

Chapter 15

Common Infections Following Lung Transplantation



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15.1 Bacteria Including Mycobacteria and Nocardia

15.1.1 Introduction

Infection accounts for around 35% of all deaths in the first year after transplantation with bacterial pathogens responsible for approximately half of all infections [1].

The risk of infection following lung transplantation is determined by a number of factors including:

- physical factors such as denervation of the allograft resulting in a reduced cough reflex and anastomotic site stenosis with distal infection
- the ‘net state of immunosuppression’—the result of all factors including host immune system, anti-rejection immunosuppressive therapy and concomitant viral infections such as cytomegalovirus that contribute to a patient’s risk of infection
- epidemiological exposure to organisms, including donor-derived infections, community acquired infections, travel related infections and healthcare associated infections
- the use of prophylactic antimicrobial agents in the post-transplant period

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15.1.2 Bacterial Infection: The Basics

Bacteria are defined by their morphology or shape and size. Most pathogenic bacterial species are spherical (cocci) or rod-shaped (bacilli) and may exist as single cells (for example many of the common bacilli such as *Pseudomonas* and *Stenotrophomonas*) or in a variety of characteristic patterns such as *S. pneumoniae* (pairs of lancet shaped cocci), *S. aureus* (large clusters of cocci forming ‘bunches of grapes’) and Streptococci (long chains of cocci).

Whilst molecular diagnostic techniques such as polymerase chain reaction (PCR) are increasingly important the basis of much microbiological diagnosis remains the characteristic appearance of the organism on a glass microscope slide when stained with dyes under a variety of conditions. Common stains include the Gram stain, first described by HC Gram in 1884 but still in everyday use, the Ziehl-Neelsen or acid-fast stain for mycobacteria and the modified Ziehl-Neelsen stain for nocardia. The Gram stain divides bacteria into Gram positive or Gram negative depending on the ability of the cell wall to prevent decolourisation after staining with crystal violet. It is important to remember that bacteria such as *S. aureus* and *Pseudomonas* species are not stained by the Ziehl-Neelsen stain and conversely mycobacteria cannot be seen on a Gram stain. Culture techniques also differ with mycobacteria often unable to grow on conventional agar plates, requiring special growth media and prolonged culture periods. Therefore if mycobacterial infection is suspected the request form for the sample must specify ‘mycobacterial culture’ so the appropriate investigations are performed by the laboratory.

The laboratory diagnosis of important bacteria in the setting of lung transplantation is summarised in Table 15.1.

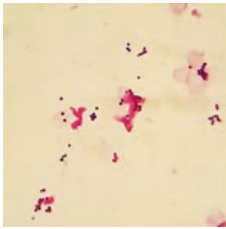
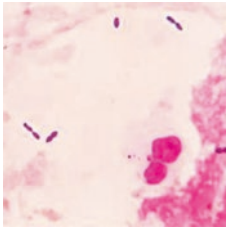
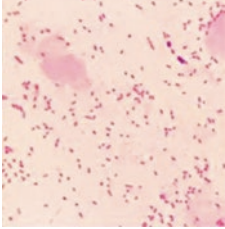
15.1.3 What You Need to Know: A Brief Summary of Important Bacteria in Lung Transplantation

15.1.3.1 *Staphylococcus aureus*

Clinical Features

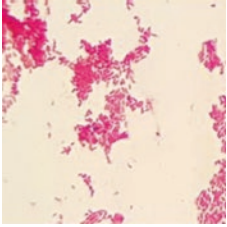
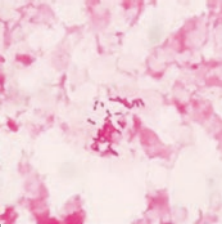
S. aureus is a common colonizer of the upper respiratory tract and skin, and is isolated with increased frequency from the sputum of patients with cystic fibrosis although the frequency decreases with age [2]. *S. aureus* can be acquired from the donor, the recipients own bacterial flora or the hospital environment as a healthcare associated infection, and is responsible for a wide range of health care-associated infections such as ventilator-associated pneumonia, bacteraemia, and surgical site infections. Isolates of *S. aureus* are characterised according to their susceptibility to methicillin, an anti-staphylococcal penicillin. Methicillin susceptible *S. aureus*

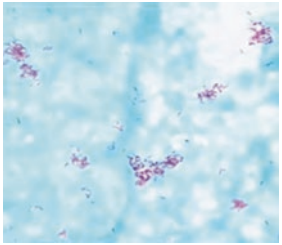
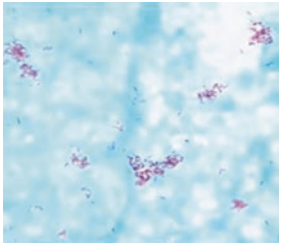


Table 15.1 Laboratory diagnosis of important bacteria

Important organisms	Gram stain appearance	Ziehl–Neelsen stain	Modified Ziehl–Neelsen stain	Polymerase chain reaction
<i>Staphylococcus aureus</i>		Not applicable	Not applicable	Rapid detection of the presence of <i>S. aureus</i> and differentiation between MSSA and MRSA
<i>Streptococcus pneumoniae</i>		Not applicable	Not applicable	Urinary antigen test for rapid diagnosis of systemic illness (not PCR based)
<i>Haemophilus influenzae</i>		Not applicable	Not applicable	Not in routine use

(continued)

Table 15.1 (continued)

Important organisms	Gram stain appearance	Ziehl–Neelsen stain	Modified Ziehl–Neelsen stain	Polymerase chain reaction
<i>Pseudomonas aeruginosa</i>		Not applicable	Not applicable	Not in routine use
<i>Burkholderia cepacia</i> complex		Not applicable	Not applicable	Not in routine use. Utilised in some specialist laboratories for rapid differentiation between species

<p><i>Mycobacteria species</i></p>	<p>May appear as 'non-staining' or colourless rods against the background</p> 		<p>Not applicable</p>	<p>PCR directly on clinical sample for rapid diagnosis of tuberculosis and differentiation from other mycobacterial species. Also performed for rapid identification of <i>M. tuberculosis</i> from culture</p>
<p><i>Nocardia species</i></p>		<p>Not applicable</p>		<p>Not in routine use</p>

Photographs courtesy of Thomas Cawsey and Maisie Cao, Department of Microbiology, St. Vincent's Hospital, Sydney

(MSSA) is more common in community acquired infections whereas methicillin resistant *S. aureus* (MRSA) occurs with greater frequency in hospital acquired infections.

The largest study of *S. aureus* following lung transplantation was a retrospective single centre study conducted over a 5 year period [3]. *S. aureus* infection developed in 109 of 596 lung transplant (18%) recipients within 90 days of transplantation. MSSA (62%) was more common than MRSA (38%) but the proportion of MRSA infections increased over time. Pneumonia (48%) was the most common infection, followed by tracheo-bronchitis (26%), bacteremia (12%), intrathoracic infections (7%), and skin/soft tissue infections (7%). Infected patients required longer hospital and intensive care unit stays ($p < 0.0001$ for both) but the 30- and 90-day mortality rates were low (7% and 12%, respectively). However infected patients had higher rates of rejection (both acute and chronic) at 1 ($p = 0.048$) and 3 years ($p = 0.002$), and higher mortality at 1 ($p = 0.058$) and 3 years ($p = 0.009$).

Treatment

MSSA

- dicloxacillin or flucloxacillin
- cefazolin or cephalothin for penicillin allergic patients (note—there is 5–10% risk of anaphylaxis in patients with documented penicillin anaphylaxis)
- clindamycin is often prescribed for deep infections because it exhibits good tissue penetration. However it is a bacteriostatic antibiotic and should only be administered to patients with *S. aureus* bacteraemia following specialist advice

MRSA

- vancomycin with appropriate therapeutic drug monitoring (TDM)
- Teicoplanin—TDM not available in most centres. Standard dosing may be inadequate, especially for bacteraemia
- Linezolid—superior to vancomycin for MRSA pneumonia. Toxicity may occur with long-term administration unless TDM is undertaken
- some isolates may be susceptible to clindamycin, cotrimoxazole and doxycycline. However these agents should not be used to treat bacteraemia

Infection Control

MSSA: no specific measures required.

MRSA: patients are usually placed on contact precautions (gown or apron, glove and careful hand hygiene as per 5 moments for hand hygiene) and may be isolated in a single room or cohorted with other colonised patients to prevent spread to other non-identified colonised patients.

15.1.3.2 *Haemophilus influenzae*

Clinical

Haemophilus influenzae is an important respiratory pathogen. In patients with cystic fibrosis it often causes infection early in life but is replaced by other organisms such as *Pseudomonas spp.* over time [4]. In contrast, patients undergoing lung transplantation for other indications may be colonized with *H. influenzae* at any stage of life. Post-transplant infection with *H. influenzae* is relatively uncommon. This is at least in part because of the wide spread practice of the administration of azithromycin and trimethoprim/sulphamethoxazole as prophylactic agents in the post-operative period. Both these antimicrobial agents have activity against *H. influenzae* thereby reducing the frequency of infection.

Treatment

- approximately 25% of *H. influenzae* isolates are susceptible to ampicillin
- ampicillin resistant isolates are generally susceptible to augmentin, cefuroxime and third generation cephalosporins (cefotaxime, ceftriaxone)
- cephalexin is ineffective

Infection Control

No specific infection control measures required other than standard precautions and hand hygiene.

15.1.3.3 *S. pneumoniae*

Like *H. influenzae* *S. pneumoniae* is an important respiratory pathogen which is uncommon in the setting of lung transplantation, again in part because of the impact of antimicrobial prophylaxis with trimethoprim/sulphamethoxazole and azithromycin. After lung transplantation a reduction in an important component of the immune system, serum immunoglobulins, is common occurring in up to 63% of lung transplant recipients [5]. It is likely that this increases the risk and frequency of severe pneumococcal infection.

Treatment

- *S. pneumoniae* is generally susceptible to penicillin
- penicillin resistant *S. pneumoniae* pulmonary infection can usually be successfully treated with penicillin as the concentration achieved in the lung is sufficient to exceed the threshold for efficacy
- alternative treatment options for penicillin resistant *S. pneumoniae* causing meningitis or blood-stream include third generation cephalosporins and vancomycin

Infection Control

No specific infection control measures required other than standard precautions and hand hygiene.

15.1.3.4 *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a Gram negative bacillus which commonly colonises the airways of patients with cystic fibrosis but is also found in other patients proceeding to lung transplantation, for example those with chronic obstructive pulmonary disease. In many centres *Pseudomonas* is the most common cause of post-transplantation bacterial infection. Prolonged pre-transplant therapy with a variety of antibiotics frequently results in highly resistant organisms colonizing the patient at the time of transplantation.

Laboratory reports may refer to ‘mucoid *Pseudomonas*’ isolated from a specimen. Mucoid *Pseudomonas* develops under certain environmental conditions following infection with non-mucoid species. The thick polysaccharide capsule gives the organism a ‘wet’ appearance when growing on an agar plate in the laboratory but more importantly renders the organism more resistant to immunological defense mechanisms such as phagocytosis and to standard anti-*Pseudomonas* therapy.

Treatment

- guided by laboratory susceptibility testing, especially in patients with extensive prior antibiotic exposure
- susceptibility testing of mucoid strains is less reliable than standard strains
- commonly used antibiotics include aminoglycosides (gentamicin, tobramycin, amikacin), antipseudomonal beta-lactams (piperacillin-tazobactam, ceftazidime, cefepime), ciprofloxacin and meropenem. Colistin may occasionally be required for extremely resistant organisms

Infection Control

Contact precautions are generally reserved for patients with multi-drug resistant *Pseudomonas aeruginosa*.

15.1.3.5 *Stenotrophomonas maltophilia*

Stenotrophomonas maltophilia is a Gram negative bacillus which is increasingly recognized as an important pathogen of the airways in the setting of lung transplantation. The organism is widespread in the environment, found in soil, water and animal and plant material. Treatment is complicated by the multi-drug resistance.

Treatment

- trimethoprim-sulphamethoxazole is the treatment of choice although resistance is increasingly described
- ciprofloxacin is active against approximately 50% of laboratory isolates

Infection Control

- no specific infection control requirements other than standard precautions and hand hygiene.

15.1.3.6 *Burkholderia cepacia* Complex

Burkholderia species are Gram negative bacilli closely related to *Pseudomonas species* (in fact they were previously called *Pseudomonas cepacia* and you will sometimes see this referred to in older literature). In the setting of cystic fibrosis and lung transplantation, the clinically important species belong to the *Burkholderia cepacia* complex (Bcc), a group of 17 genetically closely related organisms. However it has been recently recognised that not all Bcc are equally pathogenic. The most important organisms include *B. cenocepacia* (previously named Bcc genomovar III) and *Burkholderia multivorans* (previously Bcc genomovar 2) which account for up to 97% of all *Burkholderia cepacia* complex isolates from patients with cystic fibrosis [6]. One of the most feared organisms is *Burkholderia cenocepacia* which can be an aggressive pathogen that is transmissible between patients and can cause epidemics.

Recent studies have suggested that *B. cenocepacia* is associated with poor outcome and is a contraindication to transplantation in many centres. Therefore accurate detection and identification of *Burkholderia species* prior to transplantation is absolutely essential: a false positive result can lead to exclusion from the transplantation waiting list whereas a false negative result can lead to poor transplantation outcome and possible cross infection between patients if appropriate infection control measures are not put in place.

Treatment

There is no standard treatment that can eliminate Bcc. Eradication of Bcc is extremely difficult as many species of Bcc, particularly *B. cenocepacia*, are intrinsically resistant via a variety of resistance mechanisms to numerous antimicrobial agents including the aminoglycosides (gentamicin, tobramycin), most antipseudomonal beta-lactam antibiotics (piperacillin-tazobactam, cefepime, ceftazidime) and colistin. Rapid development of resistance may occur during therapy [6]. In a study of a large number of Bcc isolates, 2621 strains of *Burkholderia cepacia* complex isolated from 1257 cystic fibrosis patients were tested. Resistance to all available antimicrobial agents was demonstrated in 18% of isolates with the most active

agents, minocycline, meropenem, and ceftazidime inhibiting 38%, 26%, and 23% of strains, respectively [7]. The use of combination antimicrobial therapy to overcome these issues has not usually been successful.

Infection Control

Bcc can be spread to susceptible patients by:

- person to person contact
- contact with contaminated surfaces or objects
- exposure to Bcc in the environment

Contact precautions and isolation (see MRSA) may be implemented in hospital. Alternately, patients colonised with Bcc should not be housed next to an immunosuppressed patient.

15.1.4 *Mycobacterial Infection*

Mycobacteria are bacteria forming their own genus within the phylum Actinobacteria. Over 190 species have been identified but not all are pathogenic (that is have the potential to cause infection in humans). Mycobacteria are slender, curved rods that, unlike most bacteria, are acid fast (see preceding section). In addition, they are resistant to alkalis and dehydration meaning they can survive for long periods in the environment. The cell wall contains complex waxes and glycolipids. They multiply very slowly on special media and some clinical isolates can take 4–6 weeks to grow. Based on their growth rate, catalase and niacin production and pigmentation in light or dark conditions mycobacteria are classified as *Mycobacterium tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microtii*) and non-tuberculous mycobacterium (NTM). Molecular techniques (e.g. PCR) can now readily differentiate between them.

15.1.4.1 *Mycobacterium tuberculosis* (TB)

M. tuberculosis is transmitted from person to person. The incidence in transplant recipients is much higher than in the general population [8]. The most common cause in the transplant population is reactivation of latent infection but other causes include unrecognised transmission in the donor lungs (that is donor-derived), especially in countries where TB is endemic, and primary infection after transplantation [9]. The median time to infection from lung transplantation is 3.5 months (earlier than in renal transplant recipients) but donor-derived infections usually occur earlier, often within the first month post-lung transplant [8].

Risk factors include prior residence in an endemic country, history of untreated TB, a chest x-ray which shows evidence of old healed TB, augmented immunosup-

Fig. 15.1 Chest x-ray showing bilateral *Mycobacterium tuberculosis*. Courtesy of the Public Health Image Library, Center for Disease Control and Prevention

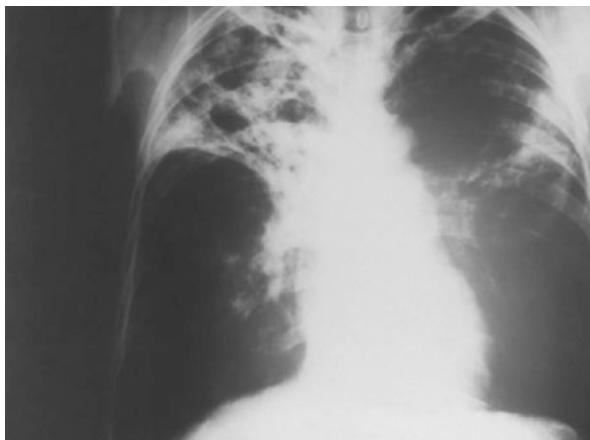
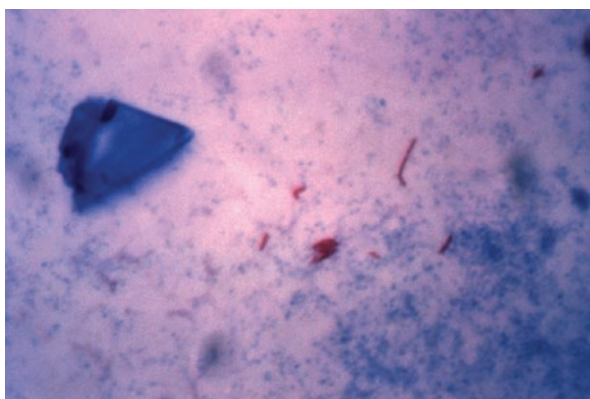


Fig. 15.2 *Mycobacterium tuberculosis* detected in a sputum smear using Ziehl-Neelsen stain ($\times 1000$ magnification). Courtesy of the Public Health Image Library, Center for Disease Control and Prevention



pression for rejection, use of T-cell depleting agents for immunosuppression and recipient age.

The lung is the most common site of infection but in up to 33% extra-pulmonary or disseminated TB can occur with unusual presentations (e.g. skin ulcers, abscesses, tenosynovitis) [9]. Fever is a very common presenting complaint as are night sweats and weight loss [9]. Instead of the classical cavity that is seen on chest x-ray in immunocompetent patients, in lung transplant recipients focal infiltrates, miliary pattern, nodules or pleural effusions are more common (Fig. 15.1) [9].

The diagnosis of active TB can be challenging in lung transplant recipients with sputum samples commonly stain and culture negative. Bronchoalveolar lavage (BAL) with the fluid sent for acid fast bacilli (AFB) staining (Fig. 15.2) and culture is ideal. PCR testing is useful to decrease the time to diagnosis given cultures are slow to grow. Biopsy of skin lesions, abscesses, soft tissue lesions or other accessible extra-pulmonary sites for AFB staining, culture, histology and/or PCR can assist in the diagnosis of extra-pulmonary TB.

Treatment

Guidelines exist for the treatment of active TB; however, there are a few specific things to note in the lung transplant setting [10–12].

- a rifamycin-based regimen (rifampicin is the most common drug used in this group) is strongly preferred because of its sterilizing capacity and ability to prevent the emergence of resistance
- rifamycins interact with immunosuppressant agents. Dose adjustments will be required at initiation and cessation with close monitoring of levels of immunosuppressant drugs whilst receiving a rifamycin
- some centres prefer rifabutin for use in the transplant setting as it has less impact on drug metabolism than rifampicin
- for localised non-severe infection and no suspicion of isoniazid resistance a fluoroquinolone could be substituted for the rifamycin with the duration extended to 12–18 months depending on the number of drugs used. Otherwise a rifamycin agent should be used in the regimen.
- the minimum duration is 6 months but some experts prefer a minimum of 9 months in the transplant setting. Longer treatment is required for severe or disseminated infection or for infection involving the central nervous system and/or bone and joint and in pulmonary disease with ongoing AFB detectable in sputum (>2 months)
- streptomycin should not be used in the lung transplant setting because of the associated high-risk of nephrotoxicity.
- immunosuppressive agents used to prevent rejection may only require minimal or no dose reduction. This is because immune reconstitution inflammatory syndrome (IRIS) can occur even when the immunosuppressant agents are not dose-reduced as the anti-TB treatment can reverse some of the immunosuppressive effects of TB.

