Susceptibility to infection in patients with neutropenia: the role of the innate immune system

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Summary
Chemotherapy-induced neutropenia increases the risk of infection. There appears to be a wide variability in the severity and length of infective episodes. Susceptibility to infections is determined by the underlying malignant disease and its treatment, environmental factors (e.g. nutritional state of the patient and hygiene) and genetically determined variations of the immune system. The majority of primary immunodeficiencies are rare (c. frequency one in 10 000), whereas some genetic polymorphisms in the innate immune system, such as profound mannose-binding lectin deficiency, are much more common (c. frequency one in 10). Here, we review the potential role of the innate immune system in determining susceptibility to infections in patients with neutropenia.

Keywords: neutropenia, cancer, innate immunity, mannose-binding lectin, infection.

In the Western world, more than one in 600 children will develop a malignancy in the first 15 years of life (Stiller, 1997). Although there have been major advances in therapy, most children have chemotherapy-associated complications, the commonest of which is infection. It is now nearly four decades since the relationship between the degree of neutropenia and the risk of bacterial and fungal infections was first recognized. Bodey et al (1966) published the first detailed account of the infectious complications of 52 patients treated with cytotoxic chemotherapy for acute leukaemia. They made the observation that, as granulocyte counts fell, the frequency, duration and severity of infections dramatically increased. This was particularly marked when neutrophil counts fell <500 cells/μl (Fig 1). Lymphocytes were similarly affected and low counts were also related to increased infections.

Infections were noted to be worse during relapse of the underlying disease and the failure of leucocytes to recover following an infection was associated with a very poor prognosis. It is now clear that this is largely determined by both the underlying disease and the potency of chemotherapy. Interestingly, however, it is apparent that patients differ in their susceptibility to infection in the context of neutropenia. This indicates that other factors are operating to protect patients from infection in their immunocompromised state. This article explores the potential role of the humoral arm of the innate immune system in providing protection from infections during neutropenia.

The innate immune system
The adaptive immune system provides highly specific recognition of both host and foreign antigens, allowing for effective handling of a multitude of microorganisms and the generation of targeted immunological memory. The innate immune system, which is a more ancient arm of immunity (Hoffmann et al, 1999), also provides host defence against a vast array of pathogenic microbes. However, the specificity of the recognition systems employed is targeted against highly conserved structures common to large groups of microorganisms. This is achieved through interactions between host-derived pattern-recognition receptors (PRR) and pathogen-associated molecular patterns (PAMP) on microbes, which are frequently the repeating sugar arrays expressed on microbial surfaces (Janeway, 1989). Whilst the adaptive and innate systems are often considered as separate entities, the fact that the adaptive immune system has evolved in the presence of the innate system suggests the probability that the two systems may be linked. This has indeed been demonstrated in many ways, not least of which is the common use of certain effector cells and soluble mediators (Janeway, 1989; Janeway & Medzhitov, 2002; Iwasaki & Medzhitov, 2004)

Pattern-recognition receptors
The PRR can be expressed on the cell surface, in intracellular compartments, or secreted into the bloodstream and tissue fluids (Medzhitov & Janeway, 1997, 2002; Uronen-Hansson et al, 2004). They are expressed on most effector cells of the immune system and, of particular relevance to innate immunity, are their presence on macrophages, dendritic cells and...
neutrophils. These receptors recognize PAMP, which functionally can be divided into three classes: (i) signalling [e.g. membrane-bound toll-like receptors (TLR) and the cytoplasmic nucleotide-binding oligomerization domain (NOD) proteins], (ii) endocytic (e.g. the macrophage mannose receptor) and (iii) secreted [e.g. collectins, C-reactive protein (CRP), anti-microbial peptides and serum amyloid protein (SAP)] (Medzhitov & Janeway, 2000).

**TLR and the NOD signalling pathways**

The TLR and NOD1 and NOD2 have an essential role in the innate recognition of PAMP and in triggering acquired immunity in higher organisms (Akira, 2003; Philpott & Girardin, 2004). So far, at least 11 mammalian TLR (TLR1–TLR11) have been identified. The TLR family is characterized by the presence of an extracellular domain containing leucine-rich repeats and a cytoplasmic toll/interleukin (IL)-1 receptor (TIR) domain similar to that of the IL-1 receptor family. Upon ligand binding, these receptors function through a family of adapter (MyD88, MAL/TIRAP, TRIF, TRAM) proteins, which lead to the recruitment of IL-1 receptor-associated kinases and appropriate members of the tumour necrosis factor receptor-associated factor family to the TLR complex. The net downstream effect is the activation of mitogen-activated protein kinases and nuclear factor-kappa B (NFkB) pathways, culminating in changes in expression of a variety of innate immune-response genes, including inflammatory cytokines, chemokines and antimicrobial peptides (AMP) (Medzhitov & Janeway, 2000; Akira & Takeda, 2004; Kelly & Conway, 2005). It is becoming increasingly clear that the TLR family plays a major role not only in the expression of innate immunity but also through activating antigen-specific lymphocytes and thereby initiating adaptive immune responses.

