KOAH Endotiplerinde İnflamatuvar Yanıtların Heterojenitesi: Tıbbi Perspektif ve Klinik Uygulamaya Aktarım Sistemleri

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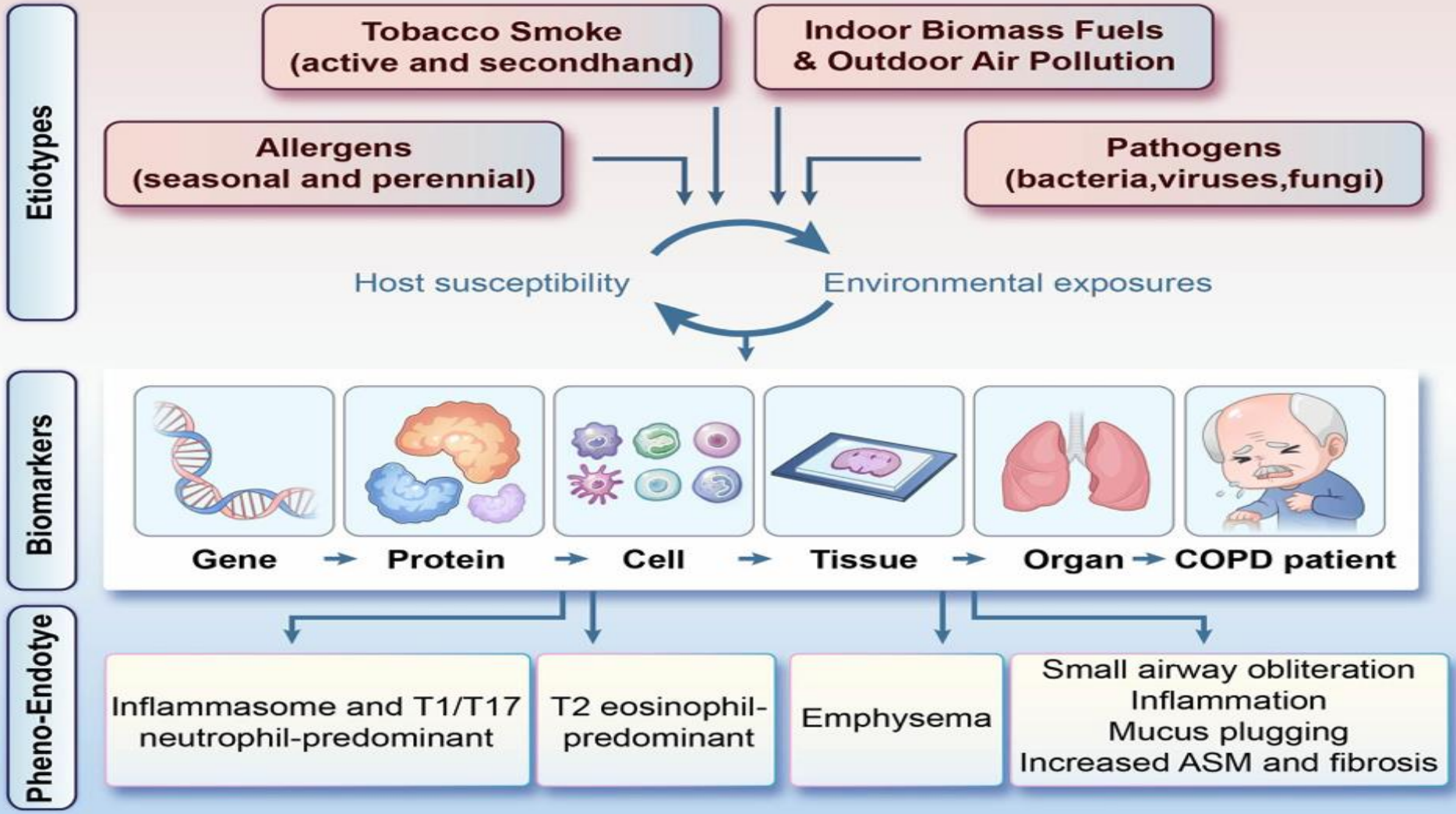
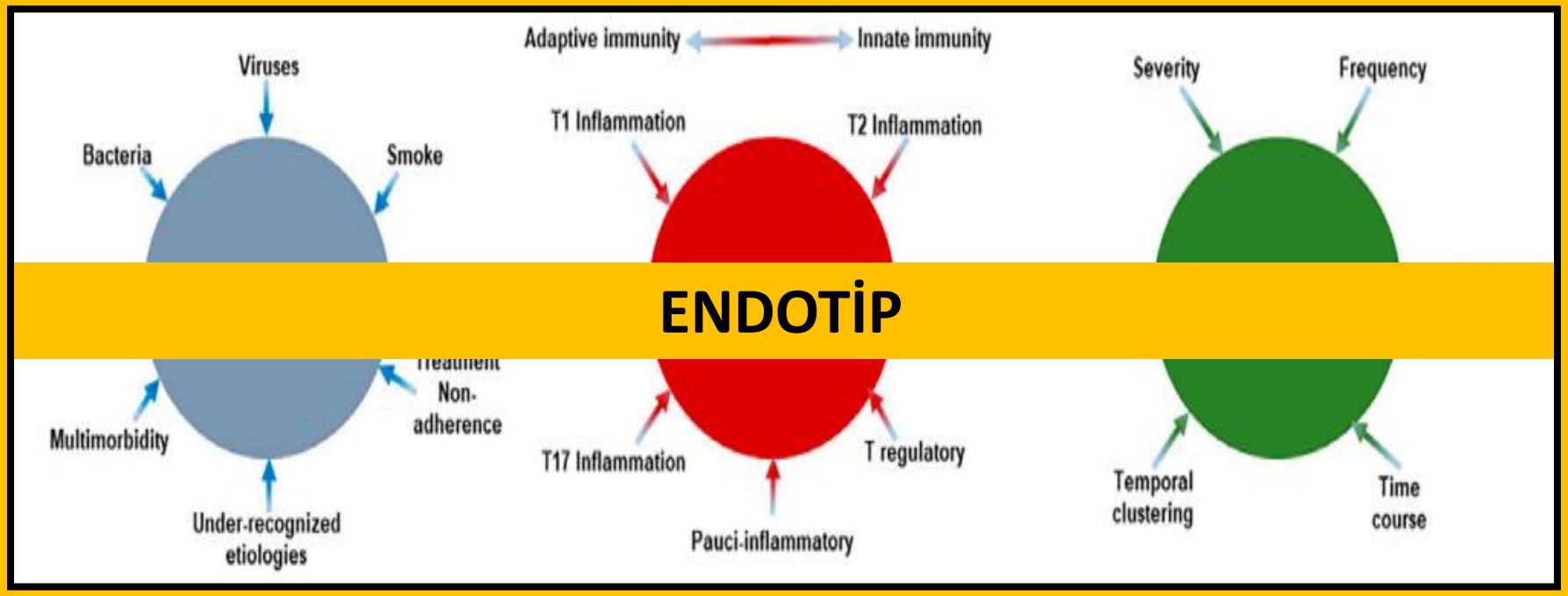


