Severe infections in neutropenic patients

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Purpose of review
Severe infections in neutropenic patients can rapidly progress to septic shock and multiorgan failure with a high associated mortality. In this article we discuss current practice, emerging trends and controversies, including the prophylactic and empiric use of antimicrobial therapy, and advances in cellular and immunotherapy.

Recent findings
Neutropenia is no longer a consistent factor predicting poor outcome in haematological patients admitted to the ICU. Severe infections in neutropenic patients are often polymicrobial, and pathogen resistance remains a challenge. Invasive fungal infection is still predictive of poor outcome. There has been a rapid expansion in the diagnostics and treatment modalities available for patients with invasive fungal infection. Use of growth factors, polyvalent immunoglobulin, and cellular therapy appear to be of value in certain groups of patients. There is a move away from the use of noninvasive ventilation and the use of high-flow nasal oxygen therapy is one of a number of novel respiratory support strategies that is yet to be evaluated in this patient population.

Summary
Translation of current advances in antimicrobial, cellular and immunotherapy, and diagnostics to aid clinical management by the bedside is important in reducing morbidity and mortality for neutropenic patients with severe infection.

Keywords
allogeneic stem cell, infection, neutropenia, sepsis, transplant

INTRODUCTION

Neutropenia is defined as an absolute neutrophil count below 1.5×10^9/l. Neutropenic patients with severe infections are being increasingly treated in the ICU environment because of severe sepsis, septic shock, and multiorgan failure with significant associated morbidity and mortality [1,2]. Around half of febrile neutropenia episodes are complicated by severe sepsis and septic shock requiring ICU admission, where the reported mortality is 35 and 50%, respectively [1–3]. The review discusses the current practice, emerging trends and controversies, including the prophylactic and empiric use of antimicrobial therapy, and concludes with the emerging role of novel cellular and immunotherapies.

HOW IMPORTANT IS NEUTROPENIA TO PROGNOSIS?

The presence of neutropenia conferred a hazard ratio of 1.7 in patients with severe sepsis or septic shock in a recent multicentre cohort of 1981 ICU patients [4▪]. Studies suggest that neutropenia *per se* does not appear to be consistently associated with inferior survival in critically ill patients with haematological malignancies or after haematopoietic stem cell transplantation (HCT) [5▪▪,6,7]. In these patients, neutropenia appears to be a less important predictor of survival than invasive ventilation, myeloablative conditioning, organ failure, and acute kidney injury [6,7].

International guidelines have adopted risk stratification of febrile neutropenia in specific patients groups, mainly with cancer or after HCT; this, together with advances in intensive care management, and the early recognition and

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KEY POINTS

- Neutropenia *per se* is not prognostic in haematology patients compared with other factors.
- Consideration of a polymicrobial cause of sepsis, particularly in the context of HCT.
- Use of serial preemptive *Aspergillus* spp. antigen testing is recommended for high-risk patients.
- Prophylaxis with G-CSF, granulocytes, polyvalent IVIg for selected patient groups.
- Limited use of NIV in favour of high-flow nasal oxygen in neutropenic patients with respiratory failure should be considered.
- There remains a pressing need for improved approaches for managing respiratory failure and ARDS.

treatment of patients with neutropenic sepsis, have contributed to improved outcomes in neutropenic patients that present with severe infections [2,7–9,10▪,11,12▪▪,13].

