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Paediatric Update

Management of infection in children with malignancy

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1. Introduction

The outcome for children with cancer has improved significantly over the last 20 years. This has been achieved by the use of combination chemotherapy, radiotherapy, surgery and haemopoietic stem cell transplant strategies. Simultaneous improvement in supportive care has also greatly contributed. Control of infection, in particular, has improved immensely and is the particular topic of this Update.

Infection is still one of the most serious complications for the immunocompromised host. Most patients with malignancy become neutropenic at some point during treatment. Many patients will also have other causes of immunodeficiency, with impairment of both cellular and humoral immunity putting them at increased risk of infection from bacterial, fungal and viral pathogens. Infections, especially with gram-negative bacilli, in the immunocompromised host may result in the rapid onset of septic shock which, without rapid and appropriate antibiotic therapy, is life-threatening [1]. Therefore, the challenge in modern antibicrobial management is prompt diagnosis and identification of the infecting organism followed by rapid institution of appropriate therapy with as few, or safely managed, side-effects as possible. This goal can be achieved by using antibacterial, antiviral and antifungal agents alone or in combination with cytokine therapy to accelerate neutrophil and macrophage recovery in some cases. In this review we aim to examine some of the recent progress in this field and its impact on clinical practice. Our view of 'current standard best practice' is summarised in Fig. 1.

2. Infections

2.1. Predisposing causes

Neutropenia is the most substantial cause of infections in children with cancer. The risk is directly related to the depth and duration of the neutropenia. Empirical treatment of neutropenic fever with broad spectrum antibiotics results in significantly reduced infection-related mortality. However, not all children are at equal risk. Risk factors include the presence of potential sites of entry for infection, such as mucosal disruption, which may result in localised or systemic infection, and indwelling central venous lines. Not only do these sites provide a potential portal of entry, but also provide an instrument for colonisation which creates difficulty eradicating the infection. Second, chemotherapy and transplant 'conditioning' protocols may include specific immunosuppressive agents such as purine analogues, antibodies (such as CAMPATH and antilymphocyte globulin) cyclosporin or tacrolimus. These drugs, together with 'chemotherapy' cause prolonged periods of lymphopenia and/or reduced lymphocyte function which result in a higher risk of infection by viruses and fungi (including *Pneumocystis carinii*). Third, the risk of infection is partly dependent on the patient's environment, both within and outside the hospital. Building work, crowded places and contact with other infected people all increase the risk of infection in the immunocompromised host.

3. Pathogens

Bacterial infections are usually caused by endogenous organisms which can be isolated in up to 40% cases [2]. Infection with gram-negative bacilli (such as *Escherichia*

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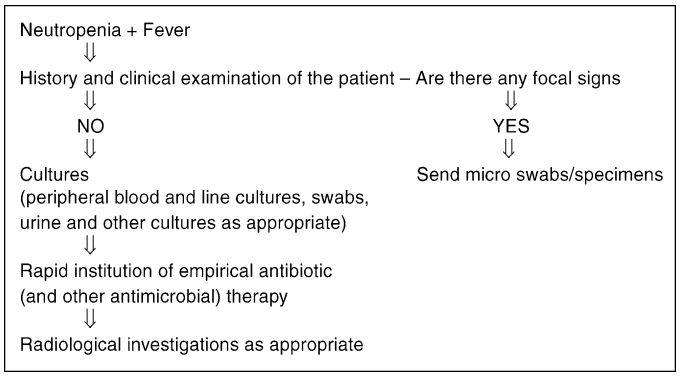

Fig. 1. Management of infection in children with cancer.

coli, *Pseudomonas aeruginosa, Klebsiella, Enterobacter*) is common. Infection with *P. aeruginosa* may be particularly worrying, with rapidly evolving skin necrosis and septic shock. Gram-positive infections (*Staphylococcus aureus* and *epidermidis*, diphtheroids and *Corynebacterium*) are also common in neutropenic patients and their incidence is increasing, partly due to the use of indwelling intravascular lines and partly because of antibiotic usage patterns, for example ciprofloxacin prophylaxis [3]). Eradication may be especially problematic if a line is colonised with an extracellular slime substance, which reduces antibiotic penetration and may result in repeated infections with the same pathogen. Some organisms now exhibit a considerable degree of antimicrobial resistance. Eradication of these is proving to be a progressively more difficult problem in immunocompromised hosts. These organisms include MRSA (methicillin-resistant *S. aureus*), VRE (vancomycin-resistant enterococcus) and ESB (extended spectrum β-lactamase bacteria). Antibiotic and infection control policies should include strategies to minimise the risk of acquiring these infections.

