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NARRATIVE REVIEW

ICU-acquired infections in immunocompromised patients

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Abstract

Immunocompromised patients account for an increasing proportion of the typical intensive care unit (ICU) case-mix. Because of the increased availability of new drugs for cancer and auto-immune diseases, and improvement in the care of the most severely immunocompromised ICU patients (including those with hematologic malignancies), critically ill immunocompromised patients form a highly heterogeneous patient population. Furthermore, a large number of ICU patients with no apparent immunosuppression also harbor underlying conditions altering their immune response, or develop ICU-acquired immune deficiencies as a result of sepsis, trauma or major surgery. While infections are associated with significant morbidity and mortality in immunocompromised critically ill patients, little specific data are available on the incidence, microbiology, management and outcomes of ICU-acquired infections in this population. As a result, immunocompromised patients are usually excluded from trials and guidelines on the management of ICU-acquired infections. The most common ICU-acquired infections in immunocompromised patients are ventilator-associated lower respiratory tract infections (which include ventilator-associated pneumonia and tracheobronchitis) and bloodstream infections. Recently, several large observational studies have shed light on some of the epidemiological specificities of these infections—as well as on the dynamics of colonization and infection with multidrug-resistant bacteria—in these patients, and these will be discussed in this review. Immunocompromised patients are also at higher risk than non-immunocompromised hosts of fungal and viral infections, and the diagnostic and therapeutic management of these infections will be covered. Finally, we will suggest some important areas of future investigation.

Keywords: Immunocompromised patients, Intensive care units, Critical illness, Cross-infection, Bloodstream infection, Ventilator-associated pneumonia, Antimicrobial resistance

Introduction

The last decades have seen a striking increase in the availability of effective therapeutic interventions for cancer, hematologic malignancies, solid organ transplantation and auto-immune diseases. In parallel, the survival of patients with these conditions as well as other immunodeficiencies has improved significantly [1]. Consequently, recent studies evaluating the use of intensive care have shown that immunocompromised patients account for a significant percentage of the typical intensive care unit (ICU) case-mix. It is estimated that around one-third of ICU patients present at least one risk factor for immunosuppression, and cancer patients currently represent approximately one in six ICU admissions [2, 3].

Immunocompromised patients may require ICU admission for several reasons, including the treatment of severe infections, immune-mediated organ dysfunction, acute bleeding and complications associated with therapies that target their disease. However, their outcomes are only partially explained by their background

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medical history and the conditions leading to critical care [2–5]. As a result of baseline immune abnormalities, exposure to broad-spectrum antibiotics, invasive devices and/or additional immune-modulating therapies during their ICU stay, immunocompromised patients may be at higher risk of acquiring new infections in the ICU.

Among ICU-acquired infections occurring in immunocompromised patients, the most prevalent include ventilator-associated lower respiratory tract infections (VA-LRTI), which are divided into ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT), and bloodstream infections (BSI) [6–10]. Importantly, these patients might also be more susceptible than non-immunocompromised counterparts to a specific range of pathogens—often described as 'opportunistic'—such as some bacteria of lower virulence, but also fungi and viruses. Finally, a special area of concern is related to the prevalence of antimicrobial resistance (AMR) in this population.

Different definitions of immunosuppression have been used across studies, which explains the important variability in reports on the incidence, microbiology and outcomes of ICU-acquired infections in this population. Furthermore, data on the infectious complications associated with the newest immunosuppressive and anti-cancer drugs are scarce. In this article, we will discuss how immunosuppression is usually defined in the critical care literature, cover the mechanisms associated with ICU-acquired infections, describe the epidemiology, diagnosis and management of the most common ICU-acquired infections in immunocompromised patients, and suggest areas of further study.

Methods

We searched the MEDLINE and PubMed databases for articles in English published between 2003 and 2023, using associations of search queries related to the concepts of immunosuppression ('neoplasm', 'cancer', 'hematologic neoplasms', 'HIV', 'immunocompromised host', 'immunosuppression', 'transplantation', 'leukopenia'), intensive care medicine ('intensive care unit', 'critical care'), infections ('cross infection', 'bacteremia', 'bloodstream infection', 'pneumonia', 'invasive fungal infections', 'virus diseases') and antimicrobial resistance ('drug resistance, microbial'). Further references were added through hand-searching in the relevant literature and verifying references of key papers. We screened titles and abstracts of papers identified by our search, and assessed the full text of potentially relevant articles. The inclusion of papers in the final manuscript was based on consensus among all coauthors.

Take-home message

Immunocompromised patients account for an increasing proportion of intensive care unit (ICU) patients and form a highly heterogeneous patient population. Recent data have challenged the common assumption that immunocompromised patients are at higher risk of ICU-acquired infections in general, and with multidrug-resistant bacteria in particular. However, these patients remain prone to opportunistic infections in the ICU, including viral and fungal infections. Future research efforts should focus on the epidemiology of ICU-acquired infections among immunocompromised patients, the role of the normal microbiota, improved tools for microbiological diagnosis and for the assessment of immune function at the bedside, and immunomodulating agents to prevent ICU-acquired infections in this population.

Definitions of immunosuppression

From the immunological perspective, immunosuppression is defined as immune dysfunctions associated with an increased susceptibility to recurrent infections by common or ordinary pathogens, and also by opportunistic microorganisms considered innocuous for non-immunocompromised hosts. Immunosuppressive conditions classically include primary inherited immunodeficiencies [11] and acquired immunodeficiencies related to cancer, hematologic malignancies and their treatment, solid organ transplantation, long-term exposure to corticosteroids and other immunosuppressive drugs, neutropenia or HIV infection. In the critical care literature, the term 'immunocompromised patients' generally refers to patients presenting with at least one of these conditions at ICU admission [8, 12]. Conversely, patients without clinical or biological evidence of immunosuppression are often, by default, and sometimes improperly, considered 'immunocompetent.' However, the assumption that all patients deemed 'immunocompetent' at ICU admission indeed have a normal immune system appears questionable, especially among those with sepsis, whose severity of infection often results from ineffective anti-infective responses [13]. Indeed, multiple conditions likely to impact immuno-inflammatory responses underlie a 'hidden' state of immunosuppression (Table 1). However, there is no validated diagnostic test to assess the actual 'net state of immunosuppression' in critically ill patients. In this review, we have used the term 'immunocompromised patients' to refer to the group of patients presenting with known risk factors of immunosuppression at ICU admission ('overt' immunosuppression), while acknowledging both the large phenotypic heterogeneity within this population and the fact that some features of ICU-acquired infections discussed here might also apply to patients falling outside of this definition (those with 'covert' immunosuppression).

