COVID CORNER
Ongoing COVID-19 updates brought to you by
The Office of CME&PD and The Physician Learning Program

UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE
Continuing Medical Education and Professional Development

Physician Learning Program

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Disclosure
Any direct financial payments, gifts, in-kind compensation or honoraria
• Employee, University of Calgary

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Disclosure of Financial Support

• The program was developed and planned to achieve scientific integrity, objectivity and balance

• This program has received educational grants from the College of Physicians and Surgeons of Alberta and Alberta Health Services

From your nose to your toes: Atypical presentations of COVID-19

• Loss of smell and taste
• Gastrointestinal symptoms
• Liver test abnormalities
• Does COVID cause strokes?
• Cardiac manifestations
• Dermatologic presentations
• What are COVID toes?
• Multi-System Inflammatory Syndrome in Children

COVID CORNER
Wednesday, May 27th, 1900-2100

https://cumming.ucalgary.ca/cme/COVID-19-Resources/COVID-Corner

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Lessons Learned from the Bonspiel Outbreak

Kelly Burak MD MSc FRCPC
Professor and Associate Dean, Continuing Medical Education and Professional Development, Cumming School of Medicine, University of Calgary

Disclosure
- Employee, University of Calgary
Curling is an ancient game that originated in Scotland. What percentage of the world’s curlers are Canadian?

1) 10%
2) 25%
3) 50%
4) 75%
5) 90%

SARS-CoV2 virus outbreak amongst physicians at a curling bonspiel in Canada

Kelly W. Burak, Sampson Law, Chris M. Rice, Jia Hu, Christopher I. Fung, Allan K.H. Woo, Bonnie L. Meatherall
From your nose to your toes: Atypical presentations of COVID-19

FIGURE 1. Number of bonspiel participants with confirmed COVID-19 (swab positive), presumptive COVID-19 (swab negative or not done), other non-specific symptoms (swab negative), or no symptoms.

- 10 reported symptoms during event
- Cases more likely to have attended buffet lunches (98.0% vs 77.3%; p=0.003)
FIGURE 2. Frequency of symptoms amongst confirmed and presumptive COVID-19 cases.

**Confirmed cases**
- 80% cough
- 50% fever
- 40% SOB
- 20% never had any of the above

**Anosmia (n=28)**
- 75% with dysgeusia
- Only symptom in one

**GI symptoms**
- 71% cases

FIGURE 3. The median onset of common symptoms amongst confirmed and presumptive COVID-19 cases.

**Median onset to symptoms**
- 6 days (IQR 4.5-8)

Note: Dysgeusia (altered taste) (n=20) includes 18 with aguesia (loss of taste).
Lessons learned from the bonspiel outbreak

- SARS-CoV2 is highly infectious (77% attack rate)
- RT-PCR tests from upper respiratory tract lack sensitivity (71%)
- Atypical symptoms (anosmia, gastrointestinal) are common and should be included in COVID-19 case definitions
- Majority of cases were mild (1 ER visit, no hospitalizations)

Does SARS-CoV2 cause stroke?

Michael Hill MD FRCPC
Professor University of Calgary, Director, Stroke Unit; Department of Clinical Neurosciences, Hotchkiss Brain Institute, O’Brien Institute for Public Health

Disclosures
- Any direct payment or honoraria: Employee, University of Calgary
- Membership on advisory board or speakers’ bureau: NoNO Inc. (unpaid); Boehringer Ingelheim.
- Grants and Clinical Trials: Multiple grants and trials
Do you think SARS-CoV2 can cause stroke?

1) YES
2) NO
3) MAYBE

Image Source: Bitmoji
Covid19 Disease and Stroke

Michael D Hill, MD MSc FRCPC

Covid19 Disease – what is it?

• Pathology shows a viral pneumonia with some mild peri-carditis and sometimes myocarditis
• No other organ system involved
• What are the neurological manifestations? Stroke?
Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China

Lung Mao, Haoyun Jin, Mengke Hong, Yi Hu, Zhengli Chen, Quarry Hill, Jing Chang, Caodong Hong, Yifan Zhou, David Wang, Keping Yue, Yanran Li, MD, PhD; Bihui, MD, PhD

