Chronic Pneumonia

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Abstract

Chronic eosinophilic pneumonia (CEP) is associated with eosinophilic lung ailment specifically/usually diagnosed by a triad of clinical warning signs together with pulmonary warning signs, eosinophilia, as well as distinguishing radiographic defects. It needs a high indicator of doubt given that it is overlain with other eosinophilic situations and be deficient in a diagnostic assay. The diagnosis is made after careful consideration of other secondary causes of eosinophilia, such as infectious, drugs, or toxic etiologies. CEP generally responds rapidly to treatment, which primarily consists of corticosteroid therapy, but relapses are common. New remedies are being investigated which are documented in new studies regarding the pathophysiology of eosinophilic illness progression. Close follow-up is important given the difficulty in weaning patients from glucocorticoids with many patients developing sequelae of chronic glucocorticoid therapy. Hence, searching for various treatments is being prioritized by the scientific community.

Keywords

Chronic eosinophilic pneumonia (CEP) · Common variable immunological disorder (CVID) · Mepolizumab · Omalizumab · BAL

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4.1 Introduction

4.1.1 About the Disease

Eosinophilic lung diseases are a group of diffuse parenchymal lung diseases characterized by the prominent infiltration of the lung interstitial and alveolar spaces by polymorphonuclear eosinophils, with conservation of the lung architecture. As a corollary, a common denominator of eosinophilic lung diseases is represented by a dramatic response to systemic corticosteroid therapy and healing without any sequelae in most cases, despite frequent impressive impairment of lung function at presentation [1]. CEP was first recognized as a unique pulmonary entity in 1969, characterized by Carrington et al., when a series of female patients were described as presenting with symptoms of dyspnea, fever, and weight loss who demonstrated pulmonary opacities on chest X-ray and had noted eosinophilic infiltration on lung biopsy specimens. The condition is thought to be idiopathic, with no known infectious or toxic etiology identified. CEP is a clinical diagnosis and has a presentation that is typically described as a triad of the following: pulmonary symptoms, abnormal chest imaging, and abnormal elevation of eosinophils in either serum or pulmonary tissue [2].

4.1.2 Epidemiology

Representing <3% of cases of varied interstitial diseases, CEP may be a rare illness. It is, however, the foremost common of the eosinophilic pneumonias in nontropical areas wherever incidence of parasitic infections is low. Most patients are nonsmokers, and it is thought that <10% diagnosed are smokers. This contrasts with acute leucocyte respiratory illness within which a smoking history is a far lot in common [3]. It is a significant reason behind death among all age groups, leading to 1.4 million deaths in 2010 (7% of the world's yearly total) and was the fourth leading reason behind death within the world in 2016, leading to 3 million deaths worldwide [4, 5].

4.1.3 Causes/Symptoms

A cluster of disorders is classified by etiology, together with secondary causes like infectious, malignant, allergic, drug, and deadly etiologies. Primary eosinophilic lung diseases can be further classified by isolated pneumonic involvement vs. general involvement, and two major isolated pneumonic white blood cell respiratory organ diseases embody acute eosinophilic pneumonia (AEP) and CEP, though these are commonly less abundant [2].

4.2 Pathophysiology of Pneumonia

4.2.1 Cell Types Involved

There is a complex balance amid the organisms residing within the lower tract and also the native and general defense mechanisms (both innate and acquired) that once disturbed give rise to inflammation of the respiratory organ parenchyma, i.e., pneumonia. Common defense mechanisms that are compromised within the pathologic process of respiratory illness include:

- Systemic defense mechanisms like body substance and complement-mediated immunity that is compromised in diseases like common variable immunological disorder (CVID), X-linked immunodeficiency (inherited), and purposeful as plenia (acquired). Impaired cell-mediated immunity predisposes people to infection by living organisms like viruses and organisms of low virulence like pneumonia (PJP), plant causes, among others.
- The mucociliary clearance that is usually impaired in cigarette smokers, post-viral state, Kartergerner syndrome, and different connected conditions.
- Impaired cough reflex seen in comatose patients, a sure indication of substance abuse.
- Accumulation of secretions as seen in mucoviscidosis or in cartilaginous tube obstruction.

