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Caroline Leech , Edward Hartley , Priyanka Pillai ,
Marius Holmes , Karen Jones , Daniel Darbyshire , RCEM COVID-19 CPD Team

Introduction

Following from the successful “RCEM weekly top five” series starting in April 2020, this is the fifth of a monthly format for EMJ readers. We have undertaken a focused search of the PubMed literature using a standardised COVID-19 search string. Our search between 1 February and 28 February 2020 returned 6712 papers limited to human subjects and English language. We also searched high-impact journals for papers of interest.

Our team have narrowed down the most interesting, relevant and important of the papers and provided a critical snapshot of five of those we felt most deserved EMJ reader attention. Importantly, we have highlighted the main findings from the papers with key limitations and considerations for EM clinicians when interpreting the work. In doing so, we have created an accessible window into pertinent research findings for our busy colleagues during this fast-paced and ever-changing COVID-19 landscape.

The papers are ranked in one of three categories, allowing 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 could/should change practice

This month’s searches were undertaken by the ED team in Coventry. Next month, we visit the historic naval city of Plymouth on the south coast and look forward to an armada of quality content.

Pulmonary embolism and deep vein thrombosis in COVID-19

Topic—Diagnosis

Rating—Head turner

This systematic review and meta-analysis of 27 studies containing 3342 patients with COVID-19 aimed to determine the incidence of pulmonary embolism (PE) and deep vein thrombosis (DVT) and to evaluate the diagnostic accuracy of D-dimers in this cohort. The pooled incidence of PE and DVT were 16.5% and 14.8%, respectively, with an increased incidence of PE in those admitted to intensive care

(24.7%) compared with non-ICU patients (10.5%). These rates are markedly higher than previously reported incidences of PE in patients with non-COVID-19 viral pneumonia admitted to intensive therapy unit (ITU) with acute respiratory distress syndrome (1.3%–7.5%). The hypothesis of in situ and microvascular thrombosis in patients with COVID-19 was supported by the findings that only 42% of patients with PE had coexisting DVT and that 60% of PE were peripheral. The sensitivity of D-dimer levels for PE (96% at 500 ng/mL and 91% at 1000 ng/mL) was similar to patients with no COVID-19 in previous studies.

The meta-analysis has several limitations. Primarily many of the included studies are of low quality, showing marked heterogeneity and many with small samples (23–400 patients). The sensitivity of the D-dimer cut-off of 500 ng/mL seems promising, but the diagnostic performance of the test is poor (area under ROC 0.737). Further studies are needed to determine whether current risk assessment tools such as the Wells’ Criteria are valid in the context of COVID-19.

Finally, while the D-dimer test may not have a high negative predictive value for PE in COVID-19, occult thrombosis may still exist in the pulmonary microvasculature or elsewhere beyond the lung. Future studies need to assess whether a raised D-dimer should influence decisions around anticoagulation even for patients with a negative CTPA.

Bottom line

Patients with COVID-19 have higher rates of PE than those with non-COVID viral pneumonitis. The role of the D-dimer in the management of anticoagulation in COVID-19 requires further evaluation.¹

Prophylactic anticoagulation for COVID-19 admissions

Topic—Treatment

Rating—Worth a peek

Continuing on the thromboembolic theme, this retrospective observational cohort study of 4297 patients admitted to US hospitals with COVID-19 examined

for a link between prophylactic anticoagulant use and 30-day survival. In total, 84% of patients received prophylactic anticoagulation within 24 hours of admission. The authors report an eye-catching 34% relative risk reduction of 30-day mortality in the group who received prophylactic doses of (mostly) subcutaneous enoxaparin and heparin (14.3% vs 18.7% cumulative incidence), with no increase in serious bleeding events. A strength of this study is the use of propensity scoring to manage confounders and their effect on survival.² However, the study’s external validity is vulnerable to criticism: participants were overwhelmingly male (93%) and likely quite different in baseline characteristics from the undifferentiated patients who present to the ED. The study also excluded all patients who ‘reached any outcome within 24 hours’. The 728 patients who were excluded could have been discharged from hospital, but may also have died from COVID-19 within 24 hours and this could have considerably affected the reported ARR. Nevertheless, continued use of prophylactic anticoagulation for patients with COVID-19 admitted to hospital seems to represent a safe, and beneficial treatment.

Bottom line

Prophylactic anticoagulation administered to inpatients with COVID-19 appears to reduce in-hospital and 30-day mortality.³

Timing of corticosteroids impacts mortality in hospitalised patients with COVID-19

Topic—Treatment

Rating—Head turner

While the RECOVERY trial produced convincing results on the mortality benefit of corticosteroids, at present there is no consensus on the most appropriate time to commence steroid therapy.⁴ This retrospective observational study aimed to assess the optimal timing for corticosteroid therapy in patients with COVID-19 admitted to eight American hospitals in March 2020.

