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Original article

Pneumonia definition in allogeneic hematopoietic cell transplant recipients: Update and challenges in 2024. Recommendations from the EBMT Infectious Diseases Working Party and Practice Harmonization and Guidelines committee

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ABSTRACT

To optimize and homogenize data on infectious diseases complications, the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation (IDWP EBMT) participated in the 2023 EBMT international workshop focusing on the standardization of the definition of specific infections, including respiratory infections [1]. This is pertinent considering that a new software for data collection, including data on post-transplant infectious disease complications, was launched in 2023 and which will remain the main tool for future epidemiological studies. In this report, we briefly discuss our proposals for pneumonia definition, predominately focusing on bacterial and fungal pneumonias. We specifically address definitions of pneumonia diagnosis, infection onset date, resolution, recurrence, and breakthrough infection, and the challenges we encountered as a group to accurately define pneumonia in hematopoietic cell transplant (HCT) recipients (Table 1). Infections with community acquired respiratory viruses and adenovirus are discussed in a separate report [1]. Definitions on CMV pneumonia have been previously described and recently updated and hence not discussed in this paper [2,3].

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Introduction – state of the art

To optimize and homogenize data on infectious diseases complications, the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation (IDWP EBMT) participated in the 2023 EBMT international workshop focusing on the standardization of the definition of specific infections, including respiratory infections [1]. This is pertinent considering that a new software for data collection, including data on post-transplant infectious disease complications, was launched in 2023 and which will remain the main tool for future epidemiological studies. In this report, we briefly discuss our proposals for pneumonia definition, predominately focusing on bacterial and fungal pneumonias. We specifically address definitions of pneumonia diagnosis, infection onset date, resolution, recurrence, and breakthrough infection, and the challenges we encountered as a group to accurately define pneumonia in hematopoietic cell transplant (HCT) recipients (Table 1). Infections with community acquired respiratory viruses and adenovirus are discussed in a separate report [1]. Definitions on CMV pneumonia have been previously described and recently updated and hence not discussed in this paper [2,3].

Methods

The structure and function of the EBMT workshop have been previously described [4]. The EBMT IDWP group, consisting of an international panel of 11 IDWP members (the authors of this manuscript), reviewed the relevant guidelines on the definitions of pneumonia and proposed an update on EBMT HCT-dedicated pneumonia definitions [5,6]. The diagnostic considerations discussed in this document pertain mainly to bacterial pneumonias, while specifications on fungal pneumonias are included in the end.

Workshop recommendations

Pneumonia definition

The panel agreed that a pneumonia should be defined as radiographic evidence of a new or worsening pulmonary infiltrate, with or without compatible clinical signs and symptoms. This is in line with the criteria of the American Thoracic Society [5]. Complicated pneumonia was defined as pneumonia with at least one of the following complications: parapneumonic effusion, empyema, necrotizing pneumonia, and lung abscess. The panel extensively discussed whether a pneumonia diagnosis should be based on imaging alone, in case of lack of compatible respiratory signs and symptoms. Although neutropenic patients with pneumonia, either bacterial or fungal, almost always present with fever, specific respiratory symptoms (e.g. cough, shortness of breath, expectorations) may be absent. For example, purulent sputum is found in only 8 % of cases of bacterial pneumonia [7]. Tachypnoea, defined as >30 and >25 breaths per minute in children >1 year and adults, respectively, may be the only sign of pneumonia [8]. Moreover, even non-neutropenic HCT recipients with pneumonia, particularly those with a diagnosis of graft-versus-host disease (GvHD) on high dose steroids, may be completely asymptomatic [5]. Finally, neutropenic patients with pleura-based lesions may occasionally present with pleuritic chest -or even referral shoulder- pain, without any other symptoms. Hence, high index of suspicion for pneumonia should be applied in severely immunocompromised or neutropenic HCT recipients, and even non-specific signs, such as fever, tachypnea, or increased non-specific inflammatory markers, such as a C-reactive protein (CRP), should alert clinicians to consider requesting a chest computed tomography (CT) imaging. A chest CT is strongly recommended and preferred to chest radiology, particularly in neutropenic patients, as a normal conventional chest x-ray in a neutropenic patient with persistent fever, even when respiratory symptoms are absent, cannot exclude a pulmonary infection. In a landmark study, a pulmonary CT scan showed evidence of

Table 1
Summary of bacterial pneumonia definitions*.

