


**Asthma and
COVID-19**

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1

COVID-19



- At the end of 2019, a novel coronavirus was determined to be the cause of a cluster of pneumonia cases in Wuhan, China
- Disease spread rapidly throughout China and numerous other countries
- In February 2020, WHO designated the resultant disease COVID-19
 - COronaVIrus Disease 2019
- COVID-19 causing virus called Severe Acute Respiratory Syndrome Coronavirus 2
 - SARS-CoV-2

2

Coronaviruses



- First identified in mid-1960's
- Large family of viruses; Named for crown-like spikes on surface
- 4 main sub-groups
 - Alpha
 - Beta
 - Gamma
 - Delta
- 7 coronaviruses known to infect humans

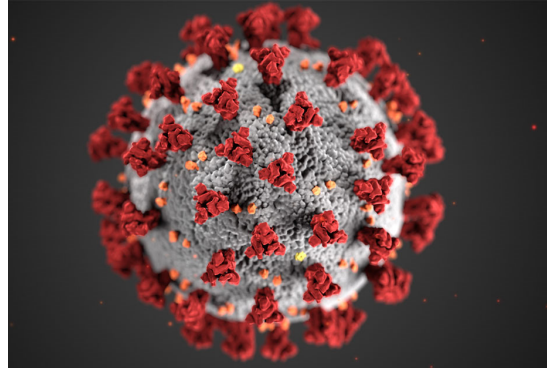


Image from [cdc.gov](https://www.cdc.gov)

3

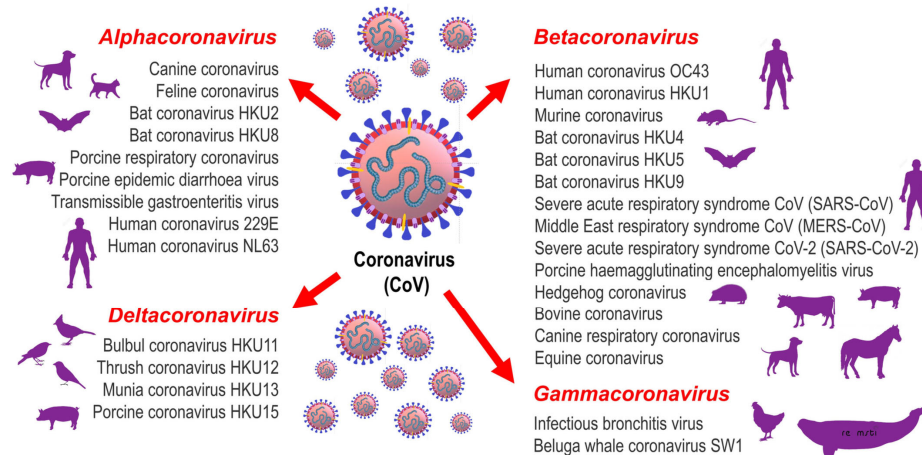
Coronaviruses



- 4 common coronaviruses that generally cause mild-to-moderate URIs
 - 229E (alpha coronavirus)
 - NL63 (alpha coronavirus)
 - OC43 (beta coronavirus)
 - HKU1 (beta coronavirus)
- 3 coronaviruses have caused more severe/fatal disease in humans
 - SARS-CoV
 - Emerged in 2002; Responsible for Severe Acute Respiratory Syndrome (SARS)
 - MERS-CoV
 - Emerged in 2012; Responsible for Middle East Respiratory Syndrome (MERS)
 - SARS-CoV-2

4

Coronaviruses



Sharun, K., Sircar, S., Malik, Y.S., Singh, R.K. and Dhama, K. (2020), How close is SARS-CoV-2 to canine and feline coronaviruses?. *J Small Anim Pract*, 61: 523-526

5

Viruses and Asthma



- Viral respiratory tract infections are the most common cause of asthma exacerbations in both children and adults ¹⁻³
- Viruses infect airway epithelium and promote an inflammatory response that can trigger wheezing illnesses ^{4,5}
- In susceptible individuals, the virus-induced immune response may mediate host responses to other microbes, infections, allergens, stress, and pollutants, resulting in asthma exacerbations ^{4,5}

