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Cytokine storm syndromes in COVID-19 and rheumatic diseases

XVth UCLouvain Review Course on Systemic Rheumatic Diseases , December 2021

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Co-chair HiHASC

Plan of the talk

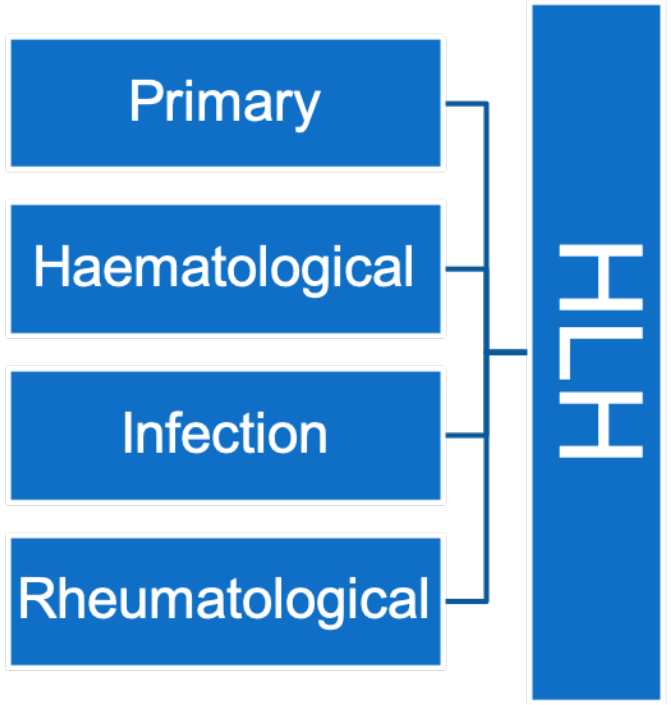
40 slides

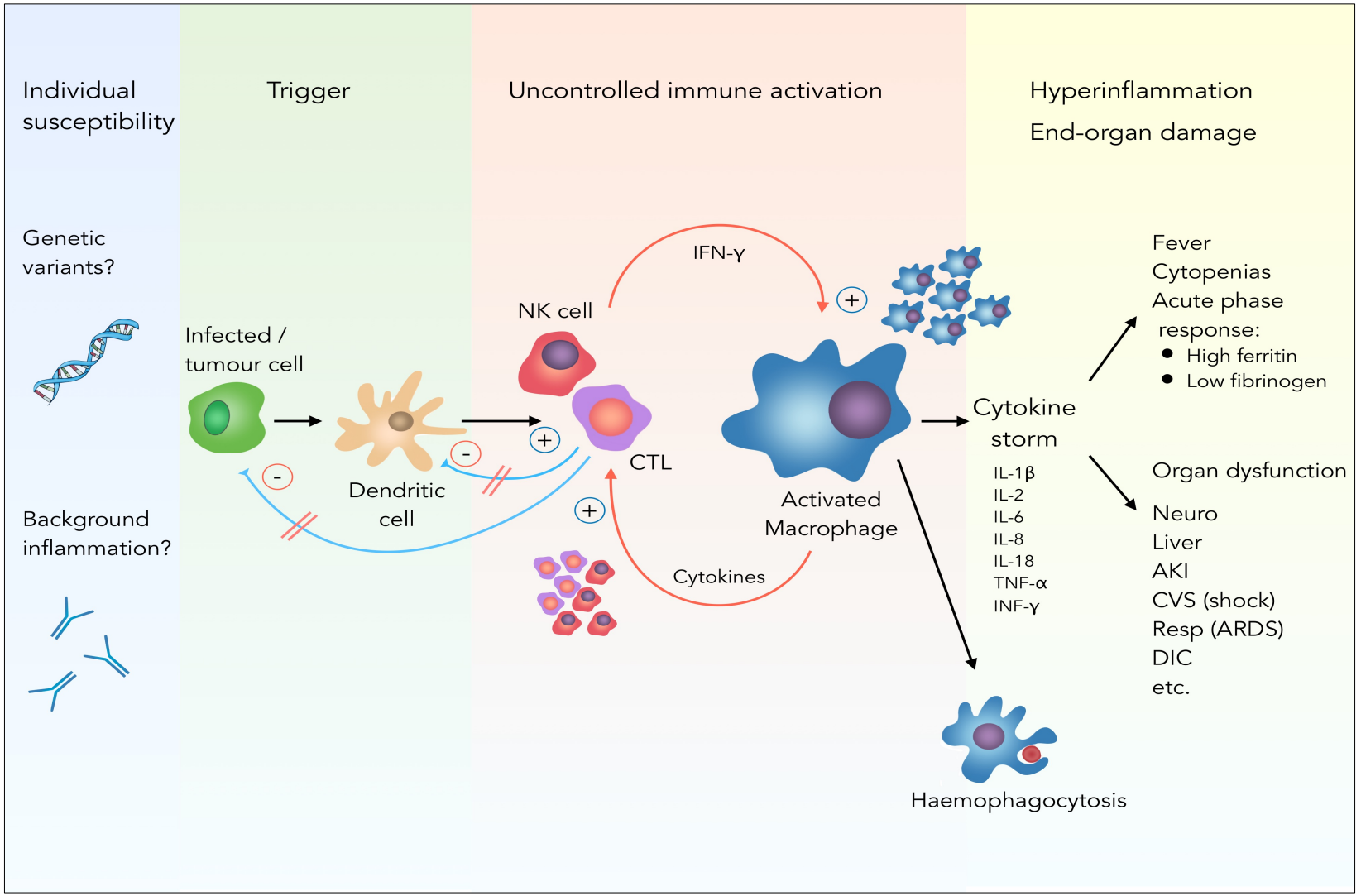
- Hyperinflammation and cytokine storm syndromes
- What is the role of a rheumatologist?
- The formation of HiHASC and the UCLH HLH MDT

- Where does COVID sit?

What is HLH?

- Lots of names for the same thing
- A hyper-inflammatory state/cytokine storm syndrome
- Defining characteristics
  - Fever
  - Haemophagocytosis by macrophages
  - High mortality
    - Multi-organ failure
    - Haemorrhage
    - Sepsis





Bauchmüller *et al*, JICS, 2020

How is HLH diagnosed?

CLINCAL FEATURES

- Unremitting fever
- Hepatomegaly
- Splenomegaly
- Lymphadenopathy
- Bleeding
- Confusion, fitting

INVESTIGATIONS

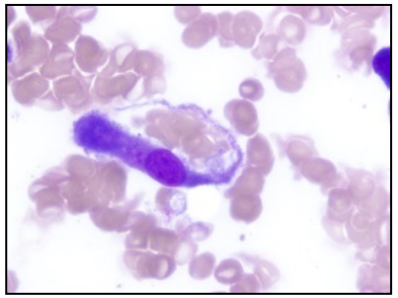
- Pancytopaenia
  - Falling platelets often first sign
- Transaminitis
- High CRP, falling ESR
- Coagulopathy
- High LDH

- **High ferritin**
- High triglycerides
- Low fibrinogen
- *Soluble CD25 (Il-2 receptor α), marker of T cell activation*

- Haemophagocytosis on BM

A rheumatologist's guide to haemophagocytosis

1. Not sensitive
   - No haemophagocytosis is not the same as no HLH
2. Not specific
3. Not just seen on BM
4. So why do one?
   - To look for malignancy/infection
   - (To convince others)



So don't let the BM replace your clinical judgement in either direction

Diagnostic criteria

2004 HLH diagnostic criteria

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled
- (1) A molecular diagnosis consistent with HLH
- (2) Diagnostic criteria for HLH fulfilled (five or more out of the eight criteria below)
  - (A) Initial diagnostic criteria (to be evaluated in all patients with HLH)
    - Fever
    - Splenomegaly
    - Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood)
      - Hemoglobin < 90 g/L
      - Platelets < 100×10^9/L
      - Neutrophils < 1.0×10^9/L
    - Hypertriglyceridemia and/or hypofibrinogenemia:
      - Fasting triclycerides ≥ 265 mg/dL
      - Fibrinogen < 1.5 g/L
    - Hemophagocytosis in bone marrow, spleen, lymph nodes
    - No evidence of malignancy
  - (B) New diagnostic criteria
    - Low or absent natural killer cell activity (according to local laboratory reference)
    - Elevated ferritin (≥500 mg/L)
    - Soluble CD25 (i.e. soluble interleukin-2 receptor) ≥ 2,400 U/mL