MANAGING SUSPECTED BACTERIAL SEPSIS

Severe bacterial infections remain the main cause of severe sepsis and septic shock in neutropenic patients admitted to ICUs. Sepsis source control can often be challenging, as fever may be the only initial symptom, inflammatory features are often lacking because of a deficit of mediator cells, polymicrobial infection is frequent, and cultures only yield an organism in around a third of cases. Gram-positive organisms predominate with an increasing incidence of life-threatening gram-negative organisms. The incidence of multiresistant organisms is also increasing: *Pseudomonas* spp., *Escherichia* spp., *Stenotrophomonas* spp., *Acinetobacter* spp., vancomycin-resistant enterococci (VRE), linezolid-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, metronidazole-resistant *Clostridium* spp., extended-spectrum beta-lactamases, carbapenem-resistant *Enterobacteriaceae*, New Delhi metallo-beta-lactamase-1 [8,13,14]; this may be because of colonization and infection of in-situ access devices, routine antibacterial prophylaxis with fluoroquinolones, and empirical broad-spectrum antimicrobial use [8,13,14]. Multidrug-resistant (MDR) gram-negative infection is associated with increased mortality in haematology cancer patients [odds ratio 3.8; 95% confidence interval (CI) 1.2–11.8] [15]. However, it is interesting that colonization with some MDR isolates in HCT recipients does not necessarily appear to affect survival, at least in a recent single centre German cohort [16▪▪].

Empirical antibiotic therapy

International guidelines recommend that febrile neutropenia may be empirically treated with an antipseudomonal beta-lactam (e.g. piperacillin-tazobactam), or carbapenem (e.g. meropenem; especially if extended-spectrum beta-lactamases infection is suspected) [2,7–9,10▪,11,12▪▪,13]. Cefepime is also a reasonable alternative, although it has been associated with inferior survival in some studies [8,10▪]. Additional anaerobic cover is usually unnecessary, unless *Clostridium difficile* or perianal infection is suspected. A dual empirical antimicrobial agent strategy is frequently used, although not supported by strong evidence. The addition of an aminoglycoside in patients with severe sepsis or suspected antibiotic resistance, and a glycopeptide in patients with suspected catheter-related infection, skin or soft-tissue infection, and/or pneumonia are recommended [13,14]. Colistin or tigecycline may be useful for suspected carbapenem-resistant *Enterobacteriaceae* and New Delhi metallo-beta-lactamase-1 infections. Linezolid, daptomycin, or tigecycline may be useful if VRE is suspected, although routine use of linezolid does not appear to improve survival [17▪▪]. A multidisciplinary approach, considering the patient population and local microbiological epidemiology, is advocated when considering empirical antibiotic therapy policies. Central venous catheter (CVC) removal should be considered in patients with septic shock, without an obvious other source of infection, but routine removal is not considered necessary [2]. Similarly, routine antimicrobial prophylaxis for long-term CVC lines is not supported [18▪]. Locking the CVC line with heparin and an antibiotic may be beneficial, particularly in high-risk groups [18▪].

The risk and type of infection post-HCT is time dependent, modulated by specific factors including the intensity and components of the conditioning regimen (mucositis and organ toxicity), donor source [cell type, degree of human leukocyte antigen match, gender mismatch, and cytomegalovirus (CMV) mismatch], disease type (length of neutropenia) and status [11]. A systemic review and meta-analysis of 1412 patients reported that prophylaxis with trimethoprim/sulfamethoxazole reduced *Pneumocystis jirovecii* pneumonia related infection by 85% [relative risk (RR) 0.15; 95% CI 0.04–0.62] and death (RR of 0.17; 95% CI 0.03–0.94) [19▪▪]. However, there was no improvement

in overall survival compared with placebo or fluoroquinolone [19▪▪]. Trimethoprim/sulfamethoxazole is also useful if *Toxoplasma* spp., *Nocardia* spp., *Pneumocystis* spp., and *Stenotrophomonas* spp. infection is suspected, particularly in patients post-HCT.