KOAH sigara dumanı,hava kirliliği,enfeksiyon,allerjen maruziyeti ile tetiklenen heterojen, kronik inflamatuar, patobiyolojik mekanizması farklı endotipleri içeren bir hastalık

Tüm KOAH hastaları aynı değildir!!!

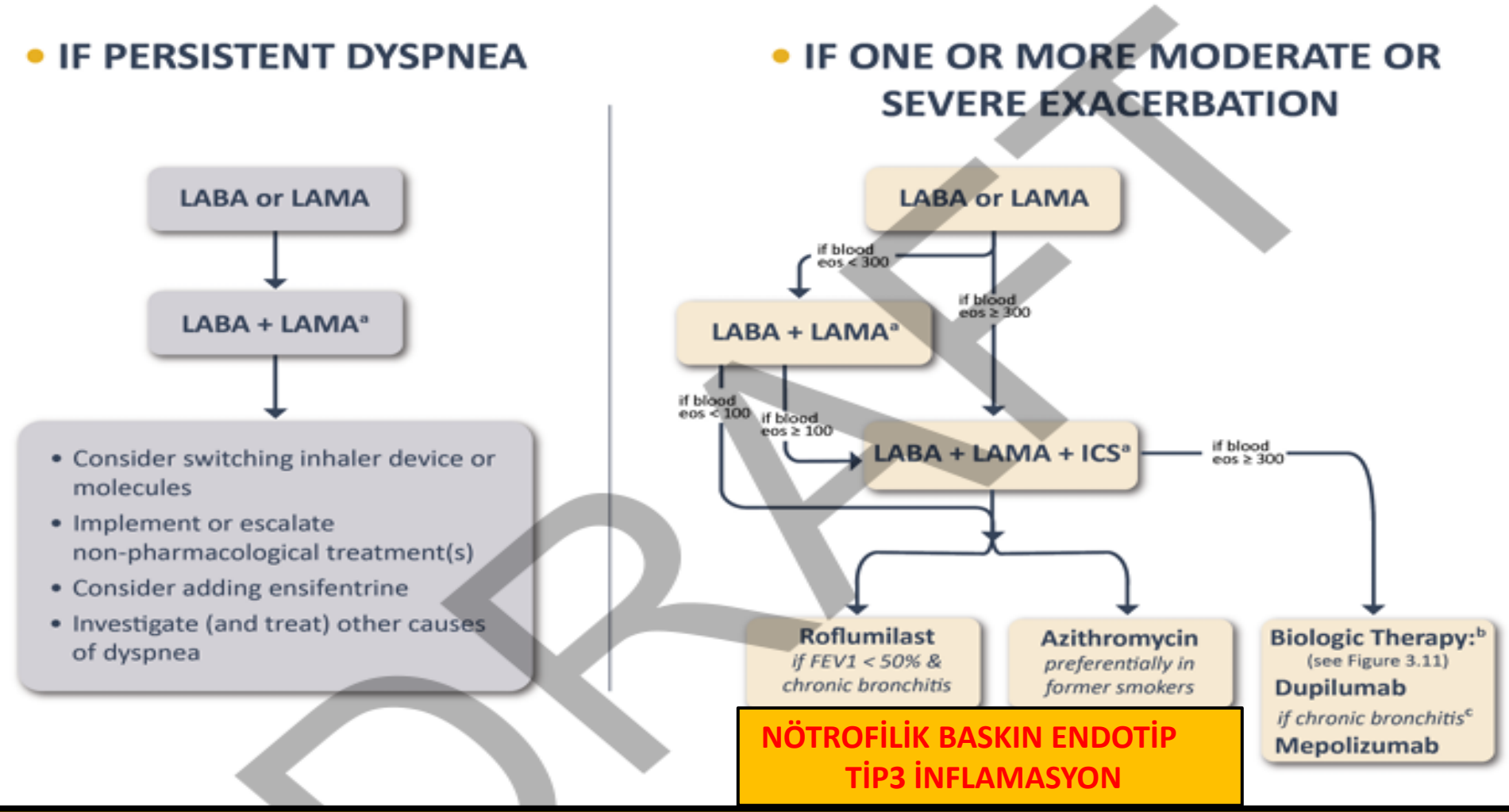


Aynı klinik fenotipi gösteren hastalar
genetik, immün yanıt, moleküler yolak,inflamasyon gibi farklı altta yatan biyolojik mekanizmalara sahip olabilir.

Nötrofil baskın (“Tip 2-düşük”) endotip

Sigara ile ilişkili kronik bronşit fenotipi ile örtüşür

- **Kronik öksürük**
- **Balgam hipersekresyonu**
- **Bakteriyel kolonizasyon**
- **Kortikosteroide direnç**
- **Hızlanmış FEV1 kaybı**
- **Sık infektif alevlenmeler ile karakterize**



Dual/Triple tedaviye rağmen yılda 1 veya daha fazla orta veya ağır alevlenmede

- **FEV1 <%50 kronik bronşit fenotip**
- **Sigarayı bırakmış olgularda**

Global Initiative for Chronic Obstructive Lung Disease [GOLD]. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2026 Report. GOLD; 2025

