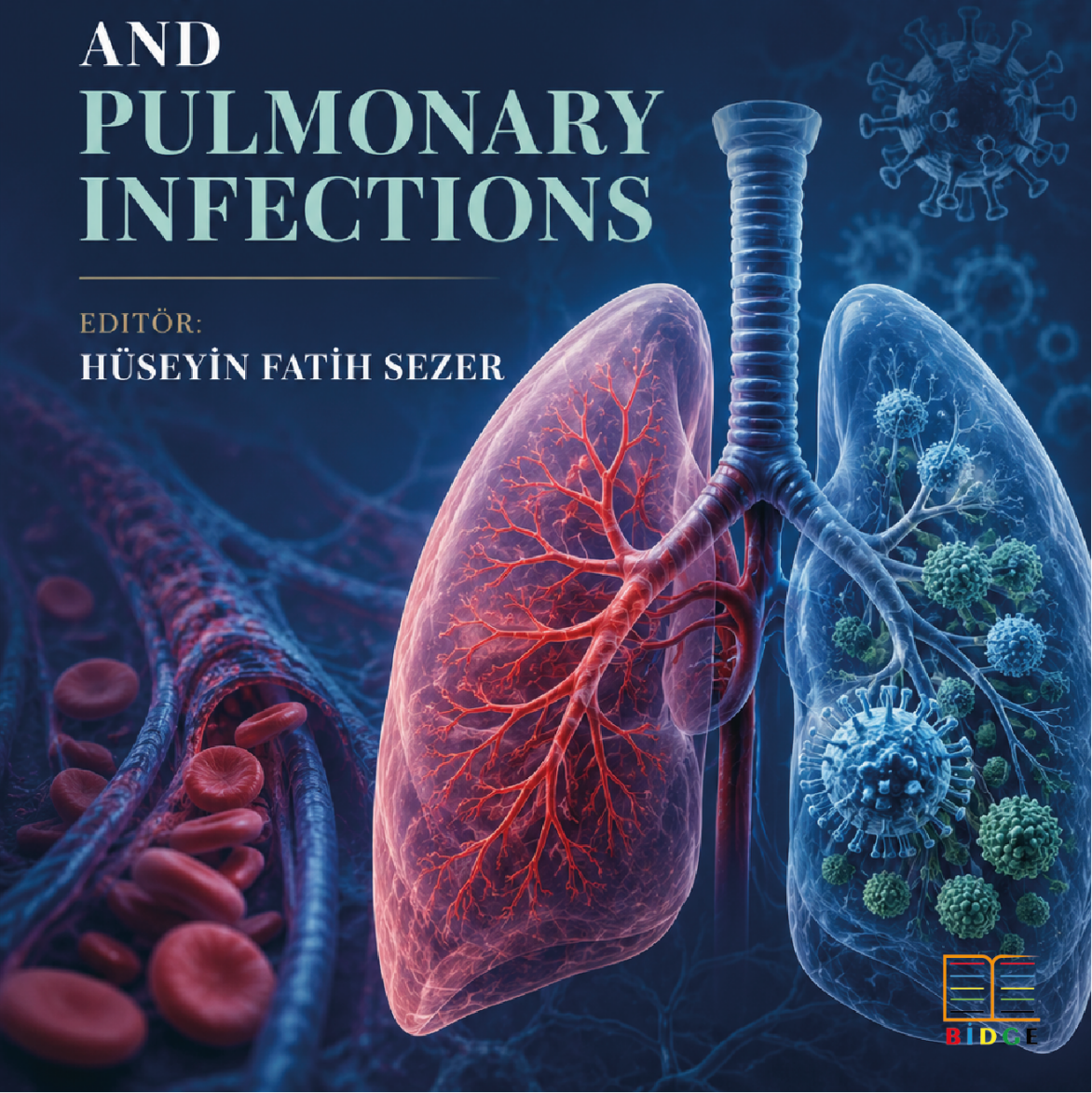
CURRENT DEVELOPMENTS IN PULMONARY VASCULAR DISEASES AND PULMONARY INFECTIONS

EDITÖR:
HÜSEYİN FATİH SEZER



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PREFACE

Today, the importance of the pulmonology branch is increasing due to factors such as changes in climatic conditions, environmental factors affecting human health, the growing elderly population. The purpose of this book is to present current developments and approaches in these branches, which are undergoing extreme changes and growth.

The respiratory system, together with the circulatory system, undertakes the most important task in providing basic life activities. In our book titled "Current Developments in Pulmonary Vascular Diseases and Pulmonary Infections'', current definitions, diagnosis and treatment methods related to this important system have been prepared by our colleagues with great devotion.

I would like to thank all the authors and the employees who contributed to the publication. I hope that the book will be useful to all our colleagues, especially in chest diseases and chest surgery, in their academic studies and clinical practice.

ASSOC. PROF. DR. HÜSEYİN FATİH SEZER

KOCAELI UNIVERSITY

İÇİNDEKİLER

BÖLÜM 1

UPFRONT OR SEQUENTIAL COMBINATION THERAPY STRATEGIES IN PULMONARY ARTERIAL HYPERTENSION

EBRU ŞENGÜL PARLAK[1]

Introduction

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological condition characterized by a resting mean pulmonary arterial pressure (mPAP) exceeding 20 mmHg, as determined by right heart catheterization (RHC). PH can occur across all age groups and currently affects approximately 1% of the worldwide population. The prevalence rises substantially with advancing age, particularly among individuals older than 65 years, reflecting the increasing contribution of underlying cardiac and pulmonary disorders. Pulmonary arterial hypertension (PAH), classified within Group 1 PH, represents a pre-capillary form of PH. The natural history of untreated PAH is marked by progressive pulmonary vascular disease, culminating in right ventricular (RV)

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decompensation, heart failure, and premature death (Humbert et al., 2023).

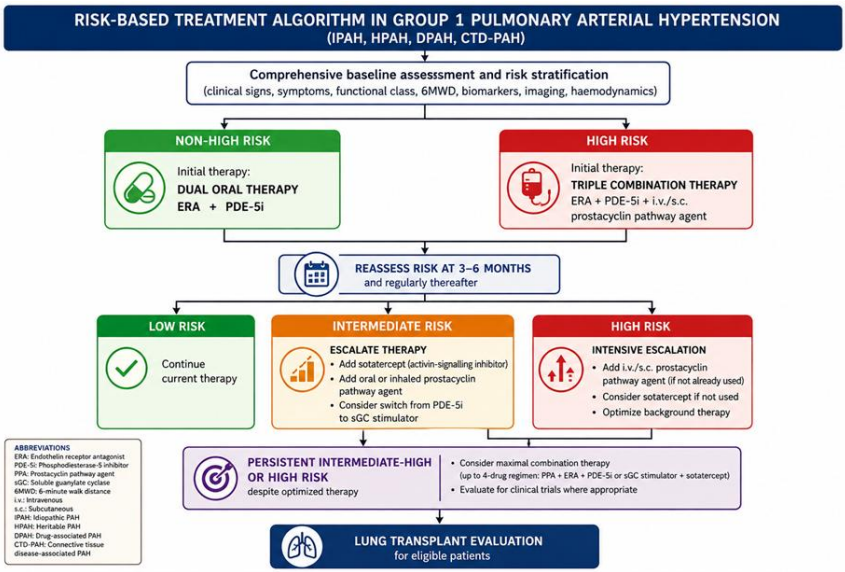
The overarching objective of PAH management is to achieve and sustain a low-risk clinical profile. Nevertheless, evidence from contemporary registries and clinical trials indicates that a considerable proportion of patients do not reach this therapeutic target despite receiving guideline-directed treatment (Humbert & Lau, 2019).

