Bacterial Pneumonias in Immunocompromised Patients

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Abstract

With the overall improvement in survival of cancer patients and the widespread use of novel immunotherapy drugs for malignant as well as nonmalignant diseases, the prevalence of immunosuppression is rising in the population. Immunocompromised patients are particularly exposed to pulmonary infections which remain a leading cause for acute hypoxic respiratory failure and intensive care unit admission. Although fungal or opportunistic infections are always a concern, bacterial pneumonia remains the most common cause of pulmonary infection, is associated with a significant mortality, and has some specificity in this population. Adequate and timely prevention, diagnosis, and management of bacterial pneumonias require knowledge about the complex interplay between host factors (type and severity of immunosuppression) and bacterial pathogenesis, to improve the outcome. We provide an overview of bacterial pneumonias in immunocompromised patients including their epidemiology, risk factors with respect to the pattern of immunosuppression, microbiological characteristics, diagnostic approach, management, and prevention.

Keywords

- pneumonia
- immunosuppression
- cancer
- bacteria
- acute respiratory failure

Epidemiology

Bacterial pneumonias in immunocompromised patients deserve a special consideration, as the population of patients with impaired immunity is growing and respiratory complications are a leading cause for their intensive care unit (ICU) admission. More than 15 million patients with a history of cancer were alive in the United States in 2016[1] and this number is expected to rise due to the combination of a growing, aging population and recent advances in treatments prolonging the life expectancy of cancer patients. About 15 to 20% of ICU patients have malignancy and acute respiratory failure (ARF) accounts for up to 60% of ICU admissions in patients with hematological malignancies[2] or solid tumors. Bacterial pneumonia in turn is the leading cause for ARF in cancer patients, accounting for approximately 30% of ICU admissions.[3,4] ►**Table 1** summarizes recent studies on immunocompromised patients with ARF that specifically reported rates of bacterial pneumonia.

Furthermore, immunosuppression is a well-known risk factor for community-acquired pneumonia; approximately 10% of patients hospitalized for community-acquired pneumonia[5] and up to 30% of those with severe hospital-acquired pneumonia requiring ICU admission have cancer.

Regarding incidence rates based on specific types of immunosuppression, approximately 20 to 30% of patients develop bacterial pneumonia after remission induction chemotherapy for acute leukemia[6] and 15% of patients do so after hematopoietic stem cell transplant (HSCT; half of the episodes occurring within the first 3 months).[7] Similarly, bacterial pneumonia is the most frequent of the respiratory complications observed in 25% of patients after chemotherapy for lymphoma.[8] A lower incidence of 5% has been reported after chemotherapy for lung cancer,[9] but data are scarce for other solid tumors. Other types of immunosuppression similarly increase the risk of developing bacterial pneumonias: human immunodeficiency virus (HIV) infection is associated with an increased incidence of bacterial

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Table 1 Recent studies involving immunocompromised patients with acute respiratory failure and specifically reporting data on bacterial pneumonia

Authors	Year	Type	Patients (*n*)	Immunosuppression	Mortality	Bacterial pneumonia (%)
Lemiale et al[76]	2015	RCT	374	All types	25.7% at day 28	45.5
Azoulay et al[3]	2017	Prospective observational	1,545	All types	44.2% in hospital	29.5
Fujiwara et al[77]	2016	Retrospective	71	Hematological malignancy	74.6% in ventilated patients with non-CPE	35.2
Lee et al[78]	2015	Retrospective	45	Hematological malignancy	62.2% in hospital	57.8
Schnell et al[79]	2013	Retrospective	424	Cancer	42% in hospital	47
Azoulay et al[52]	2010	RCT	219	Cancer	31% at day 28	39
Azoulay et al[51]	2008	Prospective observational	148	Cancer	55.4% in hospital	32.4
Azoulay et al[4]	2004	Prospective observational	203	Cancer	47.8% in hospital	29.5
Yoo et al[80]	2013	Retrospective	214	Cancer	49% in hospital	29
Azoulay et al[81]	2018	RCT	778	All types	41.3% in hospital	41.1
Mokart et al[82]	2013	Prospective observational	219	Cancer	31.1% at day 28	39
Rabe et al[83]	2004	Retrospective	30	Acute myeloid leukemia	87% in ICU	50
Depuydt et al[84]	2010	Retrospective	137	Hematological malignancy	67.9% in hospital	25.5
Rabbat et al[85]	2008	Prospective observational	121	Hematological malignancy	38% in ICU	20.7
Lemiale et al[86]	2017	RCT	353	Cancer	22.6% at day 28	43.1
Neuschwander et al[87]	2017	Retrospective	1,004	Cancer	63.7% in hospital	65.9
Decavèle et al[88]	2019	Retrospective	217	Brain tumors	47.9% in hospital	29.5