Term	Definition	
Pneumonia		Radiographic evidence of a new or worsening pulmonary infiltrate, with or without compatible clinical signs and symptoms.
Complicated pneumonia		Pneumonia with at least one of the following complications: parapneumonic effusion, empyema, necrotizing pneumonia, lung abscess.
Microbiologically confirmed pneumonia		Pneumonia with a relevant and clinically meaningful pathogen identified in lungs or other relevant specimen.
Non-microbiologically confirmed pneumonia		Pneumonia without an identified pathogen, despite a sufficient diagnostic work-up.
Non-infectious pneumonia		Lung infiltrates attributed to a non-infectious process (e.g. intra-alveolar pulmonary hemorrhage, idiopathic pneumonia syndrome, drug toxicity) in the setting of a negative detailed infectious disease work-up that fails to identify a clinically relevant pathogen.
Time of diagnosis		Day of first imaging confirming the pneumonia diagnosis. In case radiology was prompted by specific clinical signs and symptoms (hypoxia, pleuritic chest pain, dyspnea, tachypnea, but not fever alone), the day of the first documented clinical sign or symptom prompting the request of an imaging diagnostic test should be considered as the first day of pneumonia diagnosis.
Treatment response[1]	**Complete response**[2]	Survival with complete resolution of new or worsening radiological findings and signs and symptoms of infection.
	Partial response[2]	Survival with partial improvement of new or worsening radiological findings and signs and symptoms of infection.
	Failure	Radiographic progression (increase of ≥50 % of pulmonary infiltrates compared with baseline) and/or clinical deterioration (e.g. shock, respiratory failure/increase requirement for oxygen, need for invasive mechanical ventilation or death) associated with the index pulmonary infection.
Attributable mortality		Death associated with the pneumonia, even in the presence of other contributors (e.g. respiratory failure, shock).

*For the diagnosis of invasive fungal pneumonias, the panel refers to the consensus guidelines by Donnelly P et al. (reference). The definition of community acquired respiratory viruses and adenovirus are discussed in separate reports (Piñana JL, Current Research in Translational Medicine 2024 Vol. 72 Issue 3 Pages 103,461). Definitions on CMV pneumonia have been previously described and hence not discussed in this paper [2,3].

[1]In clinical practice, clinical response of bacterial pneumonia is usually assessed within 48–72 h. However, for registry purposes we would suggest that overall (clinical and radiological) response assessment should be performed after 2–4 and 6–12 weeks of appropriate treatment for bacterial and fungal pneumonia, respectively.

[2]For patients with prior scarring lesions on their imaging tests, radiological response would be resolution of new lesions and return to baseline.

pneumonia in 60 % of patients with febrile neutropenia, whose chest x-rays were normal [9].

Microbiologically confirmed pneumonia

Depending on the identification of a likely causing pathogen, pneumonia may be further classified as: microbiologically or radiologically/clinically documented. The panel strongly recommends extensive diagnostic workup to obtain a microbiological diagnosis in all cases of pneumonia in HCT recipients. Conventional microbiology tests should be routinely requested, including blood and sputum (when available) cultures, molecular testing by PCR for atypical bacterial (e.g. *Mycoplasma pneumoniae*) and viral (e.g. CMV, SARS-CoV-2, influenza, respiratory syncytial virus, parainfluenza, adenovirus, rhinovirus, other coronaviruses, metapneumovirus, etc.) pathogen detection in the appropriate specimen, and other biomarkers (e.g. serum galactomannan enzyme immunoassay -GM EIA, urinary antigen for *Legionella pneumophila* or *Streptococcus pneumoniae*). A bronchoscopy should be performed, when feasible and as early as possible, to optimize pathogen recovery and targeted antimicrobial treatment. Bronchoalveolar lavage (BAL) results may change the clinical management in >50 % of lower respiratory tract infections in immunocompromised hosts [10]. Performing a bronchoscopy may allow for additional tests to be performed on the BAL, including, but not limited to fungal specific PCR and GM EIA. Transbronchial biopsies, that may add additional information to the BAL, may not always be feasible, particularly in patients with poor graft function and persistent severe thrombocytopenia. The risk-benefit ratio for performing a diagnostic procedure with a bronchoscopy and transbronchial biopsy should be evaluated on a case-by-case basis and a decision made after discussion between hematology, infectious disease, and pulmonary services. However, retrospective data from large series suggest that bronchoscopy remains a relatively safe diagnostic procedure even in high-risk, fragile allogeneic HCT recipients [11,12].