The resident macrophages serve to safeguard the respiratory organ from foreign pathogens. Ironically, the inflammatory reaction triggered by these terrible macrophages is what is chargeable for the histopathological and clinical findings seen in respiratory illness. The macrophages engulf these pathogens and trigger signal molecules or cytokines like TNF-α, IL-8, and IL-1 that recruit inflammatory cells like neutrophils to the positioning of infection. They conjointly serve to gift these antigens to the T cells that trigger each cellular and body substance defense mechanisms and activate the targeted antibodies against these organisms. This, in turn, causes inflammation of the respiratory organ parenchyma and makes the liner capillaries leaky, resulting in oxidative congestion and underlines the pathologic process of respiratory illness [6].

4.2.2 Biology of the Disease

Eosinophils are multifunctional leukocytes involved in innate and reconciling immunity. They mature within the bone marrow beneath stimulation from cytokines. Particularly, they are influenced by IL-5, IL-3, granulocyte-macrophage colony-stimulating tissue, and transcription factors including delta-dbl-GATA-1, before disseminating into the blood and after into tissues. Eosinophils have intracytoplasmic granules containing proteins, toxins, and chemokines, and pro-inflammatory degranulation of eosinophils releases these venomous substances

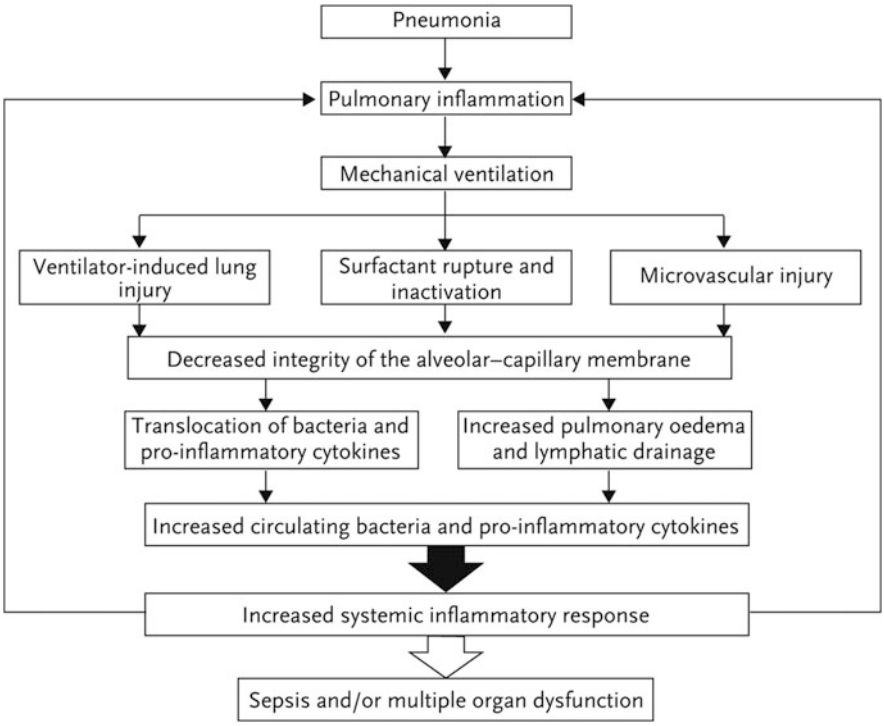

Fig. 4.1 Biology of the disease

into the tissues, which contributes to the pathophysiology of WBC disorders (Fig. 4.1). Eosinophils move with multiple cellular pathways, as well as T helper lymphocytes, mast cells and basophils, macrophages, and multiple cells. However, the white corpuscle play an important role in respiratory organ and it principally directed by IL-5 and also the eotaxin taxonomic category of chemokines [7]. Additionally, recent study suggests that IL-25 might uphold chronic WBC inflammation of the respiratory organ [8]. Histopathological lesions are associated with the toxicity of small piece discharge of eosinophils and are mostly reversible with treatment, though tissue harm and reworking will be seen [7]. Osteopontin levels are found to be elevated in bronchoalveolar lavage (BAL) fluid of patients with WBC respiratory illness as well as drug-induced eosinophilic pneumonia. They will play a role in WBC inflammation [1].

