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Pneumocystis Pneumonija. Literatūros apžvalga

Pneumocystis Pneumonia. Literature Review

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1. Abbreviations

PJP	Pneumocystis jirovecii pneumonia
HIV	human immunodeficiency virus
AIDS	Acquired immunodeficiency syndrome
NIV	non-invasive ventilation
ARF	acute respiratory failure
ICU	Intensive care unit
HEPA	High efficiency particulate air
ROS	Reactive oxygen species
NO	Nitric oxide
ARDS	Acute respiratory distress syndrome
CT	Computed Tomography
PCR	Polymerase chain reaction
BAL	Bronchoalveolar lavage
NIPPV	Non-invasive positive pressure ventilation
CPAP	Continuous positive airway pressure
BiPAP	Bilevel positive airway pressure
HFNC	High-flow nasal cannula
TMP-SMX	Trimethoprim-Sulfamethoxazole
COPD	Chronic obstructive pulmonary disease
FiO2	Fraction inspired oxygen
PaO2	Partial pressure of arterial oxygen
PaCO2	Partial pressure of carbon dioxide
CO	Carbon dioxide
Tregs	Regulatory T cells

2. Summary

This study was performed to evaluate the potential benefit of non-invasive ventilation for patient with acute respiratory failure due to Pneumocystis jirovecii pneumonia. It focuses on patients' outcomes and their mortality rates compared to patients that need to be intubated and conventionally mechanically ventilated. The study was aimed at shedding a light on the use of non-invasive ventilation for this specific patient group as it is sparsely researched and there is not enough data as of now which hinders their broad implementation into the daily clinical routine. This

study aims to provide a better understanding of the effectiveness of non-invasive ventilation methods in the treatment of acute respiratory failure for patients with pneumocystis jirovecii pneumonia infections. Another point this study is trying to bring across is that there are still substantial gaps in the current research. There are multiple studies about non-invasive ventilation which generally approach their application in patients with acute respiratory failure, which allows them to draw conclusions on their effectiveness in the applications for patients with pneumocystis jirovecii pneumonia. This study was performed as a literature review, taking a look at different non-invasive ventilation methods across different studies and comparing their patient outcomes and mortality rates compared to conventional mechanical ventilation. Throughout this it was seen that non-invasive ventilation modalities could offer great help to the treatment of acute respiratory failure in patients with pneumocystis jirovecii pneumonia, but there is still a need for research to provide solid proof of their benefit and effectiveness. After extensive review of various sources this study came to the conclusion that in order for non-invasive ventilation modalities to be readily used in the daily routine many factors need to be addressed. Factors ranging from adequate training of healthcare professionals to ensure proper use, to more research solidifying the mortality rates and improved patient outcomes.

3. Key words

Non-invasive ventilation; Pneumocystis jirovecii pneumonia; conventional mechanical ventilation; CPAP; BiPAP; HFNC

4. Introduction

Respiratory failure often presents as a clinical challenge, even more so when it is associated with an opportunistic infection such as Pneumocystis jirovecii pneumonia (PJP). This opportunistic infection is often linked to immunocompromised patients, such as HIV/AIDS patients or transplant patients. With the development of non-mechanical ventilation (NIV), an alternative to the conventional treatment approach with mechanical ventilation for patients with acute respiratory failure has emerged. However, the effectiveness of NIV is still investigated, especially for immunocompromised patients without HIV. This paper aims to explore the application of NIV in managing respiratory failure compared to the conventional approach with mechanical ventilation.

PJP presents as an opportunistic infection in immunocompromised patients and is a major cause of respiratory distress in those groups. Mortality ranged from 10-20% in HIV-positive groups and even up to 60% in non-HIV-infected groups. It is characterized by progressive dyspnea, fever, and non-productive cough, often leading to severe hypoxemia and respiratory failure needing intensive care treatment. Conventionally the treatment consists of mechanical ventilation, this approach bears substantial risks, such as ventilator-associated pneumonia and prolonged stays in the intensive care ward. To reduce these substantial risks other options such as NIV therapy have been presented as alternatives. The idea of NIV is to improve oxygenation without the need to intubate the patient.

The main focus of this study is to assess the effectiveness of NIV in patients with respiratory failure caused by PJP and to assess the possibility of NIV being an alternative to mechanical ventilation. Furthermore, this study aims to explore factors influencing the clinical outcome of patients treated with NIV therapy. This paper aims to provide insights for decision-making, optimizing patient outcomes, and streamlining further research in this area. The following question is addressed in this study: to what extent can non-invasive ventilation serve as an effective and appropriate alternative to conventional mechanical ventilation in managing PJP-related ARF? Additionally, this study highlights challenges in implementing NIV and evaluates emerging technologies that could enhance future treatment strategies.

Despite the efficient spread of PJP via air, there are specific conditions on which the colonization of the immunocompromised patient depends. For example, patients with hematological diseases immunocompromised by treatment with corticosteroids have a significantly increased risk of infection. This highlights that exposure to infection alone may not be enough to cause colonization, but that factors such as immune modulation play a significant role (9). Due to this the need for strategies to mitigate risk factors arises.

The immune response of the infected patient plays a substantial role in the pathology seen in patients. Commonly the immune-mediated response of the infected patient results in more damage to the lung tissue than the pathogen itself. Activation of macrophages and excessive release of cytokines lead to acute damage of the alveoli, further leading to impaired gas exchange in the lung (7). The overreaction of the immune response to eliminate the infection and the resulting respiratory distress highlights the importance of treatment not only targeting the pathogen but also the modulation of the immune system to reduce collateral damage. Interactions between PJP and alveolar epithelial cells further exacerbate complications. The trophic form of PJP leads to further lung damage, while its cystic form allows it to prolong its persistence within the host. These cysts also lead to further inflammatory cascades, which again lead to further hypoxemia and acute respiratory distress (12).

5. Methods

This research adopts a multidisciplinary approach, grounded in an extensive review of existing literature, including peer-reviewed studies, clinical trials, meta-analyses, and case reports. A comparative analysis of various ventilation strategies, patient outcomes, and cost-effectiveness data forms the foundation for evaluating NIV's role in this clinical context. The findings are further contextualized by exploring implementation challenges, healthcare system capabilities, and emerging technologies. This paper is organized into seven sections: Chapter 6 provides an in-depth understanding of PJP, including its pathogenesis, immune response, clinical features, and diagnosis. Chapter 7 reviews treatment approaches for PJP-related respiratory failure, focusing on pharmacological management, conventional ventilation, and NIV modalities. Chapter 8 offers a comparative analysis of ventilation strategies, examining patient outcomes, mortality rates, and cost-effectiveness. Chapter 9 highlights the challenges and success factors associated with NIV implementation. Chapter 10 discusses emerging technologies and research gaps relevant to PJP-related ARF. Lastly, the paper concludes with recommendations based on the findings and their implications for clinical practice and future research directions.

6. Fundamentals of Pneumocystis Jirovecii pneumonia

6.1 Pathogenesis and Life Cycle

As previously mentioned, PJP is an opportunistic fungal infection mainly targeting immunocompromised patients, such as patients with HIV/AIDS or transplant patients. In non-immunocompromised patients the immune system can suppress the growth of PJP, however, in immunocompromised patients, PJP can exploit the weakened immune system of the patient.

The life cycle of PJP consists of an interplay of sexual and asexual reproduction, being a central part of its persistence and pathogenicity. During an infection, the trophic form predominates on the pulmonary alveoli adhering to the alveola epithelial cells. This helps PJP to secure nutrients but also aggravates inflammation and exacerbates damage to the lung tissue. (12).

The pathogen presents remarkable adaptability to diverse host environments. In patients with HIV-related CD4+ T cell depletion, PJP can proliferate uncontrolled, however, in patients with non-HIV-related immunosuppression, an excessive inflammation often worsens the clinical presentation (10). This difference highlights that pathogenesis is linked to the type of immune deficiency present in the host. This heterogeneity leads to the necessity of a tailored approach concerning its treatment.

The main route of transmission of PJP is via airborne routes, where infectious cysts are released by infected patients and then inhaled by susceptible patients. This route of transmission raises concerns regarding healthcare-associated infections, such as ICUs (8). This necessitates the need for high-efficiency particulate air (HEPA) filtration and following infection protocols.

6.2 Host Immune response

The immune response plays a pivotal role in the progression and severity of Pneumocystis jirovecii pneumonia, particularly in immunocompromised individuals. Alveolar macrophages are present as the first line of defense. They phagocytose PJP helping to limit its growth and colonization. This first-line defense however is impaired in patients with hematological conditions or undergoing chemotherapies. Immunosuppressive effects resulting from the use of corticosteroids deprive the macrophages of the ability to recruit further immune cells, resulting in the survival of the pathogen, but also accelerating the progression of the disease.

The severity of PJP can be directly linked to the impaired function of macrophages. An unchecked proliferation of PJP in the host, caused by an insufficient response by the macrophages, leads to extensive lung damage. The uncontrolled proliferation also causes the accumulation of inflammatory mediators. This leads to a pro-inflammatory state which worsens the respiratory dysfunction. Patients with a combination of reduced macrophage activity and impaired immune regulation often lead to worse outcomes (7).

Immunocompromised patients often show a lack of reactive oxygen species (ROS) and nitric oxide (NO). These defense mechanisms are secreted by macrophages and are crucial for eradicating PJP in its cystic and trophic forms within the alveoli. This leads to a further weakened innate immune response.

Reduced amounts of CD4+ T cells due to HIV or immunosuppressive treatments cause the weakened response of the adaptive immune system. The CD 4+ T cells are essential for the activation of the macrophages as well as for the recruitment of neutrophils and other immune cells (9).

This interaction with CD4+ T cells leads to a different clinical presentation for patients with HIV and patients without HIV. In patients with HIV, the fungus can gradually proliferate without much interference from the immune system. This leads to slower progression of the disease as the lung tissue is not damaged as fast. However, in patients without HIV and normal CD4+ T cell levels, the progression of the disease is faster. This is due to a hyper-inflammatory reaction due to an overactive neutrophilic response, damaging the lung tissue next to the damage done by PJP itself. This leads to clinical worse outcomes (8). This increased cytokine release in non-HIV patients contributes to ARDS and severe respiratory failure. Elevated cytokine levels can be directly linked to hypoxemia and impaired gas exchange (8; 18).