The epidemiology of sepsis in Western countries is characterized by the significant predisposing role of age

Table 1 Conditions associated with immunosuppression in critically ill patients

Overt immunosuppressive conditions		Covert immunosuppressive conditions	
Primary immunodeficiencies*	**Chronic acquired immunodeficiencies**	**Acute acquired immunodeficiencies**	**Non-immune conditions**
- Antibody deficiency - Cellular deficiency - Combined antibody and cellular immune deficiency - Phagocytic defects - Complement defects	- Hematological malignancies - Solid tumors (especially if metastatic and/or under chemotherapy) - Solid organ transplantation - Corticosteroids and other immunosuppressive therapies - HSCT - HIV (especially if CD4 + T-cell count < 200/µL)	- Sepsis - Viral pneumonia (flu, SARS-CoV-2) - Major trauma - Major surgery - Subarachnoid hemorrhage - Cardiac arrest - Malaria	- Diabetes - Chronic pulmonary conditions (e.g., COPD) - Cirrhosis

*Simplified functional classification. The reference molecular classification is regularly updated

COPD chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *HSCT* hematopoietic stem cell transplantation, *SARS-CoV-2* Severe acute respiratory syndrome coronavirus 2

and comorbid conditions [14–16]. Beside aging-related immune cell alterations, a physiological process called immunosenescence, several patients with sepsis also harbor non-immune comorbid conditions that are likely to modulate systemic and/or organ-specific anti-infective defenses. For instance, diabetes is associated with defective phagocytic functions of neutrophils, cirrhosis impairs the essential filter functions of the liver (which is an important reservoir of macrophages, known as Kupffer cells), and chronic obstructive pulmonary disease (COPD) modulates lung immunity toward bacteria. It is illustrative that critically ill patients from the first wave of coronavirus disease 2019 (COVID-19) were generally deemed 'immunocompetent' because they lacked the classical criteria for immunosuppression. However, most of them harbored chronic non-immune comorbidities such as obesity, diabetes and arterial hypertension [17]. Further investigations revealed inappropriate antiviral responses in some of them, ascribed to immune dysfunctions (e.g., the presence of anti-interferon [IFN] antibodies) [18, 19].

Furthermore, there is now firm evidence that critically ill patients labeled as 'immunocompetent' at ICU admission are prone to further ICU-acquired infections related to opportunistic pathogens, including bacteria with limited virulence in non-immunocompromised patients (e.g., Pseudomonas spp., enterococci) and fungi (both yeasts and molds), as well as to the reactivation of latent herpesviruses [16, 22, 23]. The significance of viral reactivation is unclear, as direct organ involvement is uncommonly encountered. Interestingly, viral reactivation may not only be a consequence of immunosuppression, but may also have immunomodulatory consequences by increasing the risk of ICU-acquired bacterial and fungal infections [20]. This increased susceptibility to opportunistic infections argues for ICU-acquired profound and sustained immunosuppression, which involves quantitative and/or functional alterations in all innate and adaptive immune cells [21]. Several clinical studies have shed light on the pathophysiological mechanisms of these alterations, which have been described in the setting of various acute illnesses, including bacterial sepsis, viral infections (e.g., flu), major surgery and trauma [21–23]. Several immune biomarkers have emerged to stratify the risk of ICU-acquired infections beyond the classical clinical risk factors, including lymphopenia [24], monocyte expression of human leukocyte antigen (HLA) class II histocompatibility DR molecules (HLA-DR) [25] and immune functional tests [26]. However, these biomarkers only reflect the functionality of individual components of the immune system, have limited diagnostic and prognostic performance, and might display limited availability at the bedside. Furthermore, they have mostly been assessed in non-immunocompromised patients [27, 28]. Such acquired immune dysfunctions primarily result from the primary insult leading to ICU admission (sepsis, trauma, major surgery, etc.). Still, it is noteworthy that many interventions in the ICU also have potent immunomodulatory properties, including invasive procedures (intravascular catheters, endotracheal intubation, mechanical ventilation), drugs (corticosteroids, sedatives, catecholamines and some antibiotics, which could alter immune responses through mitochondrial toxicity [29, 30]), and blood products (including red blood cells, platelet concentrates and fresh-frozen plasma) [31–33]. Several pre-clinical studies have also documented that the normal microbiota influences the development and function of critical mediators of the immune system [34, 35]. Still, the relevance of these findings to critically ill patients is yet unclear. Thus, the primary insult and related medical interventions may mitigate the anti-infective capacities toward ICU-acquired infections and

smooth out some differences across immunocompromised and non-immunocompromised patients.

Mechanisms of infection in immunocompromised patients

The incidence, microbiology and outcomes of ICU-acquired infections in immunocompromised patients are influenced by numerous factors, which can be broadly divided into: (1) microbial factors, namely the balance between exposure to virulent and opportunistic pathogens and the integrity of the normal commensal flora; (2) the nature, duration and severity of immunosuppression; (3) the disruption of anatomical barriers; and (4) past and current antimicrobial exposure for either prophylactic or therapeutic purposes (Fig. 1).

Specific data on the microbiology of ICU-acquired infections in immunocompromised patients are scarce. In the proportion of these infections attributed to what could be defined as a set of 'typical' bacteria frequently encountered in the ICU (including but not limited to *Staphylococcus aureus*, Enterobacterales, non-fermenting Gram-negative bacteria), ICU-acquired colonization with virulent strains is believed to play a major role, similarly to what is observed in non-immunocompromised hosts. Preclinical data suggest that the disruption of the normal flora may facilitate colonization and subsequent infection with pathogenic bacteria [36–38], and while firm clinical evidence of this is limited, investigations targeting the microbiota of critically ill patients are illustrative of its potential role in the pathophysiology of ICU-acquired infections. In humans, randomized controlled trials have demonstrated that treatment with pre-/probiotics resulted in a lower incidence of VAP [39] and antibiotic-associated diarrhea [40]. However, recent reviews on their effect are inconclusive [41, 42]. Fecal microbiota transplantation (FMT) has been demonstrated to reduce the incidence of *Clostridium difficile* infections [43, 44], but not of other ICU-acquired infections. And contrarily to attempts at restoring a 'normal' flora [45], selective digestive tract decontamination (SDD) with broad-spectrum antimicrobials has also been shown in high-quality studies to reduce the incidence of VAP [46, 47] and ICU-acquired bacteremia [47, 48]. Importantly, the evidence on these interventions among immunocompromised patients is limited [49].