2016 MAS criteria for patients with sJIA

Ferritin >684 ng/ml

and any 2 of the following:

Platelet count ≤181 x 10^9/liter

Aspartate aminotransferase >48 units/liter

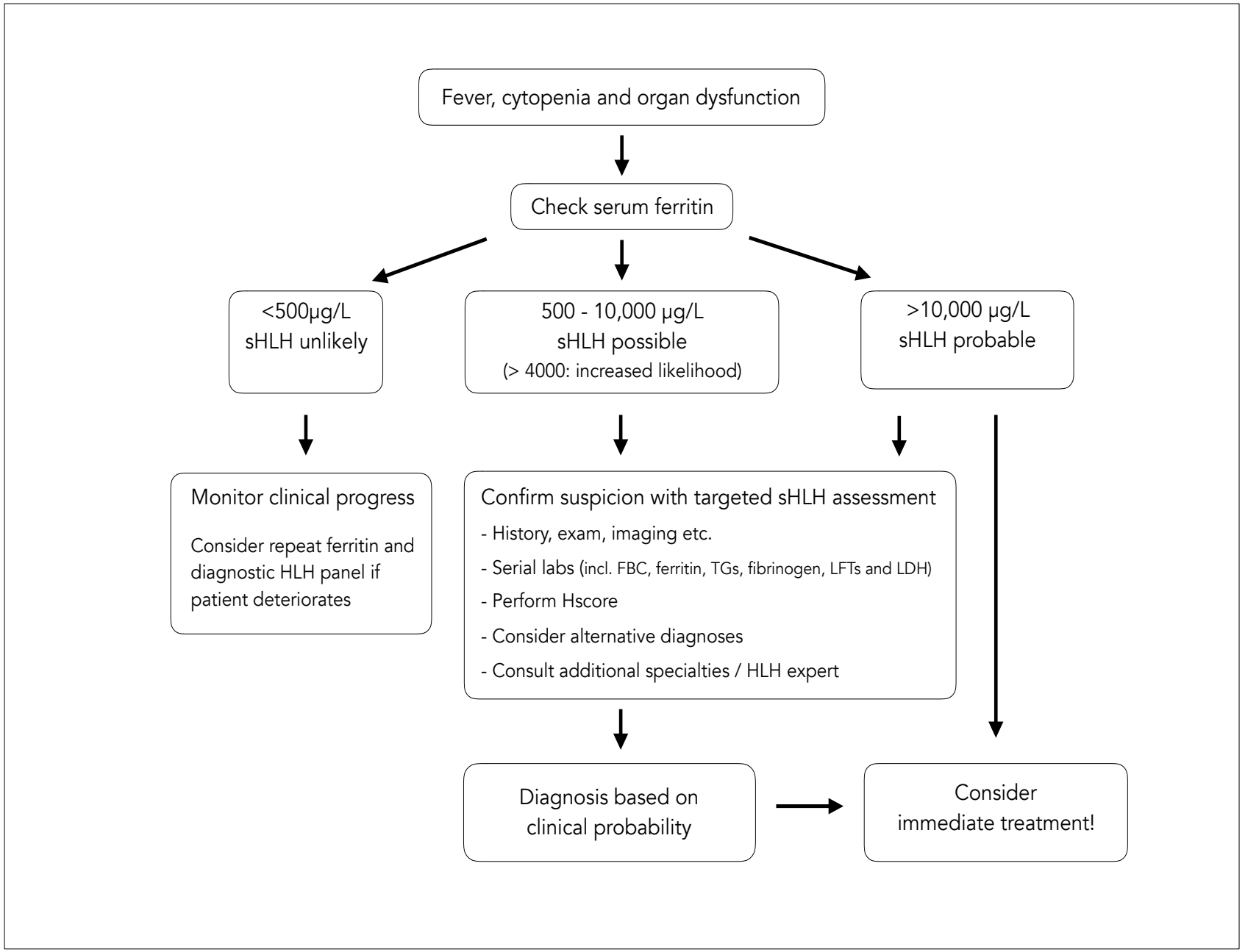
Triglycerides >156 mg/dl

Fibrinogen ≤360 mg/dl

H score
Fardet et al A+R 2014
http://saintantoine.aphp.fr/score/

Would this patient benefit from immunosuppression?

When to suspect HLH (adapted from Carter *et al*, 2018)



HLH for rheumatologists

Who do we treat?

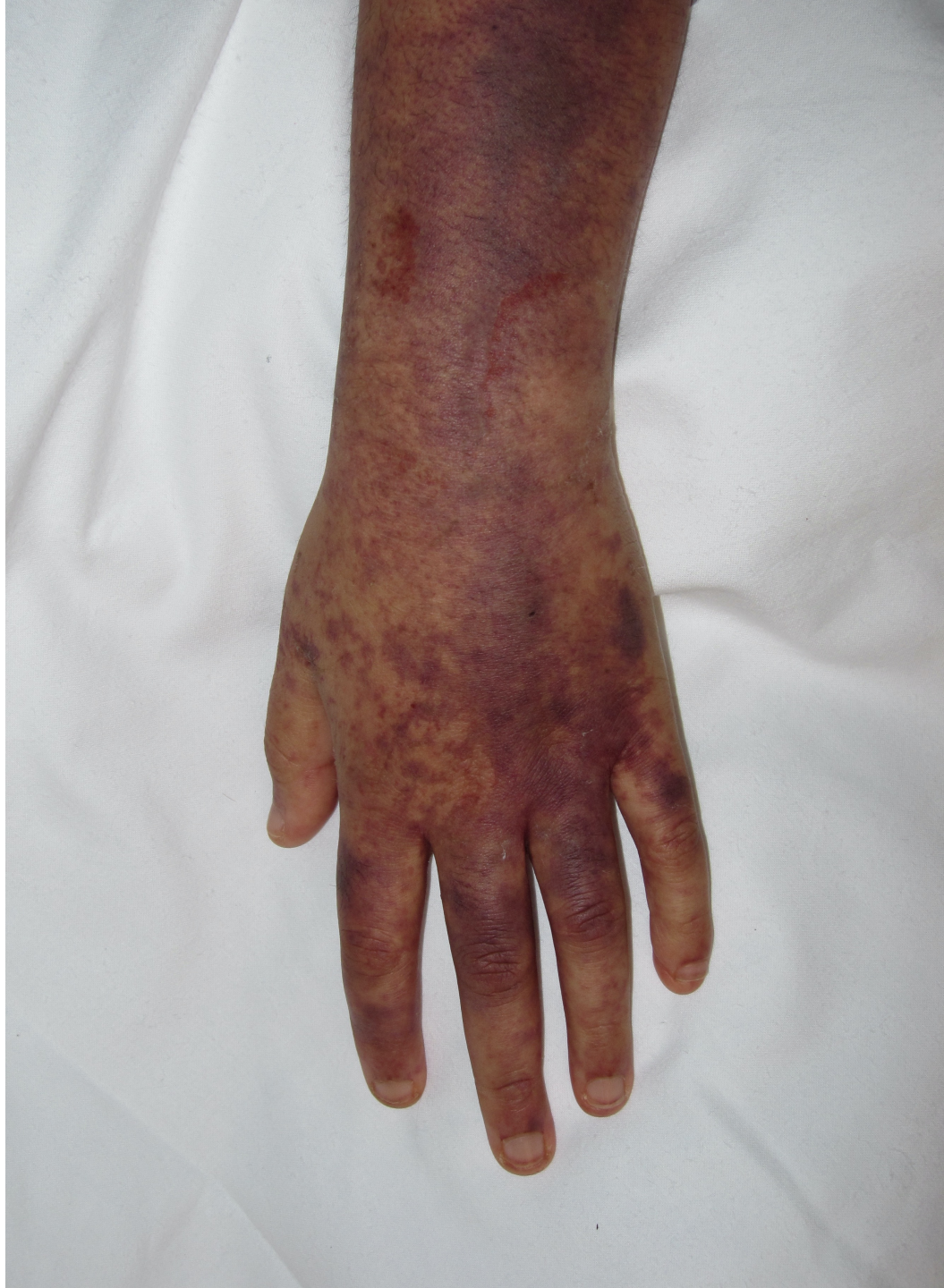
- AOSD/sJIA
- SLE

Why we are well placed to do it?

