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## **UPDATE ON GLOBAL DEVELOPMENTS ON COVID-19**

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## Summary

- A prospective cohort study conducted among adult cancer patients in UK reported 92.5% of patients who died during the course were due to COVID-19. This was also significantly associated with increasing age and being male patient. The study also revealed that those with haematological malignancies to be at significantly increased risk of COVID-19 infection and even severe form of it.
- Patients with COVID related hyper inflammation (COV-HI) at admission had been observed to be at an increased risk of dying than patients who didn't have the COV-HI.
- An alternative rapid RT-qPCR approach without RNA extraction and potential for decreasing time and cost compared with standard RT-PCR has been reported to have high sensitivity and specificity.
- Further multi-country randomized trial has reported no difference between a 10-day vs a 5-day course of remdesivir.
- U.S. FDA issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients on August 23. However, concerns have been raised from a wide group of scientists.
- WHO has published recommendation for children on masks:
  - Children aged 12 and over: should wear a mask under the same conditions as adults.
  - Children aged between 6 and 11: consider risk of transmission of the virus and whether the child is interacting with high-risk individuals such as the elderly. Adult supervision is needed if he/she wears a mask.
  - Children aged 5 years and under: they should not be required to wear masks unless in a risky setting.
  - Children with severe cognitive or respiratory impairments with difficulties tolerating a mask should not be required to wear masks.

## Recommendations

- Although the FDA authorisation should give more confidence to consider use of convalescent plasma in clinical practice, the lingering uncertainty still calls for further clinical trials.
- The evolving diagnostic procedures should be tracked systematically to select and adapt more efficient and less costly approaches.

- The WHO masking rules may offer some guidance on how children should be wearing masks. Availability of suitable masks and public education is needed.

### Update on pathogenesis

- In a recent case series, full post-mortem examinations were done on nine UK patients with confirmed COVID-19 including sampling of all major organs. One additional patient underwent percutaneous biopsy sampling (heart, lungs, pancreas, kidneys, and liver) under ultrasound guidance. Histochemical stains and immunohistochemistry were applied according to local protocols. Histopathological findings were reported by subspecialist pathologists and all cases were reviewed independently by at least two pathologists. The major findings of the study are summarized below;
  - Out of the nine full autopsies, one micro or macro-thrombosis was observed at least in one organ predominantly on lung (eight [89%]), heart (five [56%]), and kidney (four [44%]).
  - Diffuse alveolar damage was found in all ten patients.
  - Immune cell depletion particularly CD8-positive T cells was reported in hematological organs.
  - Bone marrow haemophagocytosis was prominent in two patients and focal in two patients.
  - Novel autopsy findings include; acute pancreatitis (two [22%] of nine patients), adrenal micro-infarction (three [33%]), pericarditis (two [22%]), disseminated mucormycosis (one [10%] of ten patients), aortic dissection (one [11%] of nine patients), and marantic endocarditis (one [11%]).
  - In addition, moderate to intense microglial activation was the most prominent pathological finding in all five patients with CNS features.
  - At the end, the study recommended as additional investigation is needed on the role of kidney injury, pancreatitis, pericarditis, secondary fungal infections, and pre-existing liver disease on COVID-19 [Hanley, B., et al, 2020].
- A prospective cohort study was conducted among adult cancer patients who were enrolled in the UK coronavirus cancer monitoring project cohort between March 18 and May 8, 2020. The study compared the effect of tumor subtype and patient demographics (age and sex) on prevalence and mortality from COVID-19 between 1,144 cancer patients with COVID-19 and 282,878 non-COVID-19 cancer control population from the national statistics. The major findings of the study are summarized below;

