Treatments for COVID-19

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1. **Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results** - WHO Solidarity Trial Consortium

   The solidarity trial was a large-scale, International trial, led by the WHO. Overall it includes 405 hospitals in 30 countries with ~11,300 adult participants. Interim results were released on 15 October 2020 and updated in NEJM on 2 December 2020. The 4 study drugs were: remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon-β1a. We do not focus on interferon-β1a due to the known high cost of this drug and its unlikely widespread adoption due to this limitation in the sub-Saharan African context. The primary outcome measured was 28-day in-hospital mortality. Patients were randomised to one of the trial drug regimens and open control (up to five options, four active and the local standard of care). Of note, 61% of participants were in Asia or Africa, versus 17% in Latin America and 22% in Europe and Canada.

   2750 participants were randomised to remdesivir, with 2725 controls. With similar numbers of deaths in each group, with a RR=0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control), these results show that there was no mortality benefit demonstrated with remdesivir.

   954 participants were randomised to hydroxychloroquine, with 909 controls.
   The RR was found to be 1.19 (0.89 -1.59; P=0.23; 104/947 vs 84/906), showing no mortality benefit demonstrated with hydroxychloroquine.

   1411 participants were randomised to lopinavir/ritonavir and 1372 to its control. Similar to the RECOVERY trial, the results here were disappointing. They showed quite clearly that lopinavir/ritonavir did not reduce mortality (11% in each group), duration of hospital admission or progression to mechanical ventilation (9% in each group) with a RR=1.00 (0.79-1.25, p=0.97; 148/1399 vs 146/1372). As such this arm was also closed early due to null effect. An issue that arose in both trials is that lopinavir/ritonavir can only be given orally, and is not suitable for nasogastric administration so cannot be given to those who were mechanically ventilated.

   There has been concern that antiretrovirals would be directed away from HIV services to treat COVID-19. This would have been hugely detrimental to HIV services, and now given the lack of evidence there is no justification for this.

2. **Remdesivir for the Treatment of Covid-19 — Final Report** - John H. Beigel, *et al.*

   This was a multicentre, double blind, randomised, placebo-controlled trial (ACTT-1) of IV remdesivir in adults hospitalised with COVID-19 and evidence of LRTI. Participants were randomly assigned to remdesivir or placebo for 10 days. Primary outcome was time to recovery (discharge or quarantine) which had changed from from clinical status on day 15 to time to recovery, early on in the study. 1062 participants were randomised, 541 to remdesivir and 521 to placebo. The method of randomisation not described but was stratified by site and disease severity. Median time to recovery was 10 days for those randomised to remdesivir (95%CI 9-11) and 15 days for those who received placebo (95%CI 13-18). RR 1.29, 95%CI 1.12-1.49; P<0.001). Clinical status assessed throughout on 8 category ordinal scale and NEWS. Clinical status on day 15 was a secondary outcome. Estimates of mortality were 6.7% with remdesivir vs 11.9% with placebo by day 15, with a statistically significant hazard ratio 0.55, 95%CI 0.36 to 0.83. The beneficial effect of remdesivir was not statistically significant at day 29, with mortality at 11.4% in the remdesivir group vs 15.2% in the placebo group, hazard ratio 0.73, 95%CI 0.52-1.03.

   The paper concludes that remdesivir was superior to placebo in reducing time to recover in adults hospitalised with COVID-19, especially when given early in the illness. Other limitations include the fact that corticosteroids were used in some patients- 23% and hydroxychloroquine 35.6%.

3. **Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial** - The RECOVERY Collaborative Group

   This first paper is the publication about the lopinavir/ritonavir arm of the RECOVERY trial. The RECOVERY trial is an ongoing UK randomised controlled trial aimed at identifying treatments for COVID-19. So far, over 181 sites, over 39 thousand people have taken part, randomised to study arms vs usual care with a 28 day mortality primary outcome.

   It was hoped that lopinavir/ritonavir could be a useful treatment in COVID-19 patients based on *in vitro* activity. 1616 patients received Lopinavir/Ritonavir and 3424 patients were allocated to usual care.