Abbreviations: CPE, cardiogenic pulmonary edema; RCT, randomized control trial.

pneumonia (8.5 cases per 100 patient-years), which accounted for 10% of hospital admissions in a prospective observational study of 600 HIV-positive patients.[10] Bacterial pneumonia is also frequent after solid organ transplantation: a cumulative incidence of approximately 30% at 18 months has been reported after lung transplant,[11] whereas approximately 10% of patients developed bacterial pneumonia within a year of heart[12] or liver transplant, lower incidence rates being reported after renal transplant (approximately 5%).[13] As immune checkpoint inhibitors are being increasingly used in oncology, authors have also investigated their impact on severe infection and have reported rates of bacterial pneumonia occurring during immunotherapy that ranged from 1.8% in patients with melanoma to 10% in patients with lung cancer.[14] Finally, long-term steroid use has been associated with increased risk of hospital admission for pneumonia.

Pathogenesis

Obstructive Pneumonia

Pneumonia downstream to a bronchial obstruction may be secondary to extrinsic compression caused by an extraluminal tumor (lymph node for instance) or to endobronchial obstruction caused by intraluminal tumor growth; neoplasms of the lung and bronchus are the most frequent cause but malignant lymphomas, tumors of the thyroid or larynx, esophageal tumors, and metastases from extrathoracic tumors may also be involved.[15] Obstructive pneumonia may infrequently reveal the malignancy but is responsible for approximately 50% of pneumonias in patients with established lung neoplasms. Postobstructive pneumonias are frequently polymicrobial and may be difficult to treat and require up-to-date interventional pulmonary management (laser bronchoscopy, airway stenting, electrocautery, etc.).[15]

Aspiration Pneumonia

Aspiration pneumonia has been extensively described after chemoradiotherapy in patients with head and neck cancer and may be secondary to swallowing dysfunction due to mucositis during the treatment period, or to radiation-induced fibrosis of the oropharyngeal musculature after completion of the treatment. A cumulative incidence of 15 to 20% within 1 to 2 years of treatment and an increased associated risk of death

have been reported. A link between severe mucositis and aspiration pneumonia has also been suggested in a few case reports in patients with hematological malignancies[16] and would deserve further investigation.

Hematogenous Pneumonias

Hematogenous pneumonia occurs when a blood-borne bacteria originating from a distant infectious site deposits in the lung parenchyma. Long-term central venous catheters are widely used in cancer patients, with insertion rates of 13 to 30% 2 years after the diagnosis of malignancy, depending on cancer site. Patients with cancer and implantable port systems were found to experience a median of 0.2 infections per 1,000 catheter-days (range, 0–2.7 per 1,000 catheter-days) versus 1.9 infections per 1,000 catheter-days (range, 0.6–6.6 per 1,000 catheter-days) for subcutaneous tunneled central venous catheters,[17] the presence of neutropenia being an independent risk factor for acquiring infection with incidence rates as high as 24 infections per 1,000 neutropenic-days in hematology patients. Hematogenous pneumonia itself has been scarcely described in the literature in cancer patients, but it tends to present radiologically with multiple bilateral parenchymal nodules and cavitation.

Risk Factors

Several factors, not only the type of immunosuppression but also complications of the malignancy or its treatment, may contribute to the development of pneumonia (►**Fig. 1**).