Enfeksiyöz endotip

INFLAMMATORY PATHWAY	TYPE 1	TYPE 2	TYPE 3
Primary immune cells	 Macrophage  Th1  ILC1  NK	 Th2  ILC2  Mast cell  Basophil  Eosinophil	 Neutrophil  Th17  ILC3
Key cytokines	IFNγ, TNF, IL-6, IL-12, IL-18, IL-2	IL-4, IL-5, IL-13, IL-31	IL-17, IL-6, IL-22, IL-23
Function	• Antitumor activity • Cellular immunity: antiviral/antibacterial • Suppression of type 2	• Humoral immunity: antiparasitic helminths • Neutralizes toxins • Regulates wound repair and regeneration • Suppression of type 1	• Regulation of intestinal epithelial barrier • Responses to extracellular bacteria and fungi
Examples of consequence of dysregulation and associated disease	• Ankylosing spondylitis • Atherosclerosis • Autoimmune gastritis • Diabetes mellitus • Hashimoto thyroiditis • Inflammatory bowel disease • Multiple sclerosis • Rheumatoid arthritis • Sarcoidosis	• Allergy • Anaphylaxis • Type 2 asthma • Atopic dermatitis • Chronic obstructive pulmonary disease with type 2 inflammation • Chronic rhinosinusitis with nasal polyps	• Ankylosing spondylitis • Multiple sclerosis • Psoriasis • Rheumatoid arthritis • Uveitis

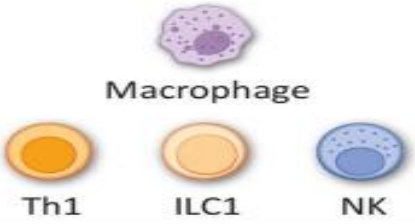
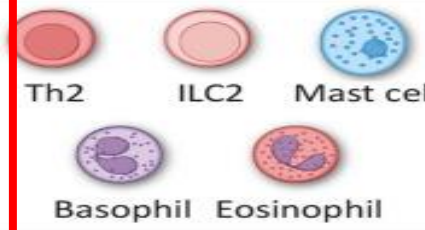
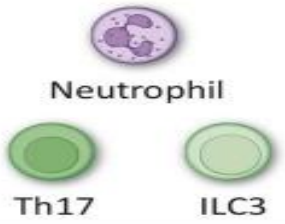
Akut ve/veya kronik hava yolu enfeksiyonları ile karakterize

Haddad EB, et al.Dermatol Ther (Heidelb). 2022 Jul;12(7):1501-1533.

İNFEKSİYON ENDOTİPİ

- Profilaktik antibiyotikler (uzun süreli makrolidler)
- Mukosiliyer klirens teknikleri
- İnhale antimikrobiyal
- Mikrobiyom modüle edici tedavi

Eozinofil-predominant (“Tip 2-yüksek”) endotip

INFLAMMATORY PATHWAY	TYPE 1	TYPE 2	TYPE 3
Primary immune cells	 Macrophage, Th1, ILC1, NK	 Th2, ILC2, Mast cel, Basophil, Eosinophil	 Neutrophil, Th17, ILC3
Key cytokines	IFNγ, TNF, IL-6, IL-12, IL-18, IL-2	IL-4, IL-5, IL-13, IL-31	IL-17, IL-6, IL-22, IL-23
Function	• Antitumor activity • Cellular immunity: antiviral/antibacterial • Suppression of type 2	• Humoral immunity: antiparasitic helminths • Neutralizes toxins • Regulates wound repair and regeneration • Suppression of type 1	• Regulation of intestinal epithelial barrier • Responses to extracellular bacteria and fungi
Examples of consequence of dysregulation and associated disease	• Ankylosing spondylitis • Atherosclerosis • Autoimmune gastritis • Diabetes mellitus • Hashimoto thyroiditis • Inflammatory bowel disease • Multiple sclerosis • Rheumatoid arthritis • Sarcoidosis	• Allergy • Anaphylaxis • Type 2 asthma • Atopic dermatitis • Chronic obstructive pulmonary disease with type 2 inflammation • Chronic rhinosinusitis with nasal polyps	• Ankylosing spondylitis • Multiple sclerosis • Psoriasis • Rheumatoid arthritis • Uveitis

