Immunopathogenesis of COVID-19

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What determines disease severity?

RNA sequence → Virus → Viral load

Cells → Mediators → Epithelial damage → Bacteria

Cell stress → Viral spread

DNA → Host → Environment

Need to study host, pathogen and co-pathogen
MOSAIC

255 patients with influenza-like illness
172 (65%) with PCR-confirmed influenza

45 page booklet (Flu-CIN)
Extensive clinical information
Samples from multiple timepoints
Respiratory, blood and other samples
Virology and genomics
Molecular bacteriology
Mediators and cellular immunology
Transcriptomics
Host genomics
8000 sample biobank

matched healthy controls, ILI controls

A comprehensive study of the causes of severe pandemic influenza

21,000,000 data points
Progression of whole-blood transcriptional signatures from interferon-induced to neutrophil-associated patterns in severe influenza

Conclusions:

1. ‘Viral’ signal is only in those with low NPA bacterial load

2. ‘Bacterial’ signal is not seen in those with low NPA bacterial load
ISARIC preparedness platform

- Developed in the wake of the flu pandemic
- Uses WHO-approved clinical data tool from MOSAIC
- Sleeping platform, launched 2011
- Pre-agreements in place with >200 UK hospitals
CO-CIN and ISARIC-4C

77 933
Number of patients (all tiers)

75 522
Number of patients (Tier 0)

697
Number of patients (Tier 1)

1 714
Number of patients (Tier 2)

Tier 0
- Demographic data
- Outcome
- Comorbidities

Tier 1
- Single biological sample set:
  - Plasma/serum
  - Nasal swabs
  - Urine + Stool

Tier 2
- Serial biological sample sets

https://isaric4c.net/sample_access.html
Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study

- People of all ages admitted to 208 hospitals in the UK
- Patient data collected and uploaded from start of admission by 2648 frontline NHS clinical and research staff and volunteer medical students

22\textsuperscript{nd} April 2020:

- **20,133 patients** with confirmed SARS-CoV-2
- **34\%** of cases in the UK
- **Median age:** 73 years, Male/Female 60/40
- **Outcome:** 41\% discharged alive
  - 26\% died
  - 34\% still in hospital at reporting date.
Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study

doi:10.1136/bmj.m1985
http://dx.doi.org/10.1136/bmj.m1985
Diffuse alveolar damage attracts macrophages and neutrophils

Hyaline deposition, endothelial infection/injury and secretion of inflammatory mediators

Microthrombi incompletely cleared by fibrinolysis (D-dimer)

Progressive occlusion of small vessels, right ventricular stress
Genetic mechanisms of critical illness in Covid-19

E Paio-Castineira, S Clohisey, L Klaric, A Bretherick, K Rawlik... The GenOMICC Investigators, The ISARIC-4C Investigators, The Covid-19 Human Genetics Initiative, ... PJM Openshaw, MG Semple, V Vitart, JF Wilson, J. Kenneth Baillie

Steroids benefit those with respiratory failure, but may harm milder cases. Severity is largely immune-mediated and is strongly heritable.

**Genome-wide association study**, 2244 critically-ill Covid-19 were ancestry-matched to UK Biobank; confirmed in GWAS comparisons with two other population control groups.

**Found three novel associations:**
1. Chr19p13.3 (p = 3.98 × 10^{-12}) dipeptidyl peptidase 9 (DPP9)
2. Chr12q24.13 (p = 1.65 × 10^{-8}) antiviral restriction enzyme activators (OAS1, OAS2, OAS3)
3. Chr21q22.1 (p = 4.99 × 10^{-8}) interferon receptor (IFNAR2)

Also confirmed 3p21.31 locus (rs73064425, p = 4.77 × 10^{-30}).

Evidence of a causal link from low expression of IFNAR2 and high expression of TYK2 to life-threatening disease.

Transcriptome-wide association in lung tissue of the monocyte/macrophage chemotactic receptor CCR2 with severe Covid-19.

https://www.medrxiv.org/content/10.1101/2020.09.24.20200048v1
INFLAMMAGE study, EMINENT consortium

Symptom scores

Effect of age on outcome of RSV human challenge

Viral load (qPCR)

Dr Chris Chiu et al.
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ISARIC

- 2648 frontline volunteers
- ISARIC outbreak lab volunteers
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- Ewen Harrison
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To the patients and their relatives