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CHALLENGES AND STRATEGIES IN MANAGING PNEUMONIA IN IMMUNOSUPPRESSED PATIENTS

Maria Luiza Cota Pereira
Pontifícia Universidade Católica de Minas Gerais (PUC Minas)
Contagem – MG
https://orcid.org/0000-0003-4488-0858

Maraiza Carneiro
Universidade Anhanguera (UNIDERP)
Campo Grande – MS
https://orcid.org/0009-0000-1808-8301

Camila Melo de Freitas
Faculdade Pitágoras de Medicina de Eunapólis (FPME)
Eunapólis – BA
https://orcid.org/0000-0003-3952-7398

Eduarda Colaço Canelada
Centro Universitário de Votuporanga (UNIFEV)
Votuporanga – SP
https://orcid.org/0009-0005-5505-7252

Amanda Carolina Zicatti da Silveira
Pontifícia Universidade Católica de São Paulo (PUCSP)
São Paulo - SP
https://orcid.org/0000-0001-8963-9553

Abstract: **Objective**: Analyze and synthesize current evidence on the challenges faced in the management of pneumonia in immunosuppressed patients, including the identification of predominant etiological agents, patterns of antimicrobial resistance, diagnostic strategies, therapeutic approaches and preventive measures, with the aim of improving clinical outcomes in this population vulnerable. Methods: Bibliographic review carried out in the PubMed database, with the terms "Immunosuppressed Patients", "Pneumonia", "treatment", "Antibacterial Drug Resistance", "Drug Resistance Treatment" with the filter for the last 5 years. 1,644 studies were found in the initial search, after applying the selection criteria, 19 articles were selected for this review. Review: With an increase in cases of immunocompromised patients, there was a need for a specific approach to the survival of these patients. These include treatment, such as corticosteroids and immunosuppressants, in which the type of pneumonia is observed, such as obstructive, aspiration and hematogenous, in addition to analyzing the type of pathogens and tests by performing a culture to analyze the medication that will be used in the treatment. Final considerations: Such patients require greater attention and need a multidisciplinary team, due to the ease of developing opportunistic diseases, due to specific treatment and the need for adjustments in the face of side effects and possible drug interactions.

Keywords: Immunosuppressed Patients; Pneumonia; Antibacterial Drug Resistance.

INTRODUCTION

Community-acquired pneumonia (CAP) represents a significant challenge in the medical field, especially in the treatment of immunocompromised patients. Medical societies around the world have developed guidelines focused on standardizing initial empiric therapy to improve treatment and outcomes in these patients. However, these guidelines often exclude immunocompromised patients due to the need for more complex and individualized therapeutic approaches (Ramirez et al., 2020).

Immunocompromised patients, when they present signs and symptoms of CAP, often receive conventional treatment, which may not consider their specific conditions or the limitations imposed by their compromised immune systems. Despite general recommendations for the initial treatment of these patients, there is an urgent need for additional research to develop new, more effective therapeutic strategies for this high-risk group (Ramirez et al., 2020).

With the increasing prevalence of immunosuppressed patients, driven by global advances and the use of new immunotherapy drugs, a significant increase in the survival of cancer patients is observed. However, these patients face an elevated risk of lung infections, which are a leading cause of acute hypoxic respiratory failure and intensive care unit (ICU) admission (Van de Louw et al., 2019).

Bacterial pneumonia, in particular, remains the most prevalent lung infection and is associated with a high mortality rate, especially among immunosuppressed patients. Understanding the complex interaction between host factors and bacterial pathogenesis is crucial to adequately conduct prevention, diagnosis and treatment to improve clinical outcomes (Van de Louw et al., 2019).

Furthermore, the condition of immunodeficient patients is aggravated by their state of

vulnerability to opportunistic infections. The etiologies of this condition range from genetic causes (primary) to systemic disorders and immunosuppressive treatments (secondary), common in patients undergoing solid organ transplants, chemotherapy, use of immunomodulatory drugs and those with HIV (Murali et al., 2022).