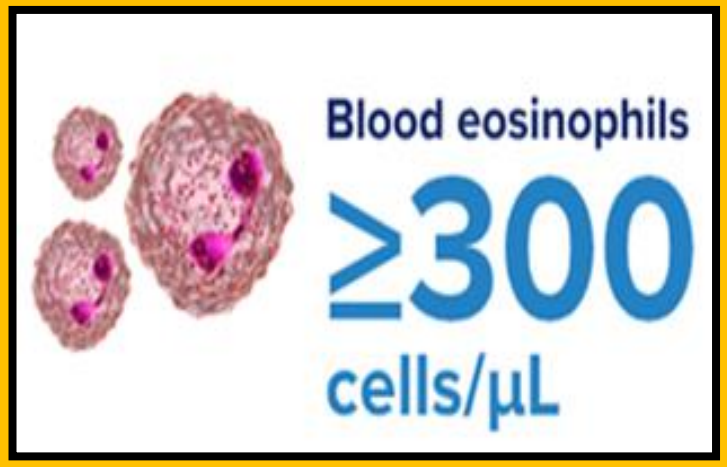
KOAH hastalarının %20–40

Haddad EB, et al.Dermatol Ther (Heidelb). 2022 Jul;12(7):1501-1533.

Comparative Study > Int J Chron Obstruct Pulmon Dis. 2016 Jul 1:11:1495-504.
doi: 10.2147/COPD.S100338. eCollection 2016.

Peripheral blood eosinophils: a surrogate marker for airway eosinophilia in stable COPD

Netsanet A Negewo [1], Vanessa M McDonald [2], Katherine J Baines [1], Peter Ab Wark [3], Jodie L Simpson [1], Paul W Jones [4], Peter G Gibson [3]



Introduction: Sputum eosinophilia occurs in approximately one-third of stable chronic obstructive pulmonary disease (COPD) patients and can predict exacerbation risk and response to corticosteroid treatments. Sputum induction, however, requires expertise, may not always be successful, and does not provide point-of-care results. Easily applicable diagnostic markers that can predict sputum eosinophilia in stable COPD patients have the potential to progress COPD management. This study investigated the correlation and predictive relationship between peripheral blood and sputum eosinophils. It also examined the repeatability of blood eosinophil counts.

Methods: Stable COPD patients (n=141) were classified as eosinophilic or noneosinophilic based on their sputum cell counts (≥3%), and a cross-sectional analysis was conducted comparing their demographics, clinical characteristics, and blood cell counts. Receiver operating characteristic curve analysis was used to assess the predictive ability of blood eosinophils for sputum eosinophilia. Intraclass correlation coefficient was used to examine the repeatability of blood eosinophil counts.

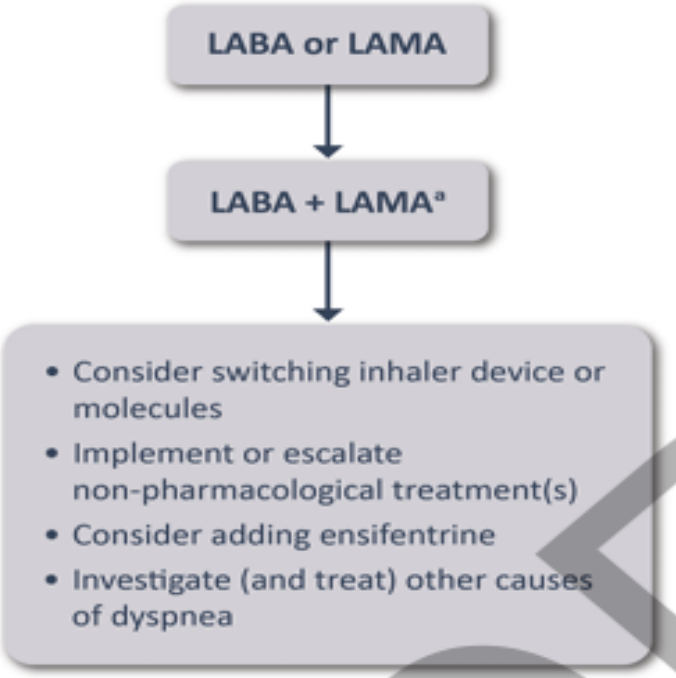
Results: Blood eosinophil counts were significantly higher in patients with sputum eosinophilia (n=45) compared to those without (0.3×10^9/L vs 0.15×10^9/L; $P<0.0001$). Blood eosinophils correlated with both the percentage ($\rho=0.535$; $P<0.0001$) and number of sputum eosinophils ($\rho=0.473$; $P<0.0001$). Absolute blood eosinophil count was predictive of sputum eosinophilia (area under the curve =0.76, 95% confidence interval [CI] =0.67–0.84; $P<0.0001$). At a threshold of $\geq0.3\times10^9$/L (specificity =76%, sensitivity =60%, and positive likelihood ratio =2.5), peripheral blood eosinophil counts enabled identification of the presence or absence of sputum eosinophilia in 71% of the cases. A threshold of $\geq0.4\times10^9$/L had similar classifying ability but better specificity (91.7%) and higher positive likelihood ratio (3.7). In contrast, $\geq0.2\times10^9$/L offered a better sensitivity (91.1%) for ruling out sputum eosinophilia. There was a good agreement between two measurements of blood eosinophil count over a median of 28 days (intraclass correlation coefficient =0.8; 95% CI =0.66–0.88; $P<0.0001$).

