ISA Journal of Medical Sciences (ISAJMS)

Homepage: https://isapublisher.com/isajms/

Volume 3, Issue 4, Jul-Aug, 2026 ISSN: 3049-1746

Neutrophilic Asthma: A Multifaceted Phenotype of Asthma

Jahun, M.M.[1], Saidu, H.[2], Aliyu, I. A.[2], Rogo, L.D.[2], Bala, J. A.[2], Magaji, B.[1], Alhassan, M.[1] and Bashari, A.[1]

[1]*Department of Medical Laboratory Science, College of health science and technology Jahun, P.M.B. 3004, Jigawa State, Nigeria.*
[2]*Department of Medical Laboratory Science, Faculty of Allied Health Sciences, College of, Health Sciences, Bayero University Kano, P.M.B. 3011, Kano State, Nigeria.*

Received: 05.06.2026 | **Accepted:** 20.07.2026 | **Published:** 22.07.2026

***Corresponding Author:** Jahun, M.M.

DOI: *10.5281/zenodo.21498322*

Abstract **Review Article**

Neutrophilic asthma is a multifaceted phenotype of severe and persistent asthma, characterized by frequent exacerbations, leading to hospitalizations, due to near-fatal asthma, fixed airflow obstruction, poor response to corticosteroids, and patient have worse quality of life, its development is driven by the participation of various immune cells and molecules. Neutrophilic asthma is caused by the interaction between genetic, environmental, innate and adaptive immune factors. Among these factors, air pollution, smoking, viral, bacteria, fungal infections and obesity contribute to the exacerbation of this type of asthma, by promoting Th17-type cell inflammation, increasing the secretion of Th17-related cytokines and chemokines, which induces the activation of neutrophils and their recruitment into the sites of inflammation. The molecular mechanisms underlying the severity of neutrophilic asthma is still not well clear or understood, making the diagnosis and treatment of this type of severe asthma an extremely challenging. The discussion of the pathophysiology, mechanism, characteristic, mediators, risk factors, biomarkers and steroid resistance of neutrophilic asthma, in this paper may provide some direction for the prevention, diagnosis and treatment of severe neutrophilic asthma. Hence this phenotype of asthma requires specific therapeutic interventions aimed at prevention and reducing airway remodeling.

Keywords: Asthma, Neutrophil.

Introduction

Asthma is defined as a chronic inflammatory disorder of the airways involving many cells and mediators. The principal associated symptoms are airway hyperresponsiveness and usually reversible airflow obstruction. These symptoms lead to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (Global health initiative for asthma 2022). It has also been defined as "a heterogeneous disease characterized by airway inflammation typified by clinical manifestations such as cough, wheezing, chest tightness, and shortness of breath that vary over time and in intensity, together with variable expiratory airflow limitations (Saidu, *et al.*, 2022).

Asthma is a chronic inflammatory airway disease with several distinct phenotypes, characterized by different immunopathological pathways, clinical

presentation, severity of the disease and response to treatment (Pavlidis *et al*., 2019). The phenotypes of asthma include eosinophilic, neutrophilic, mixed granulocytic and paucigranulocytic asthma, these are four various endotypes of asthma depending on cell counts of peripheral blood, sputum or bronchoalveolar fluid, Neutrophilic inflammations have been studied to be associated with a poor asthma control in addition to persistent asthma symptoms and atopy (Elshony *et al*., 2022). There are other several distinct clinical proposed asthma phenotypes, such as childhood-onset allergic asthma, adult-onset eosinophilic asthma, neutrophilic asthma, exercise-induced asthma (EIA), obesity-related asthma, and aspirin exacerbated respiratory disease (AERD). Among these phenotypes of asthma, there are patients whose asthma is very severe and refractory to the standard treatment including high doses of inhaled corticosteroids (ICSs), and long-acting β2- agonists (LABAs) and/or any other modifier. Severe refractory asthma encompasses several molecular phenotypes of asthma, including neutrophilic asthma phenotype. Neutrophilic asthma is characterized by severe refractory disease, with fixed airway obstruction, and poor response to standard treatment with inhaled corticosteroids (ICSs), long-acting β2-agonists (LABAs), and other modifiers (Syabbalo, 2020).

Pathophysiologic of Neutrophilic asthma

Asthma originates from complex interactions between genetic factors and environmental agents such as aeroallergens and respiratory viruses. In particular, within the airway lumen allergens can be captured by dendritic cells, which process antigenic molecules and present them to naive (Th0) T helper cells leading to the differentiation of the naïve Th0 to Th17 cells, that produce IL17A and IL-17F which cause neutrophil recruitment and expansion. Furthermore, IL-12- dependent and IFN-γ releasing Th1 cells can be activated, especially as a result of airway infections sustained by respiratory viruses. Finally, many mediators, cytokines, and growth factors produced by several different cells involved in chronic asthmatic inflammation may also affect the functions and proliferation rates of airway structural cellular elements including epithelial cells, fibroblasts, smooth muscle cells, and endothelial vascular cells (Girolamo *et al*., 2015).

