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Narrative review

Is hospital-acquired pneumonia different in transplant recipients?

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ABSTRACT

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are serious complications in transplant patients. The aim of this review is to summarize the evidence regarding nosocomial pneumonia in transplant recipients, including HAP in non-ventilated patients and VAP, and to identify future directions for improvement.A comprehensive literature search in the PubMed/MEDLINE database was performed. Articles written in English and published between 1990 and November 2018 were included.

HAP/VAP in transplant patients usually occurs early post-transplant, particularly during neutropenia in haematopoietic stem cell transplant recipients. Bacteria are the leading cause of nosocomial pneumonia for both immunocompetent and transplant recipients, being Gram negative organisms, and especially *Pseudomonas aeruginosa*, highly prevalent. Multidrug-resistant bacteria are of special concern. Pneumonia in the transplant setting may be caused by opportunistic pathogens, and the differential diagnosis needs to be extended to other non-infectious complications. The most relevant opportunistic pathogens are *Aspergillus fumigatus*, *Pneumocystis jirovecii* and cytomegalovirus. Nevertheless, they are an exceptional cause of nosocomial pneumonia, and usually occur in severely immunosuppressed patients not receiving antimicrobial prophylaxis. Performing bronchoalveolar lavage may improve the rate of aetiological diagnosis, leading to a change in therapeutic management and improved outcomes. The optimal length of antibiotic therapy for bacterial HAP/VAP has not been well defined, but it should perhaps be longer than in the general population. Mortality associated with HAP/VAP is high.

HAP/VAP in transplant patients is frequent and is associated with increased mortality. There is room for improvement in gaining knowledge about the management of HAP/VAP in this population. **C. Gudiol, Clin Microbiol Infect 2019;25:1186**

Introduction

Pneumonia involving transplant patients is a frequent nosocomial complication, with increased morbidity and mortality. Unlike in the general non-immunosuppressed population, the aetiology of pneumonia in this setting is much more diverse, the differential diagnosis needs to be extended to other non-infectious complications, and the possibility of co-infections also needs to be taken into account. Despite the existing challenges in the management of transplant patients with nosocomial pneumonia, information regarding this potentially severe complication is scarce. In this regard, the most recently published international guidelines for the management and prevention of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) excluded this patient population [1–3]. Moreover, in the scenario of increasing multidrug antibiotic resistance, these patients were also excluded from trials evaluating the efficacy of the new beta-lactam plus beta-lactam inhibitor combinations, such as ceftazidime/avibactam and ceftolozane/tazobactam, for the treatment of nosocomial pneumonia [4,5].

The aim of this review is to summarize the existing evidence regarding nosocomial pneumonia occurring in adult transplant recipients, including HAP in non-ventilated patients and VAP, and to identify future directions for improvement and the gaps to be filled

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by new research. Nosocomial pneumonia has been classified in two categories: HAP and VAP. HAP is defined as a pneumonia not incubating at the time of hospital admission and occurring 48 hr or more after admission. VAP is defined as a pneumonia occurring >48 hr after endotracheal intubation [1]. To this end, we conducted a comprehensive literature search in the PubMed/MEDLINE data base, of studies written in English published between 1990 and November 2018, using the following search terms: hospital-acquired pneumonia, nosocomial pneumonia, ventilator-associated pneumonia, transplantation, transplant patients, haematopoietic stem cell transplant, solid organ transplant and nosocomial infection.

Epidemiology

HAP and VAP involving the general population represent one of the most common hospital-acquired infections, accounting for up to 22% of all infections acquired in this setting [6]. The incidence of nosocomial pneumonia has been reported to range from five to more than 20 cases/1000 hospital admissions for HAP [1], and from two to 16 episodes/1000 ventilator-days for VAP [7]. Of note, these data come from studies that included transplant patients, although information focused specifically on this severely immunosuppressed population is scarce.

Transplant patients may be particularly susceptible to developing nosocomial pneumonia. In this line, after bloodstream infection, pneumonia is the second most frequent nosocomial infection in haematopoietic stem cell transplant (HSCT) recipients [8–11]. Pneumonia is particularly frequent during neutropenia, and is associated with increased morbidity and mortality. Most of the published reports focusing on pneumonia after HSCT include episodes acquired both in the community and nosocomial setting, and thus it is difficult to gather accurate information regarding episodes acquired only in the hospital. Nevertheless, episodes occurring during neutropenia or early after transplant (<100 days after transplant) are likely to be acquired in the nosocomial setting. In addition, in the late post-transplant period, the majority of cases of pneumonia occur as opportunistic infections in hospitalized patients with graft versus host disease (GVHD) and severe immunosuppressive therapy.

