Infectious diseases approach to immunocompromised patients in the pediatric intensive care unit

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Abstract. The diagnosis and management of infectious diseases in the immunocompromised patient can be challenging, especially when that patient is critically ill. In the diagnostic approach to the immunocompromised patient, clinicians will need to integrate the risks particular to the immunodeficiency with the risks associated with hospital-associated exposures. The potential infectious diagnoses are expanded in the immunocompromised patients, most notably to include diseases due to opportunistic infections, such as fungi, latent viruses, and opportunistic Gram-positive and Gram-negative bacteria. In addition, prior hospital and antibiotic exposure increases the likelihood that these patients will have infections due to resistant organisms. When an infection is diagnosed, the approach to treatment in the immunocompromised patient is also dependent on the degree and type of immunodeficiency, and optimal treatment strategies are often not well studied. This review focuses on general principles that can be used in the diagnosis and management of immunocompromised, critically ill patients with suspected or proven infection and highlights in detail the approach to infections of the blood stream and respiratory tract.

Keywords: Immunocompromised, infections, pediatric intensive care unit

1. Introduction

In pediatric medicine, the number of patients with immunodeficiency has increased. This increase is due in part to the increasing survival of patients treated with chronic immunosuppression, increasing success and utilization of solid organ and hematopoietic stem cell

transplantation, as well as an increase in the numbers of newly developed immunomodulator agents [1–4]. As a result, the pediatric intensive care unit (PICU) physician is routinely faced with the management of infections in a wide variety of immunocompromising states. This wide variation in at risk patients and extensive differential for possible infectious pathogens can appear overwhelming. Understanding the general categories of immunocompromising states and some of the more common infectious diseases that plague this population can help the PICU clinician frame an initial approach. This should start with identifying the

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immunocompromising condition, including type and duration of immune suppressive therapy, followed by initiation of diagnostic testing and empiric antimicrobial therapy for common and immediately life threatening infectious pathogens, and finally consideration of less common infectious disease pathogens with the support of subspecialty services (Fig. 1). This review will present a framework to serve as a general guide to help the PICU clinician establish his or her own systematic approach to these challenging patients, with a focus on two common sites of severe infection in the PICU - the bloodstream and respiratory system.

2. Types of immunocompromised patients in the PICU

Patients admitted to the PICU with an immunocompromising condition can be generally categorized into one of the following groups: hematopoietic stem cell transplant (HSCT) recipients, solid organ transplant (SOT) recipients, children receiving chemotherapy for malignancy, primary or acquired immune deficiency, and those receiving immune modulating therapy for autoimmune diseases. While it would be useful to understand the percentage of PICU patients who fall into each group, these data have not been established and will likely vary depending on the institution. Nonetheless, there are published studies that doc-

ument the frequent need for intensive care within specific immunocompromising categories. For example, a meta-analysis of pediatric HSCT patients found a range of 4–44% post-transplant PICU admission [5]. In a retrospective cohort study of pediatric HSCT patients, transplant for a nonmalignant disease was associated with an increased risk of requiring intensive cardiopulmonary support, including 50% of patients transplanted for immunodeficiency [6]. Importantly, this study found that 40% of HSCT patients overall had at least one diagnosed infection at the time of PICU admission.

In pediatric acute myeloid leukemia (AML), patients receive myelosuppressive chemotherapy resulting in prolonged periods of neutropenia; up to one third of children with AML are admitted to the PICU in the first 9 mo of diagnosis [7]. Although the risk for PICU admission is lower among other pediatric cancer patients, the fact that there are close to 13,000 new pediatric cancer cases diagnosed each year in the United States alone means that even a small rate of intensive care need would result in a substantial number of admissions [8]. A study of primary immunodeficiencies reported that 6% of patients admitted with an immunodeficiency diagnosis required PICU admission, and a 15-yr study of PICU admissions for rheumatic diseases documented 122 admissions for 90 patients [9, 10]. Of the 18 patients with rheumatic disease who died in the PICU, 50% had an infection as part of the cause of death, and 22% had infection as the sole cause of death.