1. Carroll KN, Hartert TV. The impact of respiratory viral infection on wheezing illnesses and asthma exacerbations. *Immunol Allergy Clin North Am* 2008; 28:539.
 2. Tan WC. Viruses in asthma exacerbations. *Curr Opin Pulm Med* 2005; 11:21.
 3. MacDowell AL, Bacharier LB. Infectious triggers of asthma. *Immunol Allergy Clin North Am* 2005; 25:45.
 4. Holt PG, Sly PD. Viral infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment. *Nat Med* 2012; 18:726.
 5. Gern JE. Viral respiratory infection and the link to asthma. *Pediatr Infect Dis J* 2008; 27:597.

6

Viruses and Asthma



- Respiratory viral infection and replication activates innate and adaptive immune responses
 - Proinflammatory cytokine production
 - Chemokine production
 - Recruitment of inflammatory cells to the airway

7

Viruses associated with recurrent wheezing and asthma exacerbations



| Virus | Major antigenic groups |
|-----------------------------|----------------------------|
| Rhinovirus | A, B, C |
| Respiratory syncytial virus | A, B |
| Coronaviruses | NL63, HKU1, OC43, 229E |
| Metapneumovirus | A, B |
| Parainfluenza viruses | I, II, III, IV |
| Enterovirus | D68, others |
| Influenza viruses | A, B, C |
| Bocavirus | |
| Adenovirus | Serotypes 1, 2, 3, 5, 6, 7 |
| Polyomavirus | WU, KI, Malawi |

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8

COVID-19



- Most recent global statistics from the WHO

- >500 million cases
- >6.2 million deaths

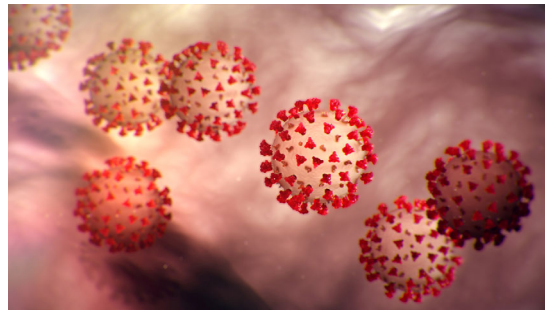


Image from [cdc.gov](https://www.cdc.gov)

9

COVID-19



- CDC outlined risk factors (original guidance)

- Age
 - >81% of deaths COVID-19-related deaths occur in patients older than 65
- Certain underlying medical conditions
 - Risk of severe illness increases as number of medical conditions increases

10

Medical Conditions Associated with Increased Risk



- Cancer
- Chronic Kidney Disease
- Chronic Liver Disease
- Chronic Lung Disease
- Cystic Fibrosis
- Dementia or other neurological condition
- Diabetes
- Disabilities
- Heart Conditions
- HIV infection
- Immunocompromised state
- Mental Health Conditions
- Overweight and Obesity
- Physical Inactivity
- Pregnancy
- Sickle Cell Disease or Thalassemia
- Smoking (current or former)
- Solid organ or blood stem cell transplant patient
- Stroke or cerebrovascular disease
- Substance Use Disorders
- Tuberculosis

11

COVID-19



- Chronic Lung Disease
 - Asthma, if it's moderate to severe
 - Bronchiectasis (thickening of the lungs' airways)
 - Bronchopulmonary dysplasia (chronic lung disease affecting newborns)
 - Chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis
 - Having damaged or scarred lung tissue known as interstitial lung disease (including idiopathic pulmonary fibrosis)
 - Pulmonary embolism (blood clot in the lungs)
 - Pulmonary hypertension (high blood pressure in the lungs)

12



Reasonable to hypothesize that asthma is a risk factor for COVID-19

BUT

What does the DATA tell us?

13



COVID-19 and Asthma

- Does asthma increase the risk of SARs-CoV-2 infection?
- Does asthma increase the risk of severe COVID-19?
- Does asthma severity impact risk?
- Do asthma medications impact risk?
- Does asthma phenotype/endotype impact risk?