Neutrophil functions in asthma

Neutrophils provide a crucial ‘first-line’ immune response and are among the first effector cells to be recruited to the lung during inflammation, irrespective of the cause, and are also the most abundant leucocyte, accounting for 70% of all circulating white cells (Summers *et al*., 2010). Once released from the bone marrow into the circulation, neutrophils patrol the blood vessels and navigate towards inflammation by sensing chemotactic gradients such as CXCL-8, which can be released due to interaction of microbial or damage associated molecular patterns. During this process, neutrophils use their cellular polarity, regulated by Rho guanosine triphosphatases, to perform amoeboid movement to accurately reach the site of inflammation (Amulic *et al*., 2012). To enable migration through dense extracellular matrices, neutrophils release proteinases, such as neutrophil elastase and proteinase 3, to cleave components of the extracellular matrix such as elastin, fibronectin, vitronectin, laminin and collagen (Crisford *et al*., 2018)

At the site of inflammation, neutrophils engulf smaller target material by phagocytosis, such as *Haemophilus influenzae* or *Streptococcus pneumoniae*. Engulfed microbes are then destroyed in the neutrophil phagosome through pH change, and exposures to reactive oxygen species (ROS) and cytotoxic enzymes. Besides phagocytosis, neutrophils can also perform microbial killing by degranulation, a process in which neutrophils extracellularly release cytotoxic ROS and proteolytic enzymes such as neutrophil elastase and proteinase 3 at the site of infection. (Crisford *et al*., 2018). Neutrophils can also release neutrophil extracellular traps (NETs), web-like structures consisting of cytosolic granule proteins embedded on a scaffold of decondensed chromatin—to capture and destroy pathogens (Papayannopoulos, 2018).

A study of neutrophilic asthma defined by raised

blood neutrophil count were associated only with moderate exacerbations and poor asthma control with low blood eosinophil counts, found that this was associated with increased levels of C-reactive protein, matrix metalloproteinase-9, IL-6, leptin, and soluble urokinase plasminogen activator receptor serum levels. (Flinkman *et al*., 2023). This non-T2 or T2-low neutrophilic phenotype does not have any targeted biologic therapies since the key driving pathways are unclear (Chung 2023). There is a need for a more granular definition of asthma phenotypes using blood biomarkers not only to inform the underlying molecular pathways but also to facilitate personalized therapeutic choices (Flinkman *et a*l., 2023).

Neutrophilic asthma is characterized by increased neutrophil airway inflammation, with Th17 cells playing a central role in this phenotype. A Th17-Treg cell imbalance leads to the release of IL-17 from Th17 cells, which indirectly induces neutrophil recruitment to sites of inflammation and decreases levels of forced expiratory volume (i.e., FEV1 %), steroid responsiveness and increases airway hyperresponsiveness. In addition to triggering the release of a range of inflammatory factors (e.g., IL-6, IL-8, IL-11, granulocyte macrophage colony stimulating factor [GM-CSF] and vascular endothelial growth factor) leading to asthma exacerbation and airway remodeling, (Zhang *et al*., 2022). Neutrophilic asthma is an adult-onset disease which usually starts after 12 years. It is the most common phenotype in adult characterized by severe persistent asthma with frequent exacerbations, Patients with neutrophilic asthma have frequent urgent visits to emergence rooms, hospitalization and intubation. This phenotype of asthma is worse at night with frequent nocturnal attacks and has been associated with sudden-onset fatal asthma in about 23% of the patients (Syabbalo, 2020).

Table 1 Characteristics of neutrophilic asthma

➢ Adult on-set, after 12 years
➢ Less atopic
➢ Th17 cytokine milieu - IL-6, IL-8, IL-21, IL-23, IL-17A, IL-17F, IL-1β, TNF-α, TGF-β
➢ Chemo attractant chemokines – CXCL1 (Gro-α), CXCL2 (Gro-β), CXCL5, CXCL6, CXCL8 (IL-8), MCP-1
➢ Prostaglandins - prostaglandin E2
➢ Low periostin levels - indicator of IL-13 inflammatory activity
➢ High hydrogen sulfide levels
➢ Fixed airway obstruction (low FEV1)
➢ Low post-bronchodilator response to β2-agonists
➢ Less responsive to methacholine bronchoprovocation tests
➢ Corticosteroid unresponsiveness

Abbreviations; FEV1, forced expired volume in 1 sec (Syabbalo, 2020)

Mechanisms of severe neutrophilic asthma

T Helper 17 as IL-17 Producing Cell

The differentiation of Th17 cells from naïve T cells is regulated by the combination of IL-6 and Transforming Growth Factor (TGF)-β (Gaffen *et al*., 2014). The presence of both IL-6 and TGF-β is required for the upregulation of a specific Th17 cell transcription factor, retinoic acid Receptor-related Orphan Receptor (ROR. The transcription factor RORγt is necessary for Th17 cytokine production and for the expression of the IL-23 receptor complex (Syaballo, 2020). Interleukin-23 is required for expansion, stabilization, and proliferation of Th17 cells in order to produce chemoattractant cytokines, and chemokines. In addition, IL-23 prolongs the expression of Th17 cells signature cytokines, such as IL-17, IL-22, and GM-CSF that induce tissue pathology and mediates chronic inflammation. It also promotes the survival, and maintenance of Th17 cells (Zhou *et al*., 2007). Interleukin-21 produced by Th17 cells themselves, acts in a positive feedback loop to differentiate more Th17 cells (Syaballo, 2020). Signal Transducer and Activator of Transcription 3 (STAT 3) appears to be essential for the differentiation of Th17 cells (Wei *et al*., 2007). Interleukin-1β is essential in the early differentiation and conversion of Fox3+ T cells into IL-17-producing cells (Chang *et al*., 2009).

