COVID19 and Pulmonary Embolism

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COVID19

- Pathological features
- Macro vs Micro
- Serological markers
- Epidemiology
- Case presentations
COVID19

• Pathological features
  • Macro vs Micro
  • Serological markers
  • Epidemiology
  • Case presentations
Alveolar fibrin in COVID19-ARDS
(like most ARDS)

1. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med. 2020;8(7):681-686.
Small *in situ* thrombosis in COVID-19-ARDS

1. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med. 2020;8(7):681-686.
Big RV dilatation in COVID19-ARDS

1. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med. 2020;8(7):681-686.
In situ arteriolar thrombosis
in COVID19-ARDS

1. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med. 2020;8(7):681-686.
1. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med. 2020;8(7):681-686.
Capillary thrombi

1. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-128.
Angiitis/angiogenesis in COVID-19

1. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-128.
COVID19

- Pathological features
- **Macro vs Micro**
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Macro vs Micro Thrombosis

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Inflammation and Hypoxia lead to Thrombosis

- The Coagulation system evolved as an effector pathway of the immune response
  - Neutrophils release NETs to trap bacteria but also lead to platelet aggregation
  - Fibrin is laid down to entrap infected cells/bacteria

Middleton EA, He X-Y, Denorme F. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. Blood. 2020;136:1169–79.
Inflammation and Hypoxia lead to Thrombosis

- The Coagulation system evolved as an effector pathway of the immune response
  - Neutrophils release NETs to trap bacteria but also lead to platelet aggregation
  - Fibrin is laid down to entrap infected cells/bacteria
- Hypoxia, via hypoxia-inducible transcriptions factors, lead to prothrombotic state

Evans CE. Hypoxia and HIF activation as a possible link between sepsis and thrombosis. Thrombosis Journal. 2019;17.
Inflammation and Hypoxia lead to Thrombosis

- Endothelial dysfunction can further impair vascular tone and drive more thrombosis
  - Endothelial injury releases tissue factor resulting in thrombin activation

Huertas A, Montani D, Savale L. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)?. European Respiratory Journal. 2020;56:2001634.
Microthrombosis vs. Macrothrombosis in COVID-19

VS.

Diffuse Alveolar Damage

Microthrombi in Small Pulmonary Arterioles

Microthrombi in Small Pulmonary Arterioles

VS.
High Compliance, High Dead Space Phenotype of COVID-19 ARDS

Gattinoni L, Chiumello D, Caironi P. COVID-19 pneumonia: different respiratory treatments for different phenotypes?. Intensive Care Medicine. 2020;46:1099–102.
Is C-ARDS really that different from ARDS?

Viewpoint

COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted?

Eddy Fan, Jeremy R Beitler, Laurent Brochard, Carolyn S Calfee, Niall D Ferguson, Arthur S Slutsky, Daniel Brodie

The COVID-19 pandemic has seen a surge of patients with acute respiratory distress syndrome (ARDS) in intensive care units across the globe. As experience of managing patients with COVID-19-associated ARDS has grown, so too have efforts to classify patients according to respiratory system mechanics, with a view to optimising ventilatory management. Personalised lung-protective mechanical ventilation reduces mortality and has become the mainstay of treatment in ARDS. In this Viewpoint, we address ventilatory strategies in the context of recent discussions on phenotypic heterogeneity in patients with COVID-19-associated ARDS. Although early reports suggested that COVID-19-associated ARDS has distinctive features that set it apart from historical ARDS, emerging evidence indicates that the respiratory system mechanics of patients with ARDS, with or without COVID-19, are broadly similar. In the absence of evidence to support a shift away from the current paradigm of ventilatory management, we strongly support the use of ARDS mechanical ventilation guidelines in the setting of COVID-19.

“Reports of phenotypic heterogeneity in patients with COVID-19-associated ARDS, although interesting, could easily be over-interpreted or inappropriately applied in the intensive care unit, potentially leading to detrimental ventilatory management strategies in these patients.”