Imaging findings in immunocompromised patients with pneumonia reveal specific characteristics that can guide diagnosis and therapeutic management. Studies indicate that the interpretation of radiological images, together with the patient's clinical history, is vital for early diagnosis and reduction of morbidity and mortality in this group (Murali et al., 2022). Therefore, this study seeks to analyze and synthesize current evidence on the challenges faced in the management of pneumonia in immunosuppressed patients, addressing the identification of the predominant etiological agents, patterns of antimicrobial resistance, diagnostic strategies, therapeutic approaches and preventive measures necessary to improve clinical outcomes in such a vulnerable population.

METHODOLOGY

This study consists of a bibliographical review carried out according to the criteria of the PVO strategy, which is based on three main aspects: the population or research problem (P), the variables of interest (V) and the expected outcomes (O). The guiding research question was formulated as: "What are the challenges and effective strategies in the diagnosis, treatment and prevention of pneumonia in immunosuppressed patients, considering the predominant etiological agents and patterns of antimicrobial resistance?". To collect data, we searched the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) database. The search terms used were combined with Boolean operators "AND", "OR", according to the following search strategy: (immunosuppressed patients) AND (pneumonia) AND ((treatment) OR (Antibacterial Drug Resistance) OR (drug resistance treatment)). Initially, this search resulted in 1644 articles. The inclusion criteria defined for the selection of articles were: articles written in English, published between 2019 and 2024, which discuss the themes proposed for this research. Review-type studies were considered eligible., retrospective observational studies, observational studies, experimental studies, clinical trials and articles available in full. The exclusion criteria applied included: duplicate articles, works available only in summary form, articles that did not directly address the proposal studied and that did not meet the requirements. other inclusion criteria. After applying these criteria, 17 articles were selected from the PubMed database to form the basis of analysis for this study.

REVISION

The diversity of pathogens that cause pneumonia in immunosuppressed patients results in a variety of resistance mechanisms and therapeutic options. Immunosuppression is of particular concern as it is associated with increased mortality in cases of pneumonia, highlighting the crucial importance of precisely identifying the pathogen to enable effective intervention (Van de Louw et al., 2019). Immunocompromised patients are at high risk of developing community-acquired pneumonia (CAP), which can be caused by both opportunistic pathogens, such as Pneumocystis jirovecii, and typical and atypical pathogens found in non-immunocompromised individuals. Streptococcus pneumoniae is frequently cited as the main agent of CAP in both immunocompetent and immunocompromised adults. However, there is a paucity of data on the clinical outcomes of

immunocompromised patients who develop pneumococcal pneumonia (Ramirez et al., 2021).

Among the classic pathogens of community-acquired pneumonia in immunosuppressed patients, S. pneumoniae and Haemophilus influenzae are commonly identified. Recipients of solid organ and stem cell transplants have a higher incidence of pneumococcal infections compared to the general population. Other community pathogens such as Mycoplasma spp., Legionella spp. and Chlamydia spp. are also relevant (Van de Louw et al., 2019).

In HIV-infected patients, an increased prevalence of Pseudomonas aeruginosa and Staphylococcus aureus as community pathogens is observed. In particular, methicillin-resistant S. aureus (MRSA) has been frequently identified, with notable community outbreaks especially among men who have sex with men, and a higher prevalence of nasal carriage of MRSA in HIV-infected individuals (Van de Louw et al., 2019).

In hospital settings, especially intensive care units (ICU), pathogens include Pseudomonas spp., enteric gram-negative bacilli, Stenotrophomonas spp. and MRSA. In addition to these classical bacteria, tuberculous and non-tuberculous mycobacteria, as well as Nocardia, are also considered significant in immunocompromised patients (Van de Louw et al., 2019).

Over the years, the composition of pathogens causing pneumonia in immunosuppressed patients has remained relatively stable, with the exception of the notable increase in multidrug-resistant (PMR) pathogens. It has been observed that immunosuppressed patients have a significantly higher rate of PMR bacteria and related infections acquired in intensive care units (ICU) compared to non-suppressed patients (Van de Louw et al., 2019).

