Chronic manifestations of CoVID 19

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"Death is not the only adverse outcome of covid-19"

- Reports suggest 30% have not fully recovered several weeks after initial illness
- Some persist for months
- Often physically fit, younger people with persistent exercise intolerance, breathlessness, cough, anxiety, palpitations, poor concentration intense fatigue, mood swings, muscle & joint pains, headaches & brain fog
- Suffer the illusion of recovery only to fall back into mental and physical exhaustion

Alwan BMJ Opinion 2020
Garner BMJ Opinion. 23 Jun 2020
Thornton BMJ 2020

Persistent symptoms in CoVID Positive Patients

- 292 patients interviewed; 94% had ≥ 1 symptom at diagnosis; of these 35% had not recovered at a median 16d post testing; 26% aged 18–34yrs, 32% 35–49yrs, 47% ≥50 yrs
- 43% of those with cough, 35% fatigue, 29% SOB initially, still had these symptoms
- Prolonged illness occurs even in young patients with mild illness
- Age ≥50 vs 18–34 aOR = 2.29 (1.14–4.58); ≥ 3 vs no comorbidities aOR = 2.29 (1.07–4.90); BMI ≥30 aOR 2.31 (1.21–4.42); psychiatric condition aOR 2.32 (1.17–4.58) associated with ongoing ill health

https://www.cdc.gov/mmwr/volumes/69/wr/mm6930e1.htm

CoVID 19: Post ICU Syndrome (PICS)

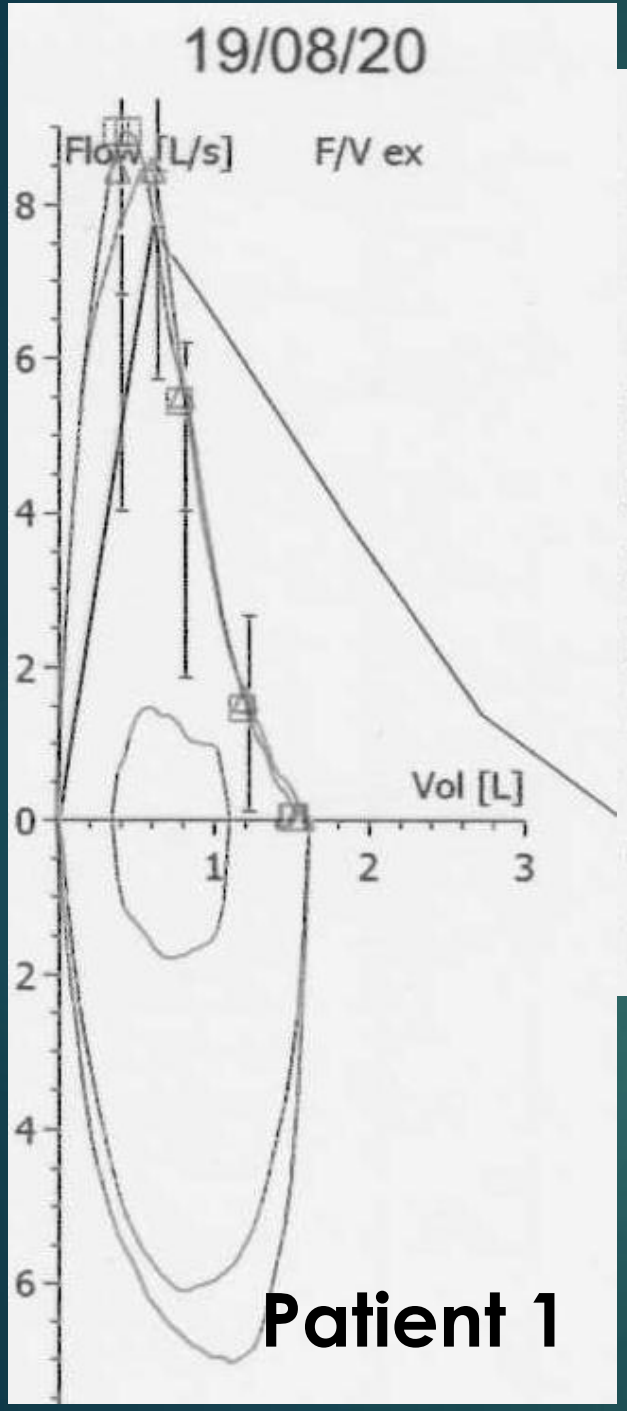
- Health problems that remain after critical illness
- Present when the patient is in ICU & may persist after the patient is discharged
- ICUAW: 50% who stay in ICU for ≥1 week may take more than 1 year to recover
- Most studies report persistent anxiety & depression at 12 months, but some report PTSD for up to 8 years
- 3-fold increase in odds of moderate/severe cognitive impairment

Davidson MyICUCare Website: Society of Critical Care Medicine
Mikkelsen Crit Care Med 2012; 185:1307
Wunsch JAMA 2014;311:1133
Huang Crit Care Med 2016; 44:954