Interleukin-17(IL-17)

Interleukin-17 Interleukin-17 (IL-17) plays a key role in the pathogenesis of neutrophilic asthma, via induction and expression of cytokines, chemokines, adhesion molecule, and growth factors which propagate neutrophil recruitment and activation into the airways (Syabbalo, 2020). Interleukin-17 (IL-17 also termed IL-17A) plays a key role in the pathophysiology of neutrophilic asthma. IL-17 and other family members are produced mainly by Th17 cells, but other cell can also secrete IL-17 in the lungs. IL-17 induces the transcription of several cytokines, chemokines, adhesion molecules, and growth factors. Chemoattractant cytokines, and chemokines recruit and activate neutrophils into the airways leading to neutrophilic asthma. The major role of neutrophils in the lung is respiratory defense against bacterial and fungi, but unfortunately, activated neutrophils can produce proteases, Reactive Oxygen Species (ROS), cytokines, and chemokines which can lead to epithelial injury, airway inflammation and hyperresponsiveness, culminating to severe neutrophilic asthma. Neutrophils upon provocation by viral and bacterial infections or allergic inflammation, can generate Neutrophils Extracellular Traps (NETs), inflammasomes, and cytoplasts, which can further orchestrate airway injury, hyperreactivity, and can lead to severe obstructive disease (Lachowicz-Scroggins *et al*., 2019).

Other IL-17 Producing Cells

Interleukin-17 is also secreted by other activated immune cells, such as dendritic cells, CD8+ T cells, δγ T cells, natural killer cells, invariant natural killer T cells, lymphoid tissue inducer cells, and type 3 innate lymphoid cells (Cua *et al*., 2010). Additionally, haematopoietic and non-haematopoietic cells, such as eosinophils, neutrophils, monocytes, macrophages, and bronchial fibroblasts can secrete IL-17, under certain circumstances (Brodlie *et al*., 2011). Because of the large number of cells producing IL-17, it becomes very difficult to target any specific cell type. Moreover, most of these cells produce a plethora of inflammatory mediators, which could make precision therapeutic targeting difficult (Syabballo, 2020).

Neutrophil extracellular traps

In neutrophilic asthma, NETs can act as a physical and biological barrier to prevent the spread of pathogens; however, NETs can exacerbate asthma severity when pathogens are eliminated. NETs reduce neutrophil migration, disrupt tight junctions between airway epithelial cells, induce airway epithelial cell death and promote IL-8 production (Zhang *et al*., 2022).

NETs are a network of extracellular DNA strips and proteins released from activated or dying

neutrophils. These are present in the airway of asthma patients, and help to eliminate invading pathogens. However, excessive NET formation (NETosis) can cause airway damage, accelerating neutrophilic asthma progression (Poto *et al*., 2022).

Studies have revealed that caspase 11-driven and GSDMD-dependent neutrophil pyroptosis is responsible for NETosis, in response to LPS stimulation or bacterial infection (Chen *et al*., 2018). Thus, blocking the GSDMD cleavage can prevent the neutrophil pyroptosis and NETosis triggered by phorbol 12-myristate 13- acetate (PMA) (Sollberger *et al*., 2018).

Interleukin 8 (IL-8)

IL-8 stimulation of peripheral blood neutrophils in patients with severe asthma enhances neutrophil autophagy and the production of NETs. NETs consist of de-agglutinated chromatin and antimicrobial factors, including neutrophil elastase (NE) and myeloperoxidase (MPO), which trap and kill bacteria, fungi and parasites (Zhang *et al*., 2022). IL18 can induce the infiltration of neutrophils and eosinophils in the lungs, causing airway hyperresponsiveness, IL-18 can also exacerbate airway inflammation by promoting Th1 and Th2 cell activation, and IFN-γ and IgE production (Hao *et al*., 2024).

NLRP3/caspase-1/GSDMD signaling pathway in neutrophils

Notably, the activation other NLRP3/caspase-1/GSDMD signaling pathway in neutrophils, in response to adenosine triphosphate (ATP) or microbial toxin pneumolysin, can lead to IL-1β secretion, without inducing pyroptosis (Karmakar *et al*., 2020). This resistance to pyroptotic cell death keeps neutrophils alive to continuously produce IL-1β, and sustain neutrophilic inflammation, which may function as a mechanism that drives the progression of severe, glucocorticoid-resistant neutrophilic asthma (Kim *et al*., 2017). The inhibition of the NLRP3 inflammasome can prevent the severe bronchial neutrophilic inflammation triggered by fungal allergen *Alternaria alternata* in mice (Killian *et al*., 2023). These findings indicate that inflammasome activation is involved in neutrophilic inflammation in asthma (Poto *et al*., 2022).

Inflammatory mediators of Neutrophilic asthma

Neutrophil elastase

Neutrophil elastase can induce goblet cell metaplasia, mucus hypersecretion, which is a hallmark of severe asthma. It can also induce airway smooth muscle proliferation (Baines *et al*., 2011) and has been implicated in airway remodeling (Vargas *et al*., 2016).

Reactive oxygen species

Activated neutrophils are the major source of reactive oxygen species, such as hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), and superoxide radical (O_2^-) in allergic inflammation. ROS act synergistically with neutrophil proteases to cause lung tissue damage, sub mucus gland hyperplasia and mucus secretion, and airway hyperreactivity (Loukides *et al*., 2002).