It is crucial to recognize the risk factors for PMR infection, which include: prior antibiotic use, prior PMR colonization or infection, travel to extended-spectrum β-lactamase endemic areas, hospitalization in long-term care facilities, use of catheter, allogeneic stem cell transplantation and graft-versus-host disease. With the increase in ESBL-producing Enterobacteriaceae, the use of carbapenems has intensified, resulting in a subsequent increase in bacteria resistant to these antibiotics (Van de Louw et al., 2019).

A retrospective observational cohort study conducted by Wu et al. (2023) compared clinical characteristics and results of immunocompromised and immunocompetent patients admitted to the ICU. It has been observed that immunocompromised patients have a lower frequency of infections with atypical pathogens, but a higher prevalence of viral infections other than influenza and cytomegalovirus (CMV), in addition to a higher incidence of fungal infections. Shi et al. (2023) point out that the prevalence of lung fungal diseases, such as invasive pulmonary aspergillosis (IPA), is on the rise, especially due to the increase in risk groups that require immunosuppressive therapy. Diagnosing Aspergillus infections remains a significant challenge, impacting the morbidity and mortality of these patients.

Additionally, Wu et al. (2023) reported a higher frequency of polymicrobial infections in immunocompromised patients, with emphasis on mixed viral-fungal infections. The most frequently identified pathogens included Pneumocystis jirovecii, CMV, Aspergillus, Staphylococcus aureus, and influenza A virus.

In the case-control study by Ramirez et al. (2021), the clinical outcomes of immunocompromised and non-immunocompromised patients hospitalized with pneumococcal pneumonia were compared. The results showed that, with

adequate antibiotic therapy, the presence of a compromised immune system does not significantly influence clinical outcomes, indicating that infection control depends primarily on the local antibiotic level. Finally, Lopez et al. (2020) evaluated the use of aminoglycosides in immunosuppressed patients with bacterial pneumonia and septic shock in ICUs in several countries, observing a high rate of overall and infection-related mortality, although there was evidence of therapeutic benefit in certain subgroups of patients.

Otani et al. (2021) retrospectively analyzed 318 immunocompromised patients not infected by HIV, who had respiratory diseases and were treated with corticosteroids and/or immunosuppressants. These patients have recently started using trimethoprim-sulfamethoxazole (TMP-SMX) as primary prophylaxis against Pneumocystis pneumonia (PcP). This pioneering study explored the efficacy and tolerability of TMP-SMX in patients treated with different dosages of this drug combination, confirming that the preventive efficacy remained unchanged.

Streptococcus pneumoniae is a Gram-positive bacterium that poses a significant health threat, especially in vulnerable populations such as children, the elderly and immunocompromised individuals. To colonize the upper respiratory tract and transition to an invasive infection, S. pneumoniae secretes a variety of surface proteins that promote adhesion to epithelial cells. We identified several proteins contributing to host cell adhesion, including neuraminidase NanA and ZmpB, which are cell wall-bound proteins interacting with host collagen IV. PsaA, a surface lipoprotein, has also shown significant intercellular host binding capacity (George et al., 2024).

Furthermore, S. pneumoniae secretes two types of lipid peptidyl-prolyl isomerase (PPIases) at the cell wall membrane interface, PrsA and SlrA, which exhibit homology to different protein families. PrsA, although widely conserved in Gram-positive bacteria and Streptococcus species, does not have PPIase activity, while SlrA belongs to the cyclophilin family and retains PPIase activity. Proteomic analysis of the complete S. pneumoniae secretome indicates that PrsA contributes to the folding and stability of proteins secreted at the membrane-cell wall interface.

S. pneumoniae persists in populations due to its ability to quickly adapt to different environments and host immune responses. This bacterium has the natural ability to absorb DNA from its environment and incorporate it into its chromosome, which is crucial for its colonization and pathogenicity.