Research | Original Investigation

Table 3. Laboratory Findings of Patients With COVID-19 With CNS Symptoms*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 28)</th>
<th>Severe (n = 27)</th>
<th>Nonsevere (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>4.6 (0.1-12.5)</td>
<td>4.9 (1.8-20.4)</td>
<td>5.1 (3.0-12.5)</td>
<td>0.75</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>2.6 (0.0-10.9)</td>
<td>3.1 (0.7-18.7)</td>
<td>3.8 (0.0-10.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Platelet</td>
<td>200.0 (180.0-220.0)</td>
<td>190.0 (180.0-220.0)</td>
<td>220.0 (180.0-220.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>141.0 (0.1-212.0)</td>
<td>144.0 (0.1-212.0)</td>
<td>140.0 (0.1-212.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>D-dimer, ng/mL</td>
<td>0.5 (0.2-3.7)</td>
<td>0.5 (0.1-2.6)</td>
<td>0.5 (0.1-2.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>79.0 (8.8-121.0)</td>
<td>104.0 (8.8-216.0)</td>
<td>64.0 (20.0-216.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>244.0 (2.2-880.0)</td>
<td>241.0 (2.2-880.0)</td>
<td>239.0 (2.2-880.0)</td>
<td>0.32</td>
</tr>
</tbody>
</table>
| Abbreviations: CNS, central nervous system; COVID-19, coronavirus disease 2019.

*P values indicate differences between patients with and without CNS symptoms, and P < 0.05 was considered statistically significant.
SARS-CoV2 Neurological manifestations

- Central – role of the olfactory bulb?
  - Encephalopathy
  - Seizures
  - Stroke

- Peripheral
  - Guillain-Barre syndrome
  - Myositis / myopathy
Cerebrovascular complications in patients with SARS-CoV-2 infection: Case series

- N=6 (5 male, 1 female)
- All 6 with elevated LDH, LFT’s
- 67% with abnormal coagulation. (elevated d-dimer, platelet count, increased aPTT)
- 67% died, 1 in coma, 1 vegetative state
- All patients with severe pneumonia

Morassi M et al. https://europepmc.org/article/ppr/ppr152878

Cerebrovascular Dis (+) Cerebrovascular Dis (-) Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
Mortality
Bai Y 2020 2 7 34 120 5.1% 1.01 [0.30, 3.27]
Cao J 2020 3 6 14 96 6.6% 3.43 [1.35, 8.74]
Chen T 2020 4 4 109 270 11.1% 2.23 [1.01, 4.89]
Luo XM 2020 22 30 78 367 11.1% 2.65 [1.86, 3.73]
Yuan M 2020 1 1 9 26 6.5% 2.13 [0.62, 5.61]
Subtotal (95% CI) 57 879 40.4% 2.38 [1.92, 2.96]
Total events 32 244
Heterogeneity: Tau² = 0.00, CH² = 13.15, df = 4 (P = 0.03), I² = 0%
Test for overall effect: Z = 7.61 (P = 0.00001)

Severe COVID-19
Guo 2020 4 15 169 1084 7.2% 1.71 [0.73, 4.00]
Hu L 2020 3 7 169 316 7.1% 0.85 [0.34, 1.90]
Li G 2020 2 2 24 232 6.9% 7.50 [4.22, 14.87]
Qin 2020 8 11 278 441 10.9% 1.18 [0.86, 1.67]
Wang Dai 2020 3 5 68 138 8.0% 1.22 [0.56, 2.64]
Wang Y 2020 3 7 35 106 6.9% 1.50 [0.83, 2.98]
Zhang Guo 2020 11 15 44 206 16.6% 3.43 [2.30, 13.53]
Subtotal (95% CI) 62 2523 59.6% 1.88 [1.09, 3.29]
Total events 34 787
Heterogeneity: Tau² = 0.59, CH² = 44.70, df = 6 (P < 0.00001), I² = 87%
Test for overall effect: Z = 1.96 (P = 0.05)

Total (95% CI) 119 3402 100.0% 2.04 [1.43, 2.91]
Total events 66 1031
Heterogeneity: Tau² = 0.27, CH² = 46.38, df = 11 (P < 0.00001), I² = 77%
Test for overall effect: Z = 3.95 (P < 0.0001)
Test for subgroups difference: CH² = 0.00, df = 1 (P = 0.48), I² = 0%

Cerebrovascular Disease

- Reported in 5% of cases [1]
- Most patients have vascular risk factors [2]
  - 39% DM
  - 54% HTN
  - Glucose intolerance 77%
- One series of 12 patients
  - 39% large vessel
  - 28% small vessel
  - 28% cardioembolic


Mao et al. JAMA NEUROL 2020 Apr 10

- Increased thrombosis as a result of viral infection
- Role of anti-phospholipid antibodies
- Relationship with "covid toes" – cold agglutinins or cryoglobulins or other similar mechanism?