Screening for latent TB (prior exposure to *M. tuberculosis* which can reactivate and cause clinical disease) needs to be performed pre-transplant in all lung transplant candidates. Two tests are available, namely, the tuberculin skin test (TST) and the interferon-gamma release assay (IGRA). The IGRA is used in most centres. Screening algorithms are available [10, 13]. As the risk of reactivation and severe infection is increased in transplant recipients and the annual risk of active TB with a positive TST is 7.4%, there is a good argument for latent TB treatment. The optimal timing for latent TB treatment is pre-transplant. Latent TB should be treated if:

- the initial or boosted TST produces induration of ≥ 5 mm or a positive IGRA;
- prior history of untreated latent TB; or
- receipt of an organ from a donor known to have untreated latent TB.

Isoniazid (with oral pyridoxine) is the treatment of choice and has a low risk of toxicity. Rifampicin for 16 weeks or isoniazid in combination with rifapentine for 12 weeks are alternative regimens, but only pre-transplantation because of drug interactions.

Infection Control

As already stated person-to-person transmission of TB can occur. The major route is by inhalation of airborne particles. There are a number of factors that increase the risk of transmission of airborne particles including presence of untreated active pulmonary or laryngeal TB, cavitory disease, smear positivity and short time to positive *M. tuberculosis* culture. A number of procedures can also increase the risk of dispersal of airborne particles including intubation and bronchoscopy. Patients with extra-pulmonary TB are not contagious; however, concomitant pulmonary or laryngeal TB needs to be excluded firstly. Immunocompromised patients with extra-pulmonary TB should be presumed to have pulmonary TB until proven otherwise.

There are numerous international and national TB control guidelines on which hospitals base infection control programs for TB [14]. If TB is suspected or untreated:

- the patient must be managed in airborne isolation rooms with negative pressure ventilation
- masks must be worn by health-care workers when in contact with the patient and by the patient when he/she leaves the room
- when TB is excluded the patient can be removed from isolation
- for patients with confirmed TB isolation can be discontinued when the patient is receiving treatment, demonstrates a clinical response and has three negative AFB smears from sputum
- close liaison with the institutional Infection Control Team is essential in cases of suspected or untreated TB.

15.1.4.2 Non-tuberculous Mycobacterium (NTM)

Common NTM affecting lung transplant recipients include *M. avium* complex, *M. kansasii* and *M. abscessus*. These are environmental organisms so infection usually occurs via acquisition from an environmental reservoir and not person to person transmission. Healthcare-associated infection from contaminated medical devices can occur and person-to-person transmission has been described with *M. abscessus* [15, 16].

Risk factors for infection include cystic fibrosis as an underlying disease, the isolation of a NTM (particularly *M. abscessus*) pre-transplant and the use of rabbit anti-thymocyte globulin. Median time to onset is later when compared with TB (1 year). The lungs are most commonly affected but cutaneous, soft tissue and

disseminated infection can be seen, especially with *M. abscessus*, *M. chelonae* and *M. kansasii* [17]. With disseminated disease constitutional symptoms (e.g. sweats, tiredness, weight loss) predominate [18]. The most common radiological features seen are fibrocavitary and cavitary, nodules, bronchiectasis, tree-in-bud, and large opacities (>2 cm) [19].

Diagnosis is very challenging as these are environmental organisms and it is difficult to determine whether isolation of these organisms reflects contamination/colonization or true infection. Guidelines for diagnosis exist for NTM [20]. Factors such as organism burden, specific species, clinical signs and symptoms and radiological features all need to be considered when determining infection category and whether or not to treat.

Treatment

Treatment is similar to the immunocompetent population. A multi-drug regimen is used (see Table 15.2); however, similar to TB a few specific points need to be considered in the transplant setting.

- susceptibility testing should be performed to direct initial and maintenance regimens.
- clarithromycin can increase serum levels of calcineurin inhibitors and rapamycin agents via the cytochrome (CYP) 3A4 pathway so with the initiation and cessation of clarithromycin the immunosuppressant agents may need dose adjustment. Close monitoring of immunosuppressant concentrations is required.
- the issues outlined above for rifamycin use in TB treatment also apply to the treatment of NTM.
- the duration of treatment is longer than for the immunocompetent population. The minimum is usually 12 months after last positive culture; but lifelong suppressive therapy may be needed in some patients.
- reduction of immunosuppression needs to be considered.
- surgical resection may be required if:

Table 15.2 Treatment regimens for commonly encountered *non-tuberculous mycobacteria* post-lung transplantation

Organism	Treatment regimens
<i>M. avium intracellulare</i>	Clarithromycin (or azithromycin), rifampicin (or rifabutin) and ethambutol (consider adding amikacin in fibrocavitary or severe nodular/bronchiectatic disease)
<i>M. kansasii</i>	Isoniazid, rifampicin, ethambutol (rifampicin resistance—high dose isoniazid and ethambutol, trimethoprim-sulphamethoxazole and streptomycin)
<i>M. abscessus</i>	Amikacin, cefoxitin and clarithromycin (or azithromycin) (very resistant organisms or disseminated disease consider adding a carbapenem, tigecycline or linezolid) [1]

- large abscesses are present
- there is a large burden of disease
- focal disease not responding to therapy
- the patient cannot tolerate therapy.

M. abscessus is a particular problem in the lung transplant setting. It is increasing in incidence and can cause disseminated infection post-lung transplant which can be very difficult to eradicate. It is also resistant to many of the available antimicrobial agents and drug-related toxicity has been detected in up to 44% post-lung transplantation [21, 22]. Treatment is complicated and prolonged.

In some centres isolation of *M. abscessus* in a lung transplant candidate is considered as a strong relative contra-indication to transplantation [23]. Other centres have determined that transplantation of patients with pre-transplant isolation of *M. abscessus* is possible with the precautions outlined in Table 15.3 [24, 25]. Currently, expert opinion indicates that transplantation in those with pre-transplant isolation of *M. abscessus* should be decided on a case-by-case basis.

Infection Control

As NTM are ubiquitous in the environment, transmission is usually from an environmental source. In addition, NTM are resistant to chlorine and have the ability to form bio-films. As a result infection control measures are directed at ensuring adequate disinfection of hospital equipment, rigorous and repeated surface cleaning and high-quality water supply. Ongoing environmental surveillance in the hospital setting and close liaison with institutional Infection Control and Engineering Teams is critical to prevent outbreaks of NTM, particularly in the setting of construction.

Table 15.3 Current recommendation for management of pre-transplant *M. abscessus* into the post-transplant period

Recommendations
Ensure meet the ATS criteria for disease
Commence triple antimicrobial therapy (according to susceptibility patterns)
Intra-operatively
Use a clam-shell approach
Irrigate the pleural cavity after removal of native lungs with betadine or amikacin
Change surgical gloves prior to insertion of allograft
Complete hilar and mediastinal lymphadenectomy
Continue therapy post-transplant for a minimum of 6 weeks
Exact duration is dependent on surveillance bronchoscopy results. If the 6 week surveillance bronchoscopy is negative for <i>M. abscessus</i> culture then stop, if it is positive then continue
Consider switching to indefinite prophylaxis with inhaled amikacin, oral ciprofloxacin and oral clarithromycin
Regular examination of wounds, skin and soft tissue for signs of disseminated infection

ATS American Thoracic Society

Adapted from Lobo et al. [16] and Robinson et al. [17]. Courtesy of Dr. Orla Morrissey and Dr. Hannah Bills

There are some evidence in the literature that *M. abscessus* has been associated with person-to-person transmission but other studies have indicated that this may not be the case [26, 27]. Careful assessment of each institution's epidemiology will assist in deciding if patients with *M. abscessus* require airborne isolation or simply rigorous cleaning of the environment [28]. Recently *M. chimera* contamination of heater-cooler units used in cardiac surgery has been reported resulting in cases of surgical-site and disseminated infection worldwide. New enhanced decontamination strategies have been developed and ongoing surveillance is required to ensure that these remain effective [29].

15.1.4.3 *Nocardia*

Nocardia are ubiquitous, saprophytic, gram-positive bacteria that belong to the aerobic actinomycetes group. They are partially acid-fast rods that grow slowly in branching chains resembling fungal hyphae. There are more than 80 species but most infections in humans are caused by *Nocardia asteroides sensu stricto*, *N. farcinica*, *N. nova*, and *N. brasiliensis*.

Infections with *Nocardia* are increasing in lung transplant recipients [30]. Whilst widespread throughout the world infections with *Nocardia* have the highest frequency in dry windy climates which facilitate aerosolisation and dispersal. Infections mostly occur in the first year after lung transplantation but are rare within the first month unless it is donor-derived infection. Risk factors include corticosteroids (particularly in the preceding 6 months), and augmented immunosuppression (high median calcineurin inhibitor levels in the preceding 30 days) [30]. Rituximab use and hypogammaglobulinaemia have also been associated with an increased risk of developing *Nocardia* infection as has the use of alemtuzumab for treatment of allograft rejection [31–33].

Inhalation is the most common route of infection therefore the lungs are most commonly affected. Dissemination to other organs, particularly the skin and central nervous system (CNS) has been reported in 50% of cases. The skin can also be infected by direct inoculation, especially if the lung transplant recipient is involved in outdoor activities. The most common signs and symptoms are fever, weight loss, cough, pleuritic chest pain and dyspnoea. Chest imaging frequently shows irregular nodular lesions which may be cavitory (Fig. 15.3) [34]. Other features include diffuse infiltrates or consolidation with associated pleural effusions.