CoVID 19: Respiratory Complications

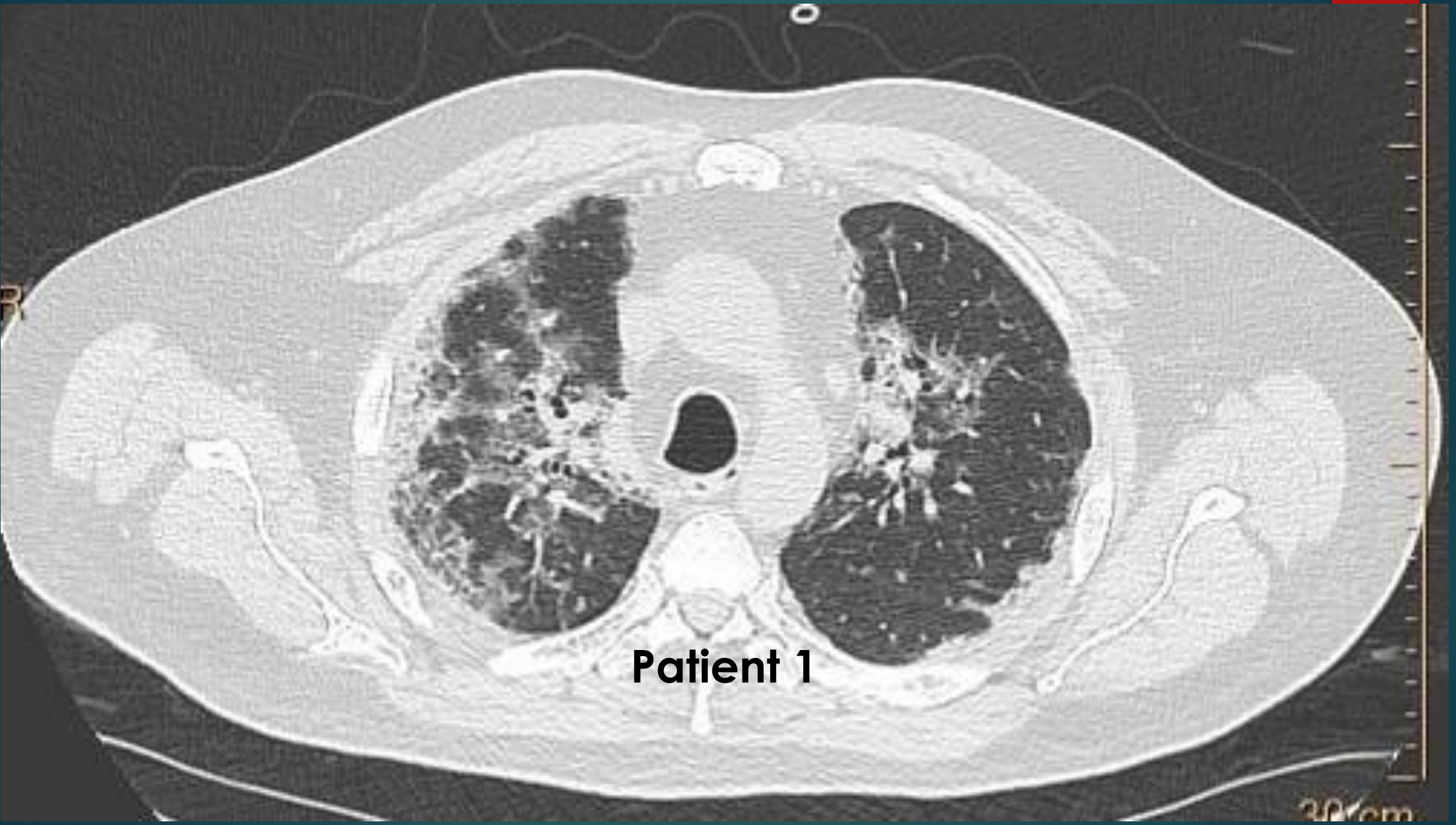
- Chronic cough, lung fibrosis, bronchiectasis, PED disease
- 30% with SARS or MERS had persistent lung abnormality, most mild with a DLCOs of 70-80%
- Risk factors for moderate/severe covid-19 are similar to IPF, (males & age) & CoVID targets alveolar epithelial cells like herpes which has been implicated in IPF pathogenesis

