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Coronavirus Disease 2019: coronaviruses and blood safety

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Abstract

With the outbreak of unknown pneumonia in Wuhan, China in December 2019, a new coronavirus, Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) aroused the attention of the entire world. The current outbreak of infections with SARS-CoV-2 is termed Corona Virus Disease- 2019 (COVID-19). The World Health Organization (WHO) declared COVID-19 in China as a Public Health Emergency of International Concern (PHEIC). Two other corona virus infections-- SARS in 2002-2003 and Middle East Respiratory Syndrome (MERS) in 2012-- both caused severe respiratory syndrome in humans. All three of these emerging infectious diseases leading to a global spread are caused by beta-coronaviruses. Although coronaviruses usually infect the upper or lower respiratory tract, viral shedding in plasma or serum is common. Therefore, there is still a theoretical risk of transmission of coronaviruses through the transfusion of labile blood products. Because more and more asymptomatic infections are being found among COVID-19 cases, considerations of blood safety and coronaviruses have arisen especially in endemic areas. In this review, we detail current evidence and understanding of the transmission of SARS-CoV, MERS-CoV and SARS-CoV-2 through blood products as of February 10, 2020 and also discuss pathogen inactivation methods on coronaviruses.

Keywords: coronavirus, blood safety, SARS, MERS, 2019-nCoV, COVID-19, SARS-CoV-2, pathogen inactivation technology.

Introduction

Since a cluster of unknown pneumonia patients was found in December 2019 in Wuhan, China, a new coronavirus (CoV), which was temporarily named 2019 novel coronavirus (2019-nCoV) by the World Health Organization (WHO) on 7 January, suddenly came into our sight [1]. The virus was subsequently renamed Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) and disease it causes named Corona Virus Disease-2019 (COVID-19). As of February 10, 2020, there have been over 43,000 patients confirmed positive by nucleic acid testing in China and 23 other countries and it has caused 1017 deaths due to acute respiratory failure or other related complications. In addition, over 21,000 suspected infected people were isolated and are waiting to be tested. On January 31, WHO announced the outbreak of COVID-19 in China as a Public Health Emergency of International Concern.

In 2002-2003 more than 8000 patients suffered from Severe Acute Respiratory Syndrome (SARS) due to a corona virus with 774 virus-related deaths reported to WHO. Since September 2012, there were 2494 laboratory-confirmed cases of infection with Middle East Respiratory Syndrome Corona Virus (MERS-CoV) with 858 virus-related deaths reported to WHO [2,3]. All three of these emerging infectious diseases leading to a global spread are caused by beta-coronaviruses.

In China, prior outbreaks of emerging infections have had an unfavorable impact on the blood supply. [4]. However, consideration must also be given to the safety of the transfusion recipient even if the emerging infection is a respiratory disease. Previous studies indicated that viral RNA could be detected from plasma or serum of patients infected with SARS-CoV [5-8], MERS-CoV [9] or SARS-CoV-2 [1] during different periods after the onset of symptoms. However, the detection of viral RNA by the polymerase chain reaction (PCR) is not equivalent to the detection of intact infectious virus. Although WHO noted in 2003 that no cases of SARS-CoV have been reported due to transfusion of blood products, there was still a theoretical risk of transmission of SARS-CoV through transfusion [10]. With more and more

asymptomatic infections being found among COVID-19 cases, blood safety is worthy of consideration. In this review, we detail current evidence and understanding of the transmission of SARS-CoV, MERS-CoV and SARS-CoV-2 via transfusion as of February 10, 2020 and discuss pathogen inactivation methods on coronaviruses.

Diversity of coronaviruses

As the largest known RNA viruses, CoVs are further divided into four genera: alpha-CoVs, beta-CoVs, gamma-CoVs and delta-CoVs [11], among which alpha- and beta-CoVs are able to infect mammals while the other two genera can infect birds and could also infect mammals [12]. So far, seven coronaviruses have been found to infect humans and cause respiratory diseases. Four of seven are common human CoVs (HCoVs) usually leading to common self-limited upper respiratory disease: HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1. These viruses can occasionally cause more serious disease in young, elderly, or immunocompromised individuals.