   The conclusion was that lopinavir/ritonavir is not an effective treatment for Covid-19. There was no reduction in mortality, hospital stay or risk of progression to ventilation.
   - In terms of mortality 23% of the treatment group vs. 22% control group died within 28 days (RR 1.03).
   - In terms of hospital stay the median admission duration was 11 days in each group, with 69% treatment group discharged in 28 days vs. 70% control group (RR 0.98).
   - And 10% treatment group vs. 9% control group progressed to mechanical ventilation (RR 1.15).

Results were consistent between subgroups of patients – which were age, sex, ethnicity, symptom duration, and respiratory support at the time of enrolment. Randomisation to this arm closed early due to the null effect demonstrated.

4. **Respiratory Support in COVID-19 Patients, with a Focus on Resource-Limited Settings** - Arjen M Dondorp, *et al.*

   Whist lots of trials are on going for drug therapies, the mainstay of managing COVID-19 is providing oxygen support. This first review is from the American Journal of Tropical Medicine and Hygiene and it lays out the logistics of this in a resource-limited setting.

   The authors refer to the 2015 The Lancet Commission on Global Surgery, which found that a quarter of hospitals in resource limited settings lack sufficient oxygen supply. They highlight that hypoxaemia is well tolerated in these patients and that the oxygen targets should be more liberal – aiming for oxygen saturations of 88%. They advise awake proning, which facilitates ventilation of posterior lung fields and improves the ventilation-perfusion mismatch. Guidelines from high resource settings advise arterial blood gas monitoring and etCO_2 monitoring; however these are not always available and pulse oximetry is a very good guide in COVID-19 patients. Lung ultrasound can also be a good alternative to chest x-rays and chest CT scans.

   They then discuss escalating to non invasive and invasive ventilation. Firstly they advise to base this on respiratory fatigue and high work of breathing – as opposed to hypoxia alone, which as mentioned before can be well tolerated. They acknowledge that CPAP and noninvasive ventilation is a grey area with limited evidence in the context of covid, and these modalities carry uncertainty around aerosolisation risk.

   In terms of mechanical ventilation it is worrying that the fatality is over 50% for intubated patients. They explain that lung protection is key here and this is done by the following measures
   - Use low tidal volumes. Limiting tidal volumes to 6 mL/ideal body weight (IBW)
   - Permissive hypercapnia. Hypercapnia should be tolerated as long as pH and SpO_2 88%/PaO_2 8
   - Limit PEEP to 10 cmH_2O
   - Monitoring and limiting driving pressure: most COVID-19 patients can be ventilated with driving pressure less than 15 cmH_2O
   - Use a low threshold for prone positioning

   Overall, this was an excellent pragmatic summary of oxygenating and ventilating COVID-19 patients.

5. **High-Flow, Noninvasive Ventilation and Awake (Nonintubation) Proning in Patients With Coronavirus Disease 2019 With Respiratory Failure** - Suhail Raoof, *et al.*

   This paper was published in CHEST in 2020. This focuses on high flow oxygen, noninvasive ventilation and proning. Early on in the pandemic the advice was to intubate

promptly – due to concerns over very rapid respiratory decline and also the aerosol generating risk of other modalities.

However, this paper suggests there may be approximately 25% of patients with COVID-19 in whom modalities such as high-flow oxygen, noninvasive ventilation, and awake proning may stabilize their respiratory function and obviate the need for intubation.

They provide a good summary table of physiologic effects, indications, precautions, technique and monitoring for these therapies. As a very brief summary they show that:

- High flow nasal oxygen provides heated, humidified oxygen, delivering a high FiO_2 at a high flow rate. It flushes the nasopharynx with oxygen in exhalation and generates extrinsic PEEP
- Proning makes ventilation more homogenous, improves ventilation-perfusion matching and shunt effects, as well as helping with secretion drainage
- Non-invasive ventilation opens collapsed lung units and improves alveolar ventilation. This increases PaO_2 and decreases $PaCO_2$ and also reduces work of breathing

This is an interesting paper to focus on the more grey area of respiratory support, that teams were reluctant to use initially but may have an important management role in this pandemic and could reduce the need for mechanical ventilation.

6. **Convalescent plasma transfusion for the treatment of COVID-19: Systematic review** - Karthick Rajendran, *et al.*

   This paper highlights that there is very little data thus far regarding convalescent plasma transfusion (CPT). The review includes five studies reporting CPT to COVID-19 patients.