Fraser BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m3001

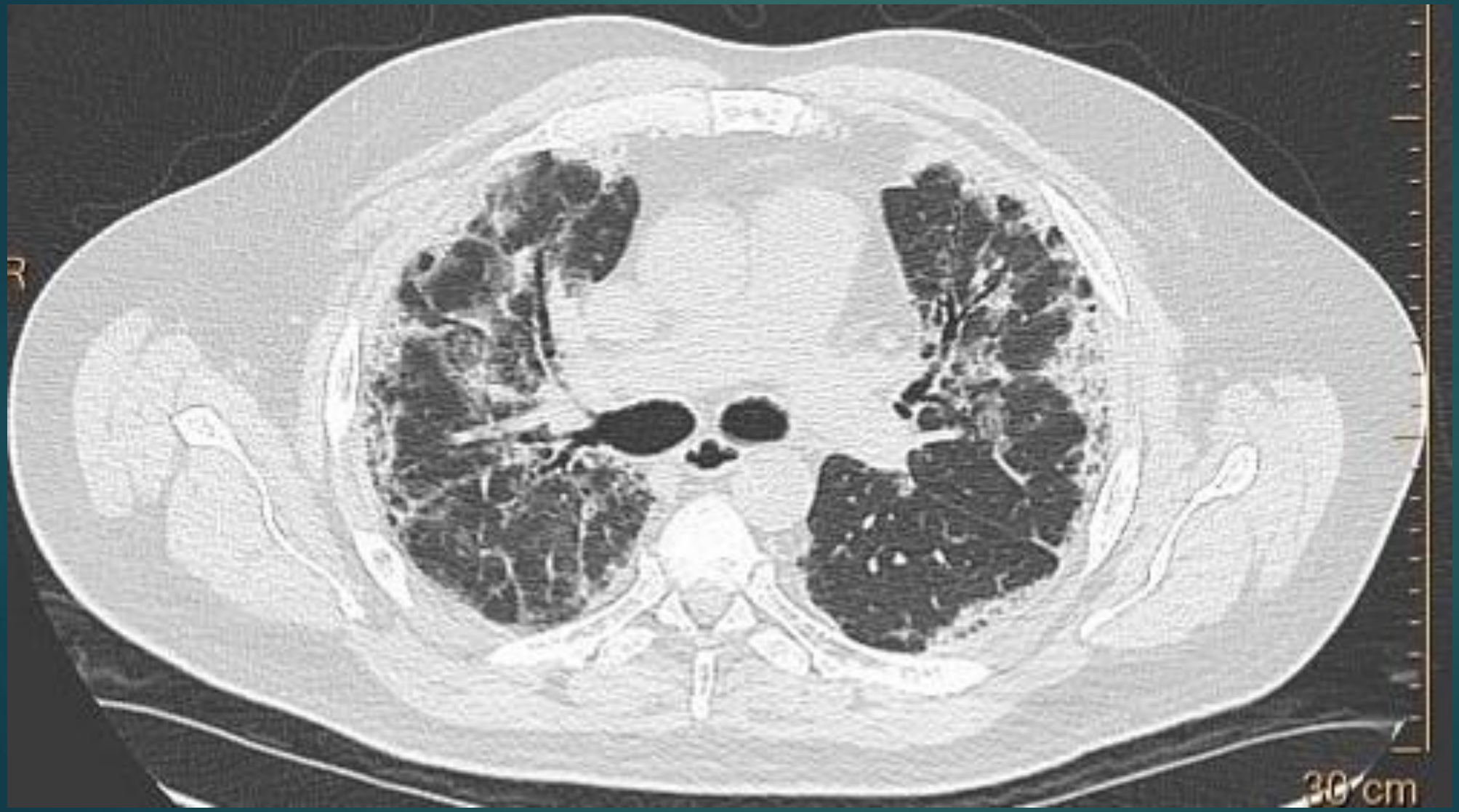


Patient 1

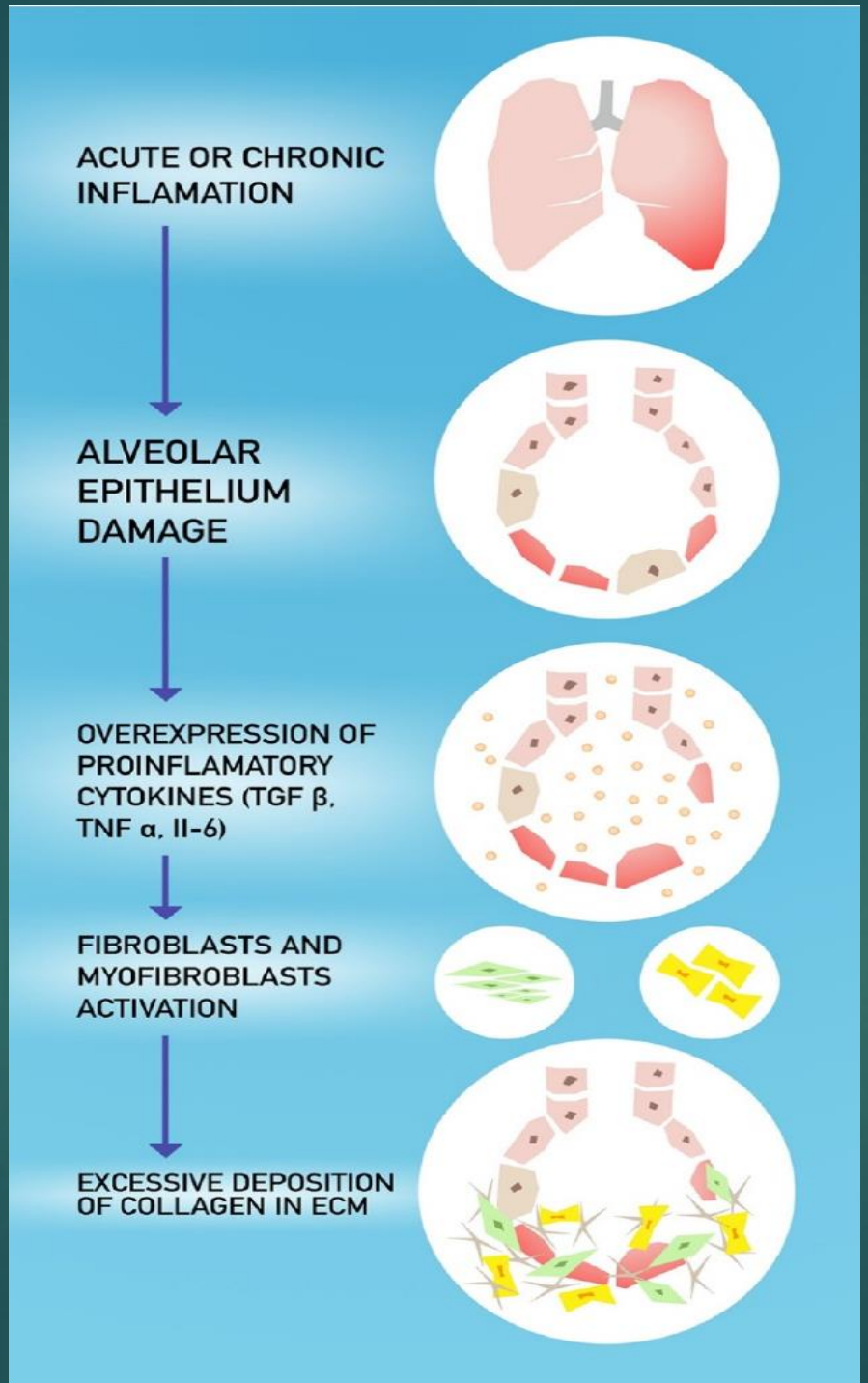
	Actual	Pred	%Pred
FVC	1.55	3.64	42
FEV 1	1.53	2.86	53
FEV 1 % FVC	98.77		
PEF	8.89	7.69	116
MEF 75	8.89	6.82	130
MEF 50	5.40	4.03	134
MEF 25	1.43	1.38	103
MMEF 75/25	3.73	3.23	115
FVC IN	1.61	3.77	43
FIF 50	6.15		
VC MAX	1.61	3.77	43
FEV 1 % VC MAX	94.72	75.87	125
DLCO SB	2.51	8.37	30.0
VA	2.05	6.11	33.6
DLCO/VA	1.22	1.34	91.6
VIN	1.60	3.77	42.4



Patient 1


R
30 cm

Fibrosis in CoVID



Lechowicz J Clin Med 2020

Prediction of Development of Fibrosis

- 32 confirmed COVID-19 patients,14 with fibrosis
- Fibrosis group: older (median age: 54.0 vs 37.0 (p=0.008), CRP 53.4 vs 10.0 (p= 0.002); IL-6 79.7pg/L vs 11.2 (p = 0.04); LO hospital stay 19.5 days vs. 10.0 (p = 0.001), pulsed steroid therapy 11.0 days vs 5.0 (p < 0.001); antiviral therapy (12.0 vs 6.5 days (p =0.012).

Yu Korean J Radiol 2020;21(6):746-755

Causes: Interaction of FIO2 & Tidal Volume

- Pre-exposure to hyperoxia for 12 hrs pre high-stretch ventilation produced severe interstitial edema, haemorrhage & PMNL infiltration in 4hrs
- High stretch ventilation without prior hyperoxia, hyperoxia alone, or both strategies combined, all produced mild changes
- Hyperoxia markedly increased lethality of Legionella & Pseudomonas pneumonia in mouse models