Conclusion: Peripheral blood eosinophil counts can help identify the presence or absence of sputum eosinophilia in stable COPD patients with a reasonable degree of accuracy.

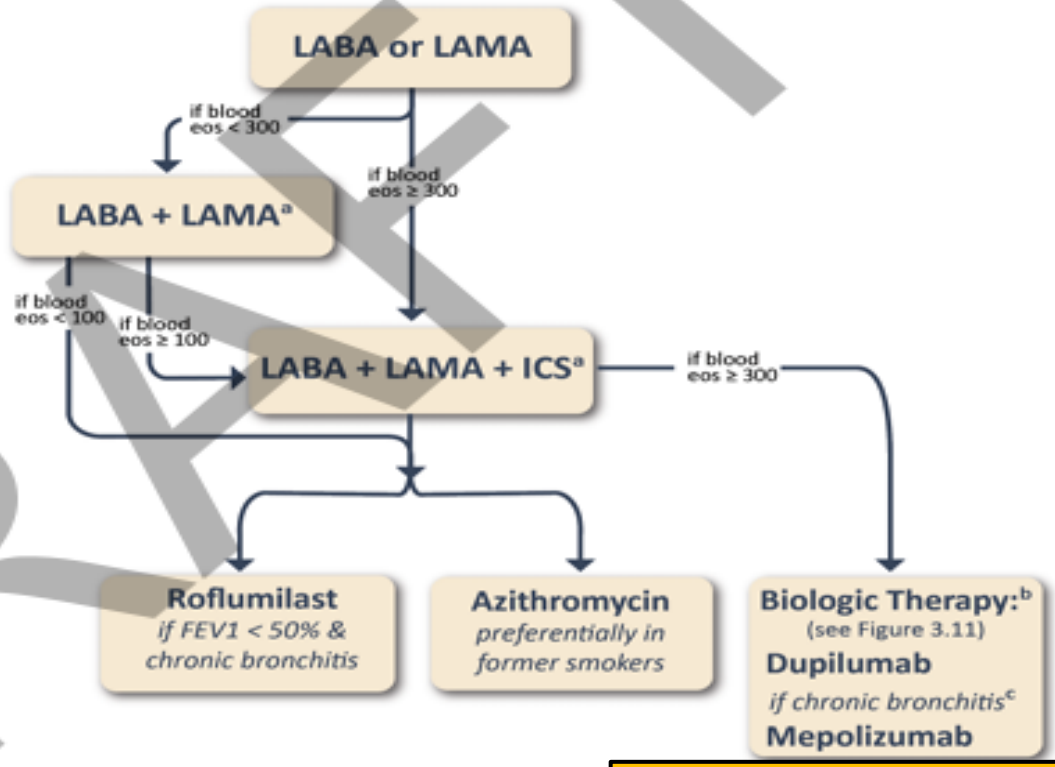
Eozinofil baskın endotip

- Persistan dispne
- Kronik öksürük
- Progresif FEV1 kaybı
- Sık akut alevlenme

IF PERSISTENT DYSPNEA



IF ONE OR MORE MODERATE OR SEVERE EXACERBATION



EOZİNOFİLİK ENDOTİP
TİP2 İNFLAMASYON

Dual/Triple tedaviye rağmen yılda 1 veya daha fazla orta veya ağır alevlenmede

- **Kan eozinofil sayısı (BEC) ≥300 cell/ml**
- **Kronik bronşit fenotip**

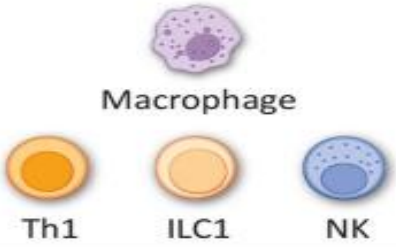
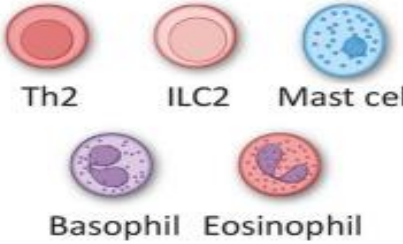
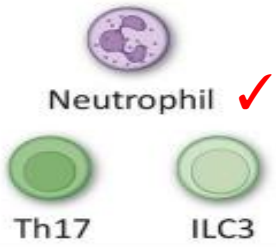
Global Initiative for Chronic Obstructive Lung Disease [GOLD]. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2026 Report. GOLD; 2025

Genetik Endotip

- **Alfa-1 Antitripsin (AAT) eksikliği endotipi**
- **Telomer kısalığı ilişkili endotip**

Stanley SE.J Clin Invest. 2015 Feb;125(2):563-70
Strnad P. N Engl J Med. 2020 Apr 9;382(15):1443-1455.

Telomer kısalığı ilişkili endotip

INFLAMMATORY PATHWAY	TYPE 1	TYPE 2	TYPE 3
Primary immune cells			 ✓
Key cytokines	IFNγ, TNF, IL-6 ✓, IL-12, IL-18, IL-2	IL-4, IL-5, IL-13, IL-31	IL-17, IL-6 ✓, IL-22, IL-23