14

COVID-19 and Asthma



- Does asthma increase the risk of SARs-CoV-2 infection?
- Does asthma increase the risk of severe COVID-19?
- Does asthma severity impact risk?
- Do asthma medications impact risk?
- Does asthma phenotype/endotype impact risk?

15

COVID-19 and Asthma



- Prevalence of asthma in initial Wuhan cohort was low
 - 140 cases of community acquired COVID-19
 - 82 cases classified as non-severe and 58 as severe
 - No self-reported allergic disease including asthma, allergic rhinitis, food allergy, atopic dermatitis and other type 2 allergic disease was documented among the 140 cases
- Additional studies revealed relatively low asthma prevalence amongst those with COVID-19 in different parts of the world

Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75:1730-1741

16

COVID-19 and Asthma



TABLE 1 Estimated asthma prevalence (%) among patients with coronavirus disease 2019 (COVID-19) in comparison with the general population asthma prevalence in various countries [13–27, 38, 46]

| Country | National asthma prevalence (%) | Asthma prevalence among SARS-CoV-2 positive patients (%) |
|-------------|--------------------------------|--|
| China | ~1.5–6.5 | ~1–1.5 |
| USA | ~8 | ~10–18 |
| UK | ~12–18 | ~14–18 |
| Australia | ~20 | ~10–14 |
| Spain | ~6–7 | ~5 |
| Italy | ~6 | ~1 |
| Ireland | ~9 | ~11 |
| Switzerland | ~5 | ~6.5 |
| Germany | ~7–8 | ~10–11 |
| Israel | ~7.5–8.5 | ~5 |
| Mexico | ~2.5 | ~2–3 |
| Brazil | ~12.5–13.0 | ~5–6 |

Adir Y, Saliba W, Beurnier A, et al. Asthma and COVID-19: an update. *Eur Respir Rev* 2021; 30: 210152

17

COVID-19 and Asthma



- Sunjaya et al published a systematic review and meta-analysis looking at asthma and COVID-19 risk
- Search of 5 electronic databases between 12/1/2019 and 7/11/2021
 - Included all primary controlled studies reporting on adults with confirmed COVID-19 based on positive RT-PCR, with a pre-existing diagnosis of asthma, published in the English language
 - Asthma was defined according to definitions in the individual studies and included those sourced from medical records, physician-diagnosed and self-reported asthma
 - Excluded studies with ≤ 15 participants, pre-prints, and those not published in English
- 51 total studies included

Sunjaya AP, Allida SM, Di Tanna GL, et al. Asthma and COVID-19 risk: a systematic review and meta-analysis. *Eur Respir J* 2022; 59: 2101209 [DOI: 10.1183/13993003.01209-2021].

18

COVID-19 and Asthma



- Meta-analysis revealed an 8.08% prevalence of asthma among those who tested COVID-19 positive based on RT-PCR
 - lower than the global prevalence of self-reported asthma symptoms of 8.6%
- The pooled analysis of 10 studies (n=785,151) showed a **risk ratio reduction** in acquiring COVID-19 of 17% for people with asthma compared to those without asthma
 - risk ratio 0.83, 95% CI 0.73–0.95; p=0.01

Sunjaya AP, Allida SM, Di Tanna GL, et al. Asthma and COVID-19 risk: a systematic review and meta-analysis. Eur Respir J 2022; 59: 2101209 [DOI: 10.1183/13993003.01209-2021].

19

COVID-19 and Asthma



- Does asthma increase the risk of SARs-CoV-2 infection?
- **Does asthma increase the risk of severe COVID-19?**
- Does asthma severity impact risk?
- Do asthma medications impact risk?
- Does asthma phenotype/endotype impact risk?