Diagnosis is by microscopy, culture and histological examination of respiratory specimens (most particularly bronchoalveolar lavage fluid [BAL]) or biopsy tissue (e.g. skin or brain tissue). *Nocardia* grows on non-selective media forming characteristic white and chalky colonies. If there is a suspicion that the infection may be *Nocardia* inform your diagnostic laboratory as the specimens require longer incubation for the growth of *Nocardia* and in samples with mixed growth (that is multiple organisms [particularly sputum]) *Nocardia* may be obscured. Selective media can be used to improve the yield of *Nocardia* growth (e.g. Thayer-Martin). *Nocardia* has characteristic features on gram stain (see Fig. 15.4). In tissue *Nocardia* appears as gram positive branching and beaded rods with surrounding pyogenic inflammatory

Fig. 15.3 Large nodule of *Nocardia* infection in a solid-organ transplant recipient

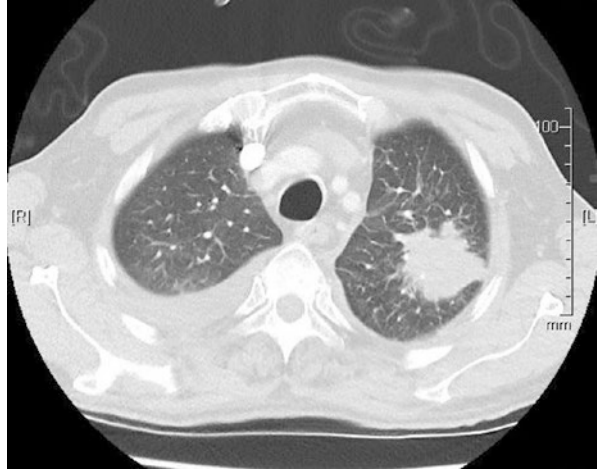
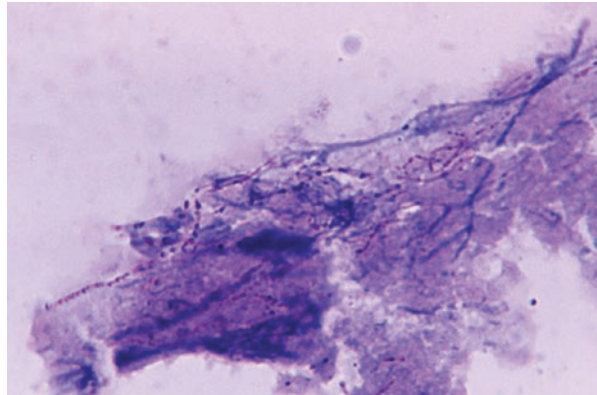


Fig. 15.4 Characteristic microscopic features of *Nocardia*. Courtesy of the Public Health Image Library, Center for Disease Control and Prevention



reaction. It is important to determine the species and susceptibility profiles as different species have different susceptibility profiles. This information is very useful in determining the treatment regimen.

Treatment

Antibiotics are the mainstay of treatment. The site(s) and burden of infection, the species and the potential drug-drug interactions all determine the antimicrobial regimen to be used for treatment [35].

- mild pulmonary infection—trimethoprim-sulfamethoxazole (TMP-SMX) for 6–12 weeks
- severe pulmonary infection (no CNS involvement)—parenteral treatment with TMP-SMX plus amikacin

- CNS infection—parenteral treatment with TMP-SMX plus imipenem
- multi-organ infection including the CNS—intravenous (IV) amikacin added to the regimen of IV TMP-SMX and imipenem.
- meropenem may be used instead of imipenem as the former is less likely to precipitate seizure activity. Sensitivity to meropenem must be demonstrated in the laboratory before use [36].
- linezolid has excellent in vitro activity against *Nocardia* and has been used with success in treatment; therefore linezolid may be used as part of a multi-drug regimen [37, 38].
- if the patient has a TMP-SMX allergy desensitisation should be performed if possible.

Parenteral treatment is continued for 3–6 week followed by oral therapy for 6–9 months. Oral agents that are commonly used include TMP-SMX, minocycline and/or amoxicillin-clavulanate. Surgery may be required in cases of cerebral nocardiosis or large soft tissue abscesses not responding to treatment, empyema or mediastinal fluid collections and for pulmonary nocardiosis that is complicated by pericarditis. Consideration should be given to reducing immunosuppression especially in cases with severe disease or those progressing on anti-microbial treatment. Indefinite secondary prophylaxis is also recommended as the immunosuppression cannot be fully reversed.

Infection Control

There are no reports of person-to-person transmission of *Nocardia* in the literature. As *Nocardia* are ubiquitous environmental organisms, acquisition is mostly from an environmental source. Similar to NTM infection control measures in the hospital setting for *Nocardia* are directed at disinfection of equipment and surfaces and ensuring high-quality water supply. Ongoing surveillance is required to prevent outbreaks, particularly in the setting of construction.

15.2 Fungal Infections

15.2.1 Introduction

Fungal infections are a significant problem in lung transplant recipients occurring in 8.6% and causing death in up 39.5% of those infected [39, 40]. The majority of infections are caused by *Aspergillus* and *Candida* species. *Cryptococcus* is the third most common cause of fungal infection. The fungi that cause mucormycosis (e.g. *Rhizopus* species), *Scedosporium*, and *Fusarium* are emerging and are associated with very high mortality rates (60.5%); thus, increasing emphasis is placed on early recognition, diagnosis and treatment [40]. *Histoplasma*, *Coccidioides* and *Blastomyces* species are important for those who live in or have previously resided

in or visited endemic areas. *Pneumocystis jirovecii*, whilst infrequent, can cause significant morbidity and mortality.

The risk factors for infection are very similar to those described above for bacterial infection. In addition, fungal infections have been implicated in triggering the development of chronic rejection (that is, chronic lung allograft dysfunction [CLAD]) [41].

Fungi are a major problem in lung transplant recipients. The importance of thinking about fungi in any lung transplant recipient suspected of having infection cannot be over-estimated. Early diagnosis and treatment is critical to optimising outcomes. Prophylaxis may reduce the impact of fungal infections in lung transplant recipients but issues such as drug intolerance and drug-drug interactions and the emergence of resistance may complicate treatment and reduce overall efficacy.

15.2.2 Microbiology

Fungi can be a single cell or complex multicellular organisms. Fungi are mainly found in soil or on dead plant matter. They can be divided up into yeasts, multicellular filamentous moulds and dimorphic fungi. Yeasts are small, lemon-shaped single cells that are around the size of red blood cells. They multiply by budding a daughter cell off from the original parent cell. Multicellular filamentous moulds are made up of very fine threads known as hyphae. They grow from the hyphal tips and divide repeatedly along their length creating long and branching chains. Some of the hyphal branches grow into the air and spores form on these aerial branches. These spores can be carried by the wind, rain or insects to new habitats where they can germinate to start growing and producing new hyphae. The process of infection is mimicked in immunosuppressed individuals where the conidia (spores) are inhaled and with impaired immune defence mechanisms the conidia (spores) can germinate and uncontrolled hyphal growth can occur. Dimorphic fungi are fungi that can exist as yeast or mould. A prime example of a dimorphic fungus is *Penicillium marneffeii*, a human pathogen that exists as a mould at room temperature but as yeast at human body temperature.

15.2.2.1 *Aspergillus* Species

Aspergillus fumigatus is the most common of all *Aspergillus* species [42]. Other species that can cause infection in the lung transplant setting include *A. flavus*, *A. terreus*, *A. niger* and *A. nidulans* [42]. The importance of identifying *A. terreus* is that it has a different susceptibility profile to the other *Aspergillus* species. It is resistant to amphotericin B [43].

Aspergillus species commonly cause 4 types of infection in lung transplant recipients:

- *Aspergillus* colonisation

- Tracheobronchial aspergillosis
- Invasive pulmonary aspergillosis (IPA) (also known as *Aspergillus* pneumonia)
- Disseminated invasive aspergillosis (IA).

15.2.2.2 *Aspergillus* Colonisation

Aspergillus colonization is defined as the detection of *Aspergillus* in respiratory secretions by culture, PCR or by the detection of *Aspergillus* galactomannan (a cell wall protein) in the absence of any symptoms, lesions in the airways seen on bronchoscopy or new changes seen on chest x-ray or computed tomography (CT) scan [44, 45]. *Aspergillus* colonization has been detected pre-transplant in 8–59% of patients (most commonly in cystic fibrosis [CF] patients) and is a risk factor for post-transplant IPA and CLAD [3, 7]. Post-transplant colonization is found in 30–40% [45].

Treatment

Some centres give antifungal agents to all lung transplant recipients (immediately post-transplant for 4–6 months) to minimize *Aspergillus* colonization and its complications [45, 46]. With the use of universal prophylaxis the time to *Aspergillus* colonisation has lengthened from 3.2 months to 6.8 months post-lung transplant [47, 48]. Other centres only give antifungal treatment (for 3 months) once *Aspergillus* is detected [45, 46]. This is known as the pre-emptive strategy. It is not known which strategy is best.

15.2.2.3 Tracheobronchial Aspergillosis

Tracheobronchial aspergillosis is defined as the detection of *Aspergillus* in respiratory secretions by culture, PCR or the detection of *Aspergillus* galactomannan with new lesions demonstrated on bronchoscopy including patches of redness (erythema), ulceration, necrosis or pseudomembranes but with no changes detected on chest x-ray or CT scan [44, 45]. The patient may be asymptomatic or may present with symptoms such as fever, cough, wheeze and/or hemoptysis [49]. It occurs in the majority of patients in the first 3 months post-lung transplant [47]. The importance of tracheobronchial aspergillosis is that the lung transplant recipient is at risk of progressing to IPA or disseminated IA [47].

Treatment

- the treatment of choice is voriconazole. Alternative agents include amphotericin B, posaconazole and itraconazole

- combine with nebulized amphotericin B for a direct local effect [50].
- repeated bronchoscopic debridement particularly in those with large amounts of necrotic debris [51]
- stenting occasionally required to maintain a patent airway

The duration of treatment is dependent on the severity of the initial infection, degree of immunosuppression and response to therapy but should be given until the lesions have completely healed and potentially life-long in those with bronchial anastomotic involvement.

15.2.2.4 Invasive Pulmonary Aspergillosis and Disseminated Invasive Aspergillosis

Proven IPA is defined as evidence of parenchymal (lung tissue) invasion by *Aspergillus* hyphae or positive culture from sterile lung tissue alone or with signs/symptoms such as fever, abnormal white cell count, new onset purulent sputum or change in the character or quantity of sputum or respiratory secretions, new onset or worsening cough, dyspnoea, tachypnoea, pleural rub, crackles or bronchial breath sounds. Probable IPA is defined as signs/symptoms (as above) and new or progressive and persistent infiltrate, consolidation, cavitation or nodules and detection of *Aspergillus* in respiratory secretions by culture, PCR or the detection of *Aspergillus* galactomannan (single positive for bronchoalveolar lavage [BAL] or 2 positives for sputum) (Fig. 15.5) [44, 45]. Average time to development is 6 months [52].