- Experience in looking after sick patients
- Experience in using corticosteroids and biologics

HLH: personal interest

- How it all began (for me)
  - Index case
- Session at BSR
  - Identified need for cross-specialty working
  - Convinced of under-recognition
  - Pockets of knowledge
  - Unfair access to treatment



The formation of HiHASC in 2018

- **Aim:**

- To improve outcome for patients with HLH by:
  - Raising awareness
  - Cross specialty working/learning
  - Research

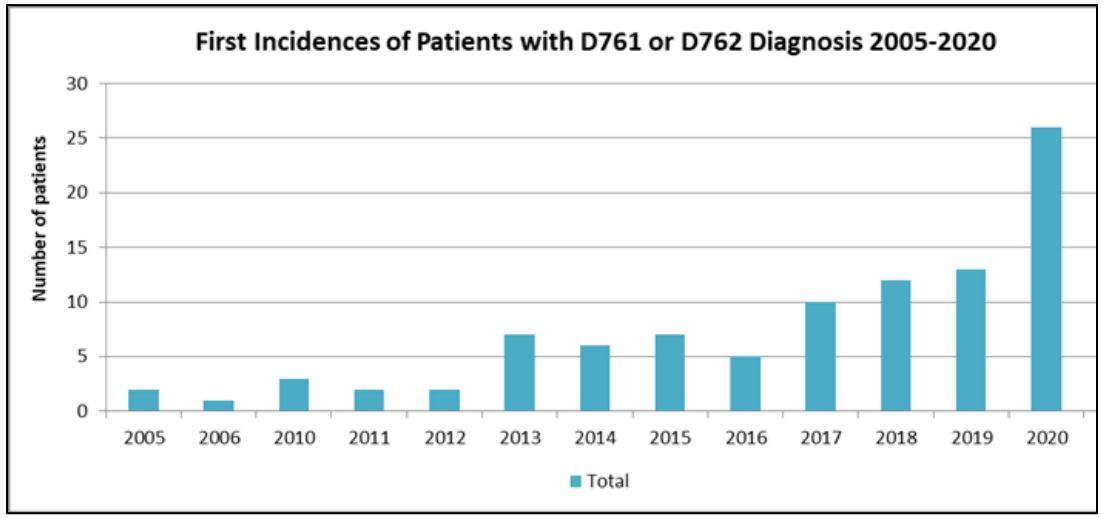
- **Who:**

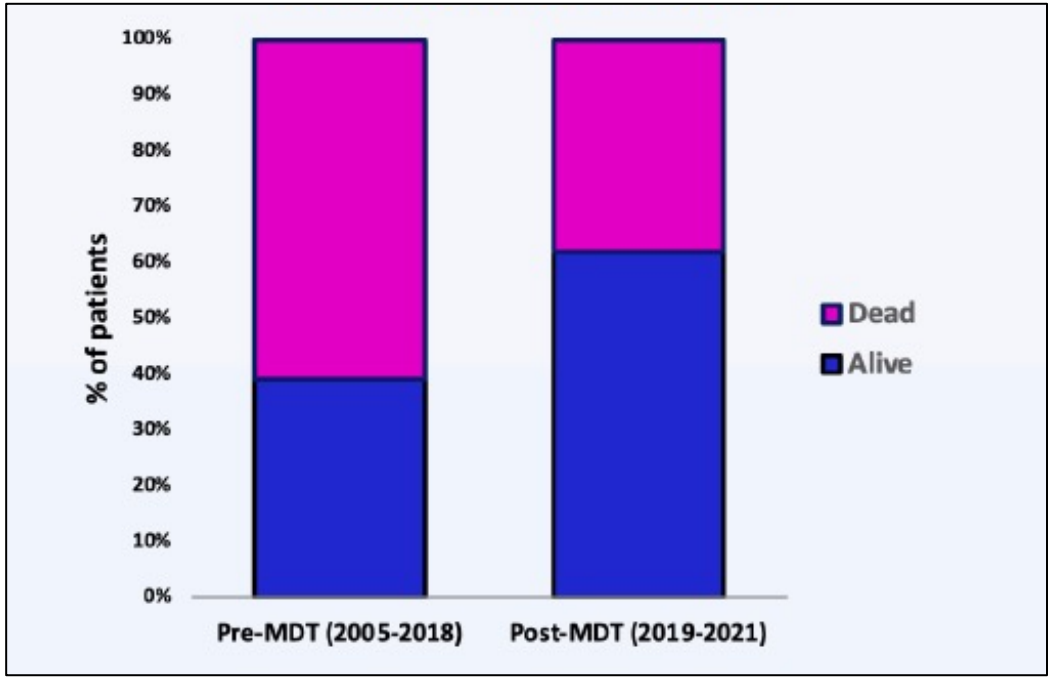
- Pan-UK
- All age groups
- Across all specialties

- Initially two meetings per year, 15 members
- And then…

www.hishasc.org

The formation of the UCLH HLH MDT in 2019





COVID and hyperinflammation

Early recognition of an unusual (and deadly) disease phenotype

	Normal Range	Died (N=68)	Discharged (N=82)	p-value
Alanine aminotransferase, U/L	9.0-50.0	170.8 (991.6)	48.68 (83.1)	0.35
C-reactive protein, mg/L	0.0-5.0	126.6 (106.3)	34.1 (54.5)	＜0.001
Interleukin-6, ng/mL	0.0-7.0	11.4 (8.5)	6.8 (3.61)	＜0.001
Serum ferritin, ng/mL	21.8-274.7	1297.6 (1030.9)	614.0 (752.2)	＜0.001
White blood cell count, $\times 10^9$/L	3.50-9.50	10.62 (4.76)	6.76 (3.49)	＜0.001
Lymphocyte count, $\times 10^9$/L	1.10-3.20	0.60 (0.32)	1.42 (2.14)	＜0.001
Haemoglobin, g/L	130.0-175.0	127.0 (16.7)	127.6 (16.3)	0.82
Platelet count, $\times 10^9$/L	125.0-350.0	173.6 (67.7)	222.1 (78.0)	＜0.001

Ruan, Qiurong et al. “Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China.” *Intensive care medicine* vol. 46,5 (2020): 846-848. doi:10.1007/s00134-020-05991-x

Do a subgroup of patients develop a hyperinflammatory response?

- What is in a name?

Controversy over terminology

- The key questions were:

Should we immunosuppress these patients?

In trials or empirical treatment?

- Role of a rheumatologist:

Which drugs to consider?

What side effects to look out for?

> Lancet. 2020 Mar 28;395(10229):1033-1034. doi: 10.1016/S0140-6736(20)30628-0. Epub 2020 Mar 16.

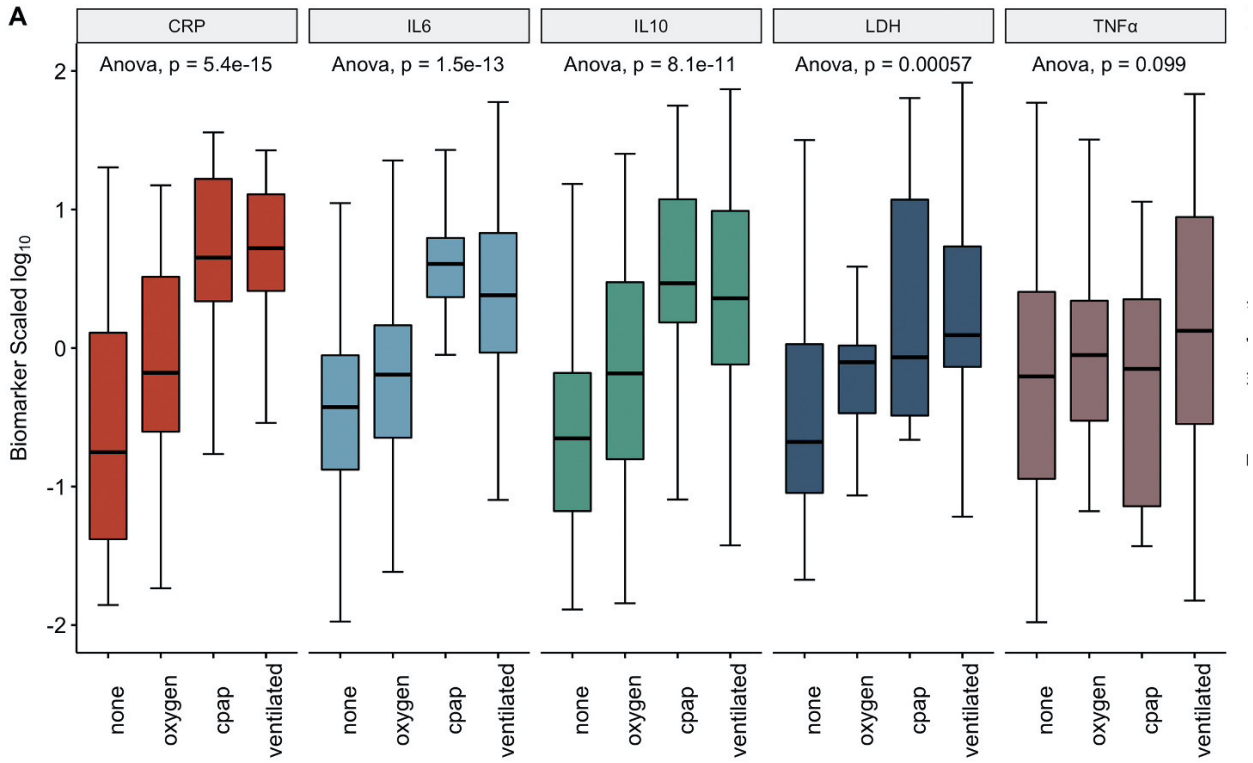
COVID-19: Consider Cytokine Storm Syndromes and Immunosuppression

