Ann Natl Acad Med Sci (India), **45(1):** 45-65, 2009

Pneumonia in Organ Transplant Recipients

G. C. Khilnani and Vijay Hadda
Department of Medicine, All India Institute of Medical Sciences,
New Delhi-110016.

Abstract

Solid organ transplant and hematopoietic stem cell transplant is an established treatment for many malignant and non-malignant end stage diseases. With advances in understanding of immunology of transplantation, the graft survival has improved but immunosuppression is still an issue. Immunosuppression puts these patients at risk of opportunistic infections. Pneumonia is amongst one of the most common infections in this population. Microorganisms causing pneumonia vary from bacterial, mycobacterial, fungal to viral depending upon the level of immunosuppression. Therefore, management of pneumonia in this group of patients is challenging. Most of the times, isolation of the causative organism is not possible at the time of presentation making selection of antimicrobials difficult. Empirical treatment is usually guided by various factors like, age of the graft, level of immunosuppression, radiological features, prevalent local pathogens and initial response to therapy. Recently, with better understanding of immunology and antimicrobial therapy, mortality and morbidity have reduced significantly.

Key words: Solid organ transplantation, hematopoietic stem cell transplantation, immunosuppression, pneumonia.

Correspondence: Dr. G. C. Khilnani, Professor, Department of Medicine, All India Institute of Medical Sciences, New Delhi, India. Phone: +91–11-26593488; Fax: +91-11-26588663. E-mail: gckhil@hotmail.com Proceedings of the NAMS-PGI Symposium on 'Community Acquired Pneumonia', held in Chandigarh, 2007.

Introduction

Solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) represent one of the greatest medical achievements of the twentieth century. With advances in basic immunobiology and clinical care, these treatment options are offered to more patients with various malignant and non-malignant diseases. According to United Network for Organ Sharing, the number of transplants has already exceeded 25,000 per year, for last five years (http://www.UNOP.org) and worldwide, 30,000-40,000 HSCTs are performed each year. Kidney (60%) is the most common SOT and others include liver (25%), heart (10%) and lung (5%). Immunosuppressive therapy in the form of corticosteroids and other drugs is an integral part of organ transplant management. Although, with advanced understanding of immunobiology, the rejection and overall survival have improved in these patients, these techniques make them more prone to developing various infections.

Although, with introduction of more effective prophylactic strategies and refined immunosuppressive regimens, the incidence of infectious complications after transplantation has declined, it still remains a common life-threatening complication in these patients. Pneumonia is the most common infection in lung and heart transplant recipients (1, 2) and is only second to intraabdominal infection in liver transplant recipients (3). Renal transplant recipients are having the lowest risk of pneumonia reflecting the less rigorous surgical procedure and the decreased level of immunosuppression required to sustain it.

Like SOT, HSCT recipients are also at high risk for pulmonary infectious complications (4). Factors affecting susceptibility to infection are pretransplant immune status, type of conditioning regimen, degree and duration of neutropenia, and development of graft versus host disease (GVHD) (4). Allogenic transplant recipients are at greater risk than autologous transplant, and matched, unrelated-donor transplant carries maximum risk (4).

Pathophysiology

In normal person lungs are well protected from pathogens by general, innate and adaptive immune mechanisms which are intricately intertwined with overlapping signaling pathways (5). The general defenses in upper airway consist of nasal pathway, sinuses and turbinates which trap inhaled pathogens. In lower respiratory tract there are cough and sneeze reflexes, glottis to cover larynx and

mucociliary clearance to prevent entry of pathogens. Surfactant lining, alveolar macrophages and lymphatic system contain pathogens in the bronchial tree, which escaped the above defenses.

Innate immunity in the form of IgA (in conducting airway) and IgG (in alveoli) activate complement cascade in response to pathogen exposure. The respiratory mucosa also secretes cytokines and chemokines which attract leukocytes and defensins (6). The final and the most affected defense in transplant recipients against pneumonia is adaptive immunity. This consists of activation and proliferation of clonal lymphocytes specific for antigenic characteristics of the pathogen (6). Subsequently, there is a complex interaction between T-lymphocytes, antigen presenting cells (APC) and class II major histocompatiblity complex protein. It results in intracellular activation of calcineurin, upregulation of nuclear activity and interleukin-2 (IL-2) production. IL-2 stimulates immune system in many ways but the most important is self-proliferatory effect on activated T-cells. Once a specific line of "helper" T-lymphocytes (Th) is activated it will mature as Th1 (control cell mediated immunity) or Th2 (control humoral immunity). The mature T-lymphocytes travel to site of inflammation and through interactions with various cells like cytotoxic T-lymphocytes, B lymphocytes, natural killer cells and phagocytes contain infection. Once the acute infection is controlled, the lymphocyte activity subsides and few cells linger as memory cells that can be summoned in future.

In transplant recipients, exogenous immunosuppression achieved with different classes of drugs leads to T-lymphocyte suppression. Various mechanisms involved are calcineurin inhibition (cyclosporine A and tacrolimus), cell cycle inhibition (azathioprine and mycophenolate mofetil), blunting of IL-2 proliferating action on T-lymphocytes (sirolimus and everolimus) or broad-spectrum immunosuppression (corticosteroids). Drugs used for induction therapy to minimize early acute rejection, i.e. antilyphocytic antibodies or IL-2 receptor antibodies, affect lymphocyte function and overall immune response. High doses of chemotherapy with or without total body irradiation are administered to ablate the bone marrow, maximize tumor cell kill and induce immunosuppression to prevent rejection of the donor stem cells. The number of other factors like anatomic location, type of transplant and comorbid conditions like diabetes and renal failure also contribute to immunosuppression. Certain viral

infections [Epstein-Barr virus, cytomegalovirus (CMV), HIV, and hepatitis C virus], along with the factors described above, result in a net "state of immunosuppression" and put these patients at high risk of pulmonary infections (5,7).