The hyper-inflammatory response of non-HIV immunosuppressed patients also intensifies respiratory failure. The excessive release of pro-inflammatory cytokines by the neutrophils and proteolytic enzymes amplifies tissue destruction. This leads to higher mortality rates for patients with non-HIV immunosuppression (8).

Regulatory T cells (Tregs) have a regulatory role in PJP infections. They balance pro-inflammatory and anti-inflammatory signals to reduce the damage done to the alveolar tissue by preventing excessive immune activation. Conversely, their suppressive effect can cause a less effective clearance of the pathogen, prolonging the infection. The use of corticosteroids for long periods of time or other immune-modulating therapies also impairs Tregs, leading to a complicated disease progression (21).

A disruption to the Tregs function often leads to worse inflammatory damage in non-HIV patients. Improper use of corticosteroids can hinder pathogen clearance and worsen clinical outcomes but are frequently employed to prevent excessive immune responses of the host (9).

The long-term use of corticosteroids therefore affects both the innate and adaptive immune system of the host, leading to a reduced ability of the host to deal with the infection. Research indicates that the use of corticosteroids within 40 days before PJP infection increases mortality significantly, especially in non-HIV immunocompromised patients (9).

Although the humoral response is less studied, it is known that it plays an important part in fighting a PJP infection. The recognition and clearance by macrophages are further facilitated by pathogen-specific antibodies. This interaction is impacted by patients who are immunocompromised as they have lower antibody production which hinders the host's ability to fight the infection (7). Treatment strategies that target the humoral immune response currently present promising avenues for complementing treatment strategies, by enhancing specific antibody responses and decreasing the overall disease burden in infected patients at higher risks (7).

Generally speaking, the immune response to PJP is a complex interplay between the innate and adaptive immune system. The interaction between the immune system, pathogen clearance, and inflammatory reactions highlights the importance of a tailored approach to managing this disease.

6.3 Clinical Manifestations and Diagnosis

PJP presents with a wide range of clinical manifestations such as dyspnea, non-productive cough, and fever as the most commonly seen symptoms. Particularly dyspnea is often seen in infected patients as it occurs in around 88% of all patients and is particularly worrying due to its correlation with severe hypoxemia. This can potentially lead to respiratory failure. As discussed earlier the immune response in non-HIV immunocompromised patients, such as patients with hematological diseases, overshoots and causes more severe damage to the lung tissue (19).

Fever and a non-productive cough are present in 69% of all PJP cases. These symptoms, however, are unspecific and often occur with other pulmonary infections. This complicates the diagnosis, especially in immunocompromised patients, as the symptoms are unspecific, highlighting the importance of taking a good immunological history before making a diagnosis (19). The severity by which the disease progresses in non-HIV immunocompromised patients further increases the need for a good anamnesis and diagnosis strategy in those patients. For patients within this group, the diagnosis of PJP should always be considered to treat it early and decrease potential damage to the lung as efficiently as possible (19).

Severe hypoxemia is a hallmark of PJP infections and correlates with damage to the lung tissues and impaired gas exchange. This is due to the pathogen's activity and due to the immune response of the host, which as discussed previously is more severe in non-HIV immunocompromised patients. Hypoxemia can be used as a severity marker of PJP infections as it strongly correlates with imaging and laboratory findings. Patients with severe hypoxemia are at high risk of severely worsening and rapidly progressing to acute respiratory failure if they are not treated immediately. (8).

Chest X-rays reveal bilateral interstitial infiltrates in 83.3% of patients and therefore play an important role in diagnosis. These findings, however, are not pathognomonic and often appear with other pulmonary conditions, such as bacterial pneumonia. Therefore it is necessary to combine clinical and laboratory findings with X-ray findings to form a diagnosis (19).

A high-resolution CT scan can enhance diagnosis-making as it can show bilateral, widespread ground-glass opacities in around 69% of infected patients. These CT findings play a pivotal role in making a diagnosis when combined with clinical symptoms and are highly specific to PJP when combined. Therefore a high-resolution CT scan plays a pivotal role in making a diagnosis and ruling out other causes for hypoxemia and the main clinical symptoms, such as fever and non-productive cough (19).

A PCR test of BAL fluid is another important diagnostic measure for diagnosing PJP in patients. It is highly sensitive and can offer additional information when the imaging studies are inconclusive. However, a PCR may also identify a colonization rather than an active infection, especially in immunocompromised patients. To limit this challenge the findings in the PCR should be correlated to the clinical symptoms and imaging findings. This helps to differentiate between colonization and an active infection in the patient. Combining these methods allows for a more accurate diagnosis of PJP and allows for choosing an appropriate implementation of therapeutic measures (18).

In challenging cases, the use of cytological staining for PJP cysts can be used. Cytological staining is less sensitive than a PCR test, but it can complement PCR findings and improve diagnosis-making.

Cytology is not always needed but can be of great help in particularly challenging cases, or the results of previously performed tests present conflicting signs (19).

A comprehensive anamnesis also plays a pivotal role in diagnosis-making. Factors such as immunological status, corticosteroid use, or preexisting hematological malignancies can give valuable hints for the diagnosis and also imply the need for different treatment approaches (14; 19). Therefore a combination of anamnesis, clinical findings, imaging, and laboratory findings is the foundation to make an accurate and timely diagnosis for PJP patients.

Non-invasive respiratory support strategies are primarily discussed as treatment methods but can also play a role in diagnostic measures. Recent studies with preterm neonates with respiratory distress syndrome have shown that treatment with non-invasive positive pressure ventilation (NIPPV) reduces the need for mechanical ventilation compared to continuous positive airway pressure (CPAP) with a risk ratio of 0.60. This ventilation method was also linked to lower cases of air leakage and decreased mortality (15). Even though this study was focused on neonates it could give possible indices for patients with PJP. It could lead to an understanding of patients' responses to non-invasive ventilation and an understanding of this could allow for early detection of treatment failure, allowing for more precise clinical decision-making in those situations.

All in all the diagnosis of PJP is based on combining the clinical symptoms combined with imaging studies and laboratory findings. This requires a multidisciplinary team and can be a complex multistep approach.

7. Treatment Approaches in PJP-related respiratory failure

7.1 Conventional treatment strategies

The primary medical treatment strategy for PJP and the first-line choice of treatment is the administration of trimethoprim-sulfamethoxazole (TMP-SMX). TMP-SMX inhibits the enzymes crucial for the production of folic acid. Reduced production of folic acid severely impacts the survival and proliferation of both cystic and trophic forms of PJP. This helps to reduce the pathogen load and also reduces the damage done by the pathogen and the immune response to the lung tissues (7). However, the timely administration of TMP-SMX is important. A delayed administration has shown increased mortality rates, especially in non-HIV immunocompromised patients (8).

In severe cases, it is often required to administer high-dose TMP-SMX for treatment. This however also bears a higher risk of complications such as renal toxicity, and bone marrow suppression among the most common complications. This has resulted in patients receiving high doses of TMP-SMX needing to be monitored even more carefully to ensure that the toxicity of the dosage is not leading to further harm, but also that the dosage is high enough to treat the pathogen adequately (7).

In recent years resistance to sulfonamides has been seen. This resistance proves as a challenge to the use of TMP-SMX and asks for the need for second-line treatment. Clindamycin-primaquine or atovaquone often can be used as second-line treatment if resistance to sulfonamides is suspected or proven. However, both of these options have a lower efficacy than TMP-SMX. (7). Better more efficient options are currently being discussed to address the rising resistance to sulfonamides.

Additionally, the use of corticosteroids as adjunctive therapy has emerged complementary to the use of TMP-SMX. This combination therapy is particularly used in patients with severe inflammatory responses in order to limit the damage to the lung tissue and prevent acute respiratory failure. By inhibiting the release of cytokines, corticosteroids help to limit the host immune response and therefore reduce the damage done by the immune system to the host lung tissue. This decreased release of cytokines is especially useful in non-HIV patients, as their immune system more commonly reacts more aggressively to a PJP infection. Preventing damage to the alveoli allows for better oxygenation and preserves lung function (8). Recent research has indicated that the use of corticosteroids within 72 hours after starting the treatment has reduced mortality in patients. Delayed use of corticosteroids also reduces their effectiveness in protecting from the survival rates of non-HIV patients who are treated with corticosteroids are significantly higher than those who are not treated with corticosteroids. This can largely be linked to the reduction of the cytokine activity caused by the CD4+ T cells (12).

However, the use of corticosteroids also bears risks of side effects, especially if used in high doses. While they are invaluable by decreasing the cytokine activity, they can also be the cause of secondary infections or a delayed immune recovery in the patient (8). To reduce these side effects guidelines recommend starting with a high dose of corticosteroids and then gradually tapering the dose used. This helps to treat inflammation while reducing the risk of adverse reactions (7).

The use of conventional mechanical ventilation remains a major part of treating severe respiratory failure. Even though it is commonly used for patients experiencing respiratory failure it still poses a significant risk for those patients. Patients receiving conventional mechanical ventilation, especially those who are immunocompromised, are at risk for ventilator-associated pneumonia barotrauma, and other complications associated with mechanical ventilation. Mortality rates for patients who are immunocompromised and receive mechanical ventilation can be up to 90%. (8). Therefore the reliance on conventional mechanical ventilation should be reconsidered and the use of non-invasive ventilation options, such as CPAP or BiPAP, should be explored. These options reduce the risks introduced by mechanical ventilation and also preserve the physiological reserves of transplants (8). The use of conventional mechanical ventilation also requires the patients to stay for more extended periods in the ICUs, which increases the risks for complications but also increases the healthcare costs. A need for close monitoring protocols is also needed to detect complications as early as possible, further increasing the risk of complications (7).

The knowledge of how to use certain non-mechanical ventilation devices also plays a crucial role in the treatment of patients. Recent studies have shown that approximately 69,1% of nurses have a good understanding of non-invasive pressure ventilation (NIPPV). However there are still gaps which persist and are especially in the areas regarding the indication and the modes of NIPPV. These gaps highlight that there is still a need for further training in this area, to improve quality and the risk of improper use of those devices (20).