Fan E, Beitler JR, Brochard L. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted?. The Lancet Respiratory Medicine. 2020;8:816–21.
Bleeding and Clotting in COVID-19

400 hospital-admitted patients with COVID-19 (144 critically ill)

Bleeding

- Overall bleeding events: 4.8% critically ill
- Major Bleeding: 5.6% critically ill

Clotting

- Overall thrombotic complications: 9.5% critically ill
- Confirmed VTE: 4.8% critically ill

Predictors of Thrombosis:
- D-dimer (ng/mL)
- PT (sec)
- aPTT (sec)
- Fibrinogen (mg/dL)
- Platelet count (x10^9/L)
- CRP (mg/L)
- ESR (mm/h)
- Factor (mg/L)
- Procalcitonin (ng/mL)
- High-sensitivity troponin (ng/mL)

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Hanny Al-Samkari, Rebecca S. Karp Leaf, Walter H. Dzik, Jonathan C. T. Carlson, Annemarie E. Fogerty, Anem Waheed, Katayoon Goodarzi, Pavan K. Bendapudi, Larissa Bornikova, Shruti Gupta, David E. Leaf, David J. Kuter, Rachel P. Rosovsky, COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection, Blood, 2020.
There are over 30 currently enrolling clinical trials for anticoagulation paradigms in COVID-19.
Operation Warp Speed: ACTIV-4 Anti-thrombotics

- **ACTIV-4 Inpatient Protocol**
  - Therapeutic vs. Prophylactic anticoagulation
  - 2000 Hospitalized patients
  - Primary Endpoint: 21 Day Organ Support (respiratory or vasopressor) Free Days
  - Secondary Endpoint: Composite endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke at hospital discharge or 28 days
  - Anticipated study completion by March 2021

- **ACTIV-4 Inpatient Protocol (ASA/Apixiban/Placebo; 7000 patients)**

- **ACTIV-4 Convalescent Protocol**
COVID19

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# APL antibodies with COVID19

## Table 1. Prevalence of antiphospholipid antibodies in serum from COVID-19 patients (n=172)

| aPL antibody | Number positive (manufacturer’s cut-off) | %     | Number positive (titer ≥40 units) | %     |
|--------------|------------------------------------------|-------|-----------------------------------|-------|
| aCL IgG      | 8                                        | 4.7%  | 2                                 | 1.2%  |
| aCL IgM      | 39                                       | 23%   | 13                                | 7.6%  |
| aCL IgA      | 6                                        | 3.3%  | 1                                 | 0.58% |
| aβ2GPI IgG   | 5                                        | 2.9%  | 3                                 | 1.7%  |
| aβ2GPI IgM   | 9                                        | 5.2%  | 7                                 | 4.1%  |
| aβ2GPI IgA   | 7                                        | 4.1%  | 3                                 | 1.7%  |
| aPS/PT IgG   | 42                                       | 24%   | 21                                | 12%   |
| aPS/PT IgM   | 31                                       | 18%   | 21                                | 12%   |
| any positive aPL | 89                       | 52%   | 52                                | 30%   |

1. Zuo Y, Estes SK, Ali RA, et al. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. Sci Transl Med. 2020.
But lots of viral infections have APL Ab

| Infection type                                            | No. of positive patients/total (%) |
|-----------------------------------------------------------|-----------------------------------|
| **Anticardiolipin antibodies**                            |                                   |
| HIV + no OI \((n = 19)\)                                  | 840/1499\(^a\) (56)              |
| HIV + all combined OI \((n = 6)\)                         | 193/306 (63)                      |
| Hepatitis C virus \((n = 20)\)                            | 368/1785 (21)                     |
| Hepatitis B virus \((n = 9)\)                             | 93/483 (19)                       |
| Epstein-Barr virus \((n = 4)\)                            | 68/137 (50)                       |
| Human T-lymphotropic virus type 1 \((n = 3)\)            | 31/191 (16)                       |
| Hepatitis A virus \((n = 1)\)                             | 2/2 (100)                         |
| Human herpesvirus type 6 \((n = 1)\)                     | 19/32 (59)                        |
| Lymphotropic viruses \((n = 1)\)                          | 8/20 (40)                         |
| Parvovirus B19 \((n = 1)\)                               | 8/60 (13)                         |
| Varicella zoster virus \((n = 1)\)                        | 8/12 (67)                         |