Myeloperoxidase

Myeloperoxidase (MPO) released from neutrophil primary granules can react with hydrogen peroxide (H2O2) generated during respiratory bursts, producing hypochlorous acid (HOCl), and other reactive oxygen species (Monteseirín, 2009). The ROS are crucial for microbial activity, and antigen presentation, but play deleterious role in causing injury to lung tissue during neutrophilic inflammatory process (Chang *et al*., 2012).

Metalloproteases

Metalloprotease-9 is one of the most investigated inflammatory mediators in asthma. Elevated levels of MMP-9 have been found in induced sputum, and BAL fluid from patients with asthma, and the levels

correlated with neutrophil numbers and asthma severity (Grunwell *et al*., 2019).

Lipid mediators

Neutrophils can synthesize lipid mediators such as and leukotrienes (LTB4), platelet activating factor (PAF), prostaglandins (PGE2), and thromboxane's (TXB2) via cyclooxygenase enzyme systems. Lipid mediators play an important role in neutrophil migration and activation in the airway inflammation process (Syabbalo, 2020).

Neutrophil and Eosinophils cross-talk

Neutrophil proteases, such as elastase, cathepsin G, and protease-3 may induce airway inflammation through activation of eosinophils to produce superoxides, cytokines, and chemokines, thus aggravating neutrophilic asthma (Hiraguchi *et al*., 2008).

T regulatory cells

Tregs are a specialized population of CD4+T cells that act to suppress the immune response, thereby maintaining the body's immune homeostasis and self-tolerance. Tregs can be divided into two main subpopulations: thymus-derived Tregs (tTregs) and peripherally-derived Tregs (pTregs). tTregs primarily recognize self-antigens, which is important for maintaining self-tolerance and preventing autoimmunity (Wang and Liu, 2024). However, pTregs are thought to be involved primarily in the tolerogenic response to foreign antigens and microbes (Lan *et al*., 2020). Reduced numbers of Tregs have been observed in the blood and induced sputum of patients with asthma, and during acute asthma exacerbations, asthmatics have a greater degree of Tregs deficiency (Mamessier *et al*., 2008). Studies by Wang and Liu (2024), support the idea that decreased numbers of Tregs and functional deficits contribute to asthma (Wang and Liu, 2024).

Risk factors associated with Neutrophilic asthma exacerbation

Air pollution

Multiple studies have recently found that air pollutants (e.g., diesel exhaust particles [DEP]) (Weng *et al.*, 2018) ozone, fine particulate matter (PM2.5) and nitrogen dioxide [NO_2] (Martin, *et al*., 2013) are involved in the inflammatory response of Th17-type asthma. These pollutants activate oxidative stress or directly induce the release of Th17 cell associated inflammatory cytokines and chemokines, thereby exacerbating the severity of allergic asthma (Zhang *et al*., 2022)

Smoking

Smoking is an important risk factor for the exacerbation of asthma. The expression of IL-17A, IL-6 and IL-8, as well as the number of neutrophils in the bronchial mucosa are significantly increased in asthmatic smokers compared with non-smokers (Siew, *et al*., 2017). IL-17A induced IL-6 and CXCL8 expression in human primary airway epithelial cells and cigarette smoke extracts were able to increase IL-17A-induced IL-6 and CXCL8 expression in a synergistic manner. (Zhang *et al*., 2022)

Bacterial infections

Pathogens such as *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*, are among colonizing bacteria of the airway mucosa, which can induce a proinflammatory immune response and promote asthma exacerbations (Larsen *et al*., 2014). According to previous reports, 41% of airway secretions from neutrophilic asthma patients, carried potentially pathogenic bacteria. Among these individuals, the infection rate of Haemophilus influenzae in patients with neutrophilic asthma was as high as 60% (Wood *et al*., 2010). The study by Essilfie *et al*. (2011), showed for the first time that a Haemophilus influenzae infection can promote the innate and adaptive response of

macrophages and Th17 cells to produce IL-17, which in turn induces neutrophil dominant inflammation and aggravates asthma. Moraxella catarrhalis infection in the airways of mice can cause substantial neutrophil infiltration, the production of elevated levels of IL-6 and TNF-a, and moderate levels of CD4+ T cell-derived IFN-c and IL-17.11 Extracellular vesicles (EVs) are spherical bilayers of phospholipids widely found in Gram-negative and some Gram-positive bacteria. PAMPs in EVs derived from Gram-negative bacteria (e.g., LPS and peptidoglycan) can induce a host adaptive immune response towards EV proteins. In addition, studies have shown that sputum LPS levels are significantly higher in patients with neutrophilic asthma than in healthy controls (Zhang *et al*., 2022).

Respiratory viral infections

Respiratory RNA viruses (e.g., rhinovirus [RV], respiratory syncytial virus [RSV] and influenza) are a major cause of respiratory infections that exacerbate asthma and other respiratory diseases (Hossain *et al*., 2020). Respiratory RNA viruses or polyinosinic acids: poly (I:C) (a viral substitute) that can be used to explore the immunological mechanisms of exacerbation in an allergen-driven model of neutrophilic asthma (Zhang *et al*., 2022).