20

COVID-19 and Asthma



- Huang et al investigated risk of severe COVID-19 in patients with asthma
- Severe COVID-19 outcomes:
 - Hospitalization
 - Intensive Respiratory Support
 - ICU admission within 30 days of diagnosis
 - Death within 60 days of diagnosis
- Found that patients with well-controlled asthma had less severe COVID-19 than those with uncontrolled asthma

Huang, B. Z., Chen, Z., Sidell, M. A., Eckel, S. P., Martinez, M. P., Lurmann, F., Thomas, D. C., Gilliland, F. D., & Xiang, A. H. (2021). Asthma disease Status, COPD, and COVID-19 severity in a large Multiethnic POPULATION. *The Journal of Allergy and Clinical Immunology: In Practice*. <https://doi.org/10.1016/j.jaip.2021.07.030>

21

COVID-19 and Asthma



- Beurnier et al reported that, among hospitalized patients with severe pneumonia due to SARS-CoV-2 infection, asthma patients were not over-represented ¹
- Avdeev et al described a low prevalence of asthma (1.8%) among 1,307 intensive care unit patients with SARS-CoV-2 pneumonia who required mechanical ventilation ²
- Terry et al found that there was no clear evidence of increased risk of COVID-19 diagnosis, hospitalization, severity, or mortality due to asthma ³
- Eggert et al showed that asthma does not independently increase the risk for hospitalization, severe disease, or long-term symptoms in COVID-19 ⁴

1. Beurnier A, Jutant EM, Jevnikar M, et al. Characteristics and outcomes of asthmatic patients with COVID-19 pneumonia who require hospitalisation. *Eur Respir J* 2020; 56: 2001875.

2. Avdeev S, Moiseev S, Brovko M, et al. Low prevalence of bronchial asthma and chronic obstructive lung disease among intensive care unit patients with COVID-19. *Allergy* 2020; 75: 2703–2704.

3. Terry PD, Heidel RE, Dhand R. Asthma in adult patients with COVID-19: prevalence and risk of severe disease. *Am J Respir Crit Care Med* 2021; 203: 893–905

4. Eggert LE, He Z, Collins W, et al. Asthma phenotypes, associated comorbidities, and long-term symptoms in COVID-19. *Allergy*. 2022 Jan;77(1):173-185.

22

COVID-19 and Asthma



- Numerous additional studies have also demonstrated no increased risk in general between adult patients with asthma and severe COVID-19 infection ¹⁻⁶

1. Terry PD, Heideil RE, Dhand R. Asthma in adult patients with COVID-19. Prevalence and risk of severe disease. *Am J Respir Crit Care Med* 2021;203: 893-905.
2. Cao L, Lee S, Krings JG, Rausedo AM, Reynolds D, Presti R, et al. Asthma in patients with suspected and diagnosed coronavirus disease 2019. *Ann Allergy Asthma Immunol* 2021;126:535-541.e2.
3. Grandbastien M, Plotin A, Godet J, Abessolo-Amougou I, Ederle C, Enache I, et al. SARS-CoV-2 pneumonia in hospitalized asthmatic patients did not induce severe exacerbation. *J Allergy Clin Immunol Pract* 2020;8:2600-7.
4. Shi L, Xu J, Xiao W, Wang Y, Jin Y, Chen S, et al. Asthma in patients with coronavirus disease 2019: a systematic review and meta-analysis. *Ann Allergy Asthma Immunol* 2021;126:524-34.
5. Ho KS, Howell D, Rogers L, Narasimhan B, Verma H, Steiger D. The relationship between asthma, eosinophilia, and outcomes in coronavirus disease 2019 infection. *Ann Allergy Asthma Immunol* 2021;127:42-8.
6. Sunjaya AP, Allida SM, Di Tanna GL, Jenkins C. Asthma and risk of infection, hospitalization, ICU admission and mortality from COVID-19: systematic review and meta-analysis. *J Asthma* 2021;1-14.