1. Abdel-Wahab N, Talathi S, Lopez-Olivo MA, Suarez-Almazor ME. Risk of developing antiphospholipid antibodies following viral infection: a systematic review and meta-analysis. Lupus. 2018;27(4):572-583.
Viral-associated APL Ab aren’t necessarily associated with VTE

| Infection type | No. of positive Patients with infection and aPL antibodies (%) |
|----------------|---------------------------------------------------------------|
| Hepatitis C virus ($n=9$) | 20/178 (11.2) |
| HIV ($n=6$) | 0/171 |
| HIV + OI ($n=3$) | 1/111 (<1) |
| Hepatitis B virus ($n=5$) | 4/75 (5) |
| Epstein-Barr virus ($n=1$) | 0/19 |
| Human herpesvirus type 6 ($n=1$) | 0/19 |
| Human T-lymphotropic virus type 1 ($n=1$) | 0/23 |

1. Abdel-Wahab N, Talathi S, Lopez-Olivo MA, Suarez-Almazor ME. Risk of developing antiphospholipid antibodies following viral infection: a systematic review and meta-analysis. Lupus. 2018;27(4):572-583.
APL antibodies in COVID19 are mostly in the first week or two.

1. Zuo Y, Estes SK, Ali RA, et al. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. Sci Transl Med. 2020.
Persistent ACL and A-PT Ab are associated with VTE

| APLA subtype          | Persistent |          | Persistent or transient |          |
|-----------------------|------------|----------|-------------------------|----------|
|                       | OR (95% CI)| P        | OR (95% CI)             | P        |
| ACLA IgG              | 10.0 (1.8-56) | .013     | 2.8 (0.5-16)           | .211     |
| ACLA IgM              | 32.7 (4.2-256) | .001     | 10.0 (1.8-56)          | .013     |
| Anti-β₂-GPI IgG       | 17.8 (2.6-116) | .065     | 10.6 (1.7-65)          | .010     |
| Anti-β₂-GPI IgM       | 0.7 (1.2-37)   | .036     | 9.2 (1.5-55)           | .015     |
| Anti-PT IgG           | 3.5 (0.7-19)   | .155     | 3.1 (0.6-18)           | .179     |
| Anti-PT IgM           | 3.6 (0.3-46)   | .358     | 2.6 (0.4-17)           | .292     |

1. Male C, Foulon D, Hoogendoorn H, et al. Predictive value of persistent versus transient antiphospholipid antibody subtypes for the risk of thrombotic events in pediatric patients with systemic lupus erythematosus. Blood. 2005;106(13):4152-4158.
Laboratory criteria for antiphospholipid syndrome

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least **12 weeks** apart.

2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype on two or more occasions, at least **12 weeks** apart.

3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype on two or more occasions at least **12 weeks** apart.

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1. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295-306.
COVID-19

- Pathological features
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High incidence of PE among COVID19 who get scanned

1. Poyiadji N, Cormier P, Patel PY, et al. Acute Pulmonary Embolism and COVID-19. Radiology. 2020:201955.

1500 Consecutive CTPA scans performed from 3/16/2020 – 4/18/2020 Across multiple hospitals

73 (22%) COVID19 with Acute PE

256 (78%) COVID19 without Acute PE

1171 Excluded

How many COVID19 patients didn’t get CT scans?
Incidence of PE among COVID-19 patients

- **RCTs**
- **Retrospective review of scans**

| Study               | Incidence |
|---------------------|-----------|
| Wang (n = 233)      | 0.9%      |
| Beigel (n = 1063)   | 0.6%      |
| Bavaro (n = 20)     | 40.0%     |
| Bompard (n = 125)   | 24.0%     |
| Leonard-Lorant (n = 106) | 30.0% |
| Poyiadji (n = 328)  | 22.0%     |
| Grillet (n = 100)   | 23.0%     |
| Mazzaccaro (n = 32) | 65.6%     |
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Case presentations