The first two HCoVs, HCoV-229E and HCoV-OC43 have been known since the 1960s. With the emergence of SARS in 2002, a novel beta-coronavirus came to attention; and subsequently HCoV-NL63 and HCoV-HKU1 were identified in 2004 and 2005, respectively [13]. MERS-CoV which was isolated in 2012, is similar to SARS-CoV-- both can infect the lower respiratory tract and usually cause a severe respiratory syndrome in humans [14] with a case fatality rate of 35.5% and 10%, respectively [15]. SARS-CoV-2 was recently isolated from human airway epithelial cells, characterized by next-generation sequencing in January 2020, and identified to be a new member of beta-CoVs [16]. SARS-CoV-2 can also infect the lower respiratory tract but the clinical symptoms are milder than SARS and MERS according to current limited evidence and reports [1].

SARS-CoV

Atypical pneumonia putatively caused by SARS-CoV was first identified following an outbreak in Guangdong Province, China in November 2002. The infection quickly

spread to Beijing, Hong Kong, Vietnam, Singapore, and Canada in March 2003. This disease proved to be highly infectious with respiratory droplets as the main route of transmission. Infected feces also played an important role in some cluster outbreak cases [17,18]. Fortunately, it has been proved that SARS patients are not infectious during the period of incubation (within 16 days of infection, usually 3-5 days).

Many studies found that SARS-CoV RNA could be detected in the plasma of SARS patients, even though it is a respiratory disease. The first report published on April 10, 2003 [5] indicated that extremely low concentrations of viral RNA existed in plasma of a SARS patient during the acute phase of illness, at 9 days after the onset of symptoms. The viral content of plasma was low. Researchers could only detect SARS-CoV RNA using a nested PCR assay established in house and the viral load was 190 copies/mL performed after ultracentrifugation of 2mL of plasma. They could not detect viral RNA in the plasma collected from two contacts, although the sputum of one was positive by three of four different PCR assays and the viral load in sputum was as high as 6.3×10^4 copies/ml. Based on this study and other information, WHO [10] and the US Food and Drug Administration (FDA) [19] drafted recommendations on blood safety and pointed out a theoretical risk of transmission of the SARS virus through transfusion of blood products. They also recommended some precautionary principles regarding the deferral of blood donation by individuals from areas with recent local transmission. In addition, blood donors should report to collection agencies if they were diagnosed as suspected or confirmed SARS patients within one month following their donation; and in such instances, efforts would be made to trace recipients or recall any blood products not transfused. Later, two studies focused on new PCR methods for detection of SARS-CoV RNA. One study was based on serial analysis of plasma viral RNA concentrations in adult SARS patients by quantitative RT-PCR with a limit of detection of 74 copies/ml. The study found that, on the first day of fever onset, 50% (6/12) of confirmed patients had detectable viral RNA in plasma; and that by day 14, the proportion fell to 25% (3/12). Overall, 78% of patients had detectable viral RNA in the first week of their illness [7]. Similar to the

first study, the average viral concentration was low at 140 copies/ml in patients who had relatively mild symptoms and did not require intensive care unit (ICU) admission in hospital. In pediatric patients, 87.5% (7/8) of children had viremia and the median concentration of plasma was 357 copies/mL based on the same PCR method used with adult SARS patients above [8]. Finally, Grant et al. [6] reported that within three days after fever onset, 79% (19/24) of patients had detectable SARS-CoV RNA in plasma. The viral load level rose fast and the maximal viral load was at around day 4 or day 5 after the onset of fever, after which the viral load quickly decreased. Their findings showed viral shedding in plasma was common when people were clinically ill with SARS virus and that plasma may be a better sample compared with nasal and throat swabs. The detection sensitivity of plasma was equivalent to that of nasopharyngeal aspirates within the first three days after the onset of fever.

In addition, researchers found that lymphocytes have a much higher concentration of SARS-CoV RNA than plasma whether tested in the acute phase or convalescent phase [20], although plasma viral RNA from only five patients in acute phase and five in convalescent phase was detected. It was subsequently shown that SARS-CoV could not only infect lymphocytes but also replicate in them in a self-limited manner [21-23]. These findings provided evidence that lymphocytes might be one of targets for SARS-CoV and indicated the potential for a transmission risk by blood products with high concentrations of donor lymphocytes (peripheral blood stem cells, bone marrow, granulocyte concentrates, etc).

Although these findings provided some evidence that SARS-CoV indeed existed in plasma or lymphocytes of SARS patients, no nation including those with local transmission of SARS, and no organizations including WHO[10] and the American Association of Blood Banks (AABB), recommended screening donors for SARS-CoV RNA or related antibodies based on the following facts: (1) SARS patients are not infectious in the period of incubation time and the incubation time is relatively short; (2) Almost all SARS-CoV infected people have severe symptoms, and few

asymptomatic carriers were found; (3) Data showed that the viral load from plasma of SARS patients was low [17,24,25]; (4) No transfusion transmission cases have been reported so far [10]; and studies that screened blood donations for SARS-CoV RNA in 2003 failed to identify any positives[26].