Prophylactic measures are commonly used, especially the prophylactic administration of TMP-SMX. The use of TMP-SMX as a prophylactic agent has proven to be highly effective in preventing infection with PJP in high-risk populations, such as transplant patients or patients with prolonged immunosuppressive therapy. It has been proven to reduce hospitalization rates as well as to improve the outcomes if infection happens (8). The compliance of patients receiving TMP-SMX as prophylaxis plays a pivotal role in its effectiveness. Improper adherence to the regime can lead to often preventable cases of infections PJP. Proper patient education combined with regular follow-ups are invaluable to maximize the effects of the prophylactic benefits.

There is also a gap in the administration of TMP-SMX as prophylactic agents in different population groups. For example, there is an incidence of 2-4% of infections with PJP for kidney transplant patients who do not receive TMP-SMX as prophylaxis (2). Especially in the high-risk period within the first 6 months after the transplant highlights the importance of the timely use of prophylactic measures to reduce infections with PJP. The emergence of resistances of TMP-SMX, as discussed earlier, also highlights the need to develop alternative treatment and prophylaxis measures that are similarly effective as TMP-SMX. It also asks for close monitoring of the resistance of PJP to TMP-SMX (8)

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Generally speaking, the conventional treatment strategy for PJP requires a timely intervention and a treatment that focuses on the pathogen but also limits the cytokine activity of the body, to limit damage to the alveoli. Significant challenges still remain, especially seen with the complications and mortality of patients receiving conventional mechanical ventilation, highlighting the need for possible alternative treatment strategies.

7.2 Non-invasive ventilation modalities

To improve patient's outcome the management of respiratory failure in patients is highly important. Therefor the usage of non-invasive ventilation is becoming more important as treatment modality. At this point there are different modalities in use, such as Continuous Positive Airway Pressure (CPAP), Bilevel Positive Airway Pressure (BiPAP), and High-Flow Nasal Cannula (HFNC), which can be used for non-invasive ventilation.

7.2.1 CPAP and BiPAP Systems

CPAP can be of great use in the management of PJP patients experiencing acute respiratory failure. It delivers a continuous airway pressure to the lungs as the patient breathes in. This increases oxygenation of the patients and helps the alveoli to stay functional. This is especially important in those patients who experience hypoxemic respiratory failure (8). The continuous positive pressure applied by the CPAP machine also has the positive effect that the collapsed alveoli can be expanded again. This can be of great help in patients with severe damage to the lung tissue done by the immune response to PJP and also PJP itself. It helps to improve and preserve the gas exchange of the lungs, to improve better oxygenation.

CPAP is particularly useful in those patients who experience purely hypoxemic respiratory failure. The continuous pressure applied by this modality helps to stabilize the alveoli, improves residual capacity and helps to reduce the effort required to breath. For Patients with PJP this treatment modality allows for an effective means to support the patients breathing without risking their defense mechanism, such as coughing which helps to remove the infective material in the patients' lungs (16). CPAP also helps to reduce the strain to the respiratory muscles, helping to improve the patients breathing. CPAP, however, is not as useful in managing hypercapnic states in patients with respiratory failure as BiPAP. This requires the need to monitor the patients' blood gas values closely to choose precisely if CPAP is the right choice or if it is more appropriate to use BiPAP.

BiPAP system allows two different pressures applied to the breathing of the patient. The "Inspiratory Positive Airway Pressure (IPAP)" and the "Expiratory Positive Airway Pressure (EPAP)" which make up the two levels used in BiPAP. This allows similarly to the CPAP for better oxygenation but also prevents the collapse of the alveoli and helps to improve the removal of CO2 from the body. The IPAP can be compared to the CPAP while the EPAP can be compared to the Positive End-Expiratory Pressure used in mechanical ventilation. The EPAP prevents the alveoli from collapsing, improves end-expiratory lung volume and oxygen saturation. It also aids with the clearance of CO2 from the body. This tailored approach can be particularly helpful for patients with chronic obstructive pulmonary disease (COPD) or patients who are hypercapnic with conditions such as acute respiratory failure in PJP infections (15). BiPAP also helps to maintain the ventilatory effort of the patient by reducing diaphragmatic fatigue, which helps to limit further decompensation of patients. Potential risks still need to be monitored carefully, such as the risk of over ventilating hypercapnic patients, which could worsen a respiratory acidosis.

The successful use of CPAP and BiPAP to treat PJP patients with respiratory failure requires adequate and early intervention timing and their use in the right settings. To identify their efficacy and also to allow for the right adjustments it is vital to introduce monitoring protocols which regularly check the patients' conditions. Regular assessment of the arterial blood gases and the oxygenation of the patients are vital control mechanisms. An early treatment start with NIV-therapy also may help to reverse inflammation and damage done to the alveoli. This helps to reduce the risk for irreversible respiratory decline (8). To achieve optimal outcomes it is vital that healthcare teams have adequate knowledge and tools to recognize declining respiratory function and also the knowledge to react accordingly. Even though NIV-therapy can have great value it is important to have structured protocols to follow in case NIV-therapy fails, so that the decision can be made to switch to conventional mechanical ventilation.

CPAP and BiPAP can be of great value, but they also have limitations. Patient adherence to the therapy with non-invasive ventilation measures still plays a very important role in the effectiveness of those modalities. Common complaints of patients, such as claustrophobia, discomfort while breathing, and pressure injuries from the mask or the straps of the mask are commonly heard and limit the adherence of the patients to the treatment. As the masks need to be placed firmly over the patient's nose and mouth, a tight fit is needed. This leads to issues with different designs of masks, how they seal around mouth and nose, and material which is light weight, but still secure (4). Studies have shown that pre-treatment education of patients have increased their adherence to therapy. It was also shown that training of healthcare personnel in mask application and problem fixing with these modalities increased the efficacy of CPAP and BiPAP, while reducing air leakage and discomfort for the patient during the therapy.

CPAP and BiPAP systems both represent great opportunities for reducing the need to mechanically ventilate patients who experience respiratory failure during a PJP infection. They help to improve oxygenation and prevent alveoli from collapsing. They, however, still have limitations, mainly the adherence of patients and also need proper protocols to improve their use and safety.

7.2.2 High-Flow Nasal Canula Therapy

High-flow nasal cannula therapy administers a high flow rate of oxygen to the patients via a nasal canula. This high flow rate of oxygen is heated and humidified to reduce complications from the therapy, such as drying of the mucosal skin of the nose. It has emerged as an alternative to therapy for patients experiencing hypoxemic respiratory failure in conditions such as PJP infections. It allows for precise control over the fraction of inspired oxygen (FiO2) and similarly to CPAP and BiPAP it improves the alveolar availability while also reducing atelectasis. As patients with PJP have ranging values of alveolar damage and inflammatory responses of the immune system, impairing oxygenation, this modality can help to improve oxygenation without the need for mechanical ventilation (6). The humidification of the air helps to reduce airway dryness, reducing complications such as thickened secretions or irritation to the mucosal tissues. These complications could worsen respiratory distress experienced by the patients if they occur.

HFNC therapy has a much better patient adherence compared to the patient adherence of CPAP and BiPAP. The non-compliance of patients with HFNC therapy measures at 1,8% while the intolerance of CPAP and BiPAP measures at around 14,0% which is significantly higher. This improved adherence can be traced back to the nasal prong used in HFNC compared to the mask in CPAP and BiPAP. The improved adherence of the therapy leads to improved outcomes when used. The usage of a nasal prong over the mask leads to lower rates of anxiety in patients which in turn enables a better respiratory effort by the patients leading to better therapeutic effectiveness of HFNC. The problems arising with CPAP and BiPAP concerning pressure injuries are also improved in HFNC, again leading to an improved adherence to the usage by the patient. This overall leads to better patient focused treatment, without compromising the efficacy of respiratory support.

Next to the increased patient tolerance to HFNC there are also measurable improvements seen in physiological parameters which are important in improving acute respiratory failure in patients with PJP. The use of HFNC helps to reduce the anatomical dead space in the upper airways, allowing for better CO2 clearance, while also increasing the gas exchange and reducing, similarly to CPAP and BiPAP, the respiratory effort. This improvement can be seen in the reduction of respiratory rates in patients receiving HFNC being at 25 ± 4 breaths per minute over 24h, while patients receiving BiPAP therapy are at 27 ± 5 breaths per minute over 24h. This decreased respiratory rate compared to BiPAP shows that HFNC reduces respiratory muscle strain and in turn allowing for an improved patient stability. The high oxygen flow also allows for continuous oxygen delivery in alternating situations. Moreover, HFNC has shown promising outcomes in Meta-analyses involving other non-invasive ventilation modalities. Compared to standard oxygen therapy HFNC has shown a reduced likelihood of treatment failure (OR: 0.51, 95% Crl: 0.29–0.81) (22).

Also the frequency of airway manipulations in HFNC treatment where shown to be lower than in other non-invasive and invasive modalities. The mean of airway interventions in patients with HFNC treatment had a mean of 6 while patients treated with other non-invasive strategies had a mean of 8 interventions. These lower airway interventions reflect the lower physical strain for the patients, as well as their improved comfort. (6). A lower rate of hands-on airway interventions also lowers the risks of secondary infections, trauma dealt to the airways, and reduced pauses in the treatment. A lower rate of complications in turn means that the burden for the patient and for the medical team, needing to properly respond to possible complications, is reduced. This reduced intervention rate also allows for better patient stability and also for more resource-effective treatment.

There is, however, the potential risk of aerosolization of infectious particles while using HFNC. It is still debated if there is a high risk for aerosolization, with some experts arguing there is not a high risk, while other experts argue for the use of precautionary measures (13). This uncertainty has limited the use of HFNC application in clinical use, even though it has been proven to be an effective tool to manage acute respiratory failure. Its aerosolization risk is described to be lower than the risk posed by CPAP and BiPAP, but the implementation of protective equipment for personnel and an adequate infrastructure of the hospital is still required (8).

The utilization of HFNC in the management of acute respiratory failure in PJP patients remains however low. This leads to gaps in standardized guidelines and not enough training provided to healthcare professionals. To improve its usage it is important to improve familiarity with HFNC and explain its application and benefits to healthcare professionals. Furthermore, educational programs and evidence-based protocols are needed to improve their usage in hospitals (8). Also, further research into the effectiveness of HFNC for specific risk populations, such as non-HIV immunocompromised patients, could help to increase its utilization (6).