Time Trend in Infections

Interestingly, the spectrum of microorganisms responsible for infections is similar among various organ recipients and these appear in fairly characteristic sequence in the post transplantation course (5). During first month the infectious risk is posed by surgery and intensive care, and immunosuppression has lesser role and nosocomial bacterial infections predominate, similar to that of the general surgical population. The period from 1 to 6 months, the period of maximum sustained immunosuppression, is characterized by the emergence of opportunistic pathogens. Beyond 6 months, stable allograft function permit reduction of immunosuppression in the majority of patients and common community-acquired pathogens are responsible for pneumonia during this period. Opportunistic infections occur less commonly in this later period but remain threat among subset of patients requiring augmentation of immunosuppression for treatment of chronic rejection or recurrent episodes of acute rejection. Modern prophylactic regimens using sulfonamides, azoles, and antivirals, have considerably changed the classical pattern of infections and the previous paradigm of predicting pathogens in certain time points post-transplantation is no longer applicable. Duncan *et al* (8) suggested modified timelines that account for the use of prophylactic regimens and their effect on the onset of infections post-transplantation (Figs. 1 and 2).

Etiology of Pneumonia

Bacterial Pneumonia

Although considerable overlap exists, there are significant differences in epidemiology and clinical presentation of these infections in SOT and HSCT recipients. Almost one third of nosocomial and community acquired pneumonia in SOT and 15% in HSCT are caused by pyogenic gram negative or gram positive bacteria (9).

Nosocomial pneumonia is almost exclusively a perioperative complication. Common pathogens are gram negative but *Staphylococcus aureus* and, in some centers, *Legionella* species are also encountered (8,9). Some studies have shown an increase in the prevalence of methicillin-resistant *Staphylococcus aureus* infections and this must be considered when initiating

empiric antibiotic therapy (10). Risk factors for nosocomial pneumonia are the need for prolonged postoperative mechanical ventilation, impairment of cough reflex, narrowing of the bronchial anastomosis, disruption of pulmonary lymphatics, and impairment in the mucociliary "escalator" because of ischemic injury to the bronchial mucosa. Passive transfer of occult pneumonia initially acquired by the donor is another circumstance unique to lung

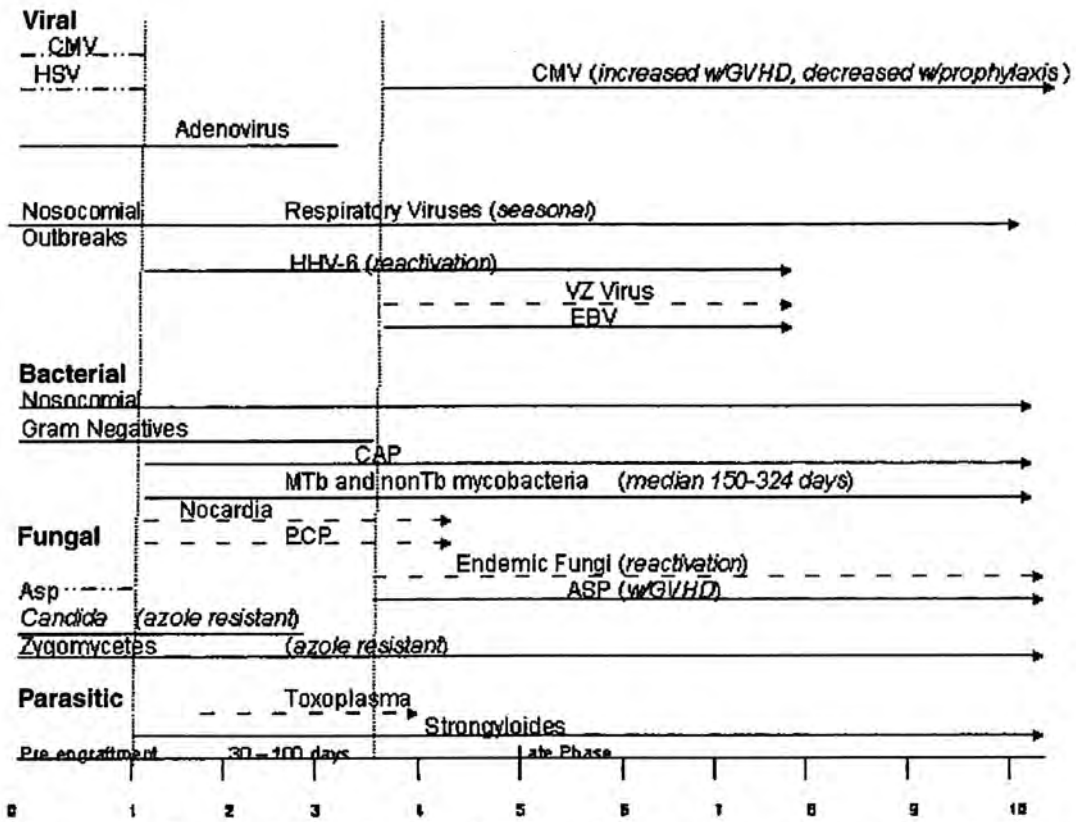

Figure 1 : Proposed infection timeline based on the use of common prophylactic antimicrobials such as sulfa, azoles, and antivirals in recipients of solid organ transplants. *Dotted lines* denote onset of infection that would occur without prophylaxis. *Solid lines* indicate the most common times to onset of infection for each pathogen. Asp = *Aspergillus*; Blasto = *Blastomyces*; CAP = community-acquired pneumonia; CMV = cytomegalovirus; Cocci = *Coccidioides*; Crypto = *Cryptococcus*; EBV = Ebstein-Barr virus; Histo = *Histoplasma*; HSV = herpes simplex virus; MTb = *Mycobacteria tuberculosis*; PCP = *Pneumocystis carinii*; Toxo = Toxoplasmosis; VZV = *Varicella zoster* virus. Zero denotes the time of transplantation. (Reproduced with permission from ATS (8))