DOI: 10.1056/NEJMoa2015432

Figure 2. Microthrombi in the Interlobular Septa of a Lung from a Patient Who Died from Covid-19.

The interlobular septa of this patient (Patient 4 in Table S1A in the Supplementary Appendix) shows slightly expanded alveolar walls with multiple fibrous microthrombi (arrowheads) in the alveolar capillaries. Extravasated erythrocytes and a loose network of fibrin can be seen in the intralveolar space (hematoxylin–eosin staining; the scale bar corresponds to 50 μm).
Stroke and Covid19 – is there a real association?

- We do not know but it is not prevalent
- Thrombophilia or some sort?
- Myocarditis and stroke?
- There is already a known clear association between URTI and stroke, influenza and stroke
- Other organisms – mycoplasma pneumonia, chlamydia pneumoniae, helicobacter pylori, CMV can all be found in atherosclerotic plaque and vascular endothelium
- Maybe we are simply better observing a known link....

Anosmia and Dysgeusia / Ageusia

Bonnie Meatherall MD FRCPC MSc DTM&H
Clinical Associate Professor Division of Infectious Diseases, Department of Medicine, Cumming School of Medicine University of Calgary

Disclosures
- Nothing to Disclose
Is the loss of smell associated with COVID-19 permanent?

1) YES
2) NO
3) MAYBE

COVID 19 - Anosmia

Bonnie Meatherall MD, FRCPC, MSc, DTM&H
Infectious Diseases
Cumming School of Medicine
Definitions and Pathophysiology

- **Anosmia and ageusia**: Inability to smell/taste, loss of all odors/flavors
- **Dysosmia and dysgeusia**: altered, distorted, hallucinations of odors/flavors


Anosmia and COVID 19 - first associations

Loss of sense of smell as marker of COVID-19 infection

There is new evidence for the loss of smell as a symptom of COVID-19 infection. We are circulating the following intelligence to Public Health England with regards to anosmia. As a result, this information highlights the importance for healthcare personnel to employ full PPE and in turn help stem the rates of infection. Full details can be read below:

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Anosmia and COVID 19 – review of the literature

- 73% developed anosmia prior to being diagnosed with COVID 19
- In 40% of cases, anosmia prompted testing
- Anosmia was the first symptoms to develop in 27% of cases
- Time to improvement/resolution was 7.2 days (+/- 3.1 days)
Anosmia and COVID 19 - Public health implications

COVID-19 Self-Assessment
novel coronavirus (COVID-19)

AHS continues to revise testing criteria in Alberta, to reflect enhanced lab testing continue to change in the coming weeks and months as the pandemic evolves.

For Albertans
Effective May 4, Albertans are now eligible for testing if they have any of the following symptoms:
- cough, fever, shortness of breath, difficulty breathing, runny nose, sore throat, chills, painful swallowing, stuffy nose, headache, muscle/joint ache, feeling unwell, fatigue, severe exhaustion, nausea, vomiting, diarrhea, unexplained loss of appetite, loss of sense of smell or taste, conjunctivitis (pink eye)

Gastrointestinal Symptoms

Sylvain Coderre MD, FRCPC, MSc (Medical Education)
Professor of Medicine, Department of Medicine (Gastroenterology)

Disclosures
• Employee, University of Calgary

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Is SARS-CoV2 spread via fecal-oral transmission?

1) YES  
2) NO  
3) MAYBE

Objectives

• At the end of this session, attendees will understand that in COVID 19 infection:
  • GI symptoms are common
  • Loss of appetite and watery diarrhea most common
  • Isolated abdominal pain uncommon, bloody diarrhea not reported
  • Pancreatitis can occur

• At the end of this session, attendees will gain understanding of the effect of IBD medications on COVID-19
  • Steroids not good
  • Biologics not bad (and ? protective)
  • 5ASA surprising

• What is not an objective: exact numbers for any of this!
What we know

- GI symptoms are prevalent:¹,²
  - Most common: loss of appetite and watery (“small bowel”) diarrhea
- GI symptoms can occur in isolation³
- The diarrhea is not bloody⁴
- Isolated abdominal pain is not common⁴
- Viral RNA is commonly found in stools (48% in one review)⁵
- COVID uses ACE2 in the gut as a cellular entry receptor⁶,⁷

¹: Pan et al, AJG April 2020;  ²: Han et al, AJG April 2020;  ³: Luo et al, Clin Gastro Hepatol, March 2020
⁴: Sultan et al, AGA review, Gastroenterology, May 2020;  ⁵: Cheung et al. Gastroenterology 2020 Apr
⁶: Effenberger et al, Gut April 2020;  ⁷: Zang et al, Science Immunology, May 2020
What we don’t know: precise numbers for any of this!

