

This week's flash update comes from the team at University Hospital Coventry Emergency Department. We are research 'newbies'! Our team started research in 2013 with very little in the way of research nurse support, and therefore to succeed it had to be the ED clinicians who were recruiting 24/7. We are proud that this has led to the present departmental culture where all our staff recognise the importance of research in developing evidence-based Emergency Medicine and have contributed to some strong recruitment into studies. As a Major Trauma Centre, the group have significant involvement in national trauma and pre-hospital research but are also focused on qualitative studies in wellbeing and civility.



We have sorted through over 600 publications this week, and here are the papers that we think deserve your attention. As in previous weeks, these have been split into 3 categories that make it easy for 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

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis by the WHO REACT working group ¹

Topic: Treatment

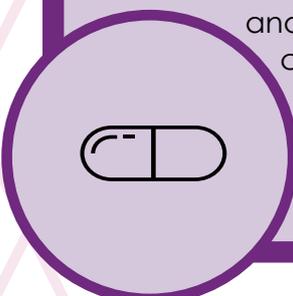
Rating: Game Changer

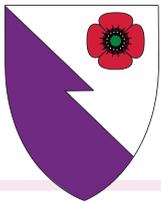
Scout: Caroline Leech



In June 2020, the RECOVERY trial group released preliminary results demonstrating a significant reduction in mortality for ventilated patients treated with Dexamethasone. This led many trials of corticosteroids to suspend recruitment because equipoise was no longer present. WHO partnered with the investigators of seven recruiting clinical trials to conduct a prospective meta-analysis to establish the association between corticosteroids and 28-day mortality. The studies randomized to usual care/placebo versus dexamethasone (3 studies – low or high dose), hydrocortisone (3 studies – low dose) or methylprednisolone (1 study – high dose). The final meta-analysis included results from two studies carried out in the UK patient population (RECOVERY and REMAP-CAP). A total of 1703 patients were randomized in the seven trials (678 to corticosteroids and 1025 to usual care/placebo). The 28-day mortality was lower in patients randomized to corticosteroids: 222 deaths/678 patients randomized to corticosteroids compared with 425 deaths/1025 patients randomized to usual care or placebo (Summary OR 0.66 [95% CI, 0.53-0.82]; $P < .001$) with little heterogeneity across studies. The reduced mortality was similar for dexamethasone and hydrocortisone (suggesting the benefit is not specific to any particular corticosteroid) and was similar with low or high dose corticosteroid regimens.

As a result of these findings WHO now recommend systemic corticosteroids as standard care for critically ill patients with COVID-19. The optimal steroid, dose, and duration of treatment or threshold at which to start treatment is not answered by this analysis.





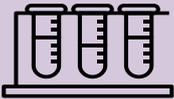
Prevalence of pulmonary embolism in patients with COVID-19 pneumonia and high D-dimer values: A prospective study by Alonso-Fernandez et al ²

Topic: Diagnosis

Rating: Head Turner

Scout: Karen Jones

The role of pulmonary embolism (PE) in the pathogenesis of COVID-19 pneumonia continues to be an area of great interest and debate. A raised D-dimer has been found to be associated with increased mortality, and retrospective and post mortem studies have shown a high prevalence of PE in patients with COVID-19 pneumonia. This prospective single-centre study in Spain performed CTPA on 30 consecutive patients with confirmed Covid-19 pneumonia and a D-dimer of > 1mcg/ml regardless of symptoms or number of days since admission. The prevalence of pulmonary embolism was 50%. Importantly, all those who only developed a raised D-dimer later in their hospital stay had been started on thromboprophylaxis at admission. This is a very small study and so the results should be viewed cautiously yet it provides another signal that D-dimer is important in prognostication and management of Covid-19.



Mortality and the use of anti-thrombotic therapies among nursing home residents with COVID-19, by Brouns et al ³

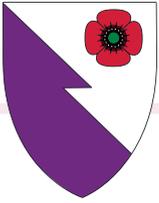
Topic: Observational

Rating: Worth a peek

Scout: Ed Hartley

The frail elderly are particularly vulnerable to mortality from coronavirus, and this year COVID-19 brought death and disease to nursing homes across the UK and Europe. This patient group remain underrepresented in the literature. Considering the emerging association between COVID-19, hypercoagulability and a high incidence of thromboembolic complications, the authors of this paper test the hypothesis that pre-existing use of anti-thrombotic or anti-platelet therapy in nursing home patients with suspected or confirmed Covid-19 infection would be associated with a lower mortality. This was undertaken through retrospective, observational analysis of 101 nursing home residents, with confirmed or clinically suspected COVID-19. 18% of the study population received either warfarin or a DOAC, with 34% on anti-platelet therapy. The devastating headline was that the authors found a mortality of 47.5% in their population, which was taken from 14 nursing homes in one of the most severely affected regions of the Netherlands. Mortality was significantly higher in men, at almost 70% of those enrolled. Whilst important confounders were overlooked, the authors matched survivors and non-survivors for a range of pre-existing conditions, finding no significant differences. Crucially, whether the patients were taking anti-thrombotic or anti-platelet therapy appeared to have no impact on mortality, either in reducing or increasing the risk of death. As winter approaches, we await effective community treatments for those frail patients in whom non-admission to hospital may be preferable.





Early outcomes with utilization of tissue plasminogen activator in COVID-19-associated respiratory distress: A series of five cases, by Christie et al⁴

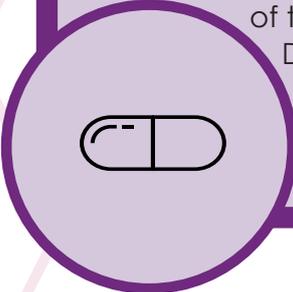
Topic: Treatment

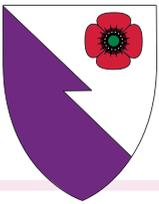
Rating: Worth a peek

Scout: Karen Jones



Patients with COVID-19 pneumonia may progress to a severe version of ARDS, often refractory to traditional supportive strategies. Current theories are that a systemic inflammatory response is triggered by the virus leading to a prothrombotic state and thrombosis in the microvasculature of the lungs. There are many recent case series in the literature where thrombolysis has provided a treatment benefit with varying impacts on final patient outcome. This American paper reports on 5 patients treated with tissue plasminogen activator (tPA) for severe respiratory failure. One patient was intubated and ventilated, three were on HFNC, and one on maximal flow rates via a non-rebreathe mask at the time of tPA administration. All had an initial increase in PaO₂ immediately post-tPA. Whilst this was followed by a small downward trend in PaO₂ over the next 24 hours, levels remained above the pre-tPA baseline allowing oxygen weaning. The patients were all at different stages in their clinical course at the time of tPA administration and the decision-making around thrombolysis was unclear. Discharge home was only mentioned in one case and the final outcome for the other four patients was not stated. This small case-series does not support a change in clinical practice but highlights the importance of future clinical studies to establish the role of thrombolytic therapy in this patient group.





Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicenter observational cohort study, by Swann et al. ⁵

Topic: Epidemiology & Prognosis

Rating: Head Turner

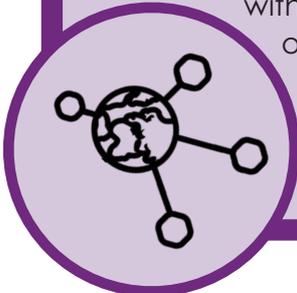
Scout: Caroline Leech



With schools going back this week there is increased anxiety about the impact of Covid-19 on the health of our children. This paper may provide some reassurance. Patients of any age admitted to hospital with laboratory confirmed SARS-CoV-2 infection were prospectively enrolled into ISARIC WHO CCP-UK and this study analysed the 651 patients aged under 19 years admitted up to 3rd July 2020. Headline figures were:

- Children accounted for <1% of all admitted patients with confirmed Covid-19.
- 18% of hospitalised children were admitted to critical care (associated with age <1 month, age 10-14 years, black ethnicity, obesity and comorbidities).
- The in-hospital mortality rate was <1% (27% in adults) and the six children who died had profound comorbidities or concurrent illness.

The study also found three distinct types of illness: the respiratory cluster of symptoms; muco-enteric symptoms (in 11% of children) which were consistent with the WHO criteria for Multi-system Inflammatory Syndrome in Children (MIS-C); and much rarer neurological symptoms (seizures and confusion). It was apparent that MIS-C can present both in children with acute SARS-CoV-2 infection and in the post-acute or convalescent phase of infection. The study also suggests that the WHO case definition for MIS-C could be refined, after finding an association with low platelet count, fatigue, headache, myalgia, sore throat, and lymphadenopathy. I found the graphics in the paper really useful to better understand the potential paediatric presentations of Covid-19 and would encourage you to take a look.



In summary

Systemic corticosteroids are now standard care for critically ill patients with Covid-19 ¹

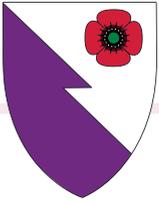
Patients with COVID-19 pneumonia and D-dimer values higher than 1 µg/mL may have a high prevalence of PE, regardless of clinical suspicion ²

There is no evidence that pre-existing anti-thrombotic and anti-platelet therapy has an impact on mortality in nursing home patients with COVID-19 ³

Case series continue to suggest thrombolysis may be beneficial for Covid-19 ARDS but further studies are needed ⁴

Severe disease is rare in UK children with Covid-19 and there is an in-hospital mortality rate of <1% ⁵





References



1. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA*. Published online September 02, 2020. doi:10.1001/jama.2020.17023
2. Alonso-Fernández A, Toledo-Pons N, Cosío BG, Millán A, Calvo N, Ramón L, et al. (2020) Prevalence of pulmonary embolism in patients with COVID-19 pneumonia and high D-dimer values: A prospective study. *PLoS ONE* 15(8): e0238216. <https://doi.org/10.1371/journal.pone.0238216>
3. Brouns SH, Bruggemann R, Linkens A, Magdelijns FJ, Joosten H et al. Mortality and the use of antithrombotic therapies in nursing home residents with COVID-19. *Journal of the American Geriatrics Society*. 2020 Aug. 68(8):1647-1652
4. Christie DB 3rd, Nemec HM, Scott AM, et al. Early outcomes with utilization of tissue plasminogen activator in COVID-19-associated respiratory distress: A series of five cases. *J Trauma Acute Care Surg*. 2020;89(3):448-452.
5. Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multi-centre observational cohort study. *BMJ* 2020;370:m3249.