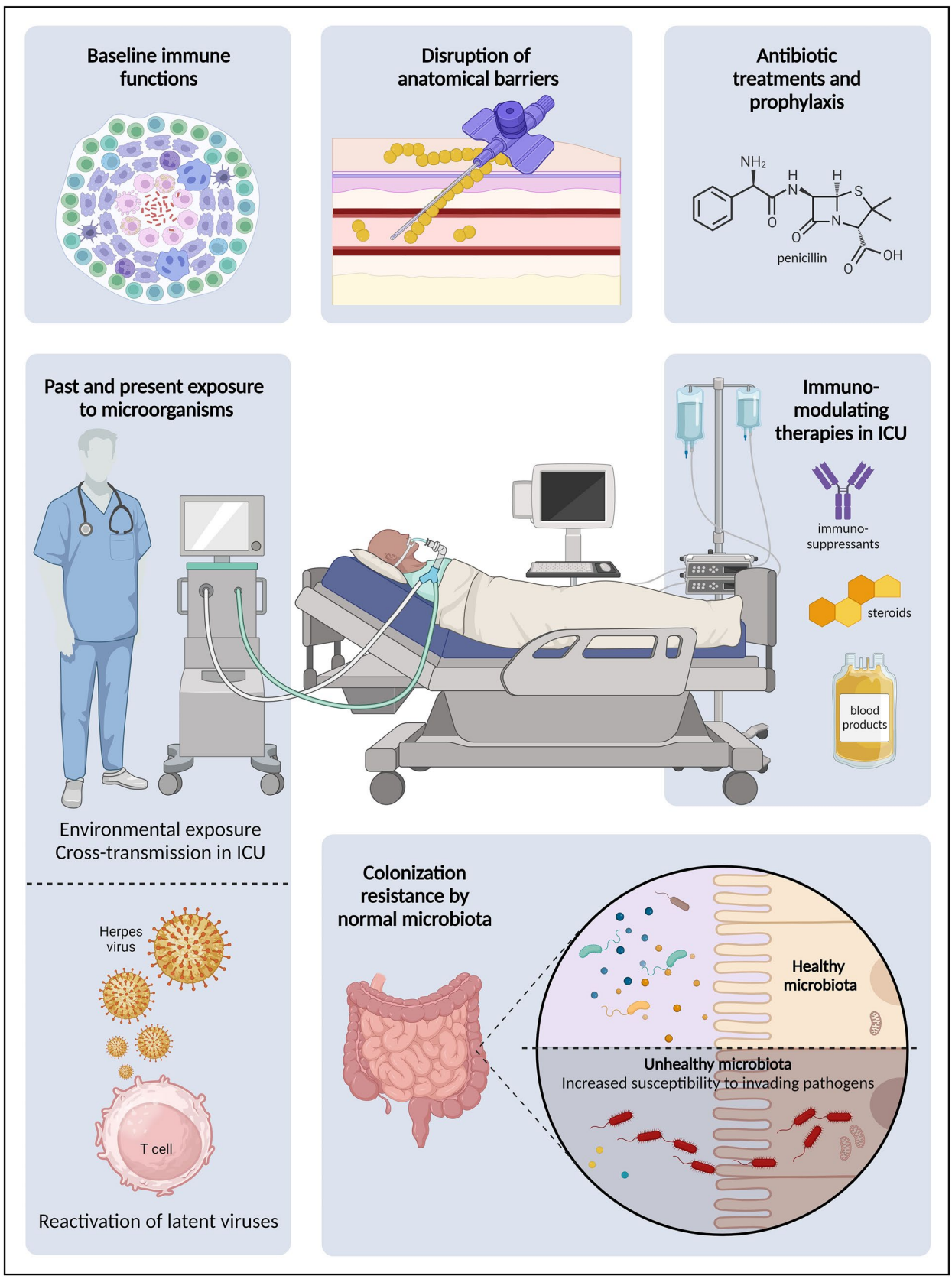
Immunocompromised patients are also prone to ICU-acquired infections with viruses, fungi and 'atypical' bacteria [8]. This can be linked to the reactivation of latent pathogens, e.g., viruses of the Herpesviridae family (such as herpes simplex virus [HSV], cytomegalovirus [CMV]) or mycobacteria; or to environmental exposure in the ICU, e.g., to opportunistic fungi (such as Aspergillus and Pneumocystis jirovecii) or respiratory viruses (such as influenza, respiratory syncytial virus [RSV] and others).

The nature, duration and severity of immunosuppression also influence the microbiology of ICU-acquired infections: prolonged neutropenia is a risk factor for invasive fungal infections [50], patients with B-cell defects are prone to infections with encapsulated bacteria [51], Pneumocystis pneumonia is classically seen in patients affected by acquired immunodeficiency syndrome (AIDS), and increasingly in patients with T-cell defects or on long-term steroids [52]. However, there is significant overlap in the list of potential pathogens typically implicated in different types of immunosuppression. Furthermore, these classical observations are made less relevant by the facts that: 1) critically ill immunocompromised patients often present multiple factors of immunosuppression simultaneously [9]; 2) as we have discussed, critically ill patients with no obvious baseline immunosuppression often develop ICU-acquired immune defects that make them prone to various opportunistic infections [22, 23, 53]; and 3) biomarkers or assays to assess the 'net state of immunosuppression' of individual critically ill patients have important limitations.

The disruption of anatomical barriers by vascular catheters, endotracheal tubes and other devices also plays an important role in the occurrence of ICU-acquired infections, essentially related to 'typical' bacterial pathogens. However, there are little data on the way immunosuppression modulates this risk, and recent investigations have challenged the common assumption that immunocompromised patients are at higher risk of 'device-associated' ICU-acquired infections. For instance (and as will be discussed in more detailed below), in an ancillary analysis of a prospective multicenter observational study, the incidence of VA-LRTI was significantly lower among immunocompromised than among non-immunocompromised patients [7], and in a retrospective multicenter analysis focusing only on immunocompromised patients, the incidence of VA-LRTI was lower among patients with hematologic malignancies than among patients with other types of immunosuppression [54]. Further, in a single-center prospective cohort study, the incidence of ICU-acquired bloodstream infections was

(See figure on next page.)

Fig. 1 Mechanisms of ICU-acquired infections in immunocompromised patients. Figure created with BioRender



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not statistically different between immunocompromised and non-immunocompromised patients [55].

Finally, the occurrence of ICU-acquired infections is influenced by past and ongoing exposure to antimicrobials. First, antifungal prophylaxis is effective at preventing Pneumocystis pneumonia in HIV-positive [56] and HIV-negative patients [57], and antiviral prophylaxis at preventing HSV reactivation in patients with hematologic malignancies [58, 59]. Thus, compliance to these regimens should be considered when evaluating immunocompromised patients suspected of ICU-acquired infection. SDD seems to be effective at preventing VAP [46, 47] and ICU-acquired bacteremia [47, 48], but its widespread use has been limited by concerns over potential negative consequences on AMR, even though implementation of SDD has not firmly been associated with increased rates of multidrug-resistant (MDR) bacteria in critically ill patients [48, 60]. Similarly, antibiotic prophylaxis in high-risk hematology patients has been evaluated in several trials, but has been associated with increased resistance rates and is therefore not recommended [61, 62]. Exposure to broad-spectrum antibiotics is considered a key driver of AMR, as it has been associated with subsequent ICU-acquired colonization and/or infection with MDR bacteria in several studies. The association between immunosuppression and AMR in the ICU will be covered in more detail in a dedicated section below.

