**COVID-19 Literature Review Newsletter Volume #45**

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**In the News:**

1. **AstraZeneca COVID-19 vaccine study paused after illness. Published September 8th, 2020**  
   [https://apnews.com/4239b8c69ba4b3703b2ca8c77810bf07](https://apnews.com/4239b8c69ba4b3703b2ca8c77810bf07)  
   a. Pause initiated from a standard review process of the vaccine phase II/III clinical trial in order to examine safety data by an independent committee after one person developed unexplained illness  
   b. AZD1222 is a chimpanzee adenovirus-vector vaccine  
   c. AstraZeneca/University of Oxford vaccine statement:

**Statement from AstraZeneca provided to STAT on Tuesday afternoon:**

As part of the ongoing randomized, controlled global trials of the Oxford coronavirus vaccine, our standard review process triggered a pause to vaccination to allow review of safety data. This is a routine action which has to happen whenever there is a potentially unexplained illness in one of the trials, while it is investigated, ensuring we maintain the integrity of the trials. In large trials illnesses will happen by chance but must be independently reviewed to check this carefully. We are working to expedite the review of the single event to minimize any potential impact on the trial timeline. We are committed to the safety of our participants and the highest standards of conduct in our trials.

**Articles:**

   [https://doi.org/10.1093/ajcp/aqaa156](https://doi.org/10.1093/ajcp/aqaa156)
Background:
- Data on underlying pulmonary pathology from COVID-19 has been limited to case reports and small case series
- Most commonly described pathology in COVID-19:
  - Acute lung injury (ALI) with hyaline membranes consistent with diffuse alveolar damage (DAD), which corresponds clinically to acute respiratory distress syndrome (ARDS)
  - Some cases reported an absence of DAD but w/had organizing PNA, chronic inflammation, congestion, and bronchopneumonia
  - Fibrin deposition and microthrombi have also been described (usually with DAD)
- This study was conducted in an academic center in NYC as an autopsy series to describe pulmonary pathology seen in decedents with confirmed severe SARS-CoV-2
  - SARS-CoV-2 confirmed by RT-PCR and correlated with imaging, clinical, and lab data

Methods:
- Autopsies performed using the Virchow technique and followed recommendations from the CDC
- Macroscopic examination of serial sections of lungs was performed
  - Samples were taken from grossly or radiographically abnormal regions
  - In the absence of abnormalities, at least one section from each lobe was collected
- Microscopic analyses were also performed
  - Frst - microscopic patterns were first categorized as “major” or “minor”
    - Major = pathologic pattern presents in ≥50% of tissue slide + present in more than one slide + encompass ≥5% of area of all slides (excluding intravascular fibrin or platelet-rich aggregates (IFPAs)) + IFPAs had to be present in at least one slide of the case
    - IFPAs = thrombi vs emboli; designated by location, quantity, size
  - Minor = pathologic pattern presents in <50% of tissue
  - Second - “novel” pathologic findings were defined as deviations from ALI (the main pathology pattern expected in COVID-19)
  - Third – “discordant” was defined as incongruity of microscopic patterns with radiographic findings
- All H&E-stained lung sections were reviewed; when available, immunohistochemical or histochemical stains were reviewed
- Imaging: all chest radiographs and CT reviewed by thoracic radiologist
  - First and last reviewed if multiple available
  - Alveolar opacities graded 0-3
  - 0=no alveolar opacities; 1=minimal <1/3 lungs involved; 2=moderate 1/3-2/3 lungs involved; 3=marked >2/3 lungs involved
- Controls – H&E slides from prepandemic, non-COVID-19 postmortem exams with ALI (n=7) and non-ALI (n=7)

Results:
- 40 sequential lung specimens from postmortem exams of patients with COVID-19 were evaluated
  - All had nasopharyngeal swabs confirming SARS-CoV-2 infection
  - Premortem, n=32; Postmortem, n=8
- The majority of patients were elderly (71.5 years) males (70%) and Hispanic/Latino (57.5%)
- More than half of patients required mechanical ventilation and 85% had HTN
- Mean time from admission to death 10.4 days (range: 0-45 days)
Major pulmonary findings: ALI (73%), IFPAs (90%), vascular congestion and hemangiomatosis-like changes (VCHL) (50%)

Eleven (27.5%) of cases did not show ALI and were categorized as “novel.”