- **GI symptoms are prevalent: up to 57% of pts in one study**
  - loss of appetite: 27%\(^5\) to 40%\(^1\)
  - watery (“small bowel”) diarrhea:
    - 0-37%\(^4\)
    - pooled 8% (18% outside of China)\(^4\)
  - nausea and vomiting: 8%\(^4\)

- **GI symptoms can occur in isolation**
  - 16%\(^3\) to 23%\(^2\) but one paper in the AGA review\(^4\) had zero such pts

- **Isolated abdominal pain is less common**
  - 3% with any abdominal pain\(^4\)

What surprised me!

- **High ACE2 levels in the pancreas**\(^8\)
- **11/67 severe COVID pts had elevated pancreatic enzymes**\(^8\)
- **17% (of 52 pts with pneumonia) had elevated pancreatic enzymes**\(^9\)
- **Case reports of pancreatitis**,\(^10\) including 2 of 3 family members admitted with COVID\(^11\)

8: Liu et al, [https://www.medrxiv.org/content/10.1101/2020.02.28.20029181v1.full.pdf](https://www.medrxiv.org/content/10.1101/2020.02.28.20029181v1.full.pdf)
9: Wang et al, Gastroenterology, April 2020
10: Anand et al, Br J Surg, April 2020
11: Hadi et al, Pancreatology, May 2020
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SECURE-IBD database

<table>
<thead>
<tr>
<th>Drug</th>
<th>Complicated ICU/Ventilator/Death with COVID (baseline 9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD</td>
<td>100/1170 (9%)</td>
</tr>
<tr>
<td>Steroids</td>
<td>23/98 (23%)</td>
</tr>
<tr>
<td>Sulfasalazine/5ASA</td>
<td>51/334 (15%)</td>
</tr>
<tr>
<td>Budesonide</td>
<td>4/31 (13%)</td>
</tr>
<tr>
<td>JAK inhibitor</td>
<td>2/18 (11%)</td>
</tr>
<tr>
<td>6MP/AZA</td>
<td>12/113 (11%)</td>
</tr>
<tr>
<td>MTX</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>Anti-TNF with AZA/MTX</td>
<td>12/117 (10%)</td>
</tr>
<tr>
<td>Anti-integrin</td>
<td>9/115 (8%)</td>
</tr>
<tr>
<td>Other drugs</td>
<td>3/45 (7%)</td>
</tr>
<tr>
<td>IL 12/23</td>
<td>3/112 (3%)</td>
</tr>
<tr>
<td>Anti-TNF alone</td>
<td>8/337 (2%)</td>
</tr>
</tbody>
</table>

https://covidibd.org/current-data/
Last updated May 18, 2020

Liver Test Abnormalities

Kelly Burak MD MSc FRCPC
Professor and Associate Dean, Continuing Medical Education and Professional Development, Cumming School of Medicine, University of Calgary

Disclosure
• Employee, University of Calgary

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What is the most common liver test abnormality associated with COVID-19?

1) ALT  
2) AST  
3) ALP  
4) GGT  
5) Bilirubin

Liver tests in COVID-19

• Angiotensin converting enzyme 2 (ACE2) receptor\(^1\)
  • highly expressed in alveolar epithelial cells of the lung
  • expressed only in 3% of hepatocytes vs 58% of bile duct cells

• AST > ALT
• ALP is least affected
• DDx
  • Shock
  • Sepsis (cytokines)
  • Drug induced liver injury
  • Other

\(^1\)Chai X, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. https://doi.org/10.1101/2020.02.03.931766


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Do liver tests predict outcomes?

<table>
<thead>
<tr>
<th>Lab test</th>
<th>Deaths (n=113)</th>
<th>Recovered (n=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT median</td>
<td>28.0 (18.0-47.0)</td>
<td>20.0 (14.8-32.0)</td>
</tr>
<tr>
<td>% &gt;ULN</td>
<td>27%</td>
<td>19%</td>
</tr>
<tr>
<td>AST median</td>
<td>45.0 (31.0-67.0)</td>
<td>25.0 (20.0-33.3)</td>
</tr>
<tr>
<td>% &gt;ULN</td>
<td>52%</td>
<td>16%</td>
</tr>
<tr>
<td>ALP median</td>
<td>76.0 (60.0-118.0)</td>
<td>64.0 (51.0-77.0)</td>
</tr>
<tr>
<td>Albumin median</td>
<td>30.1 (27.9-33.0)</td>
<td>36.3 (33.7-39.5)</td>
</tr>
<tr>
<td>Bilirubin median</td>
<td>12.6 (9.4-16.7)</td>
<td>8.4 (5.8-11.2)</td>
</tr>
</tbody>
</table>

Chen T, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020: 368; doi: https://doi.org/10.1136/bmj.m1091


Are liver disease patients at ↑ risk from COVID-19?

