Introduction

Many patients in the Intensive Care Unit (ICU) are immunocompromised. In some, immunosuppression is easily apparent, especially when caused directly by underlying disease (such as a haematological malignancy) or treatment (such as drugs to prevent organ rejection or as a side effect of cancer chemotherapy). In others, immunosuppression is less apparent and is induced by the underlying disease, for example: following traumatic injury or sepsis, or as a response to therapies provided during intensive care such as steroids ***(Murphy et al., 2010).***

Immunosuppression itself does not cause pathology but does leave the patient prone to infection. There is no good clinical test to measure the degree of immunosuppression; the clinician must simply maintain a high index of suspicion. The consequences of immune suppression in the ICU highlight the importance of infection prevention and control, as well as surveillance measures to ensure that appropriate treatment is implemented safely and quickly. Intensive care clinicians require a thorough understanding of the mechanisms of immune suppression and the management of patients with immune dysfunction ***(Murphy et al., 2010).***

The past two decades have witnessed an increase in the number of patients who are immunocompromised as a consequence of a primary or secondary immunodeficiency disorder or from the use of agents that depress one or more components of the immune system. Broadly defined, an immunocompromised host has an alteration in phagocytic, cellular, or humoral immunity that increases the risk of an infectious complication or an opportunistic process such as a lymphoproliferative disorder or cancer. Patients may also be immunocompromised if they have an alteration or breach of their skin or mucosal defense barriers that permits microorganisms to cause either a local or a systemic infection (e.g. from burns or indwelling catheters) ***(Pizzo, 1999).***

Under the influence of immunosuppression, microorganisms may become opportunistic, commensal organisms may become pathogenic, normally poorly pathogenic organisms may become more aggressive, and patients may respond poorly to treatment. For these reasons, a systematic approach to diagnosis is required ***(Montague et al., 2011).***

The assessment of the level of immune deficiency differs based on the underlying cause and may include white blood cell and CD4 cell counts as well as therapeutic drug monitoring for those on immunosuppressant

medications. Targeted testing should then be performed based on the resulting differential diagnosis. A focused assessment for common symptoms will guide testing which may include complete blood counts, liver function tests, urine analysis, cultures of blood, stool, and urine, and chest X-rays as well as specific testing for respiratory, urinary, and diarrhea pathogens ***(Jong & Freedman, 2012).***

Patients with immune deficiencies, whether primary or acquired, experience a broad spectrum of illness beyond than that seen in immunocompetent persons in a given region. Unique illnesses in the immunocompromised may result from abnormal responses to ordinarily nonpathogenic agents or atypical responses to typical pathogens ***(Montague et al., 2011).***

Several immunocompromised patients are at risk for infection with traditional nosocomial bacteria such as Pseudomonas aeruginosa, Enterobacter sp., Klebsiella sp. Escherichia coli, Acinetobacter sp. and Staphylococcus aureus ***(Franquet, 2004).***

As the population of chronically immunosuppressed individuals continues to grow, the prevalence of fungal infections is increasing. Fungal infections in this patient population represent challenges in diagnosis and management ***(Venkatesan et al., 2005).***

The leading cause of death in solid organ and hematopoietic stem cell transplant recipients is infection. The respiratory viruses, particularly respiratory syncytial virus, influenza, parainfluenza, adenovirus, and picornaviruses, are increasingly recognized as significant pathogens in these populations. Respiratory syncytial virus has been found to be the most common of the respiratory viruses causing severe infections in transplant recipients ***(Ison & Hayden, 2002).***

Aim of the essay

The aim of the essay: illustrate how to recognize the immunocompromized patient and how to implement the proper management of those patients.

Chapter 1

Recognising the Immunocompromised Patient

The past two decades have witnessed an increase in the number of patients who are immunocompromised as a consequence of a primary or secondary immunodeficiency disorder or from the use of agents that depress one or more components of the immune system.

The immunocompromised patient is at risk for developing a wide variety of life-threatening infectious diseases. Depending on the underlying immune system defect, many diverse organisms, including those handled routinely by the immunocompetent host, can become pathogens. Immunocompromised patients can have the same infections as immunocompetent people but in addition one needs to consider some more specific infections which are especially found in immunocompromised host. Patients who are immunocompromised for whatever reason are liable to contract opportunistic infections ***(Pizzo, 1999)***.

A. Causes of Immunodeficiency:

Broadly defined, an immunocompromised host has an alteration in phagocytic, cellular or humoral immunity

that increases the risk of an infectious complication or an opportunistic process such as a lymphoproliferative disorder or cancer. Patients may also be immunocompromised if they have an alteration or breach of their skin or mucosal defence barriers that permits microorganisms to cause either a local or a systemic infection, e.g. from burns or indwelling catheters, etc ***(Bodey & Bueltmann, 1992)***.