Type of Immunosuppression

Neutropenia

Rates of chemotherapy-induced neutropenia depend on tumor site and chemotherapy cycle (the risk being maximal after the first cycle) and type: low rates of 5% have been reported in colorectal cancer after the first cycle of chemotherapy,[18] whereas approximately 35 and 55% of patients with breast cancer and non-Hodgkin's lymphoma respectively develop grade 4 neutropenia (absolute neutrophil count $< 0.5 \times 10^9$/L) during the whole course of chemotherapy.[19] The association between the intensity and duration of neutropenia and the development of infections, including pneumonias, has long been recognized.[20] Recruitment of chemo-attracted neutrophils into the lungs is a key part of the host defense against invasive pneumococcal infection; besides a decreased absolute number of circulating neutrophils, impaired phagocytic and bactericidal activity, as described in patients with acute myeloid leukemia

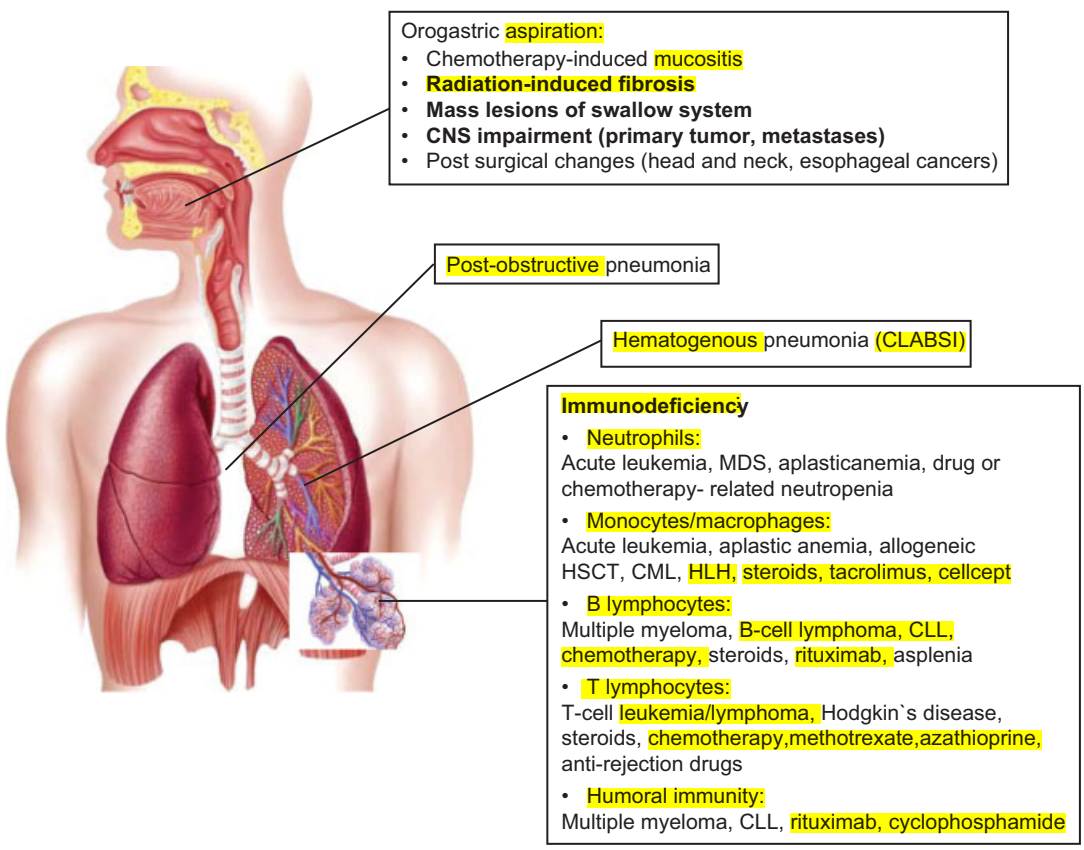

Fig. 1 Spectrum of risk factors and pathogenesis of bacterial pneumonias in immunocompromised patients. Local factors (oropharyngeal or airway lesions), systemic infections, and dysregulated defense mechanisms of the respiratory system due to the immunodeficiency may all contribute to the development of bacterial pneumonia. CLABSI: central line associated bloodstream infection; CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; CNS: central nervous system; HLH: hemophagocytic lymphohistiocytosis; HSCT: hematopoietic stem cell transplant; MDS: myelodysplastic syndrome.