MANAGING SUSPECTED INVASIVE FUNGAL INFECTION

The risk of invasive fungal infection (IFI) in patients with neutropenia has been shown to vary between 2 and 40%. *Candida* spp. and *Aspergillus* spp. comprise around 95% of fungal isolates in Europe and the United States. Critically ill patients often present with nonspecific symptoms or persistent fever despite antibacterial therapy. The risk of IFI is dependent on several factors: level and duration of neutropenia, underlying disease and status, age, comorbidities, antifungal prophylaxis, corticosteroids, presence of CVC lines, hypogammaglobulinemia, parenteral nutrition, haemodialysis, multiple broad-spectrum antibiotics, major surgery, and exposure to immunomodulatory agents [13,20]. The programmed cell death-1 T cell checkpoint inhibitor ipilimumab has recently been associated with *Aspergillus* spp. infection [21]. Furthermore, there are emerging data suggesting that patients have a genetic risk of IFI susceptibility that is clinically important. HCT recipients from a donor with long pentraxin 3 h2/h2 haplotype (adjusted odds ratio 2.78; $P = 0.03$) or toll-like receptor 4 haplotype S4 (adjusted hazard ratio 6.16; 95% CI 1.97–19.26; $P = 0.002$) are at particular risk of invasive pulmonary aspergillosis (IPA), partly because of impaired neutrophil function [22▪▪,23].

There is a trend of increasing mould infections and fluconazole-resistant *Candida* spp., such as *C. krusei* and *C. glabrata*, related to routine fluconazole prophylaxis. In most HCT centres, the incidence of *Aspergillus* spp. is twice that of *Candida* spp. [24]. Current guidelines recommend that only high-risk patients receive antifungal prophylaxis with activity against moulds [8,13,25▪]. Oral posaconazole prophylaxis is more effective than other triazoles in randomized trials of neutropenic and HCT patients, although more gastrointestinal side-effects were reported [25▪]. A phase 1 study demonstrated good tolerance of intravenous posaconazole [26▪]. Isavuconazole is a newly licenced triazole antifungal being investigated for prophylaxis and treatment [27▪▪]. Antifungal prophylaxis can generally be discontinued when severe neutropenia has resolved, and 3 months post-HCT, unless immunosuppressive therapies or graft versus host disease (GvHD) are present [28].

Empirical antifungal therapy

Despite antifungal prophylaxis, one in 20 patients post-HCT will develop IFI [25▪]. A Cochrane systematic review and meta-analysis reported that liposomal amphotericin B was superior to voriconazole for empirical therapy for fungal infections in febrile neutropenia [29▪]. Voriconazole is preferred for IPA (especially if *Aspergillus terreus* is suspected) and echinocandins (caspofungin, micafungin, or anidulafungin) for candidemia [30,31]. Liposomal amphotericin B has also been suggested for mucormycosis, *Histoplasma* spp., and *Fusarum* spp. The use of combination therapy for severe or refractory infection remains controversial and costly but has shown to improve survival in a randomized trial [32▪▪], and surgical resection has a very limited role for localized disease not responding to medical therapy. Resistance of *Aspergillus fumigatus* to triazoles has been reported *in vitro,* but has not translated to clinical resistance in most cases. Isavuconazole is a newly approval triazole that is noninferior to voriconazole for IPA, and is also useful in the treatment of mucormycosis (website: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207500Orig1s000lbl.pdf). Despite the advances in treatment, mortality for neutropenic patients with IPA or candidiasis remains high, ranging from 30 to 60% in the nontransplant population, to 90% in HCT recipients [20,33].

Diagnostic challenges of invasive fungal infection

Microbiological diagnoses with direct microscopy, histology, or culture are preferable, but differentiation between infection and colonization poses a challenge. *Aspergillus* spp. antibodies are falsely negative in the context of immune suppression. The detection of nucleic acid by the PCR has been available for over a decade but has yet to penetrate routine clinical practice. Antigen tests for *Aspergillus* spp. are routinely used in some ICUs for high-risk patients, particularly in the context of serial testing [13]. Galactomannan is a cell wall polysaccharide containing galactofuranose residues found on *Aspergillus* spp. as well other fungi such as *Penicillium* spp., *Histoplasma* spp., and filamentous ascomycetes (e.g. *Fusarium* spp.). False positives may occur with cross-reacting antigens, severe mucositis, gastrointestinal GvHD, and certain antibiotic preparations (amoxicillin–clavulanate, piperacillin–tazobactam, carbapenems, ceftriaxone, or cefepime) [8,10▪,13]. However, a cut-off value of 0.5 ng/ml for optical density in neutropenic patients is useful for preemptive monitoring and diagnosis, with bronchoalveolar lavage sampling being more useful than blood.