Combination therapy provides superior clinical benefits compared with monotherapy in PAH. Consequently, the majority of patients with PAH are considered suitable candidates for oral or parenteral combination therapy at the time of diagnosis, with early follow-up assessment and timely treatment escalation when indicated (Chin et al., 2024). This chapter summarizes the current evidence supporting combination therapy strategies and reviews contemporary recommendations for their implementation in clinical practice.

Fundamentals of Combination Therapy in PAH

The concept of combination therapy has long been incorporated into the therapeutic management of PAH. Historically, additional agents targeting complementary pathogenic pathways were introduced when the response to initial therapy proved inadequate. More recently, treatment strategies have shifted toward a structured, risk-oriented approach in which therapeutic decisions are guided by serial risk assessment and proactive escalation of treatment. Within this framework, achieving and maintaining a low-risk status remains the principal goal of PAH management (Humbert & Lau, 2019). Figure 1 summarizes current recommendations for combination therapy in PAH, based on the proceedings and treatment concepts presented at the 7th World Symposium on Pulmonary Hypertension (Chin et al., 2024).

Figure 1. Risk-Stratified Therapeutic Approach to PAH



Reference. Chin, K. M., et al. (2024).

Initial Dual Combination Therapy

Current international guidelines recommend the combination of an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE5i) as the preferred initial treatment strategy for patients with PAH who are classified as low- or intermediate-risk. In the guideline algorithm, initial oral dual combination therapy is recommended at Class I for patients with a negative vasoreactivity test and no significant cardiopulmonary comorbidities who are categorized as low or intermediate risk. In contrast, an initial oral monotherapy approach is recommended for patients with relevant cardiopulmonary comorbidities. For patients at high risk, treatment strategies incorporating intravenous or subcutaneous prostacyclin analogs in addition to ERA and PDE5i therapy are recommended (Humbert et al., 2023).

Evidence Supporting Initial Dual Combination Therapy

One of the earliest randomized studies investigating combination therapy in PAH was the BREATHE-2 trial. This double-blind, randomized, placebo-controlled study enrolled 33 patients with World Health Organization (WHO) functional class (FC) III–IV symptoms. Although patients receiving combination therapy demonstrated a trend toward greater improvement, the differences did not reach statistical significance (Humbert et al., 2004).

Among the most influential studies evaluating upfront dual combination therapy is the AMBITION trial. This multicenter, randomized, double-blind phase 3–4 study included 500 patients with WHO FC II or III PAH. A combination of ambrisentan and tadalafil significantly reduced the risk of clinical failure compared with either monotherapy (Galiè et al., 2015). Furthermore, a secondary analysis of the AMBITION trial, treatment was associated with reductions in NT-proBNP levels and improvements in six-minute walk distance (6MWD) (Hoeper et al., 2016).

The effects of macitentan, administered either alone or in combination with a PDE5 inhibitor, on RV remodeling were investigated in the REPAIR study, an open-label, single-arm, multicenter phase 4 trial. Following treatment, significant increases in RV stroke volume together with marked reductions in pulmonary vascular resistance (PVR) were observed (Noordegraaf et al., 2022).

The A DUE study compared a fixed-dose combination of macitentan and tadalafil with the corresponding monotherapies. The findings demonstrated that fixed-dose combination therapy achieved a greater reduction in PVR than either monotherapy. Improvements in 6MWD were also reported (Grünig et al., 2024).

A proportion of patients with PAH fail to achieve an adequate clinical response despite treatment with PDE5 inhibitors. In such cases, switching to riociguat, which targets the same biological

pathway through a distinct mechanism of action, has emerged as a potential therapeutic strategy.

The RESPITE study evaluated the transition from PDE5 inhibitor therapy to riociguat in patients who exhibited an insufficient response despite treatment with an ERA and a PDE5 inhibitor. Fifty-one patients with WHO FC III symptoms were enrolled. After 24 weeks of follow-up, improvements in 6DWD and reductions in NT-proBNP levels were observed. These findings suggested that reconfiguration of targeted treatment strategies may be beneficial in selected patient populations (Hoeper et al., 2017).

This therapeutic approach was subsequently examined in a randomized controlled setting in the REPLACE trial. Among patients switched from PDE5 inhibitor therapy to riociguat, 41% achieved clinical improvement, compared with 20% who continued PDE5 inhibitor therapy. Moreover, the incidence of clinical worsening events was substantially lower in the riociguat group. These results indicate that transitioning to riociguat may represent a valuable treatment-escalation strategy for intermediate-risk patients who fail to achieve an adequate therapeutic response (Hoeper et al., 2021).

In a systematic review and meta-analysis conducted by Farmakis et al., 59 studies were evaluated, of which 13 met the inclusion criteria for quantitative analysis. The pooled analysis included 880 patients. Eight studies investigated combinations of ERAs and PDE5 inhibitors; three evaluated prostanoid-containing regimens; one assessed an ERA plus a soluble guanylate cyclase (sGC) stimulator combination; and three examined initial triple-combination therapy. The analysis demonstrated that initial combination therapy was associated with an approximately 52% reduction in PVR. In studies evaluating upfront triple-combination therapy, this reduction approached 67%. These findings suggest that intensive treatment strategies initiated early in the disease course

may confer substantial hemodynamic benefits (Farmakis et al., 2022).

Guideline Recommendations for High-Risk Patients

Guidelines for Pulmonary Hypertension recommend the use of intravenous or subcutaneous prostacyclin analogs in addition to an ERA and a PDE5i as part of the initial treatment strategy for patients with high-risk PAH. The primary objective of this approach is to achieve rapid hemodynamic improvement while reducing the risk of mortality. The risk-based framework adopted by the guidelines emphasizes that treatment intensity should be tailored not only according to symptom burden but also according to prognostic indicators that determine clinical outcomes (Humbert et al., 2023).

Evidence Supporting Initial Triple Combination Therapy

Initial triple-combination therapy consisting of intravenous epoprostenol, bosentan, and sildenafil has been evaluated in newly diagnosed patients with New York Heart Association (NYHA) FC III–IV PAH. This study was a retrospective analysis of data from a prospective registry and included 19 patients. Significant improvements were reported in several clinically relevant parameters, including six-minute walk distance, cardiac index, and PVR. These findings suggest that an aggressive upfront treatment strategy may provide substantial benefits, particularly in patients with high-risk disease (Sitbon et al., 2014).

There is increasing consensus that, among patients classified as intermediate risk but exhibiting marked hemodynamic impairment, initial triple-combination therapy incorporating an intravenous or subcutaneous prostacyclin analog is one of the most promising strategies to achieve a low-risk profile and improve long-term outcomes (Boucly et al., 2021; Jin et al., 2021).

