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Title: EMJ COVID-19 monthly top five (December 2020)

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Introduction

Edited by Dr Gabrielle Prager on behalf of the RCEM COVID-19 CPD team

Following from the successful "RCEM weekly top five" series starting in April 2020, this is the third of a monthly format for EMJ readers. We have undertaken a focussed search of the PubMed literature using a standardised COVID-19 search string. Our search between 1st December and 31st December 2020 returned 1183 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 5 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 EM clinicians when interpreting the work. In doing so 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 3 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 Centre for Urgent and Emergency Care Research at the University of Sheffield. We look forward to next month's instalment by our colleagues in Leicester.

1. **Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results (1)**

Topic: **Treatment**

Outcome Rating: **Game Changer**

In March 2020, the World Health Organisation (WHO) recommended randomised trials into potential treatments for COVID-19. Experts agreed on four antiviral drugs that could be repurposed to reduce mortality in this patient group. The four drugs were remdesivir, hydroxychloroquine, lopinavir and interferon beta-1a.

Within a month a large international, open-label randomised trial was launched at 405 hospitals in 30 different countries. There was no placebo group; the control group consisted of the local usual care. Adult patients (>18) who were hospitalised with COVID-19 and not currently on a trial drug were included. The primary outcome was in-hospital mortality with the secondary outcomes being the length of stay and requirement for mechanical ventilation. The protocol specified a sub-group analysis of severe COVID-19 but did not define "severe", so sub-group analysis is limited. The trial was adaptive, dropping ineffective treatments and adding other potential candidate drugs. Hydroxychloroquine was dropped after three months, lopinavir after four, and interferon after seven months. The trial is still recruiting and has since included monoclonal antibodies into the protocol. At the time of this interim publication the study had recruited 11,266 patients into the intention-to-treat analysis. There were 954 patients randomised to hydroxychloroquine, and the rate ratio for in-hospital mortality was 1.19 (0.89-1.59) vs control. There were 1411 patients randomised to lopinavir, which had a rate ratio of 1.00 (0.75-1.25) vs. control. There were 2063 randomised to interferon which had a rate ratio of 1.16 (0.96-1.39). There have been 2750 assigned to remdesivir so far, and this interim analysis shows a rate ratio of 0.95 (95% CI 0.81-1.11) vs control.

The sub-group analysis and secondary outcomes also failed to demonstrate a reduction using these repurposed antivirals. The trial has been criticised for its open design and the heterogeneity of the population and control treatments, but it is difficult to see how the former could influence mortality. Furthermore, the latter could be considered a strength if it enhances the generalisability of the results.

Bottom line: This was a large, well-conducted trial which has shown that previously developed antivirals do not significantly reduce mortality, length of stay, or the requirement for mechanical ventilation. The severity of COVID-19 does not appear to affect these results.

2. A systematic review of corticosteroid treatment for non-critically ill patients with COVID-19 (2)

Topic: **Treatment**

Outcome Rating: **Head-turner**

Between July and September 2020, strong and widely-implemented evidence emerged that corticosteroids reduce mortality in patients with 'severe' and 'critical' COVID-19. This evidence is largely based on a systematic review and meta-analysis of seven trials, of which the RECOVERY trial was the largest (3,4). Conversely, the evidence for corticosteroids' lack of effect in non-severe and non-critical COVID-19 is based on the results of the RECOVERY trial alone (4). This paper sought to redress the balance by systematically reviewing controlled observational studies in addition to RCTs to broaden the evidence base for corticosteroids in non-critical COVID-19.

PRISMA guidelines were followed throughout. 'Non-critical' was defined as COVID-19 not requiring mechanical ventilation. Five observational studies and the RECOVERY trial were included. The observational studies used propensity matching but remained at risk of bias due to retrospective design, heterogeneous interventions (corticosteroid choice, dose and timing) and lack of placebo. Study heterogeneity precluded meta-analysis. It is worth noting that RECOVERY was by far the largest single study (n = 5,418) and that the observational studies only contributed a total of 480 patients.

Two of the observational studies assessed in-hospital mortality, one in severe (non-critical) cases, and the other in moderate cases. Neither found an association between corticosteroids and in-hospital mortality, which is concordant with the findings of RECOVERY and aligns with WHO guidance which does not advocate corticosteroids in non-severe COVID-19. Four of the additional studies assessed secondary outcomes such as duration of hospitalisation, length of viral shedding and disease progression, with mixed results.

Bottom line: the available evidence suggests that there is no mortality benefit from corticosteroids in non-severe and non-critical COVID-19.

3. **Obesity is associated with increased severity of disease in COVID-19 pneumonia: a systematic review and meta-analysis (5)**

Topic: **Epidemiology**

Outcome Rating: **Worth a peek**

A higher prevalence of obesity in younger Western patients may mean that COVID-19 will cause more severe disease in a greater number of younger patients than has previously been reported (6).

This systematic review and meta-analysis looked at the association between body mass index or obesity and outcomes in COVID-19. Twenty-two studies comprising 12,591 patients were included. The meta-analysis demonstrated that obesity was not associated with increased mortality. However, obesity was associated with a range of other adverse outcomes including disease progression (OR 1.41, 95% CI 1.26-1.58), severe COVID-19 (OR 4.17, 95% CI 2.32-7.48), intensive care admission (OR 1.57, 95% CI 1.19-2.09) and mechanical ventilation (OR 2.13, 95% CI 1.10-4.14). The association between obesity and poor outcomes was more pronounced for younger patients (aged <60 years) than older patients.

