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COVID-19 insights from transfusion medicine

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The emergence of coronavirus disease 2019 (COVID-19) in the first months of 2020 resulted in a massive surge in admissions to hospitals and intensive care units due to the nature of the respiratory pathophysiology. In some countries, healthcare systems were rapidly overwhelmed, while in others their hospitals coped with the first wave and all patients received the level of care needed, depending upon both the containment measured and the level of development of the healthcare systems.

Transfusion medicine services have prepared for possible blood shortages caused by a drop in blood donations, if donors became reluctant to participate in blood drives at the usual rate or became symptomatic and unable to donate.[1,2] However, shortages were often avoided, as the lack of donations was more than compensated for by an actual drop in blood component utilisation, as elective procedures with anticipated blood demand were postponed.[3,4] Planning with uncertain timelines and erring on the safe side had previously triggered surpluses with increased outdating of blood components.[5]

The first analyses of patients with COVID-19 in Wuhan, China did not report a substantial need for blood transfusion.[4] For the patients who did require transfusion, the component types and clinical indications remained to be discerned. In this issue, Doyle *et al.*[6] describe transfusion practice for patients with COVID-19 in intensive care units (ICUs), some requiring extracorporeal membrane oxygenation (ECMO), as one of the first reports on this topic. In this analysis of 235 patients, within 6 weeks, approximately 20% required one or more red cell transfusions, 3% required platelet transfusion and 2% each required fresh frozen plasma or cryoprecipitate. More than 50% of the patients with ECMO used blood components compared to 14% without ECMO. Plasma from convalescent donors was unavailable at the centre during these first 6 weeks.

The transfusion requirements were low, unless ECMO was necessary. And blood usage seemed almost restricted to red cell components. During ECMO, the red cell usage in patients with COVID-19[6] resembled usage in patients without COVID-19.[7] The indications for transfusion in patients without ECMO should be described in greater detail in future studies. One could explore the outcomes, for instance in those 15% of all red cell transfusions that were used for red cell exchanges alone. Which comorbidities are predisposing to blood transfusion and severity of viral disease? This short report from critical care at a large academic centre in London, UK[6] may not be representative of general clinical settings in primary care hospitals. Hence, more such descriptions of transfusion requirements could be informative, which will eventually allow us to compare the practice among patient cohorts in different countries.

There are hardly any reasons, however, to suspect blood component usage would be greater in patients with COVID-19 outside of critical care than inside. Should there be a blood shortage, this would be induced by the supply side rather than any blood demand of this pandemic. Why then should studying transfusion requirements be worthwhile in patients with COVID-19? To understand the pathophysiology of COVID-19, data analysis employs stratification of patients. Transfusion indications and requirements can serve as surrogate markers for the pathophysiology, such as disease severity. For instance, blood cell counts correlated with disease onset and recovery.[8,9] Proper patient blood management should always be applied,[10] particularly to limit blood sampling for study purposes before prompting any transfusion need.

In rapid reporting succession, patients with COVID-19 have been documented to develop cold agglutinin disease,[11] the relatively more common autoimmune haemolytic anaemia[12,13] or immune thrombocytopenia[14] and their combination as Evans syndrome.[15] Each of these clinical entities can progress to require transfusions of red cells or platelets.

Platelet transfusions occurred in <3% of all patients[6] and may seem minimal, and almost not worth analysing. However, pragmatic study designs employ such carefully conducted and documented observations. Any prospective observational study can contribute to powerful datasets of

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thousands of patients within a short time frame, when combined with many similar studies, no matter how small separately.[16]

Many platelet components contain 100% plasma. Even when produced with platelet additive solution, such components retain >30% of plasma with its residual anti-A and anti-B isoagglutinin.[17] The transfusion of ABO incompatible platelet components is considered benign for known clinical entities. More attention to ABO compatibility would limit antigen–antibody interactions and complement activation,[18] being known mediators of disseminated intravascular coagulation and systemic inflammatory response syndrome. The accumulated clinical data, if it had been accessible and suitably collated, would have sufficed to corroborate the safety of current transfusion practice in patients with COVID-19. These data would also establish a baseline for other COVID-19 therapies involving plasma.

Therapeutic plasma exchange has been applied[19] to treat hyper-inflammation in severe COVID-19, with a choice among fluids, albumin, immunoglobulin and plasma as replacement volume. The coagulopathy[20] in up to 50% of patients[21] may caution against the use of plasma from convalescent donors, despite promising reports in previous[22] and the current severe acute respiratory syndrome (SARS) infection.[23,24] The safety profile has to be established, particularly for patients in early stage COVID-19, where convalescent plasma, if safe, may be most effective. There is time for better science.[25]

The ABO blood group correlates with coagulation activities, particularly von Willebrand factor. An initial report proposed an increased risk for patients with COVID-19 and blood group A.[26] Additional data[27] and discussion indicated O individuals may be more protected than B individuals,[28,29] both carrying anti-A albeit of different titres. If higher titres correlated with delayed disease progression, plasma with high titre isoagglutinin or monoclonal anti-A might be a treatment option. Even 25% of blood group A patients, who express an A_2 phenotype, can receive anti-A_1.[30]

A large genome-wide association study established two gene loci conferring susceptibility for respiratory failure.[31] The second, smaller association signal coincided with the gene of the ABO blood group system, showing a higher risk in blood group A and a protective effect in blood group O,[31] although this conclusion was critiqued on technical merits.[32] Of course, >10 years ago, the spike protein of SARS coronavirus-1 (SARS-CoV-1, not today's SARS-CoV-2 of COVID-19) was inhibited by anti-A from binding to its receptor on cell surfaces.[33] More study is needed if human red cells express angiotensin-converting enzyme 2,[34] the target of the SARS-CoV-2 virus, which is currently not considered to directly bind to red cells. The anti-A effects observed in SARS-CoV-1[35] and now in SARS-CoV-2[26,27,31] deserve attention. As SARS-CoV-1 did not spread into a pandemic, the chance to resolve the mechanism or refute the association had been missed.

Any viral infection has a window of viraemia, which may be brief and symptomatic, when a virus is transmittable by blood transfusion. Because no signal for SARS-CoV-2 could be detected in the blood of asymptomatic patients,[36] the blood supply is considered safe without additional virus mitigation;[37,38] this situation is a fortunate coincidence. Pathogen reduction technologies could eliminate any risk posed by this novel virus and are licensed in the European Union and United States for platelet and plasma components.[39] The current pandemic should stimulate a wider implementation of safeguards for emerging and many unknown viruses, and eventually be applied to red cells, as the most widely used blood component. Several routes of research in transfusion medicine can be pursued and contribute to better understand COVID-19 pathophysiology.

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