Fungal infections are common in the neutropenic host. The more severe infections are usually seen in patients who have been immunosuppressed for long periods, especially those undergoing bone marrow transplantation. Deep seated and systemic fungal infections pose a particularly serious problem. Eradication is difficult and mortality high. The number of isolates of non-albicans Candida species (i.e. *C. topicalis, C. parapsilosis, C. krusei, C. glabrata and C. lusitaniae*) seems to be increasing [4]. Aspergillus infections are also being detected with greater frequency in BMT recipients [5]. Other fungal infections are rare in patients with malignancy, but emerging pathogens include *Cryptococcus neoformans*, *Mucorales* and filamentous fungi, (i.e. fusarium, trichosporoum and scedosporium species) [6]. Recently reclassified as a fungus [7], *Pneumocystis carinii* may also cause considerable morbidity and mortality.

Viral infections are common in very immunosuppressed patients, especially those who have undergone a haemopoietic stem cell transplant. Herpes Simplex Virus-1 (HSV-1) reactivation is relatively common. It usually causes skin lesions but oral and oesophageal mucositis may also occur. Disseminated HSV infection is uncommon, but almost any organ can be involved and is difficult to treat successfully. Primary varicella zoster virus (VZV) infection may cause chicken pox or may be reactivated, causing shingles. In patients who are seronegative for VZV, chicken pox may be life-threatening. Measles may also be life-threatening in the immunocompromised host because of pneumonitis and disseminated disease, especially in communities in which measles or Measles, Mumps, Rubella (MMR) vaccine uptake is low. Cytomegalo-virus (CMV) infection most often causes a severe pneumonitis, but gastrointestinal disease, hepatitis and retinitis may also be seen. Other herpes viruses which may cause infection in immunosuppressed individuals include Epstein–Barr virus (EBV) and human herpes viruses 6 (HHV-6). EBV infection is unusual in patients with malignancy, but posttransplantation EBV-driven B cell lymphoproliferative disorder can occur and is most often seen in patients who have received T cell-depleted grafts or solid organ transplants. HHV-6 reactivation has been described in immunosuppressed patients, particularly following transplantation, with reactivation causing pneumonitis, encephalitis or, probably most commonly, bone marrow suppression [8].

Respiratory syncitial virus (RSV), influenza A and B, parainfluenza viruses and adenovirus are other causes of pneumonitis. Adenoviruses may also cause haemorrhagic cystitis and renal disease as may CMV and reactivation of latent BK papovavirus in the kidney. Other virus infections include JC papovavirus reactivation which is rare but, can cause life-threatening progressive multifocal leucoencephalopathy following marrow transplantation.

4. Management of infection

The source of infection may not be apparent in the neutropenic child with cancer, but prompt clinical and laboratory assessment and urgent implementation of appropriate, empirical treatment are crucial. Samples should be taken for diagnostic tests prior to treatment, except in dire emergencies, and modification made, if necessary, once the results are known.

4.1. Diagnosis

Correct diagnosis of infection is the most important factor in directing appropriate treatment, but this is often one of the most difficult aspects of managing neutropenic and immunosuppressed patients. There are several problems encountered. First, the specimen should provide a high chance of isolating the organism. For example, specimens from bronchoalveolar lavage or transbronchial biopsies are often not sufficiently representative to detect fungal infections reliably. Second, the technique must be sufficiently sensitive to isolate any pathogens present and rapid enough to give a result in a clinically appropriate time-frame. Viral isolation and culture methods may take several days and therefore have limited clinical use. Faster commercial kits based on immunofluorescence, polymerase chain reaction (PCR) or fast-track culture systems are available for some organisms and may provide a rapid alternative. Third, and most important of all, is the difficulty in interpretation of laboratory results in the clinical setting. It should also be appreciated that faster and more sensitive techniques may be less reliable because the presence of a commensural organism does not always imply pathogenicity. Similarly, increased sensitivity may well be associated with a correspondingly increased false-negative rate, so interpretation of results may be difficult or even misleading. Other diagnostic tests including the use of C-reactive protein (CRP) and interleukin 6 (Il-6) may be helpful in supporting a diagnosis but are rarely, if ever, specific. CRP does not distinguish between infection, or other causes of fever and inflammation to be of much diagnostic use. Il-6 measured by enzyme-linked immunosorbent assay (ELISA) may be a more sensitive marker of gram-negative infections compared with gram-positive infections or other causes of fever [9], but is not specific enough to be of mainstream clinical use. Diagnostic radiology such as high resolution computed tomography (CT) and magnetic resonance imaging (MRI) scans often help confirm a suspected diagnosis though abnormal radiological signs often develop relatively late in infection, when the patient is already on the way to recovery.