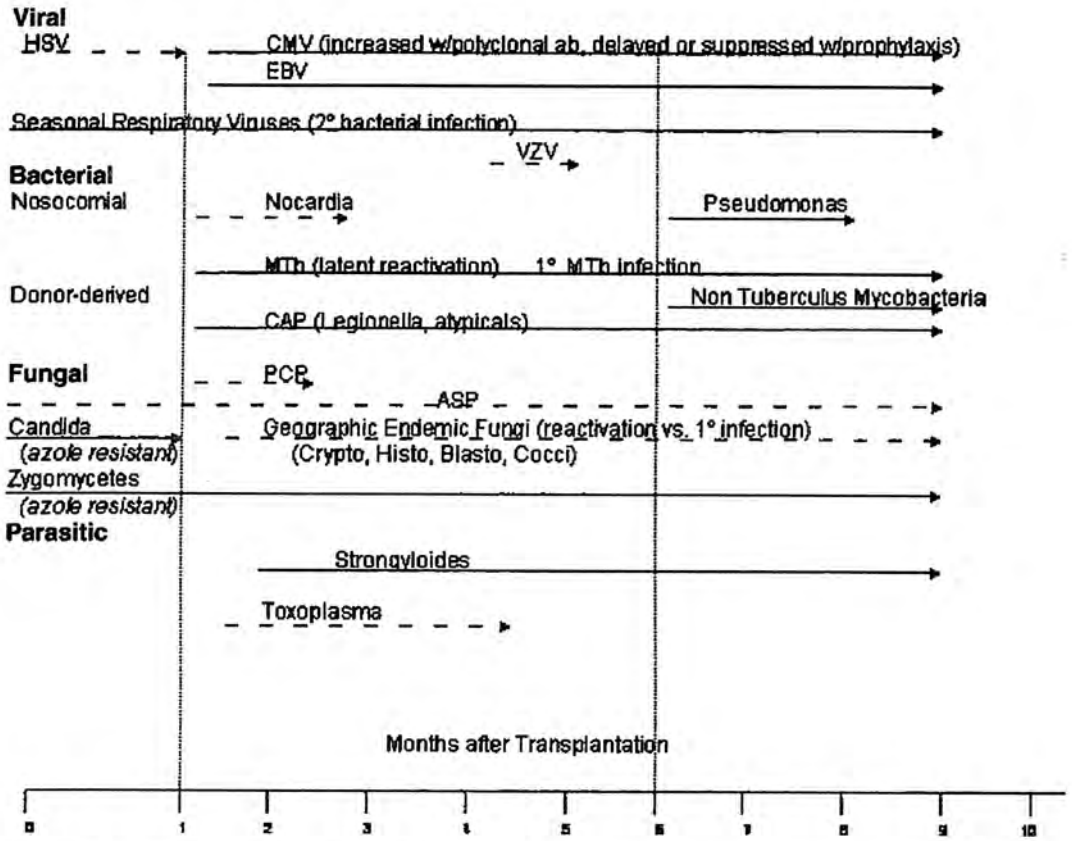

Figure 2 : Proposed infection timeline based on the use of common prophylactic antimicrobials such as sulfa, azoles, and antivirals in recipients of HSCT. *Dotted lines* denote onset of infection that would occur without prophylaxis. *Solid lines* indicate the most common times to onset of infection for each pathogen. Asp = *Aspergillus*; CAP = community-acquired pneumonia; CMV = cytomegalovirus; EBV = Ebstein-Barr virus; GVHD = graft versus host disease; HHV 6 = human herpes virus 6; HSV = herpes simplex virus; MTb = *Mycobacteria tuberculosis*; PCP = *Pneumocystis carinii*; VZV = *Varicella zoster* virus. Zero denotes the time of transplantation. (Reproduced with permission from ATS (8))

transplantation. Although the incidence of nosocomial pneumonia has declined significantly in transplant recipients (8, 9) but the mortality remains high.

Community acquired pneumonia (CAP) occurs later in the posttransplantation period. *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Legionella* species are the leading culprits responsible for CAP in these patients (7, 8). Among lung transplant recipients who have

developed bronchiolitis obliterans syndrome (BOS), *Pseudomonas aeruginosa* is identified as the etiologic agent in the majority of cases. Earlier, Nocardia infections were relatively common (11). With introduction of cyclosporine-based immunosuppressive regimens and wide spread use of sulfonamides for *Pneumocystis carinii* pneumonia (PCP) prophylaxis have reduced *Nocardia* infections markedly. Recent case series have suggested a frequency of *Nocardia* infection in the order of 0.2–2.1%. (9,12) Clinicians must remain particularly vigilant for this infection in patients in whom trimethoprim–sulfamethoxazole has either not been administered because of allergy or has been discontinued after the first year.

Mycobacterial Pneumonia

In developed countries it is relatively uncommon post transplantation infection but transplant recipients are having 30- to 100-fold higher annual risk of developing tuberculosis than that of the general population (13). In United states and Europe tuberculosis has been reported in about 0.5–2% of organ transplant recipients (13,14). In endemic areas like India it is seen in up to 15% of transplant recipients (15). Reactivation of latent infection is believed to be the predominant mechanism for development of active tuberculosis after transplantation. Other less common modes of acquisition include nosocomial outbreaks and donor transmission through infected kidney, lung, and liver allografts (13).

