

Control and Nursing in Guangdong Second Provincial General Hospital, have undergone intensive training to become familiar with the requirements for infection control in the negative pressure isolation wards. Herein, cameras cover the entire ward except for the privacy area. The infection control observer monitors medical staff in real time via computer monitors in a separate area (figure). The main responsibilities of the observer are to maintain the normal operation of the negative pressure isolation wards, supervise the implementation of disinfection, ensure a sufficient supply of protective materials, arrange specimens for inspection, and relieve anxiety of the medical personnel while treating patients.

The observers pay attention to the medical staff not only during their time in the negative pressure ward, but also during the putting on or taking off of protective equipment when they enter or leave the ward. Although the health-care providers have attended multiple training sessions and emergency drills, in operation (especially in high-stress negative pressure wards) some steps might be omitted or overlooked, thus incurring potential exposure to nosocomial infection. For example, when a nurse helped an elderly patient pull up a zipper in the negative pressure ward, the zipper unexpectedly ripped the nurse's glove. The nurse became nervous, and anxious to continue her procedures. Discovering this situation on screen, the observer immediately soothed the nurse and sent another staff member into the ward to assist. Following the occupational exposure process, the observer then instructed the nurse to remove her gloves carefully, disinfect her hands, and dispose of the ripped gloves. The observer also systematically assessed the risks for the nurse and arranged a quarantine room for medical observation

to ensure full safety before she was allowed to return to the negative pressure ward.

The observing system, as a proactive infection control tool, provides immediate prevention against nosocomial infection in negative pressure isolation wards, which offers creative assistance to combat the COVID-19 outbreak. Guangdong Second Provincial General Hospital plans to incorporate artificial intelligence image recognition into the observing system, aiming to enhance the sensitivity and accuracy of instant detection. Implementing and improving the observing system might be a promising endeavor for controlling nosocomial infection of the COVID-19 outbreak and other acute infectious diseases.

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## Convalescent plasma as a potential therapy for COVID-19

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The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which originated in Wuhan, China, has become a major concern all over the world. The pneumonia induced by the SARS-CoV-2 is named coronavirus disease 2019 (COVID-19). By Feb 22, 2020, this virus has affected more than 77700 people worldwide and caused more than 2300 deaths. To date, no specific treatment has been

proven to be effective for SARS-CoV-2 infection. Apart from supportive care, such as oxygen supply in mild cases and extracorporeal membrane oxygenation for the critically ill patients, specific drugs for this disease are still being researched. In the USA, the first patient infected with SARS-CoV-2 was treated by supportive care and intravenous remdesivir, before the patient recovered and was discharged.<sup>1</sup> However,

randomised clinical trials are needed to evaluate the safety and efficacy of remdesivir in the treatment of COVID-19.

Convalescent plasma or immunoglobulins have been used as a last resort to improve the survival rate of patients with SARS whose condition continued to deteriorate despite treatment with pulsed methylprednisolone. Moreover, several studies showed a shorter hospital stay and lower mortality in patients treated with convalescent plasma than those who were not treated with convalescent plasma.<sup>2-4</sup> In 2014, the use of convalescent plasma collected from patients who had recovered from Ebola virus disease was recommended by WHO as an empirical treatment during outbreaks.<sup>5</sup> A protocol for the use of convalescent plasma in the treatment of Middle East respiratory syndrome coronavirus was established in 2015.<sup>6</sup> In terms of patients with pandemic 2009 influenza A H1N1 (H1N1pdm09) virus infection, a prospective cohort study by Hung and colleagues showed a significant reduction in the relative risk of mortality (odds ratio 0.20 [95% CI 0.06–0.69],  $p=0.01$ ) for patients treated with convalescent plasma.<sup>7</sup> Additionally, in a subgroup analysis, viral load after convalescent plasma treatment was significantly lower on days 3, 5, and 7 after intensive care unit admission. No adverse events were observed. A multicentre, prospective, double-blind, randomised controlled trial by Hung and colleagues showed that using convalescent plasma from patients who recovered from the influenza A H1N1pdm09 virus infection to treat patients with severe influenza A H1N1 infection was associated with a lower viral load and reduced mortality within 5 days of symptom onset.<sup>8</sup> A meta-analysis by Mair-Jenkins and colleagues showed that the mortality was reduced after receiving various doses of convalescent plasma in patients with severe acute respiratory infections, with no adverse events or complications after treatment.<sup>9</sup> Another meta-analysis by Luke and colleagues identified eight studies involving 1703 patients with 1918 influenzapneumonia from 1918 to 1925 who received an infusion of influenza-convalescent human blood products, which showed a pooled absolute reduction of 21% (95% CI 15–27;  $p<0.001$ ) in the overall crude case-fatality rate at low risk of bias.<sup>10</sup>

One possible explanation for the efficacy of convalescent plasma therapy is that the antibodies from convalescent plasma might suppress viraemia.

