EMJ COVID-19 monthly top five

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Introduction

Following from the successful 'RCEM weekly top five' series starting in April 2020, this is the seventh 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 April 2021 and 30 April 2021 returned 3139 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 not only the main findings from the papers but key limitations and considerations for emergency medicine 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 Emergency Innovation Research Network (EIRN) at Cork University Hospital Emergency Department, Ireland. We look forward to next month's instalment by our colleagues from the Emergency Medicine Research Group Edinburgh.

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial
Topic: treatment
Rating: game changer

The Randomised Evaluation of COVID - 19 Therapy (RECOVERY) trial is a large randomised control trial that has been evaluating potential COVID-19 treatments in hospitalised patients in the UK NHS.[1] It has now evaluated the effect of tocilizumab in patients with severe COVID-19 characterised by hypoxia and substantial inflammation. Tocilizumab is an anti-interleukin-6 receptor antibody, it may mitigate the hyperinflammatory response and associated cytokine 'storm' seen in severe COVID-19. It has shown promise in prior observational studies.

This intervention was offered as an additional randomisation to trial participants within 21 days of initial randomisation who had severe COVID-19, defined as evidence of progressive COVID-19 with oxygen saturation <92% on room air or receiving oxygen therapy and C-Reactive protein ≥75 mg/L.

Participants were randomised to current management versus current management plus tocilizumab at a dose of 400–800 mg (weight-based).

The primary outcome was all-cause mortality at 28 days. Secondary outcomes were time to discharge from hospital and receipt of invasive ventilation or death in those patients not receiving invasive ventilation at time of randomisation.

Of the 4116 (19%) RECOVERY trial participants eligible for inclusion, 2022 were randomised to the tocilizumab group and 2094 were allocated to controls. Mortality at 28 days in the intention-to-treat analysis was significantly lower in the tocilizumab group (31% vs 35%, p=0.0028) and the proportion of patients discharged from hospital was higher (57% vs 50%, p<0.0001). Fewer patients in the tocilizumab group required invasive ventilation (35% vs 42%, p<0.0001).

The RECOVERY trial has contributed to international COVID-19 guidelines, and these results, in combination with previous studies, are already changing practice. There are, however, limitations. Clinicians were not blinded to allocations, and this could have resulted in differences in management decisions (such as whether to continue care). Additionally, 16% of the tocilizumab group did not receive the drug, with no explanation given; therefore, we may not have a true representation of its effects. We should remember that tocilizumab is also expensive and not readily available worldwide.

A preplanned 6-month analysis may help us appreciate the longer-term outcomes.

Bottom line
In hospitalised patients with COVID-19 with hypoxia and systemic inflammation, tocilizumab improved survival and discharge from hospital at 28 days.

Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study
Topic: vaccination
Rating: head turner

This prospective observational study looked at the safety profile and efficacy of the Pfizer–BioNTech and Oxford–AstraZeneca vaccines, building on data gathered during phase 3 trials.[2] This UK-based trial was conducted between December 2020 and March 2021. Anyone in the UK general population over 18 years old had the opportunity to download and sign up to the COVID Symptom Study app, which records baseline health, employment and demographic characteristics. It then prompts the user for further health updates after receiving the vaccination or being tested for COVID-19. Use of the app was driven by media, word of mouth, referrals and charities. On downloading the app, participants consented to non-commercial use of their data. Primary outcomes included the proportion of users reporting adverse events within 8 days of vaccination. Secondary outcomes included the infection rate in vaccinated individuals.

Data were collected from more than 600 000 individuals receiving either vaccine, with a subset of 28 207 having received both Pfizer–BioNTech doses. About a quarter of recipients reported systemic adverse effects and two-thirds reported local adverse effects, both lower than expected from phase 3 trial data. Allergic skin reactions were reported in less than 2% of individuals. Systemic and local adverse effects were more frequently reported in those with previous SARS-CoV-2 infection.

A reduction in risk of SARS-CoV-2 infection for both vaccinations was demonstrated from 12 days post vaccination with a risk reduction of 60% (95% CI 49 to 68) for the Oxford–AstraZeneca vaccine and 58% (95% CI 62 to 72) for the Pfizer–BioNTech. Vaccine effectiveness is difficult to comment on within an observational data set; however, the risk reduction over time is similar to that seen in previous phase 3 trials.[3] Limitations include potential information bias due to self-reported data, participants were self-selected and older than the general population and only short-term side effects were recorded. There is a possibility of response bias as users are more likely to be interested in health. The authors are clear that this paper is unable to allow an inference of causality.

Bottom line
Reassuringly, adverse events from both vaccines were usually mild and brief, occurring less frequently than previously expected in a study population considerably older than previous phase 3 trials.

Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit admission and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform
Topic: epidemiology
Rating: head turner
A large cohort study has been conducted in the UK seeking to estimate the effect of ethnicity on testing and testing positive for SARS-CoV-2, hospitalisation rates, intensive care unit (ICU) admissions and mortality.[4] Previous studies in the UK and North America have demonstrated higher levels of COVID-19 and more significant disease in minority ethnic groups in comparison to white groups. This study aimed to analyse different ethnic groups separately rather than as a single cohort, using a large general population-based sample.

The authors used the OpenSAFELY platform, an electronic record of 24 million patients registered with primary care in the UK NHS. The study comprised of data from 17 288 532 adults. 10 877 978(62.9%) White, 1 025 319 (5.9%) South Asian, 340 912 (2.0%) Black, 170 484 (1.0%) mixed ethnicity, 320 788 (1.9%) were of other ethnicity, and 4 553 051 (26.3%) were of unknown ethnicity.