ICU-acquired bloodstream infections

Few studies have specifically investigated the association between immunosuppression and the incidence of ICU-acquired BSI. Interestingly, all-cause immunosuppression at ICU admission was not a risk factor for ICU-acquired BSI in a retrospective analysis of 571 BSI episodes among 10,734 patients from the Outcomerea database (France) [63]. Similar results were obtained in a retrospective study on 1306 ICU-acquired BSI episodes among 150,948 ICU admissions in 85 American ICUs [64], and in a single-center retrospective cohort study in France (1313 patients, including 249 immunocompromised) [55]. In a retrospective study on 330 ICU-acquired BSI episodes among 6339 patients in Australia, immune deficiency and malignancies were more prevalent in patients with at least one ICU-acquired BSI than in patients without (10.6% vs. 7%, $p=0.02$ for immunosuppression and 19.1 vs. 14.8%, $p=0.04$ for malignancies), but immunosuppression (not including malignancies) was not an independent risk factor for ICU-acquired BSI in multivariate analysis [65].

Around 90% of ICU-acquired BSI occurring in unselected critically ill patients are caused by bacteria, and there are limited data related specifically to the microbiology of these infections among immunocompromised patients [63, 66–68]. Almost all microorganisms can cause BSI in these patients, including commensal microorganisms of lower virulence (such as coagulase-negative staphylococci [CNS]). Independently of immune status, the European Centre for Disease Prevention and Control has reported that CNS were the most frequently isolated microorganisms in ICU-acquired BSI (mostly associated with catheter-related BSI), followed by Enterococcus spp., Klebsiella spp. and *Staphylococcus aureus* [69]. These data are consistent with those collected in onco-hematologic patients over 15 years (2006–2020, $n=467$ BSI episodes) by Laporte-Amargos et al., although only < 5% of the cohort was admitted to ICU [9]. However, in the EUROBACT-2 study (2600 unselected ICU patients with BSI), Gram-negative bacteria were predominant (59%), and recent reports focusing on patients with cancer and hematologic malignancies [70, 71] and neutropenia [72] have also documented an increase in the proportion of Gram-negative bacteria causing BSI (although not all ICU-acquired). Differences across studies might be related to differences in local epidemiology, but most importantly to the exclusion in some studies of cases related to potential blood culture contaminants (e.g., CNS). Around 10% of ICU-acquired BSI are related to fungal pathogens, most often to Candida species [63, 66–68].

There is no specific definition or diagnosis method for ICU-acquired BSI in immunocompromised patients: according to the 2009 IDSA guidelines, "a BSI is defined by positive blood cultures in a patient with systemic signs of infection, and may be either secondary to a documented source [most often VA-LRTI or catheter-associated infections] or primary", and is considered ICU-acquired if occurring after ≥ 48 h in the ICU [73]. Aerobic and anaerobic blood cultures followed by species identification (usually by matrix-assisted laser desorption/ionization-time of flight [MALDI-TOF] mass spectrometry) remain the gold standard to identify causative microorganisms in BSI. Considering the growth time requirement for blood culture and the negative prognostic impact of a delayed pathogen-adapted antimicrobial treatment, rapid molecular assays (often based on multiplex polymerase chain reaction [mPCR]) have recently been developed as rapid alternatives to culture-based methods [74]. However, most of these syndromic mPCR assays do not alleviate the need for prior incubation, as their diagnostic performance is unacceptably low when used directly on whole blood. An inherent limitation of these tools is the limited number of PCR targets present in their panels. To this date, a clear demonstration of the clinical relevance of these molecular methods in terms of patient outcomes in the management of BSI is lacking.

The occurrence of ICU-acquired BSI has been associated with an increased mortality among unselected critically ill patients, including in Adrie et al. [63] (adjusted HR 1.40, 95% confidence interval [95%CI] 1.16–1.69), Prowle et al. [65] (adjusted HR 2.89, 95%CI 2.41–3.46), and in a retrospective study on 232 ICU-acquired BSI episodes among 3247 patients in 12 ICUs in France (odds ratio [OR] 3.20, 95%CI 2.30–4.43) [75]. Little data have been published on the impact of immunosuppression on the association between occurrence of ICU-acquired BSI and outcomes. However, in the EUROBACT study, Tabah et al. found that among patients with hospital-acquired BSI (76% of which were acquired in the ICU), immunosuppression was associated with an increased mortality risk (OR 2.11, 95%CI 1.40–3.19) [67]. Both in the general ICU population [63] and among critically ill neutropenic patients [72], inappropriate initial antibiotic treatment has been associated with an increased mortality; given the rising prevalence of AMR in ICUs, this makes the choice of empirical antibiotic regimens particularly challenging.

Key points for the management of BSI in critically ill patients—not specifically in immunocompromised patients—have been recently proposed by experts and are summarized here [74]. Both in immunocompromised and non-immunocompromised patients, empirical antibiotic treatment for suspected ICU-acquired BSI will be instructed by individual risk factors for MDR bacteria (including prior antibiotic exposure), local ecology, clinical severity (septic shock), the net state of immunosuppression (especially the presence of neutropenia) and suspected or proven candidemia. In most cases, initial empirical regimens will include broad-spectrum antibiotics. Novel beta-lactams (and associations with beta-lactam inhibitors) active against certain MDR bacteria can be used empirically in critically ill patients, mostly following local ecology. Empirical combination antimicrobial therapy—usually associating a beta-lactam and an aminoglycoside or a fluoroquinolone—is recommended until antibiotic susceptibility testing (AST) results become available. However, extending the duration of dual therapy after culture results become available is controverted, as several meta-analyses have shown that the combination of a beta-lactam and an aminoglycoside did not reduce mortality in patients with BSI, including neutropenic patients or those with sepsis, compared to the same beta-lactam alone, and might increase the risk of acute kidney injury [76–78]. Empirical antifungal treatment with an echinocandin for suspected candidemia should be considered in patients with prolonged neutropenia ($\geq$7 days), non-resolving fever after initiation of broad-spectrum antibiotics, no other source of infection and risk factors for candidemia (including Candida colonization and elevated (1–3)-Beta-D-glucan). It should be initiated promptly in neutropenic patients with septic shock. Preemptive antifungal treatment has been defined as a treatment initiated in patients with elevated fungal biomarkers, and is not recommended in non-neutropenic patients [79]. Failure to achieve source control has been clearly associated with increased mortality [67, 68], and removal of central lines should be immediate in patients with septic shock. Therapeutic drug monitoring is recommended for vancomycin, aminoglycosides and polymyxins, and could be useful for beta-lactams. Prompt de-escalation should be a cornerstone of antibiotic stewardship for all patients [80, 81]. Classically, it has been advised to continue antibiotics until evidence of bone marrow recovery in febrile high-risk neutropenic patients (until the neutrophils count is >500 cells/µL) [82]; however, recent studies have suggested that it is safe to discontinue antibiotics in patients who remain neutropenic but have been afebrile for several days (usually 3–7 days) and in whom no source of infection has been found [83, 84].

