Asthma Exacerbation and Infection:

Beyond a Simple Trigger

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Contents

- Infection in asthma exacerbation
- Viral vs. bacterial mechanisms
- Host immune phenotypes
- Infection-prone asthma
- Therapeutic implications

Why Does Infection Matter in Asthma?

- Respiratory viral infections are the **leading trigger of exacerbations**
- Identified in **~70–80% of cases**
- Exacerbations → **major driver of morbidity & healthcare burden**

- But not all infections lead to exacerbations
  → Host immune response determines outcome

➢ **Exacerbation is not pathogen-driven alone,**
but shaped by host immune susceptibility.

Kumar et al., Acta Med Acad 2020

Isolated Pathogens During Asthma Exacerbation

	Total	No obesity	Obesity	*P*
	n = 407*	*n* = 236	*n* = 171	
Virus				
Influenza	67/407 (16.5)	41/236 (17.4)	26/171 (15.2)	0.560
Human rhinovirus	37/328 (11.3)	23/196 (11.7)	14/132 (10.6)	0.751
RSV	17/326 (5.2)	10/194 (5.2)	7/132 (5.3)	0.953
Metapneumovirus	14/326 (4.3)	7/195 (3.6)	7/131 (5.3)	0.444
Coronavirus	12/328 (3.7)	9/196 (4.6)	3/132 (2.3)	0.374
Parainfluenza	10/328 (3.0)	6/196 (3.1)	4/132 (3.0)	1.000
Adenovirus	3/328 (0.9)	1/196 (0.5)	2/132 (1.5)	0.567
Enterovirus	1/264 (0.4)	0	1/105 (1.0)	0.398
Bacteria				
S. pneumoniae	25/407 (6.1)	15/236 (6.4)	10/171 (5.8)	0.833
P. aeruginosa	17/407 (4.2)	12/236 (5.1)	5/171 (2.9)	0.282
C. pneumoniae	10/217 (4.6)	9/119 (7.6)	1/98 (1.0)	0.024
K. pneumonia	9/407 (2.2)	5/236 (2.1)	4/171 (2.3)	1.000
M. pneumoniae	9/254 (3.5)	4/138 (2.9)	5/116 (4.3)	0.736
H. influenzae	8/407 (2.0)	4/236 (1.7)	4/171 (2.3)	0.725
E. coli	6/407 (1.5)	4/236 (1.7)	2/171 (1.2)	1.000
MRSA	4/407 (1.0)	2/236 (0.8)	2/171 (1.2)	1.000
M. catarrhalis	3/407 (0.7)	1/236 (0.4)	2/171 (1.2)	0.575
MSSA	2/407 (0.5)	0	2/171 (1.2)	0.176
S. maltophilia	2/407 (0.5)	2/236 (0.8)	0	0.512
B. pertussis	1/126 (0.8)	0	1/54 (1.9)	0.429

Virus

- Influenza
- Rhinovirus
- RSV
- Metapneumovirus
- Coronavirus
- Parainfluenza

Bacteria

- *S. pneumoniae*
- *P. aeruginosa*
- *C. pneumoniae*
- *M. pneumoniae*
- *H. influenzae*

S Park et al. BMC Pulm Med 2024

Spectrum of Infection in Asthma

1. Viral Infection (Primary Triggers)

다양한 respiratory virus가 천식 악화의 주요 원인으로 작용

Common viruses

- Rhinovirus (most frequent)
- Respiratory syncytial virus (RSV)
- Influenza / Parainfluenza
- Coronavirus / Adenovirus

2. Bacterial Infection / Detection

Key Pathogens

- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Streptococcus pneumoniae*
- *Pseudomonas aeruginosa*

Clinical Relevance

Post-viral bacterial overgrowth
Chronic detection
in severe asthma subset

3. Interaction Spectrum

Viral – Bacterial Interaction

Viral Infection → Epithelial Damage + Impaired Immunity → **Bacterial Proliferation**

Exacerbation Severity 증가

4. Temporal Dimension

Pattern	Characteristics
Acute viral infection	Sudden exacerbation trigger
Post-viral bacterial	Delayed worsening / Secondary peak
Persistent colonization	Recurrent exacerbation & inflammation

Asthma exacerbation reflects a spectrum of infection rather than a single mechanism

Kumar et al., Acta Med Acad 2020

Viral vs Bacterial Infection in Asthma Exacerbation

	Viral Infection	Bacterial Infection
Common organism	Rhinovirus, RSV	*Haemophilus influenzae*, *Pseudomonas aeruginosa*
Trigger role	Primary trigger of exacerbation	Secondary or persistence-driven
Onset	Rapid (acute)	Subacute / chronic
Immune response	IFN-driven antiviral response	Neutrophilic, innate immune activation
Key pathway	↓ IFN (especially in asthma) → viral persistence	Impaired clearance → bacterial colonization
Inflammation type	T2 amplification (eosinophilic)	Non-T2 / neutrophilic
Host defect	Defective antiviral immunity	Impaired innate surveillance (NK, macrophage)
Clinical pattern	Episodic exacerbation	Recurrent / persistent symptoms
Airway status	Relatively reversible	Structural damage (bronchiectasis overlap)
Treatment implication	ICS, biologics (anti-IgE, anti-IL5)	Antibiotics, macrolide, host-directed therapy

Host Phenotype Modifies Infection-Driven Exacerbation

T2-High / Atopic Asthma

- **Atopy, IgE sensitization**
- **Type 2 inflammation dominant**
- **Viral-triggered allergic inflammation**

Mechanism

- Th2 cytokine environment
- Amplified inflammatory response

Clinical pattern

- Episodic / seasonal exacerbation

Non-T2 / Infection-Prone Phenotype

- **Less atopy, recurrent infection**
- **Severe / persistent disease**
- **Infection persists due to impaired clearance**

Mechanism

- Impaired host defense (↓IFN, NK dysfunction)
- Persistent airway inflammation

Clinical pattern

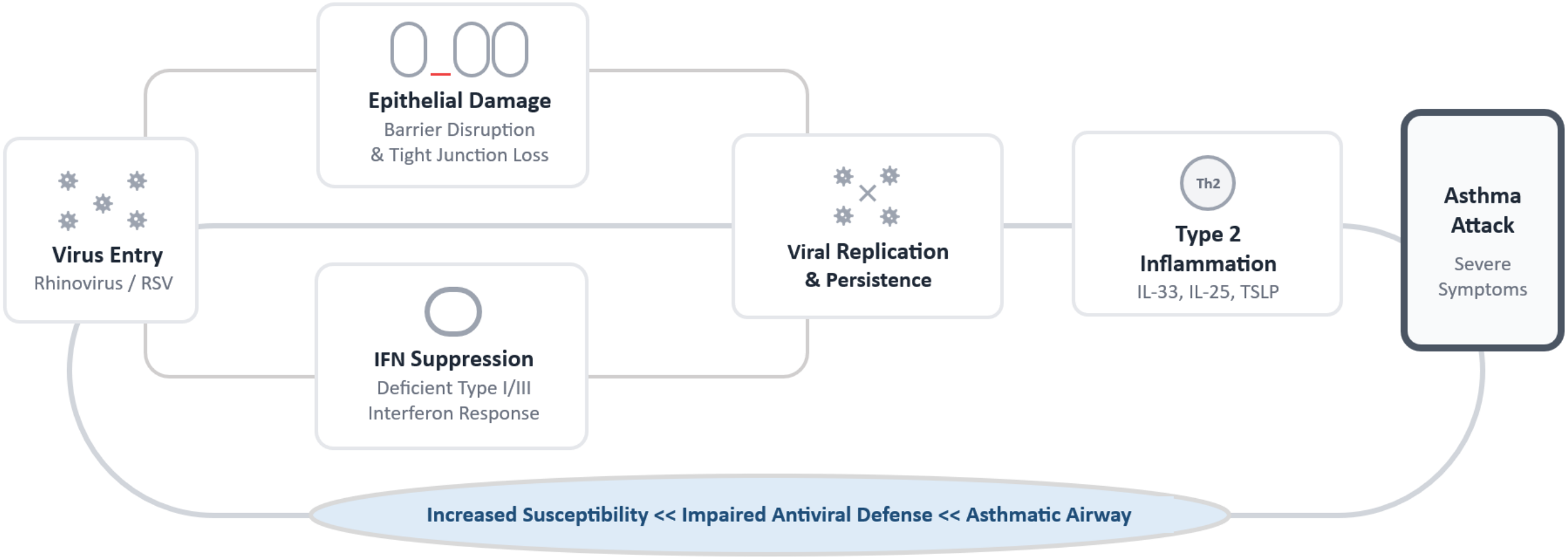
- Recurrent / progressive

Infection is a universal trigger,

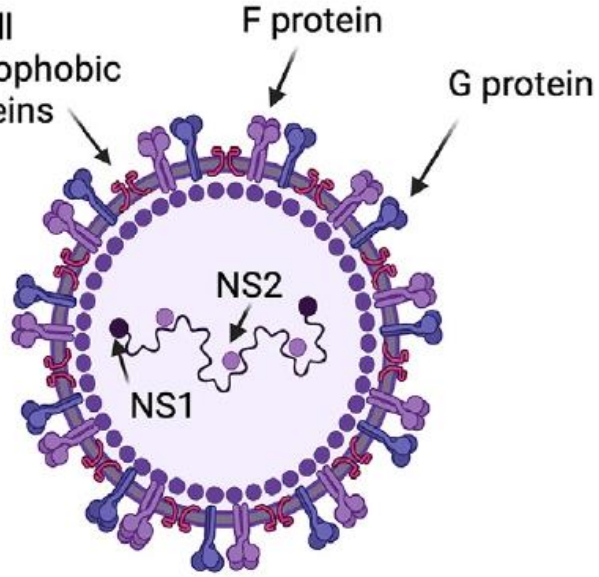
but its clinical impact depends on host susceptibility and immune phenotype.