The relationship between initial treatment strategy and long-term survival has been investigated in a cohort of 2,077 patients with PAH. Among the 1,611 patients who received targeted therapy, 61% received monotherapy, 34% received dual-combination therapy, and 5% received triple-combination therapy. Survival analyses demonstrated superior long-term survival among patients who received initial triple-combination therapy. In particular, treatment strategies incorporating intravenous epoprostenol yielded notably favorable results. These observations further support the prognostic importance of intensive prostacyclin-based treatment approaches in high-risk patients (Boucly et al., 2021).

One of the most important studies addressing whether initial triple therapy offers advantages over dual therapy is the TRITON trial. This multicenter, double-blind, randomized phase 3 study enrolled patients with WHO FC III PAH. The trial compared initial dual therapy with macitentan and tadalafil against an initial triple oral regimen created by adding selexipag to the same background therapy. The results did not demonstrate a significant advantage of upfront triple oral therapy with respect to PVR, 6MWD, or changes in NT-proBNP levels (Chin et al., 2021).

Accordingly, the 2022 ESC/ERS Guidelines do not recommend initial triple oral combination therapy consisting of macitentan, tadalafil, and selexipag. This recommendation is classified as Class III with a level of evidence B (Humbert et al., 2023).

Sequential Combination Therapy and Treatment Escalation Strategies

Although upfront combination therapy has become a cornerstone of PAH management, a substantial proportion of patients fail to achieve a low-risk profile at the time of diagnosis. Consequently, repeated risk assessment throughout follow-up and

the addition of further targeted therapies when treatment goals are not achieved have become integral components of contemporary management. The 2022 ESC/ERS Guidelines recommend treatment escalation in patients who do not attain predefined therapeutic targets (Humbert et al., 2023). While combination therapy may be initiated simultaneously at diagnosis in selected patients, the stepwise introduction of a second or third agent is often better tolerated in clinical practice. This strategy, referred to as sequential combination therapy, is now widely employed in the management of PAH (Humbert & Lau, 2019).

The SERAPHIN trial evaluates the long-term effects of macitentan on clinical outcomes in patients with PAH. A total of 742 patients were randomized to receive macitentan 3 mg, macitentan 10 mg, or placebo. Patients receiving background therapy with PDE5 inhibitors, oral or inhaled prostanoids, or calcium channel blockers were allowed to continue these treatments throughout the study. The findings demonstrated that adding macitentan to existing PAH therapies reduced long-term morbidity and mortality, thereby supporting the effectiveness of sequential combination therapy (Pulido et al., 2013).

The GRIPHON trial represents one of the most important studies establishing the role of selexipag in PAH treatment. In this phase III trial, 1,156 patients were randomized to receive either a placebo or selexipag. Most participants were already receiving an ERA, a PDE5 inhibitor, or both at baseline. The primary endpoint was a composite of death from any cause or PAH-related complications. During follow-up, the primary endpoint occurred in 41.6% of patients in the placebo group compared with 27.0% in the selexipag group, corresponding to a 40% reduction in event risk with selexipag treatment (HR 0.60; 99% CI 0.46–0.78; $p<0.001$). The majority of events consisted of disease progression and hospitalization. Although no significant mortality benefit was

demonstrated, the results established selexipag as an important option for treatment intensification in PAH (Sitbon et al., 2015).

The role of prostacyclin pathway agents in sequential combination therapy was further evaluated in the FREEDOM-EV trial. This randomized, double-blind, placebo-controlled study enrolled 690 patients who were assigned to receive oral treprostinil or placebo in addition to their existing oral PAH therapy. The addition of oral treprostinil resulted in a significant reduction in the risk of clinical worsening. Clinical worsening occurred in 26% of patients receiving oral treprostinil compared with 36% of those receiving placebo. Improvements were also observed in FC, dyspnea scores, and NT-proBNP concentrations. These findings support the efficacy of sequential combination therapy targeting the prostacyclin pathway by adding oral treprostinil to established PAH treatment regimens (White et al., 2020).

Most therapeutic agents used in PAH for many years have primarily acted through vasodilatory mechanisms and have not been able to completely reverse pulmonary vascular remodeling (Humbert et al., 2023).

As a result, novel therapeutic approaches targeting the proliferative and remodeling processes in the pulmonary vasculature have emerged in recent years. Among these, sotatercept has attracted particular attention. In the phase II PULSAR study, sotatercept treatment was associated with significant reductions in pulmonary vascular resistance, accompanied by decreases in NT-proBNP levels and improvements in 6MWD (Humbert et al., 2021).

These observations were subsequently confirmed in the phase III STELLAR trial conducted by Hoeper and colleagues. In this study, 323 patients with PAH receiving stable background therapy were randomized to receive either sotatercept or placebo. After 24 weeks of treatment, patients receiving sotatercept achieved

an increase in 6MWD that exceeded that observed in the placebo group by 40.8 meters. Significant improvements were also reported in PVR, NT-proBNP levels, FC, and clinical worsening outcomes (Hoeper et al., 2023).

The ZENITH trial further demonstrated that the addition of sotatercept to standard therapy in patients with advanced, high-risk PAH significantly reduced the risks of death, lung transplantation, and hospitalization. These findings indicate that sotatercept not only improves symptoms and functional capacity but may also favorably influence disease progression and long-term prognosis, thereby representing an important therapeutic advance in PAH management (Humbert et al., 2025).

Current PAH therapies primarily rely on vasodilatory mechanisms and do not fully reverse pulmonary vascular remodeling. With the development of sotatercept, which targets the activin signaling pathway, a novel treatment paradigm has emerged that seeks to directly modulate the underlying vascular remodeling processes responsible for disease progression in PAH (Humbert et al., 2021; Hoeper et al., 2023).

Conclusion

Combination therapy has become the standard approach in the treatment of PAH. The combination of an ERA and PDE5i is recommended for patients at low or intermediate risk, whereas triple-combination therapy incorporating a parenteral prostacyclin should be considered in patients with high-risk disease or severe hemodynamic impairment. Sequential treatment strategies, including the addition of selexipag, transitioning to riociguat, and incorporating prostacyclin pathway agents, are key components of the contemporary risk-based treatment paradigm. Furthermore, the introduction of sotatercept into clinical practice has established a novel therapeutic target in PAH. This agent, together with future

therapies acting through similar mechanisms, is expected to contribute to the further refinement and evolution of risk-based treatment algorithms in the years ahead.

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BÖLÜM 2

MEDICAL MANAGEMENT OF CTEPH

EBRU ŞENGÜL PARLAK[1]

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct subtype of pulmonary hypertension (PH) that develops within the spectrum of chronic thromboembolic pulmonary disease and is characterized by persistent fibrothrombotic obstruction of the pulmonary arterial vasculature (Humbert et al., 2023). The estimated annual incidence of CTEPH is approximately 5–6 cases per million individuals; however, rates may increase to nearly 13 cases per million when systematic surveillance is performed following acute pulmonary embolism (PE). Despite being traditionally regarded as a consequence of unresolved thromboembolic obstruction, current evidence indicates that the pathogenesis of CTEPH is considerably more complex. In addition to persistent organized thromboembolic material within the proximal pulmonary arteries, progressive alterations of the distal pulmonary microcirculation contribute substantially to disease development and progression. These two interrelated mechanisms—mechanical vascular obstruction and

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secondary microvascular remodeling—collectively promote elevations in pulmonary vascular resistance (PVR), leading to right ventricular overload and progressive functional impairment. Mechanical obstruction results from organized fibrothrombotic lesions that remain within the affected pulmonary arterial segments, whereas microvascular disease develops in both obstructed and unobstructed lung territories and may involve vascular regions that appear structurally preserved on imaging studies (Kim et al., 2024).