The incidence of pneumonia in HSCT patients has been reported to range from 15% to 30% [10,12–14], and was found to be higher during neutropenia in a prospective study (11.9 episodes per 1000 neutropenic-days vs. 1.8 per 1000 non-neutropenic days) [9]. In addition, the results of the ONKO-KISS study showed that the rate of nosocomial pneumonia was higher in allogeneic than in autologous recipients (11.0% vs. 5.4%) [15], and that it may be particularly high in those receiving an unrelated donor allogeneic transplantation [16]. A nationwide prospective study referring to data collected by the Spanish Research Network of Transplants (RESITRA) involving 427 allogeneic (allo)-HSCT recipients reported a global incidence of pneumonia of 52.2 episodes per 100 allo-HSCT/year. The median time of diagnosis after transplantation was 66.5 days, and the maximum incidence occurred in the first month post transplant (8.6 episodes per 100 allo-HSCT) [17]. In this study, acute or chronic GVHD and prior HSCT were found to be risk factors for pneumonia.

In solid organ transplant (SOT) recipients, nosocomial pneumonia usually occurs early after transplant, particularly in the post-surgical period [18–20]. The incidence of nosocomial pneumonia in SOT recipients varies widely among type of organ, with pulmonary transplant (PT) recipients being at greatest risk, with an incidence of up to 30% [21,22]. Impaired mucociliary clearance, continuous exposure to the environment, impaired cough mechanisms, the need for prolonged mechanical ventilation and gastroparesis have been identified as risk factors for nosocomial pneumonia in PT recipients [23–26]. The incidence of nosocomial pneumonia in other SOT recipients has been reported to be about 15% for heart transplant (HT) recipients [27], from 5% to 48% for liver transplant (LT) recipients [28–32] and from 4.5% to 16% in kidney transplant (KT) recipients [34,34]. Interestingly, a study comparing LT recipients with non-transplant surgical ICU patients suggested that LT itself did not increase the risk of VAP [28].

HAP/VAP in the general population increases the duration of hospitalization and healthcare costs, and impairs patients' outcomes [35–38]. In this regard, mortality due to nosocomial pneumonia is high, ranging from 20% to 50% for ventilated patients. Nevertheless, the mortality directly associated with VAP is controversial, and the most recently published data report an estimated attributable mortality of 10–13% [39,40]. Even though HAP has been considered to be less severe than VAP, serious complications have been described in patients with this condition, particularly among those who develop HAP in the intensive care unit, in whom the mortality rate may be similar to that in those with VAP [41,42].

Current data regarding the impact of nosocomial pneumonia in HSCT recipients is scarce. However, attributable mortality in these patients may be higher than in non-transplanted patients. In this line, the data available from the RESITRA study showed an overall mortality of 46.3% in allo-HSCT, with 66% of these deaths considered to be related to pneumonia [17].

The reported mortality rates of nosocomial pneumonia in SOT recipients have been as high as 50–70% [30,43–46]. In PT recipients mortality varies from 14% to 40% depending on whether HAP or VAP is considered [25,47]. Moreover, lung rejection and reduced 1-year survival have been reported [22,48]. Mortality rates of nosocomial pneumonia in other SOT recipients range from 26% to 55.6% in HT recipients [49,50], from 22% to >50% in LT recipients [28,31,32,51], and are about 35% in KT recipients [33].

Aetiology

Bacterial pneumonia is the leading cause of nosocomial pneumonia both in the general non-immunosuppressed population and in transplant patients. In addition to the usual colonizing microorganisms of the respiratory tract, such as *Streptococcus pneumoniae*, *Branhamella catharralis* and *Staphylococcus aureus*, *Pseudomonas aeruginosa* and other Gram-negative bacilli are also an important cause of HAP/VAP in both populations. Importantly, multidrug resistance has been increasingly reported among organisms causing nosocomial pneumonia [52–55]. Nevertheless, unlike the general non-immunosuppressed population, pneumonia in the transplant setting may sometimes be caused by opportunistic pathogens, and the differential diagnosis needs to be extended to other non-infectious complications, which sometimes coexist with an active infection [56]. Regarding this issue, patients with profound and prolonged neutropenia and those with acute GVHD or graft rejection are at risk for developing opportunistic infections, such as fungal and viral infections and *Pneumocystis jirovecii* pneumonia (PCP).