4.2.3 Transcriptional Regulation

The interface between the external environment (including microbes therein) and the internal environment (including leukocytes and other immune cells) is the respiratory epithelium, and immunity roles of this interface were the subject of extensive

study. We learned that an essential action of the cytokine IL-17, already well recognized for driving sterilizing immunity against extracellular bacteria and fungi, is to activate the lung's epithelial lining. IL-17 signals to cells via the IL-17RA receptor, and it has become apparent that humans with mutations in IL-17RA show greater susceptibilities to bacterial pneumonia. Although IL-17 receptors are expressed by many different cell types, the mutation of IL-17RA in lung epithelial cells selectively (in mice with CC10-Cre transgenes and floxed ***Il17ra***) was demonstrated to be sufficient to increase bacterial burdens during *Klebsiella pneumoniae* pneumonia in mice. A protective action observed was the induction of CXCL5 by epithelial cells, advancing prior studies that suggested this was an epithelial-specific product during pneumonia that elicits neutrophil recruitment. Transcriptional profiling experiments in mice with pneumococcal pneumonia have now revealed that CXCL5 is only one of many hundreds of genes that are induced preferentially in epithelial cells during infection, dozens of which are secreted products like CXCL5 that can mediate immune cell cross-talk. Another epithelial-specific product was identified as a neutrophil activator, secreted and transmembrane 1 (Sectm1), which stimulates recruited neutrophils to make more of the neutrophil-attracting chemokine, CXCL2, thereby amplifying the positive feedback of inflammation within the infected lung. Harnessing the power of epithelial innate immunity, pharmacologically triggering these cells is being pursued as a means to provide protection against diverse respiratory infections, and it now appears that this can be effective even in mice modeling leukemia patients, despite profound immune dysregulation due to both leukemia and leukemia treatment.

4.3 Current Treatment

The mainstay of treatment relies on oral corticosteroid (OCS) therapy; with a goal of causing remission further as reducing the chance of reversion [9]. Response to OCS is sometimes dramatic and fast, with each clinical improvement and backbone of infiltrates on imaging. It is worth noting that response generally happens within many days, and if fast clinical improvement is not seen, various diagnoses ought to be reconsidered [10]. Low-dose inhaled corticosteroids (ICS) were used formerly to help with tapering and discontinuing OCS. ICS have thus been planned as monotherapy, thanks to the suspected deposition of ICS in alveoli to stop the event of the aspect effects from long-run usage of OCS. However, a study performed by Minakuchi et al. suggests that ICS might not be a good monotherapy. While not treatment, spontaneous resolution happens in $<10\%$ of patients with CEP, and is a near threat of succession to fibrosis [11].

There are no firm doses or period tips. The general goal is to keep up continued clinical improvement on very cheap attainable dose of OCS so as to avoid relapse but conjointly minimize steroid-related facet effects. Initial treatment is usually with oral prednisone at 0.5–0.6 mg/kg/day with the dose narrowing down by a common fraction on confirmation of each clinical and radiologic resolution [12]. A review of this literature relating to treatment by Suzuki et al. suggests that a beginning dose

of prednisolone of around 30 mg would be adequate [10]. Treatment periods are variable from several months to 12 months, depending on the clinical response. Relapses are common, occurring in over half the patients [9]. Despite this typically accepted observe, only one study so far has prospectively evaluated the optimum treatment plan with relevance to reversion rate, in an exceedingly irregular parallel-group study. In this trial, the study cluster received the OCS treatment at a daily dose of 0.5 mg/kg/day over a shorter 3-month period compared to an equivalent dose in an exceedingly longer 6-month period. Within the 3-month cluster, the prednisolone was tapered by 20% each 2 weeks to nil by 3 months, whereas within the 6-month cluster, the prednisolone was tapered off slower over 6 months. They were determined for 2 years on completion of treatment. The relapse rates were similar between the teams (52.1% vs. 61.9%, $P = 0.56$), suggesting that a shorter treatment amount is also acceptable, with revised observation [13].