High-flow nasal cannula therapy offers advantages in patient adherence and clinical outcomes compared to CPAP and BiPAP. However, challenges such as the aerosolization risk and the unfamiliarity and lack of structured protocols for use hinders its widespread use in hospitals.

8. Comparative Analysis of Ventilation Strategies

Choosing the right modality of ventilation to treat acute respiratory failure in PJP patients is crucial. This section will compare non-invasive ventilation modalities compared to conventional mechanical ventilation. Focusing on the non-invasive modalities named above, CPAP, BiPAP, and HFNC. It will highlight clinical outcomes, patient survival rates, and look at the cost effectiveness of those modalities compared to conventional mechanical ventilation.

8.1 Efficacy of NIV versus Conventional Mechanical Ventilation

Comparing non-invasive ventilation to conventional mechanical ventilation in patients with Pneumocystis jirovecii pneumonia experiencing acute respiratory failure shows significant differences in the clinical outcomes. Patients who are treated with non-invasive ventilation strategies have shown lower rates of intubation. This lower rate of intubation is crucial as intubation in those affected patients carries a high mortality rate. The mortality rate for immunocompromised patients who are infected with PJP exceed 90%, highlighting the non-invasive ventilation approach as an important factor to reduce the need to intubate those patients. As discussed earlier non-invasive ventilation can help to improve spontaneous breathing of the patients, by reducing the strain placed on the respiratory muscles of the patients and also helps to manage hypoxemic and depending on the modality, hypercapnic states of the patient. This can help to stop the progression of acute respiratory failure, preventing the need to intubate a patient at risk (3; 8). This prevention of the need to intubate all patients who experience acute respiratory failure due to a PJP infection helps to reduce intubation and therefore helps to reduce ventilator-associated complications, such as ventilator-associated pneumonia.

Focusing on the advantages of non-invasive ventilation modalities to help to maintain proper pulmonary function, it is important to highlight the benefits of it during the early stages of acute respiratory failure. Helping to reduce respiratory effort and also improving oxygenation of the patient an early therapy with non-invasive ventilation modalities can help to reduce compounding factors worsening acute respiratory failures. The compounding factors include diaphragmatic fatigue and the collapse of the alveoli, which can be stopped or reduced by the positive pressure provided by the treatment modalities. Also patients who are treated with non-invasive modalities experience less complications compared to patients who are treated with conventional mechanical ventilation methods. They show a lower frequency of ventilator-associated pneumonia and other systemic infections, which occur more often in cases where the patient needed to be ventilated mechanically. (8). This is particularly important for patient risk groups who are immunocompromised and are especially at risk of being infected with nosocomial infections.

The ability of non-invasive ventilation modalities to support the lung mechanics, reducing the strain on the respiratory muscles and improving oxygenation plays another vital role in their application. This is particularly important in combinations of hypoxemic and hypercapnic states in patients infected with PJP. Here alveolar damage impairs the effective gas exchange. (16). The ability of CPAP and BiPAP to help the collapsed alveoli to expand again and reduce the damaged alveoli from collapsing helps to stabilize this imbalance of the gas exchange, stabilizing the patient. These modalities also allow for greater patient comfort and compliance with the treatment. (15).

The adaptability of those non-invasive ventilation modalities also plays a pivotal role in their effectiveness. While CPAP is mainly useful in hypoxemic states and does not help particularly well with patients with hypercapnic respiratory failure, the use of BiPAP can help in these specific situations. The ability of BiPAP to administer inspiratory and expiratory pressure allows for a better removal of CO_2 from the body, allowing to minimize situations where high CO_2 levels in the patient exacerbate the acute respiratory failure. Even though CPAP does not help to remove CO_2 as efficiently as BiPAP it still helps to improve hypoxemic states in the patients experiencing hypoxemic acute respiratory failure by improving alveolar patency and oxygenation. These advantages reduce the incidence of barotrauma and alveolar damage, which are common and frequent complications seen in conventional mechanical ventilation (15). Furthermore non-invasive ventilation modalities avoid complications linked to invasive procedures which go along with conventional mechanical ventilation (3).

The use of non-invasive ventilation methods also helps to reduce stays in ICUs for the patient, as well as reducing their stay in the hospital in general. Patients who are treated with conventional mechanical ventilation often stay prolonged periods of time in the ICU and the hospital in general due to the complications associated with the use of conventional mechanical ventilation. For patients who are immunocompromised, as patients with PJP infections, it is important to have shorter stays in ICU units and the hospital in general. For those patients prolonged stays on the wards mean that they have an increased risk of secondary infections or other complications, due to their immunocompromised states. (3; 8). Also the use of conventional mechanical ventilation necessitates prolonged monitoring and interventions for the patients. Non-invasive treatment modalities allow for a quicker recovery of the patients and reduce the dependency of the resources used on the intensive care units.

The notable difference in survival rates between non-invasive ventilation modalities and conventional mechanical ventilation strategies highlights the use of them to be used as a first-line intervention. Their use helps to reduce complications arising with conventional mechanical ventilation but also helps to improve patients' comfort and patient orientated goals. It allows patients to have better control over their treatment, while also reducing psychological stress which is associated with invasive procedure (16). This reduced rate of complications, such as ventilator associated injuries to the lungs and systemic infections, helps to quicken the patient's recovery and shorten their stay in the hospital, while also reducing their long-term morbidity (8).

However, it is important to note that the implementation of non-invasive ventilation modalities relies on careful selection of patients. If they are used inappropriately or their use delays the transition to conventional mechanical ventilation if they fail, they can increase the mortality risk for patients. It is important to develop standardized protocols and have experienced healthcare professionals to ensure that non-invasive ventilation modalities are monitored correctly and that the escalation to conventional mechanical ventilation strategies is done at the correct time. Therefore it is important to have clear criteria when to start the treatment with non-invasive ventilation modalities and also when to switch from them to conventional mechanical ventilation strategies. These criteria are of importance as a delayed recognition of therapy failure with non-invasive ventilation can exacerbate respiratory failure (8).

There are plenty of studies of non-invasive ventilation methods focused on other conditions, such as chronic obstructive pulmonary disease and cardiogenic pulmonary edema. However, the effectiveness of non-invasive ventilation in patients who experience acute respiratory failure due to a PJP-infection, still needs further research. Protocols that were proven effective in patients with chronic obstructive pulmonary disease and cardiogenic pulmonary edema treating impaired gas exchange and extensive lung damage, also suggest that they could yield similar effects to patients with acute respiratory failure due to PJP with the same problems. (16). However there are still gaps in the research which need to be studied in order to address their efficacy (8).

The treatment with High-flow nasal cannula (HFNC) is presents as a promising non-invasive ventilation treatment for patients with acute respiratory failure due to PJP infections. They have an unique advantage compared to CPAP and BiPAP that they have high patient adherence to it. It can provide precise FiO2 delivery to the patient and supports the upper airways, while also ensuring the patients' comfort due to its less obstructive application for the patient (6). There are yet challenges with the risk of aerosolization that need to be looked after, which still limit their broader utilization in general use. Studies with patients experiencing acute respiratory distress syndrome due to COVID-19 have shown that HFNC can be used in infectious settings with the use of negative pressure rooms (17). Further clinical trials and the development of protocols could help to integrate HFNC more effectively into the clinical routinely care for acute respiratory failure in PJP patients. This could yield particularly promising effects, as the adherence to it is higher than the adherence to CPAP and BiPAP use, therefore reducing intubation rates and improving patient outcomes (15).

Generally speaking the use and the potential benefits of non-invasive ventilation methods rely on their early implementation in the treatment, a healthcare team that is familiar with their applications and risks and benefits, and the implementation of standardized protocols to improve their usage. This is of importance as delays in their implementation to the therapy or a delayed switch to conventional mechanical ventilation can be harmful and reduce their effectiveness (8). Healthcare teams who are familiar with non-invasive ventilation modalities are more likely to recognize signs of treatment failure and therefore are able to adjust the treatment strategy more adequately, while also ensuring a better adherence of the patient to the therapy (3).

8.2 Patient Outcomes and Mortality Rates

The use of non-invasive ventilation modalities has shown significantly reduced rates of intubation compared to the use of conventional mechanical ventilation in immunocompromised patients who experience acute respiratory failure due to an infection with pneumocystis jirovecii pneumonia. This is particularly highlighted by the high mortality rate of exceeding 90% of patients with conventional mechanical ventilation in the situation of acute respiratory failure due to a PJP infection (3; 8). This increased mortality rate is inherently linked to the complications associated with conventional mechanical ventilation. These risks commonly include barotrauma, ventilator-associated pneumonia, and the worsening of respiratory mechanics. They also prolong the stay on ICU wards and hospitals in general, increasing the risk of further complications. Non-invasive ventilation modalities offer treatment options which reduce the risk of those complications, as they are not invasive for the patient, therefore reducing the risk for those complications linked to invasive procedures. This is especially helpful for immunocompromised patients, such as patients with PJP infections, as they have a higher risk for those complications. The early use of non-invasive ventilation strategies helps to reduce the rates of intubations needed in those patients, therefore reducing the rates complications can occur.

Research shows that PJP infections often lead to conventional mechanical ventilation and therefore often have high mortality. The use of conventional mechanical ventilation has a 90-day mortality of 27% which increases to 50% mortality for severe cases of PJP (18). The immunocompromised state of the patients who are infected with PJP, which often results from other conditions, increases their risk for complications from invasive ventilation even further. Infection was shown to be the most common cause of mortality in patients with low to intermediate risk hematologic malignancies. This result from retrospective studies suggests that the minimization of risks of mechanical ventilation by using non-invasive ventilation plays an important role in improving the survival rate for those patients (18).

The effective use of CPAP and BiPAP in the management of hypoxemic respiratory failure and hypercapnic respiratory failure respectively helps to reduce mortality rate for immunocompromised patients. CPAP helps to prevent alveolar collapse and enhance oxygenation, while BiPAP also enhances CO_2 clearance (16). Using those two modalities minimizes the use of conventional mechanical ventilation, when they are used at a timely and correct manner. By reducing the rates of intubation they help to reduce complications caused by intubations, especially those complications seen in immunocompromised patients. Their effectiveness however depends on their timely use and correct response to changing situations. If treatment failure with CPAP or BiPAP is not seen in a timely manner, it can harm their efficacy, worsening the patient's situation, causing more harm.