23

COVID-19 and Asthma



- Ruano et al reported that there were no differences in lung function, need for oral corticosteroids, emergency care, or hospitalizations for pediatric patients with asthma with and without COVID-19 ¹
 - This was independent of asthma severity or control in the last year
 - It was noted that in patients with probable COVID-19 there was increased use of controller and symptom reliever treatment → Suggests possible COVID-19 induced exacerbations
- Beken et al reported that in children with asthma, with or without concurrent allergic diseases, there was no association with an increased risk of hospitalization for COVID-19 ²

1. Ruano FJ, Somoza Alvarez ML, Haroun-Diaz E, Vazquez de la Torre M, Lopez Gonzalez P, Prieto-Moreno A, et al. Impact of the COVID-19 pandemic in children with allergic asthma. *J Allergy Clin Immunol Pract* 2020;8:3172-3174.e1.
2. Beken B, Ozturk GK, Aygun FD, Aydogmus C, Akar HH. Asthma and allergic diseases are not risk factors for hospitalization in children with coronavirus disease 2019. *Ann Allergy Asthma Immunol* 2021;126:569-75

24

COVID-19 and Asthma



- Does asthma increase the risk of SARS-CoV-2 infection?
- Does asthma increase the risk of severe COVID-19?
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25

COVID-19 and Asthma



- Adir et al showed that recent systemic corticosteroid use (as a marker of control/severity) was associated with both moderate to severe COVID-19 and all-cause mortality
 - This association had a positive correlation with the number of prescriptions in the previous year, with greater than 2 prescriptions having the highest hazard ratio
- Biologic therapies approved for asthma were not associated with an increased risk of SARS-CoV-2 infection or COVID-19 severity

Adir Y, Humbert M, Saliba W. COVID-19 risk and outcomes in adult asthmatic patients treated with biologics or systemic corticosteroids: nationwide realworld evidence. J Allergy Clin Immunol 2021;148:361-367.e13.

26

COVID-19 and Asthma



| Asthmatic patients with positive PCR for SARS-CoV-2 | | | |
|---|-----------------------------|-------------------|-------------------|
| | Previous treatment with SCS | ICS | Biologics |
| Infection with SARS-CoV-2 | No increased risk | No increased risk | No increased risk |
| COVID-19 severity | Increased risk | No increased risk | No increased risk |
| COVID-19 mortality | Increased risk | No increased risk | No increased risk |

FIGURE 1 Asthma medications and the risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and disease severity. COVID-19: coronavirus disease 2019; ICS: inhaled corticosteroids; SCS: systemic corticosteroids.

Adir Y, Saliba W, Beurnier A, et al. Asthma and COVID-19: an update. *Eur Respir Rev* 2021; 30: 210152

27

COVID-19 and Asthma

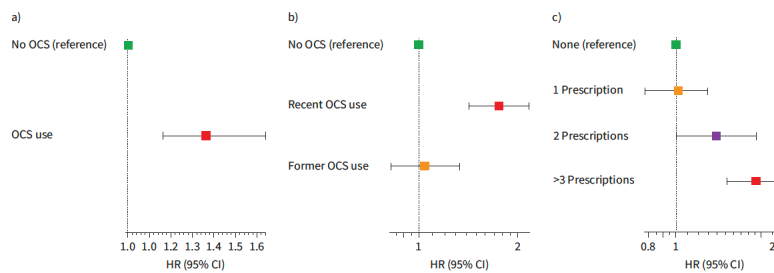


FIGURE 2 Association of oral corticosteroids use and outcomes in asthmatic patients with coronavirus disease 2019 (COVID-19). Reproduced from *Amir et al.* [30]. a) Adjusted^a hazard ratios (HRs; 95% CI) for the association oral corticosteroids (OCS) use in the prior year and the composite of moderate to severe COVID-19 or all-cause mortality within 90 days following PCR date among adult asthmatic patients with positive PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (n=8242). OCS use refers to any use in the year before baseline with no OCS use serving as reference category. b) Adjusted^b HRs (95% CI) for the association recent and former OCS use and the composite of moderate to severe COVID-19 or all-cause mortality within 90 days following PCR date among adult asthmatic patients with positive PCR for SARS-CoV-2 (n=8242). c) Adjusted^c HRs (95% CI) for the association between the number of filled steroids prescriptions in the prior years and the composite of moderate to severe COVID-19 disease and all-cause mortality within 90 days following PCR date among adult asthmatic patients with positive PCR for SARS-CoV-2 (n=8242). ^a: adjusted for age, sex, ethnicity, diabetes, hypertension, ischaemic heart disease, obesity, smoking and biologics use.