(AML),[21] might also contribute to increased susceptibility to pneumonia. In a large prospective cohort of cancer patients admitted to ICU for severe pneumonia, approximately 10% were neutropenic.[22] On the other hand, a European data registry analysis showed that 7.8% of 1,595 patients developed pneumonia during the neutropenic period following autologous or allogeneic HSCT.[23] Pneumonias also account for approximately 7 to 10% of bacteremias in neutropenic cancer patients and are associated, in this setting, with a 30-day mortality rate of 46%.[24]

Humoral Immunosuppression

Primary immunodeficiency syndromes are a group of rare and heterogeneous genetic diseases, affecting approximately 1:10,000 individuals and variably impeding B cell function and antibody production; repeat episodes of pneumonia are a warning sign of primary immunodeficiency. Pneumonia was the most common clinical feature in a large series of 2,212 patients with common variable immunodeficiency (CVID) and was associated with lower plasma levels of immunoglobulin G.[25]

Secondary humoral immunosuppression is much more frequent and hypogammaglobulinemia mainly complicates multiple myeloma or chronic lymphocytic leukemia (CLL); the association between the hypogammaglobulinemia observed during CLL and infection has been recognized since the 1960s[26] and especially involves encapsulated bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae*) because of deficient opsonization.

Cellular Immunosuppression

Although the literature on host defense against bacterial pneumonia mostly focuses on innate immunity, cellular adaptive immunity is also involved in the immune response against *Legionella pneumophila*[27] or *H. influenzae*, and CD4-positive lymphocytes, for instance, play a role in the immune response to *S. pneumoniae*.[28]

Cellular immunodeficiency is rarely primary, as in DiGeorge syndrome or other T cell deficiencies, and much more frequently secondary or iatrogenic. HIV infection is the typical example of cellular immunodeficiency and carries a risk of community-acquired bacterial pneumonia inversely related to the CD4-positive lymphocyte count.[29] However, patients with Hodgkin's disease, CLL, or certain types of lymphoma also have defects in cellular immunity. Iatrogenic cellular immunodeficiency is also very common in patients with malignancies, solid organ transplant, HSCT, or connective tissue diseases receiving corticosteroids, calcineurin inhibitors, antimetabolites, mammalian target of rapamycin (mTOR) inhibitors, or monoclonal antibodies, which can at various degrees affect T cell function.[30]

Nutritional and Performance Status

Poor performance status has been identified as a risk factor for bacterial pneumonia in patients with lung cancer[9] and is overall associated with increased hospital mortality in cancer patients admitted in ICUs for severe bacterial pneumonia.[22,31] Performance and nutritional status are often correlated and the link between malnutrition and perioperative mortality has been extensively described in patients undergoing major cancer surgery.[32] Nutritional status has been associated with overall outcome in patients undergoing chemotherapy for acute leukemia or lymphoma or after allogeneic HSCT,[33] but unlike in surgical patients its association with outcome in nonsurgical patients with bacterial pneumonia has not been specifically investigated.

Microbiology

Establishing a specific microbiologic diagnosis can be challenging but is important for optimal care. There is a wide range of pathogens causing pneumonia in immunosuppressed patients. Documentation depends on the immunosuppression subtype, the time from solid organ or stem cell transplantation, and the community or hospital acquired type of pneumonia. It should be kept in mind that immunosuppressed patients may present concomitant infections with bacteria but also viruses and fungi.[34] This population often has more than one etiology of pulmonary infiltrates or ARF.[3]

In community-acquired pneumonia, classic pathogens are often involved in immunosuppressed patients. *S. pneumoniae* and *Haemophilus* species are the most frequently identified causes of community-acquired bacterial pneumonia.[35] Higher incidence of pneumococcal infection has been reported in solid organ and stem cell transplant recipients compared with general population. In a prospective cohort, solid organ transplant recipients presented a 12.8 relative risk of invasive pneumococcal disease compared with the general population.[36]

Other community-acquired pathogens include *Mycoplasma* spp., *Legionella* spp., and *Chlamydia* spp. In HIV-infected patients, the frequency of *Pseudomonas aeruginosa* and *Staphylococcus aureus* as community-acquired pathogens is higher than in HIV-uninfected individuals. Methicillin-resistant *S. aureus* (MRSA) may be considered as a potential pathogen, given that community outbreaks of MRSA have been seen in men who have sex with men and nasal carriage of MRSA is more common in HIV-infected individuals.[37]

ICU-acquired bacterial etiologies include *Pseudomonas* spp., enteric gram-negative bacilli, as well as *Stenotrophomonas* spp., and MRSA.[38]