They also help to reduce hospital stays for patients, especially ICU stays for those patients. This reduced time spent in the hospital is linked to the ability of non-invasive ventilation modalities to quickly stabilize the patients, but also with their reduced risk of complications, which are commonly seen with conventional mechanical ventilation treatment approaches prolonging recovery time for the patients (3; 15). It is important for them to be used in a timely manner, however, as delayed implementation of them into the treatment strategy often leads to a severe acute respiratory failure which will still need to be treated with conventional mechanical ventilation and therefore loses their benefit of less invasive approaches.

The use of non-invasive ventilation methods has shown to be reducing mortality rates in conditions like chronic obstructive pulmonary disease and cardiogenic pulmonary edema. This reduced mortality rates in these two conditions can be linked the ability of the non-invasive ventilation modalities to treat hypoxemic situations and the ventilation-perfusion mismatch. These two complications can also be seen in patients with acute respiratory failure in PJP patients, therefore suggesting that the use of non-invasive ventilation has potentially similar benefits in PJP patients (16; 8). However further research is needed to particularly see the added benefits to these situations. The variability of patients with PJP who are non-HIV immunocompromised and their hyper-inflammatory response marks the need for clinical trials in order to refine protocols for treatment with non-invasive ventilation modalities (9).

High-flow nasal cannula therapy can help to improve mortality rates as well, as the adherence from patients to their use is higher compared to the use CPAP and BiPAP, as they improve the patient's comfort and induce less anxiety than CPAP or BiPAP (17; 15). Also their humidification helps to improve ciliary mucous clearance and reduce the respiratory effort, those points being helpful in the treatment of PJP in patients. The question of aerosolization still limits its potential use in the general hospital settings, even though evidence suggests it is probability to reduce treatment failure and improving outcomes.

The successful use of non-invasive ventilation treatment strategies for PJP patients with acute respiratory failure and therefore their reduction of mortality rates due to complications associated with conventional mechanical ventilation, relies on their timely use and proper selection of patients (8; 3). Choosing the right patients for treatment with non-invasive treatment modalities helps to reduce treatment failure and therefore consequent need for conventional mechanical ventilation. Proper protocols for situations like treatment failure and how to choose the right patients play an important role in ensuring the efficacy of non-invasive ventilation strategies.

Evidence that non-invasive ventilation strategies can help reduce mortality risks and improve patients' outcomes in acute respiratory failure due to PJP infections is seen, however it still needs further research, training for the healthcare teams, and proper development of protocols to be effectively used in the hospital setting, helping to reduce potential risks and high mortality rates of patients experiencing acute respiratory failure due to PJP infections.

8.3 Cost-Effectiveness and Resource Utilization

Even though cost-effectiveness should not be the prime reason to choose non-invasive ventilation as a treatment option it still plays an important role in choosing non-invasive ventilation for treatment of acute respiratory failure resulting from PJP. Non-invasive ventilation options help to reduce costs for the hospitals by reducing the time patients spent in the hospitals, especially the ICUs, und therefore also reduce the rate of complications which would also increase the costs for the healthcare providers. By also reducing the need for intubation complications such as barotrauma and ventilator-associated pneumonia are reduced, helping to mitigate the cost of the treatment of those complications (8). These options allow non-invasive ventilation as a treatment option to reduce cost and help to utilize resources efficiently where they are scarce.

The cost-effectiveness of non-invasive ventilation is particularly pronounced in patients who are immunocompromised, as they have an increased risk for complications due to invasive procedures, such as intubation for conventional mechanical ventilation. Patients who are immunocompromised due to underlying conditions, such as hematological malignancies, frequently need critical care in the ICU wards. The cost of these stays on the ICU can be reduced by the proper use of non-invasive ventilation modalities, as they reduce the prevalence of conventional mechanical ventilation associated complications, which in turn directly decreases the cost to treat those complications. The improved survival rate of non-invasive ventilation also helps to reduce cost for long-term treatments (16). This highlights the combination of cost-effectiveness and clinical benefits from using non-invasive ventilation as a first-line treatment option.

The cost of conventional mechanical ventilation also includes cost for further interventions. Such interventions include the use of an extracorporeal membrane oxygenation (ECMO) and a prolonged use of antibiotics to prevent or target ventilator-associated pneumonias. The use of non-invasive ventilation reduces the risk for those complications, by reducing the rate patients need to be intubated after treatment failure with non-invasive ventilation. This allows for better resource distribution, especially in settings where there are limited resources to be used for the patients (8).

High-flow nasal cannulas further improve resource-effectiveness even compared to CPAP and BiPAP. There are two main reason. Firstly the initial cost for acquiring such a device is comparably lower than acquiring a CPAP or BiPAP device. They also have a lower maintenance cost which helps to reduce their costs even further once they are acquired. Secondly the tolerance of HFNC is better than the tolerance to CPAP or BiPAP, with an intolerance of 1,8% compared to the intolerance to BiPAP of 14,0%. As higher tolerance leads to less treatment failures there are less costs due to patients needing to be transitioned to more invasive measures, such as conventional mechanical ventilation (6). Once the research gap about aerosolization is adequately closed and HFNC is regularly used in hospital settings in infectious settings, it can greatly help reduce costs for the healthcare provider.

Furthermore the use of HFNC is related to lower rates of invasive airway manipulations. This decreased incidence of airway manipulations has the effect that there are lower numbers of complications due to such airway manipulations. Also similarly to CPAP and BiPAP it helps to reduce the incidence of ventilator-associated pneumonias, reducing the cost needed to treat such complications, such as the cost for antibiotics (8; 6). This reduced rate of complications helps to reduce costs but also helps to reduce the strain placed on the hospital staff, allowing them to spread their resources effectively, leading to a better patient outcome and cost management.

HFNC has a relatively simple set-up and simple level required to operate it effectively. This simplicity helps to decrease training required to work with those devices, allowing for a broader introduction to most settings, especially in facilities where resources are rare, and training options are limited for more complex devices facilities (16).

Studies have proven that home mechanical ventilation compared to home oxygen therapy further reduces cost and the economic efficiency of non-invasive ventilation strategies. A combination of home mechanical ventilation with home oxygen therapy showed a reduced cost of approximately $4,000 per patient compared to home oxygen therapy alone (11). This reduced cost results from fewer hospital admissions and also fewer high-cost interventions. Similar benefits can be expected when non-invasive ventilation strategies routinely are implemented in hospitals for the treatment of acute respiratory failure in patients suffering from pneumocystis jirovecii pneumonia.

The reduced cost stemming from the use of non-invasive ventilation can also lead to better resource-effectiveness for the whole healthcare system. By reducing the cost for the whole system it allows for a better allocation of resources in times of need, such as a public healthcare crisis (16). The money that can be saved by using non-invasive ventilation methods also can be saved and be used at a later time to improve the infrastructure, make hospitals and medical care more accessible, and to generally improve the healthcare system.

High-flow nasal cannula therapy can also help to reduce costs in non-specialized care environments, making it even more valuable in settings where there are restricted resources. As its acquirement is less costly and its maintenance is lower than other non-invasive ventilation devices, such as CPAP and BiPAP. Also the infection protocols for HFNC as they are now and with possible studies proving aerosolization is of a similar or even lower risk than CPAP and BiPAP, as explained earlier with the COVID-19 study, it may be even more helpful in settings where proper infrastructure is not readily available. This can again be very helpful in the situation of the public crisis where resources need to be distributed very carefully to handle the coming cost of all the interventions correctly. (8).

Yet again the timely initiation of treatment with non-invasive ventilation methods is of great importance concerning their cost-effectiveness. If they are used to late or incorrectly the risk for treatment failure increases, leading yet again to the switch to conventional mechanical ventilation, which greatly increases the costs needed for the treatment. Guidelines helping to decide when to initiate the treatment with non-invasive ventilation and also guidelines when to escalate the treatment to conventional mechanical ventilation can help to improve patient outcomes but also helps to improve cost-effectiveness (8). These guidelines are of great importance to optimize the cost-benefit ratio of non-invasive ventilation.

Even though there are studies that prove the cost-effectiveness of non-invasive ventilation in treatment compared to conventional mechanical ventilation, its cost-effectiveness in treatment of acute respiratory failure in patients with PJP has not been specifically studied. This gap in direct and long-term data shows that there is a gap in the research proving the cost-effectiveness of non-invasive ventilation for this patient group. Research should focus on immediate cost reduction by using non-invasive ventilation but also should focus on the potential benefit by reducing long-term complications, such as chronic respiratory complications, and therefore reducing the cost associated with the treatment of those long-term complications (16).

Overall the use of non-invasive ventilation can help reduce costs, especially HFNC, by reducing hospital stays, minimizing complications, and lowering operational expenses. However there are still gaps in the research which need to be addressed, before there can be a conclusive statement made about the cost-effectiveness.

9. Implementation Challenges and Success Factors

The treatment of pneumocystis jirovecii pneumonia is complex and requires a strategic approach as well clinical decision making, training of healthcare professionals, and effective monitoring protocols. This part focuses on the main challenges of implementing non-invasive ventilation successfully, so that its benefits can be utilized while minimizing its wrongful use. By addressing those challenges this part tries to help with the implementation of improving management protocols, helping to reduce mortality rates.

9.1 Clinical Decision-Making Framework

It is critical to diagnose a pneumocystis jirovecii pneumonia infection early and to start intervention as soon as possible. To stop its rapid progression and high mortality rates, especially in the immunocompromised patients, needs the prompt initiation of antimicrobial therapy with TMP-SMX other alternatives for patients who have allergies related to those agents or for cases where resistance is proven or suspected (8). The use of corticosteroids is also recommended when the patient suffers from severe hypoxemia (PaO2 <70mmHg) to dampen the immune response of the patient and to mitigate the damage done by the immune response to the lung tissue (7). Delays in the initiation of the treatment have been shown to worsen the outcomes for patients, even reaching mortality rates of up to 60% in non-HIV immunocompromised patients (7; 8). This high mortality rate highlights the need for tools to identify patients at risk.

Making an accurate and fast diagnosis can be difficult due to the unspecific symptoms with which PJP can present. Therefore a robust diagnosis needs to include a high-resolution computed tomography combined with the clinical findings and bronchoalveolar lavage (7).