4.3.1 Drawbacks of the Current Treatment

Although the extensive tenure prognosis of the illness is highly sensitive to systemic corticosteroids, but frequently relapses if the dose is tapered or treatment discontinued. Partly patients are noted to suffer reversion, with some failure numerous times. Commencement of OCS medical therapy in relapsed cases is uniformly effective. Predictors of relapse have not been strictly evaluated; however smoking underlying bronchial asthma are double risk factors [10, 14]. These patients might need chronic steroid maintenance medical care, and efforts to mitigate aspect effects are necessary [10]. This additionally leads to efforts toward finding probable steroid-reducing therapies.

4.3.2 Future Directions in Therapeutics

Most of other therapies are delineated just in case of reports with no strong proof supporting their use in CEP. Omalizumab, an antibody against IgE, was utilized in a patient with CEP on the second reversion in 2 years. This patient had an elevated IgE and had been given omalizumab injections. The patient was deemed to be sickness-free after 15 months of medical aid [15]. During a succeeding case report, Domingo et al. delineated a fortunate use of omalizumab in a patient with CEP with distinguished asthmatic options and mud mite allergen. They were ready to taper the dose of omalizumab by 500 mg each for 6 months [16]. Clinicians ought to be tuned in to the chance of exposure to eosinophilic granulomatosis with polyangiitis (EGPA) in these patients [15].

There are many alternative potential targets for CEP, most ordinarily against IL-5. Amplified levels of IL-5 with associated discharge of cytotoxic granular proteins from eosinophils are a decisive mechanism into the pathophysiology of CEP [17].

Mepolizumab and reslizumab stop binding of circulating IL-5 to eosinophils. Benralizumab neutralizes IL-5 and operates by binding the alpha fractional subunit

of the IL-5 receptor and is additionally ready to induce programmed cell death of target cells via antibody-dependent cell-mediated toxicity [18, 19]. During a massive multicenter randomized controlled trial involving 621 patients, mepolizumab reduced the speed of asthma attack exacerbations in rigorous eosinophilic asthma [20]. It has conjointly been demonstrated to cut back the frequency of asthma attack exacerbations and is identified to be helpful as a possible steroid-sparing agent in hyper eosinophilic syndromes [21, 22]. Although anti-IL5 therapies are verified as efficacious in eosinophilic asthma attack, there is restricted knowledge on the employment of those therapies in CEP.

A recent report delineated a patient with CEP who had undergone glucocorticoid medical aid, however failing steroid taper and experienced noteworthy steroid-induced side effects together with weight gain, Cushingoid options, and muscle wasting. Eighteen months subsequent to preliminary appearance, mepolizumab was started at a dose of 100 mg each for 4 weeks. Once this medical aid commenced, her peripheral blood symptoms weakened, and her symptoms disappeared whereas tapering of glucocorticoids was found. However, she developed a gentle hypersensitivity reaction subsequent to 6 months of medical aid. Therefore, reslizumab at a dose of 3 mg/kg was initiated each for 4 weeks. Following 2 further months, she was ready for discontinuing her glucocorticoids [23]. Mepolizumab had conjointly been used effectively in another patient with CEP and a 20-year history of asthma attack throughout his second reversion at 100 mg each month [24]. However, the period of medical aid with mepolizumab in such patients remains unclear.

Other potential targets for treatment of CEP embrace IL-25, IL-33, IL-4, and IL-13. IL-25 and IL-33 are first and foremost made by airway epithelial cells that induce the assembly of Th2-type cytokines together with IL-5 and IL-13 on eosinophils. Katoh et al. examined the BAL fluid in 20 with AEP, 22 patients with CEP, 20 with idiopathic pulmonary fibrosis (IPF), and 20 with sarcoidosis. Patients with acute and chronic eosinophilic asthma attacks had higher IL-5 and eosinophil levels compared to patients with IPF and sarcoidosis. Curiously, IL-25 levels were elevated in patients with CEP, however not AEP. IL-33 levels were not considerably totally different in eosinophilic pneumonia when compared to sarcoidosis and IPF [8]. The results of this study indicate that IL-25 could also be a possible therapeutic target for CEP. Currently, antibodies to Il-25 do not seem to be commercially offered.

