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Infection in cancer and transplantation

Rosemary A Barnes

Abstract

The range of opportunist pathogens in cancer and transplant patients continues to increase. New treatment modalities and forms of immunosuppression following transplantation have improved survival from the underlying disease but can lead to prolonged immunosuppression and increased risk of infection. NICE guidelines for the management of neutropenic sepsis are now available but have aroused some controversy, particularly over the recommendation for quinolone prophylaxis in high-risk patient groups.

In addition to neutropenia, long-term defects in cell-mediated immunity are exposing patients to risk of chronic, viral, protozoal and fungal infection. Advances in diagnostic techniques have the potential to improve management and limit unnecessary empirical treatment, allowing a move towards a diagnosis-driven strategy. However, interpreting the clinical validity and utility of some of these assays can be difficult, particularly for low-prevalence infection where the positive predictive value of any diagnostic test is likely to be low and prompt empirical antibacterial therapy is still indicated in neutropenic patients.

Keywords diagnosis; immunocompromise; neutropenia; NICE guidelines; refractory fever

What's new?

- Multi-resistant Gram-negative infections increasing
- NICE guidance on neutropenic sepsis has been developed
- New treatment modalities may result in long-term impairment of cell-mediated immunity and profound immunodysregulation
- A targeted diagnostic approach is replacing empirical antifungal treatment of refractory fever
- Information on the clinical value of new molecular diagnostic tests is still evolving

Introduction

It is well recognized that cancer and transplant patients are immunocompromised by virtue of their underlying disease, chemotherapeutic and radiation treatments and need for ongoing immunosuppression. Classically, the neutropenic patient is considered most at risk with bacterial and fungal infections predominating in this period. However, the increasing use of novel aggressive chemotherapies and immunosuppressant agents, including biological response-modifying agents such as monoclonal antibodies, has led to a growing population of patients with deficits in cell-mediated immunity (CMI). This exposes them to risks of serious viral and fungal infection that may be prolonged (Table 1).

Neutropenic infection

The number of deaths from neutropenic sepsis more than doubled between 2001 and 2010 (Office of National Statistics). Neutropenic sepsis in patients having anti-cancer treatment is defined as a neutrophil count equal to or lower than 0.5×10^9/litre with either a temperature higher than 38°C or other signs or symptoms consistent with clinically significant sepsis. Mortality from untreated neutropenic sepsis ranges from 2 to 21%[1] and empirical therapy for immunocompromised patients is essential. There are several common pitfalls in the management of suspected infection, as follows.

- The concept of empirical treatment, which should be applied to patients where no source/organism is identified, is frequently misunderstood. Patients with infiltrates on chest X-ray, obvious line or soft-tissue infection, or with pathogens already isolated, should receive targeted therapy as determined by national guidelines not the 'empirical' neutropenic fever regimen.
- Differentiation between uncomplicated neutropenic fever and life-threatening neutropenic sepsis is not always made and the terms are sometimes used interchangeably. Sepsis requires additional rapid interventions and appropriate care bundles for sepsis management.
- Definition of response to antibiotics is often determined incorrectly by resolution of fever. There is an unrealistic expectation that fever will settle rapidly whereas in reality the duration of fever in documented bacterial infection is 7–10 days.[2] This leads to inappropriate addition and/or switching of antimicrobials. Markers of response should concentrate on clinical variables and include reducing fever haemodynamic stability and normalization of acute phase response markers; response should not be determined solely by rapid defervescence of fever.

Historically, immunocompromised patients succumbed to Gram-negative septicaemia but the advent of more active antibiotics, especially antipseudomonal penicillins, combined with the frequent use of long-term intravascular access devices led to a change in the spectrum of organisms in the 1980s with a rise in

Rosemary A Barnes *MD MA MSc FRCP FRCPath is Professor/Honorary Consultant, Department of Medical Microbiology and Infectious Diseases, Institute of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, UK.* *Competing interests: RAB has served on advisory boards, received sponsorship and travel expenses to attend meetings and received honoraria for lectures/symposia from Merck, Sharp and Dohme, Astellas, Gilead Sciences and Pfizer. In addition, she has received educational grants, scientific fellowship awards and independent researcher grants from Gilead Sciences and Pfizer. She is a member of the European Aspergillus PCR Initiative Working Group of the International Society for Human and Animal Mycology and a board member of the foundation European Aspergillus PCR initiative. She is a member of the Steering Group of the NISCHR funded Microbiology and Translational Infection Research Group. She served on the clinical guideline development group for the NICE Neutropenic sepsis guideline.*