The authors analysed data on demographic covariates (age, sex, deprivation, household size, primary care consultations in the past 12 months and geographical region) and clinical covariates (body mass index, glycated haemoglobin, blood pressure, smoking status and clinical comorbidities)

After accounting for all covariates, South Asian, black and mixed ethnicity groups were more likely to be tested and to test positive for SARS-CoV-2 compared with the white group. The risk of hospitalisation was increased in all minority ethnic groups. The risk of ICU admission was two–three times higher in the four broad minority groups and two–five times higher among South Asian, black, mixed and other subcategories relative to the White British group. Mortality was increased by 22%–51% in the four broad minority ethnic groups. Differences between minority ethnic groups with regard to positive testing and severe COVID-19 symptoms were small.

The causes of these excess risks in both the UK and elsewhere are likely multifactorial, with social deprivation, structural inequalities, inequitable care and uptake of testing and vaccination all playing a role. Further work is needed to better appreciate and address the underlying mechanisms at play to reduce these inequalities.

Bottom line
Minority ethnic groups in the UK have suffered disproportionally during the COVID-19 pandemic.

Methylprednisolone in adults hospitalised with COVID-19 pneumonia: an open-label randomised trial (GLUCOCOVID)

Topic: corticosteroids and COVID-19
Rating: worth a peek
Corticosteroids are a frequently used weapon in our emergency arsenal for the treatment of respiratory conditions.[5] While the RECOVERY trial found that corticosteroids were beneficial in critically ill hospitalised patients with COVID-19,[6] the role of steroids in the patient that warrants hospital admission but is not yet requiring critical care is unclear.

This open-label study was a partially randomised control trial with hospitalised patients not requiring critical care. 'Partially', in that the treating team could allocate the patient to the intervention arm if they felt this was beneficial. Patients were included if they had a symptom duration of at least 7 days, radiological

evidence of disease, met specified criteria for abnormal gas exchange demonstrating moderate to severe disease and met biochemical criteria for evidence of systemic inflammatory response. Patients were allocated to either the treatment arm (n=35) receiving intravenous methylprednisolone for 6 days or to standard of care management (n=29). Treatment was commenced the same day as inclusion in the trial.

The primary outcome was a composite endpoint of in-hospital mortality, ICU admission or progression to non-invasive ventilation. Patients were followed up for 28 days.

In the per-protocol analysis, the treatment group demonstrated a statistically significant 20% risk reduction to the control (30% vs 50%) in reaching the primary composite endpoint. In the intention-to-treat analysis, the methylprednisolone group was less likely to reach the study endpoint (relative risk: 0.68), but this was not statistically significant. Participants had symptoms for a mean of 12 days (SD: ±6) at inclusion. No significant adverse events were reported aside from hyperglycaemia in 12 patients.

While the study suggests that there may be some beneficial effect to the use of methylprednisolone in this patient group, there are some limitations. These findings represent an interim analysis due to declining patient numbers in the study location. For sufficient power, it had a requirement of 180 participants. In addition, the main driver for the endpoint was critical care admission, which possesses a degree of subjectivity. There was, however, specific, easy to follow inclusion criteria, accepted standard of care protocols with both an intention-to-treat and per-protocol analysis performed.

Bottom line
This interim analysis will not change our practice; we are still not any closer to the answer of does steroid administration worsen the disease at the viral stage of the illness. However, having the wheels in motion to examine treatments for this specific patient group is encouraging.

Effectiveness of the BNT162b2 COVID-19 vaccine against the B.1.1.7 and B.1.351 variants
Topic: prognosis
Rating: head turner
This study from Qatar looks at the effectiveness of the Pfizer–BioNTech vaccine against two COVID-19 variants of concern, the B.1.1.7, first identified in

Kent, England and B.1.351, first identified in South Africa.[7] These variants account for the majority of infections in Qatar.

The authors estimated vaccine efficacy using a test-negative case–control study. Testing in Qatar has been conducted in symptomatic individuals, as part of contact tracing, routine testing and random testing campaigns. Cases and controls were matched 1:1 by age, sex, nationality and reason for PCR testing.

After one dose, the Pfizer–BioNTech vaccine had an estimated effectiveness against subsequent SARS-CoV-2 infection of 29.5% (95% CI 22.9 to 35.5) for the B.1.1.7 variant and 16.9% (95% CI 10.4 to 23.0) for B.1.351 variant.

Fourteen days after the second vaccination dose, the Pfizer–BioNTech vaccine had an estimated efficacy of 89.5% (95% CI 85.9 to 92.3) against infection from the B.1.1.7 variant and 75% (95% CI 70.5 to 78.9) against infection from the B.1.351 variant. This is lower than the 95% efficacy against infection reported in the phase 3 trial conducted before these variants emerged.[3]

Vaccine effectiveness against severe, critical or fatal disease (14 days after second vaccination) from all variants of SARS-CoV-2 in Qatar was 97.4% (95% CI 92.2 to 99.5). Despite reduced effectiveness against infection primarily for the B.1.351 variant, it remained effective in preventing severe illness and death.

There are limitations to the study. The population demographic in Qatar is younger, with a greater proportion of males, than in other populations. However, the population is also very diverse with large number of expats from many nationalities, a potential strength.

Bottom line

This study provides reassurance that the Pfizer–BioNTech vaccine provides good protection against severe disease caused by these new variants of concern.

Check for updates

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