<table>
<thead>
<tr>
<th></th>
<th>COVID-19 with Liver Disease (n=250)*</th>
<th>COVID-19 without Liver Disease (n=2530)</th>
<th>RR (95%CI)** p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>52%</td>
<td>30%</td>
<td>1.7 (1.2, 2.0) p &lt; 0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>12%</td>
<td>4.3%</td>
<td>2.8 (1.9, 4.0) p &lt; 0.001</td>
</tr>
</tbody>
</table>

*50 had cirrhosis 42% had NAFLD


**similar RR after propensity score matching
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Dermatologic Presentations

Justin Chia MD FRCPC FAAD
Clinical Assistant Professor, Division of Dermatology, University of Calgary

Disclosures
- Nothing to Disclose

Has Maggie been drinking alcohol?
Does Maggie have cirrhosis?
Does Maggie have COVID-19?

Hb: 110
(MCV 90)
WBC: 5.0
Plts: 120
Creat: 130
Lytes: normal
Glucose: 25.0
HbA1C: 8.0%
AST: 60
ALT: 35
ALP: 200
GGT: 300

Image Source: pixabay.com

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What is the mechanism of ‘COVID toes’?

1) Direct SARS-CoV2 infection of skin
2) Viral induced thrombosis
3) Immune mediated reaction
4) Other

Learning Objectives

• Identify the most common cutaneous manifestations of COVID-19 and the time of their occurrence within the disease course
• Explore the possible pathogenesis of chilblain-like lesions (“COVID toes”)
• Work-up and management of chilblain-like lesions
Cutaneous Manifestations of COVID-19

- It is estimated that up to 20% of COVID-19 patients develop cutaneous manifestations\(^1\).
- The largest consensus study to date reported 375 cases of skin eruptions in suspected and confirmed COVID patients in Spain\(^2\).
- Classification into 5 groups:
  - Vesicular
  - Urticarial
  - Maculopapular/morbilliform
  - Livedoid/necrotic
  - Chilblain-like

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Timeline

<table>
<thead>
<tr>
<th>Very early (prior to other symptoms)</th>
<th>Early (with other symptoms)</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesicular</td>
<td>Urticarial</td>
<td>Chilblain-like</td>
</tr>
<tr>
<td></td>
<td>Maculopapular</td>
<td>Livedoid / necrotic</td>
</tr>
<tr>
<td></td>
<td>Livedoid / necrotic</td>
<td></td>
</tr>
</tbody>
</table>

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Vesicular

- Very early in disease course (prior to other symptoms)
- Middle-aged patients
- Pruritic
- Medium severity of systemic disease
- Lasts ~ 10 days
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Urticarial

- Occurs with other symptoms
- Very pruritic
- Lasts 1 week
- All patients survived in cohort

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Maculopapular

- Occurs with other symptoms
- Pruritus in 50%
- Lasts for ~ 9 days
- 2% mortality in cohort

Livedoid/Necrotic

- Different degrees of lesions
- Likely occlusive vascular disease
- Older patients
- 10% mortality
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Chilblain-like
(aka pseudo-chilblain, COVID toes, pernio-like)

- Systematic review finds chilblain-like lesions account for 40% of all reported cutaneous manifestations
- Tends to affect younger patients
- Late finding
- Less severe disease
- Painful and/or pruritic
- Can affect hands and feet
- Lasts 2-4 weeks
- Asymmetric

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1 week later I received the following email…

“Hi Dr. Chia, apologies for this email. I wanted to let you know that I developed the same symptoms as [my son]. You mentioned that chilblains is not genetic or contagious. Interested in your thoughts! Here are some pictures . . .”
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Photo used with patient's permission.

Photo used with patient's permission.