A timely initiation of treatment with non-invasive ventilation strategies helps to improve the outcomes for the patient significantly. Initiating non-invasive ventilation within hours of respiratory decompensation has proven to prevent even further clinical deterioration (8). Programs helping to train the rapid response and the details of non-invasive ventilation modalities help to increase patient comfort and improve the device setup. However the problems of non-invasive ventilation, such as patient incompliance also need to be addressed with the patient (3).

It is important to select the patients carefully and to choose which treatment modality is the best choice for each patient individually. Patients who experience moderate hypoxemia and moderate hypercapnic acute respiratory failure are favorable for the treatment with non-invasive ventilation. However patients who experience respiratory distress, impaired consciousness, or hemodynamic instability more commonly need to be intubated right away (16). Scoring systems, such as APACHE II and SAPS II may help to identify the correct treatment option for each patient. It also needs to be considered if the patient has relevant comorbidities which can impact the effectiveness of the implementation of non-invasive ventilation (1). Therefore a multidisciplinary team can help to make a more dynamic treatment option, evaluating each approach more accurately (8).

The multidisciplinary approach helps to improve patient care with each party having control in their respective part of the treatment and working together to achieve the best result. For example the pulmonologist assesses the respiratory function of the patient while a respiratory therapist oversees the device settings and has an eye for potential complications. Additionally the intensivists have a view of the general condition of the patient and decide when to escalate the treatment approach (8).

The effectiveness of non-invasive ventilation requires standardization and clearly defined criteria to maximize their benefit in clinical use. Those criteria need to include oxygen saturation levels, PaCO2 thresholds, but also need to include the possible contraindications for initiating the treatment (3). These protocols also need to address specific criteria, such as the settings for the devices used, or how frequently a patient should be monitored to see early signs of treatment failure. Based on these criteria there should also be protocols introduced on how to react to specific clinical parameters (16). Training healthcare professionals with these protocols helps to strengthen their knowledge and prevent mistakes, improving the quality of the care for the patient (8).

Training programs for healthcare professionals are indispensable. They should include theoretical parts, explaining device settings and how to react to specific situations, while it should also contain a practical part allowing healthcare professionals to get a hands-on feeling for the devices and their correct implantation. (7). To keep the team up to date with recent updates or new devices regular refreshers should be offered to the healthcare team. These updates should also involve new evidence found on the effectiveness of non-invasive ventilation in the treatment of acute respiratory distress for patients with PJP (3).

The healthcare team should, however, also know about the contraindications in the application of non-invasive ventilation. Contraindications such as severe respiratory acidosis (pH<7,22) or neurological impairment should also be included in those protocols. Thus allowing for more consistent clinical practice and reducing the amount of complications (8). These protocols should also include proper settings for the devices in use, to optimize their use and also reduce the incidence of adverse outcomes (16).

In order to ensure that there is no delayed switch from non-invasive ventilation to conventional mechanical ventilation, due to the increased mortality if this switch is delayed, indicators for those situations should also be included in those guidelines. There should also be indicators, such as worsening oxygenation or a persistent state of hypercapnia, which should trigger an immediate switch to conventional mechanical ventilation to improve the patient’s outcome and to ensure a timely response by the healthcare team to those changes (7).

The successful application of non-invasive ventilation in patients with acute respiratory failure due to PJP relies on a multifaceted approach, prioritizing an early intervention, an accurate risk identification of the patient, and the collaboration of multiple healthcare disciplines. Therefore protocols need to be in place to ensure an understandable and still adjustable approach for each patient's case.

9.2 Healthcare Team Training Requirements

To ensure an optimal outcome when utilizing non-invasive ventilation modalities for patients with acute respiratory failure during an PJP infections training of the healthcare teams plays a vital role. Programs designed to gain and improve practical skills, such as fitting the masks to the patients or adjusting the parameters on the devices as practical tasks and as theoretical skills the ability to recognize patients' intolerance or treatment failure are of great help. A proper setup of the device directly affects the efficacy of non-invasive ventilation therapy by improving oxygenation but also improving patient comfort throughout the therapy. In order to achieve these results it's vital that the healthcare teams are properly trained and are able to educate the patients (8).

It is also of importance that the healthcare teams are able to deal with ventilator-related complications which can reduce the effectiveness of the non-invasive ventilation therapy. For those situations training programs should be performed which train the response to such problems, such as ventilator-patient desynchrony or wrong parameter settings on the device. Wrong pressures, such as the PEEP can make the difference between treating hypoxia or making the patient progress to severe respiratory failure. Therefore a dynamic approach to varying clinical situations helps to reduce the need to escalate the therapy to conventional mechanical ventilation (7).
During those training modules a time for debriefing or a feedback round also has significant advantages for healthcare teams. This allows them to get real-time feedback and immediately address mistakes as they occur. This allows them to build confidence and gives the healthcare teams a feeling of preparedness for possible situations in the future.

Offering training in team building allows for better cooperation within the multidisciplinary team. In the case of PJP treatment this could involve team building exercises including the pulmonologist, the nurses and the intensivists. This allows for better teamwork, especially in critical situations, which can occur often in patients with severe acute respiratory failure due to PJP, as these patients often deteriorate quickly (3).

Such tools for training the healthcare teams could be simulated scenarios with patients. Those scenarios can prepare the team for specific situations which require quick responses and help them to anticipate the next steps and react accordingly. They also help to build confidence in dealing with high-pressure situations and can enhance confidence within the team. They also reduce the number of errors which can occur as they refine the decision-making progress (7).

Training in communication between team members also allows for better integration of specific information about the patient which can significantly influence the treatment approach. Communication about the CD4+ T cells for example can greatly influence the treatment approach if it is communicated correctly within the team (8).

Another aspect which should be taught in those training is the early recognition of treatment failure, such as dropping PaO2/FiO2 ratios or rising CO2 levels. These signs and their early recognition are important as a delayed response to such changes and a delayed switch to conventional mechanical ventilation can worsen the patient's outcome and mortality (8).

In order to ensure that healthcare teams use the most appropriate non-invasive ventilation modality it is important that the teams now the specific advantages and specific limitations of the different non-invasive ventilation modalities. This helps to promote the proper selection of the most useful modality for the right situation, for example choosing the BiPAP device for patients with hypercapnic respiratory failure (16).

There is also the need to address potential language barriers during training. There can be different languages or access to devices with which not all member of the healthcare teams are familiar with. Giving the team explanations or providing them with different formats that help the to accommodate for their different needs for learning improves the overall effectiveness.

To increase patients' comfort there is also a need to teach the healthcare team with techniques to deal with those discomforts. Discomforts such as an ill-fitting mask can reduce the patient's tolerance to the treatment and therefore reduce the overall efficacy of the treatment. Training the team in how to fix those problems for the patients firstly ensures a better adherence, but also relieves anxiety (7). Implementing hands-on training to deal with specific discomforts, such as claustrophobia caused by tight fighting masks can greatly influence efficacy. These programs can also be used to teach the team about alternative non-invasive ventilation interface, which would allow for an adjustment to the patient's need even better (8).

A comprehensive and multidisciplinary training approach is essential, greatly improves the efficacy of the clinical outcomes and reduces the instances of treatment failure. They should blend theoretical knowledge and practical skills together, so that the team gets a comprehensive understanding of the modalities and the ability to respond to the specific situations accordingly. Allowing the teams to work together and by addressing barriers and mistakes these exercises can greatly improve patient care.

9.3 Monitoring and Adjustment Protocols

In order to effectively monitor a patient treated with non-invasive ventilation the continuous assessment of their blood gases is of outmost importance. The arterial blood gas analysis allows for early recognition of the worsening of the respiratory failure and indicates when there is a treatment failure. The key parameters which should be focused on in an arterial blood gas analysis in such a situation are PaO2, PaCO2, and the pH, as they provide insight into the patient's respiratory functions (8) However arterial blood gas analysis are invasive procedures and cannot be carried out continuously. Therefore other measures, such as pulse oximetry can help to continuously monitor the patient.

The early recognition of arterial blood gas analysis abnormalities is important. This is particularly important in changes to the pH values and changes to the PaCO2 values. These changes are especially important in hypercapnic respiratory failure and often result in the need to rapidly review and change the treatment strategies. An optimization of the pressures used in non-invasive ventilation therapy can often help to improve these abnormalities (3). An increase in the IPAP can help to decrease CO2 levels in the patient by increasing the tidal volume. However, this can lead to discomfort in the patient or ventilator-induced lung damage if done incorrectly (16).

As a complimentary monitoring system the use of frequent clinical evaluation can be of great help. It can indicate even subtle changes in the patient's respiratory sufficiency. Changes such as increased respiratory rate, increased heart rate, or changed mental status can indicate insufficient effectiveness of the non-invasive ventilation therapy. They can point out an inadequate oxygen delivery to the brain which can be due to problems with the settings or adherence to the non-invasive ventilation therapy (7). When combined with the regular checks of the arterial blood gases, it can allow for a robust assessment of the patient. However, these clinical assessments are subjective and might differ from healthcare professional to healthcare professional. This subjectiveness underscores the need for adequate training with those assessment tools, so that these signs can be rated as objectively as possible.

Pulse oximetry is another supplementary tool which is of great help for monitoring the patient. It shows the real time oxygen saturation of the patient and also provides trends on how the patients' oxygen levels are progressing. The ability to immediately see that the oxygen levels in a patient are decreasing allows for fast responses and treatment adjustments. Even though this continuous evaluation of the oxygen levels of the patient is helpful, the pulse oximetry still has its limitations. Pulse oximetry is unable to provide information about the CO2 values in the patients, allowing for hypercapnia to be missed, while it also does not give information about the pH levels, allowing for an acidosis to be missed. These downsides to pulse oximetry necessitates the use of arterial blood gases alongside its use at they can give valuable insight in those areas (16). Another downside is that quite commonly in patients who are critically ill peripheral perfusion can be reduced, which reduces the effectiveness of pulse oximetry, as a relatively good peripheral perfusion is needed for it to work properly.

