspergillus species, both of which may yield positive results even when the burden of these organisms are very low. Asymptomatic colonization with both PJP and Aspergillus is well documented in immunocompromised patients, particularly in the presence of structural lung disease or recent corticosteroid exposure, rendering the distinction between colonization and active infection clinically challenging. Identifying the underlying etiology of acute respiratory failure remains undetermined in 10% to 15% of cases and is of paramount importance as it is independently associated with increased mortality.[24] While fiberoptic bronchoscopy is one invasive diagnostic strategy often employed when noninvasive tests fail to identify a diagnosis, it may be limited by low yield to assist in narrowing down antimicrobials if broad spectrum antimicrobials have already commenced or be associated with clinical deterioration in the setting of high oxygen requirements.[25] Its utility is maintained if ruling out noninfectious causes (such as diffuse alveolar hemorrhage) or identifying organisms that may not be covered by traditional broad spectrum antimicrobials (ie, Stenotrophomonas, PJP, fungal infections, Cytomegalovirus). The pursuit of tissue pathology to make a diagnosis using lung biopsy has been explored in a limited number of studies. Although some studies report achieving a diagnostic yield exceeding 60%, this is balanced with a complication rate of approximately 10% even with careful patient selection (and as high as 25% in ventilated patients).[26–28] This diagnostic yield is further reduced in patients receiving invasive ventilation. Given this unfavorable risk-benefit profile, lung biopsy is generally not recommended in critically ill patients who are ventilated.

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Finally, several noninfectious conditions may closely mimic sepsis, presenting with fever, multi-organ dysfunction, and elevated inflammatory biomarkers. These include CRS following CAR-T cell or bispecific antibody therapy, tumor lysis syndrome, hemophagocytic lymphohistiocytosis, and engraftment syndrome. Careful clinical and laboratory evaluation is essential to differentiate these entities from true infectious sepsis, as their management differs substantially (Fig. 2).

EARLY IDENTIFICATION OF SEPSIS

Early identification of sepsis in immunocompromised patients is particularly challenging, yet critically important, because delayed recognition may rapidly translate into irreversible organ dysfunction and excess mortality. Compared with immunocompetent patients, immunocompromised hosts often have reduced physiologic reserve and atypical clinical manifestations, narrowing the window in which timely intervention can alter outcomes.

Timing of ICU referral is a major determinant of prognosis. Patients initially considered "too well" for ICU admission but subsequently transferred after deterioration have significantly worse outcomes, with mortality rates reported as high as 62% in delayed admissions compared with substantially lower rates among those admitted earlier in the disease course.[4,5] Each additional day spent on the ward before ICU transfer is associated with incremental increases in mortality, underscoring the importance of early recognition and proactive triage.[5]