The beta-D-glucan assay detects 1,3-beta-D-glucan, which is a cell wall component of many fungi, but the beta-D-glucan assay is not specific for *Aspergillus* spp. The assay is positive with *Aspergillus* spp., *Candida* spp., and *Pneumocystis jirovecii* but negative with mucormycosis or *Cryptococcosis* spp. Beta-D-glucan has a high negative predictive value to rule out IPA [8,10▪,13].

THE ROLE OF VIRAL REACTIVATION

Viral infection may be a consequence of reactivation or de-novo infection, but often co-occurs with bacterial and/or fungal infection. Impaired lymphocyte function can predispose to severe infection, which is often acquired secondary to medication or HCT, and can take several months to recover. The effects of antithymocyte globulin or anti-CD52 (alemtuzumab) antibody therapy may last for months and can lead to severe viral infections. Thus, prophylaxis is advocated for certain groups of haematology patients [11].

It is becoming increasingly clear that viral reactivation in critically unwell patients, even those that are not considered to be immune suppressed, is associated with inferior outcomes. CMV reactivation in ICU patients is associated with inferior survival and is a predictor for poor outcome in patients with acute respiratory distress syndrome (ARDS) [34]. Epstein–Barr virus reactivation is associated with reduced survival and greater resource use [35]. Human herpesvirus 6 appears to be prognostic only when reactivation occurs in the context of CMV reactivation [36]. A single centre trial of 124 immunocompetent ICU patients reported that antiviral therapy reduced CMV reactivation 10-fold from 30 to 3% [37▪▪], which may emerge as a promising strategy if considerable side-effects (especially renal and bone marrow toxicity) of antiviral medications can be balanced with improved clinical outcomes.

IMMUNOTHERAPY

Granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor immunotherapy

Prophylactic or therapeutic granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor may stimulate acceleration of endogenous granulocyte recovery in the context of neutropenia. Systematic reviews and meta-analyses of randomized trials have not reported benefit of either factor in terms of survival, bacteraemia, or IFI. Reduced hospital length of stay (RR 0.65; 95% CI 0.44–0.95) and improved neutrophil recovery are reported benefits [38▪]. Despite a shorter duration of neutropenia, faster recovery from fever and shorter duration of antibiotic use, absolute clinical benefit was questionable with a greater trend toward the need to discontinue G-CSF because of adverse effects [38▪,39–41]. When G-CSF or granulocyte macrophage colony stimulating factor have been compared with placebo the incidence of severe neutropenia (RR 0.67; 95% CI 0.60–0.73), neutropenic fever (RR 0.74; 95% CI 0.62–0.89), and infection (RR 0.74; 95% CI 0.64–0.85) was reduced in adults with lymphoma [42] and solid tumours [43▪]. Greater chemotherapy doses can be delivered with G-CSF use, which is associated with improved survival [41]. Thus, guidelines recommend that prophylactic G-CSF should be used with risk stratification [9,11,13,14], if the risk of febrile neutropenia is >20% [8]. However, these recommendations may not directly translate to newer pegylated or biosimilar products.

Polyvalent intravenous immunoglobulin therapy

Studies suggest that pre-HCT polyvalent intravenous immunoglobulin (IVIg) appears to be beneficial at preventing interstitial pneumonitis (RR 0.64; 95% CI 0.45–0.89) posttransplantation, but this is balanced by an increase in veno-occlusive disease (RR 2.73; 95% CI 1.11–6.71) [44]. Patients with lymphoma or myeloma with hypogammaglobulinaemia treated with polyvalent IVIg experienced reduced infections at the expense of increased adverse events [44]. Studies have reported that polyvalent IVIg may be beneficial in treating nonneutropenic ICU patients with sepsis [45,46].