One can also evaluate the FiO2 the patient needs to be adequately oxygenated. Increases in the FiO2 while the PaO2/FiO2 ratio does not improve can give valuable insight into a worsening condition of the patient, mainly worsening lung function. This can either mean that the non-invasive ventilation therapy needs to be adjusted or that there needs to be a switch towards conventional mechanical ventilation (8). The use of FiO2 as monitoring gives insight into the oxygen demand of the patient, however if the FiO2 is over adjusted without proper control why its demand increases could lead to the problem that underlying conditions, such as pneumonia or atelectasis, could be overseen. In order to role those complications out the use of X-rays in situations like these is helpful, as they can give insights into the reason for the need to increase the FiO2.

The correct use of the PEEP allows for better management of patients with hypoxemic acute respiratory failure. The PEEP allows for an better recruitment of the alveoli while also improving oxygenation, so a careful adjustment of the PEEP is needed to stop alveoli from collapsing. While also preventing barotrauma if the PEEP is to high (7). The correct application needs to be monitored closely, necessitating the use of dynamic compliance measurements.

The parameters also need to be adjusted accordingly to the patients' comorbidities. IPAP and PEEP need to be adjusted accordingly to the patient in order to provide the best possible treatment efficacy. For example patients with chronic obstructive pulmonary disease might need an increased IPAP to counteract already existing ventilatory deficits. Patients with acute respiratory distress syndrome might benefit from a lower PEEP to minimize injury to the lung tissue (16). For this individualized treatment to work properly the multidisciplinary team is necessary to work properly together (3).

To ensure the effectiveness of non-invasive ventilation therapies a timely monitoring system and interventions adjusted to the results of those are needed. Those monitoring system also help to reduce the prevalence of patients progressing to severe respiratory failure. Studies by Yu et al. (23) proved that intervention which are aimed at preventing complications improve the patients' outcomes. They checked patients who were post-kidney transplant. It was seen that those patients who received tailored treatment specifically for them had a reduced rate of progression to acute respiratory distress syndrome, as well as shortened ICU stays and reduced rates of intubation.

In order to prevent complications such as nasogastric inflation a reduction of inspiratory pressure can be used, or a nasogastric tube can be placed to decompress the pressure in the stomach (8).

The rate at which a patient should be monitored needs to be adjusted according to the patient's severity. In the initial stages of non-invasive ventilation therapy a patient should be monitored hourly or bi-hourly. Immunocompromised patients, such as the patients with PJP, benefit from those regular check-ups, as they are prone to deteriorate rapidly (8).Patients with moderate or mild respiratory failure do not need such regular assessments, but any changes in their behavior or changes in the assessments still need to trigger a rapid response to prevent the progression of the acute respiratory failure. The advancement of new ways to assess patients, such as capnography, aids to have more precise controls in between arterial blood gas analysis (16).

These protocols must also include effective strategies to communicate in between the different specialties of the multidisciplinary teams. This aids in having better care for the patient and increases the rate at which a response to a change in the patient can be performed (16; 8).

In order to treat the patient effectively the need to use different monitoring devices and protocols, combined with flexible adjustment protocols is needed. The use of arterial blood gases still remains the cornerstone of the patient assessment but can be supported by other assessments to improve its effectiveness. Addressing problems quickly, using those assessments, can lead to a better patient outcome and improved survival.

10. Emerging Technologies and Future Perspectives

The changing care for patients with PJP highlights the urgent need for new innovative technologies that can improve patient outcomes and help to manage acute respiratory failure more effectively. New technologies such as advanced ventilation technologies, high-flow nasal cannula system for example, or AI-driven support systems show promising steps to improving the patient care and overcome current limitations to non-invasive ventilation.

10.1 Advances Ventilation Technologies

New technologies helping to reduce patient-ventilator desynchrony become more and more popular, as this is a key factor to reduced effectiveness of non-invasive ventilation therapies. Proportional assist ventilation (PAV) and neurally adjusted ventilatory assist (NAVA) represent some of the new technologies on the rise. PAV is able to calculate key respiratory mechanics, such as compliance, but also the resistance and then can aid to deliver proper assistance. NAVA checks the electrical impulses from the diaphragm and uses those impulses to synchronize the patients breathing with the device.

Those devices can be helpful for patients with acute respiratory failure due to PJP as their breathing patterns can fluctuate and thus lead to patient-ventilator desynchrony. These new system work by reducing such challenges while simultaneously reducing respiratory muscle fatigue. By doing so these new advancements aim to prolong the effective use of non-invasive ventilation therapies while also reducing the need to switch to conventional mechanical ventilation. However, as useful as these new systems are the healthcare teams using those devices need proper training as these devices are complex. Misuse or wrong device settings in those complex devices may negate their advantages, making them arbitrary, thus highlighting the need for proper introduction and training with these devices. There is also still limited research done on those devices, especially in their efficacy treating PJP patients with acute respiratory failure. Clinical trials are critical to evaluate their long-term effect on the treatment, sharing insights on their impact on patients' outcomes and their mortality rate (8).

Another newer technology previously discussed is high-flow nasal cannulas as alternatives to more commonly used non-invasive ventilation modalities, such as CPAP and BiPAP. Their delivery of heated, humidified oxygen at high rates allows to reduce respiratory effort and increased oxygenation, while minimizing risks, such as thickened secretions and patient discomfort. Similar to CPAP and BiPAP this technology generates positive airway pressure allowing for an increased recruitment of alveoli, while reducing anatomical dead space and therefore improving gas exchange. Compared to CPAP and BiPAP they also have a higher patient comfort level, as their nasal prongs are more manageable for patients than the masks used in CPAP and BiPAP devices. This reduces anxiety caused by claustrophobia for example and also decreases pressure caused injuries to the patients. This increases the comfort of HFNC compared to CPAP and BiPAP. This increased comfort also increased the tolerance of the patients to this device which leads to increased adherence to the therapy and decreased treatment failure. There are still potential risks with HFNC, especially the risk of aerosolization of infectious agents, which needs to be addressed, especially for patients with PJP. The use of negative pressure rooms may however reduce the concerns arising from aerosolization and the implementation of strict infection control measures may also help mitigate those concerns (13). Introduction of real-time oxygen flow and FiO2 adjustment technologies also helps to increase individualization and sustainability for respiratory management.

With the rise of AI the combination of AI-technology combined with non-invasive ventilation therapy became viable. They represent a novel frontier in respiratory care, having the potential to further improve the management for PJP-related acute respiratory failure. AI has the ability to specifically analyze patient's needs, such as their oxygen demands. With their constant assessment of the patients' demands, AI-driven non-invasive ventilation can than adapt its respiratory support based on the patients' needs and optimize the treatment. AI also has the ability to predict certain outcomes, which can allow for identification of treatment failure, helping to reduce time needed for decision making and thus improving patient outcomes. One of the main abilities AI also presents is to deal with patient-ventilator desynchrony. This helps, as discussed above, the patient to adhere to the treatment, as they have a higher treatment tolerance. However, there is still a need for research there. The long-term effects of the use of AI driven non-invasive ventilation strategies need to be studied and also their cost-effectiveness needs to be explored (12).

The use of wearable respiratory support devices also highlights new possibilities to deal with mild to moderate respiratory failure in PJP settings. Portable HFNC and other compact modalities allow for greater patient mobility, decreasing complications. They also allow for earlier discharges and can reduce the problem of overcrowding of hospitals, by allowing patients to be treated with non-invasive ventilation modalities at home more readily. By doing so, they also have the potential to reduce healthcare costs arising for hospitals and patients, further enhancing the quality of life for those affected patients. They can also improve physical recovery time and rehabilitation time, as they allow patients to start with those activities earlier. The risk for infections, and concerns for device reliability need to be addressed first though before they can be readily introduced in order to see their safety, efficacy, and their potential risk clinical trials need to be done. In order for them to be successful they need to be user-friendly and easy to use, while also ensuring adequate respiratory support for the patient.

In order to challenge problems with single non-invasive ventilation modalities the idea of combining multiple modalities is being researched. For example a combination of CPAP and HFNC could help to increase oxygen levels in patients, while also addressing the issue with patient adherence to CPAP therapy. The challenge lies in combining two modalities effectively into one without losing any benefit and improving the outcome compared to a single modality. Studies need to be done to prove that the combination of two modalities offers better patient outcomes and improved effectiveness compared to using a single modality. Simultaneously their use becomes more complex, meaning the healthcare teams using those devices need to be properly trained in using the combined devices (8).

Technologies such as PAV, NAVA and AI-assisted system have the potential to transform and improve the current respiratory care for patients with acute respiratory failure due to a PJP infection. As promising as they are there still is a need for research, proving their efficacy and their cost-effectiveness. They also warrant more proper training as these systems are more complex and thus can be more prone to failure, mitigating their effectiveness.

10.2 Research Gaps and Opportunities

As of today there is limited evidence focused on the efficacy of non-invasive ventilation therapy when used for the treatment of acute respiratory failure caused by PJP, this is particularly so in the non-HIV immunocompromised group. Most of the studies focus on the broader application of non-invasive ventilation for acute respiratory failure. These studies focus more on the more common causes of acute respiratory failure, such as chronic obstructive pulmonary disease or cardiogenic pulmonary edema (16). These studies might suggest similar results for the application of non-invasive ventilation when used to treat patients with acute respiratory failure due to PJP, but the specific inflammatory response observed in non-HIV immunocompromised patients highlights the need for further studies specifically for PJP patients. This could highlight differences in their response to non-invasive ventilation as treatment, such as different outcomes or mortality rates. Therefore further studies in this area are vital to fully understand and implement non-invasive ventilation to the treatment strategy for PJP patients with acute respiratory failure (8).

Furthermore, recent research current research does not address the specific modalities of CPAP and BiPAP in reducing the rate of treatment failure and therefore reducing the rate of intubation to treat non-HIV immunocompromised patients, even though there is research that shows their effectiveness in different immunosuppressed groups (8).

The emergence of HFNC also proves to be an area which needs further research, before it can be fully implemented into regular clinical use. Concerns such as aerosolization need to be researched to rule out possible sources of infection routes for infected patients, such as PJP patients. Given their higher patient tolerance and their ability to improve oxygenation similarly to CPAP and BiPAP they are promising tools for future use if the research is conducted properly (6). Comparative studies focusing on the mortality rates, complications, such as ventilator-associated pneumonia, and rates of treatment failures leading to intubation across the different non-invasive ventilation modalities are needed to provide essential data to their effectiveness treating acute respiratory failure in PJP patients.

