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Morning Brief : Scientific Review

01 July 2020

The purpose of the Morning Brief is to summarize and present key information, research articles and other relevant publications pertaining to critical care and COVID-19.

Stellenbosch University Research Response Team

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1918 · 2018

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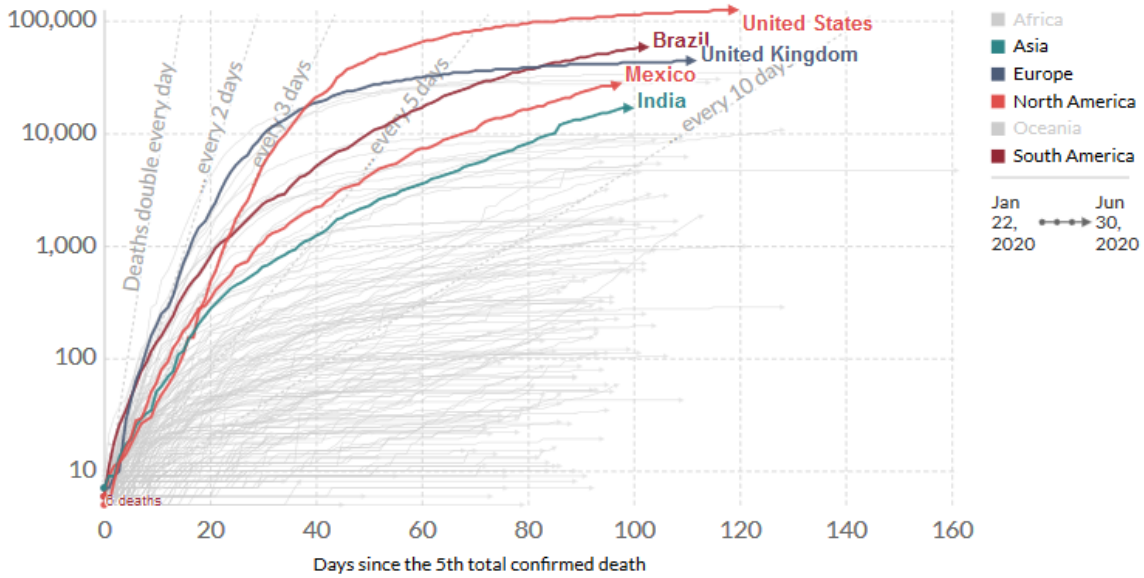
Colchicine trial

Total confirmed COVID-19 deaths: how rapidly are they increasing?

Our World in Data

Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.

LINEAR | LOG



Source: European CDC – Situation Update Worldwide – Last updated 30th June, 11:00 (London time)

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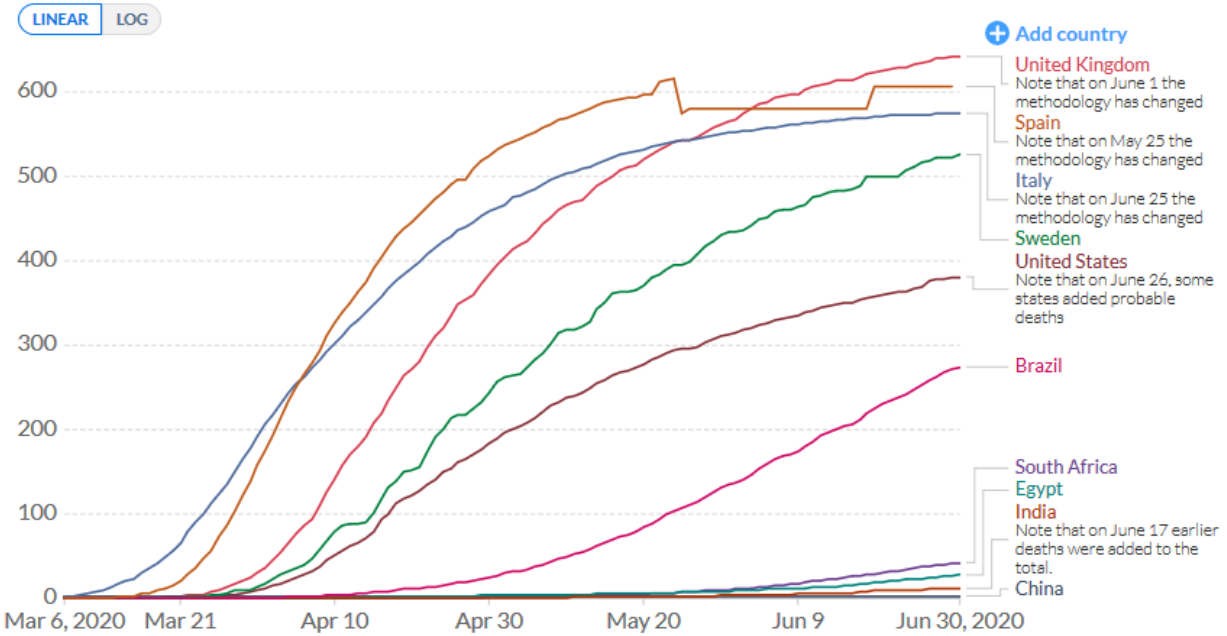
Jan 21, 2020 — Jun 30, 2020