Finally, Shi et al. (2023) investigated immunocompromised patients admitted to the ICU with suspected pulmonary aspergillosis, observing that 86% had polymicrobial pneumonia. The most frequent co-pathogen was P. jirovecii, followed by CMV, other bacteria, Mucor or Rhizopus, and M. tuberculosis. The most common modes of co-infection included Aspergillus with bacteria and Aspergillus with P. jirovecii and CMV, reinforcing the importance of empirical antifungal therapy in high-risk groups.

The study by Shi et al. (2023) showed that the majority of immunocompromised patients admitted to the ICU (80%) had mixed infections of Aspergillus with other pathogens, especially "non-cultivable" microorganisms such as CMV and P. jirovecii. This finding highlights the urgent need to develop new, more sensitive technologies for the accurate identification of Aspergillus in order to facilitate early and efficient diagnosis of co-infections, which represents a significant clinical challenge.

Pneumocystis jirovecii pneumonia (PJP), a serious fungal infection, remains a significant threat, especially in immunocompromised individuals, including those with HIV or on long-term systemic corticosteroids and immunosuppressive agents. Wang et al. (2022) carried out a retrospective study involving 122 patients diagnosed with PJP, revealing the presence of multiple pathogens in 89.3% of cases. The study also demonstrated the usefulness of next-generation sequencing which, by identifying the diversity of pathogens present, allowed adjustments to the antimicrobial regimen in almost 90% of patients. This approach influenced the addition of specific antimicrobial agents, improving the clinical management of these patients.

Furthermore, antimicrobial resistance remains a growing concern, as illustrated by the rise in carbapenem-resistant Klebsiella pneumoniae (CR-Kp) strains, which have been classified by the United States Centers for Disease Control and Prevention as an urgent health threat. public. Jung et al. (2019) highlight that cancer treatment with chemotherapy and/or hematopoietic stem cell transplantation can disrupt the intestinal microbiome, decreasing resistance to colonization and allowing the expansion of opportunistic pathogens such as K. pneumoniae. This study also highlights that dense gut colonization by K. pneumoniae is facilitated by a variety of genes, including those involved in carbohydrate metabolism and membrane proteins, which are crucial for the bacteria's adaptation and survival in adverse conditions. jointly highlight the complex challenges faced in the diagnosis and treatment of infections in immunocompromised patients, highlighting the importance of advanced diagnostic approaches and the need for constant surveillance of antimicrobial resistance to optimize treatment strategies.

A promising strategy in developing new antibacterial therapies involves identifying targets that reduce the colonization capacity of pathogens without necessarily affecting their growth or survival. Jung et al. (2019) highlight the relevance of genetic factors that influence intestinal colonization, but not bacterial growth. They propose that inhibiting the expression of these genes can decrease colonization density without exerting significant selective pressure for the development of resistance. This approach could represent a significant advance in the management of infections in clinical settings, particularly in patients with immunodeficiencies.

Furthermore, understanding the different forms of bacterial pneumonia is crucial for the effective management of immunocompromised patients. Van de Louw et al. (2019) provide a comprehensive overview of the epidemiology, risk factors, microbiological characteristics, diagnosis, management and prevention of pneumonia in this population. They classify pneumonias into three main types, based on pathogenicity: obstructive, aspiration and hematogenous, each with specific implications for treatment:

- Obstructive Pneumonia: Often found in patients with lung cancer, it is commonly polymicrobial and challenging to treat, requiring advanced pulmonary interventions.
- Aspiration Pneumonia: Associated with patients undergoing treatment for head and neck cancer, often complicated by swallowing disorders due to mucositis or post-radiation fibrosis.
- Hematogenous Pneumonia: Occurs due to bacterial dissemination via the blood, often related to the use of central venous catheters.

The diagnostic approach in immunosuppressed patients requires an individualized strategy, considering the detailed clinical history, atypical symptoms and the level of immunosuppression. Initial assessment must include thorough physical examinations and a multidisciplinary analysis, using a variety of diagnostic tools to identify subtle signs of infection. Such patients may exhibit less obvious symptoms of pneumonia, including low-grade fever and mild dyspnea, making careful surveillance for opportunistic agents such as Pneumocystis jirovecii in individuals with HIV/AIDS or Aspergillus in oncology or transplant patients essential (Ramirez et al., 2020; Wu et al., 2023).