Dupilumab may be a human anti-IL-4 receptor α-monoclonal protein that targets each IL-4 and IL-13 communication and thus TH2-type inflammation. Fidel Castro Ruz et al. at random appointed 1902 patients to varied doses of dupilumab vs. placebo and confirmed reduced frequency of asthma attack exacerbation and improvement in forced expiratory volume in 1 s. In addition, within the Liberty asthma attack Venture trial, add-on dupilumab was ready to considerably cut back the utilization of oral glucocorticoids in patients with severe asthma attack [25]. Dupilumab can also hold promise in designated relapsing cases of CEP; however it has not been utilized in these cases at this point.

4.3.3 Perspective

The short-run viewpoint for patients with CEP is mostly favorable, given the outstanding and timely clinical improvement with corticosteroids. Around half the patients at first diagnosed with CEP have clinical improvement, while there is no relapse or requirement for repeat treatment [26].

Among the remaining half of patients with relapse, repeat OCS dosing or perhaps maintenance of low-dose OCS for long is also needed [26]. In these patients, there is risk of development of steroid-related adverse effects, together with hyperglycemia, diabetes mellitus, osteoporosis, psychosis, and infectious complications like pneumonic non-tuberculoses mycobacterium [10, 14].

In terms of pneumonic status, the bulk of patients with CEP have restriction or obstruction noted on spirometry [15]. Among those with abnormal pneumonic function tests, a majority of patients improve with treatment; however, as many as 37–50% of the patients might have persistent defects after treatment [10, 27].

In summary, given the antecedently mentioned dramatic and fast response in an exceedingly giant share of patients, those who are diagnosed and treated in an exceedingly timely manner might have a good clinical response. Conversely, given the incidence of relapse and also the potential for long-standing steroid-induced side effects or fibrotic changes, more investigations of steroid-sparing therapies like anti-IL5 antibodies are required.

4.4 Toxicokinetics

The most common cause of typical bacterial pneumonia worldwide is *Pneumococcus*. The polysaccharide capsule of *Streptococcus pneumoniae* inhibits the complement binding to the cell surface and hence inhibits phagocytosis. Virulent pneumococcal proteins such as IgA1 protease, neuraminidase, pneumolysin, autolysin, and the surface protein A further help the organism to counteract the host immune response and allow it to cause infection in humans.

Genetic mutations causing an active efflux of drug and eventually resistance have led to an increase in drug-resistant *Streptococcus pneumoniae* (DRSP) over the last few years.

Alteration in penicillin-binding proteins has increased the penicillin resistance and an increased rate of penicillin-resistant *S. pneumoniae*. Penicillin resistance occurs due to failure to bind to the microbe cell wall [28, 29].

4.5 Histopathology

Pathologically, lobar pneumonia is the acute exudative inflammation of a lung lobe. It has the following four advanced stages if left untreated:

1. *Congestion*: In this stage, pulmonary parenchyma is not fully consolidated, and microscopically, the alveoli have serous exudates, pathogens, few neutrophils, and macrophages.
2. *Red Hepatization*: Here, the lobe is now consolidated, firm, and liver-like. Microscopically, there is an addition of fibrin along with serous exudate, pathogens, neutrophils, and macrophages. The capillaries are congested, and the alveolar walls are thickened.
3. *Gray Hepatization*: The lobe is still liver-like in consistency but gray in color due to suppurative and exudative filled alveoli.
4. *Resolution*: After a week, it starts resolving as lymphatic drainage or a productive cough clears the exudates [30].

4.6 History and Physical

The history findings of bacterial pneumonia may vary from indolent to fulminant. Clinical manifestation includes both constitutional findings and findings due to damage to the lung and related tissue. The following are major history findings:

- Fever with tachycardia and/or chills and sweats.
- The cough may be either non-productive or productive with mucoid, purulent, or blood-tinged sputum.
- Pleuritic chest pain, if the pleura is involved.
- Shortness of breath with normal daily routine work.
- Other symptoms include fatigue, headache, myalgia, and arthralgia.

Physical findings also vary from patient to patient and mainly depend on the severity of lung consolidation and existence or nonexistence of pleural effusion. The following are major clinical findings:

- Increased respiratory rate.
- Percussion sounds vary from flat to dull.
- Tactile fremitus.
- Crackles, rales, and bronchial breath sounds are heard on auscultation.

Confusion manifests earlier in older patients. A critically ill patient may present with sepsis or multi-organ failure [31].

