The Royal College of Emergency Medicine

RCEM COVID-19 CPD Journal club
Weekly top 5 papers

Dr Charles Reynard, Professor Simon Carley and the RCEM COVID-19 CPD team

The pace of new material has not slowed, and in this flash update we have found you the top 5 studies of the week. To source them we have sorted through hundreds of papers, and scoured high impact journals in order to find the papers that deserve your attention.

These have been split into 3 categories that will allow you to focus on the papers that are most vital to your practice.

- Worth a peek: interesting, but not yet ready for prime time
- Head turner: new concepts
- Game changer: this paper should change practice

Characterisation of 22446 patients attending UK emergency departments with suspected COVID-19 infection: Observational cohort study by Goodacre et al [1]
Topic: Epidemiology
Rating: Worth a peek
Scout: Professor Simon Carley

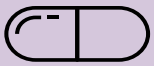
This is early data from the PRIEST study, an observational study of UK patients with suspected COVID-19 presenting to ED. We've looked at a fair few studies of patient characteristics with COVID-19 but this is the first focusing on those seen in the ED and so perhaps the most relevant to us so far. It is a pre-print so be a bit cautious as it's not yet peer reviewed, but the main findings are that the cohort is sick with high rates of admission (67.1%) and death (15.9%). Of the 8229 patients admitted to hospital with a positive COVID-19 result, the mortality was 32.7% which once again reminds us of the impact of this disease. Interestingly equal numbers of men and women were seen in the ED but men were more likely to be admitted and to have severe disease and thus die. As with other studies we have seen, those from Asian and Black ethnic backgrounds had worse outcomes in all areas and on average were over 10 years younger than UK/Irish/white patients.

The Royal College of Emergency Medicine

Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study by Biran et al [2]

Topic: Treatment
Rating: Head turner
Scout: Professor Simon Carley

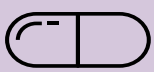
The RECOVERY trial has demonstrated that patients requiring oxygen in hospital benefit from Dexamethasone. This is great news, but when I speak to my Rheumatology colleagues there is a feeling that Dexamethasone is a bit of sledgehammer in terms of immunosuppression. The RECOVERY trial tells us that immunosuppression works, but what type and how much remains to be refined. There are now many trials in progress that seek to take a more nuanced immunomodulatory approach, and we hope to see those as randomised controlled trials soon. For now we only have observational data which will be inherently biased, but may give an indication of why there is such interest. In this multicentre observational study the authors looked at the use of tocilizumab, a monoclonal antibody directed at the IL-6 receptor. This is thought to inhibit the cytokine storm we see in the sickest COVID-19 patients and has been trialled in similar conditions in the past but with little success. However, COVID-19 is a new disease and there seems to be a good pathophysiological argument to test it. This retrospective study compared patients who received tocilizumab with those who did not and used propensity matching to try and control confounding factors. The headline figures are encouraging with an association between receiving tocilizumab and decreased hospital-related mortality (HR 0·64, 95% CI 0·47–0·87; p=0·0040), as well as other outcomes such as ventilation requirements and lab markers. We await better data from several RCTs in progress, including the RECOVERY trial which is now also randomising patients to tocilizumab.



Auxora versus standard of care for the treatment of severe or critical COVID-19 pneumonia: results from a randomized controlled trial by Miller et al [3]

Topic: Treatment
Rating: Worth a peek
Scout: Dr Charles Reynard

Another day another RCT; this phase two study of thirty patients examined the use of a novel calcium release-activated calcium channels (CRAC) inhibitor to treat COVID-19. CRAC channels are theorised to play a role in inflammation of the pulmonary epithelium and the pro-inflammatory cytokine cascade. The study was not blinded and had planned to recruit twice as many patients. Safety outcomes were comparable in each arm, but clinical outcomes were better with the intervention. The hazard ratio for death or mechanical ventilation was 0.23 (95% CI, 0.05 to 0.96; $P < 0.05$). The results give a positive signal but the width of those confidence intervals means the drug shouldn't escape through the lab door just yet. After these promising results the FDA recommended the trial be halted half way and upgraded to a blinded randomised trial; was this pragmatism in the fight against COVID-19 or should the trial have recruited the full 60 patients? Either way this is another promising therapy for the inflammatory process associated with COVID-19.