Pulmonary endarterectomy (PEA) remains the treatment of choice for eligible patients and continues to represent the only potentially curative intervention for CTEPH. Balloon pulmonary angioplasty (BPA) has emerged as an effective alternative for selected patients who are not suitable surgical candidates. Nevertheless, medical therapy has assumed an increasingly important role, particularly in individuals with inoperable disease and in those with persistent or recurrent PH following PEA or BPA (Humbert et al., 2023). Over the past decade, growing evidence supporting the use of pulmonary arterial hypertension (PAH)-targeted therapies has considerably expanded the therapeutic armamentarium available for patients with CTEPH (Delcroix et al., 2021).

Medical Therapy

Conventional medical management in patients with CTEPH consists primarily of diuretic therapy, supplemental oxygen when indicated, and lifelong anticoagulation. In addition, general supportive measures recommended for PAH, including supervised exercise and rehabilitation programs, are also applicable to this patient population (Humbert et al., 2023).

Although these supportive interventions play an essential role in symptom relief and overall disease management, they are generally insufficient to achieve complete clinical improvement

when used in isolation. Consequently, contemporary treatment strategies for CTEPH increasingly rely on a multimodal approach that integrates medical therapy with surgical and catheter-based interventions according to individual patient characteristics and disease distribution (Humbert et al., 2023; Kim et al., 2024).

Lifelong anticoagulation remains a key component of the therapeutic management of CTEPH. Current guidelines recommend continuous therapeutic anticoagulation for all patients with a confirmed diagnosis of CTEPH, irrespective of the treatment modality pursued. In patients with chronic thromboembolic pulmonary disease without documented pulmonary hypertension, however, the decision to continue long-term anticoagulant therapy should be individualized according to the patient's clinical characteristics and thromboembolic risk profile (Humbert et al., 2023). In the presence of concomitant antiphospholipid syndrome, which affects approximately 10% of patients with CTEPH, vitamin K antagonists (VKAs) continue to be the preferred anticoagulant option (Humbert et al., 2023; Kim et al., 2024).

Over the last decade, the use of direct oral anticoagulants (DOACs) has become increasingly common in clinical practice (Delcroix et al., 2021; Kim et al., 2024). Evidence available to date indicates that major bleeding rates do not differ substantially between patients receiving VKAs and those treated with DOACs. However, several reports have suggested a higher incidence of recurrent venous thromboembolic events among individuals managed with DOAC therapy (Kim et al., 2024).

In addition, studies involving patients undergoing pulmonary endarterectomy have demonstrated a greater occurrence of thrombotic and embolic complications in those receiving DOACs. The detection of acute or subacute thrombotic material at the time of surgery has also been reported to be approximately twice as frequent

among DOAC-treated patients compared with those receiving VKAs (Humbert et al., 2022; Bunclark et al., 2020; Jeong et al., 2022).

PAH-Targeted Therapies

Acute vasoreactivity testing is not recommended in the evaluation of patients with CTEPH, and current evidence does not support the use of calcium channel blockers in this setting. Owing to the contribution of microvascular remodeling to the pathophysiology of CTEPH, pharmacological therapies targeting the endothelin, nitric oxide (NO), and prostacyclin pathways have been explored. (Delcroix et al., 2021).

Riociguat is the only approved pharmacological therapy for both CTEPH and pulmonary hypertension. Riociguat enhances the NO–soluble guanylate cyclase–cyclic guanosine monophosphate pathway through direct stimulation of soluble guanylate cyclase. (Simeone et al., 2024).

The clinical efficacy of riociguat in CTEPH was established in the CHEST-1 study, which included 261 patients with inoperable disease or persistent/recurrent PH after PEA. Following 16 weeks of therapy, riociguat treatment resulted in significant improvements in six-minute walk distance (6MWD), PVR, N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations, and functional class (FC) compared with baseline values (Ghofrani et al., 2013). Sustained benefits were subsequently demonstrated in the long-term extension phase of the study, CHEST-2 (Simonneau et al., 2015).

On the basis of these data, the 2022 ESC/ERS Guidelines recommend riociguat for symptomatic patients with inoperable CTEPH or persistent/recurrent pulmonary hypertension following PEA, with a Class I recommendation and Level B evidence (Humbert et al., 2023).

The BENEFiT study assessed the effects of bosentan in patients with CTEPH. Although treatment was associated with a significant reduction in PVR, no significant improvement in 6MWD was observed after 16 weeks of therapy (Jaïs et al., 2008).

The efficacy of macitentan was later examined in the MERIT-1 trial, which enrolled patients with inoperable CTEPH. After 16 weeks of treatment, macitentan produced a significant decrease in pulmonary vascular resistance. Notably, 61% of the study population was receiving concomitant phosphodiesterase type-5 (PDE5) inhibitor therapy, raising the possibility that the combination of macitentan and PDE5 inhibitors may offer additional clinical benefit in selected patients with inoperable disease. Furthermore, MERIT-1 represented the first study to provide evidence supporting combination pharmacological therapy in patients with advanced CTEPH, particularly those classified as World Health Organization (WHO) FC III–IV (Ghofrani et al., 2017; Simeone et al., 2024).

The use of sildenafil in CTEPH has been investigated in an open-label, single-arm study involving 104 patients with inoperable disease who were treated with sildenafil at a dose of 50 mg three times daily. After three months of treatment, significant reductions in pulmonary vascular resistance were observed, accompanied by improvements in exercise capacity as assessed by the six-minute walk distance. These findings suggested that long-term sildenafil therapy may provide sustained functional benefits in patients with inoperable CTEPH (Reichenberger et al., 2007).

In the absence of randomized controlled trials and supportive registry data demonstrating its efficacy, sildenafil continues to be used as an off-label therapy in patients with inoperable CTEPH (Delcroix et al., 2021).

The CTREPH trial evaluated subcutaneous treprostinil in patients with inoperable CTEPH or persistent/recurrent PH following PEA who were in WHO FC III–IV. Compared with low-dose therapy, higher-dose treprostinil was associated with significant improvements in exercise capacity and reductions in PVR after 24 weeks of treatment (Sadushi-Kolici et al., 2019).

These findings support the role of parenteral prostacyclin therapy as a therapeutic option for patients who remain symptomatic despite other treatments or who require combination therapy (Simeone et al., 2024). Accordingly, the 2022 ESC/ERS Guidelines state that subcutaneous treprostinil may be considered in patients with inoperable CTEPH or persistent/recurrent PH following PEA who remain in WHO FC III–IV (Class IIb, Level B recommendation) (Humbert et al., 2023).

Inhaled iloprost has been studied in a randomized, placebo-controlled trial that included treatment-naive patients with PAH hypertension or CTEPH. Compared with placebo, iloprost therapy resulted in improvements in both exercise capacity and pulmonary hemodynamic parameters (Olschewski et al., 2002).

The efficacy and safety of selexipag, an oral prostacyclin IP receptor agonist, were assessed in a phase III, multicenter, double-blind, placebo-controlled trial involving 78 patients with inoperable CTEPH or persistent/recurrent PH following PEA and/or BPA. Although treatment with selexipag led to a significant reduction in PVR, no significant difference in 6MWD was demonstrated (Ogo et al., 2022).