Viral Infection Drives Asthma Exacerbation

via Immune and Barrier Dysregulation



Respiratory Syncytial Virus (RSV)



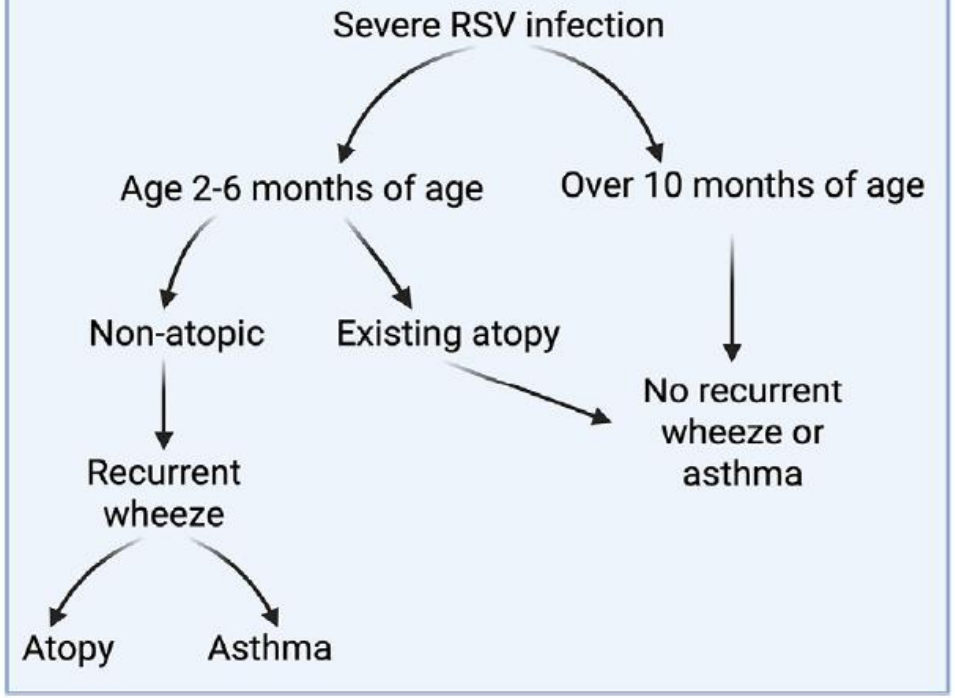
Two subtypes
RSV-A
10 genotypes
RSV-B
13 genotypes

Asthma exacerbation

Minor cause of asthma exacerbations

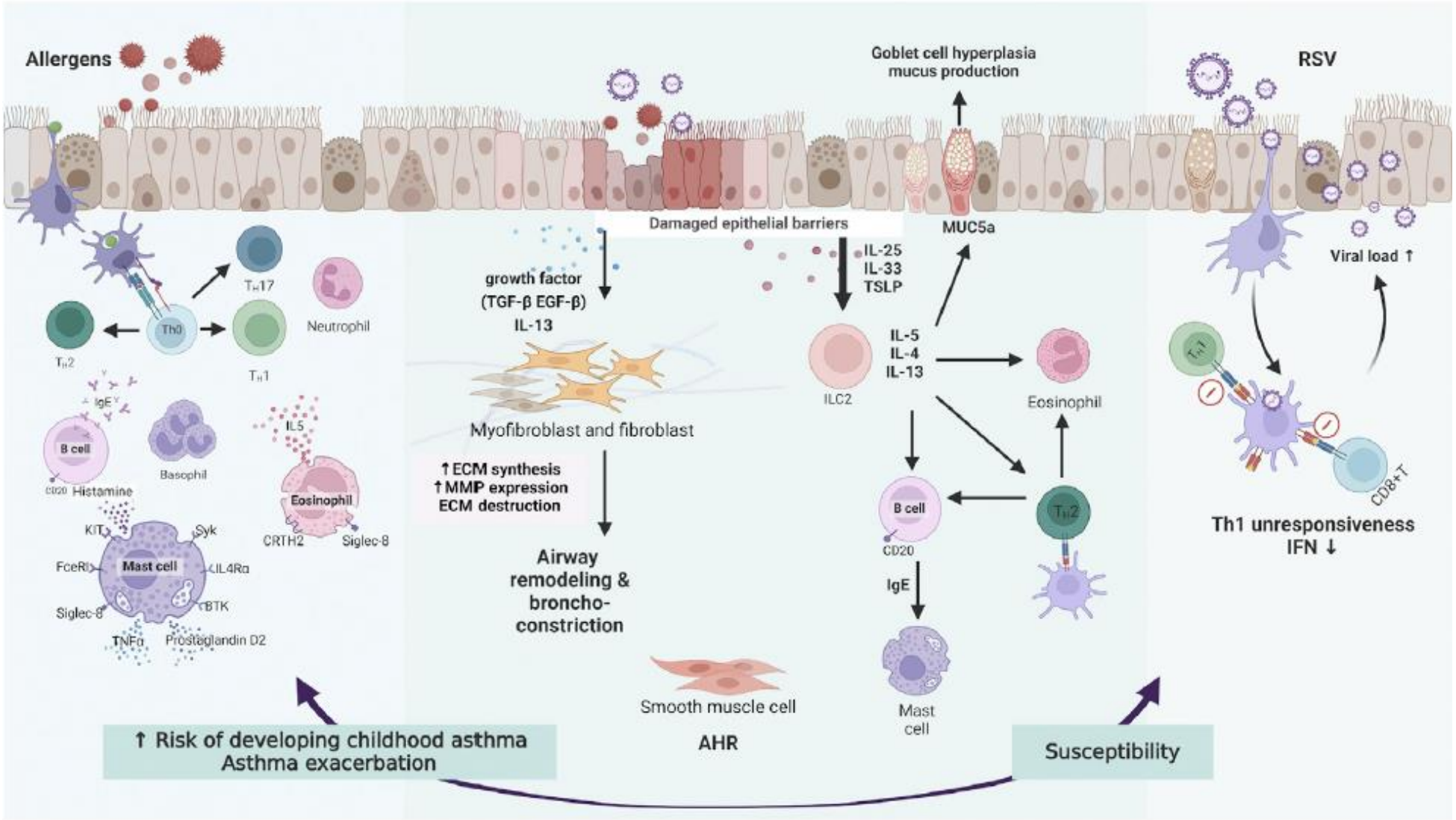
- Causes 58,000-80,000 hospitalizations and 100-300 deaths annually in children less than 5 years old
- Circulates between October-April, peaking in December
- Multiple FDA approved vaccines and anti-RSV monoclonal antibodies

Development of asthma



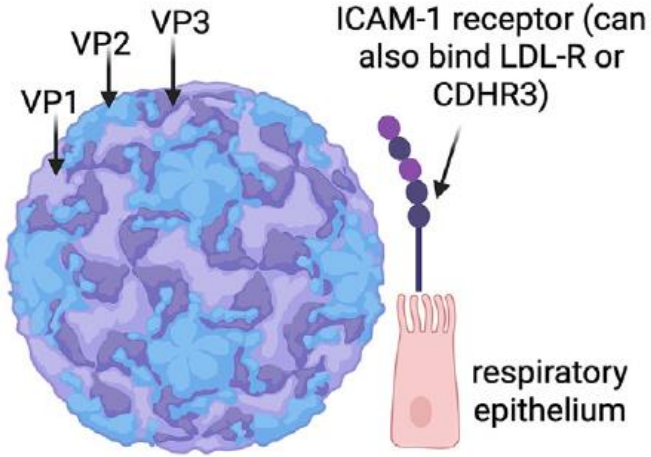
V.T. Nguyen et al. Ann Allergy Asthma Immunol 2025

RSV Infection Shifts the Immune Response from Th1 → Th2



R. Ma et al. Ann Allergy Asthma Immunol 2025

Rhinovirus (RV)



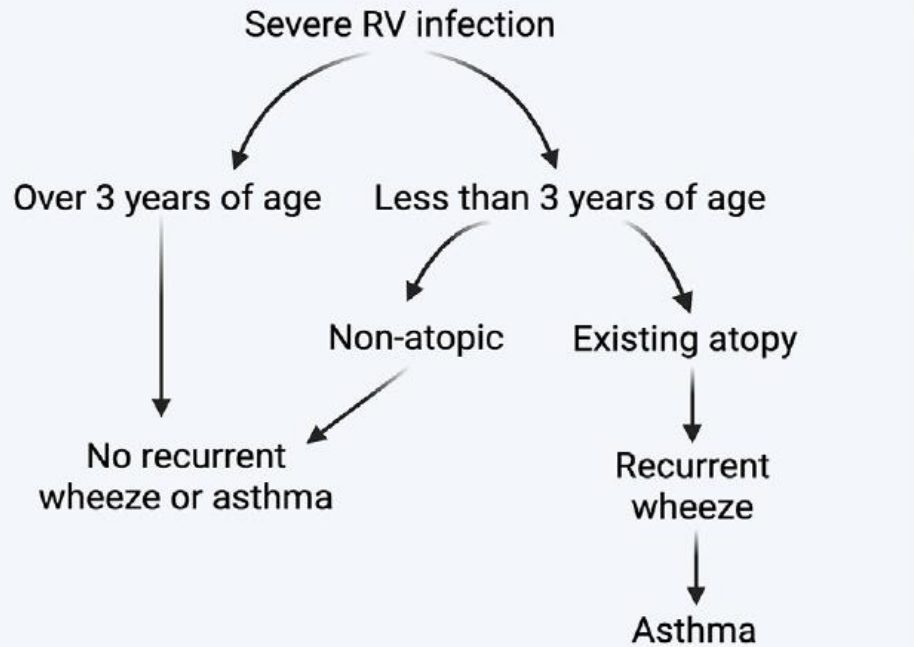
- Contributes to 30-50% of all respiratory tract infections
- The most frequently detected virus in children
- RV-A and RV-C are the predominant circulating species
- No FDA approved treatments, supportive care only