Ventilator-associated lower respiratory tract infections, including ventilator-associated pneumonia and tracheobronchitis

Recent studies have investigated the incidence of VA-LRTI in immunocompromised patients. In an ancillary analysis of an international prospective cohort study (2960 patients, including 662 immunocompromised in 114 ICUs), the 28-day cumulative incidence of VA-LRTI was significantly lower in immunocompromised than in non-immunocompromised patients (16.6% vs. 24.2%, sub-hazard ratio [sHR] 0.65, 95%CI 0.53–0.80) [7]. Similar results were obtained when considering VAT (7.3% vs. 11.6%) and VAP (9.3% vs. 12.7%) separately, and these estimates are in line with previous reports on lung and liver transplant patients [85, 86]. Furthermore, in a recent retrospective analysis of two large cohorts (n=854 immunocompromised patients), Bayon et al. have shown that patients with hematologic malignancies (n=162) had a lower 28-day cumulative incidence of VA-LRTI than patients with other types of immunosuppression (13.6% vs. 20.1%, adjusted cause-specific HR [cHR] 0.61, 95%CI 0.37–0.97), mostly due to a lower incidence of VAP (9.3% vs. 13.9%) [54].

Most cases of VAP and VAT are attributed to bacterial pathogens [87], both in the general non-immunocompromised population [88] and among immunocompromised patients [7, 54, 85, 86]. Most cases (50–80%) of bacterial VA-LRTI in immunocompromised patients are caused by Gram-negative bacteria, including non-fermenting bacilli (*Pseudomonas aeruginosa*, *Acinetobacter baumannii*) and Enterobacterales (*Escherichia coli*, *Klebsiella pneumonia*

and other less common species), which is concerning because the resistance rate of these bacteria has been rising. In the study by Moreau et al., the proportion VA-LRTI cases attributed to MDR bacteria was significantly higher among immunocompromised than among non-immunocompromised patients (72% vs. 59% of VA-LRTI episodes, OR 1.75, 95%CI 1.13–2.71), but in view of the lower incidence of VA-LRTI in immunocompromised patients, the cumulative incidence of VA-LRTI related to MDR bacteria was in fact comparable between groups (12.5% vs. 14.7%) [7]. *Staphylococcus aureus* is the most frequently encountered Gram-positive pathogen responsible for VAP [88], but the proportion of cases attributed to methicillin-resistant strains (MRSA) is low (~2%) [66, 89]. Immunocompromised patients are at higher risk of VAP related to fungi and viruses (described below). Invasive pulmonary aspergillosis is a special concern in this population, but its exact prevalence is difficult to ascertain, because formal diagnostic criteria are lacking. Candida spp. is not usually considered pathogenic when isolated in respiratory secretions.

There are no specific diagnostic criteria for VAP and VAT in immunocompromised patients [10]. The diagnosis of VAP is based on the association of signs and symptoms of respiratory tract infection in patients who have been on invasive mechanical ventilation for ≥ 48 h, have a positive semi-quantitative result from a lower respiratory microbiological sample (above specific thresholds) and a new infiltrate on chest imaging [90, 91]. The diagnosis of VAT is based on the same clinical and microbiological criteria in the absence of a new radiologic infiltrate. One of the main challenges of VAP diagnosis in immunocompromised patients lies in confirming infection and ruling out a large set of differential diagnoses, including neoplastic infiltration of the lung, pulmonary toxicities of anti-cancer treatments, fluid overload or intra-alveolar hemorrhage [2, 8]. European guidelines advocate for the use of fiber optic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) to obtain high-quality microbiological samples [91], while American guidelines support obtaining endotracheal aspirates (ETA) [90]. Of note, a randomized controlled trial on 219 critically ill cancer patients with acute respiratory failure (ARF) did not find differences in the rate of adverse events and successful microbiological documentation (except for Pneumocystis pneumonia) when comparing these two diagnostic modalities [92]. Rapid mPCR-based syndromic panels have been endorsed by recent guidelines on severe community-acquired pneumonia (CAP)[93], but not on hospital-acquired pneumonia (HAP)/VAP. A recent trial conducted on 208 inpatients with pneumonia (including 48 HAP cases and 51 patients with immunosuppression) found that an mPCR test run on BAL was effective at reducing the duration of inappropriate antibiotic therapy [94]. As mentioned, an inherent limitation of mPCR panels is their limited number of targets, making them probably less useful for ICU-acquired than for community-acquired infections. Further trials on HAP and VAP are ongoing to evaluate their impact on antibiotic prescribing [95].

Current European and American guidelines on VAP consider immunosuppression as a risk factor for MDR bacteria. Even if this likely reflects the role of confounding factors (e.g., previous hospitalization or antibiotic exposure) more than a truly causal association, these guidelines recommend using a combination of broad-spectrum antibiotics, including a beta-lactam with activity against *Pseudomonas aeruginosa*, for empirical treatment of VAP in immunocompromised patients [90, 91]. However, solid data on the microbiology and treatment modalities of VAP in this population are lacking. The choice of an empirical regimen should be based on the criteria that apply to other ICU-acquired bacterial infections, including local ecology.

Antibiotic resistance in critically ill immunocompromised patients

There is a dominant view in the literature that immunocompromised patients might present a high risk of colonization and/or infection with MDR bacteria, and recent guidelines or expert reviews on BSI, CAP and HAP/VAP advocate for the use of broad-spectrum antibiotics as empirical treatment in this population. To move away from a strict microbiological definition of resistance, it has been suggested to replace the term 'MDR' by the more clinically relevant concept of 'difficult-to-treat' (DTR), as 'DTR pathogens' refer to microorganisms that are resistant to multiple antimicrobial agents, and thus challenging to eradicate with 'standard' (first-line) antibiotic or antifungal agents. While numerous studies have sought to assess the burden of AMR in immunocompromised patients (see reviews in [96, 97]), most have not focused on ICU patients, have not included a control group of non-immunocompromised patients, and have not taken into account important confounding factors in statistical analyses.