The NOD proteins share homology with TLR in the leucine-rich repeat recognition domain but diverge in their signalling motif as NOD consist of a caspase activation and recruitment domain (CARD) rather than the TIR domain found in TLRs (Chamaillard et al, 2003; Philpott & Girardin, 2004). Bacterial activation of NODs leads to NFkB activation via recruitment of RIP-2 thus circumventing the usage of upstream signalling events described above for the TLR system. Two members of this family (NOD1/CARD4 and NOD2/CARD15) are now known to sense different motifs found in peptidoglycan, a component of bacterial cell walls (Chamaillard et al, 2003; Girardin et al, 2003a,b). NOD1, through its intracellular location in epithelial cells, is known to play an important role in sensing invasive *Shigella flexneri* (Girardin et al, 2001). It has recently been shown that NOD1 can also detect extracellular bacteria, such as *Helicobacter pylori*, by sampling bacterial products that have been ‘injected’ into epithelial cells with the aid of a type IV secretion system (Odenbreit et al, 2000; Viala et al, 2004). In contrast to direct sensing of pathogens by NOD1, NOD2 exerts a more regulatory role in modulating TLR signalling (Watanabe et al, 2004). Mutations in the NOD2 gene are now known to be linked to a subset of patients with Crohn’s disease (Ogura et al, 2001) and a rare autoimmune disease affecting the eyes and joints called Blau’s syndrome (Miceli-Richard et al, 2001).

**Endocytic pattern-recognition receptors**

The macrophage mannose receptor, which is also a member of the calcium-dependent lectin family, is an endocytic PRR. It specifically recognizes carbohydrate structures rich in mannose, which are a characteristic feature of microorganisms and mediates phagocytosis by macrophages. Another endocytic PRR, the macrophage scavenger receptor, binds to bacterial cell walls and plays an essential role in the clearance of bacteria from the circulation. The macrophage scavenger receptor mediates opsonin-independent phagocytosis of Gram-positive bacteria, such as *Staphylococcus aureus* (Suzuki et al, 1997; Thomas et al, 2000).

**Secreted pattern-recognition receptors**

Secreted pattern-recognition molecules function as opsonins by binding to microbial cell walls and tagging them for recognition by the complement system and phagocytes. Mannose-binding lectin (MBL), surfactant protein A and D (SP-A and D), CRP and SAP are secreted pattern-recognition molecules produced during the acute phase response in the early stages of an infection (Gewurz et al, 1982; Schwalbe et al, 1992; Fraser et al, 1998). The CRP and SAP are members of the pentraxin family, and both can function as opsonins upon binding to phosphorylcholine on bacterial surfaces (Gewurz et al, 1982; Schwalbe et al, 1992). CRP also has a complex role in relation to complement function. It can both promote complement activation, via the classical pathway, as well as acting as an inhibitor of the alternative pathway. The capacity of CRP to modulate complement pathways may be important in human infections (Suankratay et al, 1998).

MBL, arguably the best-characterized receptor of this class, is a member of the calcium-dependent collectin family, which also includes pulmonary SP-A and D (Holmskov, 2000) (see Table 1). However, amongst the collectins, MBL alone initiates the lectin pathway of complement activation following binding...
to mannose, N-acetyl glucosamine, fucose and glucose residues presented in the orientations and densities commonly found on microorganisms. A structurally similar group of molecules, the ficolins, also activate the lectin pathway but differ from the collectins in their carbohydrate recognition domain structure.

MBL has been shown to bind to Gram-positive and Gram-negative bacteria, to fungal species, some viruses and also to protozoa and other parasites. On binding it activates the complement system in an antibody and C1-independent manner via associated serine proteases, MBL-associated serine protease 1, 2 and 3 (MASP 1–3). MASP-2 appears to be the physiologically relevant MASP in humans. It cleaves C4 and then C2 to form the C3 convertase, C4b2a, resulting in an amplified cascade of complement activation (Fig 2).