Function	• Antitumor activity • Cellular immunity: antiviral/antibacterial • Suppression of type 2	• Humoral immunity: antiparasitic helminths • Neutralizes toxins • Regulates wound repair and regeneration • Suppression of type 1	• Regulation of intestinal epithelial barrier • Responses to extracellular bacteria and fungi
Examples of consequence of dysregulation and associated disease	• Ankylosing spondylitis • Atherosclerosis • Autoimmune gastritis • Diabetes mellitus • Hashimoto thyroiditis • Inflammatory bowel disease • Multiple sclerosis • Rheumatoid arthritis • Sarcoidosis	• Allergy • Anaphylaxis • Type 2 asthma • Atopic dermatitis • Chronic obstructive pulmonary disease with type 2 inflammation • Chronic rhinosinusitis with nasal polyps	• Ankylosing spondylitis • Multiple sclerosis • Psoriasis • Rheumatoid arthritis • Uveitis

Pulmoner vasküler endotip

INFLAMMATORY PATHWAY	TYPE 1	TYPE 2	TYPE 3
Primary immune cells	 Macrophage  Th1  ILC1  NK	 Th2  ILC2  Mast cell  Basophil  Eosinophil	 Neutrophil ✓  Th17  ILC3
Key cytokines	IFNγ TNF IL-6 ✓ IL-12 IL-18 IL-2	IL-4 IL-5 IL-13 IL-31	IL-17 IL-6 ✓ IL-22 IL-23
Function	• Antitumor activity • Cellular immunity: antiviral/antibacterial • Suppression of type 2	• Humoral immunity: antiparasitic helminths • Neutralizes toxins • Regulates wound repair and regeneration • Suppression of type 1	• Regulation of intestinal epithelial barrier • Responses to extracellular bacteria and fungi
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Teşekkür ederim...