Additional evidence supporting the use of prostacyclin-based therapies comes from a retrospective study of patients with inoperable distal CTEPH and advanced functional impairment who received long-term intravenous epoprostenol. Treatment was associated with improvements in functional status, exercise capacity,

and several hemodynamic parameters. Reported survival rates at 1, 2, and 3 years were 73%, 59%, and 41%, respectively, indicating a potential survival advantage associated with intravenous epoprostenol therapy in this high-risk population (Cabrol et al., 2007).

Multimodal Treatment Approach

Current CTEPH management relies on a multimodal therapeutic framework. The availability of three established treatment options—PEA, BPA, and targeted medical therapy—has transformed the treatment landscape, as each modality addresses different components of the disease process within the pulmonary vascular bed. As a result, contemporary management increasingly incorporates a sequential combination of two or more treatment modalities tailored to individual patient characteristics (Kim et al., 2024).

The ESC/ERS guidelines emphasize that all patients with CTEPH should be assessed by a dedicated multidisciplinary team with expertise in the full spectrum of CTEPH therapies. Such evaluation enables the development of an individualized treatment plan integrating PEA, BPA, and pharmacological therapy when appropriate, thereby addressing the diverse vascular abnormalities underlying the disease (Humbert et al., 2023).

The contribution of microvascular disease to CTEPH pathophysiology indicates that relief of proximal vascular obstruction alone may not always result in complete clinical or hemodynamic recovery. Consequently, surgical, interventional, and medical therapies should be viewed as complementary components of patient management and selected according to the distribution of vascular lesions and overall patient profile. Lifelong therapeutic anticoagulation is recommended for all patients with CTEPH, and management decisions should be guided by an experienced

multidisciplinary team. Depending on operability and lesion accessibility, treatment strategies may include PEA, BPA, targeted medical therapy, or a combination of these approaches. Following intervention, reassessment within 3–6 months is advised to determine treatment efficacy and identify residual symptoms or persistent pulmonary hypertension (Kim et al., 2024).

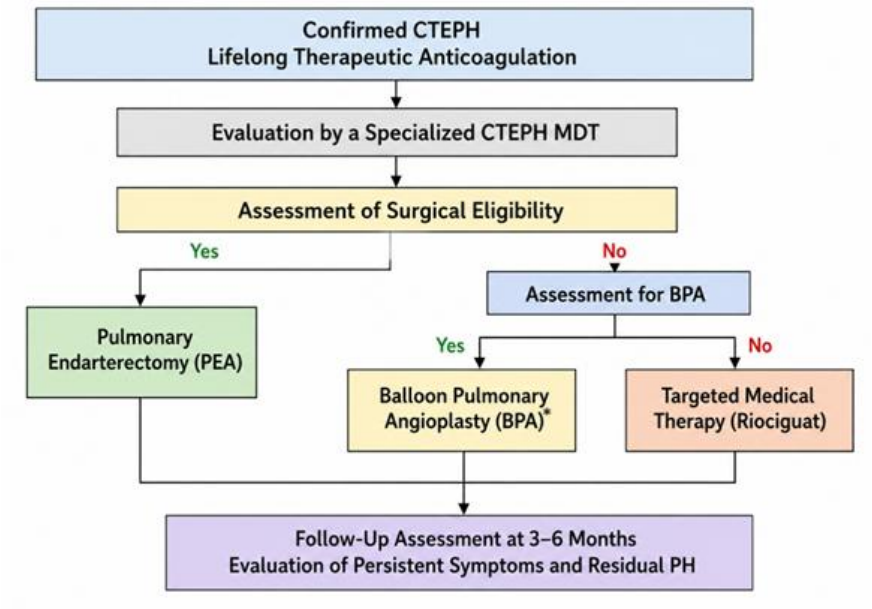
Recent data suggest that pharmacological treatment before BPA may decrease the likelihood of procedure-related complications. Therefore, the latest ESC/ERS guidelines state that pre-procedural medical therapy may be considered in patients undergoing BPA who have a pulmonary vascular resistance exceeding 4 Wood units, although the supporting evidence remains limited (Humbert et al., 2023).

The key elements of multimodal CTEPH management are summarized in Figure 1, and the proposed treatment algorithm is presented in Figure 2.

Figure 1. Principles of Management in CTEPH: The AMEND Approach

Adapted from Kim et al., 2024

Figure 2. CTEPH Treatment Algorithm



Adapted from Kim et al., 2024

**Riociguat therapy before BPA in patients with mPAP ≥40 mmHg or PVR >4 WU*

Recent advances in multimodal treatment strategies have substantially improved the prognosis of patients with CTEPH, resulting in three-year survival rates exceeding 90% in both operable and non-operable patient populations (Kim et al., 2024).

Regardless of the treatment modality employed or the immediate outcomes of PEA or BPA, all patients should undergo regular long-term follow-up. At present, there is no universally accepted definition of an optimal therapeutic target following PEA, BPA, or medical therapy in CTEPH. Nevertheless, expert consensus generally considers the achievement of a favorable clinical status, reflected by WHO-FC I–II, and/or normalization or near-normalization of resting hemodynamic parameters, as assessed by right heart catheterization performed 3–6 months after PEA or the final BPA session, to be appropriate treatment goals. Improvement

in quality of life is also regarded as a key indicator of successful therapy (Humbert et al., 2023).

Conclusion

The medical management of CTEPH has evolved considerably over the past decade. While lifelong anticoagulation remains the cornerstone of therapy for all patients, a growing understanding of the role of microvascular disease has expanded the application of pulmonary arterial hypertension-targeted therapies in this population. Among currently available agents, riociguat has the strongest evidence base and the highest level of guideline support for patients with inoperable disease or persistent/recurrent pulmonary hypertension following intervention.

In addition, endothelin receptor antagonists, prostacyclin pathway agents, and other targeted therapies have demonstrated promising results and continue to broaden the therapeutic landscape of CTEPH. As knowledge of disease mechanisms advances and treatment options expand, multimodal and individualized therapeutic strategies are expected to play an increasingly central role in optimizing clinical outcomes and long-term prognosis in patients with CTEPH.

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BÖLÜM 3

LEJYONELLA PNÖMONİSİ: TANIDAN TEDAVİYE GÜNCEL YAKLAŞIM

GÜLŞAH ETHEMOĞLU[1]

Giriş

Lejyonella pnömonisi, Legionella cinsi bakterilerin neden olduğu ve özellikle ağır seyirli toplum kökenli pnömoniler arasında önemli bir yer tutan enfeksiyon hastalıklarından biridir (Dias et al., 2025). İnsan enfeksiyonlarının büyük çoğunluğundan Legionella pneumophila sorumlu olup özellikle serogrup 1 klinik vakaların önemli bir bölümünü oluşturmaktadır (Phin et al., 2014). Hastalık, ateş, öksürük ve dispne gibi solunum sistemi semptomlarının yanı sıra gastrointestinal ve nörolojik bulgular ile çeşitli laboratuvar anormallikleri ile seyredebilmesi nedeniyle diğer bakteriyel pnömonilerden ayrılan klinik özellikler gösterebilir (Pierre et al., 2017).