- Cancer patients with COVID-19 were more likely to be men (595 [56.9%] of 1044 patients) compared to 145,034 [51.3%] of 282,878 cancer control population; OR 1.26, 95% CI 1.12–1.43.
- Out of the total 1,044 patients, 319 (30.6%) of them died during the follow up period. Of which, 295 (92.5%) of them were due to COVID-19.
- All cause case fatality rate in cancer patients with COVID-19 was significantly associated with increasing age. Similarly, it was significantly associated with sex (212 [35.6%] of 595 male patients 105 [23.6%] of 445 female patients; OR 1.92, 95% CI 1.51–2.45).
- Patients with hematological malignancies appeared to be at significantly increased risk of COVID-19 infection; leukemia (OR 2.82, 95% CI 2.21–3.55), myeloma (2.03, 1.42–2.83), and lymphoma (1.63, 1.28–2.06).
- Not only increased COVID-19 susceptibility, but patients with hematological malignancies (leukemia, lymphoma, and myeloma) had also a more severe COVID-19 trajectory compared with patients with solid organ tumors (OR 1.57, 95% CI 1.15–2.15).
- Those patients who had recent chemotherapy had an increased risk of death during COVID-19-associated hospital admission (OR 2.09, 95% CI 1.09–4.08) [Lee, L., et al, 2020].
- The association between COVID related hyper inflammation (COV-HI) and escalation of respiratory support were evaluated in a retrospective study conducted with 269 adult patients admitted between March 1 and March 31, 2020. In this study, COV- HI was defined as C-reactive protein concentration greater than 150 mg/L or a ferritin concentration greater than 1500 µg/L. Escalation for respiratory support was considered as combination of oxygen support, non-invasive ventilation and intubation. The study revealed that 90(33%) of patients were having COV-HI at admission and higher proportion of patients with COV-HI on admission died during follow-up (36 [40%] of 90 patients) compared with the patients without COV-HI on admission (46 [26%] of 179). After controlling for age, sex, and comorbidity, COV-HI was significantly associated with the risk of next-day escalation of respiratory support or death (hazard ratio 2.24 [95% CI 1.62–2.87]) [Manson, J. J.,2020].

## Update on Diagnosis

- RT-PCR testing for COVID-19 is time consuming and costly. A programme that included a rapid RTqPCR approach without RNA extraction was tested and recommended in one study. This new technique, called Direct-One-Step-RT-qPCR (DIOS-RT-qPCR) assay, is said to detect SARS-CoV-2 in less than one hour while maintaining the high sensitivity and specificity required of diagnostic tools. It is noted that this optimised protocol allows for the direct use of swab transfer media without the need for RNA extraction, achieving comparable sensitivity to the standard method that requires the time-consuming and costly step of RNA isolation. The use of fast enzymes allows RT-qPCR to be performed under standard laboratory conditions within one hour, making it a potential point-of-care solution on high-speed cycling instruments. The authors indicated their robust test is easy to perform under standard laboratory conditions in high-performance formats, which allows for a significant increase in test numbers. It was also highlighted that fast, easy, cost-effective and sensitive features of the COVID-19 testing programme is necessary for the near future that may accelerate clinical decision-making (Kriegova et al., 2020).

## Update on treatment

- Remdesivir 10-days vs 5-days: A multi-country randomized, open-label, phase 3 trial that included 584 patients with moderate COVID-19 (Spinner, Gottlieb et al. 2020) evaluated the efficacy of 5 or 10 days of remdesivir treatment compared with standard care on clinical status on day 11 after initiation of treatment. The trial included 105 hospitals in the United States, Europe, and Asia. Patients were randomized in a 1:1:1 ratio to receive a 10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199), or standard care (n = 200). Remdesivir was dosed intravenously at 200 mg on day 1 followed by 100 mg/d. The results indicated that the day 11 clinical status distribution measured on a 7-point ordinal scale was significantly better for those randomized to a 5-day course of remdesivir (median length of treatment, 5 days) compared with those randomized to standard care but the difference was of uncertain clinical importance. The difference for those randomized to a 10-day course (median length of treatment, 6 days) compared with standard care
- was not significantly different. It was also noted that nausea (10% vs 3%), hypokalemia (6% vs 2%), and headache (5% vs 3%) were more frequent among remdesivir-treated patients compared with standard care.

- On August 23, 2020, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients. The EUA authorizes the distribution of COVID-19 convalescent plasma in the U.S. and its administration by health care providers, as appropriate, to treat suspected or laboratory-confirmed COVID-19 in hospitalized patients with COVID-19 (US FDA 2020).
- However, this recommendation was preceded by some US Government health leaders, including Dr. Anthony S. Fauci, urging caution, citing weak data from the country's largest plasma study. The main concern is the lack of controls. Logistics were also additional considerations. The most recent batch of data from the program included more than 35,000 COVID-19 patients, many of them in intensive care and on ventilators, and suggested that plasma administered within three days of a diagnosis reduced mortality rates. When calculated a month after the infusions, the death rate of patients who received plasma within three days of diagnosis was lower (21.6 percent) than it was for those who received plasma after seven days (26.7 percent). But the study did not have a control group of patients given a placebo to compare with those given plasma, making it difficult for scientists to assess whether the treatment really worked. And, given the limited supply of plasma, it is not clear how realistic treating patients within three days of diagnosis would be.

