COMMENTARY

COVID-19 and Children With Diabetes—Updates, Unknowns, and Next Steps: First, Do No Extrapolation

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The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide pandemic has been devastating particularly for older adults and those from vulnerable groups, including racial and ethnic minority populations. Additionally, people with certain underlying medical conditions, including diabetes, are also at increased risk of severe illness from coronavirus disease 2019 (COVID-19) (1,2). Some children experience significant disease (3), and pediatric deaths have been reported (4). Because "diabetes" (generally grouping together type 1 diabetes and type 2 diabetes) and chronically elevated hyperglycemia have been associated with worse outcomes in adults with COVID-19 (5), the pediatric community has voiced great concerns about risk and outcomes for children with diabetes.

A foundation of pediatrics is caution about the extrapolation of adult practice to children. Many publications report poor outcomes from COVID-19 and diabetes without emphasizing that data reported are from adults, frequently older adults with additional comorbidities. Moreover, there have been warnings related to COVID-19 and immunosuppression leading to confusion, predominately outside the medical community, about the difference between immunocompromised and autoimmune. In sum, these worries have led to increases in frequency and severity of diabetic ketoacidosis (DKA), due in part to families being reluctant to enter health care settings, especially in areas where COVID-19 cases cluster (6,7).

Data scarcity regarding many aspects of how COVID-19 is affecting children with both new-onset and established diabetes has magnified these concerns. In this issue of *Diabetes Care*, Rabbone et al. (8) describe cross-sectional data from Italy, an early pandemic epicenter. This team examined diabetes diagnoses as well as reports of DKA and SARS-CoV-2 infection in children with new-onset and established type 1 diabetes from 20 February to 14 April 2020. They compare data on new presentations and DKA rates to data from the same period in 2019. They report 23% fewer new-onset cases during this time, with more children with new-onset disease presenting in DKA; they speculate that the observed decrease may be due to fear of presentation to health care facilities, implying that observed rates might rebound in a subsequent observation period. They also note that differences in exposure to other seasonal viruses associated with precipitating type 1 diabetes might have affected presentation rates.

Two additional reports in this issue also address whether SARS-CoV-2 infection affected new pediatric type 1 diabetes diagnosis rates (9,10). Interestingly, one posits an increase and the other documents no change. Unsworth et al. (9) report data from five U.K. regional inpatient units collected from late March to early June 2020. One of the five units reported an increase from two to ten cases, and a second reported an increase from four to ten cases; the other three units reported no change. Like Rabbone's report, many of the newly diagnosed children had severe DKA. The U.K. group states that these data point to an increase in incidence of pediatric type 1 diabetes of up to 80%. However, the report does not provide information on the total denominator of unit or hospital admissions, typical variability in case numbers, whether this increase is statistically significant over time, or how many newly diagnosed children regionally are typically treated at these hospitals versus other area facilities. The authors then theorize

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that a higher type 1 diabetes incidence could be related to SARS-CoV-2 infection of the pancreas and cite data showing angiotensin converting enzyme 2 (ACE2) receptor expression in β-cells from a 2010 article by Yang et al. (11). However, this assertion is based on immunofluorescence analysis of a single organ donor with limited methodologic details provided regarding reagent validation or even antibody source. Thus, at present, the presence and the level of ACE2 expression in β-cells remains controversial. Moreover, analysis of pancreata from individuals infected with SARS-CoV-2 is not available to support the notion of direct β-cell infection Additionally, rapid viral-mediated increases in incidence are not very plausible, as fulminant autoimmune-mediated diabetes does not acutely present after infection. Rather, exposures to viruses that may trigger type 1 diabetes generally predate clinical onsets by months to years (12). The higher incidence rates observed in two regional inpatient units are more likely due to other factors.

In contrast, Tittel et al. (10) examined country-wide electronic medical record data from the Diabetes-Prospective Follow-up registry (DPV). Based on population-level data from 216 of 217 DPV clinics, the rate of new-onset pediatric type 1 diabetes observed across Germany from mid-March to mid-May 2020 did not differ significantly from predicted rates based on data collected over the last decade. Taken in sum, these three articles do not provide compelling evidence that the pandemic is leading to dramatic short-term adverse changes in incidence of pediatric type 1 diabetes. Changes in viral exposure, including novel exposures to SARS-CoV-2 and fewer exposures to normally prevalent pediatric communicable diseases due to public health mitigation measures, could potentially shift future incidence rates and observed diabetes endotypes.

These articles also provide reassuring information regarding acute COVID-19 morbidity. Rabbone et al. reported on eight children with PCR-confirmed SARS-CoV-2, all of whom had mild disease or were asymptomatic, although they did not provide a population estimate of infection in children with type 1 diabetes or how this compares to peers without diabetes. Unsworth et al. included five children with evidence of current or prior SARS-CoV-2 infection by PCR or antibody testing; none had long-term adverse COVID-19–related outcomes.

Overall, the accumulating evidence suggests that children with type 1 diabetes infected with SARS-CoV-2 will have similar disease outcomes as peers without diabetes. In particular, the article by Rabbone et al. reflects observations using longitudinal, prospectively collected data from a country that was an early pandemic epicenter, with coordinated national health and insurance programs and a high underlying type 1 diabetes population prevalence. Additionally, the physicians reporting the data were embedded early in the health care provider response to COVID-19. Since their findings reflect only one country's experience during a snapshot in time, the data need to be placed in context with other emerging reports.

Routine surveillance data collection made these articles possible. As we are seeing more documented pediatric SARS-CoV-2 infections (4), providers need to ensure that the documentation of patient-level data in electronic health records continues for our children with diabetes as we monitor for both acute and longer-term disease-related morbidities. Such efforts are underway in Germany and Austria through the DPV and in the U.S. through the T1D Exchange (13).

It is important to remember that these articles only report data from children with type 1 diabetes. Given that obesity and hypertension are associated strongly with type 2 diabetes in youth and these comorbidities have been associated with more severe COVID-19 cases (14), children with type 2 diabetes may be at higher risk. Country-wide surveillance and reporting systems need to be implemented for children with type 2 diabetes.

The COVID-19 pandemic and related changes in daily life are complicating the already complex demands of blood glucose management for youth with diabetes. Countries have instituted aggressive public health measures, implementing widespread closures and other dramatic structural school, day care, and camp changes (15,16). Despite these changes, there have been reports of rapid and widespread disease dissemination in settings where children cluster with even asymptomatic children spreading the virus to other children as well as to adults (17,18).

As we write, parents and children are making difficult decisions about returning to school. These decisions impact the safety of not only children with diabetes but also those who live with them. It is critical that we work together to make sure that our children are safe at school (19). This includes following Centers for Disease Control and Prevention and other guidelines on the appropriateness of regional school reopenings, appropriate classroom distancing, use of face coverings, and cleaning procedures. Each decision about returning to school needs to be contextualized and individualized. For many children with diabetes, schools are a public health lifeline for diabetes care, daily health surveillance, and adequate nutrition.

The pandemic has had a great emotional impact. As Tittel et al. point out, stress may influence rates of new-onset disease by changing the risk of developing autoimmunity (20). Additionally, for persons with established disease, mental health symptoms coupled with decreased physical activity, dietary changes leading to poorer nutrition and weight gain, and sleep disruptions (21–23) may alter diabetes management behaviors and promote diabetes conflict. Moreover, individuals with higher levels of worry about COVID-19 and diabetes may be more vulnerable for diabetes distress, acute and chronic hyperglycemia, and the onset or exacerbation of depression and anxiety (24).

Children with diabetes are also reliant on expensive medications (including insulin), glucose monitoring, and insulin delivery technologies. The pandemic has caused some supply chain disruptions, including a shortage of metformin, and exacerbated insurance and copay concerns for many, which may increase existing disparities in diabetes care for youth (25). We need to continue to encourage and increase national pediatric access to continuous glucose monitoring systems to facilitate glycemic monitoring and data sharing with care teams and remote monitoring by school staff and other caregivers.

Since March 2020, there has been an increase in diabetes health care visits conducted via telemedicine. Although providers have had successes, there have also been difficulties collecting sufficient data for effective assessments to facilitate insulin adjustments and behavioral advice. Lack of internet and

Table 1—Pediatric diabetes during COVID-19

Needs	Recommendations
• Prospectively collected, longitudinal, retrievable public data on new-onset incidence trends, new-onset patient characteristics, and acute and long-term disease outcomes	• Collect data for children with type 1 AND type 2 diabetes following established guidelines for epidemiologic data collections and support rigorous peer review (30) • Examine effects of obesity and prediabetes • Improve data collection for racial and ethnic minority populations
• Thoughtful interpretations of emerging data reports, including thorough peer review	• Contextualize data to inform childcare decisions, including return to school and extracurricular activities • Provide a clear and unified voice for pediatric-specific diabetes concerns at the level of national and international organizations and public health messaging
• Multidisciplinary care and support including mental health and social work access	• Offer guidelines on care delivery using remote technology, including optimal clinic flow and staffing models • Provide durable insurance coverage
• Infrastructure access, including needed hardware, internet services, and data platforms for school and telemedicine	• Support virtual school education platforms and alternate ways to provide students with medical and mental health care, and nutrition services • Advocate for telemedicine platforms that are accessible by all, including communities of lower socioeconomic status
• Robust pediatric diabetes research funding	• Support diabetes federal funding (including Special Diabetes Program durable renewal) • Galvanize the volunteer diabetes advocacy and fundraising community

hardware access, particularly for children living in lower socioeconomic settings and non-English speakers, has also hampered access to multidisciplinary diabetes care.

While we await more high-quality data, clinical providers need to consider how often children with diabetes need to be seen in person and what can be accomplished virtually. Although some children may do better under lockdown due to more time to focus on self-management (26), others will require additional touchpoints. These may be especially critical for children at risk for or experiencing the economic consequences of COVID-19 including evictions and homelessness. Providers should accommodate and engage patients with limited technology and internet access. Hospital systems should prioritize telehealth for conditions such as diabetes. Payors also need to offer clearly durable telemedicine coverage that includes adequate payment structures given that virtual visits for children with diabetes, to be done properly, require multidisciplinary interactions, intensive office staff support, and the ability to obtain glycemic data and laboratory results remotely. It will also be critical that our children with diabetes continue to receive holistic care and remain current on immunizations, particularly influenza.

We are in a place where the only certainty is continued uncertainty about the course of this pandemic. We thank our international pediatric diabetes colleagues and hope their work spurs others to collaborate internationally to gather more evidence (27). We call on our community to articulate needs and refine recommended actions (Table 1). As federal diabetes funding is uncertain and many not-for-profit organizations, including the American Diabetes Association and JDRF, announce cuts in funding opportunities and staffing, we must galvanize the pediatric diabetes volunteer community (28,29) to join our efforts. We must continue to be humble and patient about what we know and advocate strenuously for coordinated, expanded, and responsive public health systems to support youth with both type 1 and type 2 diabetes.

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References

1. Cariou B, Hadjadj S, Wargny M, et al.; CORONADO investigators. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;63:1500–1515
2. Palermo NE, Sadhu AR, McDonnell ME. Diabetic ketoacidosis in COVID-19: unique concerns and considerations. J Clin Endocrinol Metab 2020;105:105
3. Feldstein LR, Rose EB, Horwitz SM, et al.; Overcoming COVID-19 Investigators and the CDC COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383:334–346
4. Children's Hospital Association, American Academy of Pediatrics. Children and COVID-19: state data report. Accessed 1 September 2020. Available from https://downloads.aap.org/AAP/PDF/AAP%20and%20CHA%20-%20Children%20and%20COVID-19%20State%20Data%20Report%208.6.20%20FINAL.pdf
5. Bode B, Garrett V, Messler J, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol 2020;14:813–821
6. Cherubini V, Gohil A, Addala A, et al. Unintended consequences of coronavirus disease-2019: remember general pediatrics. J Pediatr 2020;223:197–198
7. Kamrath C, Mönkemöller K, Biester T, et al. Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. JAMA 2020;324:801–804
8. Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A; Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes. Has COVID-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? Diabetes Care 2020;43: XXXX–XXXX
9. Unsworth R, Wallace S, Oliver NS, et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the U.K. Diabetes Care 2020;43: XXXX–XXXX
10. Tittel SR, Rosenbauer J, Kamrath C, et al.; DPV Initiative. Did the COVID-19 lockdown affect the incidence of pediatric type 1 diabetes in Germany? Diabetes Care 2020;43: XXXX–XXXX
11. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and

causes acute diabetes. Acta Diabetol 2010;47:193–199
12. Filippi CM, von Herrath MG. Viral trigger for type 1 diabetes: pros and cons. Diabetes 2008;57:2863–2871
13. Ebekozien OA, Noor N, Gallagher MP, Alonso GT. Type 1 diabetes and COVID-19: preliminary findings from a multicenter surveillance study in the U.S. Diabetes Care 2020;43:e83–e85
14. Nogueira-de-Almeida CA, Del Ciampo LA, Ferraz IS, Del Ciampo IRL, Contini AA, Ued FDV. COVID-19 and obesity in childhood and adolescence: a clinical review. J Pediatr (Rio J). 4 August 2020 [Epub ahead of print]. DOI: 10.1016/j.jped.2020.07.001
15. Esposito S, Principi N. School closure during the coronavirus disease 2019 (COVID-19) pandemic: an effective intervention at the global level? JAMA Pediat). 13 May 2020 [Epub ahead of print]. DOI: 10.1001/jamapediatrics.2020.1892
16. Centers for Disease Control and Prevention. Information for pediatric healthcare providers. Accessed 1 September 2020. Available from https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html
17. Stein-Zamir C, Abramson N, Shoob H, et al. A large COVID-19 outbreak in a high school 10 days after schools' reopening, Israel, May 2020. Euro Surveill 2020;25:2001352
18. Centers for Disease Control and Prevention. SARS-CoV-2 transmission and infection amoung attendees of an overnight camp - Georgia, June 2020. Accessed 17 August 2020. Available from https://www.cdc.gov/mmwr/volumes/69/wr/mm6931e1.htm
19. American Diabetes Association. Safe at school COVID-19 resources and information. Accessed 1 September 2020. Available from https://www.diabetes.org/resources/know-your-rights/safe-at-school-state-laws/safe-school-coronavirus-resources
20. Stojanovich L. Stress and autoimmunity. Autoimmun Rev 2010;9:A271–A276
21. Brazendale K, Beets MW, Weaver RG, et al. Understanding differences between summer vs. school obesogenic behaviors of children: the structured days hypothesis. Int J Behav Nutr Phys Act 2017;14:100
22. Loades ME, Chatburn E, Higson-Sweeney N, et al. Rapid systematic review: the impact of social isolation and loneliness on the mental health of children and adolescents in the context of COVID-19. J Am Acad Child Adolesc Psychiatry. 3 June 2020 [Epub ahead of print]. DOI: 10.1016/j.jaac.2020.05.009
23. Zhou S-J, Wang L-L, Yang R, et al. Sleep problems among Chinese adolescents and young adults during the coronavirus-2019 pandemic. Sleep Med 2020;74:39–47
24. Joensen LE, Madsen KP, Holm L, et al. Diabetes and COVID-19: psychosocial consequences of the COVID-19 pandemic in people with diabetes in Denmark-what characterizes people with high levels of COVID-19-related worries? Diabet Med 2020;37:1146–1154
25. Addala A, Auzanneau M, Miller K, et al. A decade of disparities in diabetes technology use and HbA_{1c} in pediatric type 1 diabetes: a transatlantic comparison. Diabetes Care. In press
26. Fernández E, Cortazar A, Bellido V. Impact of COVID-19 lockdown on glycemic control in patients with type 1 diabetes. Diabetes Res Clin Pract 2020;166:108348
27. International Society of Pediatric and Adolescent Diabetes (ISPAD). Summary of recommendations regarding COVID-19 in children with diabetes: keep calm and mind your diabetes care and public health advice. Pediatr Diabetes 2020;21:413–414
28. American Diabetes Association. Pathway to Stop Diabetes. Accessed 17 August 2020. Available from https://professional.diabetes.org/meetings/pathway-stop-diabetes%C2%AE
29. JDRF. Accelerating mission and becoming more volunteer powered. Accessed 17 August 2020. Available from https://www.jdrf.org/blog/2020/07/29/jdrf-accelerating-mission-and-becoming-more-volunteer-powered/
30. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Epidemiology 2007;18:800–804