Over the years, little change has been observed in pathogen documentation. Main observed changes were with the emergence of multidrug resistant (MDR) pathogens. The rate of patients with MDR bacteria and ICU-acquired infection related to MDR bacteria has been reported to be significantly higher in immunosuppressed patients compared with control.[39] This rate can reach 72% when considering ventilator-associated lower respiratory tract infection.[40] In high-risk neutropenic patients, routine prophylaxis has increased the risk for unusual pathogens that are resistant to prophylactic agents including fluoroquinolone-resistant streptococci, and MDR bacteria. Main risk factors for MDR infection are previous antibiotics exposure, previous MDR colonization or infection, travel to an extended-spectrum β-lactamase (ESBL)-endemic area, hospitalization in a long-term care facility, catheter insertion, allogeneic stem cell transplantation, and graft versus host

disease.[41] With the emergence of ESBL-producing Enterobacteriaceae, carbapenems have been increasingly used against these organisms, leading to the emergence of carbapenem-resistant bacteria.[42]

Additionally to these classical bacteria, pathogens such as tuberculous and nontuberculous mycobacteria, or Nocardia can be significant pathogens in immunocompromised patients.

Tuberculosis reactivation may occur in immunocompromised patients, especially in solid organ transplant recipients and in patients treated with high-dose steroids or tumor necrosis factor (TNF)-α inhibitors.[43] In a retrospective study, tuberculosis was diagnosed 22 months after kidney transplantation, mostly in patients born in a country with a high prevalence of tuberculosis.[43]

Nontuberculosis mycobacteria (NTM) pneumonia may occur in some specific subsets of immunosuppressed patients. Most common NTM pathogens are *Mycobacterium avium-intracellulare*, *Mycobacterium abscessus*, *Mycobacterium fortuitum*, *Mycobacterium marinum*, and *Mycobacterium chelonae*. NTM infections are most common in HIV-infected patients with profound CD4 depletion, some hematological malignancies with impaired cellular immunity like GATA2-deficiency, and solid organ and allogeneic stem cell transplantation.[44]

Nocardia species are ubiquitous saprophytic gram-positive bacteria. Nocardia infections have increased in the last two decades, due to improved identification methods and the expanding immunocompromised population. Nocardia infection most commonly involves the lung but disseminated infection can occur with bloodstream, skin, or central nervous system involvement. The risk of developing nocardiosis after transplantation varies with the type of organ transplanted and the immunosuppression regimen used. An increased risk of nocardiosis has been reported in patients with hematological or solid malignancy.[45] TNFα blocking therapies have also been reported as a risk factor for nocardiosis in patients with rheumatic diseases or inflammatory bowel diseases.[46]

Diagnosis

Clinical Presentation

Clinical presentation may be impaired in immunocompromised hosts because the usual signs of infection might be missing due to the impaired inflammatory response. During neutropenia, sputum production and radiographic infiltrated may be delayed in patients with pneumonia. In a series of cancer patients with pneumonia, neutropenic patients produced purulent sputum far less often than those without neutropenia (8 vs. 84 percent).[47] In immunosuppressed patients, infections should be largely suspected, even without fever or cough, when patients present with confusion, unexplained hypotension, or asthenia. Clinical evaluation should include extrathoracic symptoms, especially a complete skin evaluation. Skin evaluation may reveal secondary lesions of NTM or nocardiosis.

Radiological Presentation

Each immunosuppressed patients with a suspected sepsis should undergo a chest X-ray evaluation, even without respiratory symptoms. Chest X-ray may reveal pulmonary infiltrates in asymptomatic patients but also be normal in patients with pneumonia, especially neutropenic patients. Therefore, chest X-ray is not sufficient to exclude pneumonia if there are any respiratory symptoms or historical features that suggest a possible pulmonary process. Comparison with old imaging is essential. In a retrospective study of immunocompromised patients with respiratory symptoms, chest X-ray led to an accurate diagnosis in only one-third of patients.[48] Main radiological findings associated with bacterial pneumonia are asymmetric or unilateral parenchymal opacifications and pleural effusions. Minor abnormalities on a chest X-ray need further evaluation, including computed tomography (CT) scanning. CT-scan evaluation has been reported as more sensitive and superior to chest X-ray in immunosuppressed patients for the diagnosis of bacterial pneumonia and other respiratory complications. In a retrospective study of neutropenic patients, CT scan could detect pneumonia approximately 5 days earlier than chest X-ray, and during the first 7 days, the number of pneumonias detected with CT scan was six times greater than the number detected with chest X-ray.[49] The main CT-scan abnormalities associated with bacterial pneumonia in immunosuppressed patients are presence of consolidation, presence of bronchial wall thickening, and absence of mosaic pattern.