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Pathogenesis

- Likely 3 mechanisms for cutaneous manifestations:
  - Immune response to viral nucleotides
    - (Interferon may play a role in chilblain-like lesions)
  - Vasculitis
  - Thrombotic vasculopathy
**Possible workup for chilblain-like lesions**

- COVID PCR swab
- COVID serology: IgM/IgG
- CBC, diff
- ANA
- RF
- Cold agglutinins
- Cryoglobulins
- C3, C4, CH50
- CRP, ESR
- D-dimer
- Fibrinogen
- APLA

**Treatment for chilblain-like lesions**

- Reassurance
- Potent topical corticosteroids
  - (e.g. clobetasol ointment BID)
- Calcium channel blockers
- Aspirin
Summary

- COVID-19 has many cutaneous manifestations
- Chilblain-like lesions (“COVID-toes”) are common and are associated with good prognosis
- Dermatologic manifestations of COVID-19 are an active area of ongoing research (AAD International Registry, University of Calgary)

Cardiac Manifestations

Cvetan Trpkov MD MDCM
Cardiology Resident, Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary

Disclosures
- Nothing to Disclose
Are COVID-19 patients at higher risk of arrhythmias?

1) NO

2) YES

3) Only if they take hydroxychloroquine

Learning Objectives

• Share my experiences with cardiac complications of COVID-19

• Highlight cardiovascular manifestations of COVID-19 & review recent publications
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From your nose to your toes: Atypical presentations of COVID-19
Shi S, et al. JAMA Cardiol. 2020;
Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China

Table 3. Multivariate Cox Regression Analysis on the Risk Factors Associated With Mortality in Patients With COVID-19

<table>
<thead>
<tr>
<th>Factor</th>
<th>From symptom onset Hazard ratio (95% CI)</th>
<th>P value</th>
<th>From admission Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.02 (0.99-1.05)</td>
<td>.07</td>
<td>1.02 (0.99-1.04)</td>
<td>.18</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>1.51 (0.70-3.30)</td>
<td>.30</td>
<td>1.40 (0.65-3.03)</td>
<td>.39</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>1.12 (0.46-2.70)</td>
<td>.80</td>
<td>1.71 (0.71-4.09)</td>
<td>.25</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.79 (0.41-1.52)</td>
<td>.48</td>
<td>0.75 (0.38-1.50)</td>
<td>.42</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>0.37 (0.04-3.50)</td>
<td>.38</td>
<td>0.39 (0.04-3.68)</td>
<td>.41</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.10 (0.49-2.44)</td>
<td>.82</td>
<td>0.66 (0.29-1.46)</td>
<td>.30</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.75 (0.43-7.16)</td>
<td>.44</td>
<td>0.82 (0.18-3.65)</td>
<td>.79</td>
</tr>
<tr>
<td><strong>Acute respiratory distress syndrome</strong></td>
<td>7.89 (3.73-16.66)</td>
<td>&lt;.001</td>
<td>7.11 (3.31-15.25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Cardiac injury</strong></td>
<td>4.26 (1.92-9.49)</td>
<td>&lt;.001</td>
<td>3.41 (1.62-7.16)</td>
<td>.001</td>
</tr>
<tr>
<td>Creatinine ≥150 mg/dL</td>
<td>0.59 (0.29-1.23)</td>
<td>.16</td>
<td>1.22 (0.60-2.50)</td>
<td>.58</td>
</tr>
<tr>
<td>N-terminal pro-B-type natriuretic peptide ≥900 pg/mL</td>
<td>1.16 (0.54-2.47)</td>
<td>.70</td>
<td>1.52 (0.74-3.10)</td>
<td>.25</td>
</tr>
</tbody>
</table>

Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Factor Present</th>
<th>Risk Factor Absent</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥65 yr of age</td>
<td>147/1474 (10.0)</td>
<td>368/7436 (4.9)</td>
<td>1.93 (1.60-2.41)</td>
</tr>
<tr>
<td>Female sex</td>
<td>179/3571 (5.0)</td>
<td>336/5339 (6.3)</td>
<td>0.79 (0.65-0.95)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>103/1010 (10.2)</td>
<td>412/7900 (5.2)</td>
<td>2.70 (2.08-3.51)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>29/189 (15.3)</td>
<td>486/8721 (5.6)</td>
<td>2.48 (1.62-3.79)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>35/304 (11.5)</td>
<td>480/8606 (5.6)</td>
<td>1.95 (1.33-2.86)</td>
</tr>
<tr>
<td>COPD</td>
<td>32/225 (14.2)</td>
<td>483/8685 (5.6)</td>
<td>2.96 (2.00-4.40)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>46/491 (9.4)</td>
<td>469/8419 (5.6)</td>
<td>1.79 (1.29-2.47)</td>
</tr>
<tr>
<td>Receiving ACE inhibitor</td>
<td>16/770 (2.1)</td>
<td>499/8140 (6.1)</td>
<td>0.33 (0.20-0.54)</td>
</tr>
<tr>
<td>Receiving ARB</td>
<td>38/556 (6.8)</td>
<td>477/8354 (5.7)</td>
<td>1.23 (0.87-1.74)</td>
</tr>
<tr>
<td>Receiving statin</td>
<td>36/860 (4.2)</td>
<td>479/8050 (6.0)</td>
<td>0.35 (0.24-0.52)</td>
</tr>
</tbody>
</table>