4.7 Evaluation

The approach to evaluate and diagnose pneumonia depends on different modalities but primarily it is like a tripod stand which has three legs which are summed up as:

1. *Clinical Evaluation*: It includes taking a careful patient history and performing a thorough physical examination to judge the clinical signs and symptoms mentioned above.
2. *Laboratory Evaluation*: This includes lab values such as complete blood count with differentials, inflammatory biomarkers like ESR and C-reactive protein, blood cultures, sputum analysis, or Gram staining and/or urine antigen testing or polymerase chain reaction for nucleic acid detection of certain bacteria.
3. *Radiological Evaluation*: It includes chest X-ray as an initial imaging test and the finding of pulmonary infiltrates on a plain film is considered as a gold standard for diagnosis when the lab and clinical features are supportive [32, 33].

4.8 Differential Diagnosis

4.8.1 Differential Diagnosis in Children

- Asthma or reactive airway disease
- Bronchiolitis
- Croup
- Respiratory distress syndrome

4.8.2 Differential Diagnosis in Adults

- Acute and chronic bronchitis
- Aspiration of a foreign body
- Asthma
- Atelectasis
- Bronchiectasis
- Bronchiolitis
- Chronic obstructive pulmonary disease
- Fungal
- Lung abscess
- Pneumocystis jiroveci pneumonia
- Respiratory failure
- Viral [34]

4.9 Enhancing Healthcare Team Outcomes

Pneumonia is a common infectious lung disease. It requires interprofessional care and the involvement of more than one subspecialty. This patient-centered approach involving a physician with a team of other health professionals, physiotherapists, respiratory therapists, nurses, pharmacists, and support groups working together for the patient plays an important role in improving the quality of care for pneumonia

patients. It not only decreases the hospital admission rates but also positively affects the disease outcome. For healthy patients, the outcomes after treatment are excellent but, in the elderly and those with comorbidities, the outcomes are guarded.

References

1. Cottin V (2016) Eosinophilic lung diseases. Clin Chest Med 37(3):535–556
2. Crowe M, Robinson D, Sagar M, Chen L, Ghamande S (2019) Chronic eosinophilic pneumonia: clinical perspectives. Ther Clin Risk Manag 15:397–403
3. Sevim T, Aksoy E, Akyıl FT, Ağca MÇ, Kongar NA, Özşeker F (2015) Eosinophilic lung disease: accompanied with 12 cases. Turk Thorac J 16(4):172–179
4. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR (2011) Viral pneumonia. Lancet 377 (9773):1264–1275
5. WHO (2018) The top 10 causes of death. www.who.int
6. Mason RJ, Broaddus VC, Martin T, King T, Schraufnagel D, Murray J, Nadel J (2016) Murray and Nadel's textbook of respiratory medicine, 6th edn. Elsevier Saunders, Philadelphia
7. Katoh S, Ikeda M, Matsumoto N, Shimizu H, Abe M, Ohue Y, Mouri K, Kobashi Y, Nakazato M, Oka M (2017) Possible role of IL-25 in eosinophilic lung inflammation in patients with chronic eosinophilic pneumonia. Lung 195(6):707–712
8. Ueno T, Miyazaki E, Ando M, Nureki S, Kumamoto T (2010) Osteopontin levels are elevated in patients with eosinophilic pneumonia. Respirology 15(7):1111–1121
9. Suzuki YT (2018) Suda, long-term management and persistent impairment of pulmonary function in chronic eosinophilic pneumonia: a review of the previous literature. Allergol Int 67(3):334–340
10. Minakuchi M, Niimi A, Matsumoto H, Amitani R, Mishima M (2003) Chronic eosinophilic pneumonia: treatment with inhaled corticosteroids. Respiration 70(4):362–366
11. Marchand E, Cordier JF (2006) Idiopathic chronic eosinophilic pneumonia. Orphanet J Rare Dis 1(1):11
12. Oyama Y, Fujisawa T, Hashimoto D, Enomoto N, Nakamura Y, Inui N, Kuroishi S, Yokomura K, Toyoshima M, Yamada T, Shirai T, Masuda M, Yasuda K, Hayakawa H, Chida K, Suda T (2015) Efficacy of short-term prednisolone treatment in patients with chronic eosinophilic pneumonia. Eur Respir J 45(6):1624–1631
13. Ishiguro T, Takayanagi N, Uozumi R, Tada M, Kagiyama N, Takaku Y, Shimizu Y, Sugita Y, Morita S (2016) The long-term clinical course of chronic eosinophilic pneumonia. Intern Med 55(17):2373–2377
14. Kaya H, Gümüş S, Uçar E, Aydoğan M, Muşabak U, Tozkoparan E, Bilgiç H (2012) Omalizumab as a steroid-sparing agent in chronic eosinophilic pneumonia. Chest 142 (2):513–516
15. Domingo C, Pomares X (2013) Can omalizumab be effective in chronic eosinophilic pneumonia? Chest 143(1):274
16. Mukherjee M, Sehmi R, Nair P (2014) Anti-IL5 therapy for asthma and beyond. World Allergy Organ J 7(1):32
17. Lim HF, Nair P (2015) Efficacy and safety of reslizumab in patients with moderate to severe eosinophilic asthma. Expert Rev Respir Med 9(2):135–142
18. Varricchi G, Bagnasco D, Borriello F, Heffler E, Canonica GW (2016) Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: evidence and unmet needs. Curr Opin Allergy Clin Immunol 16(2):186
19. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P (2012) Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 380(9842):651–659