Clinical skills primarily underlie both the recognition of the patient at risk of immune compromise and the assessment of whether a related infection has supervened ***(Murphy et al., 2010)***.

Infection is the major cause of morbidity and mortality in patients with immunosuppression. Thorough investigation to identify the source of infection is essential.

Immunodeficiency typically manifests as recurrent infections. More likely causes of recurrent infections are inadequate duration of antibiotic treatment, resistant organisms, and other disorders that predispose to infection (eg, congenital heart defects, allergic rhinitis, ureteral or urethral stenosis, immotile cilia syndrome, asthma, cystic fibrosis, and severe 3dermatitis). Immunodeficiency should be suspected when recurrent infections are the following: severe, complicated, in multiple locations, resistant to

treatment, caused by unusual organisms and present in family members.

Initially, infections due to immunodeficiency are typically upper and lower respiratory tract infections (eg, sinusitis, bronchitis, pneumonia) and gastroenteritis, but they may be serious bacterial infections (eg, meningitis, sepsis).

Immunodeficiency should also be suspected in infants or young children with chronic diarrhea and failure to thrive, especially when the diarrhea is caused by unusual viruses (e.g., adenovirus) or fungi (e.g., Cryptosporidium sp). Other signs include skin lesions (e.g., eczema, warts, abscesses, pyoderma, and alopecia), oral or esophageal thrush, oral ulcers, and periodontitis.

Less common manifestations include severe viral infection with herpes simplex or varicella zoster virus and CNS problems (e.g., chronic encephalitis, delayed development, seizure disorder). Frequent use of antibiotics may mask many of the common symptoms and signs. Immunodeficiency should be considered particularly in patients with infections and an autoimmune disorder (e.g., hemolytic anemia, thrombocytopenia) ***(Fernandez, 2016).***

The clinical setting is extremely important in recognizing immunosuppression. Immune dysfunction induced by therapeutic intervention will be evident from

the history but immune impairment due to underlying disease may be more difficult to recognize. Inherited immune deficiencies often have characteristic patterns of disease distribution and may be associated with other clinical abnormalities (such as cardiac anomalies) ***(Murphy et al., 2010)***.

B. Diagnosis of Immunocompromised Patient:

a) History and physical examination are helpful but must be supplemented by immune function testing. Prenatal testing is available for many disorders and is indicated if there is a family history of immunodeficiency and the mutation has been identified in family members.

I. Age when recurrent infections began is important.

Onset before age 6 months suggests a T-cell defect because maternal antibodies are usually protective for the first 6 to 9 months.

Onset between the age of 6 and 12 months may suggest combined B- and T-cell defects or a B-cell defect, which becomes evident when maternal antibodies are disappearing (at about the age of 6 months).

Onset much later than 12 months usually suggests a B-cell defect or secondary immunodeficiency.

In general, the earlier the age at onset in children, the more severe the immunodeficiency. Often, certain other

primary immunodeficiencies (eg, common variable immunodeficiency [CVID]) do not manifest until adulthood.

II. Medical history: Concurrent disease, Drug or alcohol history, Current medication for example cancer chemotherapy, Weight loss, post splenectomy status, recent hospitalization or antibiotic therapy, other relatives with symptoms may provide clues as to the source of infection.

III. Family history: a young patient with recurrent infections may have an inherited immunodeficiency. A history of childhood illnesses may also be relevant.

IV. Occupational history (risk of asbestos or other carcinogen exposure).

V. Social history: HIV or viral hepatitis, homosexuality, workers in the sex industry or intravenous drug users.

VI. Travel history may be pertinent.

Patients with haematological malignancies rarely present undiagnosed to the ICU but bruising, bleeding, weight loss, night sweats or lymphadenopathy may suggest the diagnosis.

If a specific secondary immunodeficiency disorder is suspected clinically, testing should focus on that disorder (eg, diabetes, HIV infection, cystic fibrosis, primary ciliary dyskinesia).Tests are needed to confirm a diagnosis of

immunodeficiency. Initial screening tests should include CBC with manual differential, Quantitative Ig measurements, Antibody titers, Skin testing for delayed hypersensitivity.

b) Examination: if the patient have Signs of chronic disease, e.g. finger clubbing, ascites, Palpable lymphadenopathy or palpable spleen, Signs of chronic steroid therapy, if there are potential ports of entry for infection e.g. tunneled catheters, ventriculoperitoneal shunt, urinary catheter.