Fungal infection

Fungi are ubiquitous in both indoor and outdoor environments (Zhang *et al*., 2022). b-Glucan is an important component of the fungal cell wall and represents the major PAMPs of fungi. b-Glucan induces an immune response via dectin1, which promotes DCs to polarize T cells into Th17 cells, inducing potent Th17 responses and neutrophilic inflammation (Zhang *et al*., 2017). Aspergillus versicolor induces a strong Th17 response and neutrophilic inflammation due to the increased exposure of b-glucan, which depends on IL17A and dectin-1 signaling pathways this indicates that fungal exposure plays an important role in the deterioration of neutrophilic asthma (Zhang *et al*., 2022).

Obesity

Obesity plays a role in aggravating asthma symptoms. A high-fat diet increases the body weight of asthmatic mice (de Oliveira *et al*., 2019) and further increases allergen-induced neutrophilic airway inflammation, airway hyperresponsiveness, cupped cell proliferation, tissue remodeling, the production of cytokines (i.e. IL-17A, IL1b and macrophage inflammatory protein-2), and the level of MPO in the lungs (Panda *et al*., 2017) In addition, obesity increases the IL17A+ / RORcT+ Th cell population in the spleen of asthma mice, (de Oliveira *et al*., 2019) which is associated with neutrophilic inflammation and leads to a worsening of asthma symptoms. Asthma patients with an elevated visceral fat area have elevated total leukocytes, fewer eosinophil's, and increased IL-6 and IL-8 in the sputum (Deng *et al*., 2020).

Some biomarkers of neutrophilic asthma

Biomarkers can be used for a variety of purposes, such as disease diagnosis, disease process, and severity assessment or clinical response monitoring to treatment. S100 calcium binding protein A9 (S100A9) is secreted by activated neutrophils, macrophages and AECs (Wang *et al*., 2018) In addition, higher levels of S100A9 have been observed in the sera and sputa of patients with neutrophilic asthma (Lee *et al*., 2017). S100A9 stimulates NET formation, induces M1 macrophage polarization, and plays a key role in the regulation of neutrophilic asthma. Therefore, S100A9 is considered to represent a potential serum biomarker and therapeutic target for neutrophilic asthma (Quoc *et al*., 2021).

Serum YKL40 is correlated with sputum neutrophils, MPO, IL-8 and IL-6, as well as the induction of epithelial mesenchymal transition and subepithelial fibrosis through activating focal adhesion kinase and mitogen-activated protein kinase signaling pathways (Zhang *et al.,* 2022). YKL-40 has been suggested as a blood-based biomarker for airway inflammation/remodeling in neutrophilic asthma (Sun et al., 2020). All types of cells involved in the pathogenesis of severe asthma produce and secrete

exosomes. Since exosomes can be collected easily from different biofluids, they can be utilized as non-invasive biomarkers (Agache, 2019).

Why Neutrophilic asthma is steroid resistance

Mild to moderate asthma is mainly well controlled by glucocorticoids, whereas neutrophilic severe asthma is ineffective or resistant to glucocorticoids, and can make asthma more difficult to control by increasing the production of associated inflammatory factors (Ouyang *et al*., 2020). Increased miR-9 expression in the sputum of neutrophilic asthma patients reduces protein phosphatase 2A activity, which inhibits the nuclear translocation of the glucocorticoid receptor induced by dexamethasone, and renders neutrophilic asthma patients ineffective to corticosteroid treatment (Zhang *et al*., 2022).

Conclusion

Neutrophils comprise 70% of the total circulatory white cells and play a critical defense role during inflammatory and infective challenges. Neutrophilic asthma is a multifaceted phenotype of severe and persistent asthma, characterized by frequent exacerbations, leading to hospitalizations, due to near-fatal asthma and fixed airflow obstruction. The molecular mechanisms underlying the severity of neutrophilic asthma remain unclear making the diagnosis and treatment of this type of severe asthma an extremely challenging. Many clinical case studies including ex vivo and in vivo experiments needs to be conducted to explore the specific relationships between risk factors, airway epithelial cells, immune cells and cytokines. The discussion of the pathophysiology, mechanism, characteristic, mediators, risk factors, biomarkers and steroid resistance of neutrophilic asthma, in this paper may provide some direction for the prevention, diagnosis and treatment of severe neutrophilic asthma.

References

Saidu, H., Aliyu, I., A., Gwarzo, M., Y., Musa, B., P., Bala, J., A., Adeiza, M., A., Yahaya, H., Rogo, L. D., Siddeeq, I. A., Saidu, A. (2022). Pathobiological bases of asthma-COVID-19 interaction: A theoretical viewpoint: *Adesh University Journal of Medical Sciences & Research* 4: **(2)** 56-66. Doi: 10.25259/ AUJMSR_44_2022.

Global Initiative for Asthma (main report) (2022) Global strategy for asthma management and prevention. Retrieved on 12, November, 2024

Sun, Y., Shi, Z., Liu, B., Li, X., li, G., yang, F., tang, H. (2020). YKL-40 mediates airway remodeling in asthma via activating FAK and MAPK signaling pathway. *Cell Cycle* 19: **(11)**: 1378–1390.

Agache, I. (2019). Severe asthma phenotypes and endotypes. *Seminar in Immunology*, 46: 101301.

Wang, S., Song, R., Wang, Z., Jing, Z., Wang, S., Ma, J. (2018). S100A8/ A9 in Inflammation. *Frontiers in Immunology*; 9: 1298.