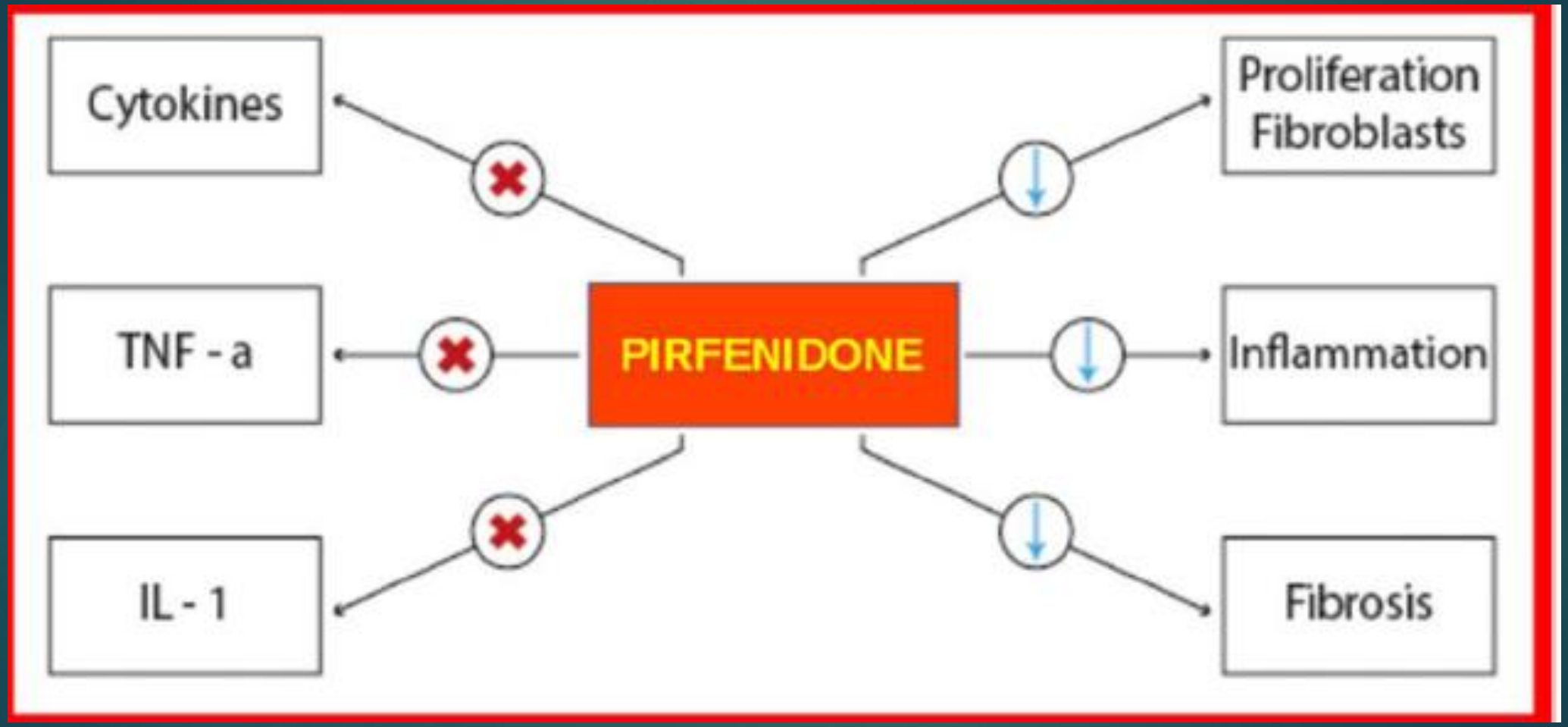
Makena Am J Physiol Lung Cell Mol Physiol 2010
Makena J Appl Physiol 2011
Tateda J Immunol 2003
Kikuchi Pulm Pharmacol Ther 2009

Prevention? Colchicine

- Inexpensive, lipid-soluble alkaloid which rapidly accumulates in granulocytes & monocytes (in multiples of plasma levels) with ensuing anti-inflammatory effects.
- It inhibits NLRP3 inflammasomes & reduces interleukin activation
- An Israeli team identified a molecule "alpha defensin", which is inhibited by colchicine, as a possible cause of CoVID 19 coagulopathy

Deftereos European Heart Journal - Cardiovascular Pharmacotherapy doi:10.1093/ehjcvp/pvaa033
JAFFE-HOFFMAN https://www.jpost.com/health-science/hadassah-doctors-crack-the-cause-of-fatal-coro

Pirfenidone



Vitiello SN Comprehensive Clinical Medicine

Pirfenidone: Case report

Covid 19: sat 88-90% treated with alluvia, polygam 20g x 5 days, methylpred 40mg dy x 3
Prescribed Pirfenidone 600mg tds on discharge. Dyspnea improved gradually & sat improved 6 wks later follow-up CT showed a substantial improvement

Zhan Xi Archives of Pulmonology and Respiratory Care 2020

Prevention Plugging

Taban and Richards AJTCCM

Prevention? Nebulised Heparin

- COVID-19 ARDS displays typical DAD with DPIC with fibrin deposition in the microvasculature & alveolar hyaline membrane formation
- Extent of coagulopathy correlates with poor outcomes.
- Nebulised UFH limits fibrin deposition & microvascular thrombosis
- In ALI inhaled UFH reduces dead space, coagulation, microvascular thrombosis, clinical deterioration & LO MV
- UFH is anti-inflammatory, mucolytic & inactivates SARS-CoV-2, preventing cell entry

van Haren Crit Care. 2020;24(454)

Prevention of Fibrosis?

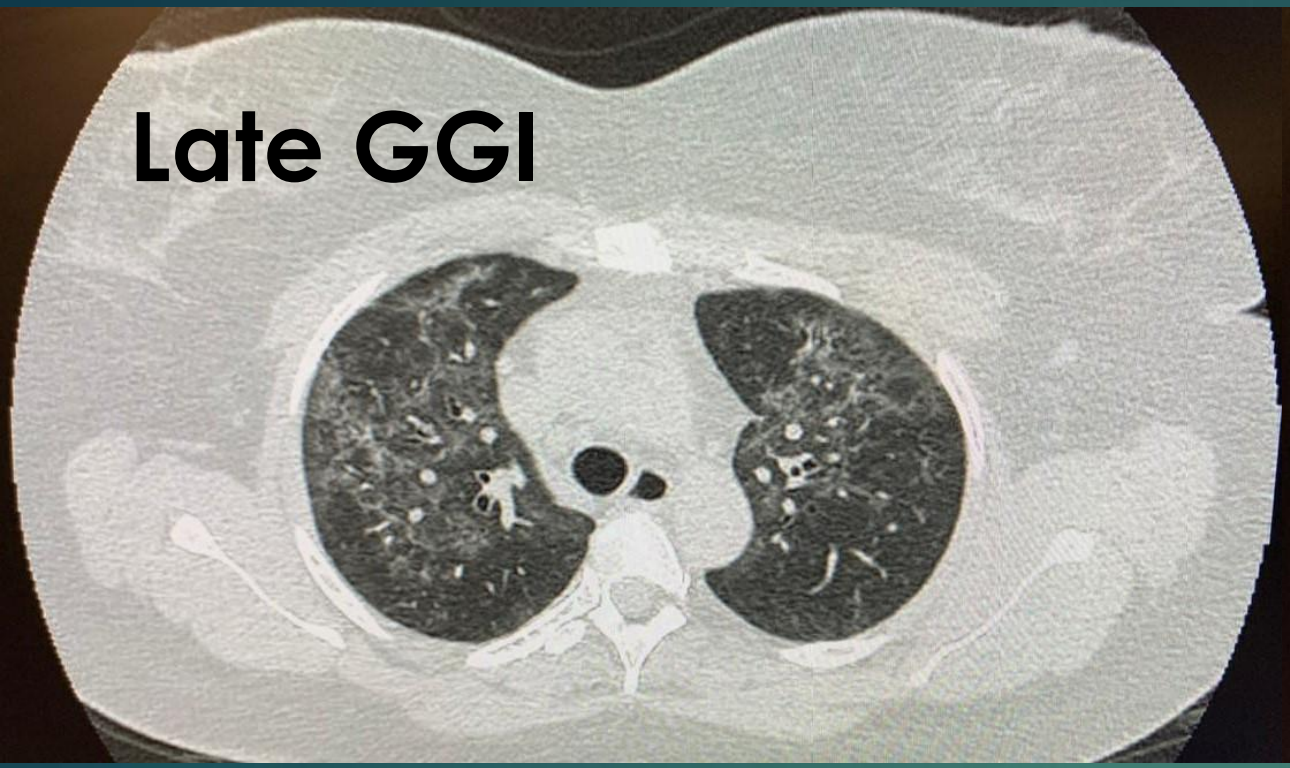
With persistently elevated CRP/IL-6: If infection excluded

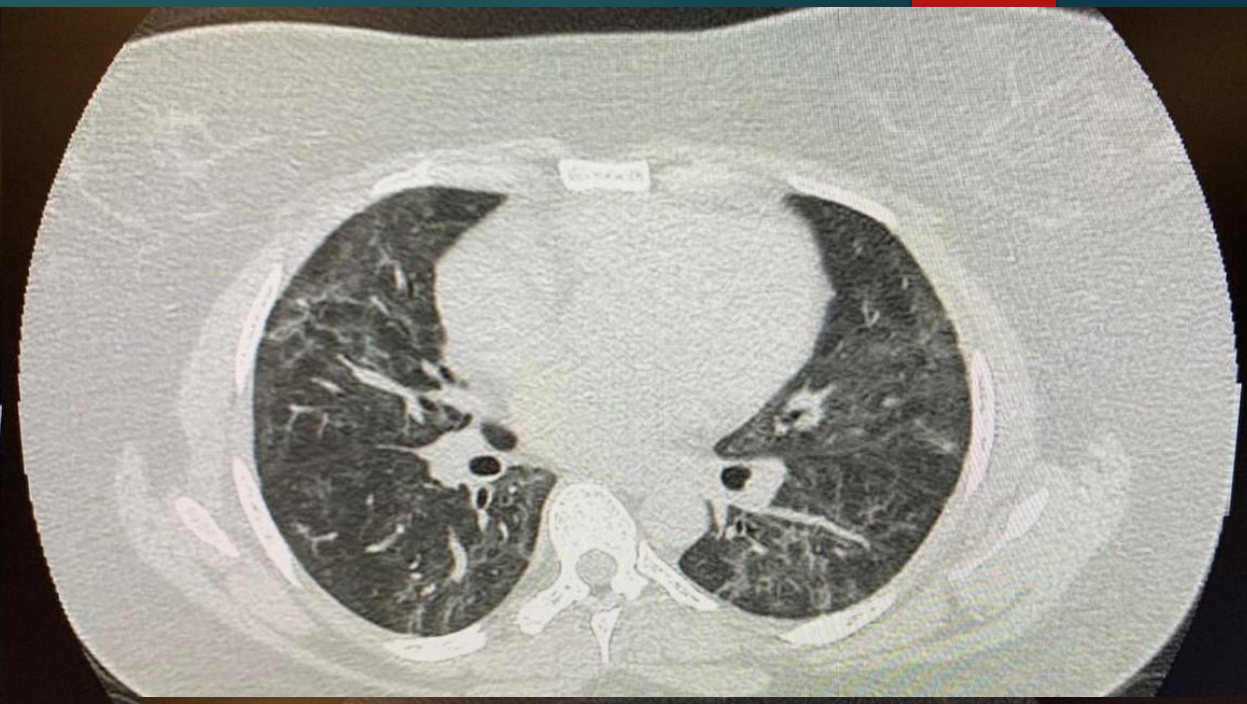
- Increase dose of steroid: methylprednisolone 125mg 8hrly x 2 days and assess response
- Add heparin nebs 5000U BD (monitor Xa and aPTT