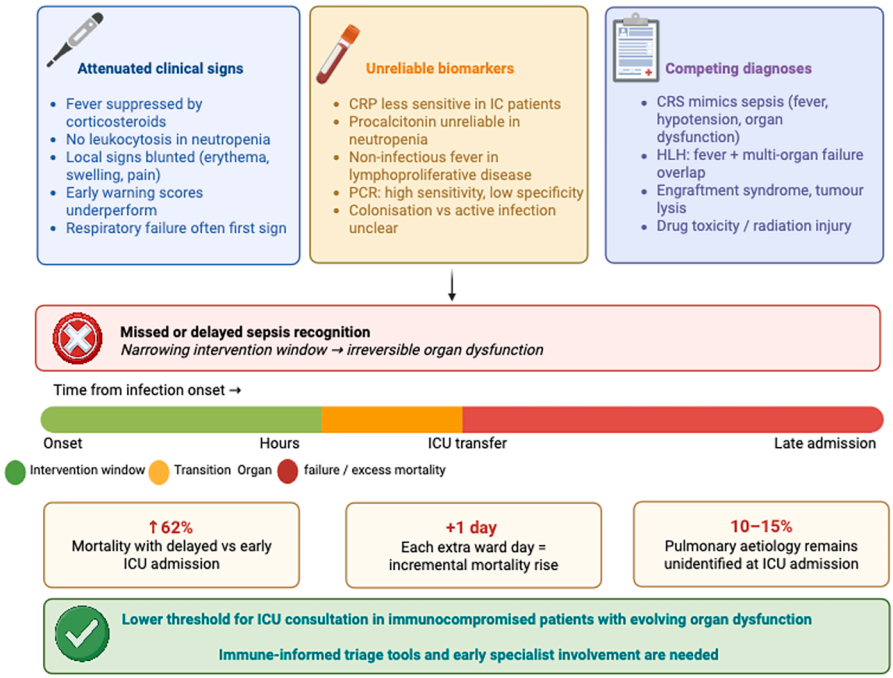

Fig. 2. Challenges and considerations in the identification of sepsis in immunocompromised patients. CRP, C reactive protein; CRS, cytokine release syndrome; ICU, intensive care unit; PCR, polymerase chain reaction. (*Created in* MS Power Point and pictograms were taken from SERVIER MEDICAL ART. Servier Medical Art is licensed under CC BY 4.0.)

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Conventional early warning tools may underperform in immunocompromised populations. In patients with hematologic malignancies, deterioration is often driven by early respiratory failure rather than circulatory collapse, and traditional triggers such as fever or leukocytosis may be absent. Modified scoring systems incorporating oxygenation parameters, such as the peripheral oxygen saturation (SpO_2)/fraction of inspired oxygen (FiO_2) ratio, have demonstrated improved discrimination in this population.[29]

Taken together, these data support a lower threshold for ICU consultation and admission in immunocompromised patients with evolving organ dysfunction. Future work should focus on developing and validating triage tools tailored specifically to this population.

SEPSIS MANAGEMENT-UNIQUE CONSIDERATIONS

The fundamental principles of sepsis management remain applicable in immunocompromised patients; however, each domain is complicated by altered pathogen range, competing diagnoses, and uncertainty regarding optimal immunosuppression management.

Empiric antimicrobial therapy: Empiric therapy is typically broader, reflecting increased risk of resistant bacterial pathogens, invasive fungal infections, and viral reactivation. Given this, it remains imperative to obtain microbiologic samples to identify the culprit pathogen before or soon after the initiation of antimicrobial therapy to tailor treatment and minimize excess duration of broad therapy. Risk-adapted strategies for invasive fungal infection diagnosis and prevention in immunocompromised hosts have been advocated in this population,[30] while epidemiologic data highlight the substantial burden of opportunistic infections in transplant and oncology populations.[31,32] Broader therapy; however, must be balanced against risks of microbiome disruption, resistance, drug–drug interactions and organ toxicities. This is particularly relevant for azole antifungals, which interact with calcineurin inhibitors and other immunosuppressants. Evidence supporting biomarker-guided de-escalation (eg, procalcitonin) remains limited in neutropenic populations, and extrapolation from immunocompetent cohorts should be approached cautiously.[7]

Hemodynamic and organ support: Optimal fluid and vasopressor strategies in immunocompromised patients are not well defined. Current practice is extrapolated from general sepsis guidelines (Surviving Sepsis Campaign).[7] Mortality increases significantly once organ failure develops—particularly among patients with cancer—highlighting the importance of early recognition, timely hemodynamic support, adequate resuscitation, and supporting consideration of early ICU admission.

Immunosuppression management: Balancing continuation versus interruption of immunosuppressive therapy is complex and highly context-dependent. Data from rheumatologic populations suggest that continuation of certain immunomodulators during infection may be safe in selected patients[33] although extrapolation to transplant and malignancy populations remains uncertain. Abrupt withdrawal may precipitate graft rejection, or autoimmune flare whereas continuation may impair pathogen clearance. In the setting of cancer, if subsequent rounds of chemotherapy were scheduled—these may be delayed until infection clearance. Engaging the specialist in the immunocompromised subspecialty is necessary to guide decision making regarding immunosuppression management.