28

COVID-19 and Asthma



- Bloom et al showed that more severe asthma was associated with more severe COVID-19 outcomes
 - Severity was based on medication requirement and exacerbation history
 - Higher risk of ICU admission and mortality in those requiring regular ICS + add-on therapy (LABA, LTRA, or theophylline) and in those with frequent exacerbation

Bloom CI, et al. *Am J Respir Crit Care Med.* 2022;doi:10.1164/rccm.202107-1704OC

29

COVID-19 and Asthma



- Does asthma increase the risk of SARs-CoV-2 infection?
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30

Asthma Phenotypes/Endotypes

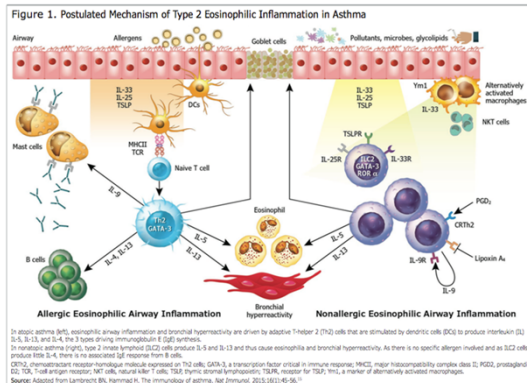


Type 2 or Th2-high asthma

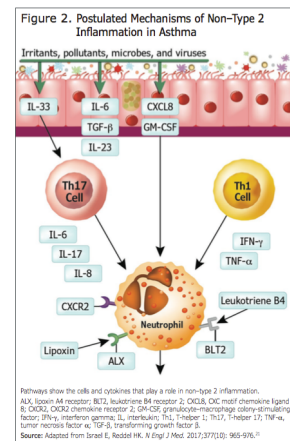
Hekking PP, Bel EH. Developing and emerging clinical asthma phenotypes. J Allergy Clin Immunol Pract. 2014 Nov-Dec;2(6):671-80

31

Asthma Phenotypes/Endotypes



T_H2-High



T_H2-Low

32

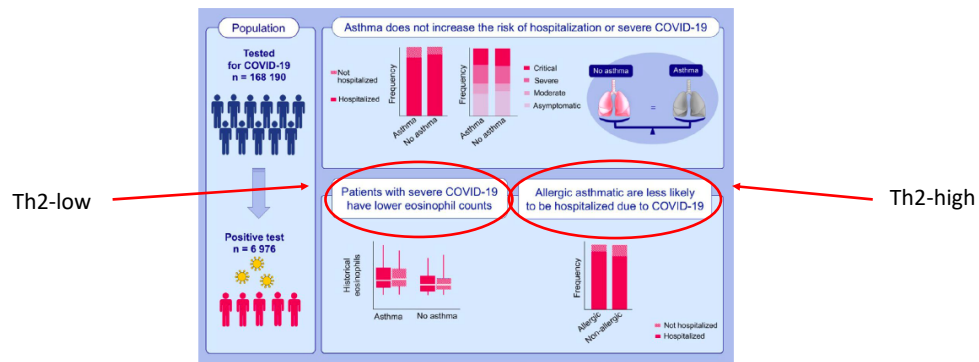
COVID-19 and Asthma



- Increasing evidence that Th2-high (type 2) inflammation may reduce the risk of SARS-CoV-2 infection and disease severity in contrast to increased risk in patients with Th2-low asthma

33

COVID-19 and Asthma



GRAPHICAL ABSTRACT

Asthma is not a risk factor for more severe COVID-19 disease. Allergic asthmatics are half as likely to be hospitalized compared with non-allergic asthmatics and lower levels of eosinophil counts (allergic biomarkers) are associated with a more severe COVID-19 disease trajectory. Recovery is similar among asthmatics and non-asthmatics.