20. Liu Y, Zhang S, Li DW, Jiang SJ (2013) Efficacy of anti-interleukin-5 therapy with mepolizumab in patients with asthma: a meta-analysis of randomized placebo-controlled trials. PLoS One 8(3):e59872
21. Garrett JK, Jameson SC, Thomson B, Collins MH, Wagoner LE, Freese DK, Beck LA, Boyce JA, Filipovich AH, Villanueva JM, Sutton SA, Assa'ad AH, Rothenberg ME (2004) Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. J Allergy Clin Immunol 113(1):115–119
22. Sarkis E, Patel S, Burns K, Batarseh H, Mador MJ (2020) Anti-interleukin (IL)-5 as a steroid-sparing agent in chronic eosinophilic pneumonia. J Asthma 57:82–86
23. To M, Kono Y, Yamawaki S, Soeda S, Katsube O, Kishi H, To Y (2018) A case of chronic eosinophilic pneumonia successfully treated with mepolizumab. J Allergy Clin Immunol Pract 6(5):1746
24. Castro M (2018) Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 378(26):2486–2496
25. Naughton M, Fahy J, FitzGerald MK (1993) Chronic eosinophilic pneumonia: a long-term follow-up of 12 patients. Chest 103(1):162–165
26. Durieu J, Wallaert B, Tonnel A (1997) Long-term follow-up of pulmonary function in chronic eosinophilic pneumonia. Groupe d'Etude en Pathologie Interstitielle de la Societe de PathologieThoracique du Nord. Eur Respir J 10(2):286–291
27. Hauswaldt J, Blaschke S (2017) [Dyspnea]. Internist (Berl) 58(9):925–936
28. Berliner D, Schneider N, Welte T, Bauersachs J (2016) The differential diagnosis of dyspnea. Dtsch Arztebl Int 113(49):834–845
29. Sattar SBA, Sharma S (2019) Bacterial pneumonia. StatPearls Publishing, Treasure Island, FL
30. Falcone M, Venditti M, Shindo Y, Kollef MH (2011) Healthcare-associated pneumonia: diagnostic criteria and distinction from community-acquired pneumonia. Int J Infect Dis 15 (8):e545–e550
31. Grief SN, Loza JK (2018) Guidelines for the evaluation and treatment of pneumonia. Prim Care 45(3):485–503
32. Franquet T (2018) Imaging of community-acquired pneumonia. J Thorac Imaging 33 (5):282–294
33. Anand N, Kollef MH (2009) The alphabet soup of pneumonia: CAP, HAP, HCAP, NHAP, and VAP. Semin Respir Crit Care Med 30(1):3–9
34. Rayees S, Mabalirajan U, Bhat WW, Rasool S, Rather RA, Panda L, Satti NK, Latoo SK, Ghosh B, Singh G (2015) Therapeutic effects of R8, a semi-synthetic analogue of Vasicine, on murine model of allergic airway inflammation via STAT6 inhibition. Int Immunopharmacol 26 (1):246–256