Lejyonella enfeksiyonları ilk olarak 1976 yılında Amerika Birleşik Devletleri'nde meydana gelen bir pnömoni salgını sırasında tanımlanmış ve etken mikroorganizma daha sonra Legionella pneumophila olarak adlandırılmıştır (Fraser et al., 1977). Bakterinin

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doğal rezervuarının tatlı su ortamları olduğu ve özellikle insan yapımı su sistemlerinde çoğalma eğilimi gösterdiği ortaya konmuştur (Mercante & Winchell, 2015). Soğutma kuleleri, klima sistemleri, sıcak su tankları ve duş başlıkları gibi aerosol oluşturan sistemler bakterinin çevresel yayılımında önemli rol oynamaktadır (WHO, 2022).

Lejyonella pnömonisi özellikle ileri yaşlı bireylerde, sigara içenlerde ve bağışıklık sistemi baskılanmış hastalarda daha ağır seyretme eğilimindedir. Kronik akciğer hastalıkları, diyabetes mellitus ve kronik böbrek hastalığı gibi komorbid durumlar enfeksiyon gelişme riskini artırmaktadır (Rello et al., 2024). Tanı yöntemlerindeki gelişmeler, özellikle idrar antijen testleri ve moleküler tekniklerin yaygınlaşması ile birlikte hastalığın daha erken ve doğru şekilde tanınması mümkün hale gelmiştir (Bai et al., 2023).

Bu bölümde lejyonella pnömonisinin epidemiyolojisi, patogenezi, klinik özellikleri, tanı yöntemleri ve tedavi yaklaşımları güncel literatür ışığında ele alınacaktır.

Epidemiyoloji

Lejyonella pnömonisi toplum kökenli pnömonilerin önemli ancak sıklıkla gözden kaçabilen etiyolojik nedenlerinden biridir. Legionella türlerinin toplum kökenli pnömonilerin yaklaşık %1–10'undan sorumlu olduğu bildirilmektedir (Bai et al., 2023). Tanı yöntemlerinin sınırlı kullanımı nedeniyle gerçek insidansın daha yüksek olabileceği düşünülmektedir (Phin et al., 2014).

Son yıllarda özellikle Avrupa ve Amerika Birleşik Devletleri'nde bildirilen lejyonella vakalarında belirgin artış gözlenmiştir (Soda et al., 2017; ECDC, 2023; Whiley, 2017). Bu artışın tanı yöntemlerindeki gelişmeler, yaşlanan nüfus ve kronik

hastalıkların artışı ile ilişkili olduğu düşünülmektedir (Soda et al., 2017).

Lejyonella bakterileri doğal olarak tatlı su kaynaklarında bulunmakla birlikte insan yapımı su sistemlerinde çoğalma eğilimi göstermektedir (Mercante & Winchell, 2015). Özellikle sıcak su sistemleri, soğutma kuleleri ve klima sistemleri bakterinin çoğalması için uygun ortam oluşturur ve aerosolize su damlacıkları yoluyla bulaş gerçekleşir (WHO, 2022). Hastalık genellikle kişiden kişiye bulaşmaz (WHO, 2022).

Hastalık erkeklerde daha sık görülmekte olup yaşla birlikte insidans artmaktadır (Phin et al., 2014). Sigara kullanımı, kronik akciğer hastalıkları ve immünsüpresyon önemli risk faktörleridir (Cunha et al., 2016). Ayrıca hastane su sistemlerinin kontaminasyonu nozokomiyal enfeksiyonlara yol açabilir ve özellikle immünsüpresif hastalarda ağır seyir gösterebilir (Soda et al., 2017; WHO, 2022).

Mikrobiyoloji ve Patogenez

Legionella türleri gram negatif, aerobik ve çomak şeklinde bakteriler olup doğal olarak su ortamlarında bulunan çevresel mikroorganizmalardır (Bai et al., 2023). Günümüzde 60'dan fazla Legionella türü tanımlanmış olmakla birlikte insan enfeksiyonlarının büyük çoğunluğundan Legionella pneumophila sorumludur ve özellikle serogrup 1 en sık izole edilen patojendir (Whiley, 2017).

Bu bakteriler göl, nehir ve yeraltı suları gibi doğal su kaynaklarında bulunmakla birlikte, insan yapımı su sistemlerinde çoğalma eğilimleri nedeniyle klinik açıdan önem kazanmaktadır. Özellikle sıcak su sistemleri, soğutma kuleleri ve klima sistemlerinde biyofilm oluşumu bakterinin uzun süre canlı kalmasına ve çoğalmasına olanak sağlar (Mercante & Winchell, 2015). Ayrıca Legionella türlerinin amipler ve diğer protozoonlar

içinde yaşayabilmesi, çevresel dayanıklılığını ve enfektivitesini artıran önemli bir özelliktir (Nisar et al., 2020).

Enfeksiyon genellikle kontamine su sistemlerinden kaynaklanan aerosolize partiküllerin inhalasyonu ile gelişir. Bakteri alveollere ulaştıktan sonra alveoler makrofajlar tarafından fagosite edilir; ancak fagolizozomal yıkımdan kaçabilme yeteneği sayesinde hücre içinde yaşamını sürdürür ve çoğalır. Bu süreçte bakterinin temel virülans mekanizmasını oluşturan Dot/Icm tip IV sekresyon sistemi aracılığıyla konak hücre fonksiyonlarını düzenleyen çok sayıda efektör protein salgılanır ve hücresel süreçler bakterinin replikasyonuna uygun şekilde yeniden programlanır (Qiu & Luo, 2017).

Legionella pneumophila, fagolizozomal füzyonu engelleyerek endoplazmik retikulum kaynaklı membranlarla çevrili "Legionella-containing vacuole (LCV)" içinde çoğalır. Bu yapı bakterinin hücre içi ortamda korunmasını sağlarken aynı zamanda çoğalması için uygun bir mikro niş oluşturur. Enfekte makrofajların lizisi bakterinin çevre dokulara yayılmasına neden olur ve bu süreç inflamatuvar yanıtın tetiklenmesi ile sonuçlanır (Liu et al., 2020).

Konak bağışıklık sistemi ile bakterinin etkileşimi hastalığın seyrinde belirleyici rol oynar. Özellikle hücresel immünite enfeksiyon kontrolünde kritik öneme sahiptir. Makrofajlar ve dendritik hücreler tarafından tanınan bakteriye karşı tümör nekroz faktörü alfa (TNF-α), interlökin-1 (IL-1) ve interlökin-6 (IL-6) gibi proinflamatuvar sitokinler salgılanır (Liu et al., 2020). Bununla birlikte bu yanıtın aşırı olması akciğer dokusunda hasara yol açabilir ve ağır olgularda akut solunum sıkıntısı sendromu (ARDS) gelişimine neden olabilir (Yue et al., 2021).

Son yıllarda yapılan moleküler çalışmalar, Legionella pneumophila'nın konak hücre veziküler taşınma sistemlerini hedef alarak organel fonksiyonlarını modüle edebildiğini ve otofaji gibi

hücresel süreçleri manipüle ederek hücre içi çoğalmasını sürdürebildiğini göstermiştir (Liu et al., 2020). Bu kompleks hücre içi adaptasyon mekanizmaları bakterinin patojenitesinin temelini oluşturmaktadır.