Eggert LE, He Z, Collins W, et al. Asthma phenotypes, associated comorbidities, and long-term symptoms in COVID-19. *Allergy*. 2022 Jan;77(1):173-185.

34

COVID and Asthma



- Eosinopenia has been noted to be a marker of early severe COVID-19 disease ¹⁻²
 - Eosinophil exhaustion
 - Viral inhibition of eosinophil production
 - Induction of eosinophil apoptosis

1. Lindsley AW, Schwartz JT, Rothenberg ME. Eosinophil responses during COVID-19 infections and coronavirus vaccination. *J Allergy Clin Immunol.* 2020;146(1):1-7.
 2. Zhao L, Zhang Y, Yang X, Liu X. Eosinopenia is associated with greater severity in patients with coronavirus disease 2019. *Allergy.* 2021;76(2):562-564.

35

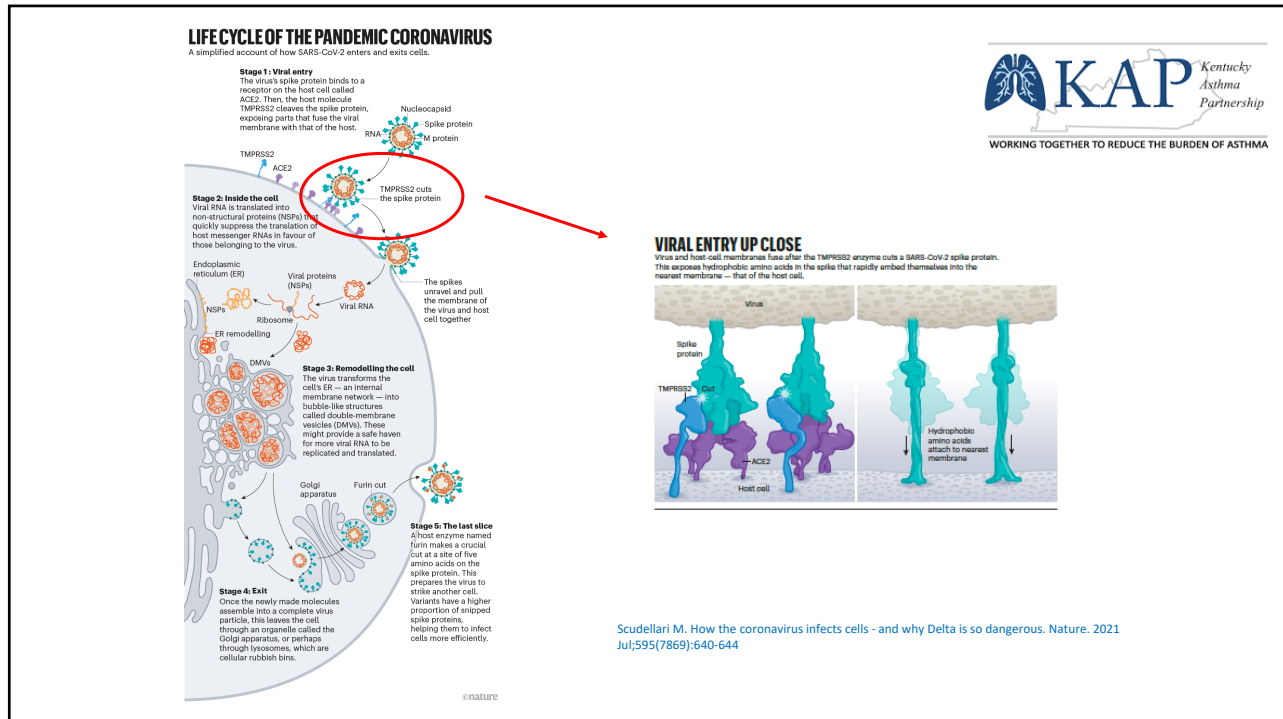
COVID-19 and Asthma



- SARS-CoV-2 utilizes the angiotensin-converting enzyme 2 (ACE2) receptor and a transmembrane serine protease (TMPRSS2) to enter host cells ^{1,2}
 - Both proteins are co-expressed in respiratory epithelia
- There is a gradient of ACE2 expression from the upper to lower airway, with higher levels expressed in the upper airway epithelium ³
 - corresponds to a greater susceptibility of upper airway cells to SARS-CoV-2 infection