Cellular receptors for MBL have been proposed and several studies have shown direct interactions of MBL with phagocytic cells, resulting in enhanced phagocytosis and modification of cellular activation (Kuhlman et al, 1989; Neth et al, 2002). Some of the biological functions of MBL are illustrated schematically in Fig 3.

**Antimicrobial peptides**

The mucosal surfaces that form the interface between the external environment and the internal organs of an organism are also major sites where both commensal and pathogenic microbes can take up residence. The first line of innate-host defence against these environmental stimuli is provided by epithelial-derived AMP present in the secretions that bathe these surfaces. Once a pathogen succeeds in breaching the integrity of the mucosal epithelia, AMPs from innate immune cells (neutrophils and macrophages) form a second source of potent antimicrobial activity. AMPs are collectively an ancient innate immune mechanism and studies in the last two decades have identified them as a critical component of host defence against infection (Ganz & Lehrer, 1998; Zasloff, 2002; Ganz, 2003; Yang et al, 2004). They have the ability to kill and neutralize Gram-negative and Gram-positive bacteria, fungi (including yeasts), parasites, cancer cells and even enveloped viruses (Hancock & Scott, 2000; Harder et al, 2001; Ganz, 2003). The cationic and amphipathic nature of these peptides promotes interaction and insertion into the negatively charged microbial membrane.

In humans and other mammals, the three main AMP families are lysozyme, defensins and cathelicidins, which are...
Defensins are a family of cysteine-rich cationic peptides with a characteristic β-sheet-rich fold (Ganz, 2003). Based on the pairing of their disulphide bridges, defensins can be divided into three subgroups termed α, β and ϕ. In humans, the respective genes of the two major (α and β) classes are clustered on the short arm of chromosome 8. Although the sequence of the human genome suggests the presence of more than 20 defensin-related genes, only six α-defensins (four present in neutrophils and two in Paneth cells of the small intestine) and four β-defensins have been identified and characterized, to date.

Studies using various in vitro and in vivo models of infection and inflammation suggest that pathogens employ a range of strategies to modulate or resist host-innate defence in a dynamic fashion. For example, enteropathogens, such as Sh. flexneri and Cryptosporidium parvum, exhibit potent inhibition of human β-defensin 1 gene and peptide expression during gastrointestinal infection (Islam et al, 2001; Zaalouk et al, 2004). These studies highlight a potential novel immune evasion mechanism employed by diverse pathogens. Reduction of host antimicrobial activity by a microbe may allow increased persistence and, ultimately disease at the site of infection. Further, bacteria can secrete molecules, such as the protein SIC from Streptococcus pyogenes, that can directly inactivate neutrophil defensins and the human cathelicidin LL-37, the major antibacterial peptide involved in bacterial clearance (Frick et al, 2003). It is becoming increasingly clear that AMPs are not only microbicidal in nature but also possess previously unknown immuno-modulatory properties, which include chemotactic activity towards a variety of immune cells [for a recent update see (Finlay & Hancock, 2004; Yang et al, 2004)], the initiation of dendritic cell differentiation (Davidson et al, 2004) and the promotion of macrophage signalling events (Bowdish et al, 2004). These studies further emphasize the contribution of AMPs towards the maintenance of tissue homeostasis both in health and disease.

Fig 3. The MBL binds to microbial surfaces and promotes opsonophagocytosis by various mechanisms. One of the most important is the activation of the complement system by the lectin pathway. This is mediated by the serine protease MASP-2 and leads to the creation of the C3 convertase C4b2a. C4b2a cleaves C3 and generates multiple C3b fragments that bind covalently to the surface of the organism. These fragments are recognized by the CR1 (CD35) receptor of phagocytes. Some C3b is converted to iC3b, which is recognized by CR3 receptors. In addition, direct uptake of MBL by phagocytes has been proposed in a number of studies but the putative collectin receptor involved has not yet been identified. MBL also promotes inflammation by a dose-dependent modulation of cytokine release from monocytes [reprinted from Molecular Immunology, 40, Turner, M.W., The role of mannose-binding lectin in health and disease, 423–429, Copyright (2003), with permission from Elsevier].