For HSCT patients, the most reliable data regarding aetiology was obtained by the RESITRA study, in which a microbiological diagnosis was made in 64.3% of all cases of pneumonia [17]. Overall, bacterial pneumonia (44.4%) was the leading aetiology, followed by fungal (29.2%) and viral (19.4%). However, pneumonias of unknown aetiology predominated in the first month after transplantation, and moulds were the earliest pathogens, followed by viruses, Gram-negative bacilli and Gram-positive cocci. The most frequent bacterial isolates were *Escherichia coli, P. aeruginosa* and *S. pneumoniae*. Pneumonia due to *S. pneumoniae* is frequent in HSCT recipients, but usually occurs late after transplant in the community setting, particularly in non-vaccinated patients [57,58]. Gram negative organisms, and particularly *P. aeruginosa,* were found to

be the leading cause of nosocomial bacterial pneumonia in some series [8,9,12,59]. *Acinetobacter baumannii* may also be a frequent cause of nosocomial pneumonia in transplant patients in some hospitals, particularly SOT recipients, and infection due to multidrug-resistant/extremely drug-resistant (MDR/XDR) strains is associated with poor outcome [59,60]. Pneumonia due to *Stenotrophomonas maltophilia* is not common, but in some cases, may give rise to pulmonary haemorrhage, leading to a fatal outcome [61–63]. Prior carbapenem use is the most important risk factor associated with *Stenotrophomonas maltophilia* infection [64,65].

In SOT recipients, nosocomial pneumonia is mainly caused by Gram negative organisms, the most common pathogens being *P. aeruginosa*, Enterobacteriaceae and *S. aureus*, frequently with multidrug-resistant (MDR) profiles [21,22,24–26,31–33,46,66]. Of note, infection due to MDR microorganisms is associated with higher rates of recurrence and mortality [67–70]. In PT recipients, lung bacterial infections can be transmitted from the donor lung and cause pneumonia in the post-surgical period. Notably, a low percentage of pulmonary infections are transmitted to the recipient if appropriate antibiotic prophylaxis is given [71].

Rarely, *Legionella* spp. can cause outbreaks in centres with an inadequate water surveillance programme [72,73]. Of note, non-pneumophila species are more frequently involved than in the general population [74–76], and atypical presentations are more frequently observed in this population [72–76].

Although very infrequent, in transplant patients with nosocomial pneumonia, opportunistic bacteria should be considered late after transplant, and mainly in patients who are severely immunosuppressed due to graft rejection or GVHD. Opportunistic bacteria reported to cause pneumonia in transplant recipients include *Nocardia* spp. [77,78] mycobacterial infections and, less frequently, *Rhodococcus* spp. [79]. *Nocardia* infections may also involve the central nervous system in immunosuppressed patients, with mortality rates reaching up to 60% [80,81]. Nocardiosis has been described in patients receiving low-dose cotrimoxazole prophylaxis for PCP, although some of the patients with nocardiosis were receiving prophylaxis with pentamidine or atovaquone [77,78,80].

Although the incidence of mycobacterial infections in transplant recipients is higher than in the general population [24,82,83], they represent a rare cause of nosocomial pneumonia. However, cases of donor transmission in SOT have been reported to develop early in the post-transplant hospital setting, especially in PT [84].

HSCT recipients are at particularly high risk of developing invasive fungal infections (IFIs), especially during neutropenia early post transplant, and mainly in those patients not receiving primary prophylaxis. Invasive aspergillosis is by far the most common cause of fungal pneumonia in HSCT and in SOT recipients, mainly in PT recipients, followed by HT recipients [85–89]. Although most cases of pulmonary aspergillosis in SOT develop after the first month after transplantation, some cases may develop in the peritransplant period [90]. Of note, infections due to cryptic species of azole-resistant *Aspergillus* spp. have been described in the last years, which may compromise the effectiveness of the treatment [91,92]. Cryptococcal infection is a rare cause of pneumonia in SOT recipients and its treatment may be associated with immune reconstitution syndrome (IRIS), which may complicate the differential diagnosis and management. Cryptococcosis is usually a late infection. When cryptococcosis is detected very early, transmission with the allograft should be considered [93,94].