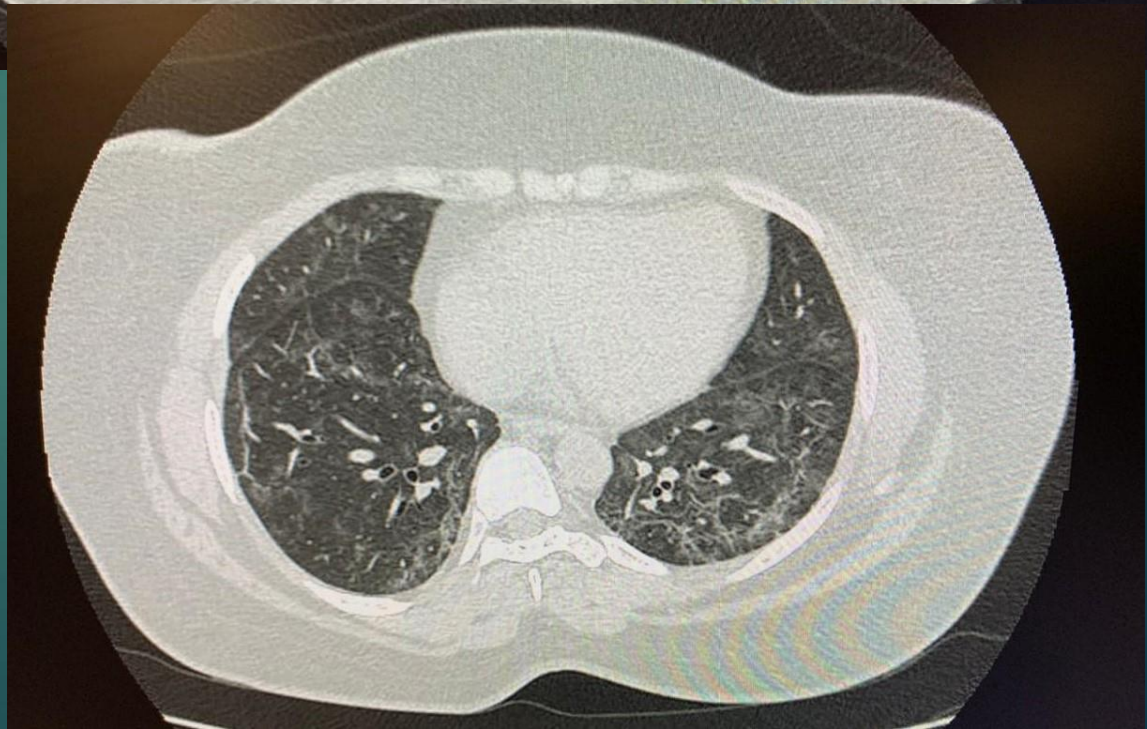
With low inflammatory markers:

- Heparin nebs 5000U BD with physio & aggressive suctioning
- Consider bronchoscopy to assess if plugs

Late GGI







35 year F, BMI 40, Covid pos 29/6,
Admission10-18/07
Discharged on Pred 15; CRP initially 55 to 11
Re-admitted 24/8; sats 93 GGI
Solumedrol 250 dly x 5 days,
Improved: ongoing Pred 30

Late development of GGI & Hypoxaemia

	Predicted	Pre Drug Reported	Pre Drug % Predicted	Post Drug Reported	Post Drug % Predicted	%Change
Test Date		2020/08/24		2020/08/24		
FVC	3.09	1.64 <	53 <	1.73 <	56 <	5
FEV1	2.67	1.56 <	58 <	1.64 <	61 <	5
FEV1/FVC	82.45	94.99	115	94.86	115	0
FEFmax	6.39	5.69	89	7.45	117	31
FEF25-75%	3.67	3.91	106	4.02	109	3
FEF25%	5.73	5.59	98	7.28	127 >	30
FEF50%	4.09	4.70	115	5.48	134 >	16
FEF75%	1.87	1.78	96	1.67	90	-6

Test Date		2020/08/24	
Dsb	24.67	11.21 <	45 <
D/VAsb	5.52	5.91	107
VAsb	4.47	1.90	42 <
BHT		13.04	

CoVID 19 Myocardial Injury

- 39 autopsies; pneumonia was the cause of death in 89.7%
- Cardiac histopathology did not meet criteria for acute myocarditis, but virus was present in 61.5% with a viral load >1000 copies/mg of RNA in 16 of 24 (66.7%)
- Active viral replication was noted & localization was most likely in interstitial cells or macrophages infiltrating myocardium not myocytes
- Using 6 proinflammatory genes, increased activity was noted in hearts with evidence of viral infection

Inciardi JAMA Cardiol.
Lindner JAMA cardiool 2020

CoVID & Myocardial Injury

- A German study in mild- moderate cases vs healthy controls & risk factor-matched controls found evidence of myocardial injury & inflammation on CMR: LVEF was lower & volumes higher, & 32% manifested late gadolinium enhancement & 22% pericardial involvement: potential selection bias & generalizability uncertain & not all may have recovered
- Ohio State University study showed CMR suggestive of myocarditis in 15% of athletes after asymptomatic/mild disease