Nontuberculous mycobacteria like *Mycobacterium avium* complex, *M. kansasii*, *M. abscessus*, and *M. asiaticum* are commonly reported among lung transplant recipients and may be more common than *M. tuberculosis* as a cause of pulmonary infections. In the largest published series encompassing 261 patients, nontuberculous mycobacteria was documented in 16 patients (6.1%) compared with only 2 cases of pulmonary tuberculosis (0.8%) (16). Thirteen of the 16 cases were due to *M. avium* complex; *M. kansasii*, *M. abscessus*, and *M. asiaticum* each accounted for one case. Pulmonary infection tended to occur late in the post transplantation course and preexistent chronic rejection is a major risk factor.

Pulmonary infection due to nontuberculous mycobacteria species is considerably less common in other solid organ transplant populations, heart transplant recipients and renal transplant recipients (0.1%) (16,17). This is only rarely reported complication after liver transplantation. *M. kansasii* and *M. avium*

complex are the prevailing pathogens responsible for pulmonary infection in these populations (17).

Viral Pneumonia

Beyond the first months post-transplant, viral pathogens emerge as the most important group of infections affecting the transplant recipients. Among lung transplant recipients they are the second most common cause of infection, accounting for 23 to 31% of all infections, but the incidence in non-lung grafts recipients varies considerably (18). As about 50% of the adult population harbor latent virus, CMV infection is considered as the most important pathogen affecting transplant recipients. Therefore, reactivation of latent infections accounts for virtually all transplant-related CMV disease. Almost 75% of solid organ transplant patients have evidence of CMV infection (19). CMV has been implicated in chronic allograft rejection - bronchiolitis oblitrans syndrome (BOS) in lung transplant recipients, though phenomenon is not observed with other allografts.

Human stem cell transplant patients are at increased risk for CMV pneumonia due to effects related to delayed reconstitution of cytotoxic T cells and immunosuppressants. Recipients of allogeneic grafts are at greater risk (20-35%), presumably due to increased requirements for immuno-suppression as compared to autologous HSCT (1-6%). Previously CMV infection onset was usually seen during first 100 days of post-transplantion. Anti-CMV prophylaxis has changed the onset of disease from the first 100 d (decreased from 35 to 6%) to beyond the first 100 d (up from 4 to15%). (9) Patients with chronic graft versus host disease (GVHD) are particularly vulnerable to CMV due to an increased need for immunosuppression. GVHD also causes an immunodeficient state by involving mucosal surfaces, reticuloendothelial system, and bone marrow (9).

Herpes simplex virus infection is commonly seen in up to 18% of transplant recipients. It may cause severe pneumonia in up to 10% of patients and can be fatal in about 20% of cases. Community-acquired viruses like, *influenza* A and B, *Para influenza*, respiratory syncytial virus, and adenovirus often lead to significant pneumonitis (up to 66%) and respiratory failure. Of these, *Para influenza*, *adenovirus*, and *respiratory syncytial virus* have been directly linked to BOS in lung transplant patients (9, 20). Human herpes virus 6 causes idiopathic pneumonia syndrome in post HSCT patients (9).

Fungal Pathogens, Protozoa, and Parasites

The incidence of invasive fungal infection in solid organ transplantation is 5–50%. *Candida* species is the most common, occurring in the early period post-transplant but it rarely causes pneumonia. The classic opportunistic fungal infection encountered in organ transplantation is *Aspergillus* species, with an incidence of 18–22%, and has a clinical presentation similar to *Mucormycosis*. *Aspergillus* or *Mucormycosis* are strongly associated with neutropenia in patients undergoing HSCT, but can occur despite adequate numbers of circulating neutrophils in solid organ recipients. Invasive disease is usually associated with a high mortality (50–100%) and localized Aspergillus infections are associated with significant morbidity in the lung transplant patient (21,22).

Less common fungi are *Cryptococcus, Histoplasma, Coccidioides* (reactivation of latent infection) and *Blastomyces dermatitidis* (primary disease). *Pneumocystis carinii* prophylaxis that includes sulfonamides has significantly reduced the incidence of *P. carinii* pneumonia and *Toxoplasma* in all transplant recipients (9,23). *Trichoderma species, Pseudallescheria boydii, Torulopsis species, Microascus species, Penicillium species, Zygomycetes, Absidia* and *Rhizopus* are few emerging fungi (24).

Approach To A Transplant Recipient With Pneumonia

When a transplant recipient presents with symptoms suggestive of pneumonia, an aggressive initial approach with broad spectrum antibiotics and comprehensive diagnostic work up is strongly recommended. Unlike CAP no triage system is recommended for these patients. Need for hospitalization is decided by the type of antimicrobial, extent of testing, and the supportive care needed. Furthermore, as this acute illness can have profound effect on long term immunosuppression as a result of drug interactions, patients may require hospitalization for drug dose modification and drug level monitoring.

Clinical presentation of pneumonia in SOT and HSCT recipients is similar to immunocompetent patient and can be mimicked by non infectious etiologies like atelectasis and pulmonary edema in many patients. Specifically, in lung transplant recipients, it is difficult to differentiate ischemia reperfusion injury and acute rejection from infective pneumonia (25).

Radiographic image, in the form of chest X-ray, can provide useful

information during initial evaluation. It corroborates the clinical suspicion of pneumonia and type of infiltrates as diffuse versus focal can help to narrow the spectrum of pathogens (2). Bacterial pneumonia is typically associated with focal consolidation, whereas diffuse interstitial pattern is often seen in viral and PCP infections (25). Exceptions also occurs for the above generalization like lung transplant patients with severe BOS manifest pneumonia as coarse diffuse infiltrates, CMV pneumonia can present with more confluent infiltrates and *Aspergillus* may present as focal consolidation, diffuse infiltrates, or multifocal nodules with cavitation. Computer tomography (CT) scan can characterize and localize infiltrates better and additionally can be used for sampling of nodules or lymph nodes. Although radiological images are helpful but the imaging pattern is not specific enough to obviate need for microbiologic or histological confirmation of suspected pathogen.