160 antigenically distinct serotypes across three species:
- RV-A
- RV-B
- RV-C

Asthma exacerbation

Major cause of asthma exacerbations

Development of asthma



V.T. Nguyen et al. Ann Allergy Asthma Immunol 2025

Role of Other Respiratory Viruses in Asthma Exacerbation

	Influenza virus	Human coronavirus (SARS-CoV-2)	Human metapneumovirus (hMPV)
Characteristics	• 모든 연령에서 asthma exacerbation 유발	• wide clinical spectrum (asymptomatic → severe)	• RSV와 유사한 paramyxovirus • 소아에서 wheezing 흔함

Clinical significance with asthma	• exacerbation의 흔한 원인 (약 10–25%)
	• severe AE risk 증가
		• generally weaker trigger compared to influenza
		• not a strong independent risk factor (early pandemic data)
			• asthma exacerbation 유발 가능
			• 일부 연구에서:
			  • recurrent wheezing 증가
			  • asthma 위험 증가 가능성

Mechanism	• IL-33 증가 • ILC2 활성화 → IL-13 증가 • airway inflammation ↑	• ACE2 ↓ (T2-high asthma) → susceptibility modulation • IFN dysregulation / epithelial injury • 일부에서 persistent airway symptoms (long COVID)	• airway epithelial infection / injury • IL-33 release → ILC2 activation (→ IL-5, IL-13) • relatively weak IFN response → delayed viral clearance

Coverstone et al. Immunol Allergy Clin N Am 2019, Khojasteh-Kaffash S et al. J Asthma 2024

Respiratory Viruses in Asthma: Key Summary

Major Viral Contributors

- Rhinovirus & RSV
  → Primary drivers of asthma exacerbation
- Human metapneumovirus (hMPV)
  → Associated with recurrent wheezing and possible asthma risk
- Human coronavirus (SARS-CoV-2)
  → wide clinical spectrum, generally weaker trigger compared to influenza
- Influenza virus
  → Contributes to exacerbation via IL-33–mediated inflammation

Shared Mechanisms

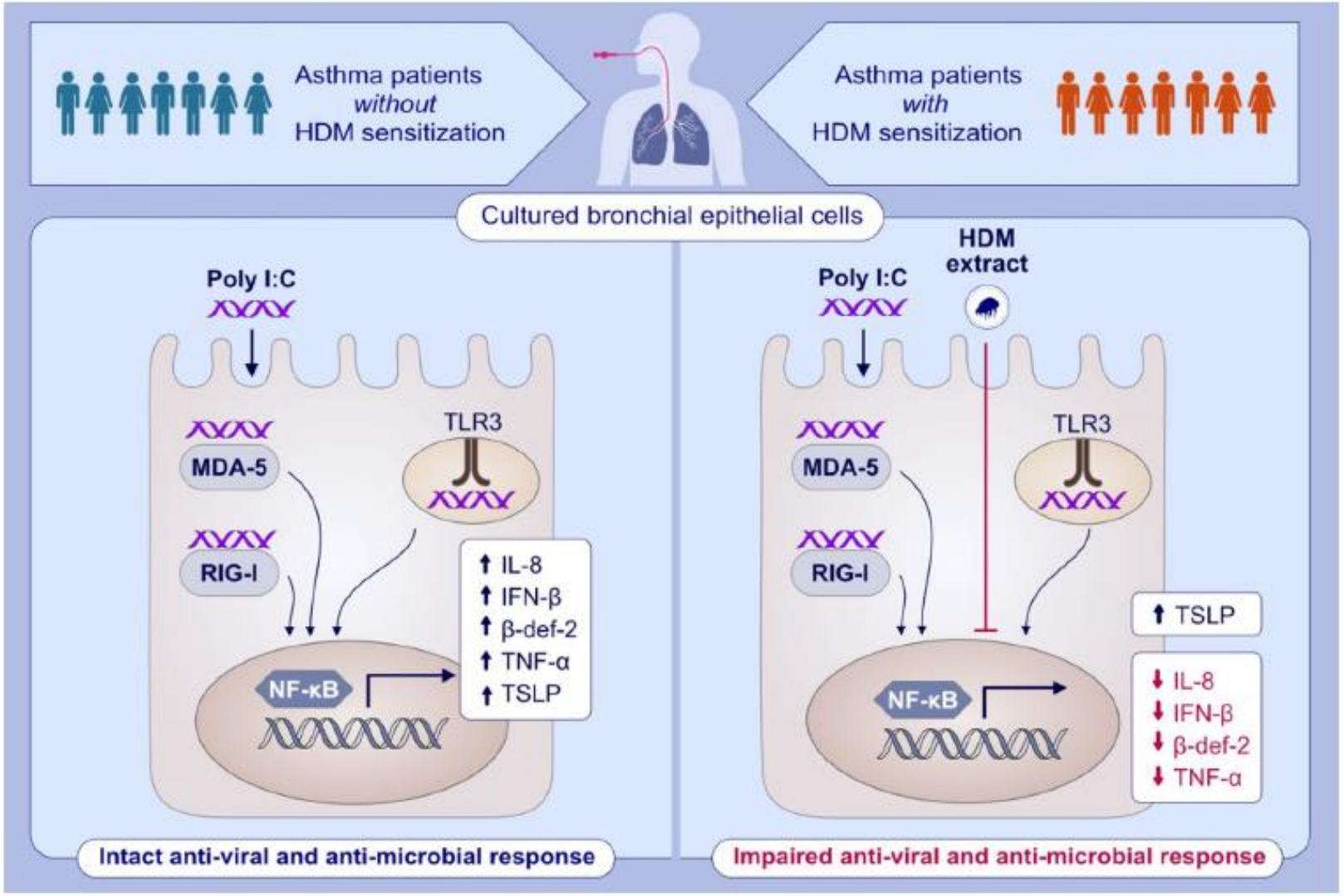
- Airway epithelial infection
- Activation of type 2 inflammation
- Increased airway hyperresponsiveness

Early-life infection burden may be more important than the specific virus type.

While multiple viruses contribute to asthma exacerbation, their roles differ, and importantly, the cumulative burden of infection may be more relevant than the specific virus

Coverstone et al. Immunol Allergy Clin N Am 2019

Allergen Exposure Weakens Infection Defense in Asthma

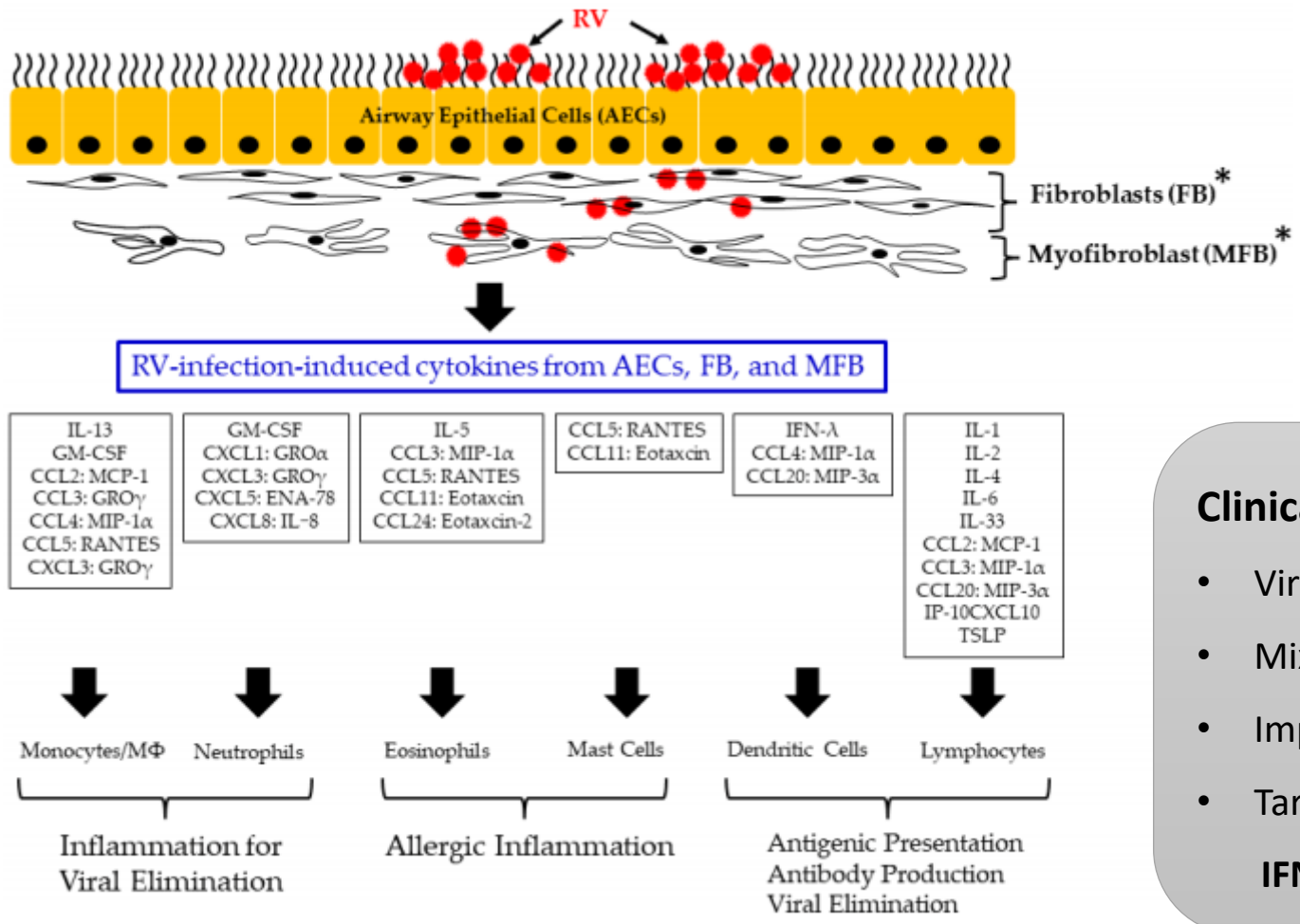


virus + HDM 에서:

- IFN ↓ → viral clearance 감소
- IL-8/TNF ↓
  → neutrophil recruitment 감소
- defensin ↓
  → bacterial defense 감소
- TSLP 유지
  → T2 inflammation 지속

Cerps et al. Allergy 2022

Rhinovirus-Induced Asthma: Beyond the Th1/Th2 Paradigm



RV infection
→ epithelial damage
→ PRR activation
→ cytokine release (Th1 + Th2)
→ immune cell recruitment
→ inflammation amplification
→ airway remodeling
→ asthma exacerbation

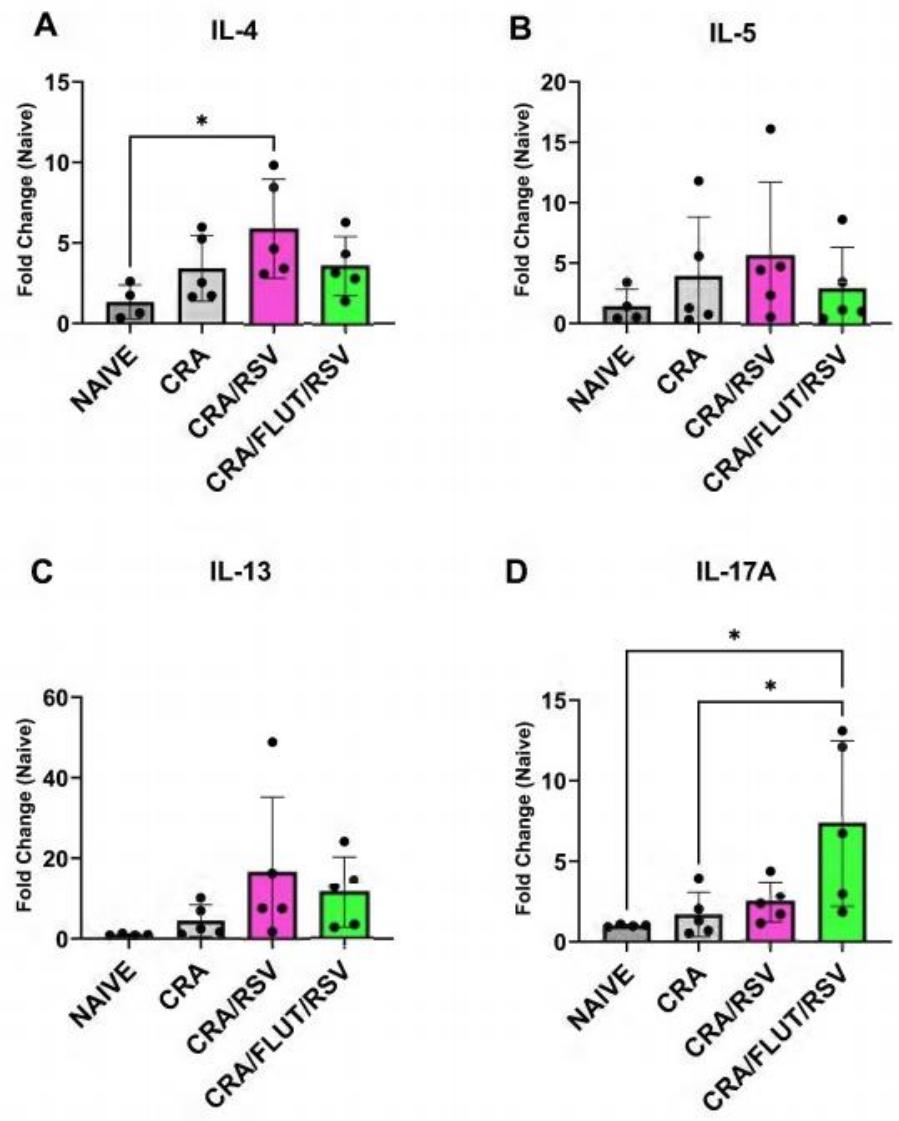
Clinical Implications

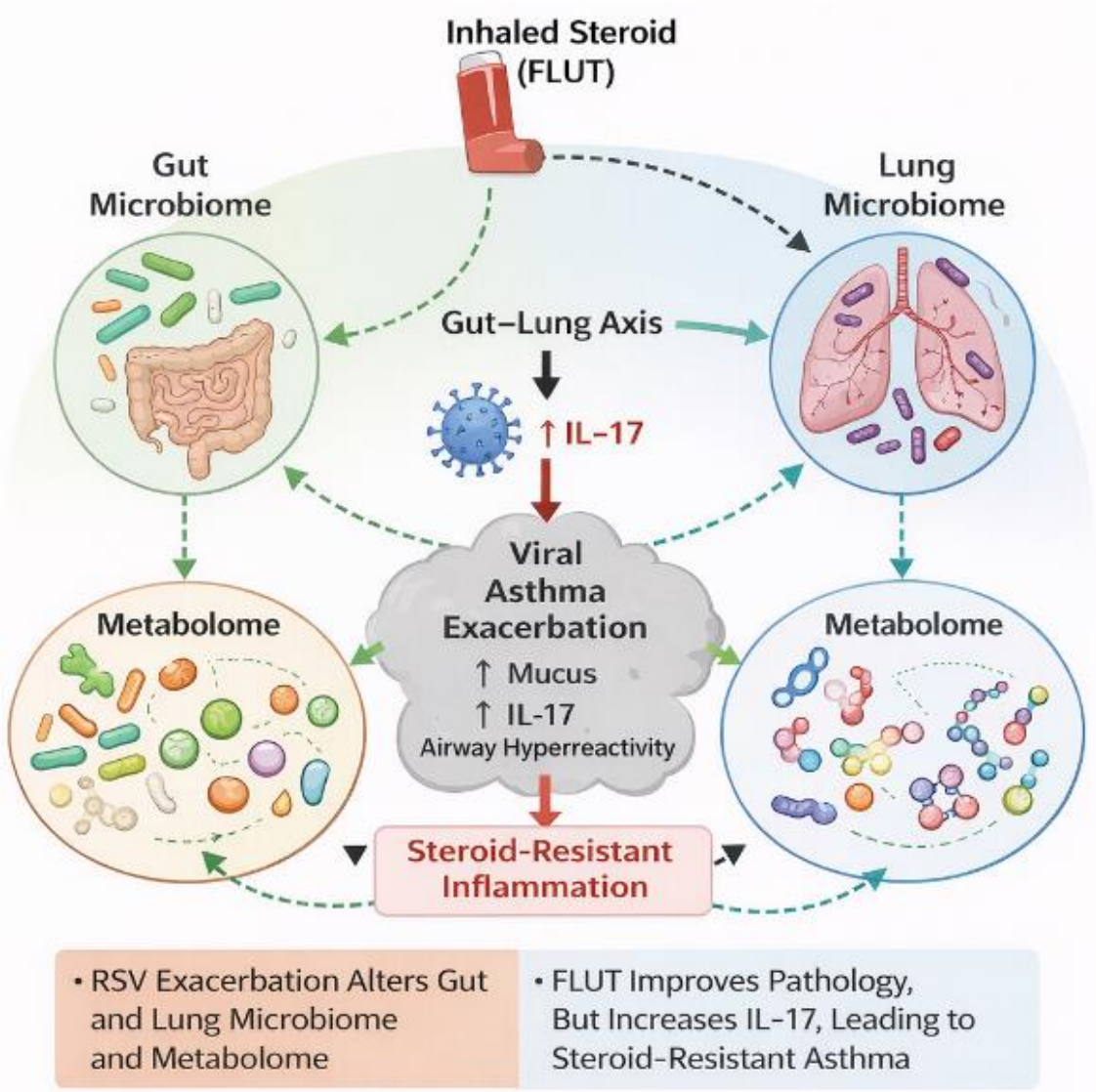
- Virus-induced asthma ≠ simple allergy
- Mixed immune phenotype disease
- Impaired **viral clearance → persistent inflammation**
- Target pathways:

  IFN signaling, epithelial immunity, type 2 inflammation

Hayashi et al. Viruses 2022

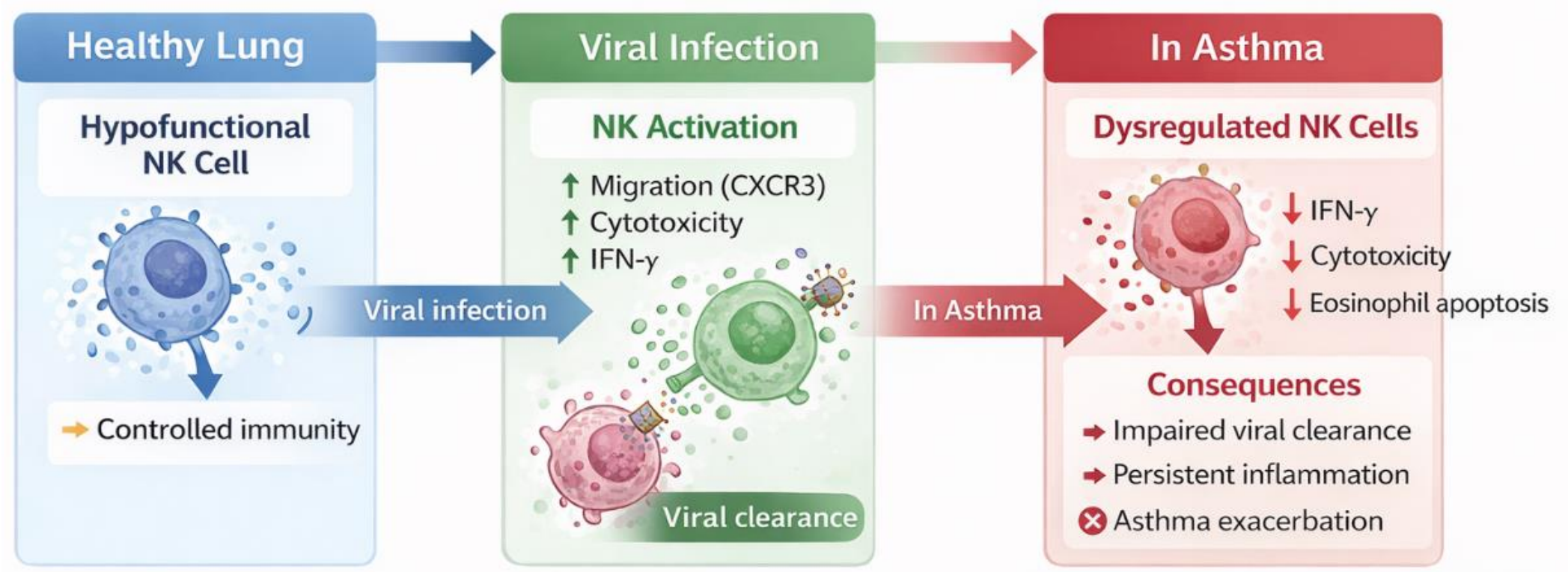
Microbiome–Metabolome Interaction in Virus-Induced Asthma Exacerbation





Yagi et al. Am J Physiol Lung Cell Mol Physiol 2024

Dysregulated NK Cells Link Viral Infection to Asthma Exacerbation



NK cells are key antiviral effectors in the lung

Normally tightly suppressed to prevent tissue damage

In asthma, NK cells show functional dysregulation

This leads to failed viral control + unresolved inflammation

Lepretre et al. Eur Respir Rev 2023

Infection-Prone Asthma Phenotype: Who are they?