Total confirmed COVID-19 deaths per million people

Our World in Data

Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true total number of deaths from COVID-19.

LINEAR | LOG



Source: European CDC – Situation Update Worldwide – Last updated 30th June, 11:00 (London time)

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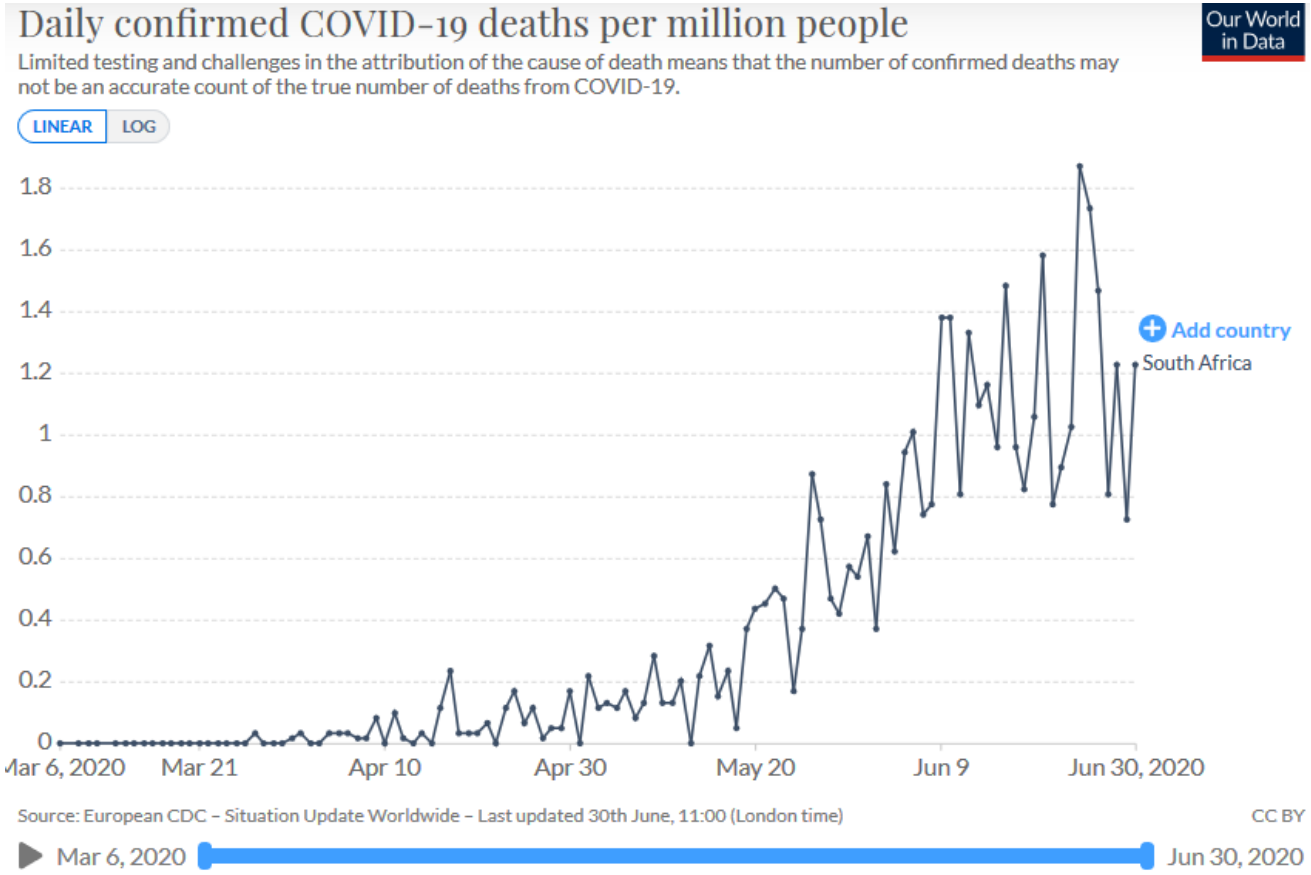
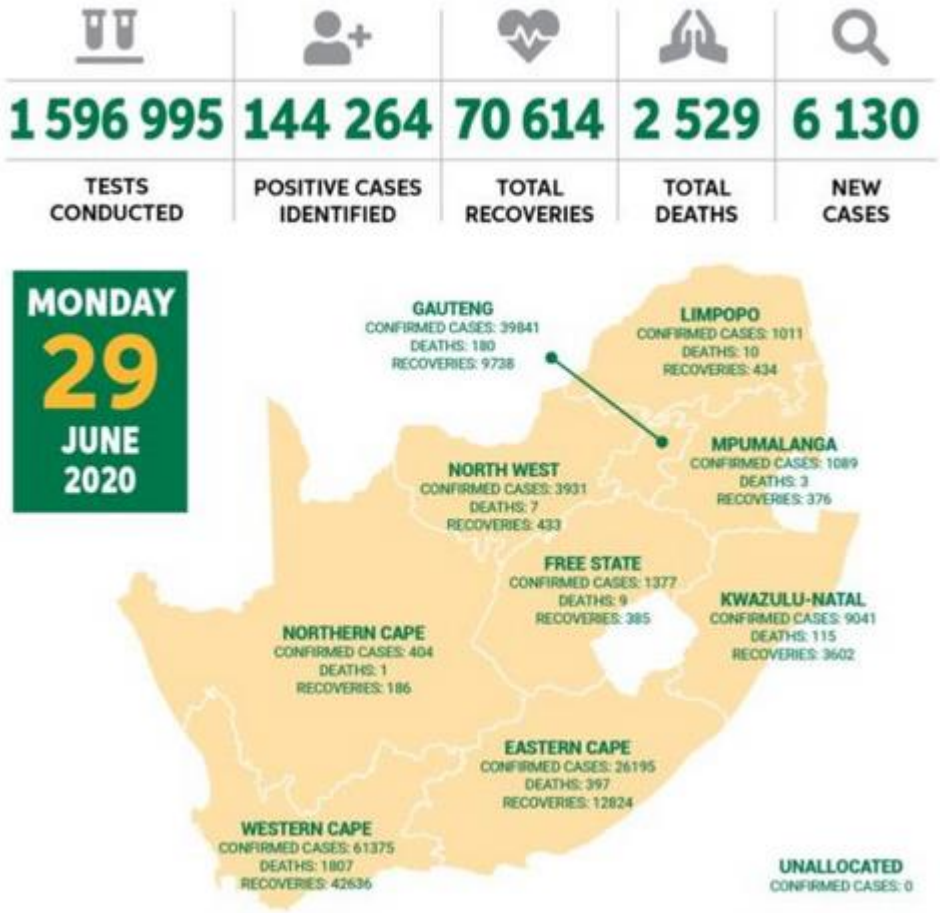
Dec 31, 2019 — Jun 30, 2020


Daily confirmed COVID-19 deaths per million people
Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.
Our World in Data
LINEAR
LOG
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Mar 6, 2020
Mar 21
Apr 10
Apr 30
May 20
Jun 9
Jun 30, 2020
Add country
South Africa
Source: European CDC – Situation Update Worldwide – Last updated 30th June, 11:00 (London time)
CC BY
Mar 6, 2020
Jun 30, 2020