Fig. 1. The initial infectious diseases approach to the immunocompromised patient who is admitted to the pediatric intensive care unit.

3. Understanding the host

The first step in an approach to immunocompromised patients is to understand the degree of immunosuppression. Table 1 documents questions to consider for each immunocompromised group of patients. The time period since immune suppression began is important for several groups. For example, in patients who have undergone SOT, the early post-transplant period (0–4 wk) is associated with typical bacterial pathogens, while the 1–6 mo period is associated with increased risk of infections due to opportunistic pathogens [11]. In patients with leukemia, longer duration of neutropenia correlates with increased risk for invasive fungal infection [12]. Understanding the infectious risks associated with primary immunodeficiencies can be more disease-specific;

Table 1
Recommendations for screening questions at presentation to the pediatric intensive care unit

Immunocompromised category	Initial patient review
Hematopoietic stem cell transplant	How long has it been since the transplant? What is the patient's absolute neutrophil and lymphocyte count? Is there any evidence of graft versus host disease? If the patient has graft versus host disease, what is their current immune suppression? Is the patient receiving antimicrobial prophylaxis? What was the cytomegalovirus/Epstein-Barr virus status of the recipient and donor?
Primary/acquired immune deficiency	What aspects of the immune system are affected? Is the patient on antibacterial or antifungal prophylaxis? What infections are known to be associated with this immunodeficiency?
Solid organ transplant	Which organ(s) has been transplanted? How far is the patient from transplant? Which conditioning agents were used? What is the maintenance immunosuppression? Is the patient receiving antimicrobial prophylaxis? What was the cytomegalovirus/Epstein-Barr virus status of the donor and the recipient? Is there any foreign material within the graft? Has the patient undergone treatment for rejection?
Children receiving chemotherapy for malignancy	What is the cancer type? What is the chemotherapy regimen (including steroids) and when was the last cycle? Does the patient have any cytopenias or are they expected to develop cytopenias within the coming days? For how long has the patient been cytopenic? Is the patient receiving antimicrobial prophylaxis?
Children receiving immunomodulators for autoimmune disease	Which immunomodulators are used? What cell type or cytokine does it target? Is the patient receiving antimicrobial prophylaxis? Is the patient receiving other immune suppression? (e.g. steroids)

therefore, while an initial approach will remain the same, consultation with subspecialty services will be critical to identify the pathogens of highest concern.

4. Initial evaluation

Once the clinician has been able to establish the general state of immune suppression, attention should focus on initial diagnostic testing and empiric antimicrobial therapy, with a focus on potentially life-threatening infections. This assessment will include blood and urine cultures in addition to symptom-specific evaluation, such as focused imaging studies or assessment for *Clostridium difficile* colitis or neutropenic enterocolitis.

A majority of infections that require PICU admission or arise while in intensive care will be hospital-associated; admission to the PICU is a risk factor itself for hospital-associated infection, as is the number of medical devices [13, 14]. For all patients, clinicians should specifically review recent infectious history, history of multi-drug resistant organisms (MDRO), as well as recent hospital and community exposures. Each patient should have a thorough exam noting the presence of foreign material, including

central venous access or urinary catheters, and the presence of any mucosal or skin break-down.

In addition to the studies noted above, non-bacterial pathogens such as primary or reactivation viral infections and invasive fungal infections should be considered. Invasive candidiasis is a significant concern in the immunocompromised PICU patient but is discussed in detail in a separate review in this issue.

5. Bloodstream infection (BSI) and central line associated BSI (CLABSI)

BSIs result in significant morbidity and mortality, and the presence of an underlying immune deficient state has been shown to be the primary predictor of mortality in PICUs [15]. Gram-negative rods (GNR) are of particular concern in neutropenic patients as they are the source of more than a quarter of bacteremia episodes in pediatric oncology patients and can result in a rapid clinical decline [16]. Gram-positive pathogens are also of concern as many of these patients have central venous access increasing the risk of infection from skin colonizers. Mucositis secondary to chemotherapy can also increase the risk of infection from pathogens, including viridans group

streptococci (VGS). VGS are particularly relevant in children with AML, where more than 20% of patients have been noted to develop VGS bacteremia [17, 18]. In HSCT patients, the risk of VGS bacteremia is highest in the pre-engraftment period [19]. Importantly, a single-center retrospective review of pediatric oncology and HSCT patients found that bacteremia with VGS was associated with a streptococcal shock syndrome in 18% of cases, some of which were fatal [20].