Clinical Clues

- Frequent antibiotics exposure
- Severe asthma subset
- Bronchiectasis overlap (CT)
- Recurrent exacerbation despite ICS

Microbiologic Pattern

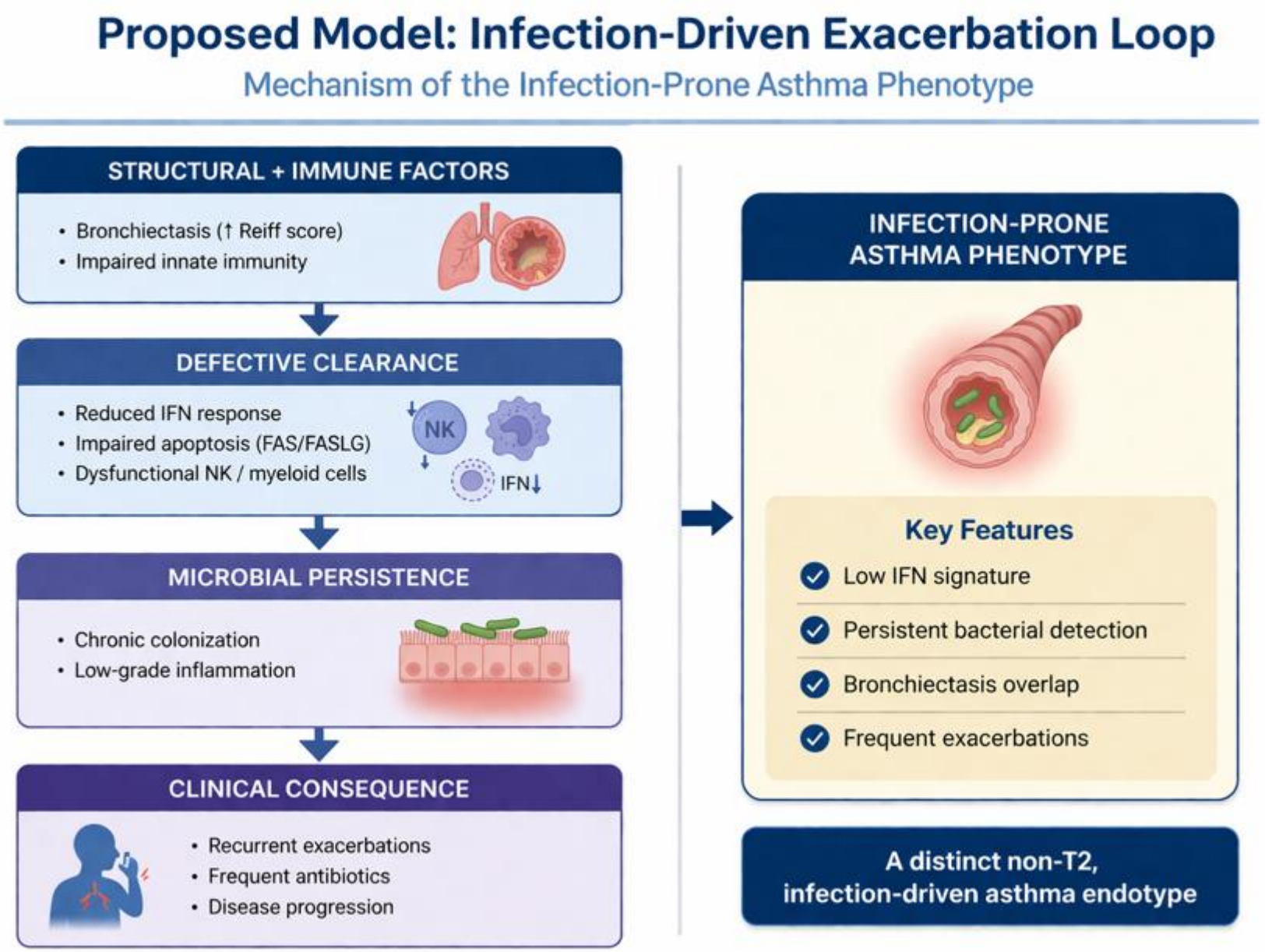
- Repeated detection of same pathogen
- Chronic airway colonization
- Often subclinical persistence

Dominant Bacterial Species

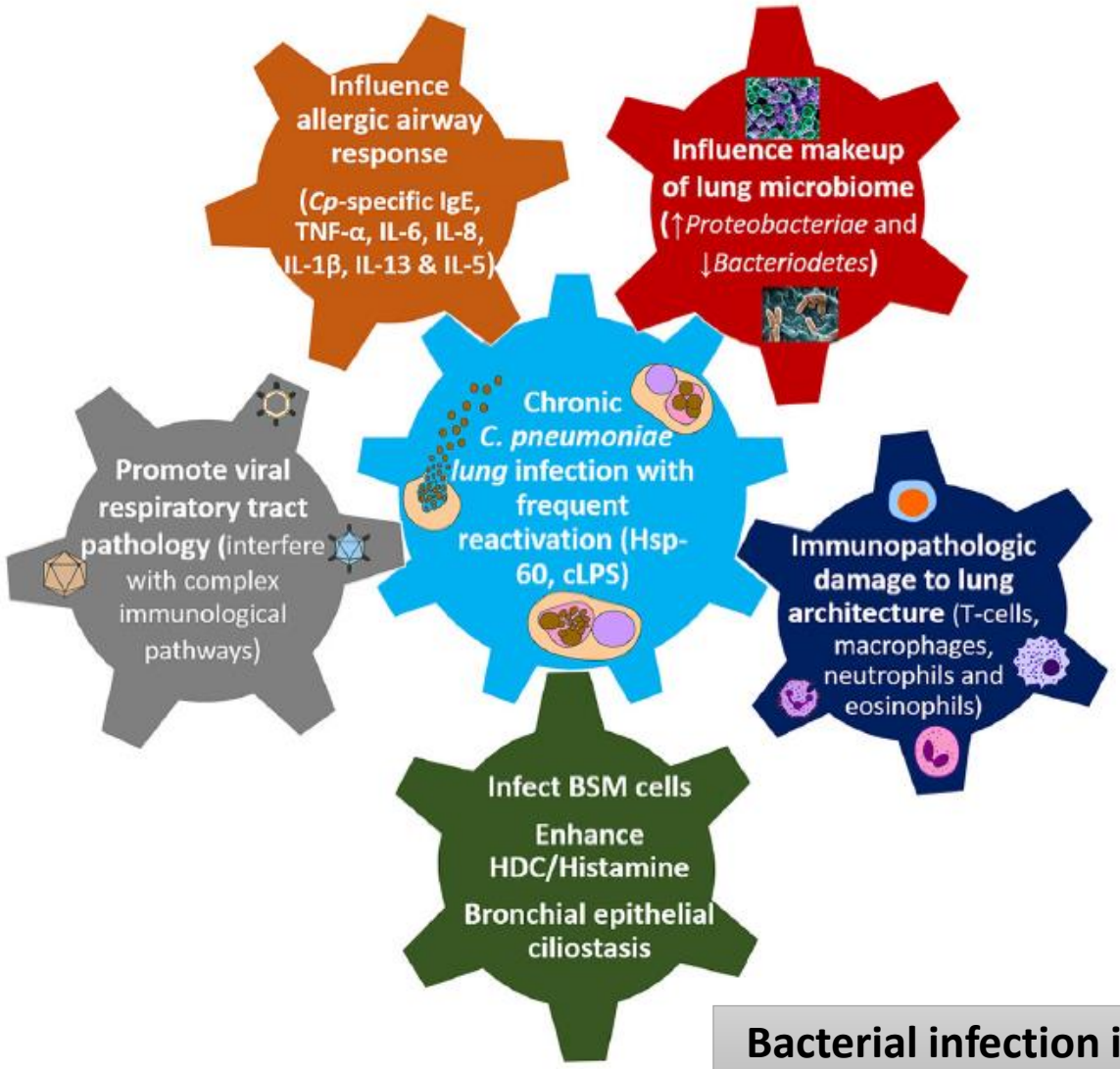
- *Pseudomonas aeruginosa*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*