In a single-center case–control study conducted to investigate the independent association of immunosuppression with AMR in the ICU, immunosuppression was only associated with ICU-acquired colonization and infection with MDR bacteria in univariate analysis, but not in multivariate analysis after adjustment for antibiotic exposure prior to and during ICU stay [98]. In the CIMDREA study, an observational prospective multicenter cohort study in France, we found that the incidence of ICU-acquired colonization with MDR bacteria was in

fact lower in immunocompromised vs. non-immunocompromised patients (adjusted sHR 0.56, 95%CI 0.40–0.79), but the incidence of ICU-acquired infection with MDR bacteria was not significantly different between groups (adjusted sHR 0.59, 95%CI 0.33–1.05) [9]. This was also true when focusing on BSI and VAP related to MDR bacteria (28-day cumulative incidence of BSI 16.7% vs. 21.3% and VAP 33.3% vs. 38.3% in immunocompromised vs. non-immunocompromised patients, respectively). This is in line with the report by Moreau et al., where the cumulative incidence of VA-LRTI cases attributed to MDR strains was similar in the two patient populations [7], and with a retrospective monocentric study on ICU-acquired BSI in immunocompromised patients [55].

Multiple factors could modulate the risk of ICU-acquired colonization and infection with MDR bacteria in immunocompromised patients—including exposure to antibiotics (especially if broad-spectrum), contact precautions and isolation measures, and the net state of immunosuppression—and further studies are necessary to better understand the dynamics of AMR in this population.

Viral infections

ICU-acquired viral infections can be secondary either to in-hospital acquisition, or to the reactivation of latent viruses [8]. The most common viruses encountered in immunocompromised ICU patients are shown in Table 2. Among them, influenza and parainfluenza viruses, human metapneumovirus, coronaviruses, adenoviruses, RSV and rhinoviruses belong to the 'core' respiratory viral pathogens that may cause CAP and HAP/VAP in immunocompromised patients [99]. For example, rhinoviruses/enteroviruses are increasingly detected among critically ill patients with hematologic malignancies (56% in reference [100]), and parainfluenza virus-3 and RSV have been reported in 71% and 12% of hematopoietic stem cell transplant (HSCT) patients, respectively [101, 102]. The Herpesviridae family is responsible for reactivation under various conditions associated with immunosuppression, and among them, CMV reactivation in respiratory secretions is common in patients under invasive mechanical ventilation (IMV). However, randomized controlled trials of CMV treatment have not demonstrated a benefit in terms of mortality or ICU length-of-stay in this population [103]. Significant CMV viremia (for which there is not established cut-off), presence of retinitis, positive tissue pathology or a positive PCR assay from BAL/tissue are indicators of disseminated CMV infection, which requires prompt treatment [104].

The diagnosis of viral infections in immunocompromised hosts relies mostly on PCR-based tests, some of them integrated in mPCR assays. In case of suspected LRTI, the recommended first-line diagnostic assay is an mPCR assay for respiratory viruses performed on a nasopharyngeal swab (or another non-invasive sample), which should be complemented by a BAL sample in cases of high clinical suspicion with a negative first-line test. In immunocompromised patients with pneumonia, swabs of vesicular or ulcerated skin lesions should be collected for viral PCR and cultures, as HSV- or varicella zoster virus (VZV)-positivity of skin lesions is highly correlated with HSV or VZV pneumonia [99]. Quantitative PCR for CMV in plasma should be obtained in high clinical suspicion. Of note, a negative plasma PCR does not exclude tissue-invasive CMV disease, especially in patients with CMV pneumonia, gastrointestinal disease, or retinitis [105, 106]. Conversely, a low viral load can be associated with non-specific CMV reactivation in the context of any acute illness. Quantitative PCR in BAL can differentiate between CMV pneumonia (high viral load) and CMV reactivation (shedding without pneumonia, low viral load). However, there is no validated diagnostic threshold to distinguish these two conditions. Of note, in lung transplant recipients, CMV viral load in BAL provides higher diagnostic accuracy compared to plasma CMV viral load [104].

Empirical therapy should be extended to cover the possibility of VZV pneumonia in patients with bilateral reticulonodular infiltrates and an accompanying vesicular rash (addition of IV acyclovir 10–15 mg/kg IV t.i.d. to the initial empirical regimen) [99]. Empirical therapy should to be extended to cover CMV pneumonitis in patients with bilateral interstitial pneumonia after a recent lung transplant or HSCT (ganciclovir 5 mg/kg IV b.d., dose adjusted for renal dysfunction) [99]. Corticosteroid use in viral syndromes has been controversial and should be used only in evidence-based indications (i.e., SARS-CoV-2 infection [107]). Lack of response to treatment (where specific treatment is available) and/or relapsing viral disease should prompt suspicion of lack of viral clearance and/or resistance to the treating agent.

Invasive fungal infections

Invasive fungal infections may develop in both immunocompromised and non-immunocompromised critically ill patients, mainly related to Candida and Aspergillus species, whereas alternative yeasts and molds are less commonly acquired in the ICU.

Invasive candidiasis is defined by the isolation of Candida spp. from sterile sites and encompasses both candidemia and deep-seated candidiasis. A number of patient- and treatment-related risk factors are associated with further development of invasive candidiasis in critically ill patients. Invasive candidiasis is commonly

Table 2 ICU-acquired viral infections in immunocompromised patients

Virus	Origin	Clinical features and complications	Treatment	Diagnosis
Influenza A and B	Nosocomial transmission	- Mild upper respiratory tract infection - Viral pneumonia and ARF - Myocarditis, pericarditis, myocardial ischemia - Myositis - Encephalitis, acute disseminated encephalomyelitis, transverse myelitis, aseptic meningitis, Guillain–Barré syndrome - Bacterial and fungal superinfections	- Oseltamivir - Zanamivir - Baloxavir - Peramivir	- PCR (upper respiratory samples, BAL, CSF) - Rapid antigen test - Viral culture - Histopathology - Serology (minor contribution)
Parainfluenza viruses 1–4	Nosocomial transmission	- Mild upper respiratory tract disease - Viral pneumonia and ARF	Supportive	- PCR (upper respiratory samples, BAL) - Rapid antigen test - Viral culture
Human Metapneumovirus	Nosocomial transmission	- Mild upper respiratory tract disease - Viral pneumonia and ARF	Supportive	- PCR (upper respiratory samples, BAL) - Rapid antigen test - Viral culture
Human coronavirus NL63, 229E, HKU1, OC43	Nosocomial transmission	Mild respiratory disease, severe pneumonia and ARDS	Supportive	PCR (upper respiratory samples, BAL)
SARS-CoV-2	Nosocomial transmission	- Fever, cough, dyspnea, myalgia, diarrhea, anosmia/ageusia, headache, non-productive cough, sore throat, nasal discharge - From asymptomatic to severe pneumonia - ARF/ARDS - Arrhythmias, acute cardiac injury, shock - Thromboembolic complications - Bacterial and fungal superinfections - Neurological complications (polyneuropathy, myositis, cerebrovascular diseases, encephalitis and encephalopathy, Guillain–Barré syndrome) - Recurrent COVID-19 in immunocompromised hosts	- Dexamethasone - Remdesivir - Tocilizumab - Anakinra - Baracitinib	- PCR (upper respiratory samples, BAL, stools) - Rapid antigen test - Viral culture - Histopathology - Serology (minor contribution)
Respiratory Syncytial virus A and B	Nosocomial transmission	- Asymptomatic or mild upper upper respiratory tract infection to bronchiolitis, severe pneumonia, ARDS - COPD and asthma exacerbation	- Ribavirin - Palivizumab	- PCR (upper respiratory samples, BAL, stools) - Rapid antigen test - Viral culture - Histopathology - Serology (minor contribution)