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Case #1
Case presentation #1

- 53 yo M with history of HTN and HLD who presented to the ED with progressive SOB following recent COVID-19 diagnosis 6 days prior to admission.
Admission vital signs

- T 100.9F
- HR 69
- BP 125/73
- RR 30
- SpO2 94% on RA
- BMI 31.6
Physical exam

- Gen: No acute distress, speaking complete sentences
- CV: Regular rate and rhythm, no murmur, rubs or gallops
- Lungs: Clear bilaterally
- GI: Abdomen soft and non-tender
- Ext: No swelling or erythema
- Skin: No rashes, wounds
Initial labs

- **CBC**
  - 6.1 > 15.1/45.6 < 158
    - 71% segs, 21% lymph, 8% mono, 0% eos/basophils
- **BMP** – 136 / 4 / 96 / 26 / 13 / 1.0 < 113
- **Liver enzymes** – Normal except AST 49, ALT 52
- **Pro-BNP** – 67 pg/ml (normal 0-899)
- **Troponin 5\text{th} Gen** – 6ng/L (normal <22 ng/L)
- **D-Dimer** – 221 ng/mL (normal <241ng/mL)
- **Rapid Covid-19 Assay** - Positive
Hospital course

- Admitted to Medicine and started on Remdesivir
  - initially saturating well on RA, overnight requiring 2-3L via NC to maintain sat >88%
- HD 4 – Increasing oxygen requirement overnight, now requiring NRB
  - Transferred to ICU and started on Dexamethasone 6mg daily
  - Over the next several days remains on NRB with intermittent self proning and occasional desaturations
- HD 9 – Increased WOB and significantly elevated D-dimer

D-Dimer (normal <241 ng/mL)
Next step?

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Hospital course

- Rx Heparin IV
- LE US: No evidence of DVT
- Oxygen gradually weaned down to NC
- HD 11 Transferred out of the ICU
- Transitioned from Heparin to Apixiban
- HD 15 Discharged home on RA
Comments

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Case #2
Case presentation #2

- 34 yo man
  - Poorly controlled non-insulin dependent T2DM
  - HTN
- Transferred from OSH with COVID-19 ARDS for consideration of VV-ECMO
Hospital course

- Admitted to OSH after 1 week of dyspnea
- Received Remdesivir, Dexamethasone and convalescent plasma
- HD 12 Intubated
- HD 15 Transferred to UCSD
Continued

- HD 16 Cannulated for VV-ECMO (P/F = 55)
  - Started on Heparin gtt (goal Xa 0.11-0.3)

- HD 26 Percutaneous tracheostomy
  - HD 26-29 Heparin held due to oozing from trach site

- HD 30-60 Required ECMO flows of ~6L/min and Sweep 6-8 lpm,
  - pulmonary compliance ~10-20 ml/cmH20
Continued

- HD 57 acute episode of hypotension
  - Previously on no vasopressors now requiring norepinephrine 26mcg/min, epinephrine 0.06mcg/kg/min, and phenylephrine 200mcg/min despite IVF boluses
- Unstable for transport
Next step?

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• Concern for possible PE
  • Empiric treatment with therapeutic heparin (Xa 0.2-0.45)
Case 2, CT slide 1
Case 2, CT slide 3
Hospital course

• Serial TTE with continued concern for RV thrombus

• Platelets drop from ~250 -> 120 over 4 days
  • PF4 0.446 (normal <0.400 OD) -> transitioned to bivalirudin gtt (Goal PTT 60 to 90 seconds)
Next step?

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Hospital course

- HD 66 - Patient’s left pupil is fixed and dilated
Hospital course

- HD 71 – Transitioned to Comfort Care
Comments

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Open discussion: COVID-19 and PE