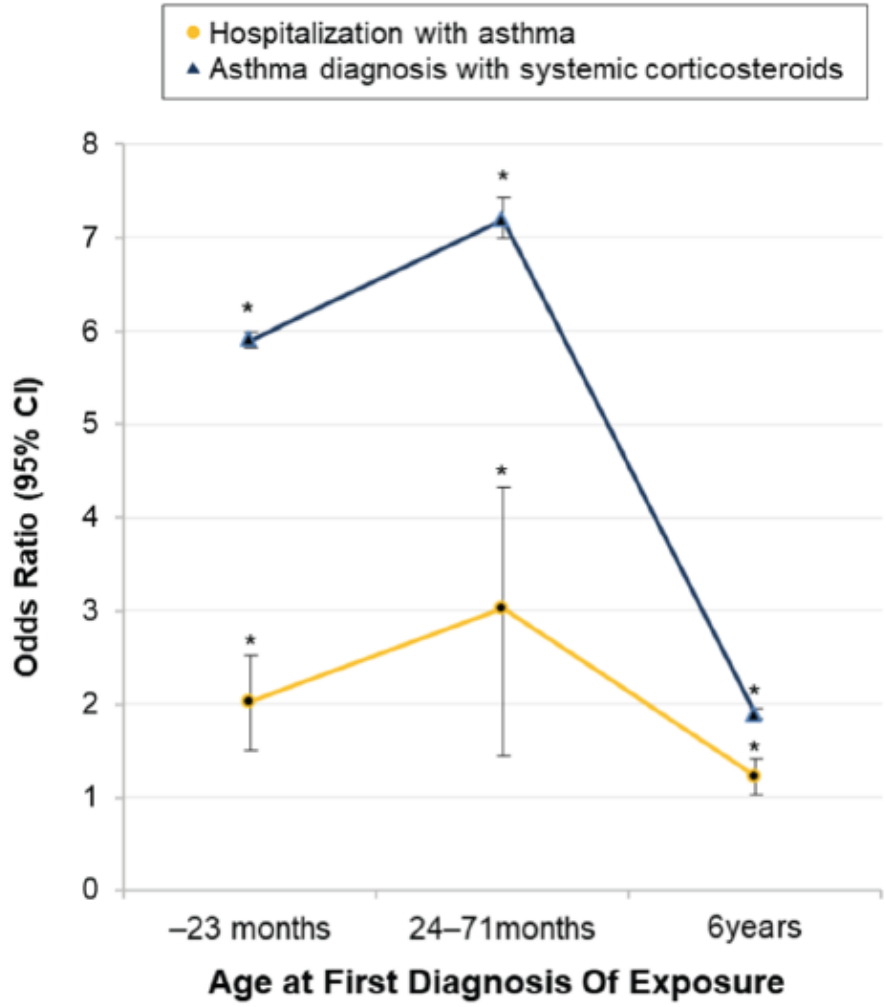
Not just infection-prone, but clearance-impaired phenotype

Mechanistic Model: Infection–Exacerbation Cycle



Bacterial Infection–Driven Asthma Exacerbation



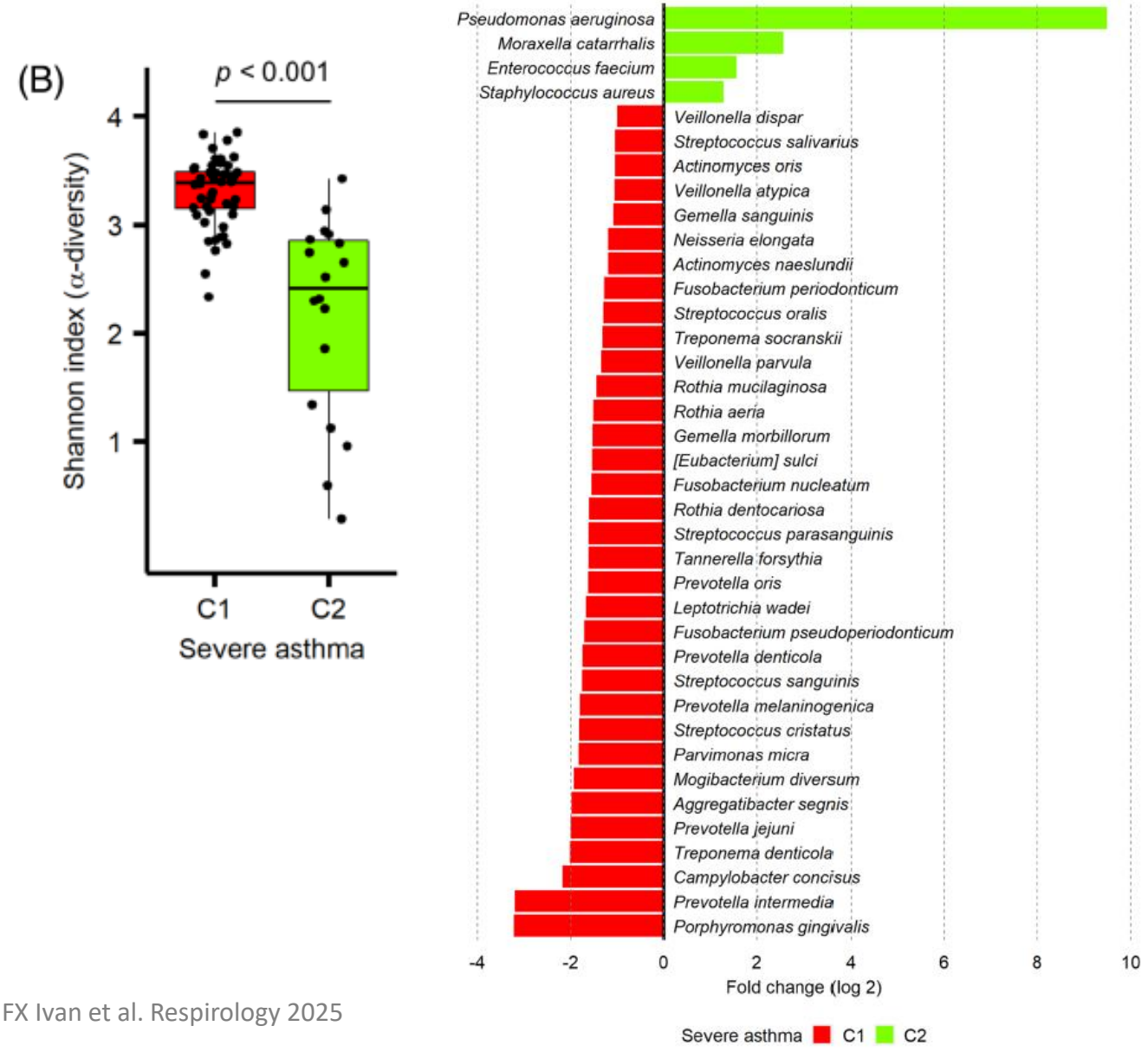


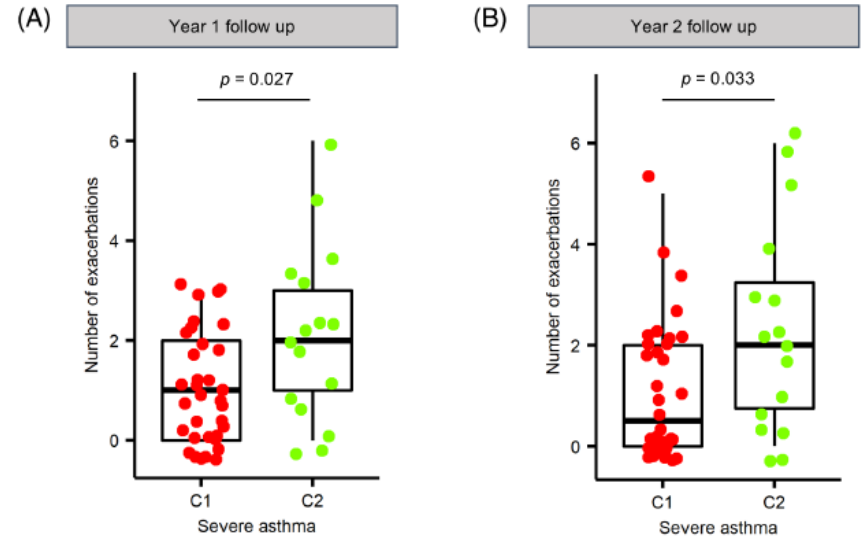
Bacterial infection is not just a trigger — it is a disease-modifying factor in asthma

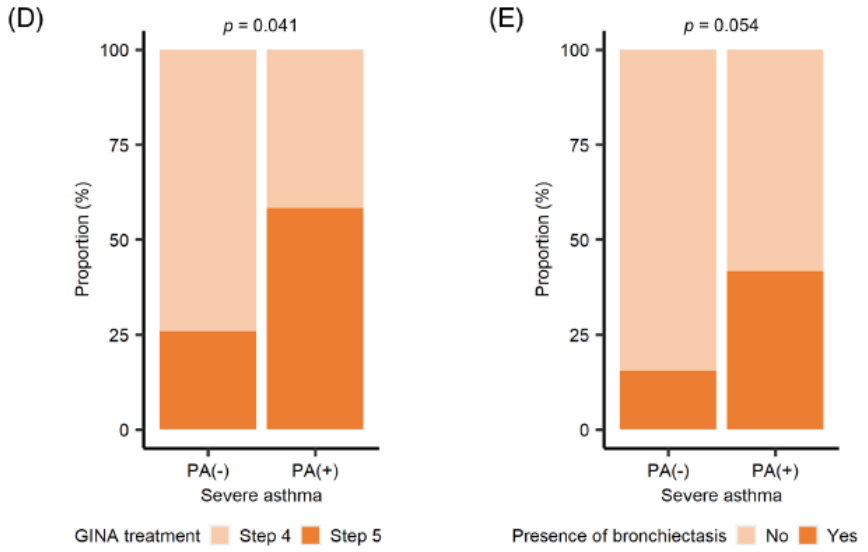
1. Webly et al. Respiratory Research 2017, 2. EK Ha et al. Pediatric Pulmonology 2024