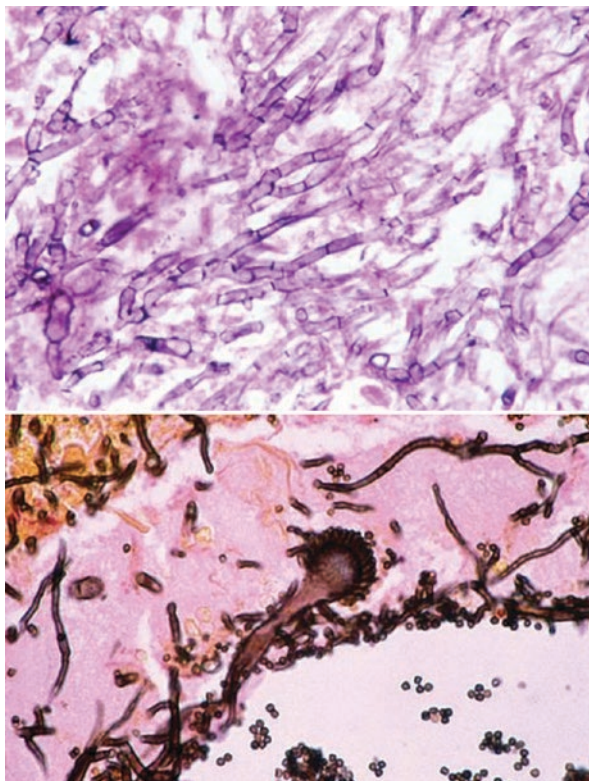
In disseminated IA, respiratory disease can be associated with infection in the sinuses, orbits and central nervous system (CNS). Other sites where *Aspergillus* can rarely cause infection include skin, bones, eyes (endophthalmitis), in the intra-abdominal cavity or retroperitoneum (e.g. abscess) and in the pericardium [42, 47].

Treatment

- voriconazole is the treatment of choice [53]
- an echinocandin (anidulafungin, caspofungin, micafungin) can be added for synergy in those with extensive disease or who are very unwell (e.g. hypoxic at presentation) [53]
- treatment of disseminated disease is the same as for IPA and as for IPA treatment continues until complete resolution

It is important to remember that when giving voriconazole (or other azole anti-fungal agents) in lung transplant recipients there are significant interactions with the immunosuppressant (e.g. tacrolimus, cyclosporine and sirolimus). Dose adjustments of the immunosuppressants are required at initiation and cessation of voriconazole (or other azole) and regular monitoring of serum immunosuppressant levels is required.

Fig. 15.5 Aspergillosis of the lung. Lung biopsy tissues stained with methenamine silver. With permission from A/Prof. David Ellis and Dr. Sarah Kidd. From Mycology Online, University of Adelaide, South Australia



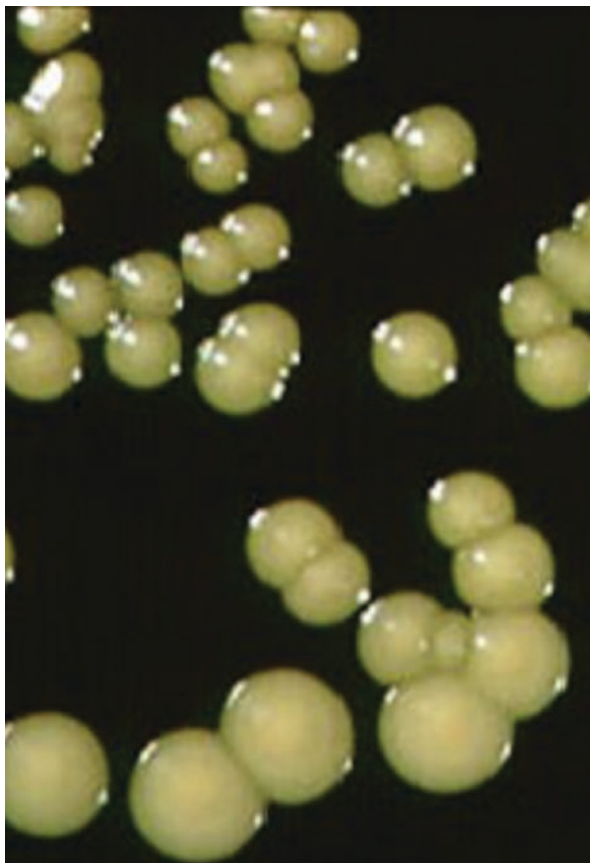
Infection Control

No specific infection control measures required.

15.2.2.5 *Candida* Species

The most common infection type seen with *Candida* species is candidaemia (infection in the bloodstream; Fig. 15.6). This is most common during the first month post-transplant and is usually related to the recent surgery, intensive care unit stay and broad-spectrum antibiotic use peri-transplant. Tissue infections can also occur and include infected pleural effusion, pleural space infection, infection of the incision sites and bronchial anastomotic site infections [50, 54]. *Candida* species are frequently isolated from the mouth, pharynx, sputum and BAL specimens but almost never spread to invade the lung tissue. Universal prophylaxis targeting *Candida* species during the first month post-transplant have been shown to be effective [55]. However, universal prophylaxis may be associated with the emergence of resistant *Candida* strains [56].

Fig. 15.6 A positive blood culture showing typical moist colonies. With permission from A/Prof. David Ellis and Dr. Sarah Kidd. From Mycology Online, University of Adelaide, South Australia



Candidaemia can manifest as fever or as severe sepsis (e.g. hypotension, tachycardia, requirement for inotrope support). Invasive candidiasis is related to the site of the infection. For example, if disseminated to the skin invasive candidiasis cause skin pustules or to the eye results in endophthalmitis. Blood cultures are still the gold-standard for the diagnosis of candidaemia; therefore a blood culture is required for all patients in whom candidaemia is suspected. In patients with invasive candidiasis a biopsy of the relevant tissues for staining, culture and histological examination is useful. Some centres have access to beta-D-glucan testing. This non-culture based assay detects a cell wall protein of *Candida* species and is a useful as an additional test (in addition to blood cultures and biopsy) in some patients, particularly those with intra-abdominal candidiasis.

Treatment

- echinocandin or liposomal amphotericin B for the treatment of candidaemia and serious *Candida* infection [45].

- once the *Candida* is detected and the sensitivity profile is known antifungal therapy can be altered [45]. If the isolate is sensitive to fluconazole then a change to this agent is recommended [45]
- if *Candida* is causing symptomatic infection of the urinary tract an echinocandin is not recommended as it has poor penetration into the urinary tract [45]. In this setting, fluconazole (if the isolate is sensitive) or amphotericin B and 5-flucytosine in combination (if the isolate is fluconazole-resistant) is recommended [45].

Infection Control

No specific infection control requirements.

15.2.2.6 *Cryptococcus*

Cryptococcus causes infection in 2% of lung transplant recipients. The most common site of cryptococcal infection is the lung (Fig. 15.7) but disseminated infection can also occur with a predilection to the central nervous system. Skin involvement including cellulitis [57] and infection transmitted in the donor lungs has also been described. The median time to infection onset is 190 days.

In addition to the usual diagnostic tests of culture and biopsy cryptococcal antigen assay is very useful as it is sensitive and specific and can be used to monitor disease treatment response.

Pre-transplant cryptococcosis has been described and is not a contra-indication to transplantation so long as disease control has been achieved with no positive cultures and cryptococcal antigen level is declining. Fluconazole is continued throughout the transplant procedure and for a minimum of 6 months post-transplantation.

Immune reconstitution inflammatory syndrome (IRIS) is common with treatment of cryptococcal infection (5–14%) [58] and manifests as an apparent flare of



Fig. 15.7 X-ray showing pulmonary cryptococcal infection involving the right upper lobe. With permission from A/Prof. David Ellis and Dr. Sarah Kidd. From Mycology Online, University of Adelaide, South Australia

infection including worsening of clinical and radiological manifestations of the infection, negative microbiology and no other explanation. It is most likely with CNS infection. Discontinuation of calcineurin inhibitors is a pre-disposing factor. It is recommended that calcineurin inhibitors are only dose-reduced and not ceased to minimise the risk of IRIS.

Treatment

The antifungal agents used depend on the site and burden of infection, indicating that diagnosis/exclusion of CNS disease by CT scan or MRI scan of head, a lumbar puncture for culture and cryptococcal antigen testing and CT of chest to determine extent of disease is critically important.

- CNS infection, disseminated infections or severe lung disease—liposomal amphotericin B and 5-flucytosine for a minimum of 2 weeks followed by fluconazole at high dose for 8 weeks and fluconazole at lower doses from 6 months to 1 year is recommended.
- small volume pulmonary disease—fluconazole alone for 6–12 months is recommended [59].

Infection Control

No specific infection control requirements.

15.2.2.7 Mucormycosis

The most common manifestation is pulmonary infection or infection of the CNS and sinuses but gastrointestinal infection (likely through ingestion) has also been described [60]. The cumulative incidence is 0.07% and it accounts for 2% of all fungal infections. Risk factors for infection include renal failure, diabetes and prior voriconazole and/or caspofungin use [61].

Mucormycosis is particularly associated with tissue infarction and necrosis due to invasion of the tissue blood vessels with the growing hyphae (Fig. 15.8). The fungi also spread rapidly along tissue planes. Both these factors contribute to the high mortality rates of up to 87% seen with this infection.

Treatment

In view of the aggressive nature of the fungus and high mortality rate treatment requires a multi-pronged approach.

- anti-fungal therapy

Fig. 15.8 Mucormycosis involving the palate. With permission from A/Prof. David Ellis and Dr. Sarah Kidd. From Mycology Online, University of Adelaide, South Australia



- first-line therapy is liposomal amphotericin B.
- caspofungin can be added if the infection is severe.
- posaconazole or isavuconazole can be given as maintenance therapy or if the patient is intolerant of liposomal amphotericin B.
- surgical debridement of all the necrotic tissue (Fig. 15.8),
- reduction of immunosuppression
- reversal of underlying factors (e.g. diabetes mellitus)

Infection Control

No specific infection control measures required.