1. M. Hoffmann et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 181, 271–280.e8 (2020).
 2. W. Sungnak et al.; HCA Lung Biological Network, SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat. Med.* 26, 681–687 (2020).
 3. Hou YJ, Okuda K, Edwards CE, Martinez DR, Asakura T, Dinnon KH III, et al. SARS-CoV-2 reverse genetics reveals a variable infection gradient in the respiratory tract. *Cell* 2020;182:429-46.e14

36



37

COVID-19 and Asthma

- Jackson et al showed downregulation of ACE2 expression in nasal and bronchial epithelial cells from patients with allergic sensitization and allergic asthma
 - Inverse association between the levels of aeroallergen sensitization and ACE2 expression in asthmatics
 - Those with the greatest levels of allergen sensitization had nearly 50% lower ACE2 expression compared with those with little or no allergen sensitization
 - Interestingly, allergen exposure was associated with further reductions in ACE2 expression in both the upper and lower airway

Jackson DJ, Busse WW, Bacharier LB, et al. Association of respiratory allergy, asthma and expression of the SARS-CoV-2 receptor, ACE2. J Allergy Clin Immunol. 2020;146(1):203-206.e3

38

COVID and Asthma

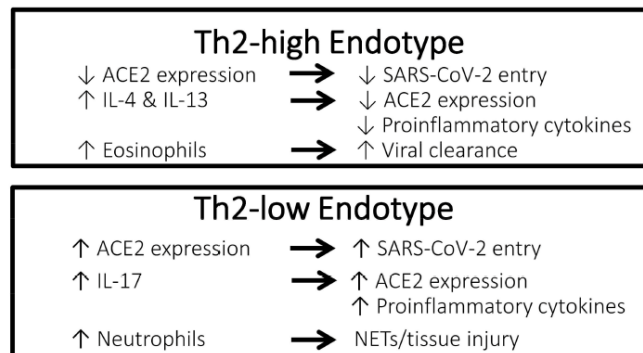


- Multiple type 2 biomarkers associate with lower ACE2 expression ¹⁻²
 - Appears to be driven by IL-13 inflammatory pathways (Th2-high)
- Additionally, treatment of airway epithelial cells with IL-13 significantly diminished viral shedding and cellular damage by affecting viral entry and replication ³
 - Appear to play an important role in the protective effects against SARS-CoV-2 infection

1. Sajuthi SP, DeFord P, Li Y, Jackson ND, Montgomery MT, Everman JL, et al. Type 2 and interferon inflammation regulate SARS-CoV-2 entry factor expression in the airway epithelium. *Nat Commun* 2020;11: 5139.
 2. Kimura H, Francisco D, Conway M, Martinez FD, Vercelli D, Polverino F, et al. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. *J Allergy Clin Immunol* 2020;146:80-88
 3. Morrison CB, Edwards CE, et al. SARS-CoV-2 infection of airway cells causes intense viral and cell shedding, two spreading mechanisms affected by IL-13. *PNAS* 2022; 119 (16);

39

COVID-19 and Asthma



Wang, C.-J.; Cheng, S.-L.; Kuo, S.-H. Asthma and COVID-19 Associations: Focus on IgE-Related Immune Pathology. *Life* 2022, 12, 153.

40

Summary



- Asthma does not appear to increase risk of SARS-CoV-2 infection
- Well-controlled asthma does not appear to increase risk of more severe COVID-19
- Poorly controlled and/or moderate-to-severe asthma (as evidenced by medication requirement and exacerbation history) may increase risk of more severe COVID-19
- Asthma phenotype may play a role in outcomes
 - Th2-high inflammatory pattern may be “protective”

41

COVID-19 and Asthma



- We still have a lot to learn

42