Puja Mehta [1], Daniel F McAuley [2], Michael Brown [3], Emilie Sanchez [4], Rachel S Tattersall [5], Jessica J Manson [6], HLH Across Speciality Collaboration, UK

Cytokine storms hit the headlines

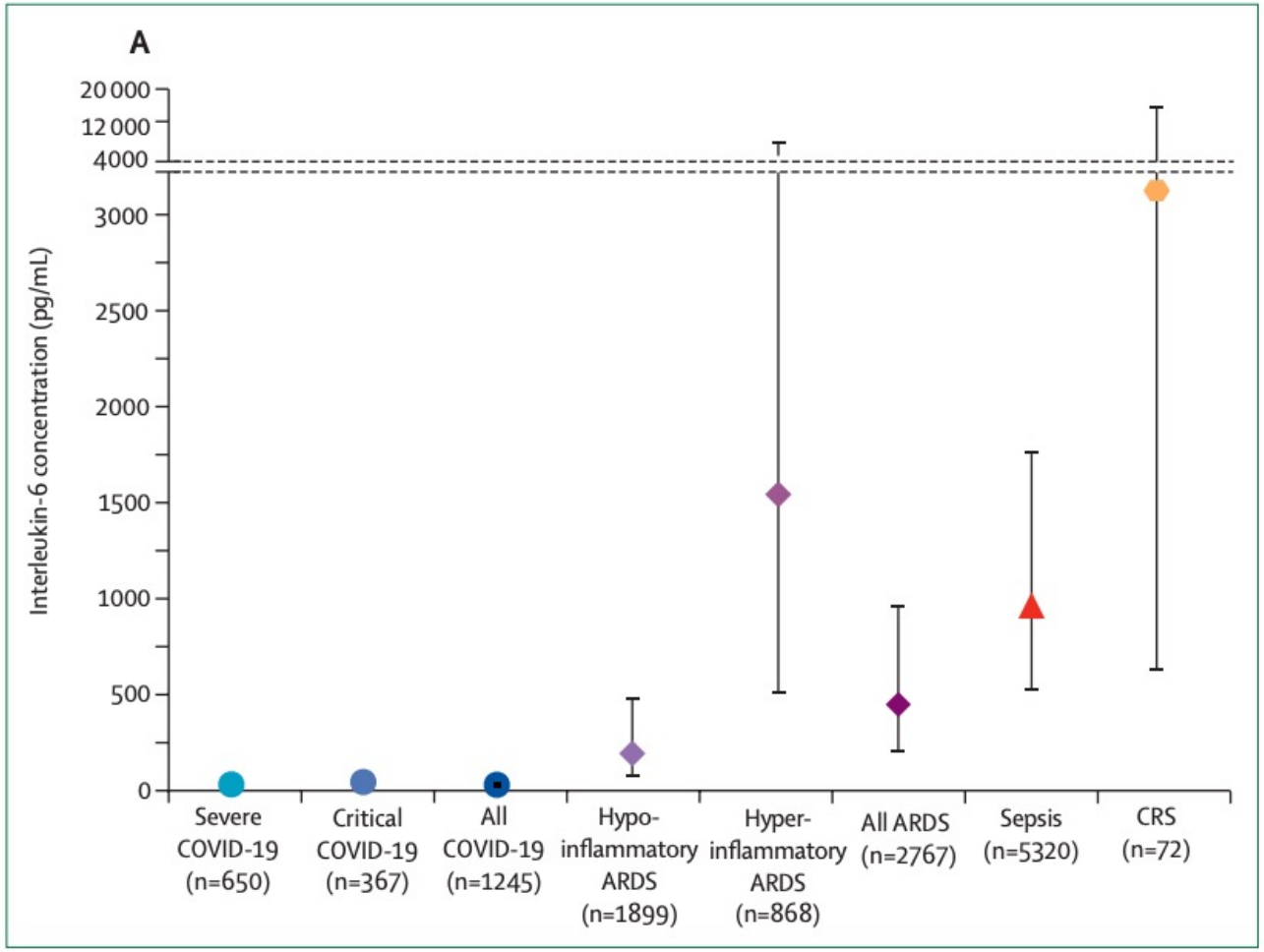
- HiHASC membership shot up
- We were asked to treat patients and produce guidelines
- Trials of immune modulation took off

Cytokine levels and need for ventilatory support



Keddie *et al*, Clinical Immunology, 2020

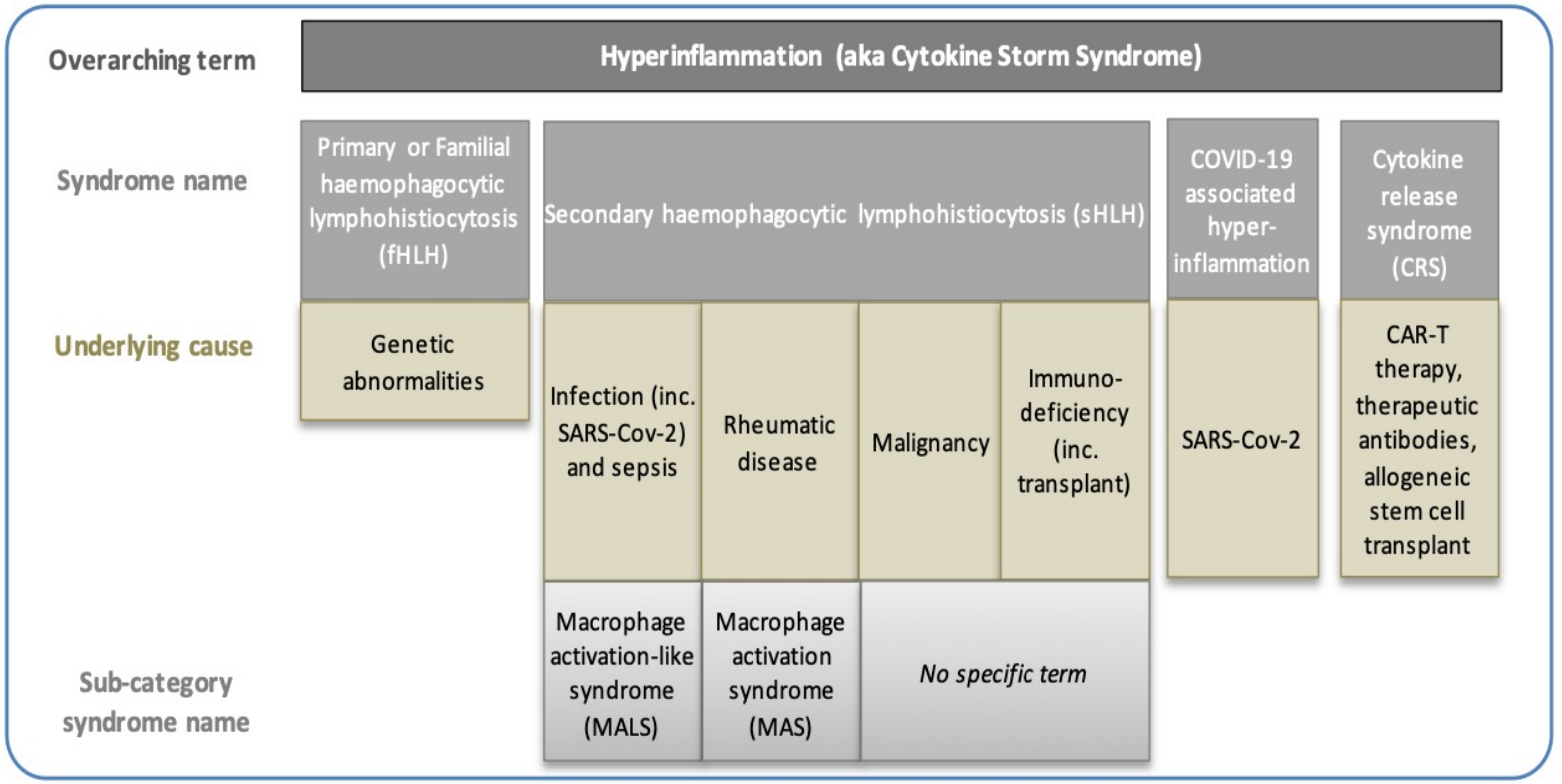
A storm about a storm



Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes

Daniel E Leisman, Lukas Ronner*, Rachel Pinotti, Matthew D Taylor, Pratik Sinha, Carolyn S Calfee, Alexandre V Hirayama, Fiore Mastroiani, Cameron J Turtle, Michael O Harhay, Matthieu Legrand, Clifford S Deutschman*

Cytokine storm syndromes: where does COVID-19 fit?



https://ctag-support.org.uk/docs/immunomodulators.pdf

Subtypes of hyperinflammation in COVID-19

New syndromes

- Severe COVID pneumonia
  - High CRP
  - Moderately high ferritin
- PIMS-TS/MIS-C (also adults)
- Neurological inflammatory disease

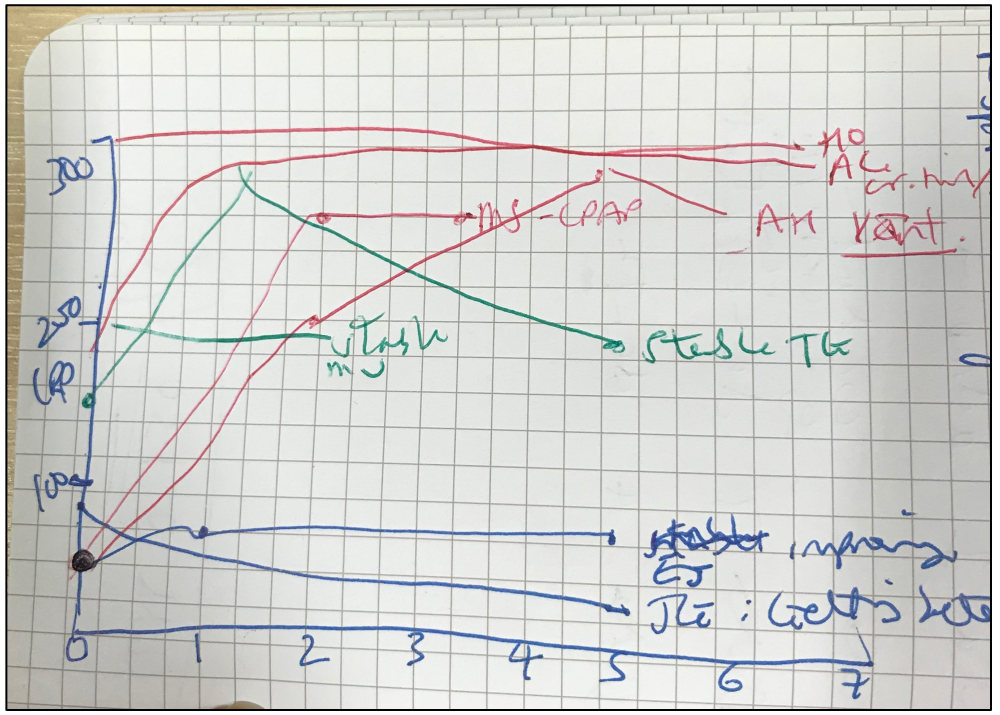
Recognized diseases

- HLH
- Vasculitis
- Chronic fatigue/long COVID???

COV-HI

Defining the COV-HI phenotype

- COVID pneumonia and HI response:
  - 7-10 days into infection
  - High CRP
  - Moderately elevated ferritin
  - Raised D-dimer
  - Need for respiratory support
  - Risk of death



Defining the HI response to COVID: Why does it matter?

- Important to recognize and define disease patterns
  - understand the aetiopathogenesis
  - extrapolate to other (rare) HI conditions

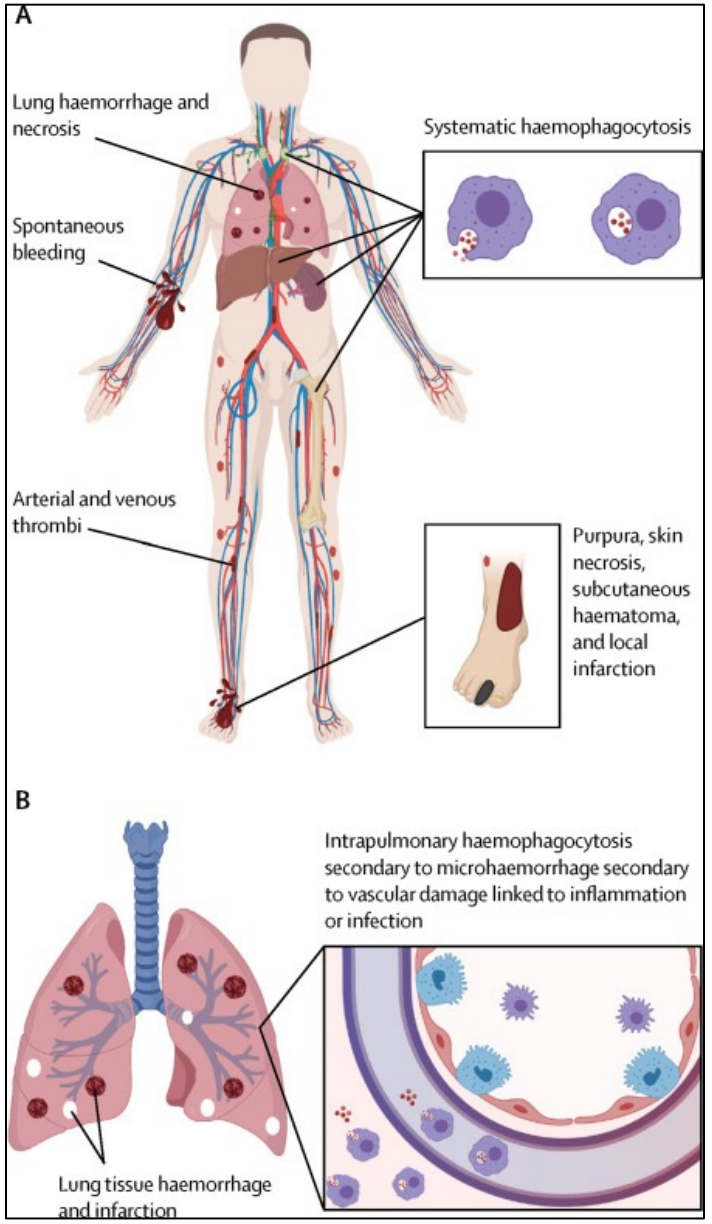
- Phenotyping of COVID hyperinflammation important
  - clinical and therapeutic benefit
  - stratify patient groups in trial design

What is the pathology?

- Early post-mortem studies:

- Alveolar damage, lung vessel thrombosis, pulmonary infarction
- Marked inflammatory cell infiltrate into vessel walls and tissue haemophagocytosis

➢ **Pulmonary intravascular coagulopathy**



Hanley *et al*, Lancet Microbe 2020
McGonagle *et al*, Lancet Rheum 2020

COV-HI: retrospective cohort study

- Aiming to
  - Define hyperinflammatory phenotype of severe COVID "COV-HI"
  - Understand COV-HI relationship to need for ventilatory support/death
- Retrospective cohort study across 2 UK centres (UCLH, Newcastle)
- Inclusion criteria
  - 18yrs+, +ve Sars-Cov2 swab, community acquired infection
  - First wave of pandemic: March 2020
- Consensus definition of **COV-HI**
  - **Ferritin>1500, CRP > 150 (or daily doubling from 50)**
- **Initial and repeated COV-HI criteria analysed against need for next day respiratory support or death**
  - **(multi-level logistic regression model)**

COVID-19-associated hyperinflammation and escalation of patient care: a retrospective longitudinal cohort study

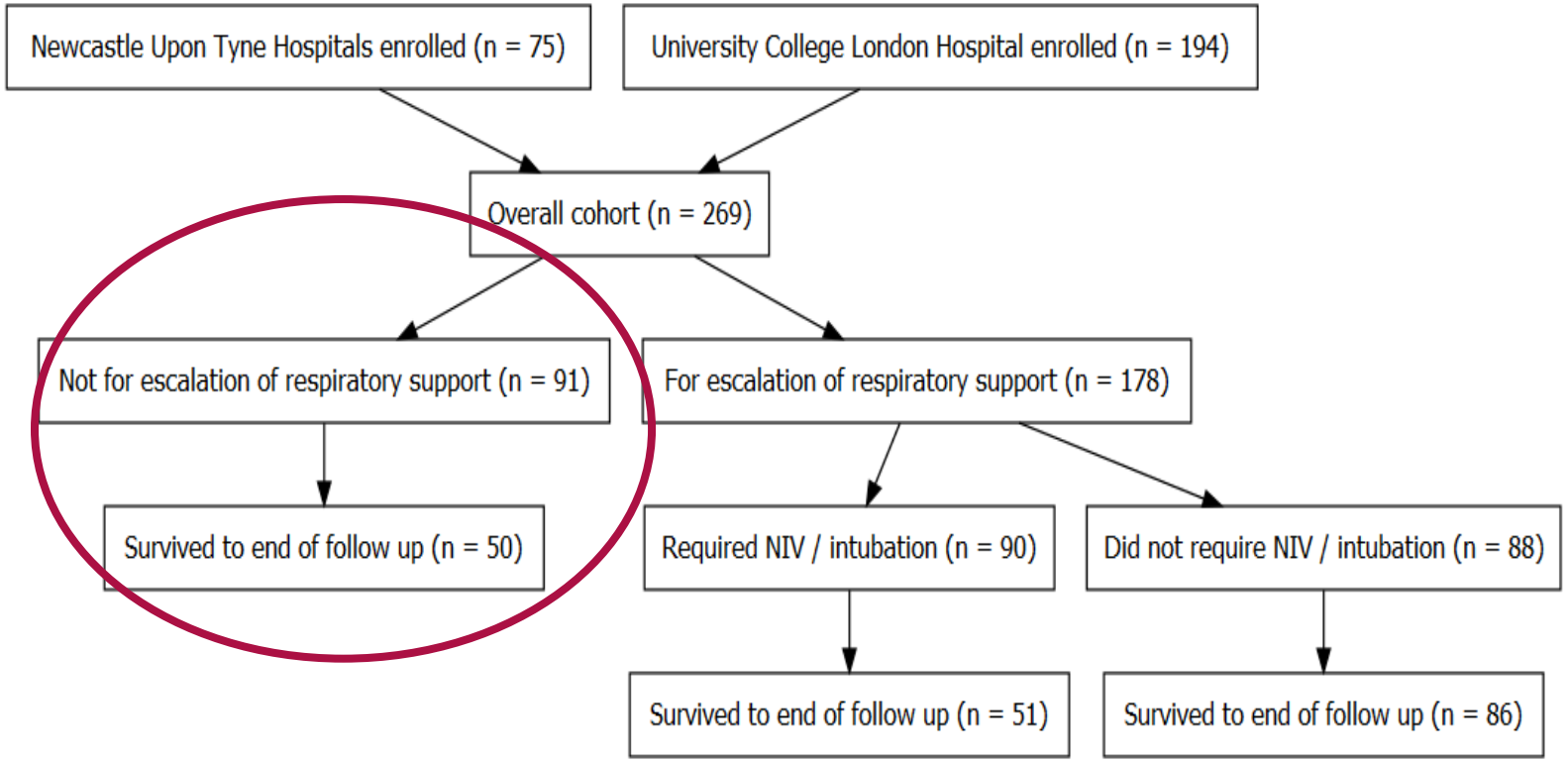
Jessica J Manson, Colin Crooks*, Meena Naja, Amanda Ledlie, Bethan Goulden, Trevor Liddle, Emon Khan, Puja Mehta, Lucia Martin-Gutierrez, Kirsty E Waddington, George A Robinson, Liliana Ribeiro Santos, Eve McLoughlin, Antonia Snell, Christopher Adeney, Ina Schim van der Loeff, Kenneth F Baker, Christopher J A Duncan, Aidan T Hanrath, B Clare Lendrem, Anthony De Soyza, Junjie Peng, Hajar J'Bari, Mandy Greenwood, Ellie Hawkins, Hannah Peckham, Michael Marks, Tommy Rampling, Akish Luintel, Bryan Williams, Michael Brown, Mervyn Singer, Joe West†, Elizabeth C Jury†, Matthew Collin†, Rachel S Tattersall†*

Lancet Rheumatol 2020; 2: e594–602

Published Online August 21, 2020 https://doi.org/10.1016/S2665-9913(20)30275-7

What happened to the patients?

Total cohort - death approx. 30%



COV-HI results: headlines

- 90/269 (33%) met COV-HI criteria at admission
  - This COV-HI group were younger with lower frailty scores than the non-COV HI group but were more likely to die (40% cf 26%)

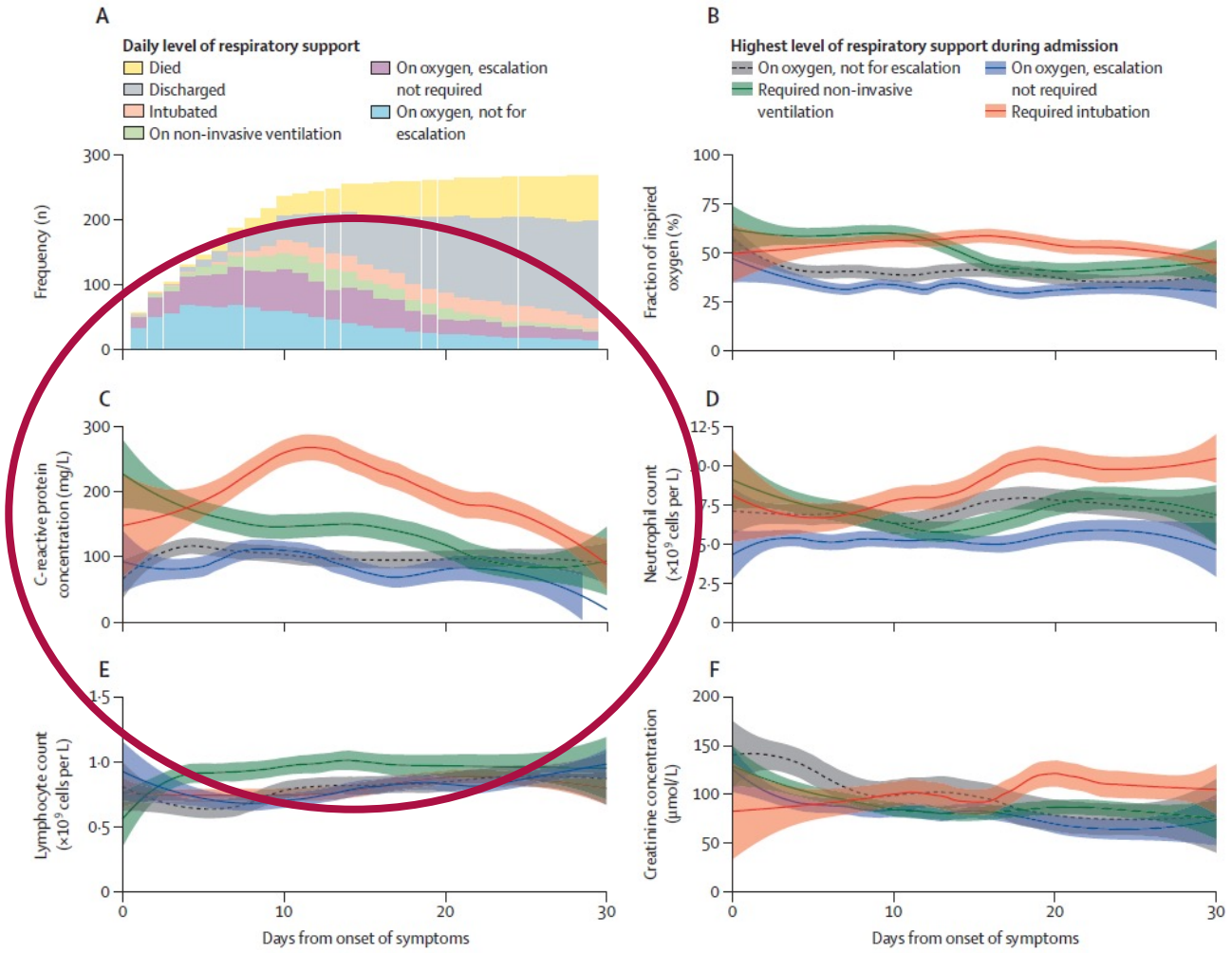
- 90/178 (50%) patients care was escalated to respiratory support (either NIV or mechanical ventilation)
  - 67 (74%) of this group met COV HI criteria by the day of escalation