15.2.2.8 *Scedosporium* Species

Scedosporium is an environmental organism that is recognised worldwide but has a higher incidence in specific geographical areas such as Spain, The Middle East and Australia. It is a common fungus in floods, tsunamis and tornados resulting in a risk for transmission if the donor drowned [62]. It is commonly isolated from CF patients pre-transplant. Risk factors for invasive *Scedosporium* disease post-transplant include pre-transplant colonisation, prior receipt of amphotericin B and augmented immunosuppression. *Scedosporium* is prone to disseminate and can be detected in blood cultures unlike other moulds such as *Aspergillus*.

In lung transplant recipients *Scedosporium* mainly causes colonisation with invasive infection occurring in about 25%. The most common clinical manifestations of invasive disease include pneumonia, mediastinitis, fungaemia or disseminated disease [63].

Progression to invasive disease is more likely in those with pre-transplant isolation; thus, if *Scedosporium* is isolated prior to transplantation it should be treated [63].

Treatment

- *Scedosporium* is innately resistant to many of the available antifungal agents including amphotericin B.
- *S. apiospermum* is sensitive to some of the azole antifungal agents, particularly voriconazole
- a combination of voriconazole and terbinafine may be the only option against *S. prolificans* (now known as *Lomentospora prolificans*) [63].

Infection Control

No specific infection control measures required.

15.2.2.9 *Fusarium* Species

Fusarium accounts for <1% of all invasive fungal disease in solid organ transplant patients with lung transplant recipients most commonly affected. Like *Scedosporium* whilst *Fusarium* occurs worldwide it has a higher incidence in some countries such as in Brazil, where the incidence of *Fusarium* is second only to *Aspergillus*. Infection usually occurs within a year of transplantation and most commonly affects the lungs. Outcome is poor with a 67% mortality rate.

Treatment

Voriconazole is the most effective agent.

Infection Control

No specific infection control measures required.

15.2.2.10 Endemic Fungi

Histoplasma is endemic to the states bordering the Ohio River Valley and the lower Mississippi River, USA but it has also been detected in Montana and Idaho. Other countries and regions where it has been isolated include Canada, Mexico, Central and South America, parts of eastern and southern Europe, Africa, eastern Asia and

Australia. Pulmonary and disseminated infections are the most common manifestations post-transplant. Infection can range from asymptomatic to severe. The diagnosis is made by using a combination of serology (antigen and antibody), culture of respiratory secretions and biopsy with histological examination of the affected tissue [64].

Routine screening pre-transplant is not recommended. Serial monitoring or the administration of prophylaxis is recommended in those who had active infection prior to transplantation [65].

Treatment

- mild disease—itraconazole
- more severe infection—amphotericin B [66]

Infection Control

No specific infection control measures required.

15.2.2.11 *Coccidioidomycosis*

Coccidioides are fungi that endemic to the Southwest of the United States particularly the San Joaquin Valley, and the Sonoran desert of southern California, Arizona and northern Mexico. In the lung transplant recipient these fungi can cause severe pneumonia or disseminated infection. Disseminated infection is most commonly characterized by skin, bone and joint lesions and/or meningeal involvement. Diagnosis is established by serological testing, culture or histopathology.

Pre-transplant assessment is required and includes a detailed past history [65]. Any history of residence or travel to an endemic area requires evaluation with serological testing and chest x-ray [65]. Any transplant candidate with past infection requires assessment by a specialist infectious diseases physician for clearance for transplantation [65]. In the case of active infection transplantation is deferred until the infection is quiescent (on radiology, clinically and serologically) [65].

Treatment

- focal pneumonia can be treated with fluconazole
- diffuse disease is treated initially with amphotericin B until clinical response followed by fluconazole or itraconazole
- coccidioidal meningitis is treated with fluconazole

Infection Control

No specific infection control measures required.

15.2.2.12 Blastomycosis

Blastomyces is endemic to parts of eastern North America, particularly northern Ontario, south-eastern Manitoba, Quebec, south of the St. Lawrence River, parts of the Appalachian mountains and the interconnected eastern mountain chains, the west bank of Lake Michigan, the state of Wisconsin and the entire Mississippi River including the valleys of the major tributaries (e.g. Ohio River). It also occurs in Africa, the Arabian Peninsula and the Indian subcontinent. Similar to *Histoplasma* and *Coccidioides* it causes pneumonia and skin involvement (with verrucous or wart-like lesions) and is also common in the transplant recipient. Diagnosis is made by culture of sputum, BAL or tissue or by histopathological examination of biopsy tissue.

Pre-transplant assessment includes symptom assessment and chest radiography for those who live in endemic areas [65]. Prophylaxis is given on a case by case basis.

Treatment

- liposomal amphotericin B until clinical improvement followed by oral itraconazole

Infection Control

No specific infection control measures required.

15.2.2.13 *Pneumocystis jirovecii*

Pneumocystis jirovecii was previously classified as a protozoan but with modern molecular techniques it has recently been reclassified as a fungus [67]. It was previously named *P. carinii* (which infects rats) but has been renamed *P. jirovecii* as this is the species that infects humans [68, 69].

If prophylaxis is not universally administered 5–15% of all solid organ transplant recipients develop *P. jirovecii* pneumonia (PJP) with the highest incidence occurring in the lung and heart-lung transplant recipients [70]. Most centres administer PJP prophylaxis and as a result very few cases are now seen. The most important risk factor for PJP is corticosteroid use in combination with other immunosuppressive agents [71]. There are no good data as to a dose and duration

of corticosteroids to decide when to give prophylaxis. The period of highest risk is the first 6 months post lung transplantation but most centres recommend indefinite prophylaxis [72].

Previously, patients presented in respiratory failure with fever and a dry cough but as the awareness of the significance of the infection has increased and as more sensitive diagnostic tests have been developed diagnosis is made earlier when the disease is mild or indolent (that is less severe cough and dyspnoea). Chest x-ray or CT scan of thorax usually demonstrates diffuse bilateral infiltrates. It is important to make a microbiological diagnosis so obtaining a respiratory specimen (induced sputum or ideally a BAL) is best. A lung biopsy is rarely required. The best test is PCR although it is very sensitive so false positive results can occur. Serum beta-D-glucan testing may be a useful adjunct if available [73].

Treatment

- trimethoprim-sulfamethoxazole (TMP-SMX) 15–20 mg/kg (based on the trimethoprim component) intravenously or orally in 3–4 divided doses daily is recommended as first-line treatment
- if the patient is allergic to TMP-SMX desensitization should be performed where possible
- if TMP-SMX cannot be used the alternative include TMP in combination with dapsone, primaquine in combination with clindamycin, atovaquone or intravenous pentamidine
- adjunctive corticosteroids are recommended if arterial blood gases show a partial pressure of oxygen of ≤ 70 mmHg

Like the treatment of PJP the first-line agent for prophylaxis is TMP-SMP but at lower doses (1 double-strength tablet 3 times a week or a single-strength tablet daily). Alternatives include dapsone, atovaquone or aerosolized pentamidine.

Infection Control

Several clusters or outbreaks of PJP have been reported, particularly in renal transplant patients. In some of these clusters or outbreaks person-to-person transmission was postulated as the cause [74]. Consequently hospitalised patients with PJP should not be placed in the same room as other immunocompromised patients. Otherwise standard precautions apply [75].

This review clearly illustrates that fungi are a major problem in lung transplant recipients. The importance of thinking about fungi in any lung transplant recipient suspected of having infection cannot be under-estimated. Early diagnosis and treatment is critical to optimising outcomes. Prophylaxis may reduce the impact of fungal infections in lung transplant recipients but issues such as drug intolerance and drug-drug interactions and the emergence of resistance may complicate and reduce its overall efficacy. Further multicentre research is required to determine the optimal prophylactic strategies for lung transplant recipients.

15.2.3 Viruses and Lung Transplantation

Viruses are organisms that are much smaller than bacteria and are unable to be detected on routine microscopy. They are only able to survive and replicate within a living cell, using the chemical machinery of that cell to reproduce. Viruses contain either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). Important DNA viruses in the setting of transplantation include the Herpesvirus family whilst the RNA viruses include most significant respiratory pathogens. Viral infection, either primary or following reactivation of latent virus, remains an important cause of morbidity and mortality following lung transplantation.

Viral culture is extremely laborious and difficult and is restricted to specialist laboratories. Increasingly the diagnosis of viral infection is made by PCR of peripheral blood or affected tissue with PCR available for all the members of the herpesvirus family listed below.

15.2.4 The Herpesvirus Family

The members of the Herpesvirus family are:

- Herpes simplex 1 and 2 (HSV-1 and HSV-2)
- Varicella (Herpes) zoster (VZV)
- Cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)
- Human herpesvirus 6 (HHV6)
- Human herpesvirus 7 (HHV7)
- Human herpesvirus 8 (HHV8)

EBV and HHV8 are both recognised as oncogenic or cancer-inducing viruses whereas CMV has immunomodulatory properties. The Herpesviruses all exhibit the phenomenon of latency where the virus lies dormant after initial infection and reactivates causing a variety of clinical presentations during periods of altered immunity.

15.2.4.1 Herpes Simplex Type 1 and 2

HSV-1 and HSV-2 cause oral and genital ulceration but occasionally cause disseminated infection, particularly in the immunocompromised host. As a rule, HSV-1 causes 80% of oral infection and 20% of genital ulceration whereas HSV-2 is responsible for 20% of oral infection and 80% of genital infection. Infection may be primary, which can be severe, or reactivation from the site of latency in the neurons. The incidence of prior infection increases with age and varies according to socio-economic status, race and country of residence, with 50–96% of the general population having antibodies to HSV-1 and therefore at risk of reactivation [76, 77].

The most common manifestation of HSV-1 and HSV-2 in lung transplant recipients are mucocutaneous ulcers involving either the oral cavity or genital tract. Less commonly, pneumonia, hepatitis or encephalitis may result from viral reactivation.

The introduction of acyclovir in the 1980s marked the first highly effective anti-viral therapy and resulted in a significant reduction in morbidity and mortality from post-transplant HSV infections. The incidence of HSV-1 and HSV-2 has fallen dramatically since ganciclovir, an anti-CMV agent with activity against HSV, has been widely used as prophylaxis against CMV infection in the transplant setting.