1 596 995
TESTS CONDUCTED
144 264
POSITIVE CASES IDENTIFIED
70 614
TOTAL RECOVERIES
2 529
TOTAL DEATHS
6 130
NEW CASES
MONDAY
29
JUNE
2020
GAUTENG
CONFIRMED CASES: 39841
DEATHS: 180
RECOVERIES: 9738
LIMPOPO
CONFIRMED CASES: 1011
DEATHS: 10
RECOVERIES: 434
MPUMALANGA
CONFIRMED CASES: 1089
DEATHS: 3
RECOVERIES: 376
NORTH WEST
CONFIRMED CASES: 3931
DEATHS: 7
RECOVERIES: 433
FREE STATE
CONFIRMED CASES: 1377
DEATHS: 9
RECOVERIES: 385
KWAZULU-NATAL
CONFIRMED CASES: 9041
DEATHS: 115
RECOVERIES: 3602
NORTHERN CAPE
CONFIRMED CASES: 404
DEATHS: 1
RECOVERIES: 186
EASTERN CAPE
CONFIRMED CASES: 26195
DEATHS: 397
RECOVERIES: 12824
WESTERN CAPE
CONFIRMED CASES: 61375
DEATHS: 1807
RECOVERIES: 42636
UNALLOCATED
CONFIRMED CASES: 0

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Original Investigation | Infectious Diseases

Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019

The GRECCO-19 Randomized Clinical Trial

Background

- Colchicine has been traditionally used to treat gout and rheumatic disease
- Number of studies show a favorable safety-benefit profile among patients with cardiovascular disease, including pericarditis
- The anti-inflammatory action is mediated by different pathophysiologic routes than that of corticosteroids and nonsteroidal anti-inflammatory agents
- Rapid onset of anti-inflammatory effects as shown by its use in gout flares

- Colchicine inhibits neutrophil chemotaxis and activity in response to vascular injury, inhibits inflammasome signaling and reduces the production of active interleukin-1β, and reduces neutrophil-platelet interaction and aggregation

Hypothesis:

- Colchicine's combined anti-inflammatory action and acceptable safety profile led to the hypothesis that it might be a safe and effective anti-inflammatory treatment choice for COVID-19

Objective:

To evaluate the effect of treatment with colchicine on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with COVID-19

Methods

- Prospective, open-label, randomized clinical trial involving 16 tertiary hospitals in Greece
- Randomly assigned in a 1:1 allocation either into the intervention or control group

- *Control group*
  - Optimal medical treatment according to local protocols

- *Intervention group*
  - Colchicine in addition to optimal medical treatment
  - **Loading dose** - 1.5 mg followed by 0.5 mg 1 hour later if no adverse gastrointestinal effects were observed.
  - **Loading dose if AZA is co-administered** - a single 1.0 mg
  - **Maintenance dosage -** 0.5 mg colchicine twice daily (reduced to once daily among patients with body weight <60 kg) until hospital discharge or a maximum of 21 days

Inclusion / exclusion criteria

Inclusion criteria

- Hospitalized adult patients diagnosed with SARS-CoV-2 infection, confirmed with PCR-RT testing with a body temperature ≥ 37.5 °C

AND

- 2 or more of the following:
  - Sustained coughing
  - Sustained sore throat
  - Anosmia and/or ageusia
  - Fatigue and/or tiredness
  - Arterial oxygen partial pressure lower than 95 mmHg on room air

Exclusion criteria

- Pregnancy or lactation
- Known hypersensitivity to colchicine
- Known hepatic failure
- Estimated GFR < 20 ml/min/1.73m^2
- Corrected QT interval ≥ 450 milliseconds
- Clinical assessment indicating that ventilatory support would be inevitable in the following 24 hours because of rapidly declining respiratory status

Endpoints

- *Primary end point* assessed in 2 phases:
  - Biochemical (early)
    - Difference in maximal high-sensitivity cardiac troponin (hs cTn) levels between the 2 groups
    - Time for c-reactive protein to reach levels greater than 3 times the upper reference limit
  - Clinical (late)
    - Time from baseline to clinical deterioration, defined as a 2-grade increase on an ordinal clinical scale, based on the World Health Organization R&D blueprint ordinal clinical scale

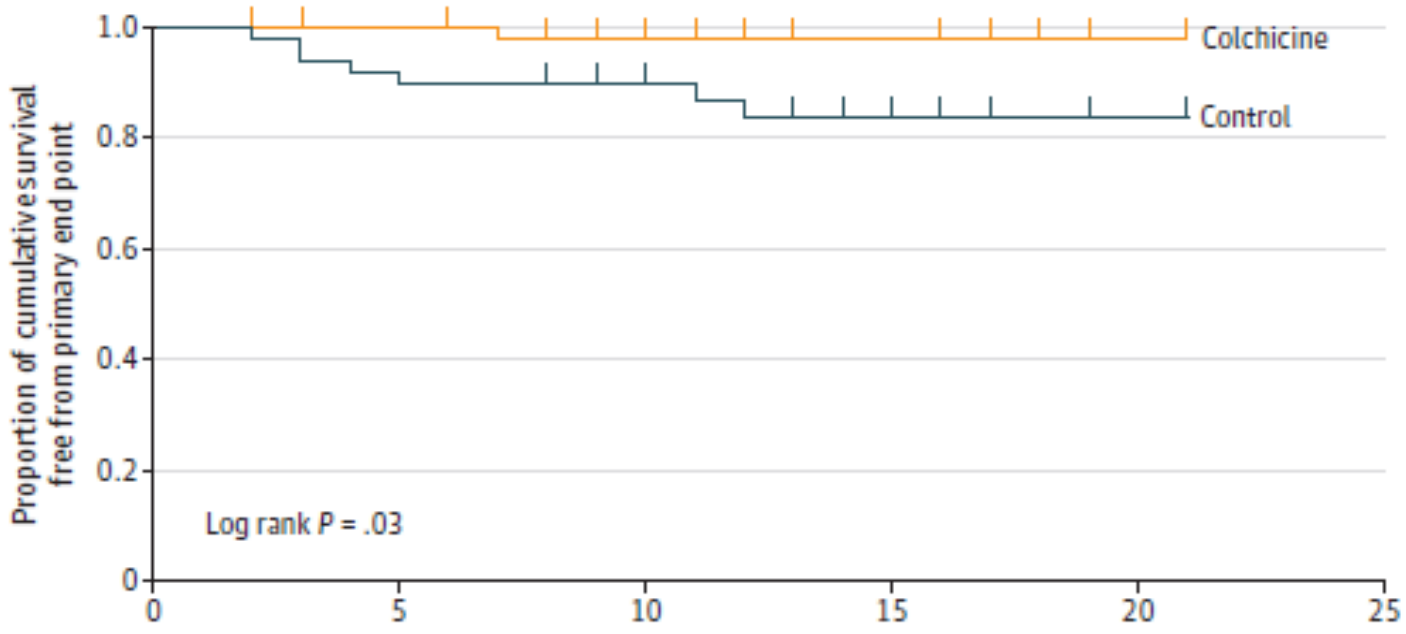
- *Secondary end points*
  - Percentage of participants requiring mechanical ventilation
  - All-cause mortality at the end of follow-up
  - Number, type, severity, and seriousness of total adverse events and treatment-related adverse events

Results

Assuming a median event-free survival of 30 days and an accrual time of 30 days, it was calculated that 180 patients were needed to have a 90% probability to detect a 50% reduction in the primary clinical end point at α = .05

- Clinical primary end point occurred in 7 patients (14.0%) in the control group and in 1 patient (1.8%) in the colchicine group (P = 0.02)
- Odds ratio of 0.11 (95%CI, 0.01-0.96; *P* = 0.046)

Figure 2. Kaplan-Meier Curves for Survival From the Primary Clinical End Point



No. at risk					
Colchicine	55	52	26	15	8
Control	50	43	36	15	6

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For the biochemical analysis, it was estimated 85 patients were needed to have a 90% probability to detect a 30% reduction in peak hs cTn level, assuming a median hs cTn level of 0.05 ng/mL in the control group, at α = .05

Table 2. Maximum and Minimal Levels of Selected Laboratory Parameters With Potential Prognostic Significance During Treatment