Immunocompromised patients with signs of severe pneumonia may require a broad empiric regimen that includes broad-spectrum antibiotics and antifungals, given the variety of potential pathogens and the increased risk of serious complications such as respiratory failure and Acute Respiratory Distress Syndrome (ARDS). Immunocompromised status is a critical risk factor that influences mortality in cases of severe community-acquired pneumonia (SCAP), requiring careful and adapted management in the intensive care unit (ICU) (Wu et al., 2023).

The diagnosis of pneumonia in immunocompromised hosts requires an integration of multiple clinical and diagnostic data, including the use of biomarkers and immunophenotyping techniques to assess the host's immune response. Analysis of immune cells via flow cytometry or immunostaining in biopsy or sputum samples can provide crucial insights into the nature of the immune response and disease progression (Cheng et al., 2023).

The diagnostic approach must be meticulous and personalized, emphasizing the importance of detailed clinical assessment and multidisciplinary collaboration. These patients often do not manifest typical symptoms of pneumonia and may present more subtle signs. Therefore, identification and quantification of specific inflammatory cells, such as neutrophils and T lymphocytes, are essential to understanding the extent and nature of the immune response. The use of advanced immunostaining techniques allows for accurate detection of pathogens in tissues, which is crucial for targeting therapeutic interventions (Cheng et al., 2023).

Blastomycosis, caused by the fungus Blastomyces dermatitidis, illustrates the complexity of managing fungal infections in immunocompromised individuals. McBride et al. (2021) highlight that the severity of the disease and mortality are accentuated in transplant patients, highlighting the importance of early diagnosis and effective treatments, such as the use of Isavuconazole. Tissue culture, in conjunction with antigen detection, is recommended to increase the diagnostic accuracy of blastomycosis.

Furthermore, management of primary prophylaxis for Pneumocystis pneumonia with trimethoprim-sulfamethoxazole (TMP-SMX) reveals challenges related to drug tolerability. Otani et al. (2021) identify multiple factors that may lead to discontinuation of TMP-SMX, including adverse side effects and the complexity of the dosing regimen. This underscores the need for careful strategies to improve treatment adherence in a vulnerable population, considering underlying medical conditions and potential drug interactions. These aspects highlight the unique challenges in diagnosing and treating pneumonia in immunosuppressed patients, requiring a highly specialized and adapted approach to ensure the best clinical management and favorable outcomes.

Research into amino acid biosynthetic pathways in Klebsiella pneumoniae reveals promising opportunities for the development of new antimicrobial therapies. These

strategies aim to disrupt the bacteria's ability to synthesize essential amino acids, such as histidine, whose biosynthetic enzymes can be inhibited to prevent bacterial growth. Silver et al. (2019) demonstrate how the manipulation of these pathways can be effective, particularly with the use of glyphosate to inhibit the synthesis of 5-enolpyruvyl esquamate-3-phosphate, significantly reducing the viability of K. pneumoniae in infection models. These approaches offer new horizons for the treatment of serious infections in immunocompromised patients where conventional options are limited due to antimicrobial resistance.

On the other hand, Pseudomonas aeruginosa represents a persistent challenge in critically ill patients due to its highly adaptive virulence mechanism and resistance to treatments. The study by Wagener et al. (2020) highlights the importance of exovirulence factors, particularly ExoY, which was found in high prevalence in clinical isolates. This exoenzyme is associated with significant pathogenic processes, such as edema, and its presence in clinical isolates suggests a crucial role in the pathogenesis of P. aeruginosa infections in patients undergoing mechanical ventilation. Understanding these virulence factors provides a basis for developing more specific and effective interventions tailored to the virulence profile of the pathogen.