   The main findings from available data are as follows:

   - Convalescent plasma may reduce mortality in critically ill patients
   - Increase in neutralizing antibody titers and disappearance of SARS-CoV-2 RNA was observed in almost all the patients after CPT therapy
   - Beneficial effect on clinical symptoms after administration of convalescent plasma.

   Based on the limited scientific data, CPT therapy in COVID-19 patients appears safe, clinically effective, and reduces mortality. Going forwards, well-designed large multicenter clinical trial studies should be conducted urgently to establish the efficacy of CPT to COVID-19 patients.

7. **Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial (PREPRINT)** - The RECOVERY Collaborative Group

   This preprint reports on the results of the convalescent plasma transfusion study arm from the RECOVERY trial which is an ongoing UK randomised controlled trial aimed at

identifying treatments for COVID-19. So far, over 181 sites, over 39 thousand people have taken part, randomised to study arms vs usual care with a 28 day mortality primary outcome.

5795 patients were randomly allocated to receive convalescent plasma and 5763 to usual care alone. No significant difference in 28-day mortality was found between the two groups: 1398 (24%) of 5795 patients allocated convalescent plasma and 1408 (24%) of 5763 patients allocated usual care died within 28 days (rate ratio [RR] 1·00; 95% confidence interval [CI] 0·93 to 1·07; p=0·93).

Allocation to convalescent plasma had no significant effect on the proportion of patients discharged from hospital within 28 days (66% *vs*. 67%; rate ratio 0·98; 95% CI 0·94-1·03, p=0·50). Among those not on invasive mechanical ventilation at baseline, there was no significant difference in the proportion meeting the composite endpoint of progression to invasive mechanical ventilation or death (28% *vs*. 29%; rate ratio 0·99; 95% CI 0·93-1·05, p=0·79).

These results show that there is no survival benefit conferred to patients hospitalised with COVID-19 by treatment with convalescent plasma.

8. **Evidence-Based Practical Guidance for the Antithrombotic Management in Patients With Coronavirus Disease (COVID-19) in 2020** - Eduardo Ramacciotti, *et al.*

COVID-19 increases risk of arterial and venous thrombotic complications. This paper sets out some evidence-based guidance on managing the thrombotic complications of COVID-19. There is an increased risk of strokes, severe venous and arterial thrombosis, particular pulmonary embolisms/thrombus, and microvascular thrombosis. What this paper outlines as being unknown includes extended DVT management, and the utility of d-dimers in the investigation of thrombotic complications. It's possible that many of the pulmonary embolisms do not originate from DVTs as there is a low incidence of DVT seen amongst inpatients. Microthrombi are seen in other organs on post-mortem examination.

The paper references Klok who reported that 49% of COVID-19 patients on their ICU had a thrombotic event which increased the risk for all cause mortality, with a hazard ratio of 5.4, (95% CI: 2.4 to 12) despite all patients receiving pharmacological thromboprophylaxis.

The authors recommend that all patients with COVID-19 should be risk stratified and given thromboprophylaxis. They also recommend mechanical prophylaxis in immobile patients if pharmcological prophylaxis is not suitable or available. Extended VTE prophylaxis should be considered on discharge. In the absence of any specific new guidance on anticoagulation, standard anticoagulation doses as recommended by WHO Interim Guidance should be followed. There is limited data on strategies using full dose or intermediate dose parenteral anticoagulation for routine care. Further studies are awaited on the subject of anticoagulation in COVID-19.

9. **Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19** - The RECOVERY Collaborative Group.

   This paper reports on the hydroxychloroquine arm of a study into evaluating treatments to reduce 28-day mortality from COVID-19. The RECOVERY trial is an ongoing UK randomised controlled trial aimed at identifying treatments for COVID-19. So far, over 181 sites, over 39 thousand people have taken part, randomised to study arms vs usual care with a 28 day mortality primary outcome. Eligible patients were those admitted with clinically suspected or laboratory confirmed SARS-CoV-2 infection

   Patients were randomly assigned to hydroxychloroquine or to usual care alone. Secondary outcomes were time until discharge and whether patients received invasive mechanical ventIlation/ECMO. 1561 received hydroxychloroquine and 3155 received usual care.