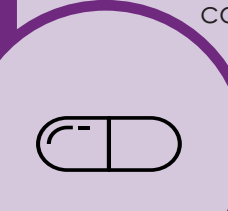
The Royal College of Emergency Medicine

COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing by To et al [4]
Topic: Epidemiology
Rating: Worth a peek
Scout: Dr Charles Reynard

There is always someone worse off than yourself; and this case study hammers that home. A poor patient from Hong Kong got SARS-CoV-2 twice. Levity aside this is not as bad as it seems at first glance, the patient's first infection was symptomatic but the second, despite being a different lineage, was asymptomatic. Remembering that n=1, this could signal that some immunity and protection was gained from the first infection. The possible negative connotation from this case is that whilst asymptomatic during the second episode the patient may still have been infective. If this case holds true it may mean that herd immunity will not prevent the spread of the virus and that a vaccine, potentially preventing re-infection, is still the only way out.

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19 by Spinner et al [5]
Topic: Treatment
Rating: Head turner
Scout: Professor Simon Carley

There is a real question about how effective antivirals might be in the management of the COVID-19 pandemic. Antivirals have been overshadowed by the results from immunomodulatory treatments for severe patients (i.e. dexamethasone). We have seen data on the ineffectiveness of hydroxychloroquine and lopinovir/ritonivir in randomised controlled trials, but there remains an enthusiasm for remdesivir which has been reported to show some benefit. The question remains as to whether that benefit is clinically important, and whether it changes the eventual outcome (death) for our sickest patients. In this randomised controlled trial 596 hospitalised patients were treated with placebo or either a 5 or 10-day course of remdisivir. The trialists did find an effect in clinical status by day 11 in the 5-day treatment group but the magnitude of that effect was small and by the end of the trial there was no difference in survival. Some will spin this trial as a positive effect of remdesivir, but in our opinion the difference is clinically unimportant in a disease with such a high mortality.



The Royal College of Emergency Medicine

In summary

Goodacre et al shocked us with an inpatient COVID-19 mortality rate of 32.7% [1]
Biran et al hint that tocilizumab could be the next breakthrough treatment [2]
Miller et al are racing to see if CRAC inhibitors fulfil their early promise [3]
To et al demonstrated that re-infection can occur [4]
Spinner et al found little or no effect for the expensive remdisivir [5]

References

1. Goodacre, S., Thomas, B., Lee, E., Sutton, L., Loban, A., Waterhouse, S., Simmonds, R., Biggs, K., Marincowitz, C., Schutter, J. and Connelly, S., 2020. Characterisation of 22446 patients attending UK emergency departments with suspected COVID-19 infection: Observational cohort study. medRxiv.

2. Biran, N., Ip, A., Ahn, J., Go, R.C., Wang, S., Mathura, S., Sinclaire, B.A., Bednarz, U., Marafelias, M., Hansen, E. and Siegel, D.S., 2020. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. The Lancet Rheumatology.

3. Miller, J., Bruen, C., Schnaus, M., Zhang, J., Ali, S., Lind, A., Stoecker, Z., Stauderman, K. and Hebbar, S., 2020. Auxora versus standard of care for the treatment of severe or critical COVID-19 pneumonia: results from a randomized controlled trial. Critical Care, 24(1), pp.1-9.

4. Kelvin Kai-Wang To, Ivan Fan-Ngai Hung, Jonathan Daniel Ip, Allen Wing-Ho Chu, Wan-Mui Chan, Anthony Raymond Tam, Carol Ho-Yan Fong, Shuofeng Yuan, Hoi-Wah Tsoi, Anthony Chin-Ki Ng, Larry Lap-Yip Lee, Polk Wan, Eugene Tso, Wing-Kin To, Dominic Tsang, Kwok-Hung Chan, Jian-Dong Huang, Kin-Hang Kok, Vincent Chi-Chung Cheng, Kwok-Yung Yuen, COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing, Clinical Infectious Diseases, , ciaa1275, https://doi.org/10.1093/cid/ciaa1275

5. Spinner, C.D., Gottlieb, R.L., Criner, G.J., López, J.R.A., Cattelan, A.M., Viladomiu, A.S., Ogbuagu, O., Malhotra, P., Mullane, K.M., Castagna, A. and Chai, L.Y.A., 2020. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA.