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References

1. 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.
2. Sunjaya AP, Allida SM, Di Tanna GL, Jenkins C. Asthma and risk of infection, hospitalisation, ICU admission and mortality from COVID-19: systematic review and meta-analysis. *J Asthma* [online ahead of print] 8 Feb 2021; DOI: 10.1080/02770903.2021.1888116.
3. Edwards MR, Strong K, Cameron A, Walton RP, Jackson DJ, Johnston SL. Viral infections in allergy and immunology: how allergic inflammation influences viral infections and illness. *J Allergy Clin Immunol* 2017;140:909–920.
4. 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, e8.
5. Peters MC, Sajuthi S, Deford P, Christenson S, Rios CL, Montgomery MT, *et al*. COVID-19-related genes in sputum cells in asthma. Relationship to demographic features and corticosteroids. *Am J Respir Crit Care Med* 2020;202:83–90.
6. Baraniuk C. Covid-19: people with mild asthma won't get early vaccination. *BMJ* 2021;372:n430.
7. Kenyon CC, Hill DA, Henrickson SE, Bryant-Stephens TC, Zorc JJ. Initial effects of the COVID-19 pandemic on pediatric asthma emergency department utilization. *J Allergy Clin Immunol Pract* 2020;8:2774–2776, e1.
8. Simoneau T, Greco KF, Hammond A, Nelson K, Gaffin JM. Impact of the COVID-19 pandemic on pediatric emergency department utilization for asthma. *Ann Am Thorac Soc* [online ahead of print] 4 Dec 2020; DOI: 10.1513/AnnalsATS.202007-765RL.
9. Olsen SJ, Azziz-Baumgartner E, Budd AP, Brammer L, Sullivan S, Pineda RF, *et al*. Decreased influenza activity during the COVID-19 pandemic-United States, Australia, Chile, and South Africa, 2020. *Am J Transplant* 2020;20:3681–3685.
10. Patel S, Thompson MD, Slaven JE, Sanders DB, Ren CL. Reduction of pulmonary exacerbations in young children with cystic fibrosis during the COVID-19 pandemic. *Pediatr Pulmonol* [online ahead of print] 12 Jan 2021; DOI: 10.1002/ppul.25250.
11. Sykes DL, Faruqi S, Holdsworth L, Crooks MG. Impact of COVID-19 on COPD and asthma admissions, and the pandemic from a patient's perspective. *ERJ Open Res* 2021;7:00822-2020.
12. McAuley H, Hadley K, Elneima O, Brightling CE, Evans RA, Steiner MC, *et al*. COPD in the time of COVID-19: an analysis of acute exacerbations and reported behavioural changes in patients with COPD. *ERJ Open Res* 2021;7:00718-2020.
13. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000;343:538–543.

A, B, and C Rhinoviruses: New Knowledge from an Impressive Consortium

A Step Forward for Rhinovirus Vaccine Efforts or a Step Back?

Rhinovirus (RV) infections cause asymptomatic infections, wheezing, and nonwheezing lower respiratory tract infections in young children (1) and the majority of acute attacks of asthma (2) and chronic obstructive pulmonary disease (3), resulting in substantial morbidity and deaths. There are 157 numbered RVs, which are divided into A, B, and C species based on sequence homology (4). One hundred RV-As and RV-Bs have been serotyped, and most do not crossneutralize (5). Studies with RV-Cs have been prevented by difficulties growing these viruses, but given the sequence divergence between A/B and C strains, it is unlikely the 51 numbered C strains will crossneutralize. The need for >150 strains in RV vaccines has hampered vaccine development. However, if certain RVs were more common causes of severe disease, could vaccine efforts be focused on these RVs to help move vaccine development forward?

RV-Bs are less likely to cause severe illness in children than RV-A or RV-C (1). However, data on RV-A/Cs and severe respiratory illnesses are not consistent, as studies in children have reported more RV-Cs than RV-As (6), whereas studies in adults reported more RV-As than RV-Cs (7).

In this issue of the *Journal*, Choi and colleagues (pp. 822–830) have made significant progress in understanding the importance of different RV species and strains in respiratory illnesses in children (8). They analyzed nasal and plasma samples from birth to age 18 in the COAST (Childhood Origins of ASThma) study, which studied 289 children from Madison, Wisconsin, at birth, 210 of whom were followed to age 18. They partially sequenced >8,000 RV-positive samples from asymptomatic and illness visits to compare RV-A and RV-C frequencies at ages 0–3, 4–8, 9–13, and 14–18 and found that RV-A and RV-C were similarly common at ages 0–3, but thereafter, RV-A was approximately twice as

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common as RV-C ($P < 0.001$). The authors hypothesized that this change in frequency might result from differences in neutralizing antibody (nAb) responses with age, as nAbs protect against reinfection with RVs. nAbs to RV-C had not previously been analyzed because infection of permissive cells with RV-Cs *in vitro* does not result in visible cytopathic effect (CPE), so there was no suitable system to assay infectivity and its neutralization by observing CPE.

The authors therefore developed a novel RV-C neutralization assay using RV-C2, RV-C15, and RV-C41, which were clinical isolates they had cloned and produced as live viruses by reverse genetics. These RV-Cs were preincubated with serial dilutions of plasma and inoculated onto HeLa-E8 cells, which are permissive to RV-C replication (9). Viral replication was measured by qPCR and inhibitory concentration 50% (IC_{50}) nAb titers calculated.

The same qPCR-based assay was used to measure IC_{50} nAb titers to RV-A16, which were then compared with standard neutralization titers against RV-A16, measured by CPE visualization using traditional methods to generate tissue culture infective dose 50% ($TCID_{50}$) titers. IC_{50} and $TCID_{50}$ nAb titers correlated very well ($r_s = 0.83$, $P = 0.006$), thus validating this novel and very useful tool for studying RV-Cs.

The authors then analyzed nAbs to RV-A7, RV-A16, RV-A36, and the three RV-Cs in plasma from 20 COAST study participants, measured at 2, 10, and 16 years. At age 2, only 5% of samples had nAbs to any of the three RV-As, whereas 27% had nAbs to the three RV-Cs. The corresponding figures for age 10 were 25% and 70%, and for age 16, they were 18% and 78% ($P < 0.001$ at each age). Thus, nAbs to these RV-Cs were much more common and much more durable to age 16 than nAbs to the three RV-As.

The low frequencies of nAbs against the RV-As may have been skewed by very low frequencies of titers against RV-A7 at all ages tested, as these were present in only 5% at ages 2 and 10 and 10% at age 16, suggesting this strain was possibly unrepresentative because it was clearly much less prevalent in the Wisconsin area during recruitment to COAST than RV-A16 and RV-A36, which each had titer frequencies of 35% at age 10. The frequency of 35% at age 10 for RV-A16 is consistent with the experience that ~50% of adults have detectable nAbs against RV-A16.

The low frequencies of nAbs against the RV-As may also have been skewed by unexpectedly low frequencies of titers against RV-A16 at age 16, as these were only 10%, considerably lower than at age 10 and against RV-A36 at age 16 (both 35%). Thus, more representative frequencies for RV-A strains would likely be ~35% at age 10 and ~35% or higher at age 16. Nonetheless, such figures are still considerably lower than those against the RV-Cs at the same ages (70% and 78%). The number of RVs tested was low (3 RV-As and 3 RV-Cs) and the number of samples was low (20 at each age). More data will be needed to confirm these findings and to extend them into greater numbers of RVs and children and into adulthood, but the authors' conclusions that RV-Cs become less common with age because of development of higher titers of durable nAbs is interesting and provides a logical explanation for the prevalence data in childhood and adulthood (6, 7).