Genetic polymorphisms within the innate immune system are increasingly being identified and their role in a clinical setting is under investigation. Mutations in the macrophage mannose receptor results in downregulation and enables opportunistic organisms, such as Pneumocystis carinii, to cause disease (Fraser et al, 1998). More recently, it has been shown that there is a strong genetic association between polymorphisms in the macrophage mannose receptor and susceptibility to infection with leprosy (Siddiqui et al, 2001).

Mutational inactivation of an unknown component in the toll and IL-1 receptor signalling pathways has been described in a patient with increased susceptibility to bacterial infections (Kuhns et al, 1997). Numerous polymorphisms have now been described in human TLRs and some appear to have clinical significance (Cook et al, 2004; Hoebe et al, 2004).

The ubiquitous and overlapping nature of endogenous AMPs suggests that deficiency of antimicrobial function in disease is likely to be a rare event. Therefore, it was of great interest when Putsep et al (2002) were able to associate specific deficiency of neutrophil LL-37 and reduced expression of defensins in patients with Kostmann’s syndrome (a severe congenital neutropenia) and susceptibility to recurrent infections and periodontal disease. A defect in the human defensins has also been described and has been implicated in the pathophysiology of cystic fibrosis (Goldman et al, 1997).

Recent data indicates that CRP levels can be influenced by polymorphisms in the CRP gene (Suk et al, 2005). However, the implications of such polymorphisms in relation to clinical infection are far from clear. It would appear that depending on circumstances, CRP can be both beneficial as well as detrimental (e.g. protecting mice from lethal doses of...

High levels of CRP have also been shown to promote atherosclerosis (Han et al, 2004). Further studies are required to establish the role of CRP in infectious susceptibility and outcome.

The best-understood and investigated defect of innate immunity is MBL deficiency. Human deficiency of MBL was first identified in association with a common defect of opsonization in children (Super et al, 1989). Subsequent studies of consecutive and prospective series of children have confirmed that MBL deficiency predisposes to infectious illness. Human deficiency of MBL is now known to be predominantly caused by point mutations within exon 1 of the MBL gene at codons 52, 54 or 57 (termed D, B and C variants, respectively) which results in aminoacid substitutions that compromise assembly of functional oligomers. Individuals heterozygous for these mutations have reduced concentrations of MBL in their serum, whereas the protein is almost absent from the serum of homozygotes and compound heterozygotes. In addition to the exon 1 mutations there are three major polymorphisms in the promotor region of the MBL gene, and one of these variants (XY) also profoundly influences expression of the protein. The MBL promotor polymorphisms are expressed as four haplotypes called HYP, LYP, LXP and LYQ. These are in linkage disequilibrium with the exon 1 polymorphic variants, so that the D variant is linked to the HYP promotor haplotype, the B variant is linked to the LYP haplotype and the C variant is linked to LYQ. The wildtype (A) exon 1 sequence is found in association with all four promotor haplotypes. More than a third of the population will have haplotypes that predispose to low MBL concentrations, and very low concentrations are expected in c. 12%. MBL deficiency is thought to be clinically most apparent in the context of co-existing immune defects, including primary and secondary immune deficiencies. The young, elderly and immunocompromised seem to be most at risk. MBL is able to modulate disease progression in various clinical settings, such as human immunodeficiency virus infection (Garred et al, 1997), rheumatoid arthritis (Garred et al, 2000) and cystic fibrosis (Garred et al, 1999). In addition, it has been shown that MBL modulates the inflammatory response of phagocytes to Neisseria meningitidis serogroup B, responsible for the majority of cases of meningococcal septicaemia in the UK (Jack et al, 2001a). Recently, MBL deficiency was also shown to be associated with increased severity of sepsis and incidence of systemic inflammatory response syndrome (Garred et al, 2003; Fidler et al, 2004). The main defects in innate immunity associated with an increased incidence of infections are listed in Table II.

Although most disease association studies have only considered deficiency of MBL there have been reports of pathology associated with normal or elevated levels of the protein. These have focused on (i) studies of patients with renal disease associated with MBL deposition in the glomeruli (e.g. post-streptococcal glomerulonephritis) and (ii) studies of myocar-