These studies emphasize the need for innovative and targeted therapeutic approaches to manage infections in immunocompromised patients, considering both the complexity of the lung environment and the resilience and adaptation of pathogens. Exploring these new strategies has the potential to significantly improve clinical outcomes for this vulnerable population.

Colistin resistance among multidrug-resistant (MDR) Klebsiella pneumoniae strains is increasing globally, severely limiting treatment options. Alternatives include conventional antibiotics with restricted pharmacokinetic/pharmacodynamic profiles and newer agents such as ceftazidime/avibactam, which are already facing emerging reports of resistance. New developments, such as mycinoderophores, eravacycline and meropenem/vaborbactam, not yet commercialized, promise to reinforce the fight against colistin resistance. However, emerging resistance is a growing concern, especially for ceftazidime/avibactam and meropenem/vaborbactam (Petrosillo; Taglietti; Granata, 2019).

Surveillance programs are essential to monitor carriers of resistant organisms, allowing for more timely infection control interventions. Microbiology laboratories must perform susceptibility testing for new antimicrobials using phenotypic and genetic/molecular methods, informing prescriptive treatments. Furthermore, innovative approaches, such as the use of bacteriophages and monoclonal antibodies, are being explored, presenting potential as future alternatives to traditional antibiotics. However, before the widespread adoption of phage therapy, significant issues need to be resolved (Petrosillo; Taglietti; Granata, 2019).

Bloodstream infections caused by carbapenem-resistant Gram-negative bacteria (CRGNB-BSI) represent a serious clinical concern, associated with high rates of morbidity and mortality, especially in immunosuppressed patients. A retrospective study analyzed 427 patients with CRGNB-BSI, identifying Klebsiella pneumoniae as the most prevalent cause. Factors such as acute kidney injury and septic shock have been associated with significant adverse outcomes. This research highlights the need for robust strategies to manage and mitigate risks in vulnerable populations (Gao et al., 2022).

Streptococcus pneumoniae is a serious threat, especially to at-risk individuals such as children, the elderly and the

immunocompromised. Chaperone proteins such as PrsA, SlrA and HtrA are crucial for secretion and virulence, influencing adhesion and invasion in infections. Recent research has investigated the role of these proteins in pneumococcal pathogenicity, revealing that modifications in the expression or function of these chaperones can significantly impact bacterial physiology and response to antimicrobial treatment (Geoger et al., 2024). Such issues highlight the complexities of diagnosing and managing infections in immunosuppressed patients, highlighting the importance of innovative approaches and the implementation of surveillance and control strategies to combat growing antimicrobial resistance.

FINAL CONSIDERATIONS

Immunosuppression is a concern in cases of pneumonia, although there are therapeutic benefits in certain subgroups from the use of a broad empiric regimen, studies and data still show a high morbidity rate and mortality. In view of this scenario, it is worth highlighting the importance of identifying each patient's pathogenic agent and choosing a medication that suits each patient. Some classifications of pneumonia analyzed, including community-acquired, hospital-acquired or mechanical ventilation-associated pneumonia, are mostly caused by pathogenic agents, such as S. pneumoniae, Pneumocystis jirovecii, Pseudomonas aeruginosa, Staphylococcus aureus, Blastomyces dermatitidis. Diagnosis of pneumonia in immunocompromised hosts has been using immune cell analysis techniques such as flow cytometry or immunostaining to help identify disease in these tissues and in treatment planning, for example: trimethoprim-sulfamethoxazole as primary prophylaxis against Pneumocystis pneumonia has brought excellent results. In contrast, pneumonia in Klebsiella pneumoniae strains showed resistance to carbapenem treatment and colistin. Already Pseudomonas aeruginosa is a challenge for critically ill patients due to its virulence mechanism and high resistance. It is necessary to use new techniques and methods, since the use of conventional therapies is limited due to the high prevalence of resistant microbial agents, and conducting research both in analyzing the patient's immunological response, and the way in which pathogens adapt, could optimize the patient's immunological response with the use of ideal medication, and furthermore, the enhancement of such immunological responses would lead to a reduction in the various complications due to opportunistic diseases.

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