- **Meeting the COV-HI criteria was significantly associated with the risk of next-day escalation of respiratory support or death (hazard ratio 2·24 [95% CI 1·62–2·87]) after adjustment for age, sex, and comorbidity.**

Longitudinal data: trajectories of disease

- Daily bloods
- Daily clinical data

- CRP: separate on basis of need for ventilatory support

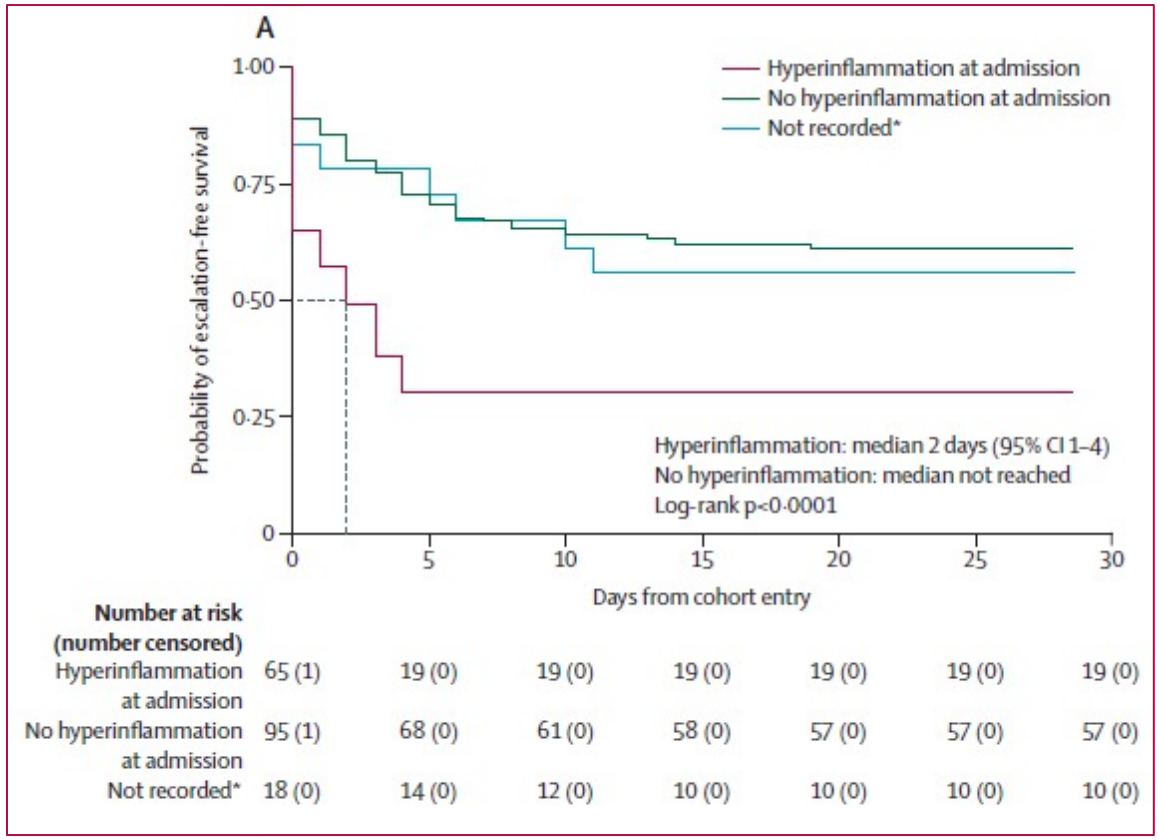


COV-HI on admission: mortality

	Patients, n (%)	Died by end of follow-up, n	Crude mortality, %
Not eligible for escalation (n=91)			
Hyperinflammation	25 (27%)	17	68%
No hyperinflammation	60 (66%)	22	37%
Unrecorded	6 (7%)	..	..
Eligible for escalation (n=178)			
Hyperinflammation	65 (37%)	19	29%
No hyperinflammation	95 (53%)	19	20%
Unrecorded	18 (10%)	..	..

Patients were stratified according to eligibility for treatment escalation at admission and whether they met the criteria for hyperinflammation at admission (C-reactive protein concentration >150 mg/L or ferritin concentration >1500 µg/L).

Table 1: **Summary of patient mortality**



Use of COV-HI criteria

- Can we predict outcome on the basis of meeting our pre-set criteria?
  - Study not designed or big enough for final answer
  - Some data to suggest these criteria might be important
- CRP was the main factor in most of these patients
  - About 20% met the ferritin cut-off (this was early in the pandemic)
- H score not obviously useful but too few to be sure

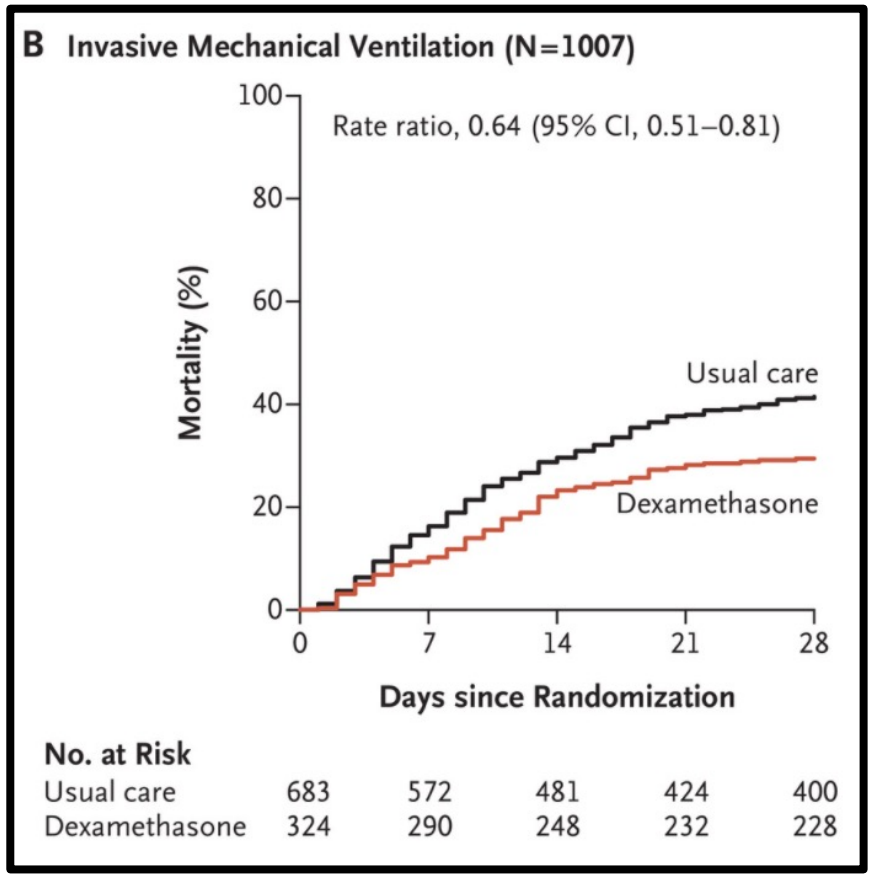
It wasn’t just us doing this..