Corticosteroids: Major trials of corticosteroids in septic shock included few profoundly immunocompromised patients, and subgroup data are lacking.[7] Whether steroid responsiveness differs by immune phenotype or baseline immunosuppression remains unknown.

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Growth-colony stimulating factor (*G-CSF*)*:* Meta-analyses have not demonstrated consistent mortality benefit in sepsis with the use of G-CSF, although faster neutrophil recovery is observed.[34] Current oncology guidelines recommend selective use in high-risk febrile neutropenia,[35] rather than routine use in all septic patients.

Granulocyte transfusions: While evidence remains limited, preliminary studies demonstrate the possible role of granulocyte transfusions in select patients with severe neutropenia with refractory infection and anticipated marrow recovery.[36] Their role in critically ill patients is uncertain.

Immune modulation: Emerging strategies—including interferon-γ, checkpoint modulation, and immune adjuvant therapies—aim to restore immune competence. However, without validated tools to define immune state, the risk of misaligned therapy (eg, augmenting inflammation in hyperinflammatory states) remains possible.[37] Current phenotyping strategies remain incompletely validated and as a result, not yet ready for routine bedside use.

Future trials should prioritize biomarker-guided and phenotype-driven designs rather than syndromic enrollment.

SEPSIS MIMICKERS

A major diagnostic challenge is distinguishing infection from noninfectious inflammatory syndromes. Conditions such as CRS, hemophagocytic lymphohistiocytosis (HLH), engraftment syndrome, and tumor lysis syndrome may closely mimic sepsis, presenting with fever, shock, and multiorgan dysfunction. These syndromes are particularly relevant in patients receiving modern immunotherapies, including CAR-T cell therapy.[38] Failure to distinguish these entities may result in inappropriate therapy. For example, CRS requires immunomodulatory treatment (eg, tocilizumab), whereas delayed antimicrobial therapy in true sepsis is associated with worse outcomes.

Given the overlap, diagnosis requires integration of clinical trajectory, treatment exposure, microbiologic data, and disease-specific biomarkers. In many cases, early management may require simultaneous empiric antimicrobial therapy and investigation for immune-mediated syndromes (**Table 2**).

OUTCOMES

Outcomes following sepsis in immunocompromised patients have improved but remain heterogeneous. ICU mortality in patients with malignancy ranges from approximately 40% to 60% depending on disease type and severity of organ failure.[6,39] One-year mortality remains high, particularly among patients with hematologic malignancies. Importantly, contemporary data challenge the perception that critical illness in these patients is uniformly futile. Selected patients may achieve outcomes comparable to immunocompetent populations when adjusted for illness severity.[39] Survival alone, however, is insufficient as an endpoint. Functional recovery, quality of life, and ability to resume disease-directed therapy are increasingly recognized as critical outcomes.[40] These considerations are particularly relevant in oncology populations, where ICU survival may serve as a bridge to further treatment. Prognostication should therefore incorporate not only acute illness severity but also reversibility of the underlying condition and patient-centered goals. Delayed ICU admission and therapeutic nihilism may adversely influence outcomes, reinforcing the importance of timely and individualized care. Future research priorities can assist in improving ICU outcomes of this population (**Table 3**).

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Table 2
Sepsis mimickers in the immunocompromised host