However, an alternative view was expressed in 2004. Researchers in Hong Kong [27] found that tests of the plasma from 3 of 400 healthy blood donors and 1 of 131 non-pneumonic pediatric inpatients collected during the outbreak of SARS tested positive for IgG antibody to SARS-CoV. The results were confirmed by two western blot assays. The presence of antibody does not imply infectious material. Nevertheless, because Hong Kong was among the worst-hit regions in the world during the 2002-2003 outbreak of SARS, they concluded that in Hong Kong subclinical or non-pneumonic SARS-CoV infections existed indicating a potential transmission risk of SARS virus via blood products. Soon afterward, four different groups raised questions and objections to the Hong Kong study focusing on the specificity of the assays and the representativeness of the population [28-31]. To provide additional information the theoretical the risk of SARS-CoV transmission through blood transfusion was estimated in Shenzhen, Guangdong Province in China. The estimate used data from Shenzhen, Hong Kong, and Taiwan in 2003 and calculated the mean risk was 14.11 (95% CI: 11.00-17.22) per million and the maximum risk was 23.57 (95% CI: 6.83-47.69) per million on April 2, 2003 [32].

MERS-CoV

In 2012, the MERS virus was first identified from a 60-year-old man who had acute pneumonia and renal failure with a fatal outcome in Saudi Arabia [33]. At that time, MERS-CoV was the sixth human coronavirus identified. MERS is a highly lethal respiratory disease and had a higher case fatality rate than SARS [3]. It caused large nosocomial outbreaks in Jeddah, Kingdom of Saudi Arabia in 2014 and the Republic of Korea in 2015 [34].

In a study on the viral load in different samples among 37 MERS patients, investigators found that nearly half of serum samples tested yielded a viral RNA signal during the first week after diagnosis and that the viral load ranged from about 2.1×10^2 to 2.51×10^5 copies/ml. However, they failed to isolate virus from these sera. Therefore, it is not known whether or not there was live MERS virus in the serum, and the patients' blood may not have been infectious [9]. Although almost all MARS patients have severe clinical symptoms, atypical patients were found during the 2015 outbreak of South Korea. One individual had infection of MERS-CoV confirmed by real-time RT-PCR but he had no symptoms in the following four days. However, it is worthy of note that each of the individuals tested were immunocompromised inpatients. Therefore, the findings are not directly related to risks among blood donors.

In the document from AABB [35], it was noted that populations such as persons in close contact with a confirmed case, camel workers who were visiting or residing in the Middle East, and healthcare personnel during a nosocomial outbreak were at increased risk of MERS-CoV infection. Since detection of virus from blood was rare and MERS viral load was low, the FDA recommended some deferral criteria similar to the SARS epidemic: 14 days from last exposure or 14 days after arrival in the US following travel/residence exposure, or 28 days after complete symptom resolution and cessation of a treatment.

SARS-CoV-2

In December 2019, an unknown pneumonia rapidly spread in Wuhan, China, and most initial cases were related to source infection from a seafood wholesale market [36]. Quickly, researchers sequenced and identified a new beta-coronavirus, the genome of which has 86.9% identity to a previously published bat SARS-like CoV genome (bat-SL-CoVZC45, MG772933.1), and is distinct from human SARS-CoV and MERS-CoV [16]. Individuals with COVID-19 infection usually have a fever and lower respiratory tract symptoms and the estimated incubation time is within 14 days.

Limited data have shown that virus RNA could be detected in plasma or serum from COVID-19 patients. In the first 41 patients in the city of Wuhan, viremia was found in 6/41 (15%) patients. The median PCR cycle threshold value was 35.1 (95% CI: 34.7-35.1) suggesting a very low RNA concentration with no difference found between ICU patients and patients with mild symptoms. Of note, one of 41 patients was positive for SARS-CoV-2 RNA but did not have a fever [1]. A family cluster of COVID-19 was reported from Shenzhen, China and found that serum from one of six patients in one family member showed a weak positive result for SARS-CoV-2 RNA and a 10-year-old child was confirmed to be an asymptomatic carrier [37]. With the virus spreading all over the world, reports from Vietnam [38], Germany [39] and the United States [40] have described the clinical symptoms, diagnosis and treatment of COVID-19. One controversial report suggested transmission by contact with an asymptomatic carrier in Germany [39]: A individual from China attended business meetings in Germany and infected at least two business partners during the incubation period. This report suggested that, in contrast to SARS, COVID-19 patients might be infectious during an asymptomatic incubation period. However, in this report, the authors did not directly interview the Chinese traveler who later was found to have been symptomatic at the time of the contact. Moreover, the researchers did not detect viral RNA of samples taken from the index patient during the period of incubation.