양산부산대학교병원
Pusan National University Yangsan Hospital

Pseudomonas-dominant microbiome defines a high-risk severe asthma phenotype







FX Ivan et al. Respirology 2025

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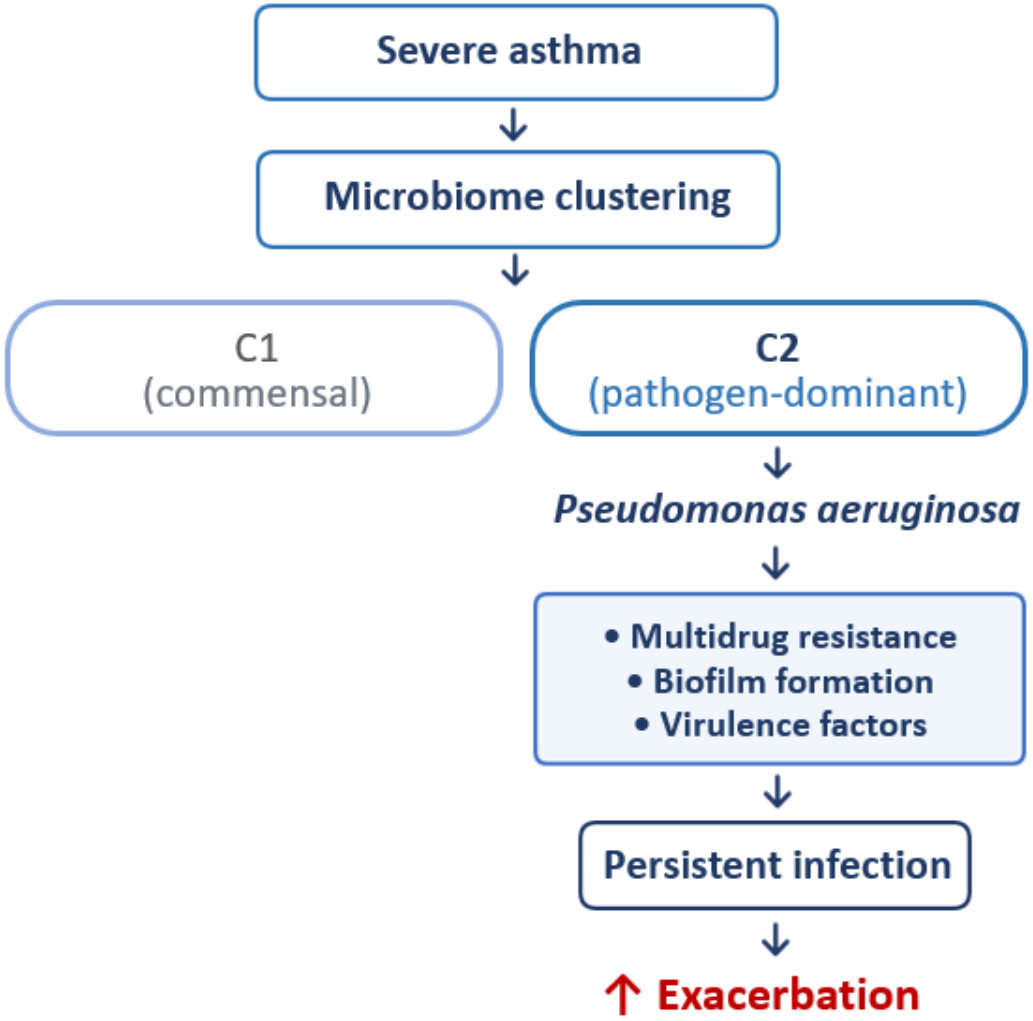
Pseudomonas-dominant microbiome defines a high-risk severe asthma phenotype

Mechanism / Concept



Key Findings

Analysis Results

↑ **Pseudomonas abundance**
Significant increase observed

2 Distinct Clusters
C1 (Commensal) vs C2 (Pathogen)

Cluster C2 Impact:
↑ **Exacerbations (IRR ~2.4)**
** Independent of bronchiectasis*

↑ **Multidrug resistance** genes

↑ **Virulence** (biofilm, secretion)

FX Ivan et al. Respirology 2025

Immunodeficiency-Driven Infection and Asthma Exacerbation

Table 2. Variations of selected features after 1 year of IRT in the T2-low group (panel A) and in the T2-high group (panel B)

	Baseline	After IRT	*p* value
Panel A			
Exacerbations/year	5.5 (1–16)	1.5 (0–7)	<0.01
Respiratory infections	3 (1–14)	1 (0–5)	<0.001
OCS	1/12 (8.3)	1/12 (8.3)	NS
OCS dose, mg	7.5	5	NS
BEC, cells/μL	80 (30–140)	115 (70–520)	<0.05
ACT	16 (10–19)	22 (18–25)	<0.01
ACQ5	2.4 (1.7–3.5)	0.4 (0.1–1.1)	<0.01
	Baseline	After IRT	*p* value
Panel B			
Exacerbations/year	7 (2–20)	1 (0–6)	<0.001
Respiratory infections	5 (0–20)	1 (0–5)	<0.001
OCS	5/21 (23.8)	2/21 (9.5)	<0.005
OCS dose, mg	17 (5–25)	3.75 (2.5–5)	NS
BEC, cells/μL	200 (50–760)	170 (10–1,400)	NS
ACT	15 (11–18)	23 (18–25)	<0.01
ACQ5	2.6 (1.9–3.3)	0.5 (0.2–1.3)	<0.01

Results:

36.4%가 T2-low phenotype

IVIg 효과
- 감염 & 악화 감소
- infection:4 → 1 (p<0.001)
- exacerbation:6 → 1 (p<0.001)

Phenotype 변화
T2-low 환자에서:
- eosinophil 증가 (80 → 115, p<0.05)
- 일부는 T2-high로 이동

Vivarelli et al. Respiration 2025

Infection as a Phenotype-Modifying Driver in Asthma

① Immunodeficiency

↓ IgG / PAD

impaired humoral immune response

reduced pathogen clearance

② Recurrent Infections

Frequent viral (e.g., HRV, RSV) and/or bacterial (e.g., *H. influenzae*, *S. pneumoniae*) exacerbations

③ Airway Inflammation & Remodeling

Persistent inflammation (Type 2 and/or non-T2)

Structural changes (e.g., goblet cell hyperplasia, smooth muscle thickening)

④ Dysbiosis & Chronic Colonization

'unbalanced'

Reduced microbial diversity

Emergence of pathogenic bacteria

Creation of a pro-inflammatory microenvironment

⑤ Severe, Treatment-Resistant Asthma

Persistent symptoms

Frequent, severe exacerbations

Corticosteroid resistance

Need for biologics or other advanced therapies

> **RECURRENT INFECTIONS** and the associated immune responses can **DRIVE** the progression to a more **SEVERE, INFLAMMATORY,** and **TREATMENT-RESISTANT** asthma phenotype.

KEY CORRELATIONS:

Higher infection rate → ↑ FeNO levels

↑ Sputum neutrophils → ↓ FEV1 % predicted

Antibiotic use → Altered airway microbiome

Phenotype-Based Therapeutic Approach in Infection-Associated Asthma

1. Universal infection response (all asthma)

- Viral/bacterial trigger → epithelial injury + inflammation
- Standard care: ICS ± LABA Short-term OCS (exacerbation)

2. T2-amplified phenotype

- Virus → ↑ IL-33 / TSLP → ↑ IgE / eosinophilia
- Key feature: exaggerated T2 response
- Treatment focus: Anti-IgE (omalizumab), Anti-IL5 / IL5R (mepolizumab, benralizumab), Anti-IL4R (dupilumab)
  Anti-TSLP (Tezepelumab)
- Effect:↓ exacerbation frequency↓ virus-induced amplification

3. Immune-impaired / infection-prone phenotype

- ↓ IFN response
- impaired NK / macrophage function
- chronic bacterial persistence
- Treatment focus:
  NOT inflammation suppression alone
  → host defense restoration

Expanding Treatment Strategies: Beyond Anti-Inflammation

1. Macrolide Therapy (Azithromycin)

Anti-inflammatory + Antibacterial

- ↓ **Exacerbation (esp. non-T2 / neutrophilic)**

Key Mechanism

- ✓ ↓ IL-8 / neutrophil recruitment
- ✓ Modulation of airway microbiome

Best Candidates

- Frequent exacerbators
- Chronic bacterial detection

2. ICS Balance — Critical Issue

Dual Effect

- ✓ ↓ T2 inflammation
- ⚠ **BUT → ↑ Infection risk (bacterial, viral)**

Clinical Implication

- › Overuse in non-T2 → **Harmful**
- › Need precision dosing

> ❗ **ICS Overuse Risk**

3. Biologics

Primary Benefit

- ★ **Strong effect in T2-high asthma**
- ⊕ Additional benefit: ↓ Virus-induced exacerbation (e.g., anti-IgE)