Girolamo, P., Alessandro V., Maria T. B., Luca G., Cecilia C., Rosa T. and Rosario M. (2015) Cellular Mechanisms Underlying Eosinophilic and Neutrophilic Airway Inflammation in Asthma. *Mediators of Inflammation*; 1-8 Article ID 879783, http://dx.doi.org/10.1155/2015/879783

Lee, T. H., Chang, H. S., Bae, D. J., et al. (2017). Role of S100A9 in the development of neutrophilic inflammation in asthmatics and in a murine model. Journal *Clinical Immunology*; 183: 158– 166.

Quoc, Q. L., Choi, Y., Thi Bich, T. C., Yang, E. M., Shin, Y. S., Park, H. S. (2021). S100A9 in adult asthmatic patients: a biomarker for neutrophilic asthma. *Experimental Molecular Medicine*; 53: 1170–1179

Lan, F., Zhang, N., Bachert, C., Zhang, L. (2020). Stability of regulatory T cells in T helper 2-biased allergic airway diseases. *Allergy*;75(8):1918–26.

Wang and Liu (2024). Immunological factors,

important players in the development of asthma *Biomed central Immunology*, 25:50

Mamessier, E., Nieves, A., Lorec, A. M., Dupuy, P., pinot,D., Pinet, C., Vervloet D., Magnan, A. (2008). T-cell activation during exacerbations: a longitudinal study in refractory asthma. *Allergy*;63**(9):**1202–10.

Larsen, J. M., Brix, S., Thysen, A. H., Birch, S., Rasmussen, M. A., Bisgaard, H. (2014). Children with asthma by school age display aberrant immune responses to pathogenic airway bacteria as infants. *Journal of Allergy and Clinical Immunology*; 133: 1008–1013.

Wood, L. G., Simpson, J. L., Hansbro, P. M., Gibson, P. G., (2010). Potentially pathogenic bacteria cultured from the sputum of stable asthmatics are associated with increased 8- isoprostane and airway neutrophilia. *Free Radical Research*; 44: 146–154.

Essilfie, A. T., Simpson, J. L., Horvat, J. C., Preston, J. A., Dunkley, M. L., Foster, P. S., Gibson, P. G., Hansbro, P. M. (2011). Haemophilus influenzae infection drives IL-17-mediated neutrophilic allergic airways disease. *Plos Pathogenes*; 7:(10): e1002244.

Kim, Y. K., Oh, S. Y., Jeon, S. G., Park, H. W., Lee, S. Y., Chun, E. Y., Bang, B., Lee, H. S. Oh, M. H., Kim, Y. S., Kim, J. H., Gho, Y. S., Cho, S. H., Min, K. U., Kim, Y. Y., Zhu, Z. (2007). Airway exposure levels of lipopolysaccharide determine type 1 versus type 2 experimental asthma. *Journal of Immunology*; 178 **(8)** 5375–5382.

Weng, C. M., Lee, M. J., He, J. R., Chao, M. W., Wang, C. H., Kuo, H. P. (2018). Diesel exhaust particles up-regulate interleukin-17A expression via ROS/NF-kB in airway epithelium. *Biochemistry and Pharmacology*; 151: 1–8.

Martin, R. A., Ather, J. L., Lundblad, L. K. A., Suratt, B. T., Boyson, J. E., Budd, R. C., Alcorn, J. F., Flavell, R. A., Eisenbarth, S. C., Poynter, M. E. (2013). Interleukin-1 receptor and caspase-1 are required for the Th17 response in nitrogen dioxide-promoted allergic airway disease. *American Journal of Respiratory Cell and Molecular biology*; 48**(5)** 655–664.

Deng, K., Zhang, X., Liu, Y., Cheng, G. P., Zhang, H. P., Wang, T., Wang, L., Li, W. M., Wang, G., Wood, L. (2020). Visceral obesity is associated with clinical and inflammatory features of asthma: a prospective cohort study. *Allergy Asthma Proceedings*; 41:(5): 348–356

Siew, L. Q. C., Wu, S. Y., Ying, S., Corrigan, C. J. (2017). Cigarette smoking increases bronchial mucosal IL-17A expression in asthmatics, which acts in concert with environmental aeroallergens to engender neutrophilic inflammation. *Clinical Experimental Allergy*; 47: 740–750.

de Oliveira, E. E., de Castro, E. S. F. M., Cacador Ayupe. M., Ambrosio, M. G. E., de Souza, V. P., Macedo, G. C., Ferreira, A. P. (2019). Obesity affects peripheral lymphoid organs immune response in murine asthma model. *Immunology*; 157: **(3)**: 268–279.

Panda, L., Gheware, A., Rehman, R., Yadav, M. K., Jayaraj, B. S., Madhunapantula, S. V., Mahesh, P. A., Ghosh, B., Agrawal, A., Mabalirajan, U. (2017). Linoleic acid metabolite leads to steroid resistant asthma features partially through NF-kB. *Journal* of *Scientific Report*; 7: 9565.

Hossain, F. M. A., Park, S. O., Kim, H. J., Eo J. C., Choi, J. Y., Uyangaa, E., Kim, B., Kim K., Eo, S. K. (2020). CCR5 attenuates neutrophilic airway inflammation exacerbated by infection with rhinovirus. *Cell Immunology*; 351: 104066.