Infections associated with biological response-modifying agents

Action	Drugs	Infectious complications
TNF inhibition	Etanercept, adalimumab, infliximab	Bacterial infections (especially tuberculosis) fungal infection, hepatitis B reactivation
IL-1 receptor antagonism	Anakinra	Pneumonia, skin and soft-tissue infection
B-cell depletion	Rituximab	Severe mucositis, hepatitis B reactivation, severe respiratory virus infection, gastrointestinal infection
T-cell/B-cell depletion	Alemtuzumab (Campath®)	Bacterial, viral, fungal, and protozoan infections particularly herpes virus infection (cytomegalovirus reactivation) and *Pneumocystis jirovecii* pneumonia (PCP)
CD33 inhibition	Gemtuzumab	Bacterial infections, fungal infections
T-cell/B-cell interaction inhibition	Abatacept	Upper respiratory tract infections, nasopharyngitis, serious bacterial infections
IL-2 receptor antagonism	Basiliximab, daclizumab	No significant increase in serious opportunistic infection reported
HER2 neu receptor antagonism	Trastuzumab (Herceptin®)	No significant increase in serious opportunistic infection reported
Endothelial growth factor receptor antagonism	Bevacizumab	No significant increase in opportunistic infection reported
Epidermal growth factor receptor antagonism	Panitumumab, cetuximab	No significant increase in serious opportunistic infection reported

HER2, human epidermal growth factor receptor 2; IL, interleukin; TNF, tumour necrosis factor.

Table 1

Gram-positive infection, due particularly to coagulase-negative staphylococci. More recently the pendulum has swung back with the re-emergence of Gram-negative organisms producing extended spectrum beta-lactamases and carbapenemases, resulting in infection with multi-resistant organisms.

Recent NICE guidance has attempted to standardize practice.[3] Early recognition of and rapid intervention in sepsis is crucial. It must be remembered that severe infection may present with hypothermia. Monotherapy with extended-spectrum beta-lactam agents has been shown to be equivalent to and less toxic than aminoglycoside combinations in several meta-analyses and is recommended in most guidelines.[4] Concerns regarding these analyses remain, in that they compared different β-lactam agents in different studies and did not take into account the changing spectrum of diseases over time. These concerns have been addressed by a mixed treatment analysis demonstrating a benefit for monotherapy with ureidopenicillins such as piperacillin/tazobactam (Tazocin®).[3] This treatment was associated with the lowest mortality (although not necessarily infectious mortality) and was not affected by year of study. Empirical use of glycopeptides is now discouraged. However, when deciding on initial empirical therapy, it is most important to consider clinical and microbiological findings. Combination therapy may still be indicated and centres with a high incidence of resistance should undertake a risk assessment. Key NICE recommendations are outlined in Practice points.

Refractory fever

Current NICE guidance does not go beyond the initial empirical phase to cover refractory fever. Many problems arise with patients with unresponsive fever where fungal and/or viral infection may be suspected. Empirical antifungal therapy is still considered by many as a standard of care for patients with refractory fever but it inevitably results in massive overuse of costly and potentially toxic antifungal drugs in patients who do not actually have invasive fungal disease. In solid organ transplantation, the incidence of invasive fungal disease (IFD) varies, being lowest in renal transplantation and highest in small bowel transplantation.[5] Most infections are caused by *Candida* species[6] except in lung transplant patients where aspergillosis causes invasive disease and tracheobronchitis in up to 9% of patients.[7] Liver transplant patients are often considered at high risk of mould infection but the incidence is relatively low (1–9%) unless specific risk factors (re-transplantation, renal failure) are present. In haematology and stem cell transplant patients where azole prophylaxis against *Candida* is widely used, invasive aspergillosis is the major IFD seen with rates ranging from less than 5 to 15%.[8]

Improved radiological techniques and introduction of biomarkers (antigen testing and polymerase chain reaction) have allowed a move away from empirical therapy towards a targeted or pre-emptive approach.[9,10]

Infections associated with defects in cell-mediated immunity

In addition to neutropenia, patients undergoing treatment for malignancies are frequently also lymphopenic. It was recognized nearly half a century ago that concomitant lymphopenia doubled the risk of severe infection.[11]

Use of immunosuppressants to prevent rejection and graft-versus-host disease and increasing use of monoclonal antibody therapies such as rituximab and alemtuzumab (Campath®) have profound and long-lasting effects on CMI.

Viral infections, particularly cytomegalovirus, herpes viruses, adenovirus, respiratory and gastrointestinal viruses predominate

but the range of emerging pathogens including acanthamoebae and algal (prototheca) infections continues to grow.

Despite advances in the treatment of HIV disease, pneumocystis infections are increasing and are now seen in groups not previously considered at high risk of this infection.[12]

Post-transplantation lymphoproliferative disorder (PTLD) is frequently driven by Epstein–Barr virus (EBV) and is seen following all forms of transplantation. An increase in central nervous system EBV has been reported. Traditional treatment involves removal of immunosuppression, which may mean sacrificing the organ transplant. Other therapies include rituximab and the recent availability of EBV-specific cytotoxic T-cell infusions and the prospect of effective EBV vaccines should improve outcomes.[13]

The major burden of invasive fungal disease is now associated with defective CMI and two-thirds of patients with invasive aspergillosis are not neutropenic.[14] Onset is seen around 100 days following stem-cell transplantation (SCT), usually in the context of on-going immunosuppression and immune dysregulation.