Schoofs and colleagues reported that 3BNC117-mediated immunotherapy, which is a broad neutralising antibody to HIV-1, enhances host humoral immunity to HIV-1.<sup>11</sup> An in vivo trial also showed that the effects of this antibody were not only limited to free viral clearance and blocking new infection, but also included acceleration of infected cell clearance.<sup>12</sup> Viraemia peaks in the first week of infection in most viral illnesses. The patient usually develops a primary immune response by days 10–14, which is followed by virus clearance.<sup>4</sup> Therefore, theoretically, it should be more effective to administer the convalescent plasma at the early stage of disease.<sup>4</sup> However, other treatments might have an effect on the relationship between convalescent plasma and antibody level, including antiviral drugs, steroids, and intravenous immunoglobulin.<sup>10</sup>

According to WHO,<sup>13</sup> management of COVID-19 has mainly focused on infection prevention, case detection and monitoring, and supportive care. However, no specific anti-SARS-CoV-2 treatment is recommended because of the absence of evidence. Most importantly, the current guidelines emphasise that systematic corticosteroids should not be given routinely for the treatment of COVID-19, which was also the recommendation in a Comment in *The Lancet*.<sup>14</sup> Evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events. Therefore, it might be worthwhile to test the safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients.

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## COVID-19: combining antiviral and anti-inflammatory treatments

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See Online for appendix

Both coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome (SARS) are characterised by an overexuberant inflammatory response and, for SARS, viral load is not correlated with the worsening of symptoms.<sup>1,2</sup> In our previous Correspondence to *The Lancet*,<sup>3</sup> we described how BenevolentAI's proprietary artificial intelligence (AI)-derived knowledge graph,<sup>4</sup> queried by a suite of algorithms, enabled identification of a target and a potential therapeutic against SARS coronavirus 2 (SARS-CoV-2; the causative organism in COVID-19). We identified a group of approved drugs that could inhibit clathrin-mediated endocytosis and thereby inhibit viral infection of cells (appendix). The drug targets are members of the numb-associated kinase (NAK) family—including AAK1 and GAK—the inhibition of which has been shown to reduce viral infection in vitro.<sup>5,6</sup> Baricitinib was identified as a NAK inhibitor, with a particularly high affinity for AAK1, a pivotal regulator of clathrin-mediated endocytosis. We suggested that this drug could be of use in countering SARS-CoV-2 infections, subject to appropriate clinical testing.

To take this work further in a short timescale, a necessity when dealing with a new human pathogen, we re-examined the affinity and selectivity of all the approved drugs in our knowledge graph to identify those with both antiviral and anti-inflammatory properties. Such drugs are predicted to be of particular

importance in the treatment of severe cases of COVID-19, when the host inflammatory response becomes a major cause of lung damage and subsequent mortality. Comparison of the properties of the three best candidates are shown in the table. Baricitinib, fedratinib, and ruxolitinib are potent and selective JAK inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis. All three are powerful anti-inflammatories that, as JAK-STAT signalling inhibitors, are likely to be effective against the consequences of the elevated levels of cytokines (including interferon- $\gamma$ ) typically observed in people with COVID-19.<sup>2</sup> Although the three candidates have similar JAK inhibitor potencies, a high affinity for AAK1 suggests baricitinib is the best of the group, especially given its once-daily oral dosing and acceptable side-effect profile.<sup>7</sup> The most significant side-effect seen over 4214 patient-years in the clinical trial programmes used for European Medicines Agency registration was a small increase in upper respiratory tract infections (similar to that observed with methotrexate), but the incidence of serious infections (eg, herpes zoster) over 52 weeks' dosing was small (3·2 per 100 patient-years), and similar to placebo.<sup>7</sup> Use of this agent in patients with COVID-19 over 7–14 days, for example, suggests side-effects would be trivial.

Other AI-algorithm-predicted NAK inhibitors include a combination of the oncology drugs sunitinib and