4.2. Treatment

Urgent implementation of antibacterial therapy with antibiotics is of paramount importance in the neutropenic host. A step-wise approach to antimicrobials is usual, commencing with empirical combined treatment (usually a β-lactam and aminoglycoside [10–13]) or monotherapy (usually carbapenem, cephalosporin or ciprofloxacin [14,15] depending on clinical circumstances). In non-responding patients, changes are made in the light of clinical and or microbiological information, for example addition of a broad spectrum agent (carbapenem) to cover anaerobes or a glycopeptide in the face of suspected or proven gram-positive infection. Empirical monotherapy should only be used where there is a clear understanding of the local micro-epidemiology. Thus, each unit should follow an antibiotic policy which is appropriate to sensitivities within the geographical region and is agreed between clinical and microbiological colleagues.

Antifungal therapy may instituted either empirically or because of direct evidence of a fungal infection. Empirical treatment is instituted if a patient has failed to respond second-line antibiotics after 48–72 h. The drug of choice is amphotericin B. Mucosal candidiasis or systemic infection with *Candida albicans* may treated with azoles, most commonly fluconazole or itraconazole. Newer agents such as voriconazole, posaconazole and echinocandins are currently under trial. Itraconazole has a broader spectrum than fluconazole with activity against non-albicans Candida and filamentous fungi. It is currently licensed in tablet form, as an oral solution and an intravenous preparation. The oral forms have limited use in patients with malignancy as absorption is variable and mucositis may limit oral intake but the oral solution is superior to the tablet form in terms of attaining reliable serum concentrations. Levels may be measured, although only in specialist centres at present, and dosage adjusted to achieve therapeutic serum concentrations. The intravenous preparation potentially provides a more reliable method of administering itraconazole. Amphotericin B has a broad spectrum of activity and is the treatment of choice for infection with non-albicans Candida, aspergillosis or other fungal infections. Side-effects are common and include hypersensitivity reactions, renal toxicity, renal tubular leak and disturbance of liver function tests. Gastrointestinal disturbances, neurological symptoms and cardiovascular arrythmias are also described. Toxicity has been reduced by the development of lipid-associated formulations which include a liposomal preparation (AmBisome), amphotericin B lipid complex (ABLC, Abelcet) and amphotericin B colloidal dispersion (ABCD, Amphocil). All these preparations have similar efficacy to amphotericin and their reduced toxicity (especially in the case of amBisome) allows higher doses to be tolerated and thus improves the treatment of fungal infections [16–19]. Lipid preparations are expensive, however, so most patients are started on 'native' amphotericin B. Absolute indications for

changing to a lipid preparation include a severe reaction, unacceptable renal toxicity or a clinical need for dose escalation.

The drug of choice for treatment of PCP is intravenous co-trimoxazole (trimethoprim and sulphamethoxazole) for a minimum of 14 days. Intravenous or inhaled pentamidine is an alternative for those sensitive to co-trimoxazole, but in treatment doses several worrying toxicities, particularly severe hypotension.

Aciclovir is the drug of choice for treating infections caused by HSV and VZV. Ganciclovir has comparatively greater activity against CMV, but it causes bone marrow suppression, creating a particular problem in those patients, particularly stem cell transplant recipients, most at risk of CMV infection. The alternative, intravenous foscarnet, causes renal impairment in up to 50% of patients. Foscarnet and cidofovir may be used to treat herpetic infections resistant to treatment with aciclovir, but severe renal toxicity is also seen with cidofovir which must be given with probenecid. Clinical trials have shown ribavirin to be helpful when treating immunocompromised infants with RSV infection, but the benefit is less clear-cut when used in older patients posttransplant.