Legionella pneumophila'nın başlıca virülans faktörleri ve bu faktörlerin enfeksiyon patogenezindeki rolleri Tablo 1'de özetlenmiştir.

Tablo 1. Legionella pneumophila virülans faktörleri ve patogenez mekanizmaları

Virülans Faktörü	Mekanizma	Patogenezdeki Rolü	Kaynak
Dot/Icm tip IV sekresyon sistemi	Konak hücre sitoplazmasına efektör proteinlerin salınması	Hücre içi yaşam döngüsünün sürdürülmesini sağlar	Qiu & Luo, 2017
Legionella-containing vacuole (LCV) oluşumu	Fagolizozomal füzyonun engellenmesi	Hücre içinde bakterinin korunmasını ve çoğalmasını sağlar	Liu et al., 2020
Hücre içi çoğalma	Endoplazmik retikulum kaynaklı vakuol içinde replikasyon	Makrofaj lizisi ve bakterinin yayılımı	Qiu & Luo, 2017;
Protozoon içinde yaşam	Amip ve protozoonlarda çoğalma	Çevresel hayatta kalma ve virülansın artması	Nisar et al., 2020; Mercante & Winchell, 2015
Konak immün yanıtının modülasyonu	Sitokin üretiminin düzenlenmesi	Enflamatuvar yanıt ve doku hasarı	Rello et al., 2024

Kaynak:Yazar tarafından literatürden derlenmiştir.

Klinik Bulgular ve Tanı Yaklaşımı

Lejyonella pnömonisi, toplum kökenli pnömonilerin önemli etiyolojik nedenlerinden biri olup klinik olarak geniş bir spektrumda seyredebilir. Hastalık genellikle akut başlangıçlıdır ve yüksek ateş,

titreme, halsizlik ve miyalji gibi belirgin sistemik semptomlarla ortaya çıkar (Miyashita et al, 2017). Solunum sistemi bulguları arasında öksürük, dispne ve plöritik göğüs ağrısı yer alır; öksürük başlangıçta kuru karakterde olup ilerleyen dönemde balgamlı hale gelebilir (Phin et al., 2014; Chahin et al., 2017).

Lejyonella pnömonisini diğer pnömonilerden ayıran en önemli özelliklerden biri ekstrapulmoner bulguların belirginliğidir. Özellikle gastrointestinal semptomlar (diyare, bulantı, abdominal ağrı) ve nörolojik bulgular (konfüzyon, bilinç değişikliği) klinik tabloda sık görülür ve tanısal açıdan önemli ipuçları sağlar (Pierre et al., 2017). Ayrıca relatif bradikardi ve standart beta-laktam antibiyotik tedavisine yanıt alınamaması lejyonella etiyolojisini düşündüren klinik özellikler arasında yer alır.

Laboratuvar bulguları özgül olmamakla birlikte tanıya katkı sağlayan bazı karakteristik anormallikler mevcuttur. Hiponatremi en sık bildirilen bulgulardan biri olup uygunsuz antidiüretik hormon salgısı ile ilişkilidir. Bunun yanı sıra karaciğer enzim yüksekliği, C-reaktif protein ve prokalsitonin düzeylerinde artış ile kreatin kinaz yüksekliği görülebilir (Chahin et al., 2017). Bu bulgular tek başına tanı koydurucu olmamakla birlikte klinik tablo ile birlikte değerlendirildiğinde lejyonella pnömonisini düşündürmelidir.

Radyolojik bulgular değişken olmakla birlikte genellikle lobar veya multilobar konsolidasyon şeklinde izlenir ve hızlı progresyon gösterebilir. Bazı olgularda kısa sürede bilateral tutulum gelişebilir. Bilgisayarlı tomografide konsolidasyon alanlarına ek olarak buzlu cam opasiteleri ve interstisyel infiltrasyonlar görülebilir (Cillóniz et al., 2016). Ancak bu bulgular özgül değildir ve diğer pnömonilerle ayırıcı tanı klinik ve laboratuvar verileri ile birlikte yapılmalıdır.

Lejyonella pnömonisinin tanısı, klinik şüphe ile birlikte uygun mikrobiyolojik testlerin seçilmesine dayanır. Klinik ve

radyolojik bulgular özgül olmadığından, kesin tanı laboratuvar yöntemleri ile konulmalıdır. Bu nedenle özellikle ağır toplum kökenli pnömoni, immünsüpresyon varlığı ve epidemiyolojik risk faktörlerinin bulunduğu hastalarda Legionella için özgül tanı testlerinin uygulanması önerilmektedir (Allgaier et al., 2021).

Günümüzde en yaygın kullanılan tanı yöntemi idrar Legionella pneumophila antijen testidir. Bu test hızlı sonuç vermesi, kolay uygulanabilir olması ve yüksek özgüllüğü nedeniyle klinik pratikte geniş kullanım alanı bulmuştur. Özellikle serogrup 1 enfeksiyonlarının tanısında duyarlılığı %70–90, özgüllüğü ise %95'in üzerindedir (Viasus et al., 2022). Bununla birlikte testin yalnızca serogrup 1'i saptaması önemli bir kısıtlılık olup diğer Legionella tür ve serogruplarının gözden kaçmasına neden olabilir (Sulaiman et al., 2024).

Moleküler tanı yöntemleri son yıllarda lejyonella enfeksiyonlarının tanısında önemli bir yer kazanmıştır. Polimeraz zincir reaksiyonu (PCR) temelli testler, solunum yolu örneklerinde bakteriyel DNA'nın hızlı ve duyarlı şekilde saptanmasına olanak tanımakta ve geniş bir Legionella tür yelpazesini kapsayabilmektedir. PCR yöntemleri özellikle idrar antijen testine kıyasla daha yüksek duyarlılığa sahip olup erken tanı açısından avantaj sağlamaktadır (Sulaiman et al., 2024; Viasus et al., 2022).

Kültür yöntemi, Legionella enfeksiyonlarının tanısında altın standart olarak kabul edilmekle birlikte özel besiyerleri (BCYE agar) gerektirmesi ve sonuçların geç elde edilmesi nedeniyle klinik pratikte sınırlı kullanım alanına sahiptir. Bununla birlikte kültür, epidemiyolojik incelemeler ve su kaynaklı salgınların araştırılmasında kritik öneme sahiptir (Rello et al., 2024).

Serolojik testler günümüzde tanıda sınırlı bir rol oynamaktadır. Akut ve konvalesan serum örnekleri arasında antikor artışı tanı koydurucu olmakla birlikte sonuçların gecikmesi

nedeniyle akut klinik yönetimde tercih edilmemektedir (Bai et al., 2023).

Tanısal yaklaşımda tek bir test yerine kombine yöntemlerin kullanılması önerilmektedir. Özellikle ağır pnömoni olgularında idrar antijen testi ile birlikte PCR uygulanması tanısal duyarlılığı artırmakta ve farklı Legionella türlerinin saptanmasına olanak sağlamaktadır (Viasus et al., 2022). Klinik şüphe yüksek ise negatif idrar antijen sonucu lejyonella enfeksiyonunu dışlamaz ve ileri tanı yöntemlerine başvurulmalıdır.