Table 2 (continued)

Virus	Origin	Clinical features and complications	Treatment	Diagnosis
Adenovirus	- Reactivation - Nosocomial transmission	- Viral pneumonia and ARF - Hemorrhagic cystitis, nephritis, colitis, hepatitis, encephalitis, disseminated disease	- Cidofovir - Brincidofovir	- Viral culture (nasal, blood, urine, CSF, tissues) - EIA - Immunofluorescence - PCR - Serology - Histopathology
Rhinovirus	Nosocomial transmission	Viral pneumonia and ARF	Supportive treatment	- Viral culture (nasal, blood, urine, CSF, tissues) - EIA - Immunofluorescence, - PCR - Serology - Histopathology
HSV (HSV-1, HSV-2)	- Reactivation in patients with T-cell defects - Donor transmission to transplant recipient	- Viral pneumonia and ARF - Skin and genital ulcers - Encephalitis - Esophagitis - Keratitis	- Acyclovir - Famciclovir - Valacyclovir - Corticosteroids for cerebral edema	- PCR (blood, BAL, CSF, tissue) - Viral culture - Histopathology - Serology
VZV	- Nosocomial transmission (rare) - Reactivation in patients with T-cell defects - Donor transmission to transplant recipient	- Viral pneumonia and ARF - Varicella, herpes zoster - Encephalitis, cerebellitis, hepatitis, myelitis - Herpes zoster ophthalmicus	- Acyclovir - Famciclovir - Valacyclovir - Corticosteroids for varicella vasculopathy	- PCR (blood, BAL, CSF, tissue) - Direct fluorescent antibody testing - Viral culture - Histopathology
CMV	- Reactivation in patients with T-cell defects - Reactivation in haematologic patients with febrile neutropenia - Donor transmission to transplant recipient	- Viral pneumonia and ARF - Viremia - Esophagitis, gastritis, colitis - Retinitis, encephalitis, myelitis, polyradiculopathy - Neutropenia, susceptibility to bacterial infections	- Gancyclovir - Valganciclovir - Foscarnet	- PCR (blood, BAL, CSF, tissue) - Histopathology - Serology

ARDS acute respiratory distress syndrome, *ARF* acute respiratory failure, *BAL* bronchoalveolar lavage, *COVID-19* coronavirus disease 2019, *COPD* chronic obstructive pulmonary disease, *CMV* cytomegalovirus, *CSF* cerebrospinal fluid, *EIA* enzyme immunoassay, *HSV* herpes simplex virus, *PCR* polymerase chain reaction, *SARS-CoV-2* Severe acute respiratory syndrome coronavirus 2, *URTI* uper respiratory tract infection, *VZV* varicella zoster virus

preceded by multisite colonization. Candidemia results from digestive translocation or catheter-related infection, and imposes additional investigations by echocardiography and fundoscopic eye examination to rule out associated endocarditis and endophthalmitis. Deep-seated candidiasis is usually related to the disruption of anatomical digestive barriers, resulting in peritonitis (perforative sus-mesocolic peritonitis or tertiary peritonitis) or infections of pseudocysts complicating pancreatitis. Candiduria is usually considered as colonization, but may occasionally reflect pyelonephritis in kidney transplant recipients. The epidemiology of candidiasis is switching toward an increased prevalence of non-albicans strains, largely driven by previous exposure to antifungals, as observed in patients with hematologic malignancies [108, 109]. Regardless of the underlying immune status [108, 110], the overall mortality associated with ICU-acquired candidemia is about 50% [109]. The treatment of invasive candidiasis relies on antifungal treatment associated with source control (surgery, removal of intravascular catheters). Guidelines in neutropenic and non-neutropenic patients concur to primary echinocandin treatment, with subsequent assessment of de-escalation toward azoles antifungals whenever possible [79, 111]. Use of echinocandins as first-line agents is justified in high-risk immunocompromised patients (especially those with hematological malignancies) who receive antifungal prophylaxis with azoles, as emergence of Candida strains resistant to azoles has been described as a result of these prophylactic regimens [112, 113]. Of note, Mucorales infections should be considered in patients under azoles prophylaxis who develop an invasive mold infection.

Aspergillus is an airborne fungus which primarily affects the respiratory tract of patients with defective systemic or local antifungal immunity. Extra-pulmonary involvement may occasionally occur due to bloodborne dissemination. Invasive pulmonary aspergillosis (IPA) exhibits two different angio-invasive and airway-invasive clinical presentations, resulting from phagocytosis defects (prolonged neutropenia following intensive chemotherapy in acute leukemia or allo-HSCT recipients) and cellular immunodepression (e.g., solid organ transplantation, prolonged corticosteroid treatment, allo-HSCT with graft-versus-host disease [GVHD]), respectively [114]. Besides, new situations at risk have emerged among critically ill patients, including sepsis, COPD and the acute respiratory distress syndrome (ARDS), especially in the setting of corticosteroid treatment prior to or during ICU stay [115–117]. Pulmonary aspergillosis has been described as a complication of severe viral pneumonia, namely influenza-associated pulmonary aspergillosis (IAPA) [115] and COVID-19-associated pulmonary aspergillosis (CAPA) [116], albeit with a highly variable reported incidence. The diagnosis of IPA is based on the EORTC/MSG criteria that define proven invasive aspergillosis if there is histologic proof of fungal tissue invasion, or alternatively probable or possible, depending on the combination of predisposing immunodeficiency, clinical or radiological factors and microbiological findings [118]. The observation that IPA might affect patients devoid of classical risk factors led to extending definitions, all derived from the AspICU algorithm in critically ill patients [119]. In contrast with the classical EORTC/MSG criteria, those ICU-adapted diagnostic algorithms are initiated when Aspergillus is retrieved from tracheobronchial samples, and include the specific entities of IAPA and CAPA [120]. Of note, the AspICU diagnostic algorithm requires a positive Aspergillus culture; however this is not essential in subsequent algorithms. In a single-center prospective cohort study on 110 patients, Aspergillus BAL culture was only positive in 58% of the 21 patients with histology-proven IPA [121]. The diagnostic performance of mycological biomarkers is highly dependent on the clinical situation [122]. The sensitivity of serum antigen galactomannan in IPA is about 70% in neutropenic patients, but remains below 20% in non-neutropenic critically ill patients. In critically ill patients, the sensitivity is much higher in the BAL fluid [121, 123]. (1–3)-Beta-D-glucan is a pan-fungal biomarker with limited sensitivity and specificity but interesting negative predictive value [124]. Regardless of underlying conditions, azoles antifungals active on Aspergillus (voriconazole or isavuconazole) are recommended as first-line treatment of IPA. Aspergillus resistance to voriconazole is emerging, owing to the widespread environmental use of pesticides. Preventive measures comprise air filtration in ICUs and prophylactic antifungal treatment with posaconazole in immunocompromised patients at high-risk of IPA, including patients with acute leukemia or allogeneic HSCT [125]. For critically ill patients with other types of immunosuppression, the demonstration of a clinical benefit of prophylactic antifungal treatments remains elusive.