Identification of pathogen

Various noninvasive tests are available to identify different pathogenic organisms and some times obviate need for invasive test like fibroptic bronchoscopy (FOB). Respiratory secretions i.e. sputa can be examined for gram stain, culture and acid fast staining (for bacteria, mycobacteria, nocardia, fungi and virus); for viral antigens (respiratory syncytial virus, para influenza, adenovirus) ; and direct fluoresce antibody (PCP). Serum tests are available for CMV (nucleic acid amplification or antigen (pp65) level), *Histoplasma* and *Cryptococcus* (antigen) and *Aspergillus* (galactomannan antigen). Urine can tested for presence of *Histoplasma* or *Legionella* antigen.

Role of fibroptic bronchoscopy (FOB)

Bronchoscopy is an important tool in diagnosis of pneumonia in immunocompromized patients like organ recipients. Bronchoalveolar lavage (BAL) and protected-specimen brushing samples have excellent yield of culturing various organisms in these patients (2,26,27). In patients with lung transplant showing lung infiltrates on chest X-ray FOB guided transbronchial biopsy can be used to exclude acute rejection of lung. When used with other tests, it can provide complimentary results. Large studies (27) involving 300 lung transplant patients demonstrated a direct impact of FOB on management of these patients. In our experience BAL has a high diagnostic yield (75.8%) in patients with kidney transplant (28).

Several authors have advocated different strategies for FOB with

limited experiences (9,27), but it can be deferred for an empirical treatment in cases where high likelihood of bacterial process like, focal consolidation, where noninvasive testing can identify a cause or when risk outweigh benefits of FOB. In these cases empiric therapy for bacterial pneumonia is safe with reassessment in 2-3 days. Infections with resistant nosocomial pathogens, opportunistic organisms and multiple organisms are more common during first 6 months after transplantation (2, 8, 9). Early FOB is justified more in patients with lung transplant recipients as acute graft rejection, post transplant lymphoproliferative disease, and tracheal stenosis can be confused with pneumonia. Rarely, surgical lung biopsy may be required when FOB technique do not reveal diagnosis.

Unfortunately, many patients are having poor lung functions so may not be fit for FOB. Therefore, before considering for FOB, risk-benefit should be assessed and where risks outweigh benefits conservative approach with empirical antibiotics is justified. The isolates from sputa or previous FOB specimen can help in selection of antibiotics. In absence of this information broad-spectrum therapy, particularly covering *Pseudomonas aeruginosa* should be initiated. In such cases, FOB can be done if there is no response with this therapy.

Treatment Of Pneumonia

To describe whole treatment of pneumonia is beyond the scope of this article. Therefore we have described only the salient features. For detailed treatment readers may take information from references.

Hospital acquired pneumonia

Infection control measures like standard precautions, isolation of resistant pathogens, routine intensive care unit (ICU) surveillance minimization of aspiration, avoidance of unnecessary and prolonged intubation and aggressive pulmonary toileting are recommended to prevent HAP (29,30). Empiric broad spectrum antibiotics should be started immediately in all suspected cases of HAP. Choice of antimicrobial agent depends on institutional patterns. As all bacterial pneumonia are treatable, an early, aggressive effort to achieve etiological diagnosis is recommended so that definite therapy can be administered (29,30). In patients with HSCT pneumonia may not be recognized radiologically because of blunted inflammatory response (9), but are treated similarly with broad spectrum antibiotics.

Community acquired pneumonia

For prevention of CAP pneumococcal, influenza and *H.infleunza* B (HIB) vaccines should be given to each candidate prior to SOT or HSCT (31). Although pneumococcal revaccination is recommended every 5 yearly, in patients with SOT it may be considered every 2-3 year interval. *H.infleunza* B revaccination is recommended based on the HIB antibody titres (31). In most cases, identification of organism by gram stain or cultures is not possible. So, American Thoracic Society (ATS) and Infectious Disease Society of America have provide guidelines for empiric treatment of CAP (32). Beta-lactam plus macrolide or quinolones are recommended as first choice of therapy in SOT. In patients who are at high risk like with lung transplant recipients who have cystic fibrosis or BOS should be treated using beta-lactam with anti-pseudomonal activity (32). Similar therapy is recommended for CAP in HSCT recipients.

Legionella pneumonia is a fatal disease, if treatment is delayed. Therefore, prompt empiric therapy is recommended in all patients with suspected cases of *Legionella* (31, 33). The preferred therapy for *Legionella* is azithromycin or a flouroquinolones. Erythromycin is not used routinely because of its interaction with calcineurin inhibitors. Initially, recommended duration of therapy was 21 days, but now 10-14 days is accepted as standard therapy (31,33). For *Nocardia*, trimethoprim-sulfamethoxazole (TMP-SMX) is drug of choice and the recommended dosing is 15 mg/kg/day of trimethoprim divided in 2-4 doses either orally or intravenously (34). Other drugs like sulfonamides alone, imipenem, meropenem, amikacin, minocycline, 3rd generation cephalosporins, linezolid, ciprofloxacin and amox-clavulanate are less studied options (34). HSCT recipients are also similarly treated and in cases with myelosupression or sulfa drug allergy, second line drugs can be used.

Tubercular pneumonia

The treatment of TB pneumonia is complicated by a number of factors present in the SOT patient, as both disease and its therapy have been attributed for high mortality in SOT (9). Rifamycins dramatically increase hepatic metabolism of calcineurin inhibitors and consequently lower the blood levels of these agents. This may lead to rejection and graft loss in significant number of patients receiving rifamycins (35). Isoniazid (INH) has also been reported to interact with calcineurin inhibitors. This interaction generally is not clinically significant

and should not preclude the use of INH. Drug induced hepatotoxicity remains an important side effect with INH. In liver transplant recipients, INH induced hepatotoxicity may lead to discontinuation of drugs in 41% to 83% of the patients (9).