Zhang, Z., Biagini Myers, J. M., Brandt, E. B., Ryan, P. H., Lindsey, M., Mintz-Cole, R. A., Reponen, T., Vesper, S. J., Forde, F., Ruff, B., Bass, S. A., LeMasters, G. K., Bernstein, D. I., Lockey, J., Budelsky, A. L., Khurana, Hershey, G. K. (2017). b-Glucan exacerbates

allergic asthma independent of fungal sensitization and promotes steroid-resistant TH2/TH17 responses. *Journal of Allergy Clinical Immunology*; 139: **(1):** 54-65 e8.

Zhou, L., Ivanov, I. I., Spolski, R., Min, R., Shenderov, K., Egawa, T., Levy, D. E., Leonard, W. J., littman, D. (2007) IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathway. *Nature Immunology* 8: **(9)**:967-974.

Brodlie, M., McKean, M. C., Johnston, G. E., Anderson, A. E., Hilkens, C. M. (2011) Fisher. Raised interleukin-17 is immunolocalized to neutrophils in cystic fibrosis. *European Respiratory Journal* 37: 1378-1385

Cua, D. J., Tato, C. M. (2010) Innate IL-17 producing cells: the sentinel of the immune system. *Nature Review in Immunology* 10: 479-489.

Chung, Y., Chang, S. H., Martinez, G. J., Yang, X. O., Nurieva, R., Kang, H. S., Ma, L., Watowich, S. S., Jetten, A> M., tian, Q., Dong, C. (2009). Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. *Immunity* 30: 576-587.

Wei, L., Laurence, A., Elias, K. M., O'Shea, J. J. (2007). IL-21 is produced by Th17 cells and drives IL-17 production in a STAT3-dependent manner. *Journal of Biological Chemistry;* 282: 34605-34610.

Syabbalo, N. (2020). Neutrophilic asthma: a complex phenotype of asthma. *Journal of Lung Pulmonary and Respiratory Research* 7: 18-24**.**

Gaffen, S. L., Jain, R., Garg, A. V., Cua, D. J. (2014). The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nature Review in Immunology* 14: 585- 600

Hiraguchi, Y., Nagao, M., Hosoki, K., Okuda, R., Fujisawa, T. (2008). Neutrophil proteases activate eosinophil function in vitro. *International Archives Allergy and Immunology;* 146: 16-21.

Loukides, S., Buoros, D., Papatheodorou, G., Siafakas, N. M. (2002). The relationships among hydrogen peroxide in expired breathe condensate, airway inflammation, and asthma severity. *Chest* 121: 338-346.

Chang, Y., Al-Alwan, L., Risse, P. A. (2012). Th17-associated cytokine promote human airway smooth muscle cell proliferation. *FASEB Journal* 26: 5152-5160

Monteseirín, J. (2009). Neutrophil in asthma. *Journal of Investigation in Allergy and Clinical Immunology* 19: 340-354

Baines, K. J., Simpson, J. L., Wood, L. G., Scott, R. J., Gibson, P. G. (2011). Systemic upregulation of neutrophil α-defensins and serine proteases in neutrophilic asthma. *Thorax* 66: 942-947.

Vargas, A., Roux-Dalvai, F., Droit, A., Lavoie, J. P. (2016). Neutrophil-derived exosomes: a new mechanism contributing to airway smooth muscle remodeling. *American Journal Respiratory and Cell Molecular Biology* 55: 450-46.

Grunwell, J. R., Stephenson, S. T., Tirouvanzian, R., Brown, L. A. S., Brown, M. R., Fitzpatrick, A. M. (2019). Children with neutrophil-predominant severe asthma have proinflammatory neutrophils with enhanced survival and impaired clearance. *Journal of Allergy and Clinical Immunology* 7: 516-525.

Lachowicz-Scroggins, M. E., Duncan, E. M., Charbit, A. R., Raymond, W., Looney, M. R., Peter, M. C., Gordon, E. D., Woodruff, P. G., Lefrancais, E., Phillipds, B. R., Mauger, D. t., Comhair, S. A., Erzurum, S. C., Johansson, M. W., Jarjour, N. N., Coverstone, A. M., Castro, M., Hastie, A. T., Bleecker E. R., Fajt, M> L., Wenzel, S. E., Israel,E. Levy, B. D., Fahy, J. (2019). Neutrophils extracellular traps, and inflammasome activation in severe asthma. *American Journal of Respiratory and Critical Care Medicine* 199: **(9):**1076-1085.

Syabbalo, N. (2020). Mechanisms of Interleukin -17 in The Pathogenesis of Neutrophilic Asthma. *Journal of Pulmonary Medicine and Respiratory Research* 6: 032.

Ouyang, S., Liu, C., Xiao, J., Chen, X., Lui, A. C., Li, X. (2020). Targeting IL-17A/glucocorticoid synergy to CSF3 expression in neutrophilic airway diseases. *Junior Chamber International Insight*; 5: e132836.