The risk of developing invasive aspergillosis depends on several factors, such as the local epidemiology, the use of broad-spectrum antifungal prophylaxis, and some other factors related to the host (neutropenia, type of transplant, immunosuppression state, cytomegalovirus coinfection, renal failure, *Aspergillus* spp. colonization, hypogammaglobulinaemia and acute and chronic graft rejection) [82,95–97]. Recently, new risk factors for aspergillosis have been reported, such as the use of tyrosine kinase inhibitors and influenza virus infection [98,99]. Mortality due to invasive aspergillosis in transplant recipients is high, ranging from 30% to 70% [89,90].

The current incidence of PCP in the era of widespread prophylaxis with cotrimoxazole is low [19,100]. However, PCP may also develop in hospitalized patients not receiving cotrimoxazole prophylaxis in situations of increased immunosuppression, or in those receiving second-line (inhaled pentamidine or atovaquone) prophylaxis [100–103]. Of note, PCP in transplant recipients presents with more severe clinical presentations and higher mortality compared to HIV + patients. Interestingly, nosocomial outbreaks of PCP have been reported in transplant recipients, raising the possibility of person-to-person transmission, although controversy exists regarding this issue [104–106]. This finding suggests the need for environmental control policies in patients with PCP.

Endemic fungi as *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Coccidioides* spp. are extremely rare causes of pulmonary infection in the nosocomial setting in transplant patients, and may be related to donor transmission or reactivation of latent infection [107].

In transplant patients, the use of a pre-emptive approach or universal prophylaxis in high-risk patients has reduced the incidence of cytomegalovirus (CMV) pneumonia [17,108–112]. Importantly, CMV pneumonitis has been reported in the hospital setting in transplant recipients in situations of especially increased immunosuppression without prophylaxis [108,112–114]. CMV pneumonia in this population could be associated with bacterial or fungal coinfections.

Other viruses than can cause nosocomial pneumonia in transplant patients are the influenza virus and other respiratory viruses [115–117]. Nevertheless, they usually produce infection in the community setting, or during a nosocomial outbreak. Herpes simplex virus can also cause VAP, due to aspiration of oropharyngeal secretions, or HAP, due to reactivation of the virus triggered by immunosuppression [118–121].

Disseminated infection and/or pneumonia due to toxoplasmosis in the transplant setting are extremely rare. However, and due to the dramatically increased mortality, a high index of suspicion is needed in patients at risk without prophylaxis, particularly in allo-HSCT recipients with GVHD, and seronegative SOT recipients, especially HT [122–125].

Diagnosis

The differential diagnosis of nosocomial pneumonia in transplant recipients includes congestive heart failure, non-cardiogenic pulmonary oedema, drug-induced and radiation-induced toxicity, malignancy, pulmonary haemorrhage, engraftment syndrome, IRIS and cryptogenetic organizing pneumonia. These non-infectious complications should be ruled out with the combination of a patient's detailed medical history and the use of imaging and specific diagnostic tests.

Transplant patients with nosocomial pneumonia should undergo a chest computed tomography (CT) scan in order to detect less evident lesions or infiltrates, to better localize them and to detect complications [126]. Although specific radiological patterns may suggest certain aetiologies [127,128], atypical presentations are frequent, and imaging should not be a surrogate for microbiological diagnosis.

Blood cultures should be performed in all transplant patients with nosocomial pneumonia, and analysis of the sputum should be performed whenever possible. Nevertheless, the diagnostic yield of sputum samples in this setting is usually very poor, especially due to poor-quality samples and the use of antibiotics prior sample collection. In the general population, the IDSA/ATS guidelines

Table 1
Suggested computed tomography imaging patterns

Radiological pattern	Possible aetiology
Diffuse ground glass opacities	*Pneumocystis jirovecii*
	Viral pneumonia
Alveolar consolidation. Air bronchogram	Bacterial pneumonia
Abscesses, cavitation	Anaerobic bacteria
	Staphylococcus aureus
	Pseudomonas spp.
	Nocardia spp.
	Mycobacterium tuberculosis
	Aspergillosis and other filamentous fungi
Nodules with peripheral ground glass (halo sign)	Aspergillosis and other filamentous fungi
Miliary pattern	Miliary tuberculosis
Tree in bud	Aspergillosis[a]
	Respiratory viruses (respiratory syncytial virus and metapneumovirus)
	Mycobacterium tuberculosis