Data of 1461 consecutive COVID-19-positive patients (confirmed by RT-PCR



nasopharyngeal swab) admitted over a 31-day period were analysed with the authors using propensity score methods to minimise confounding. Moreover, 42.1% (615) received steroid therapy compared with 57.9% (846) who did not. Patients received various regimes of steroids including dexamethasone, hydrocortisone, methylprednisolone or prednisolone. Steroid therapy initiated >72 hours after hospitalisation was associated with a marked reduction in mortality (HR 0.56, 95% CI 0.38 to 0.82, $p=0.003$) compared with the first dose at earlier time intervals. Analysis also revealed that time to therapy from onset of symptoms was relevant: treatment initiated >7 days from symptom onset was associated with a reduction in mortality (HR 0.56, 95% CI 0.33 to 0.95, $p=0.03$) compared with those who received earlier treatment. The data in this cohort also suggested that hypoxia alone, prior to 72 hours of hospitalisation, may not be an indication for initiation of corticosteroid therapy: a significant mortality benefit was only seen in those patients requiring invasive ventilation (HR 0.38, 95% CI 0.24 to 0.60, $p<0.001$) with a marginal effect on patients receiving high-flow oxygen. Limitations of the study include the retrospective design, the variety of steroid regimes/doses, and the potential lack of generalisability due to population differences.

Bottom line

This study recommends delaying steroid therapy when admitting COVID-19-positive patients unless symptom onset was >7 days or the patient requires mechanical ventilation.⁵

Effect of vitamin D₃ on hospital length of stay in moderate-severe COVID-19

Topic—Treatment

Rating—Head turner

Vitamin D for the prevention or treatment of COVID-19 has been a focus for high-profile controversy during the pandemic. It has been postulated that vitamin D₃ supplementation could improve the function of macrophages and dendritic cells to enhance the overall immune response. This double-blind randomised controlled trial (RCT) from Brazil recruited 237 hospitalised patients with moderate-severe COVID-19 who were randomised to receive either a single dose of 200 000 IU oral vitamin D₃ or placebo. The patients were not well matched for baseline characteristics, with more males, BMI>30 and black patients in

the treatment arm. The study found no statistically significant difference in the median length of stay, in-hospital mortality or rates of ITU admission between the groups. In a subgroup analysis, the study also found no benefit in patients who had low levels of 25-hydroxyvitamin D at admission and therefore the authors concluded it does not support the use of vitamin D₃ for the treatment of COVID-19.

In view of the lack of harm from these supplements, further RCTs in vitamin D are justified with several currently in progress. Any future trials should consider different doses, duration of dosing in relation to onset of symptoms, baseline vitamin D levels in participants (perhaps concentrating on those who have low levels at recruitment) and the potential effects on different patient subgroups (older, comorbidities such as obesity, or ethnic minority patients). UK national guidance currently recommends routine vitamin D supplementation of 400 IU a day during the winter months with no change for COVID-19.

Bottom line

This study does not support the use of a high single dose of vitamin D₃ for treatment of moderate to severe COVID-19 in hospitalised patients.⁶

Effect of tocilizumab on patients with severe COVID-19

Topic—Treatment

Rating—Worth a peek

This multicentre Brazilian RCT investigated the potential benefit of single-dose tocilizumab over standard care in adult patients with COVID-19. Tocilizumab inhibits interleukin 6, an inflammatory cytokine, which is raised in other viral infections and is approved for conditions such as rheumatoid arthritis and giant cell arteritis. Reduction of this interleukin is hypothesised to reduce the inflammatory response and pathophysiology of lung and organ dysfunction in COVID-19. Recruited patients had confirmed COVID-19 with positive lung imaging, requiring oxygen supplementation or mechanical ventilation, and had at least two abnormal biomarkers (CRP, LDH, D-dimer or ferritin). The primary outcome was the clinical status at day 15 (using an ordinal scale) with secondary outcomes including 28-day mortality and organ failure.

A total of 129 patients were recruited (80% power $n=150$) before the trial

was prematurely stopped by the data monitoring committee due to excess deaths in the tocilizumab treatment arm $n=11:3$ (17%:3% OR 6.42, 1.59 to 43.2). All patients were followed up in this trial and at 28 days there was no statistical difference in overall mortality. Although appropriately stopped for safety, this dataset suffers from being so small and therefore not conclusive. Additional limitations include a lack of blinding, variable concomitant treatment used for standard care (antibiotics, antivirals or corticosteroids) and deaths being in those patients who were mechanically ventilated.

The results of this study vary from the findings of the REMAP-CAP, EMPACTA and COVACTA trials where there was suggestion of less clinical deterioration or a mortality benefit from tocilizumab in COVID-19. Results of the upcoming RECOVERY trial of tocilizumab may help answer the question.

Bottom line

Tocilizumab plus standard care was not superior to standard care alone in improving clinical outcome at 15 days and may increase mortality.⁷

Twitter Caroline Leech @leechcaroline, Edward Hartley @DrEdHartley, Karen Jones @KJonesey78 and Daniel Darbyshire @dsdarbyshire

Collaborators RCEM COVID-19 CPD Team: Dr Charles Reynard, Dr Anisa Jafar, Dr Govind Oliver, Dr Gabrielle Prager.

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ORCID iDs

Caroline Leech <http://orcid.org/0000-0002-5301-9798>

Edward Hartley <http://orcid.org/0000-0001-5873-5307>

Priyanka Pillai <http://orcid.org/0000-0002-8576-4477>

Marius Holmes <http://orcid.org/0000-0001-9813-0329>

Karen Jones <http://orcid.org/0000-0003-0667-210X>

Daniel Darbyshire <http://orcid.org/0000-0001-5619-0331>

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