- Suggests 2 broad phenotypic patterns of pulmonary pathology
- 96% of pts with ALI had alveolar infiltrates in imaging and disease progression in more than half (59%)
- For non-ALI group, 83% lacked alveolar infiltrates on imaging, none had evidence of disease progression on CXR
- There was significant negative correlation between ALI & pulmonary VCHL (r = –0.62; adjusted 95% CI, –0.87 to –0.11; P = .005)
- No statistically significant correlation between ALI and IFPAs
- All non-ALI cases had VCHL & IFPA
- Cause of death (COD) in non-ALI phenotype included cardiac arrest, cardiorespiratory arrest, or vascular causes

Conclusion:

- Two distinct pulmonary phenotypic patterns (ALI and non-ALI) were noted, and COD in non-ALI cases are likely COVID-19 related but needs further study
- This is a small autopsy series and may not be externally valid


Background:
Data on new-onset type 1 diabetes during the coronavirus disease 2019 (COVID-19) pandemic, particularly in children, is limited. The angiotensin converting enzyme 2 (ACE2) receptor is the binding site for SARS-CoV-1 and -2 and is strongly expressed in pancreatic endocrine cells. Previous evidence suggests that SARS-CoV-1 virus may have entered pancreatic islet cells via the ACE2 receptor leading to b-cell damage and new-onset, mainly transient diabetes.

**Methods:**
- The authors report multicenter regional data from North West London (NWL) of new onset type 1 diabetes and diabetic ketoacidosis (DKA) in children up to the age of 16 years during the peak of the COVID19 pandemic. The investigators collected data from five inpatient units (four National Health Service [NHS] Trusts) comprising the NWL Pediatric Diabetes Network between 23 March (coinciding with the commencement of the U.K. Government lockdown) and 4 June.

**Results:**
- Thirty children aged 23 months to 16.8 years presented with new-onset type 1 diabetes (Table 1). The authors observed an apparent increase in two units, with 10 cases each (versus typically 2 and 4 cases, respectively, for April/May combined in the previous 5 years). Rates in the other three units were similar to previous years. Only three children with known type 1 diabetes presented with DKA during the same time period. In comparison with a typical year, the authors estimate this represents an additional 12–15 new type 1 diabetes cases (80% increase) during the COVID-19 pandemic, with apparent clusters of cases observed in two units.
- A high proportion of children (21/30, 70%) presented with DKA, with severe DKA (pH range 6.82–7.05) in over half (11/21, 52%). Twelve children presented with clinical shock and four were managed in pediatric intensive care. Two children presented with reduced conscious level, one received hyperosmolar therapy, and both recovered without complications.
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR was performed from nasopharyngeal swabs in 21 children meeting local testing criteria; two tested positive. SARS-CoV-2 serum IgG antibody was tested in a subgroup of children attending one of two units; 3 of 16 children (19%) tested positive. Of the five children with positive results, three presented with severe DKA and refractory hypokalemia, and one child with positive SARS-CoV-2 PCR suffered a hypokalemia-related cardiac arrest but recovered fully following 1 day of ventilation. SARS-CoV-2 also affects the renin angiotensin-aldosterone system through reduced ACE2 expression, leading to decreased degradation of angiotensin II and increased secretion of aldosterone and renal potassium loss. Although hypokalemia is not uncommon during treatment of DKA, particularly in cases of renal impairment, it is possible that reduction in ACE2 expression may have contributed in the reported cases.
Conclusion:

- This is the first report to describe an apparent increase in new-onset type 1 diabetes in children during the COVID-19 pandemic, with evidence of SARS-CoV-2 infection or exposure in a proportion of those tested.

- Limitation: testing was not universal across NWL, and 14 children did not have SARS-CoV-2 IgG testing. This limited the ability to identify possible cases, particularly in children with recent suspected symptoms or known COVID-19 contacts. In addition, SARS-CoV-2 serology was tested soon after diagnosis and did not report IgM, and as antibody responses may not develop until 14–21 days post infection, further cases may have been missed. While their data does not prove a link, they postulate that SARS-CoV-2 exposure contributed to the observed increase in cases by precipitating or accelerating type 1 diabetes onset. Further studies are required to establish a definitive link and any possible impact on the severity of type 1 diabetes presentation, including severe hypokalemia.

### Table 1—Children presenting with new-onset type 1 diabetes or with DKA and known type 1 diabetes

<table>
<thead>
<tr>
<th></th>
<th>New onset type 1 diabetes (n = 30)</th>
<th>SARS-CoV-2 not tested/negative* (n = 25)</th>
<th>SARS-CoV-2 PCR or IgG positive (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not in DKA (n = 8, 32%)</td>
<td>DKA (n = 17, 68%)</td>
<td>Not in DKA (n = 1, 20%)†</td>
</tr>
<tr>
<td>Median age (IQR), year</td>
<td>10.9 (6.8)</td>
<td>12.0 (6.0)</td>
<td>10.3 (6.2)</td>
</tr>
<tr>
<td>Male</td>
<td>22 (68)</td>
<td>6 (75)</td>
<td>11 (65)</td>
</tr>
<tr>
<td>Median weight for age z score (IQR)</td>
<td>0.12 (1.44)</td>
<td>0.90 (2.09)</td>
<td>0.04 (1.62)</td>
</tr>
</tbody>
</table>

**Ethnicity**

- White European: 12 (36) Not in DKA (n = 3), DKA (n = 7) 4 (12) Not in DKA (n = 1), DKA (n = 1) 2 (50) 0 (0)
- Black African: 8 (24) Not in DKA (n = 2), DKA (n = 6) 4 (24) 0 (0) 1 (25) 1 (33)
- Arab: 6 (18) Not in DKA (n = 1), DKA (n = 5) 3 (18) 1 (100) 1 (25) 0 (0)
- Asian: 3 (9) Not in DKA (n = 1), DKA (n = 2) 2 (12) 0 (0) 0 (0) 0 (0)
- Other: 4 (12) Not in DKA (n = 1), DKA (n = 3) 1 (6) 0 (0) 0 (0) 2 (67)

**Family history of type 1 diabetes**

- 11 (33) Not in DKA (n = 6), DKA (n = 5) 4 (24) 1 (100) 0 (0) 0 (0)

**Comorbidities**

- 2 (6) Not in DKA (n = 1), DKA (n = 1) 1 (6) 0 (0) 0 (0) 0 (0)

**Median duration of symptoms (IQR), days**

- 7 (10) Not in DKA (n = 14), DKA (n = 7) 4 (24) 1 (100) 0 (0) 0 (0)

**Median plasma glucose on presentation (IQR), mg/dL**

- 432 (200) 354 (155) 465 (177) 475 484 (135) 427 (87)

**HbA1c, median, % (mmol/mol)**

- 11.6 (103) 11.2 (99) 11.6 (103) 11.3 (100) 12.5 (113) 10.0 (88)

**Median pH on presentation (IQR)**

- 7.19 (0.28) 7.37 (0.06) 7.14 (0.29) 7.42 6.90 (0.08) 7.24 (0.11)

**Severe DKA (pH <7.1)**

- 12 (36) — 8 (47) — 3 (75) 1 (33)

**Median plasma lactate on presentation (IQR), mmol/L**

- 1.9 (2.5) 1.0 (0.04) 2.1 (2.3) 1.5 4.6 (0.8) 1.3

Data are n (%) unless otherwise indicated. IQR, interquartile range. *Eight children had no testing, six had SARS-CoV-2 PCR testing only, two had SARS-CoV-2 IgG testing only, nine had both SARS-CoV-2 PCR and IgG. †Positive for SARS-CoV-2 IgG. ‡Two positive for SARS-CoV-2 PCR and two positive for SARS-CoV-2 IgG. §One child had no testing, two children had negative SARS-CoV-2 PCR testing only.