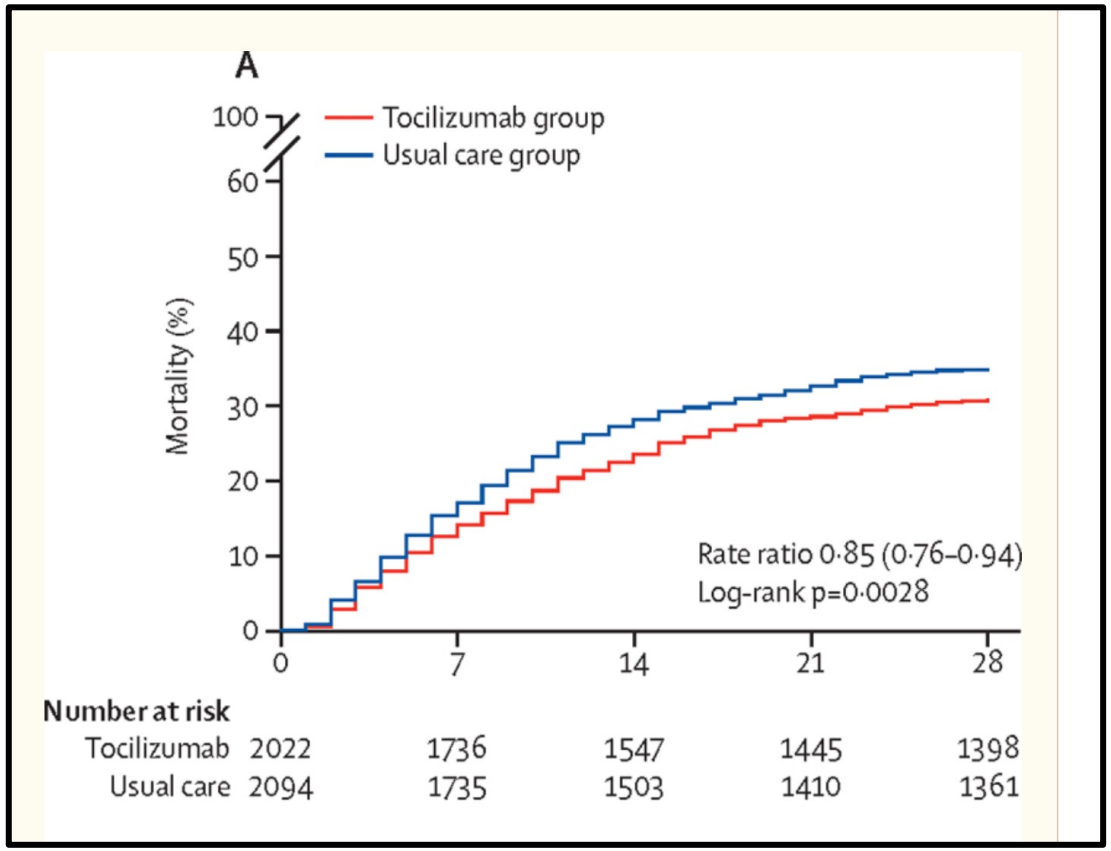
- cHIS:
  - Fever
  - Macrophage activation (ferritin)
  - Haematological dysfunction
  - Coagulopathy
  - Cytokinaemia
  - >2 features associated with increased mortality (OR 1.6)

Webb et al, Lancet Rheum, 2020

Treating COVID-19 with immune suppression

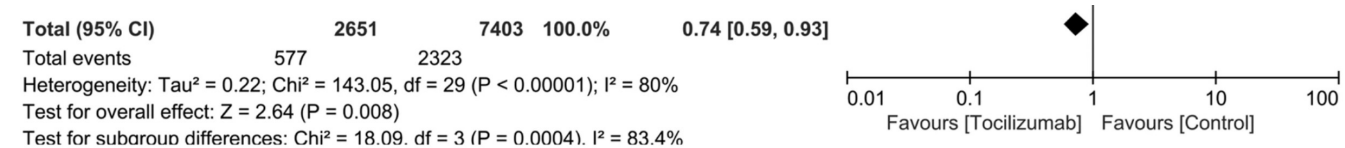
RECOVERY: dexamethasone and tocilizumab





Tocilizumab in COVID: not everyone is convinced

- Systematic review of trials
- 11,487 people
- Relative Risk (RR) of death = 0.74 (95% Confidence Interval [CI], 0.59, 0.93; $P = 0.008$; $I^2 = 80\%$).
- Studies with historical controls (RR = 0.28) or with an otherwise matched cohort (RR = 0.68) reported significant survival improvement.
- In contrast, RRs of death in studies with concurrent controls (RR = 1.10) and randomized trials (RR = 1.18 (0.57, showed no significant improvement in survival.



Risk of death.

Chen CX *et al*. Systematic review and meta-analysis of tocilizumab in persons with coronavirus disease-2019. Leukemia. 2021.

COV-HI next steps

- Larger cohort to see if:
  - COV-HI definition holds
  - We can generate a better one

- Establish whether defining a HI response and selecting out these patients improves response to immune therapy and thus limits unnecessary toxicity

- Linked to ISARIC
  - Understanding the immunology

COVID-HLH

HLH and COVID

	Sex	Age, years	Notable comorbidities	Time from admission to secondary haemophagocytic lymphohistiocytosis diagnosis, days	Peak ferritin, µg/L	Mechanical ventilation	Inotropic support	Renal replace-ment therapy	Other treatments received	Final patient outcome (days to death or discharge)
Patient 1	Male	40	Acute lymphoblastic leukaemia	28	76 225	Yes	No	No	Piperacillin and tazobactam preparation, meropenem, and liposomal amphotericin B	Died (74)
Patient 2	Male	28	Recurrent pneumonias	6	3164	Yes	Yes	No	Cefuroxime	Died (7)
Patient 3	Male	36	Acute lymphoblastic leukaemia	12	17 085	No	No	No	Meropenem, liposomal amphotericin B, and filgrastim	Discharged (31)
Patient 4	Male	36	No medical history	1	5736	Yes	Yes	No	Potassium clavulanate and amoxicillin preparation	Discharged (16)
Patient 5	Female	60	Systemic lupus erythematosus	3	12 402	Yes	Yes	Yes	Glucocorticoids (ie, for systemic lupus erythematosus)	Died (42)
Patient 6	Male	56	Asthma	3	9245	Yes	Yes	No	Potassium clavulanate and amoxicillin preparation and meropenem	Discharged (43)
Patient 7	Male	63	Type 2 diabetes and atrial fibrillation	0	17 790	Yes	Yes	No	Potassium clavulanate and amoxicillin preparation and piperacillin and tazobactam preparation	Discharged (11)
Patient 8	Male	54	Asthma	0	19 078	Yes	Yes	Yes	Glucocorticoids, potassium clavulanate and amoxicillin preparation, piperacillin and tazobactam preparation, and meropenem	Died (32)
Patient 9	Male	52	Previous deep vein thrombosis	1	12 607	Yes	Yes	Yes	Piperacillin and tazobactam preparation, clarithromycin, meropenem, vancomycin, and ciprofloxacin	Discharged (96)
Patient 10	Female	22	Sickle cell trait	9	45 864	No	Yes	No	Piperacillin and tazobactam preparation, ciprofloxacin, clindamycin, metronidazole, meropenem, linezolid, ceftazidime, and fluconazole	Discharged (40)

Table: Summary of patient demographics and treatments received that were not specific to secondary haemophagocytic lymphohistiocytosis by patient

Flower *et al,* Lancet Rheum 2021

COVID and HLH

- Relatively young cohort
- All required ICU admission
- 4/11 deaths
- Still possible to make the diagnosis with clinical confidence

- We mustn't forget the medicine we already know

SUMMARY:

COVID induces hyperinflammation with recognizable phenotypes

COV-HI may be ‘localized pulmonary cytokine storm’

COVID can also cause frank sHLH

Rheumatologists have a clear role in the management of patients with hyperinflammation

Multi-centre trials of immune modulation in very sick people are possible

Acknowledgements

- Dr Rachel Tattersall
- Prof Liz Jury
- COV-HI collaborators
- The UCLH HLH MDT
- All of HiHASC

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Any questions?