In January 2020, the European center for disease prevention and control (ECDC) [41] and AABB [42] published rapid risk assessments of the outbreak of SARS-CoV-2 and blood safety. ECDC implied a precautionary deferral of donation of blood and cells for 21 days after possible exposure to a confirmed patient or anyone who returned from Wuhan, China—applying the approach used for SARS-CoV and MERS-CoV. In addition, recovering confirmed COVID-19 patients should be deferred for at least 28 days after symptom resolution and completion of therapy [41]. AABB updated their website to state that considering the concern regarding SARS-CoV-2 and blood safety, that they

would continue to closely monitor the outbreak of respiratory illness. AABB, FDA and CDC do not currently require any action on blood collection and testing since there are no data suggesting a risk of transfusion transmission of SARS-CoV-2 [42].

As the infection continues to demand urgent attention in China and is being very closely monitored worldwide, the following points may be relevant to considerations regarding transfusion and organ transplantation: (1) Viral RNA in plasma or serum could be detected in COVID-19 patients on the first two or three days after onset of symptoms; (2) Most patients, especially younger adults who can donate blood, had milder symptoms than the older adults; (3) Patients with no fever and asymptomatic carriers have been identified in China, which increases the possibility that a COVID-19 patient or virus carrier could donate blood; (4) The rate of infectivity of patients who are in the incubation period remains uncertain and there are no data on the viral load in plasma, serum or lymphocytes among individuals in the incubation period. Therefore, whether the risk of transfusion transmission of SARS-CoV-2 is higher than other coronaviruses, especially in endemic areas such as Wuhan China, should be further explored as soon as possible. There still needs to be careful assessment on any measures regarding deferral of donors, screening for SARS-CoV-2 RNA, testing for virus-related antibodies, or use of pathogen-inactivated blood products.

Inactivation of coronavirus in blood products

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses. Usually, coronaviruses are vulnerable to acid-pH, basic-pH and heat [43] but seem to be more stable at 4°C [44]. The infectious titer of virus did not show any significant reduction after 25 cycles of thawing and freezing [44]. After the outbreak of SARS and MERS, a few studies investigated pathogen inactivation/reduction technologies (PRTs) based on in-house or commercial methods with the aim to decrease or completely eradicate the potential risk of transmission of coronaviruses via blood products or blood derivatives [45-54]. These studies are summarized in Table 1.

Generally, no single PRT technology is suitable for all blood products, since some blood components are damaged by the PRT treatment [55,56]. In-house studies of methods to inactivate coronaviruses in plasma and platelet concentrates focused mainly on heat and solvent/detergent (S/D) treatment. Usually, 60°C for 15-30 minutes is enough for reduction of SARS-CoV from plasma without cells [49], and inactivation could be achieved by the 60 °C for 10 hours for plasma products [52]. In the other study, 56°C for 25 minutes heating could reduce more than 4 $\log_{10}$ $TCID_{50}$/ml of MERS virus [53]. Since heating could denature protein in blood products, it could only be used in manufactured plasma-derived products. In addition, SARS-CoV was found to be sensitive to solvent and detergent, such as TNBP/Triton X-100, TNBP/Tween 80, sodium cholate [49]. After 30min treatment using S/D produced by Octaplas (Octapharma), the virus was reduced more than 5.75±0.3 $\log_{10}$ $TCID_{50}$/ml [50].

Illumination with different wavelengths also influenced activities of SARS and MERS virus in blood. Ultraviolet (UV)-A [46,47,51]and UV-B light [54] in the presence of amotosalen or riboflavin could inactivate the pathogens' nucleic acids, while a third PRT method uses UV-C light only [45,48]. These commercial systems could reduce the activities of SARS and MERS virus in plasma or platelet concentrates to different degrees. Methylene blue plus visible light also has the ability to inactivate coronaviruses in plasma [45,48]. Cost remains a major administrative obstacle to PRT use [55]. Therefore whether or not these PRTs should be implemented in response to SARS-CoV-2depends on the severity and prevalence of COVID-19 in different regions and on the actual risk of transfusion transmission of SARS-CoV-2.

Conclusions

Although coronaviruses cause primarily mild to severe respiratory infections, the potential for transmission by transfusion is worthy of consideration. In China, most of blood centers or blood banks have taken the following measures during the current outbreak: (1) Taking body temperature before blood donation; (2) Additional

questions in the donor screening questionnaire regarding whether the donor or relatives have related symptoms, have traveled to areas with local transmission of SARS-CoV-2 (Wuhan or Hubei province) within 28 days, or are donors with high risk; (3) Calling back to all blood donors and asking the donors and their family about their current physical condition after donation; (4) Recalling un-transfused blood products from infected donors [57]. However, given the differences between SARS, MERS, and SARS-CoV-2, it is not known if the prior recommendations used for SARS and MERS are sufficient. We are facing many unknowns, and careful monitoring and further studies should continue. Stricter measures could be implemented if necessary, such as viral RNA and virus-related antibody screening of blood donations or use of PRT in some region. As we know, Wuhan Blood Center and all blood banks in Hubei province have started to test SARS-CoV-2 RNA from blood donations since February 10. Meanwhile, because coronaviruses RNA could be detected in plasma or lymphocytes, staff in blood centers and laboratories should improve biosafety protection during the epidemic. The coming months will provide an enormous amount of new information on SARS-CoV-2 and COVID-19—information which will allow us to make decisions regarding this new virus and public safety.

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Table 1. Different methods on inactivation of coronavirus in blood products and laboratory tissue culture

Methods	Commercial Systems	Mechanism of action [56]	SARS-CoV	MERS-CoV
Heat	N/A	Denaturing the secondary structures of proteins	Products without cells 56°C 20min in serum 65°C 10min in serum 60°C 25min in 25% BSA solution [49] Plasma products 60°C 10hr [52]	DMEM+5%FBS 56°C 25min (reduction of 4 $\log_{10}$ $TCID_{50}$/ml) [53]
S/D treatments	Octaplas (Octapharma)	Disruption of lipid membranes	Products without cells 2hr for TNBP/Triton X-100 in PBS or 10% BSA 2hr for TNBP/Tween 80 in PBS or 10% BSA 24hr for sodium cholate in 10% BSA [49] Products without cells 30min (reduction of > 5.75±0.3 $\log_{10}$ $TCID_{50}$/ml) [50]	N/A
Amotosalen + UV-A light	INTERCEPT Blood system for plasma and platelets (Cerus)	Amotosalen (S-59) intercalates into nucleic acid and induces covalent cross-linking upon UV-A exposure	MEM+10% FBS (reduction of >5.8 $\log_{10}$ PFU/ml) [51]	Platelet concentrate (reduction of 4·48±0.3 $\log_{10}$ PFU/ml) [46] Fresh-frozen plasma (reduction of 4.67±0.25 $\log_{10}$ PFU/ml) [47]
Riboflavin + UV-B light	MIRASOL PRT system for plasma and platelets (Terumo)	Riboflavin associates with nucleic acids and mediates an oxygen-independent electron transfer upon UV exposure	N/A	reduction of >4.07 $\log_{10}$ PFU/ml for pooled plasma reduction of >4.42 $\log_{10}$ PFU/ml for individual donor plasma[54]
UV-C light	THERAFLEX UV-Platelets (Macophar	UV-C directly interacts with nucleic acids, causing the	Platelet concentrates (reduction of >=3.4 $\log_{10}$ $TCID_{50}$/ml) [45]	Platelet concentrates (reduction of >=3.7 $\log_{10}$ $TCID_{50}$/ml) [48]

	ma)	formation of nucleotide dimers		
Methylene blue + Visible light	THERAFEX MB (Macopharma)	MB intercalates into nucleic acid and mediates the formation of singlet oxygen upon illumination	Plasma (reduction of >3.1 log_{10} $TCID_{50}$/ml [45]	Plasma (reduction of >3.3 log_{10} $TCID_{50}$/ml) [48]

Note: N/A, not available.

BSA: bovine serum albumin

DMEM: Dulbecco's modified Eagle's medium

FBS: fetal bovine serum

TCID: tissue culture infective dose

S/D: solvent/detergent

TNBP: tri-n-butyl phosphate

PBS: phosphate buffered saline

UV: ultraviolet

PFU: plaque forming units

MB: methylene blue

Highlights

1. Review current information and understanding (as of February 10, 2020) of the potential for transmission of SARS-CoV, MERS-CoV and SARS-CoV-2 (2019-nCoV) through blood products.

2. Summarize current understanding of pathogen inactivation methods on coronaviruses.

3. Review measures that Chinese blood banks are taking during the outbreak of COVID-19.