The American Thoracic Society published guidelines for treatment of TB in SOT recipients, though many issues remain unresolved (36). In general, rifampicin either alone or in combination is not used in patients with SOT, therefore duration of therapy extends beyond the standard six month course. The patients on INH should be monitored for hepatotoxicity. Asymptomatic elevation of transaminases less than five times of normal range should prompt close monitoring rather stopping INH.

HSCT recipients are also treated similarly and rifampicin is generally not recommended because of its interactions with corticosteroids, fluconazole, analgesics and calcineurin inhibitors which are commonly used in these patients (36).

Non tubercular mycobacteria are treated with rifamycins and clarithromycin both of which have significant effects on metabolism of calcineurin inhibitors. Thus these patients require close monitoring. Other drugs like aminoglycosides which are recommended for therapy are also toxic. Initiation of treatment with two drugs and in severe cases three or more drugs are recommended (37).

CMV pneumonia

Drugs which are approved by Food and Drug Administration (FDA) are acyclovir and its valine prodrug valacyclovir; ganciclovir and its valine prodrug valgancyclovir; cidofivir and foscarnet. Leflunomide has some activity against CMV but is not approved by FDA. CMV immunoglobulins (CMVIG) are used for prevention of infection and disease.

Overall CMV therapy is more effective in SOT population than in the HSCT population. Ganciclovir is considered first line therapy for all SOT recipients and has shown benefit in renal, heart, heart-lung, and lung transplant recipients who have CMV disease and pneumonia (38-40). In lung transplant recipients, combination of ganciclovir plus intra venous immunoglobulins (IGIV) or CMVIG is associated with increased survival and is preferred therapy (40,41). Cidofivir and foscarnet, both with little experience, are associated with nephrotoxicity and dehydration and magnesium wasting, respectively.

In the HSCT population, CMV pneumonia is treated with ganciclovir

alone or in combination with foscarnet or CMVIG (42, 43). The combination of foscarnet plus ganciclovir may provide antiviral synergy but requires careful monitoring (43). Cidofivir and foscarnet are considered second line therapies because of toxicities. CMVIG either alone or ganciclovir demonstrated variable results (40,41,44).

Fungal pneumonia

The mainstay of treatment has been antifungal drugs supplemented with reversal of underlying immunosuppression, when indicated and feasible. In some cases surgery and only rarely, immune modulation is required. Various antifungal drugs against *Aspergillus* species currently available are amphotericin B (liposomal and lipid formulations), itraconazole, voriconazole, and caspofungin. Length of therapy is not standardized, but many courses continue 10 to 12 weeks or several weeks after clinical and radiographic resolution.

Amphotericin B has been the main antifungal drug in use for *Aspergillus* infection, but voriconazole is now considered a first line therapy and is being used increasingly. In one study involving 277 immunocompromised patients (including 9 HSCT and 14 solid organ transplant recipients) with confirmed or probably invasive aspergillosis, the use of voriconazole was associated with a greater complete or partial response at 12 weeks, lower mortality, and lesser need of other drugs (45). A few other small studies also indicate that voriconazole seems to be equivalent to amphotericin B (46). With availability of lipid preparation of amphotericin B (lipid complex, liposomal and colloidal dispersion amphotericin), a higher dose (5 mg/kg/d) is used as initial treatment. High doses may be more effective in select situations, but superior efficacy has not been proven. Though there are conflicting data in the transplant population but one retrospective study in 41 liver transplant recipients showed mortality benefit in patients receiving lipid forms of amphotericin (33%) compared to conventional amphotericin (86%) (47). Liposomal preparations do seem to have a more favorable side-effect profile than standard amphotericin B, particularly with respect to risk of nephrotoxicity.

Voriconazole leads to inhibition of the P-450 cytochrome system resulting in increased levels of cyclosporine, tacrolimus, or sirolimus. The interaction may be severe particularly with sirolimus so this combination is discouraged. Also, intravenous voriconazole is contraindicated in patients whose creatinine clearance is less than 50 ml/min. Itraconazole is also useful, but its oral absorption is less

reliable. Posaconazole is a newer triazole with a significant activity against *Aspergillus*.

Caspofungin is a member of the new echinocandin family of drugs. It acts on the fungal cell wall rather than the cell membrane and is approved as second-line therapy for refractory aspergillosis. HSCT and SOT recipients have shown a favourable response in approximately 45% of patients who were not responding or were intolerant to amphotericin (48,49). The drug was well tolerated in all studies. Cyclosporine resulted in increased concentration of caspofungin but no change in cyclosporine level, when used concurrently. It can reduce levels of tacrolimus and it needs to be monitored. Elevations of liver enzymes can occur, but significant hepatotoxicity is rare.

Few clinical studies showed combination of amphotericin B with capsofungin or voriconazole with capsofungin was associated with improved response (49-52). Though, there has been concern about combining azoles and amphotericin because some animal studies showed antagonism (49,52). This antagonism was assumed to be caused by alterations of the sterol composition induced by azoles that made an amphotericin less effective. With echinocandins, antagonism would not be anticipated. Some animal studies of echinocandins combined with either amphotericin or caspofungin have been very promising.

The efficacy of combination therapy using multiple antifungal agents is yet to be proved by large trials. However, limited data suggest that combination antifungal therapy may be considered in subsets of high-risk patients e.g. those on renal and replacement therapy in whom mortality rates have typically exceeded 90% (49,52).