Treatment

- acyclovir/valaciclovir/famciclovir
- suppressive therapy may be appropriate for frequent recurrences
- the development of resistant virus is uncommon

Infection Control

Standard precautions apply to patients with active HSV lesions; however contact precautions may apply in healthcare settings if lesions are not covered and for 3 days post initiation of treatment or until crusting occurs. If HSV is disseminated contact precautions required until lesions are dried and crusted. Immunocompromised staff should not care for patients. Infected staff in high risk clinical areas require urgent review for leave/ redeployment.

15.2.4.2 Varicella Zoster Virus

VZV primary infection results in chicken pox. The virus then lays dormant in neural tissue prior to reactivating as shingles, in particular during periods of immunosuppression. Shingles may follow a single nerve pathway or dermatome, may involve multiple dermatomes or the virus may disseminate involving a variety of organs including the liver, lungs, brain and spinal cord.

Approximately 90% of adults in Australia and the United States have antibody against VZV indicating prior infection. However, the incidence of antibody positivity varies between geographic areas with the incidence lower in tropical regions. Patients who do not have antibodies to VZV should be considered for vaccination prior to transplantation. As the vaccine is a live vaccine it should not be administered after transplantation as there is insufficient safety data in immunosuppressed transplant recipients [78].

Treatment

- high dose acyclovir/valaciclovir/famciclovir
- ganciclovir
- potential role for zoster immune globulin

Infection Control

Contact precautions for patients with active VZV lesions and for 3 days post-initiation of treatment or until crusting occurs.

15.2.4.3 Epstein Barr Virus

EBV is the causative agent of infectious mononucleosis (glandular fever), a common infection in the general population. It is also associated with the development of two cancers, nasopharyngeal carcinoma and Burkitt's lymphoma. Like other herpesviruses, EBV is associated with latent infection; in the case of EBV, B lymphocytes in the blood and lymphoid tissue which sets the scene for lymphoproliferative disorders.

In the setting of transplantation, EBV has a clearly established role in the pathogenesis of post transplantation lymphoproliferative disorder (PTLD) with up to 90% of cases associated with EBV latent infection. PTLD is a spectrum of disease caused by the abnormal proliferation of lymphoid cells, with clinical manifestations varying from asymptomatic to tissue infiltration and/or focal masses in a variety of organs. Figure 15.9 is a PET-CT scan from a patient with PTLD and demonstrates the widespread involvement that can occur. Diagnosis is made by excisional biopsy and histological examination. High levels of EBV DNA measured by PCR in peripheral blood provide supportive evidence.

Treatment

- reduce the level of immunosuppression
- no good data to support a role for antiviral therapy (acyclovir, ganciclovir)
- immunomodulatory agents such as anti CD20 (rituximab)
- resection of localised lesions

Infection Control

No specific precautions are required.

15.2.4.4 Cytomegalovirus (CMV)

CMV infection is defined as the detection of CMV replication (usually by PCR to detect CMV DNA or RNA in plasma or whole blood) regardless of the clinical presentation or symptoms. As with other herpesviruses, CMV infection may be

Fig. 15.9 PET-CT scan of a patient with extensive PTLD (the dark areas on the scan represent deposits of EBV-related PTLD). Image courtesy of Professor Allan Glanville

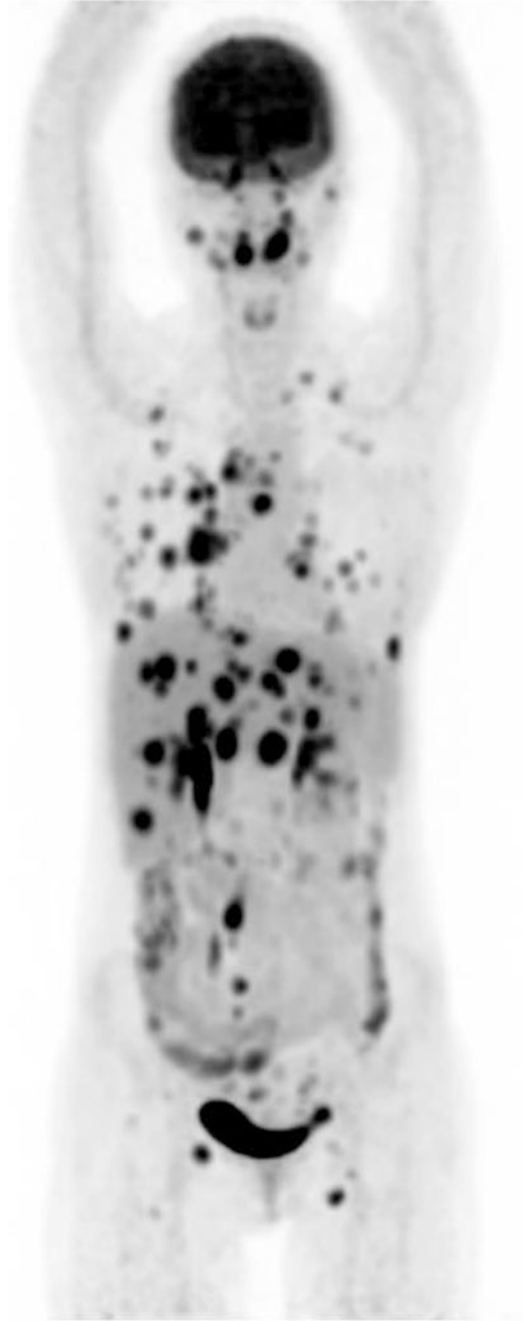
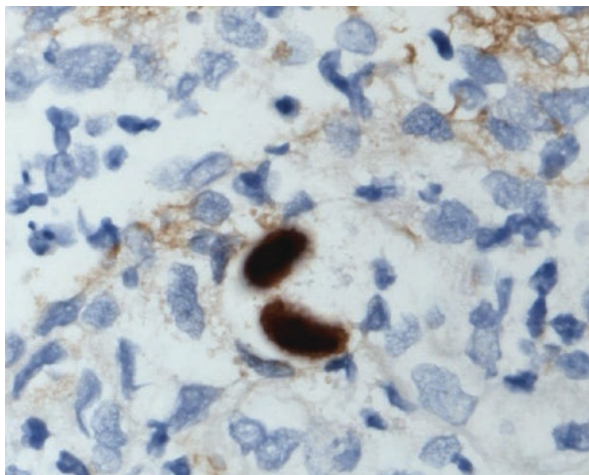


Fig. 15.10 CMV inclusion body in a gut biopsy from a patient with CMV enteritis. Image courtesy of Dr. Wade Barrett, St. Vincent's Hospital, Sydney



primary, donor-derived or reactivation of latent infection. The CMV status of donor (D) and recipient (R) is abbreviated to D+ (donor CMV seropositive), D- (donor seronegative) R+ (recipient CMV seropositive) and R- (recipient seronegative). Possible combinations include D+/R-, D-/R-, D-/R+ and D+/R+. Primary CMV infection is most likely in the setting of D+/R- whilst reactivation can occur in D-/R+ and CMV superinfection with a different strain can be seen in D+/R+.

The effects of CMV infection may be due to either direct tissue damage to a variety of organs (e.g. colitis) or indirect effects on the graft and the immune system (e.g. induce CLAD). Figure 15.10 demonstrates the 'owl's eye' appearance of CMV inclusion bodies in the bowel of a patient with CMV enteritis.

There are two approaches to the prevention of CMV disease.

- prophylaxis strategy—prescribing anti-CMV drugs for a defined period after transplantation (usually 6–12 months).
- pre-emptive therapy—treatment with anti-CMV drugs only when the plasma or blood CMV PCR becomes positive during regular monitoring

The choice of strategy varies between transplant centres and will in part be determined by the ability to rapidly and regularly perform CMV PCR on blood or plasma. In the setting of lung transplantation the prophylaxis strategy is the most frequent approach. In addition, high risk D+/R- patients are more likely to receive prolonged CMV prophylaxis.

Treatment

Despite the various approaches to prevent CMV disease, active infection occurs in up to 30% of transplant recipients [79]. Treatment options include:

- intra-venous ganciclovir
- oral valganciclovir
- CMV immunoglobulin
- reduction in immunosuppression

Treatment failure due to the development of resistant virus is well recognised and may in part be due to sub-therapeutic dosing of ganciclovir/valganciclovir. Resistance may be detected by specific testing for genetic mutations, the most common of which are UL97 and UL54.

Options to treat resistant CMV disease include alternative and experimental drugs such as:

- foscarnet
- cidofovir
- leflunomide
- brincidofovir
- maribavir
- letermovir

Infection Control

No specific infection control measures required.

15.2.4.5 Human Herpesvirus 6

HHV-6 is very common in the community with approximately 95% of the general population demonstrating serological evidence of prior infection [80]. As with other herpesviruses it remains latent after primary infection and frequently reactivates after transplantation. However the significance of reactivation is uncertain as it is not reliably associated with any specific clinical syndrome. Infection is most commonly asymptomatic but encephalitis, hepatitis, gastro-duodenitis and pancytopenia have been described. CMV prophylaxis does not appear to prevent HHV-6 reactivation [81].

Treatment

There is limited clinical treatment data available but ganciclovir, valganciclovir and foscarnet appear to have activity against HHV-6 in laboratory testing. There may be a role for reduction of immunosuppression.

Infection Control

No specific infection control measures required.

15.2.4.6 Human Herpesvirus 7

Like HHV-6, HHV-7 infection is very common in the community and reactivation can occur following transplantation. However the clinical importance of this is uncertain with no syndromes regularly associated with this virus. For this reason most laboratories do not perform PCR for HHV-7.

Treatment

There is minimal anecdotal data and no controlled trials for the treatment of HHV-7 although anti-CMV drugs such as ganciclovir, foscarnet and cidofovir may be effective.

Infection Control

There are no specific infection control procedures required.

15.2.4.7 Human Herpesvirus 8

Along with EBV, HHV-8 is an oncogenic or cancer-causing herpesvirus. Clinical manifestations include Kaposi's sarcoma (KS), body cavity lymphoma and Castleman's disease, a rare lymphoproliferative disorder. The prevalence of HHV-8 varies greatly, from 0 to 5% in North America and Northern Europe to up to 70% in regions of sub-Saharan Africa and the southern Mediterranean where the virus is endemic [82].