[a] In non-neutropenic patients following non-angionvasive bronco/airway-invasive infection.

recommend performing non-invasive procedures with semi-quantitative cultures in order to obtain respiratory samples for microbiological diagnosis, whereas the ERS guidelines recommend that invasive procedures should also be considered [1,2]. In transplant patients, the possibility of performing invasive procedures may be limited due to the underlying condition and/or the presence of cytopenias. However, performing bronchoalveolar lavage and protected-specimen brushing has been shown to improve the rate of the aetiological diagnosis of severely immunosuppressed transplant patients, leading to a change in their therapeutic management and improved outcomes [27,44,46,129,130]. In some selected patients with difficulties in diagnosis and/or unfavourable evolution it may be necessary to perform transbronchial lung biopsy or open lung biopsy. Recently, molecular methods such as PCR techniques have been increasingly used in the diagnostic armamentarium, which may improve the diagnostic yield when used in combination with the standard techniques [131,132].

Galactomannan monitoring is only useful in HSCT recipients who do not receive antimould prophylaxis [133]. In the remaining patients, galactomannan and (1-3)-β-D-glucan should be determined only if there is clinical suspicion of invasive aspergillosis, cryptococcosis or PCP. Monitoring of CMV PCR in the blood is recommended in high-risk transplant patients who undergo a pre-emptive treatment approach (see Treatment and prevention).

Tables 1 and 2 show the suggestive CT imaging patterns and the microbiological diagnostic procedures recommended for each aetiology.

Treatment and prevention

Prompt empirical antibiotic therapy based on the local epidemiology should be administered to transplant recipients with suspected VAP/HAP. In these patients, therapeutic decisions require consideration for MDR organisms and drug interaction with immunosuppressive agents. The initial empirical antibiotic therapy of transplant patients with HAP/VAP should not differ significantly from the management of the general population. Importantly, the local epidemiology has to be taken into account when choosing the empirical antibiotic treatment [1]. Therefore, the empirical antibiotic therapy should include coverage against *P. aeruginosa* and other Gram-negative bacilli, and also against *S. aureus* (particularly in SOT recipients) [134,135]. An agent active against methicillin-resistant *S. aureus* (MRSA) such as vancomycin or linezolid has been suggested to be included in the empirical treatment for previously colonized recipients or in those treated in units where >10–20% of *S. aureus* isolates are methicillin-resistant [1,134]. In severely ill patients, and particularly in centres with a high rate of multidrug resistance among Gram negative organisms, the

Table 2
Diagnostic techniques

Diagnostic procedure	Test types	Clinical examples
Sputum	Gram stain and culture	Bacterial pneumonia
	Direct fluorescent antibody	*Aspergillus* spp. and other filamentous fungi
	PCR	*Legionella* spp.
	Ziehl–Neelsen stain	*Nocardia* spp.
	Modified Ziehl–Neelsen or Kinyoun acid fast	*Mycobacterium tuberculosis*
		Non-tuberculous mycobacteria
		Pneumocystis jirovecii
Nasopharyngeal swab	PCR (single or multiplex)	Influenza and other respiratory viruses
Bronchial aspirate or Bronchoalveolar lavage	Gram stain and culture	Bacterial pneumonia
	Mycological culture	*Aspergillus spp.* and other filamentous fungi
	Ziehl–Neelsen stain	*P. jirovecii*
	Modified Ziehl–Neelsen or Kinyoun acid fast	Cytomegalovirus Influenza and other respiratory viruses
	PCR	*Nocardia* spp.
	Direct fluorescent antibody	*Mycobacterium tuberculosis*
	Galactomannan	*Toxoplasma gondii*
Blood sample	Culture	Bacterial pneumonia
	PCR	Cytomegalovirus
		Toxoplasma gondii
Urine	Soluble antigen testing	*Streptococcus pneumoniae*
		Legionella pneumophila serogroup 1
Fungal serum markers	Galactomannan, (1-3)-β–D-glucan	*Aspergillus* spp.
	Cryptococcal antigen	*P. jirovecii*
		Cryptococcus spp.