Non-microbiologically confirmed pneumonia

Despite all the currently available diagnostic tests, there remains a significant proportion of patients with pneumonia, whose diagnosis cannot be confirmed microbiologically and are hence classified as a radiologically/clinically diagnosed pneumonia. This may be due to the fact that: (a) an invasive diagnostic procedure (e.g. bronchoscopy, lung tissue biopsy) is required but not feasible, (b) diagnostic tests were performed after initiation of empirical antibacterial and/or antifungal treatment or prophylaxis, (c) pneumonia is caused by pathogens not easily retrievable (e.g. *Nocardia* spp., *Stenotrophomonas maltophilia*, non-*Aspergillus* rare molds, etc.), or (d) pneumonia due to rare unusual pathogens that are not always considered, such as lung toxoplasmosis. The majority of those pneumonias are considered to be infectious and empirically treated as such. In contrast, positive microbiological results may not always indicate a related infectious disease process. The identification of a pathogen in a respiratory sample may merely represent colonization, rather than actual disease. Careful evaluation of microbiological results by experienced infectious disease specialists may help differentiate pathogens from mere contaminants or colonizers.

Although radiographic abnormalities are required for a diagnosis of infectious pneumonia, not all radiographic findings represent infection ([5] EBMT Handbook, Chap 52). There is a long list of agents, that can produce drug-related pneumonitis, such as ibrutinib, idelalisib, panobinostat, mTOR inhibitors, methotrexate, carmustine, bleomycin, cyclophosphamide, gemcitabine, or more recently checkpoint inhibitors and antibody–drug conjugates [13–15]. Moreover, non-infectious pulmonary syndromes are frequent complications in allogeneic HCT recipients, who present with pulmonary infiltrates and associated symptoms, such as fever, with a broad array of clinical entities described in the literature [16,17]. These include intra-alveolar pulmonary hemorrhage, pulmonary edema, drug or radiation toxicity, idiopathic pneumonia syndrome (IPS), and immunologic causes (e.g. late-onset interstitial lung diseases including organizing pneumonia). These diagnoses should be considered in the absence of an identified pathogen but can also co-exist with infectious pneumonia (EBMT Handbook, Chap 52).

Day of pneumonia diagnosis

The panel suggested that the day of the first imaging test should be considered as the day of pneumonia diagnosis. In case radiology was prompted by specific new clinical signs and symptoms (hypoxia, pleuritic chest pain, dyspnea, tachypnea, but not fever alone), the day of the first documented clinical sign or symptom (if available) prompting the request of an imaging diagnostic test should be considered as the first day of pneumonia diagnosis.