A further interesting finding was the detection of 94% of known RV-As in the COAST study analysis, indicating there has been very little change in circulating RV-A strains over ~50–60 years (the RV-As were characterized and numbered in the late 1960s to early 1980s) (5). They also detected 98% of known RV-Cs, but this is less surprising, as the RV-Cs were characterized in the last 10–15 years and to a large degree in samples from the COAST study (10). Further analyses of RV-Cs in future years and in different study populations will be needed to inform on turnover of RV-C strains over time.

The authors then collected 17,664 samples from 14 cohorts studying children from birth to 18 years in the United States, Finland, and Australia; 10,185 samples were positive for RV, 6,643 from sick visits and 3,542 from asymptomatic visits, allowing for the investigation of frequencies in sickness and in health. There were slightly more positives during sick visits for RV-Cs (72.4%) than RV-As (66%), whereas only 37.8% of RV-Bs were at sick visits. Thus, at least in children, RV-Bs were strikingly less pathogenic than either A or C, and RV-Bs were detected more frequently on asymptomatic than on symptomatic visits.

The authors detected 178 RV types, identifying 21 more RV strains circulating than previously identified (157) (4). They also showed certain strains (RV-A12, 78, and 101 and RV-C02 and 11) were more commonly detected consistently over the 12-year time span of sample collection. However, the most frequently detected type (RV-A78) was only detected in 2.7% of samples, so no single RV strain accounted for more than a very small percentage of RV infections.

Consistent with the COAST findings, RV-Cs were more common than RV-As until 4–5 years old, but thereafter, RV-A infections became progressively more common, outnumbering RV-C by ~2:1 from age ~15.

Consistent with previous reports, RV-Cs were more likely associated with wheeze, and the CDHR3 rs6967330 asthma risk allele significantly increased the risk of RV-C illness, both relationships being independent of age.

I congratulate the authors for performing these extensive and detailed investigations and for significantly extending our understanding of RV species in childhood. I hope their work will stimulate further similar work in different age groups and with greater numbers of virus strains to increase our understanding even further.

The authors hope their work may assist vaccine development strategies for RV-C strains for use in early life. However, by *1*) showing that RV-A strains outnumber RV-C strains by 2:1 after age 15, and thus that RV-A vaccines are desperately needed in addition to RV-C vaccines, and *2*) identifying that 21 more RV strains than previously known were actively circulating (as were almost all the previously known strains), thus requiring any pan-RV vaccine to cover 178 strains rather than 157 strains, they may have made the job of actually developing effective RV vaccines that little bit harder! ■

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References

1. Lee WM, Lemanske RF Jr, Evans MD, Vang F, Pappas T, Gangnon R, *et al*. Human rhinovirus species and season of infection determine illness severity. *Am J Respir Crit Care Med* 2012;186:886–891.
2. Custovic A, Johnston SL, Pavord I, Gaga M, Fabbri L, Bel EH, *et al*. EAACI position statement on asthma exacerbations and severe asthma. *Allergy* 2013;68:1520–1531.
3. Seemungal T, Harper-Owen R, Bhowmik A, Moric I, Sanderson G, Message S, *et al*. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164: 1618–1623.
4. McIntyre CL, Knowles NJ, Simmonds P. Proposals for the classification of human rhinovirus species A, B and C into genotypically assigned types. *J Gen Virol* 2013;94:1791–1806.
5. Hamparian VV, Colonno RJ, Cooney MK, Dick EC, Gwaltney JM Jr, Hughes JH, *et al*. A collaborative report: rhinoviruses--extension of the numbering system from 89 to 100. *Virology* 1987;159: 191–192.
6. Erkkola R, Turunen R, Räisänen K, Waris M, Vuorinen T, Laine M, *et al*. Rhinovirus C is associated with severe wheezing and febrile respiratory illness in young children. *Pediatr Infect Dis J* 2020;39: 283–286.
7. Linster M, Donato C, Mah MG, Grau ML, Low JG, Ooi EE, *et al*. Genetic diversity of respiratory enteroviruses and rhinoviruses in febrile adults, Singapore, 2007-2013. *Influenza Other Respir Viruses* 2020;14:67–71.
8. Choi T, Devries M, Bacharier L, Busse W, Camargo CA Jr, Cohen R, *et al*.; program collaborators for Environmental influences on Child Health Outcomes. Enhanced neutralizing antibody responses to rhinovirus C and age-dependent patterns of infection. *Am J Respir Crit Care Med* 2021;203:822–830.
9. Bochkov YA, Watters K, Ashraf S, Griggs TF, Devries MK, Jackson DJ, *et al*. Cadherin-related family member 3, a childhood asthma susceptibility gene product, mediates rhinovirus C binding and replication. *Proc Natl Acad Sci USA* 2015;112:5485–5490.
10. Lee WM, Kiesner C, Pappas T, Lee I, Grindle K, Jartti T, *et al*. A diverse group of previously unrecognized human rhinoviruses are common causes of respiratory illnesses in infants. *PLoS One* 2007;2:e966.