Lung ultrasound has been developed for the quick diagnosis of pneumonia.[50] This technique seems efficient to diagnose pulmonary infiltrates but cannot distinguish the different patterns to help clinicians in differential diagnosis for immunosuppressed patients.

Noninvasive Tests

Routine tests for bacterial pneumonia like sputum sampling, urine analysis, and blood culture should be performed in immunosuppressed patients. However, as described earlier, these patients may have reduced sputum production. Microbiological testing should also include antigen detection and/or nucleic acid detection-based assays as well as cultures. Serologic testing is generally not useful in the acute management of immunocompromised patients. These patients often fail to generate an adequate antibody response to infection.

The cause of pneumonia must be identified as the risk of death is higher when the cause of ARF remains unknown in ICU patients.[4,51] The diagnosis strategy may include noninvasive and/or invasive tests. A noninvasive strategy has been reported as noninferior to an invasive strategy with fiberoptic bronchoscopy with bronchoalveolar lavage (FO-BAL).[52]

Beside the culture-based sputum analysis, nucleic acid-based detection has been developed. During the past few years, several polymerase chain reaction (PCR) panels were developed to detect frequent viruses and some bacteria. Bacteria detected depend on the panel used but may include *S. pneumoniae*, *H. influenzae*, *Bordetella pertussis*, *Chlamydophila pneumoniae*, *Moraxella catarrhalis*, *Mycoplasma pneumonia*, *S. aureus*, *K. pneumoniae*, *L. pneumophila*, and *P. aeruginosa*. These PCR tests are used on nasopharyngeal swab specimen for the noninvasive testing of patients with suspected pneumonia. More recently, a more accurate diagnosis performance has been suggested for these PCR panels when

used on sputum versus nasopharyngeal swab. In a prospective study including patients with community-acquired pneumonia, a comprehensive molecular testing for respiratory pathogens in sputum led to bacteria detection in 81% of patients versus 39% of patients with a culture-based method.[53] PCR-based identification is also useful in patients previously treated with antibiotics which may reduce the sensitivity of culture-based identification.[54] Moreover, PCR-based identification methods may include resistance gene detection which may guide antibiotic treatment. These PCR-based pathogen identification methods are useful in community-acquired pneumonia. They may be used in health care-associated pneumonia and ventilator-associated pneumonia (VAP) if they include pathogens often implied in a nosocomial setting.

Nocardiosis diagnosis relies on pathogen identification as no clinical or radiological signs are specific. Microbiology laboratory must be informed of the suspicion of nocardiosis, as specific techniques are required to check the growth of Nocardia. Nocardia-specific PCR has also been developed for the diagnosis.[55]

All the PCR-based methods raise the problem of the distinction between colonization and infection with the different pathogens. The results are often qualitative (positive or negative) and a positive result may imply only a colonization, especially on a nasopharyngeal swab. The result should be interpreted clinically. Semi-quantitative results may lack of sensibility to distinguish colonization from infection.[56] More recently, real-time PCR (RT-PCR) allowed obtaining a quantitative result which may help to distinguish colonization and infection.

New tools are being used for the diagnosis of pneumonia including next-generation sequencing (NGS). NGS could identify bacteria, fungi, and viruses in respiratory samples and could improve the diagnosis of concomitant infections.[57]

Invasive Tests

Invasive tests include FO-BAL and pulmonary biopsy.

FO-BAL has been reported to induce respiratory deterioration or cardiovascular alterations, most notably in patients with severe hypoxemia, and ventilator support may be required after the procedure. However, when FO-BAL is needed, probably in up to 25% of patients, the use of noninvasive ventilation may avoid mechanical ventilation rate requirement.[52] FO-BAL can provide profound and directed samples. These samples can be analyzed for bacteria identification but furthermore for differential diagnosis including, viral, fungal, inflammatory processes, or drug toxicity.[52] Bacteria identification may be performed with culture-based procedures but also with molecular tests like RT-PCR tests as previously described.