Pneumonia resolution, treatment failure and mortality

Treatment response criteria have been proposed for patients with invasive fungal infections [18]. The panel adjusted those criteria to further define bacterial pneumonia resolution in HCT recipients. In clinical practice, clinical response of bacterial pneumonia is usually assessed within 48–72 h. However, for registry purposes we would suggest that overall (clinical and radiological) response assessment should be performed after 2–4 and 6–12 weeks of appropriate treatment for bacterial and fungal pneumonia, respectively [19]. The panel proposed that complete or partial resolution of a bacterial pneumonia be defined as survival with complete resolution or partial improvement, respectively, of CT radiological findings and signs and symptoms of infection. For patients with prior scarring lesions on their imaging tests, radiological response would be resolution of new lesions and return to baseline. In case of partial resolution and doubt about the persistent activity of lesions on the CT scan, FDG-PET/CT could be helpful [20]. Treatment failure was defined as radiographic progression (increase of the size with ≥50 % of pulmonary infiltrates compared with baseline) and/or clinical deterioration (e.g. shock, respiratory failure/increase requirement for oxygen, need for invasive mechanical ventilation or death) associated with the initial pulmonary infection. Special note was made for patients with a pneumonia diagnosed during neutropenia and the potential imaging and clinical deterioration with engraftment, in the context of an immune reconstitution inflammatory syndrome [21–23]. In such cases, treatment response should not be assessed at the time of neutropenia resolution but rather several weeks afterwards. Attributable mortality was defined as death associated with the pneumonia, even with other contributors (respiratory failure, shock), while definition of the non-related to pneumonia mortality requires a clear alternative cause of death unrelated to the pneumonia.

Fungal pneumonia

The panel unanimously endorsed and strongly recommends the use of the most recent consensus guidelines for the definition of invasive mold infections (IMI) and *Pneumocystis jirovecii* pneumonia (PJP) [24]. For IMI, the panel acknowledges that these guidelines have introduced stricter diagnostic criteria for serum and BAL GM EIA and PCR results, than commonly used in clinical practice. Higher cut-off values for GM EIA are recommended in the definitions to increase certainty of IMI diagnosis as the definitions are primarily developed for research purposes. However, the panel agrees that less strict GM EIA definition criteria may be used for the definition of probable invasive aspergillosis in clinical practice. Breakthrough mold infections are increasingly diagnosed, particularly in allogeneic HCT recipients on long-term antifungal prophylaxis in the setting of GvHD [25]. Breakthrough mold infections were defined following the proposed definition by Lionakis et al., as any fungal infection diagnosed within 7 days of antifungal treatment or prophylaxis initiation or discontinuation [26]. Cornely et al. specified that breakthrough IFI occur during exposure to antifungal drug including those caused by fungi outside the spectrum of activity of

an antifungal and have suggested that the time of antifungal agent exposure prior to the diagnosis of a breakthrough fungal infection should be adjusted to the pharmacokinetic properties of the administered agent [27]. However, considering the minor variabilities and ease of a universal definition, this panel suggested a diagnosis of breakthrough fungal infection within 7 days of prior antifungal administration.

Discussion

Although the panel was able to agree on the adoption of consensual definitions, there is a need for specific definitions for pneumonia according to different pathogens and several points remained challenging and unresolved. The numerous causes of both infectious and non-infectious pulmonary infiltrates in HCT recipients, as well as their frequent co-existence, make specific diagnosis difficult. Although lung imaging cannot be considered pathognomonic for a specific cause, several signs are suggestive of a diagnosis, such as ground-glass opacities for PJP or viral pneumonias, centrilobular micronodules for community acquired respiratory viruses, nodules with halo or reverse-halo signs for IMI, or peripheral consolidations for organizing pneumonia [24,28–31]. The association of those different signs with different clinical entities is also important to take into consideration in the diagnostic process. Moreover, the identified pathogen should sufficiently and adequately explain the observed CT scan pattern. Although the panel strongly recommends that lower tract respiratory samples be taken to microbiologically document pneumonia as accurately as possible and to differentiate infection from a non-infectious condition, we all agreed that a bronchoscopy may not be always possible to perform. Non-invasive diagnostic tests, such as blood cultures, serum biomarkers, sputum specimens, and nasopharyngeal swabs should always be considered to achieve a microbiological diagnosis. Although BAL remains the cornerstone for diagnosing pneumonia in immunocompromised patients, recent data suggest that bronchial aspirates may be more sensitive to diagnose both *Aspergillus* infections and PJP [32]. Clearly, more data are required on this topic, before clinically meaningful and definitive conclusions can be drawn.