Son yıllarda geliştirilen çoklu patojen panelleri (multiplex PCR) ve metagenomik yaklaşımlar, solunum yolu enfeksiyonlarının hızlı ve kapsamlı tanısında yeni ufuklar açmıştır. Bu yöntemler aynı anda birden fazla etkeni saptayabilmekte ve özellikle yoğun bakım hastalarında etiyolojik tanının hızlandırılmasına katkı sağlamaktadır (Ramanan, 2018).

Tedavi ve Klinik Yönetim

Lejyonella pnömonisinin tedavisinde erken tanı ve uygun antibiyotik tedavisinin zamanında başlanması prognozu belirleyen en önemli faktörlerden biridir (Garcia-Vidal et al., 2017; Vergis et al, 2000). Legionella pneumophila hücre içi çoğalan bir patojen olduğundan, tedavide hücre içi penetrasyonu yüksek antibiyotiklerin kullanılması gereklidir. Bu nedenle beta-laktam antibiyotikler tek başına etkili değildir ve tedavi yaklaşımının temelini makrolidler ve solunum florokinolonları oluşturmaktadır (Gershengorn et al., 2015).

Makrolidler arasında özellikle azitromisin, güçlü hücre içi penetrasyonu, uzun yarı ömrü ve iyi tolere edilebilirlik profili nedeniyle sık tercih edilmektedir. Florokinolonlar ise bakterisidal etkileri ve yüksek biyoyararlanımları ile önemli bir alternatif oluşturur. Levofloksasin ve moksifloksasin gibi ajanlar, hızlı klinik yanıt ve etkin bakteriyel eradikasyon sağlamaları nedeniyle yaygın

olarak kullanılmaktadır (Torres, A., & Cillóniz, C. 2021). Bazı çalışmalarda florokinolonların özellikle ağır olgularda daha hızlı klinik düzelme ile ilişkili olabileceği bildirilmiştir (Gershengorn et al., 2015).

Tedavi seçimi hastalığın şiddetine ve hastanın klinik durumuna göre belirlenmelidir. Hafif ve orta şiddette pnömoni olgularında oral azitromisin veya levofloksasin genellikle yeterlidir ve tedavi süresi çoğu hastada 7–10 gündür. Ağır enfeksiyonlarda veya immünsüpresif hastalarda tedavi süresi 10–14 gün veya daha uzun olabilir (Viasus et al., 2022). Yoğun bakım gerektiren olgularda intravenöz tedavi tercih edilmeli ve klinik stabilite sağlandıktan sonra uygun hastalarda oral tedaviye geçiş yapılmalıdır.

Prognoz

Lejyonella pnömonisi hafif klinik tablodan ağır solunum yetmezliğine kadar değişen geniş bir spektrumda seyredebilir (Cunha et al., 2016). Prognoz; yaş, komorbid hastalıklar, immün durum ve tedavinin zamanında başlanması ile yakından ilişkilidir (Viasus et al., 2022). Özellikle ileri yaş, kronik hastalıklar ve immünsüpresyon varlığında hastalık daha ağır seyretmekte ve mortalite artmaktadır (Vergis et al., 2000).

Literaturde hastane kaynaklı enfeksiyonu olan hastaların daha karmaşık bir klinik seyir izlediği, klinik stabiliteye ulaşma süresinin daha uzun olduğu, hastanede kalış süresinin daha uzun olduğu ve diğer risk faktörlerinden bağımsız olarak enfeksiyonla ilişkili ölüm oranının anlamlı derecede daha yüksek olduğu görülmüştür. (Dagan, et al., 2021). Gecikmiş antibiyotik tedavisi de mortaliteyi artıran en önemli bağımsız risk faktörlerinden biridir (Jespersen et al., 2010).

Lejyonella pnömonisi çeşitli pulmoner ve sistemik komplikasyonlara yol açabilir. Pulmoner komplikasyonlar arasında akut solunum yetmezliği ve ARDS en sık görülen durumlardır

(Hauffe et al., 2025). Sistemik komplikasyonlar arasında sepsis, septik şok, akut böbrek yetmezliği, rabdomiyoliz ve nörolojik bulgular yer almaktadır. Özellikle rabdomiyoliz, kreatin kinaz düzeylerinde belirgin artış ile karakterize olup erken tanınması önemlidir (Cunha et al., 2016).

Lejyonella pnömonisinde prognoz büyük ölçüde erken tanı ve uygun tedaviye bağlıdır. Riskli hasta gruplarında erken klinik şüphe ve zamanında müdahale mortalitenin azaltılmasında kritik rol oynamaktadır.

Korunma ve Kontrol

Lejyonella enfeksiyonlarının önlenmesi, su sistemlerinin uygun şekilde yönetilmesine dayanmaktadır. Bu nedenle özellikle sağlık kurumları ve büyük ölçekli su sistemlerinin bulunduğu yapılarda düzenli çevresel izlem ve kontrol programlarının uygulanması önerilmektedir (WHO, 2022; ECDC, 2023).

Sağlık kurumlarında Legionella kolonizasyonu nozokomiyal enfeksiyonlar açısından risk oluşturabilir. Bu nedenle su sistemlerinin mikrobiyolojik izlenmesi, uygun sıcaklık kontrolünün sağlanması ve gerekli durumlarda dezenfeksiyon uygulanması temel korunma yaklaşımları arasında yer almaktadır (Bédard,et al., 2015).

Toplum düzeyinde ise oteller ve benzeri konaklama tesislerinde su sistemlerinin düzenli bakımı, biyofilm oluşumunun engellenmesi ve periyodik kontrol programlarının yürütülmesi önerilmektedir (ECDC, 2023).

Sürveyans sistemleri, olası salgınların erken tespiti ve kontrolünde önemli rol oynamaktadır (Beauté et al., 2016).

Sonuç

Lejyonella pnömonisi, klinik ve epidemiyolojik özellikleri nedeniyle tanısal açıdan dikkat gerektiren ve özellikle ağır seyirli

olgularda mortalite ile ilişkili önemli bir enfeksiyon etkenidir. Hastalığın özgül olmayan klinik bulgularla seyretmesi ve ekstrapulmoner semptomların eşlik edebilmesi, tanıda klinik farkındalığın önemini artırmaktadır.

Güncel tanı yöntemleri, özellikle idrar antijen testi ve moleküler teknikler, etkenin hızlı ve güvenilir şekilde saptanmasına olanak sağlayarak klinik yönetimi doğrudan etkilemektedir. Erken tanı ile birlikte hücre içi etkili antibiyotiklerin zamanında başlanması, hastalığın klinik seyrini ve sonuçlarını belirleyen temel unsurlar arasında yer almaktadır.

Hastalık prognozu büyük ölçüde konak faktörlerine bağlı olup ileri yaş, komorbid hastalıklar ve immünsüpresyon varlığında daha ağır klinik tablolar ve artmış mortalite riski söz konusudur. Bu nedenle riskli hasta gruplarında erken tanı ve uygun tedavi stratejilerinin gecikmeden uygulanması kritik öneme sahiptir.

Lejyonella enfeksiyonlarının kontrolü ise yalnızca klinik yönetim ile sınırlı olmayıp, çevresel su sistemlerinin etkin yönetimi ve sürveyans uygulamalarını içeren çok boyutlu bir yaklaşım gerektirir. Klinik farkındalık ile çevresel kontrol stratejilerinin birlikte uygulanması, hastalık yükünün azaltılmasında belirleyici rol oynamaktadır.

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