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**CORRESPONDENCE**

Table 1. Comparison of Hospital Admissions for Acute Coronary Syndrome (ACS) in Northern Italy between the Onset of the Covid-19 Outbreak and Two Control Periods.

<table>
<thead>
<tr>
<th>ACS Subtype</th>
<th>Study Period (N = 547)</th>
<th>Control Periods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Same Year (N = 899)</td>
</tr>
<tr>
<td>All ACS</td>
<td>2202</td>
<td>13.3</td>
</tr>
<tr>
<td>No. of daily admissions</td>
<td>0.74 (0.66–0.82)</td>
<td>0.70 (0.63–0.78)</td>
</tr>
<tr>
<td>Incidence rate ratio (95% CI)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**CORRESPONDENCE**

Out-of-Hospital Cardiac Arrest during the Covid-19 Outbreak in Italy


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COVID-19 myocarditis

Inciardi RM, et al. JAMA Cardiol. 2020

STIR sequence in short-axis view

STIR sequence in 4-chamber view

Inciardi RM, et al. JAMA Cardiol. 2020
From your nose to your toes: Atypical presentations of COVID-19


CORRESPONDENCE


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Pulmonary Embolism in COVID-19

- Lille University Hospital, France, reported pulmonary embolism in 22/107 (20.6%) COVID-19 ICU patients

- PE among COVID-19 series was twice higher than during control period (20.6% vs 6.1%)
  - PE frequency among 40 influenza patients in 2019 was 7.5%

- PE despite prophylactic anticoagulation in 20/22 patients

ST-Elevation Myocardial Infarction in COVID-19

- All consecutive STEMI patients with COVID-19 over 6 weeks in the Lombardy region (N=28)

- Culprit lesion in 17/28 patients (60.7%); 11 patients (39.3%) had no obstructive CAD

- STEMI represented the first clinical manifestation of COVID-19 in 24 patients (85.7%)
Summary

- COVID-19 patients with cardiovascular disease have adverse outcomes
- COVID-19 is associated with multiple cardiovascular complications
- SARS-CoV-2 infection induced cytokine storm may contribute to cardiovascular complications
Pediatric Multisystem Inflammatory Syndrome

Susa Bensler MD PhD
Professor Department of Paediatrics University of Calgary, ACHRI Director; Child Health & Wellness Researcher, Child Health Data Science Program; ACHF Chair in Pediatric Research; Husky Energy Chair in Child and Maternal Health

Disclosures
• Employee, University of Calgary

Which of the following is NOT required to diagnose Pediatric Multisystem Inflammatory Syndrome?

1) Persistent fever
2) Markers of inflammation
3) Organ(s) dysfunction
4) Positive NP Swab

Image Source: Bitmoji
Atypical Presentations in Children Multisystem Inflammatory Syndrome in Children temporally related to COVID MIS-C

Susa Benseler, Rheumatology

China: Survivors versus non-survivors


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China: Survivors versus non-survivors


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China: Hyperinflammation


Infection —— immune response —— immune dysregulation/hyperinflammation

Cytokine release
- Systemic inflammation (fever, malaise)
- Vessel inflammation (hyperemia, rashes, vascular leakage, LN)
- Inflammatory shock (hypotension, myocardial dysfunction/myocarditis)

https://www.mirror.co.uk/news/uk-news/mum-details-kawasaki-disease-symptoms-22045811

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Many names KD, MAS, sJIA

- Kawasaki Disease Shock Syndrome (KDSS): incidence 2.60 to 6.95%
- Higher levels of IL-1, IL-6, IL-10, TNF-α and IFN-γ than in typical KD patients
- Hypovolemic shock, refractory to fluid resuscitation and often requiring ICU.