Hao, Y., Wang, W., Zhang, L and Li, W. (2024). Pyroptosis in asthma: inflammatory phenotypes, immune and non-immune cells, and novel treatment approaches. *Frontiers in Pharmacology*. 15:1452845. doi: 10.3389/fphar.2024.1452845

Chen, K. W., Monteleone, M., Boucher, D., Sollberger, G., Ramnath, D., Condon, N. D., von Pein, J. B., Broz, P., Sweet, M. J., Schroder, K. (2018). Noncanonical inflammasome signaling elicits gasdermin D-dependent neutrophil extracellular traps. *Science Immunology*. 3, eaar6676. doi:10.1126/sci immunol. aar6676

Karmakar, M., Minns, M., Greenberg, E. N., Diaz-Aponte, J., Pestonjamasp, K., Johnson, J. L., Rathkey, D. W., Abbott, K. W., Feng, S. S. D., Catz, G. R. D. and Eric, P. (2020). N-GSDMD trafficking to neutrophil organelles facilitates IL1β release independently of plasma membrane pores and pyroptosis. *Nature Communication.* 11, 2212. doi:10.1038/s41467-020-16043-9

Killian, K. N., Kosanovich, J. L., Lipp, M. A., Empey, K. M., Oury, T. D., and Perkins, T. N. (2023). RAGE contributes to allergen driven severe neutrophilic airway inflammation via NLRP3 inflammasome activation in mice. *Frontiers in Immunology*. 14, 1039997. doi:10.3389/fimmu.2023.1039997

Kim, R. Y., Pinkerton, J. W., Essilfie, A. T., Robertson, A. A. B., Baines, K. J., Brown, A. C., Mayall J. R., Ali, M. K., Starkey, M. R., Hansbro N. G., Hirota, J. A., Wood L. G., Simpson, J. L., Knight D. A., Wark P. A., Gibson P. G., O'Neill, L. A. J., Cooper, M. A., Horvat, J. C., Hansbro, P. M. (2017). Role for NLRP3 inflammasome-mediated, IL-1β-dependent responses in severe, steroid-resistant asthma. *American Journal of Respiratory and Critical Care Medicine*. 196, 283–297. doi:10. 1164/rccm.201609-1830OC

Zhang, X., Xu, Z., Wen, X., Huang, G., Nian, S., Li, L., Xiyuan, G., Yingchun, Y., Qing Y. (2022). The onset, development and pathogenesis of severe neutrophilic asthma. *Immunology and Cell Biology*. 100, **(3)**:144–159. doi:10.1111/imcb.12522

Poto, R., Shamji, M., Marone, G., Durham, S. R., Scadding, G. W., and Varricchi, G. (2022). Neutrophil extracellular traps in asthma: friends or foes? *Cells* 11, 3521. doi:10. 3390/cells11213521

Sollberger, G., Choidas, A., Burn, G. L., Habenberger, P., Di Lucrezia, R., Kordes, S., Menninger, S, Eickhoff, J, Nussbaumer, p., Klebl, B., kruger, R., Herzig, A., Zychlinsky, A. (2018). Gasdermin D plays a vital role in the generation of neutrophil extracellular traps. *Science Immunology*. 3, eaar6689. doi:10.1126/sciimmunol.aar6689

Elshony, M. M., Farag, T. S., Eltrawy, H. H., Abdul-Muhaymen, A. M. (2022). Neutrophil to lymphocyte ratio as a predictor biomarker for asthma control level. *Joint resource allocation method*; 3 (2): 162-168. DOI: 10.21608/jram.2021.113151.1156

Syabbalo, N. (2020). Clinical Features and Management of Neutrophilic *Asthma Journal Pulmonary Medicine and Respiratory Research* 6: 036.

Flinkman, E., Vähätalo, I., Tuomisto, L. E., Lehtimaki l., Nieminen, p., Niemela, O., Hamalainen, M., Moilanen, E., Kankaanranta, H., IImarinen, P. (2023). Association between blood eosinophils and

neutrophils with clinical features in adult-onset asthma. *Journal of Allergy Clinical and Immunology Practical*;11**(3):**811–821.e5.

Chung, K. F. (2023). Type-2-low severe asthma endotypes for new treatments: the new asthma frontier. *Current Opinion in Allergy and Clinical Immunology*; 23**(3)**:199–204

Summers, C., Rankin, S. M., Condliffe, A. M., Singh, N., Peters, A. M., Chilvers, E., R. (2010). Neutrophil kinetics in health and disease. *Trends in Immunology*; 31:318–24.

Amulic, B., Cazalet, C., Hayes, G. L., Metzler, K. D., Zychilinsky, A. (2012). Neutrophil function: from mechanisms to disease. *Annual Review in Immunology*; 30:459–89.

Crisford, H., Sapey, E., Stockley, R. A. (2018). Proteinase 3; a potential target in chronic obstructive pulmonary disease and other chronic inflammatory diseases. *Respiratory Research*; 19:180.

Papayannopoulos, V. (2018). Neutrophil extracellular traps in immunity and disease. *Nature Review in Immunology*; 18:134–47.

Pavlidis, S., Takahashi, K., Kwang, F. N. K., Xie, J., Hoda, U., Sun, K., Elyasigomari, V., Agapow, P., Loza, M., Baribaud, F., Chanez, P., Fowlers, S. J., Shaw, D., E., Fleming, L. J., Howarth, P. H., Sousa, A. R., Corfield, J., Auffray, C., De Meulder, B., knowles, R., Fan, Chung, K., on behalf of the U-BIOPRED study group. (2019). "T2- high" in severe asthma relate to blood eosinophil, exhaled nitric oxide and serum periostin. *European Respiratory Journal* 53: **(1):**1800938