4.3. Haemopoietic growth factors and surgery

It might be expected that reduction of the duration of neutropenia following chemotherapy would reduce the number, morbidity and mortality of bacterial and fungal infections. Colony stimulating factors have therefore been evaluated as a therapeutic strategy in this context. Granulocyte colony stimulating factor (G-CSF) acts on more committed cells (primarily neutrophil precursors) to enhance neutrophil colony formation, promote neutrophil maturation and increase neutrophil cytotoxicity. Side-effects include headache, bony pain and fatigue. Granulocyte-macrophage colony stimulating factor (GM-CSF) acts on a larger number of immature progenitors than G-CSF, enhances function of neutrophils and granulocytes and potentiates the production of other cytokines by neutrophils, monocytes and eosinophils. It is used in a similar range of clinical settings to G-CSF, but has a wider side effect profile with a higher incidence of allergic reactions, serositis, oedema and a capillary leak syndrome which have limited its use [20]. Stem cell factor (SCF) acts on stem cells, progenitor cells, and in some lineages, precursor cells and mature cells and could also be potentially useful after chemotherapy. It accelerates the entry of stem cells into cell cycle and expands the number of progenitor cells. At present (November, 2002), clinical trials especially in view of a toxicity profile that includes allergic urticaria and laryngeal oedema [21,22].

Both G-CSF and GM-CSF may be given intravenously or subcutaneously in children although the intravenous route is often preferred to minimise discomfort and risk of bruising if the patients are thrombocytopenic. Both have been shown to reduce the duration of neutropenia in children undergoing chemotherapy [23–25]. The potential benefits of this observation are two-fold. CSFs can be used as a strategy to allow dose intensification of chemotherapy, or to reduce the morbidity and mortality associated with neutropenia and infection. Several studies have shown a reduction in the number of days in hospital and reduced days of neutropenia [23,25], but there is no evidence that CSF administration reduces the number of infective complications, overall morbidity or mortality. In randomised studies in adults [26–28], administration of growth factors does not been seem to reduce mortality following BMT/PBSC. 'Routine' administration of growth factors following chemotherapy has major cost implications and there is currently insufficient evidence of benefit to support this policy. However, in the seriously ill child with life-threatening infection, the use of growth factors may be justified because reduction of the period of neutropenia by several days may, in individual cases, reduce morbidity or mortality.

In general, surgery is usually best avoided unless required urgently in a life-threatening situation since surgical wounds act as a further source of sepsis and may delay the administration of further chemotherapy. However, as with any 'good rule' there are exceptions. For example, resection of amenable single or small areas of pulmonary aspergillosis in patients requiring further chemotherapy or bone marrow transplant is a valuable procedure and is carried out as an elective procedure after count recovery. Surgical biopsy may be required in certain circumstances, especially if decisions regarding the possibility of further treatment (e.g. transplant) are required. Surgical drainage of infection is not usually required as abscesses are rare in neutropenic patients and lines of demarcation of infection may not be clear.

4.4. Prevention, prophylaxis and pre-emptive treatment

4.4.1. General measures

Simple measures such as avoiding crowded areas and contact with infected people should be advised. Maintenance of nutritional status [29] and meticulous attention to personal and dental hygiene [30,31] also reduces the number of infections in children with cancer. The ward 'routine' should include regular cleaning of clinical areas, especially between patients. Rigorous hand washing and barrier nursing of severely immunosuppressed patients should be mandatory. Flowers and plants, as well as certain foodstuffs (e.g. ground pepper, nuts, etc.), may contain fungal spores and are usually best avoided. Nearby construction work liberates high numbers of fungal spores into the atmosphere. In these

circumstances, patients should be protected by the use of HEPA (high efficiency particulate air) filters with laminar airflow which have been shown to reduce Aspergillus infections and are commonly used for patients undergoing allogeneic marrow transplant.