In the case of nodular pneumonia, a transbronchial or CT-guided fine-needle biopsy must be considered, especially for the diagnosis of nocardiosis and the differential diagnosis with invasive fungal infections or tuberculosis. Nocardia may also be identified on extrapulmonary samples with culture or molecular testing, and biopsy of skin lesions or other organs should be considered in patients with suspected nocardiosis.[58]

Open lung biopsy is a procedure associated with complication and may be difficult in critically ill hypoxemic patients with frequent hemostatic abnormalities. Lung biopsy is not necessary in patients with bacterial pneumonia but may be considered and useful for the differential diagnosis, especially for malignant infiltrates, invasive fungal infections, or organized/cryptogenic pneumonia.[59]

Treatment

Antimicrobial Treatment

Initial treatment Algorithms exist for empiric antibiotic therapy in immunocompromised hosts. Initial therapy is empiric. However, careful attention to individual patient characteristics allows an empiric antibiotic therapy tailored to treat the most likely pathogens and minimize toxicity and cost. The objective is to avoid unnecessary broad-spectrum antimicrobial coverage. Antimicrobial agents used for prophylaxis should be avoided in empiric therapy as resistance may emerge.

Initial treatment for community-acquired pneumonia, health care-associated pneumonia, and VAP should follow locally adapted guidelines to improve patients' care.[60] For all patients, past medical history, especially of infection and colonization, and antimicrobial prophylaxis should be considered for empirical treatment.

In community-acquired pneumonia requiring ICU management, coverage for *S. pneumonia* and *Legionella* species should be ensured, and it is recommended to treat patients with a β-lactam associated with azithromycin or a respiratory fluoroquinolone.[60] Treatment of a suspected MRSA or *P. aeruginosa* infection is the main reason to modify the standard empirical regimen.

In VAP, recommendations are to cover for *S. aureus*, *P. aeruginosa*, and other gram-negative bacilli in all empiric regimens.[61] Adding an agent active against MRSA for the empiric treatment of suspected VAP is recommended only in patients with risk factor for antimicrobial resistance or in patients being treated in units where greater than 10 to 20% of *S. aureus* isolates are methicillin-resistant. Recommended treatments are piperacillin-tazobactam, cefepime, imipenem, or meropenem. Guidelines also suggest the use of levofloxacin, but the authors are reluctant about the empirical use of fluoroquinolones.

Definitive Therapy

After documentation (which occurs in about half of the cases), the choice of antibiotic for definitive therapy is based upon the results of antimicrobial susceptibility testing.

De-escalation after documentation is still debated in some high-risk population like febrile neutropenia. Studies have shown that de-escalation is safe in febrile neutropenia without documented infections. Current European recommendations favor treatment de-escalation using narrower-spectrum agents, guided by in vitro susceptibility tests.[62] However, these studies and recommendations did not include patients with severe infections. A retrospective study reported that antibiotic de-escalation in neutropenic patients with severe infection did not impact patients'

outcome.[63] A randomized clinical trial is currently recruiting patients to confirm these results (NCT03683329).

Treatment duration for community-acquired, health care, and ventilator-associated pneumonia is 7 days.

Antibiotic Stewardship

Antibiotic stewardship programs have been developed over the past few years. These programs are associated with reduced antibiotic consumption, especially broad-spectrum antibiotics, without affecting outcome. In neutropenic patients, antibiotic stewardship programs are associated with an increase in appropriate antimicrobial use, a reduced overall antimicrobial consumption, and reduced bacterial and *Candida* infections. These programs have also been associated with a reduced mortality.[64]

Prevention

Reducing the intensity and duration of immunosuppression as much as possible, regularly reassessing the benefit/risk ratio of long-term central venous catheters, and carefully evaluating patients at risk for aspiration pneumonia (head and neck cancers, mucositis) are all general measures aimed at preventing bacterial pneumonia.

Current guidelines recommend primary prophylaxis with hematopoietic colony stimulating factors in patients receiving chemotherapy who have an approximately 20% or higher risk for febrile neutropenia based on patient-, disease-, and treatment-related factors[65]; recommendations are based on a reduction in episodes of febrile neutropenia and infections in patients receiving growth factors; however, pneumonia has not been specifically addressed in clinical studies and there is no definite evidence of a benefit of growth factors on survival.[65] Similarly, fluoroquinolone prophylaxis has been suggested in patients with expected prolonged and profound neutropenia (<100 cells/mm^3 for >7 days),[66] based on a benefit on survival, but whether it specifically prevents pneumonia has not been investigated.