Future lines of research

Important knowledge gaps still exist in the epidemiology, pathophysiology, diagnosis and management of ICU-acquired infections among immunocompromised patients, and we envision that future research efforts will focus on the following questions:

1) How can we assess the degree and nature of immunosuppression among critically ill patients in a reproducible, affordable and longitudinal manner? As we have discussed, existing biomarkers of immunosuppression (e.g., lymphopenia [24], HLA-DR [25]) have important limitations, and there is no validated way

of assessing the 'net state of immunosuppression' of individual critically ill patients at the bedside [26]. Much effort has been invested to develop transcriptomics tools to better characterize the immune system of ICU patients, but solid clinical data on their use are lacking [126, 127].

2) Can we gain a more precise understanding of the epidemiology of ICU-acquired infections—namely their risk factors, incidence, microbiology and associated outcomes—among immunocompromised patients?
3) What is the role of the normal microbiota in preventing ICU-acquired infections? This should be dissected mechanistically in pre-clinical models, and the potential impact of strategies to modulate this flora (pre-/probiotics, FMT, SDD) in immunocompromised patients should be investigated in randomized trials. In the same line, more data on the association between these strategies and the prevalence of AMR should be collected.
4) How can we improve the diagnosis of ICU-acquired infections? The classical diagnostic microbiology workflow still mostly relies on techniques invented in the early twentieth century, and it is likely that antimicrobial stewardship could be enhanced if the diagnosis of infection was faster, cheaper and more accurate. This could in turn lead to improved outcomes at the individual level, and a lower burden of AMR at the community level. New molecular assays have demonstrated a positive impact on antibiotic exposure among inpatients with pneumonia [94], and their clinical utility among immunocompromised ICU patients needs to be further evaluated.
5) Can we use 'immunosuppression biomarkers' to design clinical trials of immune-stimulating therapies in a precision medicine framework? Several clinical trials have attempted to reverse ICU-acquired immune deficiency using immune agonists (e.g., granulocyte macrophage-colony stimulating factor [GM-CSF] [128], IFN-gamma [129, 130]), but have failed to demonstrate a positive impact on patient-centered outcomes, which could be related to a failure to specifically target subpopulations of patients with a higher likelihood of response to these drugs. We envision that better diagnostic tools could enable predictive enrichment of such trials [131], and help assess the effectiveness of immunomodulating strategies to prevent the occurrence of ICU-acquired infections among critically immunocompromised patients [22, 23, 132].

Table 3 offers ten suggestions of studies that could be conducted in the upcoming years to enrich the knowledge base in this field.

Conclusion

Immunocompromised patients account for an increasing proportion of ICU patients and form a highly heterogeneous patient population. Recent data have challenged the common assumption that immunocompromised patients are at higher risk of ICU-acquired infections in general, and with MDR bacteria in particular. However, these patients remain prone to opportunistic infections in the ICU, including viral and fungal infections. Future research efforts should focus on the epidemiology of

Table 3 Potential future studies on ICU-acquired infections in immunocompromised patients

Incidence of ICU-acquired colonization and infection with MDR bacteria in immunocompromised patients (in comparison to non-immunocompromised patients) [9]
Incidence, risk factors and outcomes of invasive pulmonary aspergillosis in ventilator-associated pneumonia (in immunocompromised and non-immunocompromised patients) [133]
Impact of novel multiplex PCR-based assays for the diagnosis of ICU-acquired invasive fungal infections in immunocompromised patients
Impact of multiplex PCR-based diagnostic assays on antibiotic stewardship in ICU-acquired and ventilator-associated pneumonia in immunocompromised patients [95]
Microbiological yield of metagenomic sequencing in cases of ICU-acquired and ventilator-associated pneumonia with negative microbiology (in immunocompromised and non-immunocompromised patients)
Impact of probiotics (or fecal microbiota transplantation) on the incidence of ICU-acquired colonization and infection with MDR bacteria in immunocompromised patients [134]
Predictive value of gut microbiota perturbations on the risk of ICU-acquired infections in immunocompromised patients
Prospective evaluation of a PCR-based assay of an immune-related transcriptomics signature to predict ICU-acquired infections in immunocompromised patients
Impact of immune-enhancing treatments administered to mechanically ventilated patients stratified on immunosuppression biomarkers (e.g., low HLA-DR expression on monocytes) to prevent or to treat VAP [135]
Evaluation of de-escalation of empirical antifungal treatment of ICU-acquired infections with negative microbiology in immunocompromised patients (especially neutropenic patients)

ICU-acquired infections among immunocompromised patients, the role of the normal microbiota, improved tools for microbiological diagnosis and for the assessment of immune function at the bedside, and immunomodulating agents to prevent ICU-acquired infections in this population.

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Declarations

Conflicts of interest
LK has received speaking fees and a research scholarship from BioMérieux, and has been employed by Transgene. JH has received honoraria for lectures from Diagnostica Stago, Pfizer PFE France, Sanofi Aventis France, Inotrem, MSD, Octapharma and Shionogi. IML, JS, and GP have no conflict of interest related to this work. FP has received speaking fees and consultancy honoraria from Gilead and Alexion, and is a member of the steering committee in a study to assess an immune diagnostic test developed by bioMérieux. SN has received speaking fees from MSD, Pfizer, BioMérieux, Fischer and Paykel, and Medtronic.

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