Table 3
Antimicrobial prophylaxis for the most common opportunistic pathogens causing nosocomial pneumonia in transplant recipients

Pathogen	Recommended	Alternate	Duration	Comments
Solid organ transplant recipients				
Aspergillosis	Liver: High risk LT recipients Echinocandin	Intravenous lipidic formulations of AmB Voriconazole	2–4 weeks or until resolution of risk factors	High-risk LT recipients: Retransplantation, fulminant hepatic failure, MELD ≥30 renal failure, MELD score 20–30, choledochojejunostomy, high transfusion requirement, early reintervention
	Lung or lung/heart: all recipients or guided prophylaxis determined by the presence of risk factors Nebulized Amphotericin B lipid complex	Intravenous lipidic formulations of AmB Voriconazole	Indefinite or for a minimum of 12 months; or guided prophylaxis	Risk factors: Induction with alemtuzumab or thymoglobulin, acute rejection, single-lung transplant *Aspergillus* colonization pre-transplant or during first year post-transplant, and acquired hypogammaglobulinaemia
	Heart: High risk HT recipients Voriconazole, posaconazole	Itraconazole Echinocandins Intravenous lipidic formulations of AmB	Determined by the presence of risk factors, minimum 4 months	High-risk heart transplant recipients: acute rejection, haemodialysis, re-exploration after transplantation, heavy Aspergillus spp. airway colonization
Cytomegalovirus	All SOT D−/R− monitoring for clinical symptoms Kidney, liver D+/R−: 3-6 months of VGCV or pre-emptive therapy D+/R+: 3 months of VGCV or pre-emptive therapy Pancreas, heart D+/R−: 3–6 months of VGCV D+/R+: 3 months of VGCV or pre-emptive therapy Lung D+/R−: 6–12 months of VGCV D+/R+: minimum 6 months of VGCV Intestinal D+/R− minimum 6 months of VGCV D+/R+: 3-6 months of VGCV			
Pneumocystis jirovecii	80 mg TMP/400 mg SMX or 160 mg TMP/800 mg SMX by mouth (single or double strength), daily or three times a week	Dapsone Atovaquone Aerosolized pentaminidine Clindamycin plus pyrimethamine	3–12 months	Prophylaxis should be reinitiated to patients with graft rejection, recurrent CMV infection, prolonged corticosteroid therapy or prolonged neutropenia. Longer durations should be considered for lung and small bowel transplant patients, previous PCP or chronic CMV disease
Mycobacterium tuberculosis	Isoniazid (300 mg/day), with oral pyridoxine 25–50 mg daily for 6–9 months If possible before transplant. If contraindicated (liver transplant candidates) after transplant	Isoniazid plus rifampicin for 3 months Rifamycins for 4–6 months Fluoroquinolones		Treatment of latent TB infection should be provided to patients with a positive tuberculin skin test and/or a positive IGRA, a history of untreated TB or chest radiograph findings compatible with untreated TB, and/or a history of contact with a patient with active TB
Haematopoietic stem cell transplant recipients				
Aspergillosis	Posaconazole, voriconazole	Itraconazole, micafungin, caspofungin, aerosolized L-AmB, and intravenous lipidic formulations of AmB		Allogeneic HSCT recipients during the neutropenic phase, and in those with moderate to severe GVHD and/or intensified immunosuppression
Cytomegalovirus	Pre-emptive therapy	Prophylaxis with GCV or VGCV	100 days after transplant	Most centres prefer pre-emptive therapy due to the high risk of neutropenia with the use of VGCV/GCV >100 after transplant if history of CMV reactivation, GVHD, or mismatched, cord blood or haploidentical donors
Pneumocystis jirovecii	Aerosolized pentamidine 300 mg every 3–4 weeks during neutropenia After engraftment: 80 mg TMP/400 mg SMX or 160 mg TMP/800 mg SMX by mouth (single or double strength) daily or three times a week	Dapsone (50–100 mg by mouth every day) Atovaquone (1500 mg by mouth every day, as single dose) Aerosolized pentaminidine (300 mg every 3–4 weeks) Clindamycin (up to 300 mg by mouth every day) and pyrimethamine 15 mg by mouth every day)	6–12 months	>6–12 months if GVHD or severe immunosuppression
Mycobacterium tuberculosis	Isoniazid (300 mg/day), with oral pyridoxine 25 to 50 mg daily for 9–12 months	Rifampin for 4 months Rifampin plus isoniazid for 3 months Fluoroquinolones		If possible before transplant