The authors note that the complex relationship between obesity and mortality has been observed in previous studies of pneumonia, but also draw attention to the fact that heterogeneity in their included studies may under-estimate the mortality in obese patients. The most important additional limitations include: varying definitions of obesity used by included studies (28-30kg/m^2), the reliance of studies on estimated or patient-reported data, and the lack of sufficient data to perform an analysis on overweight (as opposed to obese) patients. Nonetheless, the increased severity of disease in obese young patients may have significant implications for healthcare systems treating populations in which obesity is prevalent among younger patients.

Bottom line: emergency physicians should consider obesity a risk factor for severe illness in patients with COVID-19.

4. Decontamination of N95 masks for re-use employing 7 widely available sterilization methods (7)

Topic: **Personal Protective Equipment**

Outcome Rating: **Head turner**

Healthcare providers around the world continue to face a shortage of personal protective equipment (PPE), including N95 respirator masks, which offer protection for respiratory viruses such as SARS-CoV-2. The standard manufacturers' recommendation is that N95 masks are single-use products. However, developing safe and effective methods to decontaminate the masks has the potential to enable re-use and reduce shortages.

In this study the authors experimentally contaminated four different mask models with SARS-CoV-2 and assessed several decontamination methods. The mask models were: VFlex 1804, Aura 1870, 1860 (The 3M Company, St Paul, Minnesota) and AO Safety 1054S (Pleats Plus) Respirator (Aearo Technologies, Indianapolis). The methods of decontamination were: autoclave treatment, vaporous hydrogen peroxide exposure, peracetic acid dry fogging, ultraviolet C radiation and moist heat. The authors also evaluated the number of decontamination cycles that the masks could tolerate without affecting their structural and functional integrity. This was achieved through quantitative fit testing and laboratory particulate filtration testing.

All the decontamination methods except ultraviolet C radiation were effective in sterilising the masks without affecting the structure and functional integrity for at least one cycle. Autoclave treatment was effective in all models for at least one cycle, and in some models for up to 10 cycles. Finally, three of the effective methods (vaporous hydrogen peroxide, peracetic acid dry fogging and moist heat treatment) were associated with both fit and filtration integrity in all mask models up to at least ten cycles.

This study provides evidence on decontamination practices for N95 masks when it is not possible to follow the ideal single use recommendation for each patient encounter. The authors emphasise that since access to autoclaves is ‘near universal’ the findings may be highly relevant in resource-poor settings where PPE procurement remains a daily problem.

Bottom line: emergency physicians facing resource shortages should be aware of the potential of safe, efficacious and widely available techniques for decontaminating single-use PPE.

5. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine (8)

Topic: **Prevention**

Outcome Rating: **Game changer**

The development of candidate vaccines against COVID-19 has been an unprecedented scientific effort, and the subsequent demonstration of their efficacy is a landmark moment in the course of the pandemic. The Pfizer/BioNTech mRNA vaccine was the first to complete phase 3 trials, publish its results and become licensed for use in the UK.

The authors conducted a randomised, placebo-controlled, observer-blinded multinational trial. Adults >16 years who were either healthy or had stable chronic health conditions received two intramuscular injections of BNT162b2, or an equivalent volume of saline, 21 days apart. Patients were excluded if they had a history of COVID-19 or if they were immunosuppressed. Safety assessment was conducted through solicited and unsolicited methods and will continue up to 2 years after the second dose was administered (although only safety up to 14 weeks is included in this paper).

44,820 participants were randomised of whom 21,720 received the candidate vaccine. Adverse reactions were reported 21% of vaccinated participants compared to 5% of placebo recipients. Almost all reactions were mild or moderate local or systemic reactions such as pain at injection site, headache or fatigue. There were four serious related adverse events in vaccinated participants: a shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia and right leg paraesthesia. There were no related deaths in either the vaccine or placebo group.

The trial assessed efficacy by comparing the rates of illness from COVID-19 in the vaccinated and placebo groups. Between the first and the second dose there were 39 cases of symptomatic COVID-19 in the vaccination group compared to 82 cases in the placebo group, yielding an overall efficacy of 52% (95% CI 29.5 - 68.4). Among patients who had two doses, there were 8 cases of COVID-19 which occurred at least 7 days after the second dose in the vaccination group compared to 162 cases in the placebo group, yielding a vaccine efficacy of 95% (95% CI 90.3 - 97.6) by 12 days after the second dose.

There are some important limitations to consider. The study did not routinely test people for COVID-19; they only tested people if they became symptomatic. In other words, they could not say if people had asymptomatic disease in the vaccine group. As a result, it is currently

unknown whether someone with the vaccine can acquire COVID-19 and transmit it to others, even if the person vaccinated remains asymptomatic. For this reason, people fully vaccinated are still asked to quarantine if they become a close contact to someone with COVID-19.

In addition, no data are reported on the efficacy of a single dose of vaccine beyond 21 days after administration, and nor are there any data on the efficacy of two doses delivered more than 21 days apart.

Finally, 82.9% of participants were white, the median age was 52 years with 42% of participants over 55 years, and 130 of the 152 trial sites were in the USA. Exclusion criteria have left some questions about how the vaccines will work in those previously infected by COVID-19 or immunosuppressed.

Bottom line: emergency physicians can be confident that the Pfizer/BioNTech vaccine is safe and effective in preventing illness but should remain alert to how these findings translate into real-world practice.

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