Laboratory parameter	Median (IQR)		Difference (95% CI)[a]	*P* value
	Control group (n = 50)	Colchicine group (n = 55)		
Maximum creatinine phosphokinase, U/L	107 (55 to 179)	105 (55 to 167)	1 (-28 to 30)	.76
Maximum high-sensitivity cardiac troponin, ng/mL	0.0112 (0.0043 to 0.0193)	0.008 (0.004 to 0.0135)	0.0017 (-0.0015 to 0.0049)	.38
Maximum C-reactive protein, mg/dL	4.5 (1.4 to 8.9)	3.1 (0.8 to 9.8)	4.75 (-9.6 to 19.1)	.73
Maximum D-dimer, μg/mL	0.92 (0.68 to 2.77)	0.76 (0.41 to 1.59)	0.3115 (0.01 to 0.613)	.04
Minimum platelet count, $\times 10^3/\mu L$	213 (148 to 261)	226 (164 to 296)	-21 (-55 to 13)	.32
Minimum estimated GFR, $mL/min/1.73m^2$	86.7 (55.8-114.3)	100.9 (64.2-120.5)	-10 (-25 to 5)	.21
Maximum white blood cell count, /μL	7189 (5490 to 9040)	6366 (5370 to 8240)	672 (-336 to 1680)	.15
Minimum lymphocyte count, /μL	920 (676 to 1293)	1141 (796 to 1477)	156 (-355 to 43)	.11

Table 3. Adverse Events[a]

Adverse Event	No. (%)		*P* value
	Control group (n = 50)	Colchicine group (n = 55)	
Vomiting	1 (2)	1 (1.8)	>.99
Diarrhea	9 (18)	25 (45.5)	.003
Diarrhea requiring study drug stop	0 (0)	2 (3.6)	.50
Nausea	1 (2)	2 (3.6)	>.99
Abdominal pain	0 (0)	5 (9.1)	.06
Muscle spasm	0 (0)	1 (1.8)	>.99
Headache	1 (2)	1 (1.8)	>.99
Other	3 (6)[b]	6 (10.9)[c]	.50

Conclusion and limitations

Conclusion

Participants who received colchicine had statistically significant improved time to clinical deterioration compared with a control group that did not receive colchicine. However, the observed difference was based on a narrow margin of clinical significance. Therefore, these observations should be considered hypothesis generating.

Limitations

- Co-treatments with other investigational medications such as LPV/RTV, TCZ, AZA, CQ and HCQ
- Trial's small sample size combined with the low event rate make these data underpowered and hypothesis generating
- Larger RCTs are required to effectively evaluate colchicine in COVID-19

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Invited Commentary | Infectious Diseases

Colchicine for the Treatment of Myocardial Injury in Patients With Coronavirus Disease 2019 (COVID-19)—An Old Drug With New Life?

Amir B. Rabbani, MD; Rushi V. Parikh, MD; Asim M. Rafique, MD

- No significant reduction in troponin levels with colchicine - can be partly explained by the trial's inclusion criteria, which did not require an elevated troponin level.
- Median troponin levels were low and not clinically meaningful. This coupled with the trial's low event rate and very low mortality rate reflect a reasonably healthy study population in which troponin levels are likely to be in the reference range.
- **Novel finding:** Significant reduction in D-dimer levels in the colchicine group - given that it suggests colchicine's mechanism of action to treat COVID-19 may be antithrombotic as well as anti-inflammatory.
- Currently 12 colchicine trials have been registered and are ongoing.

References

1. Deftereos SG, Giannopoulos G, Vrachatis DA, et al. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. *JAMA Netw Open.* 2020;3(6):e2013136. doi:10.1001/jamanetworkopen.2020.13136

2. Rabbani AB, Parikh RV, Rafique AM. Colchicine for the Treatment of Myocardial Injury in Patients With Coronavirus Disease 2019 (COVID-19)—An Old Drug With New Life? *JAMA Netw Open.* 2020;3(6):e2013556. doi:10.1001/jamanetworkopen.2020.13556

This summary was prepared by Dr Veshni Pillay-Fuentes as part of the daily brief to the TBH ICU team.