A Potential New Treatment Option for Asthma in the Setting of Obesity or Insulin Resistance?

The epidemic of obesity now affects ∼42% of U.S. adults, whereas metabolic syndrome affects approximately 37% of adults in the country, including over 60% of obese individuals (1–3). Both disorders can contribute to increased asthma risk and morbidity (4, 5). "Obesity-related asthma," a heterogeneous asthma phenotype, results from various contributing factors and mechanisms, such as insulin resistance and metabolic dysregulation (6). Although there is ongoing research and debate on whether obesity leads to asthma or vice versa (or whether both result from a shared, earlier causal process), the pressing reality is that many obese patients with asthma have a more severe disease that does not fully respond to the usual treatments. Weight loss—whether medically or surgically induced—can lead to improved asthma outcomes, especially if metabolic dysregulation resolves (7, 8). However, weight loss is difficult to achieve and even more challenging to sustain, and therefore identifying better therapeutic options for patients with obese asthma constitutes a critical research need.

In this issue of the *Journal*, Foer and colleagues (pp. 831–840) tackle this need by evaluating the association between glucagon-like peptide-1 receptor agonists (GLP1-RAs) and asthma outcomes (9). Using data from 4,373 patients with type 2 diabetes (T2D) and asthma, they compared asthma exacerbation rates between patients starting GLP1-RAs and those initiating other medications as part of T2D treatment escalation. After adjusting for propensity scores and other covariates, they report that patients starting GLP1-RA therapy have lower asthma exacerbation rates than those initiating sulfonylureas, insulin, SGLT2 inhibitors, or DPP4 inhibitors over a 6-month period. The findings were robust to adjustment for changes in body mass index and HbA1c, suggesting the associations are independent of improvements in weight or glycemic control. Even more importantly, the estimated effect sizes were larger when the analysis was restricted to patients with moderate and severe asthma, and the associations remained significant despite the fact that the sample was markedly smaller. They also report that GLP1-RAs are associated with fewer healthcare encounters for asthma symptoms, although those findings were somewhat less robust in the sensitivity analyses. The study has several important strengths, including the use of detailed clinical data extracted from the electronic record database of a large academic healthcare organization, which allowed the authors to adjust for important covariates at different time points. The large database allowed for the exclusion of numerous comorbidities and conditions that may confound or mimic the diagnosis of asthma, and the authors also took care in adjusting for a propensity score calculated based on the probability of initiating GLP1-RA versus other T2D medications.

The report builds on existing preclinical evidence of a potential role of GLP1 signaling in asthma. GLP1 receptors are expressed in airway epithelium and airway smooth muscle. In murine models of asthma, liraglutide reduces IL-33 release and mucus secretion in response to allergen challenges as well IL-4 and IL-13 production by group 2 innate lymphoid cells (10). In *ex vivo* human airways, GLP1 receptor activation modulates airway hyperreactivity (AHR), and treatment with GLP1-RA exendin-4 prevents AHR in response to both histamine and high glucose concentrations (11). GLP1-RAs

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