   421 (27%) patients died within 28 days in the hydroxychloroquine group, and 790 (25%) in the usual care group. RR 1.09, 95%CI 0.97-1-.23; P=0.15. There was evidence of harm as those who received hydroxychloroquine were less likely to be discharged from the hospital alive within 28 days when compared with those in the usual care group (59.6% vs 62.9%; RR 0.9, 95%CI 1.03 - 1.27). There was no difference in major cardiac arrhythmia amongst those who received hydroxychloroquine. Those who received hydroxychloroquine did not have a survival benefit.

10. **Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis** - The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group.

    This was a prospective meta-analysis of 7 RCTs including 1703 patients. Trials were done across 12 countries. Patients were randomised to receive systemic dexamethasone, hydrocortisone or methylprednisolone (678 patients) or usual care/placebo (1025 patients). The primary outcome was all-cause mortality at 28 days. 6 of 7 papers had low risk of bias, one had some concerns due to randomisation. Not all trials reported death at 28 days. One reported at 21 days, and one at 30 days. 222 out of 678 patients on corticosteroids, 425 deaths out of 1025 randomised to placebo or usual care (Summary OR 0.66, 95%CI 0.53-0.82; P<0.01, based on fixed-effects model) OR 0.7, 95%CI 0.48-1.01, P=0.053, based on random effects model.

    Dexamethasone was the only one drug to show statistically significant improvement with OR 0.64, 95%CI 0.5-0.82, p<0.001. It showed no increase in adverse events. Limitations include possible ‘publication bias’ - with some trials not participating in the prospective meta-analysis because of negative results. Only one paper held some concerns for bias, with a small sample size of 47 patients, looked at methylprednisolone. These trials were all conducted in high income settings, and only on adults which makes the findings less generalisable to the sub-Saharan African context, and amongst children. There was reduction in 28 day mortality with dexamethasone in adults who were critically unwell,

regardless of whether they required NIV or IMV. Absolute mortality risk with dexamethasone was 30% vs 40% with usual care or placebo.

This paper provides an affordable and available therapeutic option for critically unwell COVID-19 patients. There have been reports in some African countries of high demand on oral steroids by **all** COVID-19 patients, including those self-medicating at home and leading to other patients (e.g. with rheumatological diseases) struggling to find them. Therefore, while oral steroids should be a key component of national protocols for management of severe COVID patients based on this paper, better governance needed to ensure appropriate use and prescription.

11. **Dexamethasone in Hospitalized Patients with Covid-19** - The RECOVERY Collaborative Group.

    This paper reports on the arm of the trial evaluating dexamethasone as a treatment to reduce 28-day mortality from COVID-19. The RECOVERY trial is an ongoing UK randomised controlled trial aimed at identifying treatments for COVID-19. So far, over 181 sites, over 39 thousand people have taken part, randomised to study arms vs usual care with a 28 day mortality primary outcome. Eligible patients were those admitted with clinically suspected or laboratory confirmed SARS-CoV-2 infection.

    This paper looks at the dexamethasone arm of the study. Patients were randomly assigned to oral or IV dexamethasone for up to 10 days or to usual care alone. The primary outcome was 28-day mortality. 2104 received dexamethasone compared with 4321 received usual care.

    Randomisation was unstratified and conducted using a web-based method, with demographic data, respiratory support and comorbidities recorded using a web-based case-report form. Follow up forms were completed online when each trial patient was discharged, at 28 days from randomisation, or at the time of death. Other treatments, duration of admission, respiratory support and dialysis/haemofiltration support was documented. 482 (22.9%) died within 28 days in dexamethasone group, and 1110 (25.7%) died in usual care group.

    There were significant differences between these groups in the level of respiratory support that they received. Comparing only those who received invasive mechanical ventilation, mortality was 29.3% in the dexamethasone group vs. 41.4% in the usual care group. A smaller benefit was seen in those receiving oxygen but without invasive mechanical ventilation (23.3% vs 26.2% mortality) and no difference seen in those who did not require any respiratory support. This study supported the use of dexamethasone to reduce 28 day mortality in those receiving any respiratory support.

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