Hyperinflammation: example HLH

Cytokine storm

Clinical phenotype of cytokine storm/hyperinflammation

This material is for individual use only and not to be used for further dissemination.
WHO: Preliminary Case Definition

Multisystem Inflammatory Syndrome in Children temporally related to COVID

Children 0-19 years of age with Fever ≥3 days

AND one/two of the following:

a) Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)

b) Hypotension or shock, or features of myocardial dysfunction, or pericarditis, or valvulitis, or coronary abnormalities (ECHO findings or elevated Troponin/NT-proBNP)

c) Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)

AND

Elevated markers of inflammation such as ESR, C-reactive protein or procalcitonin

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes

AND

Evidence of Covid (RT-PCR test positive or serology), or likely contact with patients with COVID

Kawasaki and Coronavirus

Association between a Novel Human Coronavirus and Kawasaki Disease

Lack of Association between Infection with a Novel Human Coronavirus (HCoV), HCoV-NH, and Kawasaki Disease in Taiwan

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Kids with hyperinflammation at ACH

Diagnosing hyperinflammation

**Clinical features**
- Typical clinical features: fevers, fatigue, malaise/crankiness
- KD features: red eyes, cracked lips, swollen lymph nodes, puffy hands/feet, rash
- COVID in kids phenotypes:
  - GI symptoms (abdominal pain, nausea/vomiting, diarrhea)
  - Loss of smell/taste, headaches, neck pain, chilblain-like rashes toes
- **Inflammatory shock**: hypotension, tachycardia, myocardial dysfunction, HSM, non-responsiveness to fluid resuscitation

**Laboratory and other tests**
- Blood/urine:
  - Inflammation: CRP, ferritin, D-Dimers, CBC – lymphopenia, platelets low normal, low albumin, (high procalcitonin)
  - Heart/vessels/coags: troponin, BNP, PTT, INR, fibrinogen
  - Organ function: LFTs including bili, LDH, creatinine, urine, electrolytes
- COVID: PCRs NPS, stool, blood
- Chest x-rays, ECG
- Cytokines and receptors * (IL1/6/18, CXCL10, macrophage markers)

* APL permission needed
Managing hyperinflammation

**Multidisciplinary team, early testing**
- ED/ICU/Hospital Paediatrics, Infectious Diseases, Cardiology, Rheumatology/Immunology, others as appropriate (GI, Neurology)
- Include peds COVID study coordinator, commitment to peds COVID studies
- Rapid completion of testing (store serum/plasma for further testing)
- Early ECHO, early repeat

**Treatment of hyperinflammation**
- Shock management, early start of vasopressors
- IVIG 2g/kg for KD management
- Antithrombotic therapy
  - High dose ASA for KD, low dose when afebrile
  - Escalation to heparin, if coronary aneurysms
- Corticosteroid pulses (30mg/kg) x 3 days
- Biologic therapies – options IL-1 inhibition (anakinra) or IL-6 inhibition (tocilizumab) after team considerations (high risk child, failure to other immunosuppression) or anti-TNFα (advanced coronary artery disease)

* being hired
**APL permission needed

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Il-1 inhibition

72% of patients had clinical improvement

![Graph A](image1)

![Graph B](image2)

Il-6 inhibition

Xiaoling Xu, et al., Effective treatment of severe COVID-19 patients with tocilizumab PNAS May 19, 2020 ;

Thank you
On behalf of the Alberta Children’s Hospital COVID team

Panelists

Kevin Colleaux MD FRCSC
Associate Clinical Professor, University of Saskatchewan; Vitreoretinal Surgeon, Saskatoon City Hospital; Senior Managing Partner, Saskatoon Retina Consultants.
Disclosure
- Direct financial payments, gifts, in-kind compensation or honoraria: Bayer
- Membership on advisory boards or speakers’ bureau: Bayer, Novartis
- Grants or clinical trials: Novartis

Sarah Weeks MD FRCPC
Associate Clinical Professor, Cardiac Sciences; Director, Cumming School of Medicine, University of Calgary
Disclosure
Alberta Health Services, University of Calgary

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Questions to the Panelists

• What about eye manifestations of COVID-19?

• Are patients at higher risk of non-COVID related cardiovascular mortality because of the pandemic?

Q&A

Kevin Colleaux
Sarah Weeks
Kelly Burak
Michael Hill
Bonnie Meatherall
Sylvain Coderre
Justin Chia
Cvetan Trpkov
Susa Bensler
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After the session, you will receive an email with the link

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Consequences of COVID: Impact of Isolation

- Substance misuse / abuse
- Domestic violence
- Child abuse

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