Limitation

- ⊘ **Limited effect in infection-driven / non-T2 phenotype**

4. IFN Augmentation — Emerging

Target: Impaired antiviral response

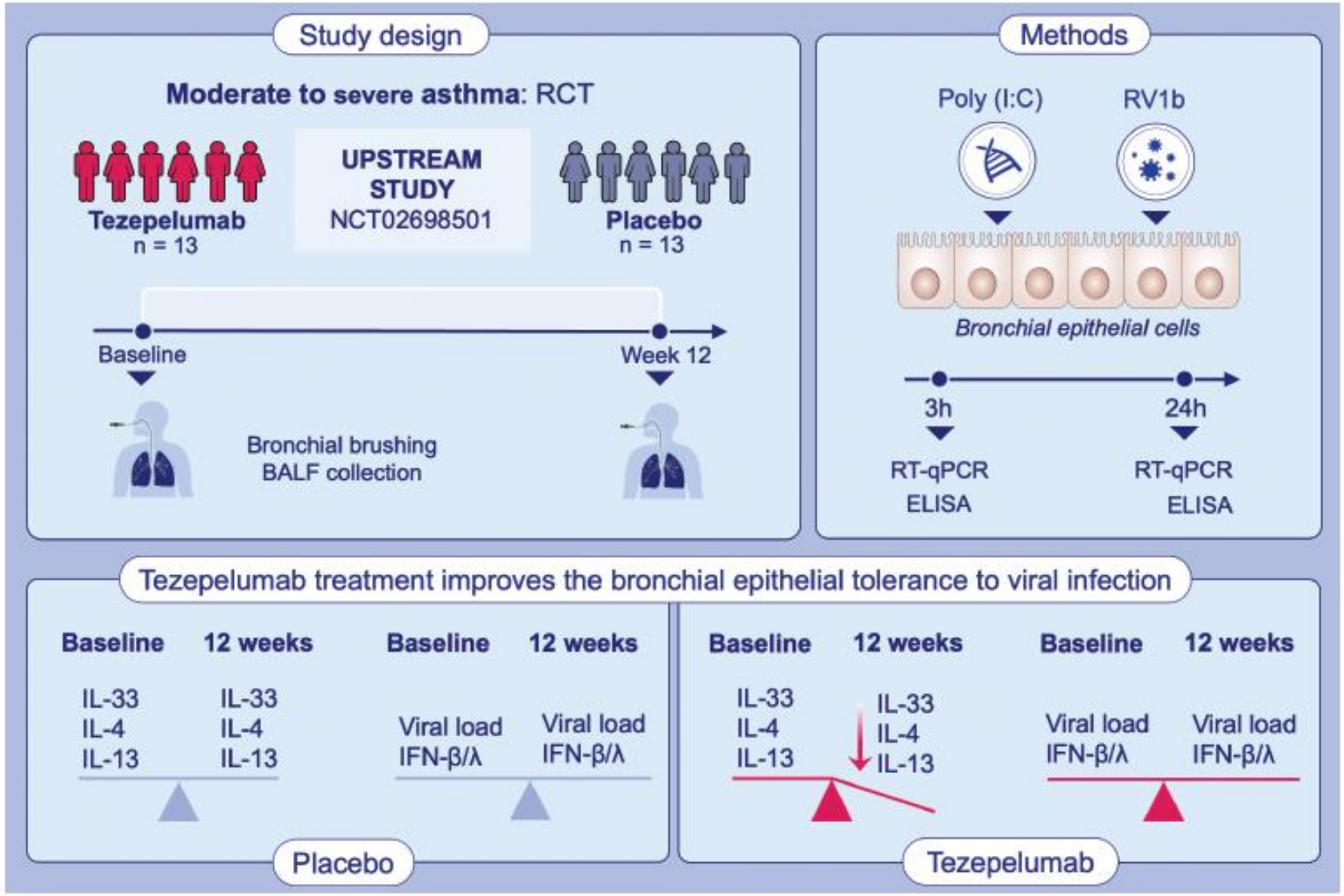
Examples

- Inhaled IFN-β (clinical trials)
- TLR agonists

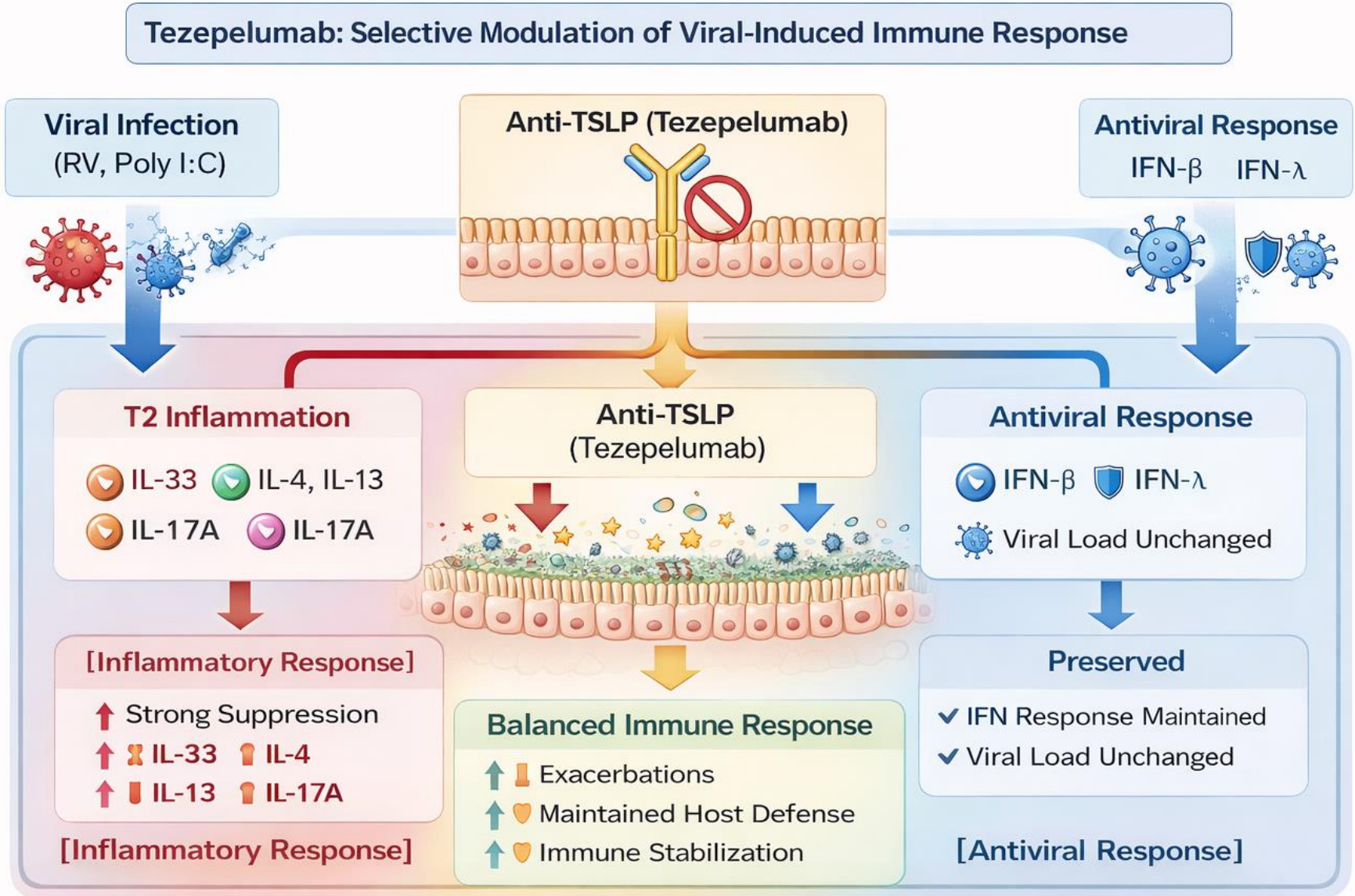
Potential Role

- Infection-prone asthma
- Early viral infection phase

Tezepelumab:
Modulating Viral-Induced Inflammation Without Impairing Antiviral Defense



Sverrild et al. Allergy 2024



Tezepelumab suppresses inflammatory amplification while **preserving antiviral immunity.**

European Academy of Allergy and Clinical Immunology (EAACI) EAACI | 2024

Toward Precision Therapy in Infection-Prone Asthma

Candidate biomarkers

- ✓ IFN signature (↓ = infection-prone)
- ✓ Blood transcriptomics
  - immune suppression pattern
  - interferon pathway downregulation
- ✓ NK cell function
  - cytotoxicity ↓
  - impaired viral/bacterial clearance
- ✓ Microbiome profiling
  - chronic colonization pattern
  - dysbiosis

Future directions

Define **infection-prone asthma cohort**

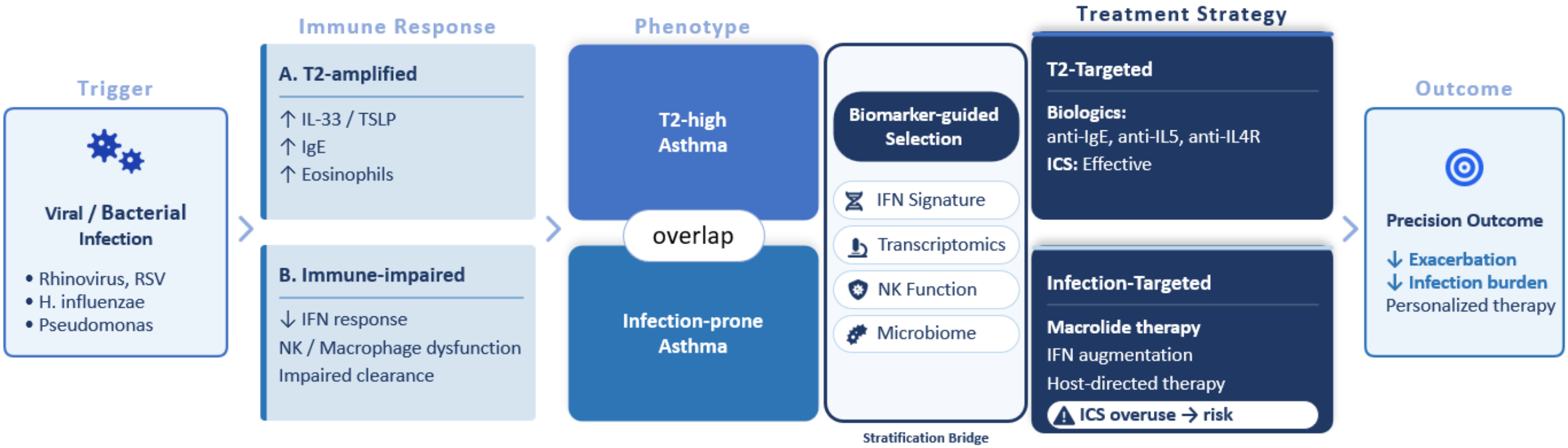
Integrate:

immune profiling
microbiome
transcriptomics

Goal:

Mechanism-based, not symptom-based treatment

Precision Treatment in Infection-Associated Asthma



Summary

- Infection ≠ single mechanism
- Host immunity determines outcome
- T2-high → inflammation amplification
- Infection-prone → impaired clearance
- Bacterial persistence → disease progression
- **→ Phenotype-based precision therapy is essential**

경청해 주셔서 감사합니다.