There are anecdotal reports of immunomodulation with granulocyte transfusion from donors stimulated with granulocyte-stimulating factor and gamma interferon during treatment of invasive pulmonary aspergillosis, with some safety issues (53). Surgical resection is usually required for infection resistant to medical therapy, massive hemoptysis, and sometimes to improve outcome of medical therapy (54,55). Many studies have shown that surgical resection can be performed with acceptable mortality, but indications are not well defined (54,55).

Conclusion

Management of pneumonia in transplant recipient can not be generalized. Also, it is not possible to give algorithm for antimicrobials to be

used in all cases. Like, immunocompetent patients with pneumonia, organ transplant recipients also require aggressive investigation for microbial diagnosis. However, antimicrobial therapy should be started without delay in all cases of clinically or radiologically suspected pneumonia. Choice of antimicrobials depend on type of organ transplant, severity of illness, use of immunosuppressive agents, radiological appearance, information about local microbiology and its resistance pattern. Duration of antimicrobial therapy should be individualized depending on severity of illness, causative micro-organism and extent of lung involvement. It would always be beneficial to involve a person who is trained and interested in treatment of infections in immuno-compromised patients.

References:

1. Maurer JR, Tullis E, Grossman RF, Vellend H, Winton TL, Patterson GA (1992). Infectious complications following isolated lung transplantation. *Chest* **101**:1056–1059.
2. Cisneros JM, Munoz P, Torre-Cisneros J, *et al* (1998). Spanish Transplantation Infection Study Group. Pneumonia after heart transplantation: a multi-institutional study. *Clin Infect Dis* **27**:324–331.
3. Kusne S, Dummer JS, Singh N, *et al* (1988). Infections after liver transplantation: an analysis of 101 consecutive cases. *Medicine (Baltimore)* **67**:132–143.
4. Soubani AO, Miller KB, Hassoun PM (1996). Pulmonary complications of bone marrow transplantation. *Chest* **109(4)**:1066-77.
5. Fishman JA, Rubin RH (1998). Infection in organ-transplant recipients. *N Engl J Med* **338**:1741–1751.
6. Welsh DA, Mason CM (2001). Host defense in respiratory infections. *Med Clin North Am* **85(6)**:1329-47
7. Snydman DR (2001). Epidemiology of infections after solid-organ transplantation. *Clin Infect Dis* **33**:S5–S8.
8. Duncan MD and Wilkes DS (2005). Transplant-related immunosuppression: A review of immunosuppression and pulmonary infections. *Proc American Thoracic Society* **2**:449-455
9. Robert MK, Vivek NA, Stephen WC (2004). Pulmonary Complications of Solid Organ and Hematopoietic Stem Cell Trans-

plantation. *Am J Respir Crit Care Med* **170(1)**:22-48.

10. Singh N, Paterson DL, Chang FY, *et al* (2000). Methicillin-resistant *Staphylococcus aureus*: the other emerging resistant gram-positive coccus among liver transplant recipients. *Clin Infect Dis* **30**:322–327.
11. Chapman SW, Wilson JP (1990). Nocardiosis in transplant recipients. *Semin Respir Infect* **5**:74–79.
12. Roberts SA, Franklin JC, Mijch A, Spelman D (2000). *Nocardia* infection in heart–lung transplant recipients at Alfred Hospital, Melbourne, Australia, 1989–1998. *Clin Infect Dis* **31**:968–972.
13. Singh N, Paterson DL (1998). Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. *Clin Infect Dis* **27**:1266–77.
14. Korner MM, Hirata N, Tenderich G, *et al* (1997). Tuberculosis in heart transplant recipients. *Chest* **111**:365–369.
15. John GT, Shankar V, Abraham AM, *et al* (2001). Risk factors for post-transplant tuberculosis. *Kidney Int* **60**:1148–1153.
16. Malouf MA, Glanville AR (1999). The spectrum of mycobacterial infection after lung transplantation. *Am J Respir Crit Care Med* **160**:1611–1616.
17. Queipo JA, Broseta E, Santos M, *et al* (2003). Mycobacterial infection in a series of 1261 renal transplant recipients. *Clin Microbiol Infect* **9**:518–525.
18. Alexander BD, Tapson VF (2001). Infectious complications of lung transplantation. *Transpl Infect Dis* **3**:128–137
19. Pereyra F, Rubin RH (2004). Prevention and treatment of cytomegalovirus infection in solid organ transplant recipients. *Curr Opin Infect Dis* **17**:357–361.
20. Khalifah AP, Hachem RR, Chakinala MM, *et al* (2004). Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. *Am J Respir Crit Care Med* **170**:181–187.
21. Bag R (2003). Fungal pneumonias in transplant recipients. *Curr Opin Pulm Med* **9**:193–198.
22. Oner-Eyuboglu F, Karacan O, Akcay S, *et al* (2003). Invasive pulmonary fungal infections in solid organ transplant recipients: a four-year review. *Transplant Proc* **35**:2689–2691.
23. Fishman JA(2001). Prevention of infection caused by Pneumocystis