Treatment of a suspected BSI in an immunocompromised patient typically begins with empiric, broad-spectrum antibiotics targeting Gram-positive and -negative organisms, including *Pseudomonas* species. The exact empiric coverage will vary by patient type and institution and requires consideration of factors that may predispose to resistant organisms. For instance, GNRs cultured from oncology patients undergoing HSCT, from patients hospitalized for ≥ 48 hr, or from those who had a history of a resistant GNR in the previous 12 mo were more likely to be highly antibiotic resistant [16].

For high-risk neutropenic oncology patients, there are pediatric specific guidelines to aid clinicians in choosing empiric antibiotic regimens [21]. Initial therapy for these patients should always include an anti-pseudomonal beta-lactam or carbapenem [21]. When a patient is clinically unstable or additional data suggest an increased risk for a resistant pathogen, the guidelines recommend addition of an agent from a second class of antibiotics to increase breadth of Gram-negative coverage while awaiting blood culture results. A known history of methicillin resistant *Staphylococcus aureus* colonization or infection, history of resistant VGS infection, and/or clinical deterioration would also warrant the empiric addition of vancomycin while awaiting blood culture results. When a patient is in extremis and at high risk for invasive candidiasis (as described in a separate review in this issue), empiric addition of an echinocandin can be considered but is not routine.

When an organism is identified in the setting of a central line, the recommendations for line removal are similar regardless of immune status. The Infectious Diseases Society of America recommends that CLABSI with *S. aureus*, *Pseudomonas aeruginosa*, *Candida* species, or an MDRO should be treated with line removal in conjunction with systemic antimicrobial therapy [22]. Monotherapy is considered appropriate for many pathogens. In the past, there was significant interest in providing dual therapy in the setting of certain GNRs, most notably for *P.*

aeruginosa. Early publications suggested a synergistic benefit of dual-agent therapy throughout the course of CLABSI treatment; however, further studies in neutropenic adults have not consistently identified benefit of two-drug regimens [23–25].

In most cases, the duration of treatment of a CLABSI in the immunocompromised patient is the same as treatment in the immunocompetent host. In patients with persistent neutropenia, there is not consensus from published guidelines on definitive management of BSI. Some centers continue antibiotic therapy throughout the duration of neutropenia while others administer antibiotics for a finite duration regardless of persistent neutropenia. Additionally, some centers will narrow empiric therapy in a neutropenic patient to target the isolated pathogen while other centers will continue broad-spectrum anti-pseudomonal coverage. Unfortunately, there are no pediatric data to support or refute any of these practices. Patients with persistently positive cultures, especially if they remain positive after line removal, should be evaluated for disseminated foci of the infection. Depending on organism, host characteristics, and the clinical presentation, such a workup could include echocardiogram, targeted ultrasound for non-cardiac endovascular infection, eye exam, and/or chest and abdominal imaging.

6. Pulmonary infection and hospital or ventilator associated pneumonia

Pulmonary infections are commonly encountered among immunocompromised children, especially in those requiring PICU care. Both presence of underlying immunodeficiency and exposure to immunosuppressive therapies have been identified as independent risk factors for hospital or ventilator acquired pneumonia (HAP or VAP) [26]. Among children with a primary immunodeficiency, pneumonia is the second leading cause of death, second only to sepsis [27].