Cellular immunotherapy

Donor granulocytes can be harvested from healthy donors either via apheresis ('granulocytes') or from whole blood ('buffy coats'). In addition to providing functional neutrophils they also contain other cell types including lymphocytes and monocytes. Randomized data support prophylactic granulocyte transfusions during neutropenia post-HCT, with a reduction in the incidence of infection and septicaemia [47]. Cell dose may be important for determining the efficacy of granulocytes for neutropenia-associated infection. Treatment of neutropenic fever in patients with acute leukaemia with a cell dose of $>1 \times 10^{10}$ (1.43×10^{8}/kg for a 70 kg adult) was associated with reduced mortality (RR 0.36; 95% CI 0.14–0.96) in a recent systematic review and meta-analysis [48,49]. A higher cell dose can be

achieved by treating donors simultaneously with G-CSF and/or corticosteroids. However, a German–Austrian multicentre randomized trial failed to show any benefit; patients with septic shock or ARDS were excluded [50]. These cellular component products carry the usual risks associated with blood component therapy, including possible transmission of infections, transfusion reactions, and human leukocyte antigen alloimmunization. Furthermore, they are not leucodepleted so must be irradiated to prevent transfusion-associated GvHD. Changes in blood component manufacture and allogeneic HCT practice from bone marrow donors and myeloablative conditioning toward reduced intensity conditioning with peripheral blood stimulated stem cell donors, means that some of these data may not translate into modern clinical practice.

Intravenous mesenchymal stromal stems have been used in haematology patients for GvHD for over a decade. However, they have recently been repurposed for the possible treatment of ARDS in recent phase 1 and 2 trials [51▪▪,52▪▪]. Intratracheal administration has also been reported [53]. These cells are bone marrow, adipose, and umbilical cord derived with heterogeneous preparation and administration, making direct comparisons problematic. Furthermore, preclinical studies suggest that these may also be useful for septic shock, and may also be directly bactericidal without the presence of antibacterial agents (Patel A, personal communication).

ACUTE RESPIRATORY FAILURE AND ACUTE RESPIRATORY DISTRESS SYNDROME

Recent guidelines and cohort studies suggest that patients with haematological malignancy with acute respiratory failure should not routinely receive noninvasive ventilation (NIV) on a general ward as this appears to be associated with delayed intubation, ARDS, and poorer outcomes [12▪▪,54]. A recent multicentre randomized trial reported that high-flow nasal oxygen may be superior to NIV for acute type 1 respiratory failure, which included 10 patients out of 310 with immune suppression [55▪▪]. In recent years, our practice has moved away from NIV toward high-flow nasal oxygen.

HCT may be complicated by idiopathic pneumonia syndrome [56]. Idiopathic pneumonia syndrome is a frequent cause of admission to the ICU for invasive ventilation and has a poor prognosis [57▪▪]. A recent cohort study reported that at least half of these cases are actually not idiopathic but attributable to undiagnosed infections, detected when more sensitive PCR-based molecular techniques are utilized [57▪▪]. Indeed, 90% of cancer patients that develop ARDS have an underlying infection, with a third attributed to fungal infection [54]. Thus, even in the absence of an organism, empirical broad-spectrum antimicrobial coverage is recommended [12▪▪,14].

There have been encouraging results in 12 children with cancer or post-HCT that were treated with high-frequency oscillatory ventilation, a group excluded from recent randomized trials and a meta-analysis [58]. The use of extracorporeal membrane oxygenation in patients with ARDS and a haematological malignancy has been reported from a small Austrian cohort of 15 patients [59▪]. New approaches to respiratory support are needed to improve the outcome of this subgroup of patients.

CONCLUSION

Severe infections in neutropenic patients are often polymicrobial and can be associated with nonspecific symptoms and signs. Pathogen resistance remains a persistent challenge. Improvements in the diagnosis and treatment of IFI may help to reduce the very high associated mortality in patients presenting with IFI. Antiviral prophylaxis in ICU patients, and monitoring for viral reactivation, may contribute in the future to a reduction in mortality. Multitargeted immunotherapies, including cellular therapies, are an exciting advance. However, the poor outcome of neutropenic patients with respiratory failure necessitating invasive ventilation remains a major clinical challenge.

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Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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