Removal of any indwelling source of sepsis (e.g. central venous lines and urinary catheters) should be considered if infection is severe or recurrent. The decision as to whether or not to remove a line depends on the severity and type of infection and the ability to otherwise support the patient. Certain organisms (e.g. *Stenotrophomonas maltophilia, Pseudomonas* spp, *Klebsiella* spp) are difficult to eradicate once a device is colonised. Positive identification of a fungus in blood cultures always requires line removal.

4.4.2. Chemoprophylaxis

Chemoprophylaxis with antibiotics, antifungal and antiviral agents has been used in patients receiving chemotherapy who are likely to become neutropenic, but increases the risk of the emergence of resistant organisms. Use of ciprofloxacin, particularly, has resulted in an increase in gram-positive infections [3]. Similarly, polyene use with nystatin or amphotericin suspension and pastilles have been shown to be of no benefit in reducing the incidence of oral candidiasis, fungal colonisation or systemic fungal infections [32–34]. Fungal prophylaxis with azoles has been shown to reduce the risk of infection [33,35–37], albeit with a concomitant risk of the emergence of Candida species resistant to fluconazole [38,39]. This form of prophylaxis should therefore be reserved for neutropenic patients at enhanced risk of a serious fungal infection. PCP prophylaxis is with cotrimoxazole and has clearly been shown to be of benefit in reducing the incidence of infection when given to 'at risk' patients [40,41]. Prophylaxis with aciclovir is routinely given to patients at risk of reactivating CMV who are undergoing bone marrow transplantation.

4.4.3. Surveillance cultures and pre-emptive treatment

The benefit of weekly surveillance cultures in patients at high risk of infection, such as those undergoing stem cell transplantation, is controversial. These include Candida and Aspergillus antigen in blood together with cultures (nasal swab, line exit swab, perineal swab, etc.). Detection of an organism may allow earlier 'targeted' treatment of infection in febrile neutropenia rather than the use of empirical treatment. However, the clinical applicability of results and optimal laboratory methods for screening are still uncertain. Currently, ELISA methods are most often used, but PCR-based tests are under evaluation. It is important to recognise that colonisation may not imply pathogenicity and care must be taken not to miss, or fail to treat, other potential causes of infection.

Prophylaxis with ganciclovir has been shown to reduce the incidence of CMV reactivation [42–45]. However, ganciclovir is myelotoxic with a high incidence of neutropenia and an alternative strategy is to aim at detecting evidence of CMV reactivation as early as possible in order to institute pre-emptive therapy. This strategy has also been shown to substantially reduce the incidence of CMV disease and mortality following allogeneic bone marrow transplantation [46,47]. Methods to detect early evidence of CMV reactivation include antigen detection tests and more sensitive PCR tests, both of which can be quantified. A rising titre of CMV antigen or viral transcripts should prompt consideration of pre-emptive ganciclovir therapy in order to reduce the risk of developing CMV disease.

5. New ideas

Daily aminoglycoside dosing is now often used in treating adults with febrile neutropenia. This practice was the consequence of evidence that the efficacy of aminoglycosides is independent of the dosing frequency and that higher peak concentrations may lead to better outcomes, without an increase in toxicity [48,49]. Several groups have now demonstrated the safe and effective use of single daily dosing regimens for both amikacin and gentamicin [50–53] in children with febrile neutropenia.

Liposomal antibiotics have the potential to increase efficacy with reduced toxicity. The most promising is liposomal amikacin (MiKasome). Amikacin is encapsulated in unilamellar low-clearance liposomes which results in increased 'area under the curve' and increased plasma and tissue half lives [54,55]. In rats, half lives are of the order of 24 h in plasma and 60–460 h in tissues [54], so twice-weekly dosing or less may be appropriate for therapy and even longer intervals for prophylaxis. Subcutaneous and intramuscular administration is also feasible in animals [56], although these routes may have limited application in children with cancer. Clear benefits of liposomal preparations include better tissue delivery and reduced renal exposure, resulting in reduced nephrotoxicity [55]. *In vitro* experiments have also suggested that liposomal ciprofloxacin and polymixin B and have better activity against *P. aeruginosa* than either liposomal amikacin and free ciprofloxacin or polymyxin B alone [57].