Puntmann JAMA cardiology
Rajpal JAMA Cardiology

Myocardial Injury

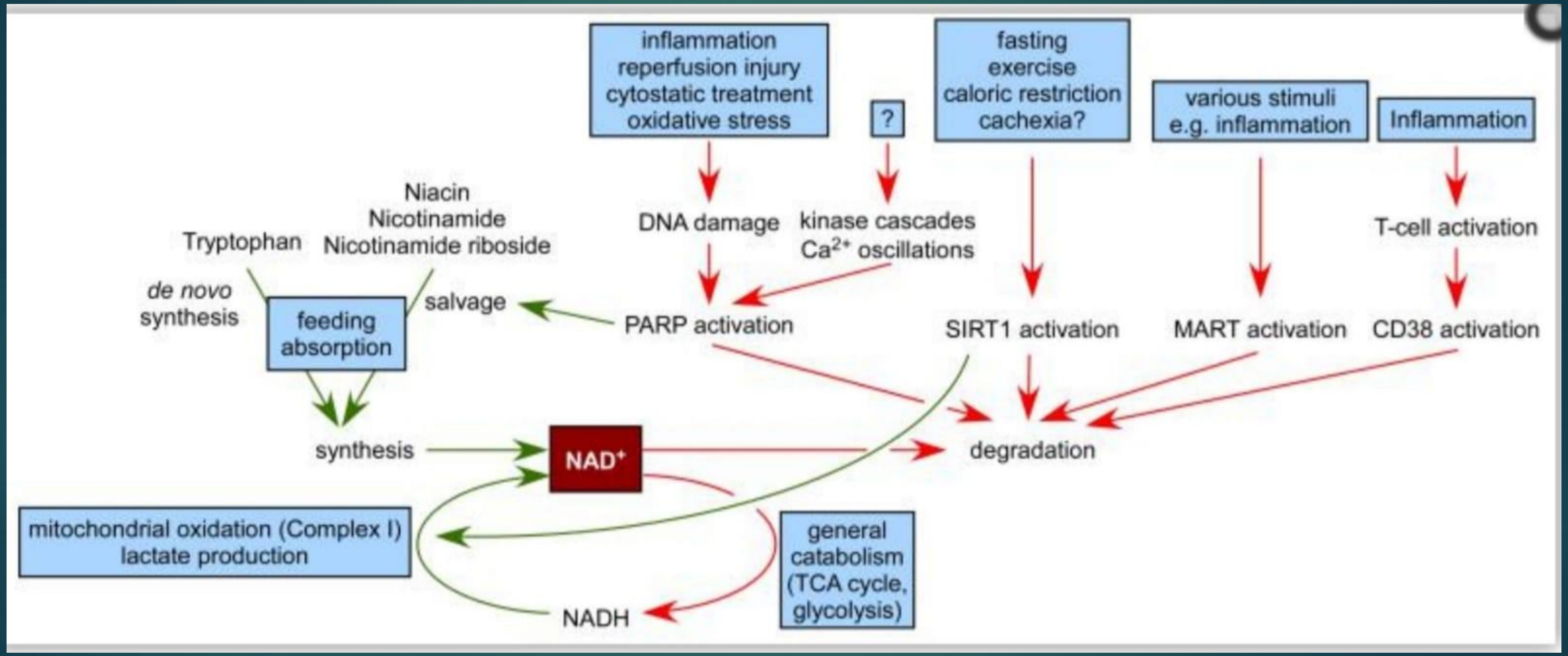
- Possibility exists of residual LV dysfunction & ongoing inflammation, with potential for new-onset heart failure other CVS complications
- But: Open letter from 50 cardiologists stated “prevalence, clinical significance & long-term implications" are not known
- If acute myocarditis refrain from sport x 3 months and restart based on HR, CRP, LV function

Yancy JAMA Cardiol 2020
https://assets.documentcloud.org/documents/7208864/Letter-About-Asymptomatic-COVID19-CMR.pdf

Long or Chronic CoVID

- Symptoms may be due to NAD+ deficiency with decreased SIRT 1 activity
- Zn^{++} & NAD^{+} imperative for function of SIRT1 which modulates TNFa, IL1b & IL6
- Hyperactivity of PARP1 depletes cellular NAD^{+} pools, leading to ATP deficiency, energy loss & subsequent cell death
- Replenishment of NAD^{+} by nicotinic acid plus zinc have the potential to ameliorate the pro-inflammatory cascade

Treatment of Chronic CoVID



Mechanically Ventilated Patients

- Prevent VILI: PEEP, Peak/plateau pressure, tidal volume, driving pressure
- Minimise oxygen requirements: Recruit (APRV), avoid fluid overload, early mobilisation, breathing trials, minimise sedation
- Difficult in busy ICU & isolation procedures interfere with usual care
- BTS guidelines: CXR & O_2 sat 3mnths post discharge for those with moderate/ severe disease or persistent symptoms

Therapy for “Long CoVID”

- Nicotinic 35mg daily
- Zinc 5-10mg daily
- Vitamin C 500mg BD
- Vitamin D 1000 IU daily