Humoral defects

Hypogammaglobulinaemia is not infrequently seen following transplantation and in certain haematological malignancies such as chronic lymphocytic leukaemia, where immunoglobulin V_H chain mutation can lead to functional disorders. Immunoglobulin subclass deficiency is recognized following SCT and complement deficiencies can also occur. The risk of overwhelming infection with capsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Neisseria meningitidis* and certain strains of *Escherichia coli* can persist indefinitely. Immunoglobulin replacement therapy, immunization using conjugate vaccines and antibiotic prophylaxis may be warranted.

Diagnosis

Opportunist infections have often gone undiagnosed and traditional methods cannot always distinguish colonization or contamination from true infection. Blood culture and sampling of other sterile sites remain useful tools in the investigation of neutropenic fever but positive diagnostic yields are often low. Rapid molecular and mass spectroscopic techniques are improving sensitivity markedly but problems with interpretation remain.

Interpretation of molecular assays

With any diagnostic test, clinicians must consider what they want from the test result.[15] When diagnosing opportunist infection, a screening test to rule out a diagnosis rather than a test to rule in a specific infection may be more useful, as it will allow empirical treatments to be safely withheld. Sensitivity of the assay is most important in this situation, often at the expense of specificity as the pre-test probability of disease is likely to be low. This will result in false-positive results but the approach may still be superior to empirical therapy.

Specimen type is important. Specimens that are difficult to obtain and require invasive techniques, such as tissue biopsies and lavage fluids, are not suitable as part of screening. They are generally obtained only when clinical signs suggest abnormalities and can be justified by the higher pre-test probability of disease. Molecular testing should be regarded as diagnostic. Here, specificity is most important in order to maximize the positive predictive value.

Other tests may have better utility as prognostic assays, or for quantitative monitoring of response to treatment or efficacy of prophylaxis.

Healthcare providers should endeavour to ensure that all new assays have been rigorously assessed with respect to analytical validity, clinical validity, clinical utility and economic benefits.[16]

With molecular tests the interpretation of clinical significance may be complex. The introduction of novel multiplex targets and new detection platforms has provided information on infectious agents whose pathogenic potential is sometimes unclear. For example, whilst we appreciate the significance of influenza A and B virus, respiratory syncytial virus and parainfluenza viruses 1 and 3, the morbidity and attributable mortality associated with metapneumovirus, coronavirus, rhinovirus, bocavirus, parainfluenza 4 and, more importantly, dual infections with these pathogens, remains to be fully elucidated in different patient groups.[17] Similarly, the multiplex gastrointestinal panels may include novel targets such as sapovirus, *Dientamoeba* sp. and norovirus. Even with known opportunist pathogens, the levels of detection are now so sensitive that patients may remain positive for prolonged periods whilst being otherwise asymptomatic.[18] This not only has serious infection control implications for healthcare providers but may also impact on patient management and cause delays in treatment and/or transplantation. Validated algorithms for testing and for interpreting results need to be developed.

Prevention

Quinolone prophylaxis, which had fallen out of favour due to concerns regarding risk of *Clostridium difficile* infection, is recommended in NICE guidance for high-risk acute leukaemias, stem cell transplants or solid tumours.[3] The recommendation is supported by meta-analyses and full health economic analysis, which showed that it:

- reduced short-term mortality and incidence of neutropenic sepsis
- outweighed the potential for emergence of antibiotic resistance
- was the most cost-effective intervention in patients with solid tumours.

However on-going surveillance for *C. difficile* infection is required.

Conclusions

Cancer and transplant patients remain at increased risk of a growing spectrum of opportunistic pathogens. The combined insult of underlying disease, newer treatment modalities and recurrent infection can lead to profound and prolonged immunoparesis. Major advances have been made in molecular diagnosis allowing a move away from empirical therapy of refractory fever. However, diagnostic accuracy is not a fixed feature of a specific test but rather a reflection of how that test is used in a particular patient population. Understanding test performance in different groups is fundamental to maximizing clinical benefits of improved diagnostic methods. ◆

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Practice points

- Neutropenic fever requires prompt initiation of treatment with piperacillin and tazobactam*
- Empirical aminoglycosides and glycopeptides are not indicated*
- Modification of the initial empirical antibacterial treatment of fever should be clinically and diagnostically driven and not based solely on persistent fever
- Prophylaxis with quinolones is indicated for high-risk groups
- New molecular diagnostic tests require interpretation of clinical value before they are used to influence patient management

* Unless there are patient specific or local microbiological contraindications (e.g. penicillin allergy or local antimicrobial resistance patterns).