## Update on personal protective equipment

### *Face mask use*

- WHO has published an advice for children on masks. The advice covers three age groups:
  - Children aged 12 and over: should wear a mask under the same conditions as adults, in particular when they cannot guarantee a distance of at least one meter from others and there is widespread transmission in the area
  - Children aged between 6 and 11: the WHO advises taking into account how widespread the transmission of the virus is and whether the child is interacting with high-risk individuals such as the elderly. It also stresses the need for adult supervision to help children use, put on and take off masks safely. It is also noted access to masks, as well as laundering and replacement of masks in certain settings (such as schools and childcare services) and potential impact of wearing a mask on learning and psychosocial development, in consultation with teachers, parents/caregivers and/or medical providers should be taken into account.

- Children aged 5 years and under: they should not be required to wear masks. This is based on the safety and overall interest of the child and the capacity to appropriately use a mask with minimal assistance. It is highlighted there may be local requirements for children aged 5 years and under to wear masks, or specific needs in some settings, such as being physically close to someone who is ill. In these circumstances, if the child wears a mask, a parent or other guardian should be within direct line of sight to supervise the safe use of the mask.
- In addition, it is advised the use of masks for children of any age with developmental disorders, disabilities or other specific health conditions should not be mandatory and be assessed on a case by case basis by the child's parent, guardian, educator and/or medical provider. In any case, children with severe cognitive or respiratory impairments with difficulties tolerating a mask should not be required to wear masks. It is also advised that children with underlying health conditions such as cystic fibrosis or cancer are should wear a medical mask in consultation with their medical providers but that children who are in general good health can wear a non-medical or fabric mask(WHO, 2020).
- In one study large-pore membranes obtained from three-ply surgical mask, which offer high breathability but low bacteria capture, were functionalized to have a uniform salt layer on the fibers. The middle membrane (active filtration unit) and outer protective membrane were discarded; the innermost polypropylene membrane (typically used against the wearer's face for mechanical protection of the middle filter) was used to produce the salt filter samples. The membranes were coated with different salt types to obtain the salt-functionalized filters: sodium chloride (NaCl), potassium sulfate (K<sub>2</sub>SO<sub>4</sub>), and potassium chloride (KCl). To prepare the coating solutions, the salts were dissolved in filtered (0.22 μm pore size) DI water under stirring at 400 rpm and 90 °C for NaCl, and 400 rpm and room temperature for K<sub>2</sub>SO<sub>4</sub> and KCl. Surfactant (Tween 20) was added at 1 v/v%. The salt filters were prepared by completely pre-wetting the membrane samples with ~ 350 μL of a given coating solution. The salt filter samples were dried overnight in an incubator at 45 °C. The results showed that uniformly functional filters were successfully fabricated with NaCl, K<sub>2</sub>SO<sub>4</sub> or KCl salts at controlled thicknesses. It was revealed the salt-functionalized membranes achieved high filtration efficiency as opposed to the bare membrane, with differences of up to 48%, while maintaining high breathability (> 60% increase compared to commercial surgical masks even for the

thickest salt filters tested). The salt-functionalized filters quickly killed Gram-positive and Gram-negative bacteria aerosols in vitro, with colony forming unit reductions observed as early as within 5 min, and in vivo by causing structural damage due to salt recrystallization. The salt coatings retained the pathogen inactivation capability at harsh environmental conditions (37 °C and a relative humidity of 70%, 80% and 90%). It was concluded that the combination of these properties in one filter will lead to the production of an effective device, comprehensively mitigating infection transmission globally (Rubino et al., 2020).

- An observational study from Shiraz, Iran, compared the average number of touches to the mucosal zone between mask wearers with those who were not wearing a mask. A total of 1000 people were observed for 15-30 minutes in public places between 22 April and 9 May 2020. Of these 568 were wearing mask while 432 did not wear a mask and the average number of touches to the mucosal zone was calculated per hour. The results showed that 92% were observed touching their face at least once an hour and averaged 10 (SD 6) touches per hour. Non-mask wearers touched their face significantly more often than mask wearers (11 vs 8 times per hour,  $P < 0.001$ ). Non-mask wearers were 1.5 (95%CI OR 1.2-2.0) times more likely to touch their mucosal zone than mask wearers ( $P < 0.001$ ). In the absence of hand hygiene, touching the mucosal zone may have a role in covid-19 transmission and mask use decreases the frequency of touching the mucosal zone on the face which in turn plays a role in reducing the transmission of the virus (Shiraly et al., 2020).

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