There are limited data on the distribution of pathogens causing pulmonary infection in immunocompromised children and few studies in adults to define the epidemiology. A Swiss report of 1,066 bronchoalveolar lavages (BAL) in adult immunocompromised patients with clinical diagnosis of pulmonary infection illustrates the diversity of potential pathogens [28]. The study included patients with human immunodeficiency virus, hematologic malignancy, autoimmune disease or interstitial lung

disease on immunosuppression, as well as HSCT and SOT recipients. In HSCT recipients and patients receiving chemotherapy for malignancy, 20% of the clinical diagnoses were due to bacteria, 12% to cytomegalovirus (CMV), and 3–4% each were due to pulmonary aspergillosis, *Pneumocystis carinii*, and respiratory viruses. More than half of the BALs did not yield an infectious etiology. SOT patients were more likely to have diagnostic yield from BAL, at more than 80%. Approximately one quarter of pulmonary infections in this group were due to bacteria and CMV, with 13–15% due to *Pneumocystis pneumonia* (PCP) and respiratory viruses and only 4% due to invasive aspergillosis. Patients in the “other immunosuppressed” category that largely included autoimmune diseases also had 80% infectious diagnostic yield from BAL and were commonly diagnosed with bacterial infection (37%) but also had notable rates of CMV infection (23%), other respiratory viruses (7%), PCP (8%), and pulmonary aspergillosis (3%). Mycobacterial infections were almost exclusively detected in the human immunodeficiency virus group with only one of the 64 mycobacterial infections being diagnosed in an “other immunosuppressed” patient.

Pediatric studies to determine the epidemiology of lung infections in immunocompromised are needed since the organism breadth and frequency may differ from that reported in adults. Despite the lack of epidemiology, the pediatric intensivist should consider the following sources of pulmonary infection: community and hospital acquired bacterial infections (including atypical infections such as *Legionella pneumophila*), respiratory viral infections, CMV pneumonia, PCP, Cryptococcal pneumonia, endemic mycoses, mycobacteria and *Aspergillus* as well as other mold pathogens.

Bacterial pneumonia in this patient population is often hospital or ventilator associated. Pediatric VAP occurs approximately once per 1000 ventilator days, down from 2/1000 in 2007 [29]. An adult study demonstrated that immunocompromised status was one of the five comorbidities that is associated with increased mortality from VAP, and thus early initiation of appropriate antimicrobial therapy is critical [30]. Unfortunately, identifying the microbiologic etiology of pediatric HAP/VAP can be difficult due to challenges in obtaining lower respiratory samples that reflect pneumonia without contamination from upper respiratory or endotracheal tube colonizers. The most common causes of HAP/VAP are GNR, *S. aureus*,

and typical respiratory pathogens like *Streptococcus pneumoniae* and *Haemophilus influenzae* [31].

The choice of empiric antibiotic therapy should include coverage for these typical community and hospital-acquired pathogens and thus a beta lactam or carbapenem agent with anti-pseudomonal activity is often recommended [31]. When there are risks for MDRO (patient with known history, pneumonia onset after 5 days of hospitalization, transfer from a facility or country with known high incidence, receipt of antimicrobial therapy in the preceding 90 days), adult guidelines suggest a second agent active against Gram-negative organisms, such as a fluoroquinolone or aminoglycoside in addition to vancomycin or linezolid to cover MRSA [31, 32]. Adult guidelines also suggest that all patients with cancer and neutropenia be approached as patients with a risk for MDRO, but this is not as standard in pediatrics [32].

Treatment duration for VAP in immunocompetent adults has been well delineated, with a randomized trial demonstrating that 8 days of antibacterial therapy was as good as 2 wk, with the exception of infections due to *Pseudomonas* and *Acinetobacter* spp. [33]. Unfortunately, this study did not include immunocompromised patients. As a result, caution should be used when extrapolating the results. The duration of HAP/VAP treatment may need to be modified depending on the degree of immunosuppression; for profoundly neutropenic patients, the duration of therapy is typically through count recovery. Published data and/or guideline recommendations do not exist to guide treatment duration of patients with other types of immunosuppression and therefore continued clinical assessment of response and consultation with an infectious disease specialist can be helpful for determining a safe duration of therapy.