carinii in transplant recipients. *Clin Infect Dis* **33**:1397–1405

24. Brown JM (2004). Fungal infections in bone marrow transplant patients. *Curr Opin Infect Dis* **17**:347–352.
25. Guilinger RA, Paradis IL, Dauber JH, *et al* (1995). The importance of bronchoscopy with transbronchial biopsy and bronchoalveolar lavage in the management of lung transplant recipients. *Am J Respir Crit Care Med* **152**:2037-2043
26. Sileri P, Pursell KJ, Coady NT, *et al* (2002). A standardized protocol for treatment of severe pneumonia in kidney transplant recipients. *Clin Transplant* **16(6)**:450-54.
27. Chan CC, Abi-Saleh WJ, Arroliga AC, *et al* (1996). Diagnostic yield and impact of flexible bronchoscopy in lung transplant patients. *J Heart Lung Transplant* **15**:196-205.
28. Kalra V, Agarwal SK, Khilnani GC, *et al* (2005). Spectrum of pulmonary infections in renal transplant recipients in the tropics: A single center study. *Int Urology and Nephrology* **37(3)**:551-59.
29. American Thoracic Society. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2005). *Am J Respir Crit Care Med* **171:** 388-416
30. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R (2004). Healthcare Infection Control Practices Advisory Committee. Guidelines for prevention of health care associated pneumonia, 2003 : recommendation of CDC and health care advisory committee. *MMWR Recomm Rep* **53(RR-3)**:1-36.
31. Avery RK, Ljungman P (2001). Prophylactic measures in the solid organ recipient before organ transplantation. *Clin Infect Dis.* **33(Suppl 1):** S15-21.
32. Mandell LA, Bartlett JG, Dowell SF, *et al* (2003). Infectious Diseases Society of America. Update of practice guidelines for the management of community acquired pneumonia in immunocompetent adults. *Clin Infect Dis.* **37(11)**:1405-33.
33. Singh N, Stout JE, Yu VL (2004). Prevention of Legionnaires' disease in transplant recipients: recommendations for a standardized approach. *Transpl Infect Dis.* **6(2)**:58-62.

34. Nocardia infections (2004). *Am J Transplant* **4(Suppl 10)**:47-50.

35. Aguado JM, Herrero JA, Gavaldá J, *et al* (1997). Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain. Spanish Transplantation Infection Study Group, GESITRA. *Transplantation* **63(9)**:1278-86.

36. Centers for Disease Control and Prevention; Infectious Disease Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients (2000). *MMWR Recomm Rep.* **49(RR-10)**:1-125.

37. Nontuberculous mycobacteria (2004). *Am J Tranplant* **4(Suppl 10)**:42-46

38. Cerrina J, Bavoux E, Le Roy Ladurie F, *et al* (1991). Ganciclovir treatment of cytomegalovirus infection in heart-lung and double lung transplant recipients. *Transplant Proc* **23**:1174-5.

39. Hecht DW, Snydman DR, Crumpacker CS, Werner BG, Heinze-Lacey B (1988). Ganciclovir for treatment of renal transplant associated primary cytomegalovirus pneumonia. *J Infect Dis* **157**:187-90.

40. Snydman DR (2001). Historical overview of the use of cytomegalovirus hyperimmune globulin in organ transplantation. *Transpl Infect Dis* **3(Suppl 2)**:6-13.

41. Valantine HA, Luikart H, Doyle R, *et al* (2001). Impact of cytomegalovirus hyperimmune globulin on outcome after cardiothoracic transplantation: a comparative study of combined prophylaxis with CMV hyperimmune globulin plus ganciclovir versus ganciclovir alone. *Transplantation* **72**:1647-52.

42. Crumpacker CS (1996). Ganciclovir. *N Engl J Med* **335**:721-9.

43. Bacigalupo A, Bregante S, Tedone E, *et al* (1996). Combined forcarnet-ganciclovir treatment for cytomegalovirus infection after allogenic hemopoietic stem cell transplantation (HSCT). *Bone Marrow Transplant.* **18(Suppl 2)**:110-4.

44. Reed EC, Bowden RA, Dandliker PS, Gleaves CA, Meyers JD (1987). Efficacy of cytomegalovirus immunoglobulin in marrow

transplant recipients with cytomegalovirus pneumonia. *J Infect Dis* **156**:641-5.

45. Herbrecht R, Denning DW, Patterson TF, *et al* (2002). Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med.* **347(6)**:408-15.
46. Denning DW, Ribaud P, Milpied N, *et al* (2002). Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis.* **34(5)**:563-71.
47. Linden PK, Coley K, Fontes P, Fung JJ, Kusne S (2003). Invasive aspergillosis in liver transplant recipients: outcome comparison of therapy with amphotericin B lipid complex and a historical cohort treated with conventional amphotericin B. *Clin Infect Dis.* **37(1)**:17-25.
48. Maertens J, Raad I, Petrikkos G, *et al* (2004). Caspofungin Salvage Aspergillosis Study Group. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Infect Dis.* **39(11)**:1563-71.
49. Marr KA, Boeckh M, Carter RA, Kim HW, Corey L (2004). Combination antifungal therapy for invasive aspergillosis. *Clin Infect Dis.* **39(6)**:797-802.
50. Singh N, Limaye AP, Forrest G, *et al* (2006). Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. *Transplantation.* **81(3)**:320-6.
51. Maertens J, Glasmacher A, Herbrecht R, *et al* (2006). Caspofungin Combination Therapy Study Group. Multicenter, noncomparative study of caspofungin in combination with other antifungals as salvage therapy in adults with invasive aspergillosis. *Cancer.* **107(12)**:2888-97.
52. Singh N, Pursell KJ (2008). Combination therapeutic approaches for the management of invasive aspergillosis in organ transplant recipients. *Mycoses.* **51(2)**:99-108.
53. Catalano L, Fontana R, Scarpato N, *et al* (1997). Combined

treatment with amphotericin-B and granulocyte transfusion from G-CSF-stimulated donors in an aplastic patient with invasive aspergillosis undergoing bone marrow transplantation. *Haematologica.* **82(1)**:71-2.

54. Habicht JM, Matt P, Passweg JR, *et al* (2001). Invasive pulmonary fungal infection in hematologic patients: is resection effective? *Hematol J.* **2(4)**:250-6.

55. Matt P, Bernet F, Habicht J, *et al* (2004). Predicting outcome after lung resection for invasive pulmonary aspergillosis in patients with neutropenia. *Chest.* **126(6)**:1783-8.