Pneumococcal vaccination is recommended in adult patients with newly diagnosed cancer before chemotherapy but studies have shown poor adherence overall[67]; the Centers for Disease Control and Prevention (CDC) recommendations are to administer a dose of conjugated 13-valent pneumococcal vaccination (PCV 13) followed by a dose of 23-valent polysaccharide vaccine (PSV 23) 8 weeks later. Given the uncertainty about the adequacy and duration of immune response in patients who have already received chemotherapy or a HSCT, guidelines are less clear in these settings.

Beside vaccination, other interventions aimed at preventing pneumonias have shown promising effects even though they are not part of guidelines: prophylactic professional oral care before chemotherapy has been associated with a decreased incidence and severity of oral mucositis in breast cancer patients and with a decreased incidence of pneumonia after major cancer surgery.[68] Patient education, daily spirometry as an early warning tool, and use of positive end-expiratory pressure have been associated with a decreased incidence of pneumonia in a small randomized controlled trial in neutropenic AML patients after induction chemotherapy.[69]

Although randomized controlled trials demonstrating a benefit of immunoglobulin replacement in CVID or other primary immunodeficiency syndromes are not available, there is enough indirect evidence to support recommendations to administer immunoglobulins every 3 to 4 weeks in patients with CVID[70]; a lower level of evidence exists for other types of primary immunodeficiencies, including those with normal levels of plasma immunoglobulins, and indications should be discussed on a case-by-case basis, as the rarity of these diseases precludes clinical trials. Prophylactic use of intravenous immunoglobulins to prevent infections in secondary immunodeficiencies is more debated: prophylactic immunoglobulin administration has been associated with a decreased rate of serious bacterial infections in patients with CLL or multiple myeloma in small randomized trials and may therefore be considered in these patients when hypogammaglobulinemia and recurrent infections are present; however, no benefit on survival has been demonstrated so far.[70]

Outcome

Immunosuppression is associated with a higher mortality when pneumonia develops: the overall mortality due to community-acquired pneumonia in a prospective cohort study was 12% for immunocompromised patients $\geq$65 years versus 3% for immunocompetent patients ($p < 0.01$).[71] Other studies have reported similar mortality in all age cancer patients hospitalized for pneumonia (19% for instance in Ahn et al[31]). The type of immunosuppression seems to affect mortality rates, as a study reported a 20% mortality in high-risk patients (immunosuppression associated with malignancy) versus 4% in low-risk patients (HIV infection, solid organ transplant, or immunosuppressive drugs)[72] after controlling for pneumonia severity index and as compared with immunocompetent patients, high-risk patients had in this study an odds ratio of 2.8 for hospital mortality whereas the odds ratio was not increased for low-risk patients.[72] A 28% 6-month mortality has been reported in patients with hematological malignancy developing pneumonia in wards[73] but a higher mortality was observed in neutropenic cancer patients with bacteremic pneumonia (46% in Gudiol et al[24]). Finally, in the most severe cases of pneumonia requiring ICU admission, mortality rates as high as 65% have been reported[22] in immunocompromised patients, whereas lower rates (ranging from 20 to 40% depending on the population included) have been observed in immunocompetent patients.

Another important outcome to consider is whether the occurrence of bacterial pneumonia in immunocompromised patients affects subsequent treatment (mostly chemotherapy), which could potentially impede overall survival. This point has not been really addressed: several studies have reported that administration of chemotherapy for acute leukemia or lymphoma in ICU patients requiring vital organ support (and sometimes with co-existing infections) was feasible and could be associated with long-term survival and continuation of

intended chemotherapy after ICU stay.[74] Similarly, a retrospective study in patients ≥65 years with solid tumors admitted to the ICU for various reasons (30% of patients being admitted for sepsis) showed that about half of the ICU survivors with potential indication for additional chemotherapy received treatment.[75] However, oncologists may be reluctant to pursue chemotherapy as planned (in terms of timing and dosage) in this setting, and the impact of bacterial pneumonia on subsequent anticancer therapy remains to be investigated.

Conflict of Interest

Dr. Azoulay reports personal fees and non-financial support from Pfizer, personal fees from Alexion, personal fees from MSD, grants and personal fees from Baxter, grants from Ablynx, outside the submitted work.

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