In addition to bacterial pathogens, mold infections also need to be considered in the immunocompromised pediatric patient with respiratory distress. *Aspergillus* is by far the most common invasive pulmonary mold infection in immunocompromised patients [28, 34]. Risk factors for invasive fungal disease have been well described and include prolonged neutropenia, dysfunctional neutrophils (chronic granulomatous disease), high dose steroids, lung transplantation, and other conditions or treatment regimens that result in prolonged and significant immunosuppression (e.g. severe combined immunodeficiency) [34]. It is important to note that while the classic radiographic indicators of pulmonary aspergillosis include nodules, cavitation, and

the halo sign, these are not always present. A retrospective multicenter analysis of 139 pediatric cases demonstrated that these radiographic findings were present in only 59%, 24.5%, and 11% of patients, respectively [35]. Therefore, it is important to consider more invasive diagnostic measures (e.g. BAL or lung biopsy) when a pulmonary mold infection is suspected.

Patients are occasionally too ill to safely undergo invasive diagnostic testing and thus non-invasive testing can be helpful in establishing the presence of invasive mold infection. Galactomannan serum testing is a useful tool for diagnosing pulmonary aspergillosis among patients with prolonged neutropenia. A prospective observational study in pediatric patients with anticipated prolonged neutropenia comprised mainly of HSCT patients demonstrated a serum galactomannan sensitivity of 95% with a high negative predictive value when tests were serially negative [36]. The performance of galactomannan assays in other settings may not be as reliable. In adult patients with SOT, a meta-analysis found the serum galactomannan sensitivity to be 41% with an 85% specificity [37]. The operating characteristics of the fungal biomarker beta-D-glucan have not been defined in children, and thus routine use in children should be avoided. When primary or reactivation infection from endemic mycoses is suspected, the relevant urine and serum markers should be assessed.

Voriconazole is considered the drug of choice for pulmonary aspergillosis [38]. However, achieving therapeutic levels of voriconazole can be difficult and thus it would be reasonable to provide a second anti-*Aspergillus* agent such as an echinocandin until therapeutic voriconazole levels are established. Additionally, dosing for voriconazole is not available for patients less than 2 yr of age and thus it is not an ideal agent in this age group. When empiric antifungal coverage is needed for a pending diagnosis, there are no guidelines to direct therapy, and there is considerable variation in practice. If there is significant concern for an invasive mold infection, one could initiate broad antifungal therapy with lipid formulation of amphotericin and provide a second agent such as voriconazole until the diagnostic work-up can be executed. In cases of pulmonary mold infections when the neutropenia or immunodeficiency is expected to be prolonged (e.g. AML and relapsed acute lymphoblastic leukemia) resection of the infected lung tissue may be required as a life-saving measure. Surgical and infec-

tious disease consultations are suggested in the early stages of management to help with therapeutic choices.

Viral pathogens are a common cause of respiratory illness requiring PICU admission for immunocompromised patients. A retrospective cohort study of respiratory viral infections in pediatric immunocompromised patients demonstrated that SOT and HSCT recipients have increased morbidity and mortality. Of 78 SOT patients with a respiratory viral infection, six (8%) had disability at discharge attributed to the viral infection, and death in 12 of the 160 SOT and HSCT recipients was either entirely or partially attributed to the viral pathogen [39].

Therapeutic options for respiratory viral infections in high-risk immunocompromised patients are limited, and there are little data to support the effectiveness of the few available agents. Most experts would support the administration of antiviral therapy such as oseltamivir or zanamivir for immunocompromised patients with influenza [40]. Each season the Center for Disease Control and Prevention documents the resistance profile of circulating influenza strains and may provide different therapeutic recommendations. Antiviral medications for other viral pathogens are less well supported. Recent observational data have suggested the potential utility of ribavirin for RSV among immunocompromised children, and some now recommend its use [41]. Adenovirus has been associated with high mortality rates in immune suppressed patients, and cidofovir is a DNA polymerase inhibitor with *in vitro* activity but limited comparative effectiveness data. Some experts do recommend cidofovir use given the significant adenovirus-related mortality rates in certain immune suppressed populations, but the benefits should be weighed against toxicities [42]. Additional antiviral agents are being developed, including brincidofovir, a pro-drug of cidofovir with decreased renal toxicity, DAS-181 (activity against parainfluenza and influenza), and ALN-RSV01 (activity against RSV); they may help change the future landscape of antiviral therapy options for immunocompromised patients [43–45].