The critically ill patient is frequently unconscious or unable to give a good history. Look for visual evidence of immunosuppression e.g. arterio-venous fistula, sternotomy scar for heart transplant, 'Mercedez Benz' scar following liver transplantation, transplanted kidney.

c) Nutritional status: if the patient appears to be malnourished, consider the possibility of gastrointestinal disease e.g. inflammatory bowel disease or unusual diseases such as helminth and tropical parasites.

d) The investigation of infection in patients with immune suppression involves the identification of the cause of infection (using imaging, microbiological and serological testing) and the investigation of the degree of immunosuppression.

Imaging: Plain x-rays, ultrasound, CT, MRI

Microbiological examination: culture, microscopical examination of fluid or tissue specimens.

Serological investigations: identification of antibody or antigen ***(Daniels and Nutbeam, 2010).***

Fever in the Immunocompromised Host:

Fever in the immunocompromised host is generally defined as a single reading over 38.3°C or a temperature over 38°C for a period of 1 hour or more. Fever is often the sole finding, and the incidence of serious disease in this group of patients is high. HIV disease, transplant medicine, cancer therapy and rheumatologic therapy have contributed to the increased prevalence of immunocompromise in the general population. Although a number of fever patterns have been associated with various infectious or noninfectious illnesses, no pathognomonic pattern or degree of fever has been clearly associated with a specific infection in immunocompromised patients. There is also no pattern of fever that can be used to rule out a noninfectious cause. Furthermore, patients who are profoundly immunocompromised can (albeit rarely) have serious local or systemic infections in the absence of fever. Fever can also be suppressed or muted by immunosuppressive agents that may be part of the therapeutic regimen, especially steroids and non-steroidal anti-inflammatory agents.

However, patients with infection usually have fever despite the use of these agents ***(Arsura, 1990).***

Fever is a manifestation of the release of proinflammatory cytokines (interleukin-1α, interleukin-1b, interleukin-4, interleukin-6, and tumor necrosis factor-α) from macrophages, lymphocytes, fibroblasts, epithelial cells and endothelial cells as a consequence of infection or inflammation. Analogs of these cytokines are inherent in the innate immune response throughout phylogeny as well as being part of the acquired immune system that confers antigen-specific immune defence. Although endogenous pyrogens are classically thought to originate from polymorphonuclear leukocytes (PML), patients with profound neutropenia have high fevers when they have infections, so reservoirs of pyrogens other than neutrophils are also important ***(Kumar et al., 2006)***.

One of the most important decisions with respect to an immunocompromised patient is whether a fever requires urgent evaluation and prompt empirical antimicrobial therapy. We should develop a systematic approach for patients with compromised immune systems who present with fever, including historical and physical findings pertinent to these patients, with attention to details that are atypical or specific to the immunocompromised state; a diagnostic workup applicable to most patients with immune

system dysfunction, a knowledge of common clinical scenarios of immunosuppression, focusing on unique presentations and treatment strategies ***(Harbarth, Nobre & Pittet, 2007).***

Although the causes of fever in immunocompromised hosts are numerous, some guidance is given by the specific immunologic defect or defects present in the patient. In addition, the length of time that the immune defenses are altered has an extremely important effect on the types of infectious complications that are likely to occur.

Among the clinical conditions associated with a risk of life-threatening infections are profound neutropenia (i.e. an absolute neutrophil count of less than 500/ml) or a history of splenectomy. In patients with these characteristics, rapidly progressive infection may be life-threatening if untreated. Because of the blunted inflammatory response in patients with neutropenia, the signs and symptoms of infection can be minimal, so a heightened index of suspicion for infection is essential. Patients, in whom neutropenia develops after a viral infection, do not have the same risk of acute bacterial infection, as those who have neutropenia after chemotherapy or preparative therapy for transplantation. Presumably this is because they do not have concurrent

breaches of mucosal integrity. Similarly, although patients with aplastic anemia or congenital neutropenia are vulnerable to acute bacterial infections, they are generally at lower risk for the acute life-threatening bacterial infections seen in patients who have neutropenia after cytotoxic chemotherapy.

The development of fever in a HIV-infected patient who also has neutropenia suggests the possibility of an infectious complication ***(Fridkin et al., 2005).***

C. Understanding the Immune Response in the Critically Ill Patient:

The immune system is a complex, multiorgan network that protects the body from pathogenic invasions by microbes. When part of the immune system functions in a compromised state, infectious complications can be sudden and fulminant. A defect at one site in the system can elicit dysfunction throughout the system.

Host defences include various physical barriers, such as skin, mucosa, secretory substances, and normal flora. The complexity of the system increases greatly at the level of cellular and molecular defence mechanisms. Lymphocytes perform a variety of functions central to competent immune function. B lymphocytes produce immunoglobulins that are critical for phagocytosis, bind to bacterial toxins, and prohibit microorganism entry from