Syndrome	Clinical Context	Key Clinical Features	Distinguishing Clues	Diagnostic Tests	Initial Management
CRS	CAR-T, bispecific antibodies	Fever, hypotension, hypoxia	Temporal relationship to immunotherapy; very high ferritin/CRP	IL-6 (if available), ferritin	Tocilizumab ± steroids
HLH	Heme malignancy, infection, autoimmune disease	Fever, cytopenias, organ failure	Ferritin often >10,000; hepatosplenomegaly; hypertriglyceridemia	Ferritin, triglycerides, sCD25	Steroids ± etoposide
Engraftment Syndrome	Post-HSCT (neutrophil recovery phase)	Fever, rash, pulmonary edema	Occurs at neutrophil recovery; noninfectious	Clinical diagnosis	Steroids
Tumor Lysis Syndrome	Hem malignancy, high tumor burden	AKI, arrhythmia, metabolic abnormality	Hyperuricemia, hyperkalemia, hyperphosphatemia	Electrolytes, uric acid	Fluids, rasburicase
Drug Reaction (DRESS, SJS/TEN)	New medication	Fever, rash, organ dysfunction	Eosinophilia, skin findings	Clinical ± biopsy	Stop drug ± steroids
Vasculitis Flare	Autoimmune disease	Fever, organ dysfunction	Known disease; ANCA or complement abnormalities	Autoimmune panel	Immunosuppression
Leukemic progression	Hem malignancy	Cytopenias, fever	Blasts on smear, marrow progression	Peripheral smear, bone marrow	Disease-directed therapy
Immune checkpoint toxicity	ICI therapy	Pneumonitis, colitis, hepatitis	Subacute course, exposure to ICI	Imaging, labs	Steroids

Abbreviations: AKI, acute kidney injury; ANCA, anti-neutrophil cytoplasmic antibody; CART, Chimeric antigen receptor T cell therapy; DRESS, Drug reaction with eosinophilia and systemic symptoms; ICI, immune checkpoint inhibitor; SJS/TEN, Stevens-Johnson syndrome/Toxic epidermal necrolysis.

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Table 3
Research gaps

Domain	Key Gap	Why It Matters	Proposed Direction
Definitions of immunocompromise	No consensus classification	Heterogeneous cohorts limit trials	Standardized, immune-based taxonomy (beyond disease labels)
Immune phenotyping	Static, single time-point measures	Immune state is dynamic	Longitudinal profiling (transcriptomics, biomarkers)
Trial inclusion	Underrepresentation in randomized controlled trial (RCTs)	Poor generalizability of guidelines	Dedicated trials or enriched subgroups
Precision antimicrobials	Overuse vs under-treatment	Resistance, toxicity, microbiome disruption	Biomarker-guided duration and de-escalation
Infection vs inflammation	Poor discrimination (eg, CRS vs sepsis)	Delayed or inappropriate therapy	Integrated diagnostic frameworks
Steroid strategies	One-size-fits-all approach	Variable immune phenotypes	Immune-aligned steroid use (phenotype-guided)
Microbiome preservation	Antibiotic-driven dysbiosis	Secondary infection risk	Microbiome-sparing strategies
ICU triage tools	Existing tools underperform	Delayed ICU admission worsens outcomes	Tailored prediction models (eg, oxygenation-based)
ICU admission thresholds	Variable across centers	Impacts mortality	Early escalation strategies
Prognostication	Survival-focused metrics	Ignores functional recovery	Long-term, patient-centered outcomes

SUMMARY

In summary, sepsis in immunocompromised patients represents a fundamentally distinct clinical entity, shaped by altered host defenses, unique pathogen profiles, and competing risks related to the underlying disease and its treatment. These differences challenge conventional sepsis paradigms and underscore the need for tailored diagnostic, prognostic, and therapeutic approaches. Advancing care in this population will require integration of clinical insight with biologic understanding to move toward more precise and individualized management strategies.

CLINICS CARE POINTS

- Pearl: Early ICU referral is often more important than the underlying immunocompromising diagnosis in determining outcome.

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- Pitfall: Excluding sepsis because fever, leukocytosis, or elevated inflammatory biomarkers are absent.
- Pearl: Frame the patient according to their dominant immune defect (barrier disruption, innate dysfunction, adaptive dysfunction, or immune reprogramming) to guide diagnostic testing and empiric therapy.
- Pitfall: Attributing all fever and shock to infection without considering immune-mediated syndromes such as CRS or HLH.
- Pearl: In acute respiratory failure, prioritize early high-yield diagnostics and pursue a microbiologic diagnosis whenever possible before prolonged exposure to broad-spectrum antimicrobials.

DISCLOSURE

No conflicts to declare.

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