Finally, pulmonary disease with CMV and PCP can result in significant morbidity and mortality in immunocompromised children [46]. Both tend to be opportunistic in patients with prolonged and profound lymphopenia or in patients receiving therapies that suppress T cell function. Comprehensive reviews for these infections in immunocompromised patients have recently been published, and thus this review will not

provide additional discussion about the approach to these pathogens [47–49].

7. Advanced care of the deteriorating patient

Importantly, infections in the immunocompromised host can be fatal even in the optimal care environments. As a result, the care team may be routinely faced with decisions regarding the need for advanced care measures in this patient population. Weighing the risks and benefits of advanced care measures can be challenging, but understanding existing prognostic or effectiveness data can be helpful. One such advanced measure is the use of extracorporeal life support (ECLS) for pulmonary infection. A retrospective case series of pediatric patients whose respiratory failure led to ECLS demonstrated that 8% of patients had an underlying immunocompromised state, including HSCT and SOT recipients, children with cancer, and children with primary immunodeficiency [50]. Survival in these patients was 30–40%, with the exception of HSCT patients, of whom only 5% (1/22) survived. Of the infectious reasons for ECLS initiation, fungal pneumonia was associated with the highest adjusted odds ratio of death.

Another commonly considered measure is donor granulocyte transfusion (GTx) and/or granulocyte stimulating interventions in the profoundly neutropenic patient with an invasive bacterial or fungal infection. A Cochrane review of adult studies published in 2005 determined that there was inconclusive evidence either for or against the use of GTx in patients who were neutropenic due to chemotherapy and/or HSCT [51]. In 2006, a pediatric phase II study of 27 neutropenic children reported that transfusion of granulocyte-colony stimulating factor - elicited granulocytes resulted in clearance of infections in 92% of patients, with one-month survival of 81% [52]. However, to date there has been no published randomized trial using the either intervention. In addition, there are also no randomized safety data, and the safety results of non-randomized trials have been varied. While the pediatric Phase II trial observed no pulmonary complications among the 27 patients receiving GTx, a retrospective study of adult patients with hematologic malignancy, neutropenia, and invasive aspergillosis observed that more than half of 53 patients who received GTx developed a pulmonary reaction [53]. The same adult study used a multivariate competing risk analysis and found better

outcomes in the 75 patients who did not receive GTx. Despite these conflicting data, when a severe infection is sustained and count recovery is not expected in the near future, GTx remains an important consideration as a life-saving measure.

Close attention to the patient's current immunosuppressive regimen is also necessary. In the setting of an invasive infection it may be helpful to hold administration of immunosuppressive therapy to preserve a transplanted organ or to treat graft-versus-host disease. Unfortunately, for many of these decisions there is a paucity of published data to serve as guidance. Therefore, it is paramount that these discussions take place with relevant specialty services in a multi-disciplinary approach.

8. Conclusions

Care of the critically ill patient with an immunocompromising condition and a possible or proven infection is challenging, and there is a clear need for more clinical research to guide diagnosis and treatment in the pediatric population. Still, we advocate for a systematic approach that focuses on the following actions: a basic categorization of the immunodeficiency and associated risk, initial studies based on the clinical presentation and most common sites of infection, timely empiric antimicrobial coverage, rapid source control when appropriate, and a high index of suspicion for opportunistic pathogens. Importantly, while this review focuses on infections of the blood and respiratory systems, there are other foci of infection that can lead to fever and/or critical illness, including intrabdominal infections such as *C. difficile* colitis, focal skin and soft tissue bacterial infections, urinary tract infection, invasive mold infections of the skin and sinuses, and post-transplant lymphoproliferative disorder. Management of each of these conditions is based on the degree of immunocompromise, and therefore integration of care with the patient's primary service and infectious diseases can be critical for optimal management in the PICU.

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