Differentiating between a pulmonary infection and colonization is sometimes challenging. Threshold values for culture specimens used in the diagnosis of pneumonia have not been established for immunocompromised patients, i.e. $\geq 10^4$ CFU/mL for BAL, $\geq 10^5$ CFU/mL for bronchial aspirates, $\geq 10^7$ CFU/mL for sputum [6,33]. Otherwise, some laboratories report semi-quantitative results which do not necessarily match the quantitative thresholds and complicate interpretation. Biomarkers may be helpful in the diagnosis of pneumonia. However, in HCT recipients, current scarce data do not support the role of inflammatory biomarkers in the diagnosis of pneumonia, although CRP and procalcitonin can be elevated in bacterial infections [34]. For non-immunosuppressed adults, the ATS/IDSA guidelines do not recommend the determination of procalcitonin to decide the need for initial antibacterial therapy [35]). Finally, biomarkers, such as the *Legionella pneumophila* or *Streptococcus pneumoniae* urine antigen, have not been validated specifically in HCT recipients.

One of the greatest challenges in the etiological diagnosis of pulmonary infiltrates after HSCT is to diagnose non-infectious pulmonary involvement alone or associated with an infection (The EBMT Handbook, Chap 52). The etiology varies depending on the time of occurrence post-transplant. Besides frequent pulmonary edema due to fluid overload, acute non-infectious lung infiltrates include IPS and diffuse alveolar hemorrhage (DAH). Idiopathic pneumonia usually occurs in the first 120 days following HSCT and is defined as the presence of multilobar pulmonary infiltrates with no pathogens identified on BAL, after ruling out cardiac dysfunction, acute renal failure, and iatrogenic fluid overload. DAH occurs at a median of 23 days post HSCT and is diagnosed with a progressively bloodier return of BAL fluid aliquots. Late onset pulmonary complications include interstitial lung diseases (ILD) and bronchiolitis obliterans. Bronchiolitis obliterans occurs between 6 months and 2 years following HSCT, whereas ILD can be diagnosed months to years after HSCT. The CT scan pattern of bronchiolitis obliterans includes attenuation in mosaic, bronchiectasis and bronchial wall thickening, air trapping by expiratory CT but no lung parenchymal abnormalities (i.e. bronchiolitis obliterans is not a differential diagnosis for pneumonia). Conversely, ILDs including organizing pneumonia and others, manifest as diffuse pulmonary opacities that are difficult to differentiate from infectious pneumonia. The BAL is particularly useful in this setting.

Conclusions

The panel was able to retain a consensus definition for the diagnosis of bacterial pneumonia and outlined the need to attain a microbiologically confirmed diagnosis of pneumonia by rigorous diagnostic efforts when feasible, to differentiate infectious from non-infectious pneumonia. More diagnostic studies, dedicated to HCT recipients, are required in the future to improve the diagnostic accuracy of infectious pneumonia in this setting.

Contributions

DN, PV, DA, MM, JS, JLP, SC, ISO, PL, RdC and AB: conceptualized the subject for this workshop; participated in the face to face meeting and wrote the original manuscript draft; RG, FO, ISO and IYA developed the methodology and edited the manuscript. All co-authors: played an important role in interpreting results, revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. They also accepted final responsibility for the decision to submit for publication.

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Declaration of competing interest

DN: No conflict of interest to declare.

PV: Participation in advisory boards and speaking honoraria for Gilead Sciences, Pfizer, Mundipharma, F2 G and Shionogi. Honoraria were paid to my institute. None of these conflicts were related to this manuscript.

DA: No conflict of interest to declare.

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FO: Declares no conflict of interest related to this work. For nonprofit organization, he is a co-chair of the EBMT pH & G committee.

IYA: Declares no conflict of interest related to this work. For nonprofit organization, he is the current chair of the EBMT pH & G

committee.

PL: Participation in advisory boards for Astra-Zeneca and Moderna. Speaker for MSD. None of these conflicts were related to this manuscript.

RdC: Participation in advisory boards for Astra-Zeneca, Astella, Moderna and MSD. Speaker for MSD, Gilead. None of these conflicts were related to this manuscript.

AB: No conflict of interest to declare.

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Further reading

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