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<th>Immune defects</th>
<th>Pathogen susceptibility</th>
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<td>Neutrophils</td>
<td>Bacteria: Gram +ve and Gram −ve</td>
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<td>Fungi: Candida, Aspergillus</td>
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<tr>
<td>Complement system</td>
<td>Bacteria: Gram +ve and Gram −ve,</td>
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<td>Fungi: Pneumocystis carinii</td>
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<td>Parasites: Cryptosporidium</td>
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<td>MBL</td>
<td>Bacteria: Gram +ve and Gram −ve,</td>
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<td>Mycobacterium tuberculosis</td>
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<td>Viruses: HIV, IAV, HSV</td>
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<td>Fungi: Pneumocystis carinii, Candida, Aspergillus</td>
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<td>Parasites: Trypanosoma cruzi,</td>
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<td>Cryptosporidium parvum, Plasmodium falciparum</td>
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<td>Defensins</td>
<td>Bacteria: Gram +ve and Gram −ve,</td>
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<td>Fungi: yeast</td>
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<td>Viruses: Adenoviruses</td>
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MBL, mannose-binding lectin; HIV, human immunodeficiency virus; IAV, influenza A virus; HSV, herpes simplex virus.

dial ischaemia-reperfusion injury. Both are reviewed briefly in Turner (2003). A recent study has also suggested that MBL may contribute to the pathogenesis of rheumatic heart disease (Schafranski et al, 2004).

It should also be stressed that there may be some biological advantage associated with low levels of MBL in certain population groups. Two hypotheses have been proposed to explain the possible survival advantages of the low level phenotype (reviewed in Turner & Hamvas, 2000). In one case the MBL deficiency simply reduces complement activation and the occasionally serious damage associated with mediator release. The alternative hypothesis proposes a role in the regulation of uptake of intracellular parasites, such as leishmania, with low levels being protective. However, a full consideration of these aspects is outside the scope of the present review.

**MBL and malignancy**

From the studies of Bodey, it has been recognized that the degree and length of neutropenia has a profound effect on the risk of infection. However, what is less clear is why, within any given episode of neutropenia, there is considerable variability in infectious susceptibility. It was on this basis that a potential role for MBL in patients suffering from haematological/oncological diseases was investigated.

The first studies were published in 2001. In one publication, MBL levels were measured in 54 adults treated with chemotherapy for a range of malignancies (Peterslund et al, 2001). No differences were observed between the distribution of MBL levels in this population and an apparently healthy population of local blood donors. However, in 16 patients who developed either bacteraemia, pneumonia or both within 3 weeks of starting chemotherapy, MBL levels were significantly lower.
than in patients without serious infections. Further analysis revealed that it was patients with an MBL concentration of 500 ng/ml or less that were particularly at risk of severe infection. In a prospective study, MBL phenotype and genotype were determined for 100 children receiving chemotherapy for a range of malignancies (Neth et al., 2001). The largest clinical groups were acute lymphoblastic leukaemia (n = 55) and non-Hodgkin lymphoma (n = 18). The MBL genotype and MBL plasma level of all patients were correlated with the causes, frequency and duration of febrile neutropenic episodes. Children with variant MBL alleles suffered from twice as many days of febrile neutropenia compared with patients with a wild type genotype. The relationship between MBL levels at diagnosis and total days of febrile neutropenia in the first 6 months from diagnosis is illustrated in Fig 4.

In addition, the mean duration of each febrile neutropenic episode was significantly longer in patients who were MBL-deficient compared with MBL wild-type patients. MBL gene polymorphisms have also been associated with major infection following haematopoietic stem cell transplantation. In one study, in which patients underwent allogeneic transplantation, invasive bacterial, viral and fungal infection occurred more frequently among those with variant MBL alleles (Mullighan et al., 2002). The presence of the HYA promoter (high MBL level-producing) haplotype protected against infection. Interestingly, MBL deficiency of donor and recipient were independently associated with an increased risk of major infection following transplantation. In another study, in which 113 patients were treated with high dose chemotherapy and autologous stem cell transplantation, MBL deficiency was also shown to significantly increase the risk of serious infection (Horiuchi et al., 2005).

Not all studies support a role for MBL in this setting. Bergmann et al. (2003) studied 80 patients with acute myeloid leukaemia (AML) and found no differences in frequency, severity or duration of fever in MBL-replete or -deficient patients. In another report, Kilpatrick et al. (2003) studied 128 patients, more than half of whom were diagnosed with lymphoma or AML. Two thirds of the cohort were receiving intensive conditioning prior to bone marrow transplantation. Only severe MBL deficiency (concentrations ≤100 ng/ml) was found to influence infectious susceptibility, and this effect was modest. In a third study, Rocha et al. (2002) found no relationship between MBL structural mutations and post-transplant infections in over 100 donor–recipient pairs following human leucocyte antigen-identical sibling bone marrow transplantation.