Antimicrobial catheters (for intravenous use) are now available and have been investigated as a means of reducing the incidence of local and systemic infections. Three catheters are currently licensed in Europe, ARROWgard (Arrow) is coated with chlorhexidine and silver sulphadiazine whilst two other catheters Vantex (Edwards Life Sciences) and Expert (Vygon) are coated in silver ions. A meta-analysis has shown that in patients with a high risk of line infections, chlorhexidine

and silver sulphadiazine catheters resulted in significantly fewer line-related infections, although these catheters were used only for short periods of up to 11 days [58]. A minocycline- and rifampicin-coated line is also currently under trial. There are some potential drawbacks with the use of coated lines, including potential alteration of antibiotic resistance patterns and allergy to the coating substance [59]. It is not yet known whether these problems will limit their use.

Several studies are now underway evaluating new approaches to the management of viral infections. New agents include antiherpes simplex and VZV drugs (penciclovir, famcilovir, idoxuridine [60]), fomivirsen (an antisense oligonucleotide) which is licensed for treatment of CMV retinitis and drugs under evaluation for treatment of CMV (bendimidazole, maribavir). Several of these current treatments are licensed or under evaluation for treatment of patients with a primary diagnosis of HIV infection, but they may also become applicable to profoundly immunosuppressed children following chemotherapy or transplantation. Improved treatment of respiratory viral infections would also reduce morbidity, but, because of the low frequency of severe viral respiratory infections are rare in cancer patients, even after bone marrow transplant. It is therefore difficult to conduct prospective trials of antiviral agents to examine their efficacy. However, small studies suggest some benefit in using cidofovir to treat adenoviral infections [61,62].

6. Future developments

Future developments must and will include the early and reliable detection of fungal and viral infections with improved diagnostic tools that give a rapid and accurate diagnosis. In addition, epidemiological studies should be designed to identify trends and emerging pathogens in order to develop necessary counter-strategies before a serious problem arises. Similarly, identification of nosocomial infections and patterns of resistance must also be monitored. Better detection, prophylaxis and pre-emptive treatment of viral infections is also urgently needed as well as more effective treatment for established viral infection, particularly in patients following allogeneic marrow transplantation, in order to minimise both morbidity and mortality.

Outpatient or home antimicrobial therapy may be appropriate in some patients, with antimicrobial single daily dosing strategies once infections are under control. This approach will surely reduce the risk of cross-infection from other patients. Novel therapeutic strategies with CSFs to limit the period of neutropenia may also emerge.

7. Conclusions

It is now considered a clinical disaster if patients succumb to infection, either within or outside hospital, whilst neutropenic. It is therefore imperative for the clinical team to remain vigilant for signs and symptoms of infection and, with their microbiology colleagues, be alert to evidence of the emergence of resistant pathogens. Sensible use of antimicrobial strategies, prolonging the useful lifespan of antibiotics such as quinolones, will enlarge the repertoire of antibiotics that are available when infections occur. We certainly require improvement in microbiological techniques and strategies to give a rapid and accurate diagnosis. This will to allow the fastest possible administration of appropriate therapy with the minimum use of unnecessary empirical agents. If this can be achieved, the risk of emergence of resistant pathogens can also be minimised. In addition, treatments must be designed to have maximal efficacy with the least achievable side-effects. Potential serious long-term toxicities should not be tolerated as the quality of life of survivors is crucial.

We are still a long way from 'getting it right'. Patients still succumb to infection and there is no room for complacency. Some 'take home' messages from this articles are listed in Fig. 2.

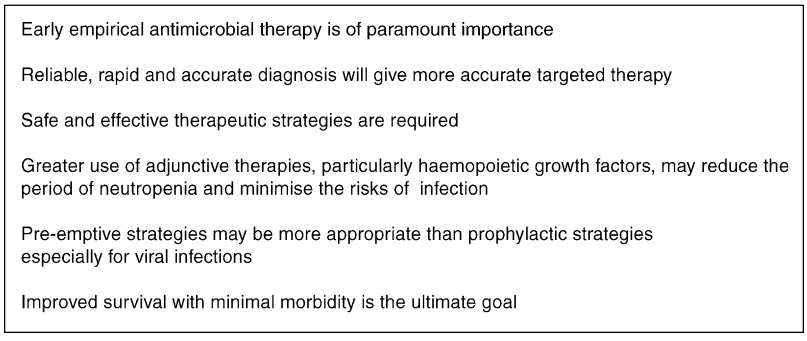

Fig. 2. Take home messages.

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