Previously recognized as an uncommon malignancy of elderly Mediterranean men, African children, and Ashkenazi Jews, KS became the most common neoplasm of patients with HIV infection with an incidence >20,000 times that of the general population [83]. Seropositive transplant recipients have a small risk of reactivation of latent virus and donor-derived infection has been infrequently reported. KS is the most common manifestation and body cavity lymphoma and Castleman's disease are rare presentations of HHV-8.

Diagnosis of HHV-8 reactivation is generally by PCR whilst KS, body cavity lymphoma and Castleman's disease require histological diagnosis.

Treatment

Antiviral drugs do not appear to be clinically effective. The mainstay of treatment includes:

- reduction of immunosuppression or reversal of underlying immune deficiency
- chemotherapy
- rituximab for Castleman's disease

Infection Control

No specific infection control procedures required.

15.2.4.8 Respiratory Viruses

Respiratory viruses circulate within the community with seasonal and geographic variability. Serious complications are uncommon in the non-immunocompromised host but in the setting of lung transplantation respiratory virus infections are associated with secondary bacterial infections, acute rejection and chronic graft dysfunction. Increased susceptibility to respiratory viruses in lung transplant recipients is multifactorial and includes immunosuppression, impaired cough reflex, poor mucociliary clearance, altered lymphatic drainage and the direct exposure of the lung allograft to the environment.

A prospective study compared 50 lung transplant recipients with respiratory virus infection with 50 uninfected recipients and demonstrated that those with a respiratory virus infection had a greater risk of acute rejection, bronchiolitis obliterans syndrome and death [84].

Important respiratory viruses include:

- respiratory syncytial virus (RSV)
- influenza
- parainfluenza
- human metapneumovirus (hMPV)
- coronavirus/rhinovirus
- adenovirus

Respiratory viral infections are common in lung transplantation. A recent study of 112 lung transplant recipients over a 2 year period found an infection rate of 19.3% with 61% having one or more viral infections over the study period [85]. Asymptomatic carriage was uncommon (<10%) and was mainly associated with coronavirus/rhinovirus. The hospitalisation rate was 50% for influenza and parainfluenza and 16.9% for other viruses.

Infection control precautions for respiratory viruses include droplet precautions (single room, mask, gown and gloves for room entry) until asymptomatic and hand hygiene as per 5 moments. Staff should not come to work if they have a respiratory illness and unwell visitors should not be allowed patient contact. Chemoprophylaxis may be administered to patients following exposure where appropriate (see below for specific viruses).

Many microbiology laboratories perform a respiratory pathogen PCR diagnostic panel which includes the common respiratory viruses such as Influenza A, Influenza B, Enterovirus, Rhinovirus, Coronavirus, hMPV, Parainfluenza, Adenovirus, RSV and non-viral organisms including *Bordetella pertussis*, *Bordetella parapertussis*, *Mycoplasma pneumoniae* and *Pneumocystis jirovecii*. Testing is generally performed on nose and throat swabs (both required), a nasopharyngeal aspirate or bronchial washings.

15.2.4.9 Respiratory Syncytial Virus

Like many respiratory viruses, RSV is seasonal with a winter predominance. In healthy adults RSV is usually associated with mild, self-limited infection but in lung transplant recipients RSV can cause bronchiolitis, pneumonia and respiratory failure with a significant acute mortality up to 20% [86] and decline in lung function associated with the subsequent development and progression of bronchiolitis obliterans syndrome (BOS) [87]. RSV has also been associated with acute rejection but a recent prospective study failed to confirm this finding [85].

Treatment

Ribavirin is a nucleoside analogue with broad range of activity against many RNA viruses and, despite a lack of randomised trial data, is the cornerstone of treatment for RSV. Ribavirin can be administered in 3 ways:

- oral
- intra-venous
- aerosolised (negative pressure room and specific equipment required)

Advice regarding administration and dosing regimen should be sought as ribavirin has significant toxicity (primarily haematological), is teratogenic and has a very long half-life.

Infection Control

Standard and droplet precautions required. Patients should be managed in a single room.

15.2.4.10 Influenza

Influenza is a seasonal virus with the greatest incidence of infections during the winter months, although it is detectable year-round in the community. The two most frequent types are influenza A followed by influenza B. Influenza viruses characteristically undergo ‘antigenic drift’ or minor annual changes in the surface glycoprotein that allows reinfection due to inadequate immunity. Every 10 years or so ‘antigenic shift’ occurs secondary to the reassortment of genes between species. Major outbreaks of influenza occur at this time as there is little immunity present in the community.

The rate of influenza is higher after lung transplantation than other solid organ transplants [88] and may be community acquired, nosocomial or donor-derived infection. Complications such as viral and bacterial pneumonia occur more frequently than in the general population. Annual vaccination of transplant recipients,

transplant candidates and their families is strongly recommended although the antibody response may be impaired in immunosuppressed patients [89].

Treatment

Treatment should be initiated in all transplant patients with suspected or proven influenza and ceased if an alternative diagnosis is made. Therapeutic options include:

- oseltamivir (oral, influenza A and B)
- zanamivir (inhaled, influenza A and B)
- amantadine (oral, influenza A only)
- rimantadine (oral, influenza A only)

Chemoprophylaxis should be offered to patients known to be exposed to influenza virus either in the hospital or the community setting.

Infection Control

Droplet and standard precautions for duration of symptoms or until 3 days of active influenza treatment.

15.2.4.11 Parainfluenza Viruses

Parainfluenza viruses (PIV) consist of a group of 4 serotypes, PIV 1–4, which circulate year-round in the community and cause a variety of clinical presentations from the ‘common cold’ to bronchiolitis and pneumonia. PIV 3 has been associated with large hospital outbreaks of infection due to person-to-person transmission, especially in haematology wards, with mortality rates up to 30% in outbreaks [90]. In lung transplant recipients PIV infection can lead to loss of lung function and bronchiolitis obliterans syndrome. Figure 15.11 shows extensive interstitial pneumonia in a patient with severe PIV infection.

Treatment

There are no randomised studies of antiviral therapy. However there are reports published primarily in the haematology setting suggesting ribavirin, either orally or intravenously administered, may be effective treatment. A small single centre study of RSV and PIV in lung transplant recipients indicated that 33% of lung transplant patients with lower respiratory tract paramyxoviral infections who were treated with inhaled ribavirin died or did not return to baseline lung function [91].

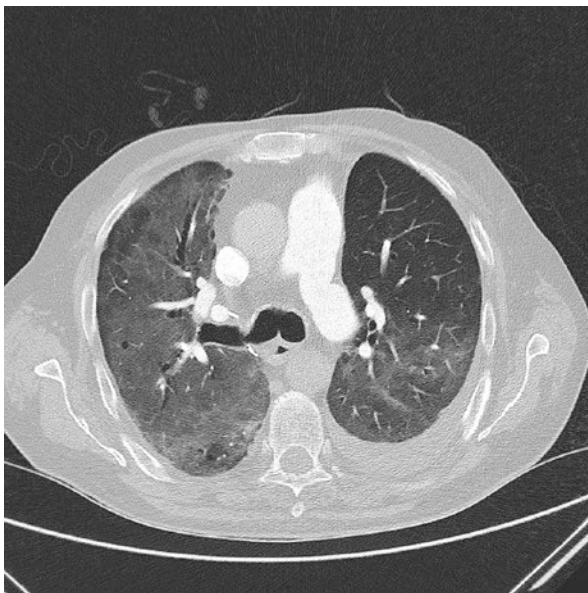


Fig. 15.11 CT scan of a patient with severe PIV infection. Courtesy of Professor Allan Glanville

Infection Control

Droplet and standard precautions.

15.2.4.12 Human Metapneumovirus (hMPV)

hMPV was first described as recently as 2001 and has been increasingly recognised as a seasonal (predominantly late winter) respiratory pathogen causing both upper and lower respiratory tract infection. About 100% of school aged children have antibodies to this virus indicating the widespread nature of hMPV [92].

HMPV is closely related to RSV and in lung transplant recipients is thought to result in graft dysfunction. However there was mainly anecdotal data to support this until a recent review by Dosanjh [93] who conducted a literature search to identify cases of both hMPV and allograft rejection within 6 months of the initial infection. 1007 lung transplantation recipients, with a total of 2883 samples, were identified. Of these, 57 had hMPV without co-infection with other agents. The results of the study indicated that 35% of acute hMPV infections without co-infection were associated with acute cellular rejection within 3 months and 9.4% of the cases subsequently developed chronic allograft dysfunction/bronchiolitis obliterans syndrome suggesting that hMPV is an important pathogen in the lung transplant setting.

Treatment

Ribavirin has been shown to have activity against hMPV in vitro [94] and in animal models of infection [95]. However no human studies in hMPV infection have been performed and the use of ribavirin remains controversial. Case reports have supported ribavirin therapy with concomitant intravenous immunoglobulins (IVIG) for improving symptoms.

Infection Control

Droplet and standard precautions.

15.2.4.13 Coronavirus/Rhinovirus

Coronavirus and rhinovirus are the most frequent cause of the ‘common cold’ in the general population. However in immunocompromised patients these viruses can cause pneumonia which may be fatal, particularly in bone marrow transplant recipients [96]. Persistent rhinovirus infection associated with graft dysfunction has been described in lung transplant recipients [97].

Treatment

There are no specific treatment options available. Decreasing immunosuppression may have a role but there is little data to support this.

Infection Control

Droplet and standard precautions.

15.2.4.14 Adenovirus

Adenoviruses consist of a large group of DNA viruses with over 50 types known to cause a variety of illnesses including gastroenteritis, encephalitis, hepatitis, haemorrhagic cystitis, upper and lower respiratory infections and conjunctivitis. In immunosuppressed patients adenovirus infection can develop at any time after transplantation and is associated with significant morbidity and mortality rates up to 75% [98]. Adenovirus infection has been reported to be associated with organ rejection following cardiac and renal transplantation. Bridges et al. reported 4 of 9 patients with adenovirus infection alone developed bronchiolitis obliterans syndrome and graft failure [99].

Treatment

There are no randomised studies of treatment. Anecdotal case reports suggest cidofovir may have a role but results are mixed.

Infection Control

Droplet and standard precautions.

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