AmB, amfotericin B; LT, liver transplant; MELD, model for end-stage liver disease; CMV, cytomegalovirus GCV, ganciclovir; VGCV, valganciclovir; TMP, trimethoprim; SMX, sulfamethoxazole; TB, tuberculosis; GVHD, graft versus host disease.
Pre-emptive therapy involves monitoring for CMV at blood at regular intervals to detect early viral replication before infection progress to invasive disease. A positive assay triggers the initiation of antiviral therapy.

association of a second antibiotic may be considered (quinolone, aminoglycoside, colistin, fosfomycin, etc.). Nevertheless, some of these drugs may not be available in some transplant units (e.g. iv fosfomycin), and the potential nephrotoxicity of the great majority of them may limit their use. Although there is no solid evidence to recommend their use in transplant patients, the recently available drugs ceftazidime/avibactam and ceftolozane/tazobactam should be considered in patients with pneumonia due to carbapenemase-producing Enterobacteriaceae and MDR-*P. aeruginosa*, if susceptible *in vitro*. Whenever possible it is crucial to accurately target antibiotic therapy and then de-escalate antibiotics based upon microbiological results.

In the scenario of a nosocomial outbreak of legionellosis or influenza affecting the transplant unit, levofloxacin and oseltamivir should be administered empirically while waiting for microbiological confirmation.

The most recent published guidelines recommend a 7–8-day course of antibiotic therapy for patients with VAP, except for patients infected with non-fermenting Gram-negative bacilli, and for those who received initially inappropriate therapy [1,2]. However, the optimal length of antibiotic therapy in transplant patients with nosocomial pneumonia has not been addressed, but it should be probably longer than for non-immunocompromised patients, particularly when treating infections due to MDR organisms. For neutropenic patients, therapy should be maintained until resolution of the symptoms and signs of infection and microbiological eradication, and after at least 4 days of apyrexia with a minimum of 7 days of antibiotic treatment [136–138].

Table 3 details the antimicrobial prophylaxis for the most common opportunistic pathogens causing nosocomial pneumonia in transplant recipients.

Future directions for research

Management of transplant patients with nosocomial pneumonia is a challenge for physicians caring for these patients, since there are no specific guidelines for this topic, it is often difficult to reach an aetiological diagnosis, and the associated mortality remains unacceptably high.

In order to improve the management of these patients, efforts need to be made to improve knowledge regarding the current risk factors, and the optimal prevention and treatment strategies based on randomized clinical trials. Based upon these results, the development of accurate tools to identify patients at highest risk for nosocomial pneumonia would be useful in order to establish optimal preventive strategies.

The role of the currently available biomarkers should be defined in this patient population. Also, although molecular methods are increasingly being used in bronchoalveolar lavage, they still have limitations regarding standardization and sensitivity. Improvement of these techniques could help differentiate between colonization and infection.

There are no data regarding the validation of the cut-offs of conventional quantitative respiratory cultures for the immunosuppressed population. These should be addressed in future research.

Uncertainty remains regarding the role of coinfections as true pathogens in this setting. Therefore, greater understanding is needed of the physiopathology of mixed infections and their impact on diagnosis and outcomes.

Gaining knowledge on the pathogenesis of some opportunistic infections, the host immune mechanisms involved, and the inflammatory responses would facilitate the development of new tools or strategies to modulate them beneficially.

Immunosuppressed patients have been excluded from studies of novel antibiotics. Nevertheless, the need for clinical trials assessing the usefulness of these drugs in this population is mandatory.

Studies regarding the level of resistance and the mechanism of resistance of MDR organisms causing infection in transplant patients are urgently needed to improve management of patients.

The optimal length of antibiotic therapy for VAP/HAP in transplant patients has not been addressed to date. Limiting exposure to unnecessary antibiotics is crucial in the fight against antibiotic resistance. This is particularly important in immunosuppressed transplant patients who often receive consecutive cycles of broad-spectrum antibiotics.

Finally, there is still some way to go in the development of new effective and safe drugs for the prevention and treatment of the most frequent opportunistic infections, as well as for MDR bacteria that cause pneumonia in transplant patients.

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