A further field which needs to be researched is the interaction between non-invasive ventilation and the use of long-term corticosteroids. Long use of corticosteroids has shown to increase the mortality rate in PJP patients due to their immunosuppressive effects. This leads to concerns about the clinical outcomes of their use when non-invasive ventilation strategies are used (9). Corticosteroids suppress key immune functions of the body, such as T-cell proliferation and macrophage activation, which can be useful in limiting the body’s immune response to the infection but could also impede the necessary balance for an effective non-invasive ventilation strategy (9). It is also unclear if the use of corticosteroids could potentially worsen the intolerance of patients towards CPAP and BiPAP, particularly in those patients who already have a feeling of discomfort or those who have weakened respiratory effort.

By reducing inflammation corticosteroids help to alleviate the burden placed on the lungs by the immune system, especially in non-HIV immunocompromised patients. This reduced immune response can however lead to a reduced pathogen clearance by the immune response which can delay the recovery of the patient while they are treated with non-invasive therapy. This interaction between corticosteroids and non-invasive therapy treatments also requires further research (8).

As discussed previously there is a need for careful patient selection when deciding to treat acute respiratory failure due to PJP with non-invasive ventilation methods. There are still research gaps in this field which need to be closed. There are a lot of different groups of patients with PJP and therefore there are a lot of variants which can influence the effectiveness of its treatment with non-invasive mechanical ventilation (8). Research into specific thresholds as to when to initiate non-invasive ventilation needs to be performed. Values regarding oxygen saturation, respiratory rate, and arterial blood gases values could help to give clear guidelines when to initiate the therapy with non-invasive ventilation and when other options should be considered.

There is also a lack of research focused on the influence of comorbidities on non-invasive ventilation therapy. Underlying conditions like pneumonias, cardiogenic pulmonary edema or other opportunistic infections could potentially undermine the effectiveness of non-invasive ventilation therapies, necessitating further research in this area (8). In a study focusing on the variation of COVID-19-asscoiated PJP cases showed a wide range of different outcomes of those patients. These different outcomes came from different immunological profiles of those patients, further strengthening the need for research in this area (5). Developing risk identification models combining clinical findings and laboratory parameters could help physicians to better decide which patients could benefit from non-invasive ventilation and which patients would benefit from other approaches, such as conventional mechanical ventilation.

The economic impact of non-invasive ventilation as treatment for acute respiratory failure in PJP patients is still largely unexplored. There are studies that have proven that non-invasive ventilation has shortened ICU stays in patients with acute respiratory failure generally, but these studies did not specifically address the economic value of PJP patients (16). HFNC as a less resource intensive non-invasive ventilation modality is largely unstudied in its economic impact (6). The use of standardized treatment strategies for patients with PJP experiencing acute respiratory failure could also drastically reduce cost, as there would be less delayed interventions or inappropriate escalation of the therapy (8). These studies es especially important in settings where there are shortages in the healthcare system or sparce resources in general, so that hospitals could more effectively implement non-invasive ventilation as a cheaper, yet still good alternative to more expensive treatment modalities.

New technologies such as HFNC and AI-driven non-invasive ventilation systems could be promising new modalities improving overall patient comfort and outcomes. These new technologies could help address key challenges in nowadays practice, such as real-time oxygenation monitoring and adjusting the flow of the machine accordingly without intervention of the patient or the healthcare team in the case of AI-driven non-invasive ventilation. Next to the possibility of oxygen flow adjustment AI-driven non-invasive ventilation could help to predict treatment failure, allowing for quicker and more adequate responses (13). However, for these technologies to be implemented into daily use However, before these technologies can be used in daily practice, they need to be studied carefully and clinical trials with those devices need to be performed to see their effectiveness in treatment of acute respiratory failure for patients with PJP.

Hybrid devices combining the functionality of two different non-invasive ventilation modalities could also be useful in the treatment of acute respiratory failure in PJP patients. However their safety and efficacy are still not validated. For those hybrid devices to be used safely in the clinical routine there need to be thorough clinical trials testing them (8). The use of portable non-invasive ventilation methods could also help to improve the outcomes of patients with acute respiratory failure suffering from PJP, but their efficacy for this specific patient group must also still be examined (12).

The overall long-term outcomes for patients treated with non-invasive ventilation therapy due to an infection with PJP and acute respiratory failure are not adequately understood. Evidence exists pointing to patients with PJP infections, especially those who have HIV, are at an increased risk of chronic respiratory complications, like fibrosis and reduced perfusion capacity when they are compared to patients who had bacterial pneumonia (8). The possibility of non-invasive ventilation strategies reducing those long-term chronic outcomes is still unclear. Studies focusing on comparing different modalities, such as CPAP compared to HFNC could give insight into different outcomes of preserving lung function and could therefore help to individualize patients' treatment strategies.

To fully implement non-invasive ventilation therapy into the daily clinical routine these research gaps need to be studied. This will help to improve clinical decision making and will help physicians to make more adequate decision when using which modality, improving patients' outcomes.

11. Conclusion

Acute respiratory failure caused by infection with PJP poses a great challenge as the mortality and morbidity rates are very high in those patients. Even though there have been many advancements in the recent years improving critical care these mortality and mortality rates still are high. This paper aimed to look at non-invasive ventilation methods compared to conventional mechanical ventilation, as patients who are intubated with this condition have very high mortality rates. Findings discussed in this paper underscore the value non-invasive ventilation can offer when utilized correctly. This study has shown that patients who are carefully selected can benefit from non-invasive ventilation therapy by reducing their hospital stays, especially their stays in ICUs and overall improving their outcomes.

It was shown that non-invasive ventilation can be a good alternative to conventional mechanical ventilation as it has a high mortality rate, especially for the non-HIV immunocompromised group. It showed that CPAP, BiPAP, and HFNC each offer their own distinct advantages which can be utilized and given the right selection very effective. CPAP was shown to effectively work for patients with solely hypoxemic acute respiratory failure, while BiPAP was shown to be useful for patients with hypercapnic respiratory failure, while HFNC was shown as an alternative for patients who were struggling with the masks of CPAP and BiPAP improving their adherence to the treatment. The study also showed that the was a lower risk to ventilator-associated complications, such as barotrauma or ventilator-associated pneumonia, while being more patient focused on the same time.

It was also shown that the effectiveness of non-invasive ventilation to treat patients with acute respiratory failure due to PJP was based on several factors. It was shown that patients with moderate hypoxemia should be selected, and the absence of contraindications should be evaluated for non-invasive ventilation to function properly. It was also shown that the healthcare team are largely responsible for the efficacy of the therapy, by making sure the device is correctly set up, the patient is continuously monitored, and the swift reaction to complications and treatment failure. The successful use of non-invasive therapy relies on patient tolerance, which often represents as a challenge, but also relies on the knowledge of the healthcare team to correctly implement it.

It was discussed that upcoming new technologies have the potential to favorably change the management of PJP-induced acute respiratory failure. Systems such as non-invasive ventilation systems aided by AI, which can monitor and adjust respiratory parameters accordingly and could also help to improve synchronization with the patient, could drastically improve the patients' outcomes. Similarly the combination of two different non-invasive ventilation modalities into a hybrid modality can help to address multiple different needs which one device on their own could not provide. Systems such as PAV and NAVA were discussed highlighting their superior synchronization with the patient, similarly to the AI-assisted devices, improving patient adherence to the treatment and improving their overall outcomes. HFNC were shown to be helpful in reducing patient discomfort, by relieving anxiety which can be caused by the masks of CPAP and BiPAP and helping to humidify their air inhaled by the patient. It was also highlighted that these modalities need further research in order for them to be fully integrated into clinical practice.

This study shows that patients can benefit from non-invasive ventilation as a therapy, mainly by reducing the mortality and improving the care for specifically selected patients. It also acknowledges that there is limited data which specifically researchers to efficacy of non-invasive ventilation as a therapeutic approach for patients with PJP and acute respiratory failure. Most of the evidence is drawn from secondary data which stems from clinical research studying acute respiratory failure broadly but not focusing on patients with PJP. There is a lack of studies done on patients with PJP, especially those who are non-HIV immunocompromised. This leads to difficulty making general statements about PJP treatment efficacies with non-invasive ventilation. It also shows that the integration of standardized treatment protocols remains difficult, as there are many different patient groups, which influence the formation of those protocols.

Another factor which influences the integration of non-invasive ventilation into the treatment of acute respiratory failure for PJP patients is the lack of research about their cost-effectiveness. This study has shown that non-invasive ventilation has the potential to reduce the cost of treatment for those patients, allowing for better resource allocation, but there is limited data for cost-effectiveness in the treatment of PJP patients. Most data were collected from different studies proving non-invasive ventilation had lower resource-costs in patients with acute respiratory failure generally.

To strengthen the use of non-invasive ventilation in the daily clinical routine there are still many gaps in the research which must be addressed. There is a need to perform prospective clinical trials to evaluate the efficacy of non-invasive ventilation across different patient groups with PJP, especially those who are non-HIV immunocompromised. This study also highlighted that criteria for selecting which patients could benefit from non-invasive ventilation need to be developed. These criteria need to be based on criteria's such as immune status, respiratory severity, and underlying comorbidities. The lack of longitudinal studies focusing on the long-term benefits of non-invasive ventilation for patients with PJP experiencing acute respiratory failure needs to be addressed. New and emerging technologies like AI-assisted devices or hybrid devices also need further studies to be implemented into the clinical routine. Therefore their efficacy and also their potential benefits and downsides need to be clearly discussed and looked at.

Despite the challenges encountered in this study the finding proves the potential of non-invasive ventilation to generate a patient-centered treatment approach by addressing the different challenges this diverse group presents. It was highlighted that for the implementation of non-invasive ventilation as a standard therapy to be implemented a multidisciplinary team needs to be involved and that this team needs to be well trained and have effective communication within itself. Moving forward for non-invasive ventilation to be successful implemented standardized protocols and international guidelines for their application, ensuring consistent and fair care for patients, need to be developed. By highlighting all those factors, this study aims to highlight the importance of non-invasive ventilation as a treatment option for acute respiratory failure in PJP patients, but also to incentivize further research and development in this area.

12. Sources

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