From the studies performed to date, the influence of MBL in the context of chemotherapy-induced neutropenia is unclear and this has been reviewed by Klein and Kilpatrick (2004). There are many potential reasons why these studies report conflicting results. These include the type of MBL assay employed, sample size and different protocols including the use of granulocyte colony-stimulating factor and prophylactic antibiotics. However, the most likely explanation lies in the patient populations used, particularly with respect to age and underlying disease. In the studies in which MBL status did not influence infectious susceptibility the patients are likely to have received more intensive chemotherapy. The majority of the patients had AML, which is associated with a particularly high rate of bacterial infections as a result of prolonged episodes of neutropenia. In contrast, in the studies by Neth et al. (2001); Peterslund et al. (2001) and Horiuchi et al. (2005), AML was less common, with a predominance of conditions considered at a lower risk for infectious complications. Support for the view that some phagocytic function is required for MBL to be functionally effective against bacteria comes from Mullighan et al. (2002) who found that MBL coding mutations in stem cell donors only influenced infections following phagocytic recovery.

For future studies it will be important to elucidate how MBL is operating in these patients and to clarify whether MBL can be effective in the absence of neutrophils. At present we have only limited mechanistic information on how MBL could be involved in protecting neutropenic patients from infection. Nevertheless, we have shown that MBL can bind to a wide range of microorganisms, including those that are responsible for serious infections in chemotherapy patients (Neth et al., 2000) (see Fig 5).

Furthermore, at MBL levels >600 ng/ml, this binding can lead to significant complement deposition on the microbial surface and, for some organisms, can lead to enhanced killing (Neth et al., 2002). However, the majority of bacterial pathogens cultured from the blood of neutropenic patients are normally engulfed and killed by phagocytes. It would therefore be surprising if complement alone would have a major effect on the rate of infection in these patients. Indeed few organisms appear to be predominantly killed by the complement system alone. The exception is N. meningitidis, which is seen more commonly in terminal complement component deficiencies and for which MBL has been shown to enhance killing in the absence of phagocytes (Jack et al., 2001b). This organism is rarely seen in neutropenic patients. It may therefore be
reasonable to assume that MBL would not influence the susceptibility/course of bacterial infection in the complete absence of phagocytes.

However, it is important to note that not all phagocytes are completely destroyed by chemotherapy. Shi et al. (2004) demonstrated that MBL significantly enhanced the function of resident peritoneal macrophages in mice rendered neutropenic by administration of cyclophosphamide. Optimizing phagocytic function, both locally and systemically, may be the key to effective MBL utilization/function. Indeed, MBL can enhance the uptake of staphylococci by phagocytes both directly and through an increase in opsonic C3 fragments (Neth et al., 2002). Such mechanisms could explain how MBL might be operating when phagocytes are present at low numbers or are functionally impaired. In the light of these observations it may be rational to combine MBL therapy with stimulating factors, such as granulocyte-macrophage colony-stimulating factor, that could enhance the activity of surviving phagocytes following chemotherapy. Clearly other mechanisms may also influence non-bacterial causes of infection. MBL has been shown to inhibit viral infectivity and has also been implicated in susceptibility to Aspergillus infection (Crosdale et al., 2001).

While it seems likely that patients with AML who are at a high risk of bacterial infection are unlikely to benefit from MBL therapy, the studies are also consistent with the possibility that, under some circumstances, MBL could be important. Paradoxically, MBL could prove to be most beneficial in those patients receiving chemotherapy associated with a lower risk of infectious complications. A number of studies have attempted to identify subsets of patients with febrile neutropenia and at lower risk of significant infection and/or complications who can be managed safely at home or following early discharge from hospital (Klaassen et al., 2000; Mullen, 2001).

This approach potentially reduces the risk of nosocomial infection and the development of bacterial resistance. It also has obvious cost benefits and would enable patients to spend more time at home with their families, thereby improving quality of life.

Further studies are required to identify the role of MBL in this patient population and determine whether MBL replacement therapy (purified or, better, genetically engineered human MBL) as first described by Valdimarsson et al. (1998) could be cost-effective in an appropriately targeted population. The role of other innate immune components in this context requires further investigation but could potentially provide a new avenue for managing infections in patients with malignancy.

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References


Fig 5. MBL-binding to microorganisms isolated from immunocompromised children (Neth et al, 2000). Inset: foci of binding of MBL to one clinical isolate of Candida albicans developed with fluorescein isothiocyanate-labelled anti-MBL.


