

Review Article

Covidaemia and its implications

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Received: 06 October 2020

Accepted: 13 November 2020

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ABSTRACT

Coronavirus disease 2019 (COVID-19) pandemic has taught many lessons to the medical fraternity. Academicians and the general population have been through phases of anxiety, panic, and trail and errors. The growing assumption at the onset of the pandemic that COVID infection may spread by blood has not found its roots deep enough for any clinical consequences. As all the symptoms of COVID relate to its local invasion at the alveolar level and its immunological sequelae, this article discusses the possibilities with the research available over the last 10 months. So far, the plasma viral load detected by reverse transcriptase polymerase chain reaction (RT-PCR) seems immaterial in comparison to the viral concentration from nasopharyngeal swabs. So the recommendations to prefer caesarean section for positive mothers, deferring blood donations by COVID patients, frequent antigen testing from blood serum and body fluids like breast milk or amniotic fluid, may really need to be given a second thought. Also, this article concludes about giving up the panic around the viremia-related possibility of vertical transmission from mother to fetus and other clinical implications of testing of blood for the same. This will help in saving the resources heavily to be used only selectively. Newborns in neonatal intensive care unit (NICU) may be permitted to be handled without gloves and using simple practices of handwashing, saving further resources and reducing neonatal infections.

Keywords: Viraemia, Vertical transmission, COVID-19, Neonatal COVID, RT-PCR

INTRODUCTION

A novel beta-coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that originated in Wuhan, China in December 2019 is responsible for the recent outbreak of pneumonia cases that the World Health Organization (WHO) proclaimed as the global coronavirus disease 2019 (COVID-19) pandemic on 11th March, 2020. With its spread spanning across 213 countries and territories, affecting over 34.2 million people to date and, taking the lives of over a million, there is a rising need to amplify the diagnostic testing and understand this virus better to control the spread. Also, the practice of doing newborn reverse transcriptase polymerase chain reaction (RT-PCR) need to be discontinued as covidaemia (SARS-CoV-2), is also rare in amniotic fluid. This will also help save resources for better use.

As per current Centers for Disease Control and Prevention (CDC) guidelines, RT-PCR of an upper respiratory specimen (nasopharyngeal specimen, oropharyngeal specimen, mid-turbinate nasal swab, nasal swab, or a nasopharyngeal/nasal wash/aspirate) is the diagnostic method of choice. However, it is associated with significant disadvantages, one of them being the risk-prone nature of this procedure necessitating the use of high-quality protective equipment by the healthcare professionals. A safer possible alternative could be testing of viral load in blood/serum, as has been seen for other viruses. More than half a year into the pandemic caused by SARS-CoV-2, the question still stands: does this newly found virus cause viraemia? If it does, does its infective nature bring forth numerous practical implications like possibilities of vertical transmission, easier diagnosis, new screening criteria and multiple possible routes of spread? Existing data (given below) show that there is

unconvincing evidence on the presence of viraemia or viral genetic material in the blood. This has prevented the testing of blood/serum samples for diagnosis of COVID-19. An incline to the absence of viraemia has closed doors on its choice as a diagnostic procedure, but even this supposed absence calls for multiple changes in our current practices like testing protocols in neonates of COVID-19 infected mothers. In this article we intend to review the evidence pertaining to the existence of viraemia in COVID-19, its significance and throw light on the numerous new avenues it opens up for a more ingenious and effective response to this pandemic.

VIRAEMIA IN BETA-CORONAVIRUSES

Respiratory pathogens like adenovirus causing viral pneumonia, influenza type A, avian influenza, and many more have manifested viraemia in the past. Substantial evidence exists over other β -coronaviruses like SARS coronavirus (2002-2003) and Middle eastern respiratory syndrome (MERS) coronavirus (2012) presenting viraemia, or viral ribonucleic acid (RNA) specifically, in the plasma or serum of patients, during different periods after the onset of symptoms possibly due to viral shedding as shown in Table 1.

Table 1: Evidence of SARS-CoV and MERS-CoV RNA in blood.

Author ³⁻¹¹	Serum/blood samples tested (n) age group (adult/ paediatric)	Serum samples positive for viral RNA (%)
Chan et al	n=26, adult	100
Ng et al	n=23, adult	78
Peiris et al	n=50, adult	45
Lau et al	n=120, adult	28
Poon et al	n=50, adult	40
Eko Ng, et al	n=8, paediatric	87.5
Grant et al	n=24, adult	79
Corman et al	n=108, adult	33
Kim et al	n=21, adult	33

In SARS-CoV, levels of RNAemia in various studies of varied sample sizes ranged between 28%-100%. For Middle eastern respiratory syndrome coronavirus (MERS-CoV), this was around 33%. Some studies indicated plasma to be a better sample than nasal and throat swabs as nasopharyngeal aspiration is regarded as a risk-prone procedure and shedding of virus in plasma is common in clinically ill patients with SARS-CoV.² Since the onset of the ongoing pandemic, various studies have been conducted to detect viral RNA in serum samples of patients diagnosed with COVID-19. These studies have

shown monumental disparities in their results. 10%-80% of the samples showed the presence of viral RNA in blood. These studies have been enumerated in Table 2.

Table 2: Evidence of SARS-CoV-2 RNA in blood.

Author ¹²⁻¹⁹	Serum/blood samples tested (n) age group (adult/paediatric)	Serum samples positive for viral RNA (%)
Huang et al	n=41, adult	15
Lescure et al	n=5, adult	20
Duan et al	n=10, adult	70
Chen et al	n=48, adult	10.4
Christensen et al	n=5, adult	80
Bermejo - Martin et al	n=250, adult	51.6
Zheng et al	n=96, adult	41
Chen et al	n=57, adult	10.53

Such wide variations in the results indicate that blood is an unreliable standard diagnostic medium for COVID-19. However, viraemia has shown to be a very useful predictor of severity. Studies employing samples of severely ill patients showed higher levels of viraemia.^{15,17,19} Additionally, this was associated with higher mortality.¹⁷ Thus, even though not for diagnosis, addition of testing of serum sample to the current myriad of laboratory investigations needs to be added for symptomatic patients. However, the above-mentioned evidence of viral RNA in the blood must be taken with a pinch of salt as firstly, evidence of RNAemia is not equivalent to the presence of the viable infectious virus in the blood. In the limited studies done around this subject, proof of infectiousness has not been found. Secondly, so far, the plasma viral load detected by RT-PCR seems immaterial in comparison to the viral concentration from nasopharyngeal swabs.

PATHOPHYSIOLOGY

As depicted in figure 1, the symptoms of SARS-CoV-2 have been attributed to various mechanisms like cytokine storm, immune dysregulation, and antibody formation but surprisingly not to viraemia. Per se COVID behaves like a local viral infection. But the absence of the direct pathogenicity by the virus may be the reason for it not eliciting symptoms like rash despite being detected in the blood of some cases. It is imperative that we check the significance of the viraemia in SARS-CoV-2 due to its wide-ranging practical implications. These include blood transfusion, vertical transmission, sexual transmission, modification of current testing guidelines, and the presence of virus particles in other body fluids to name a few.

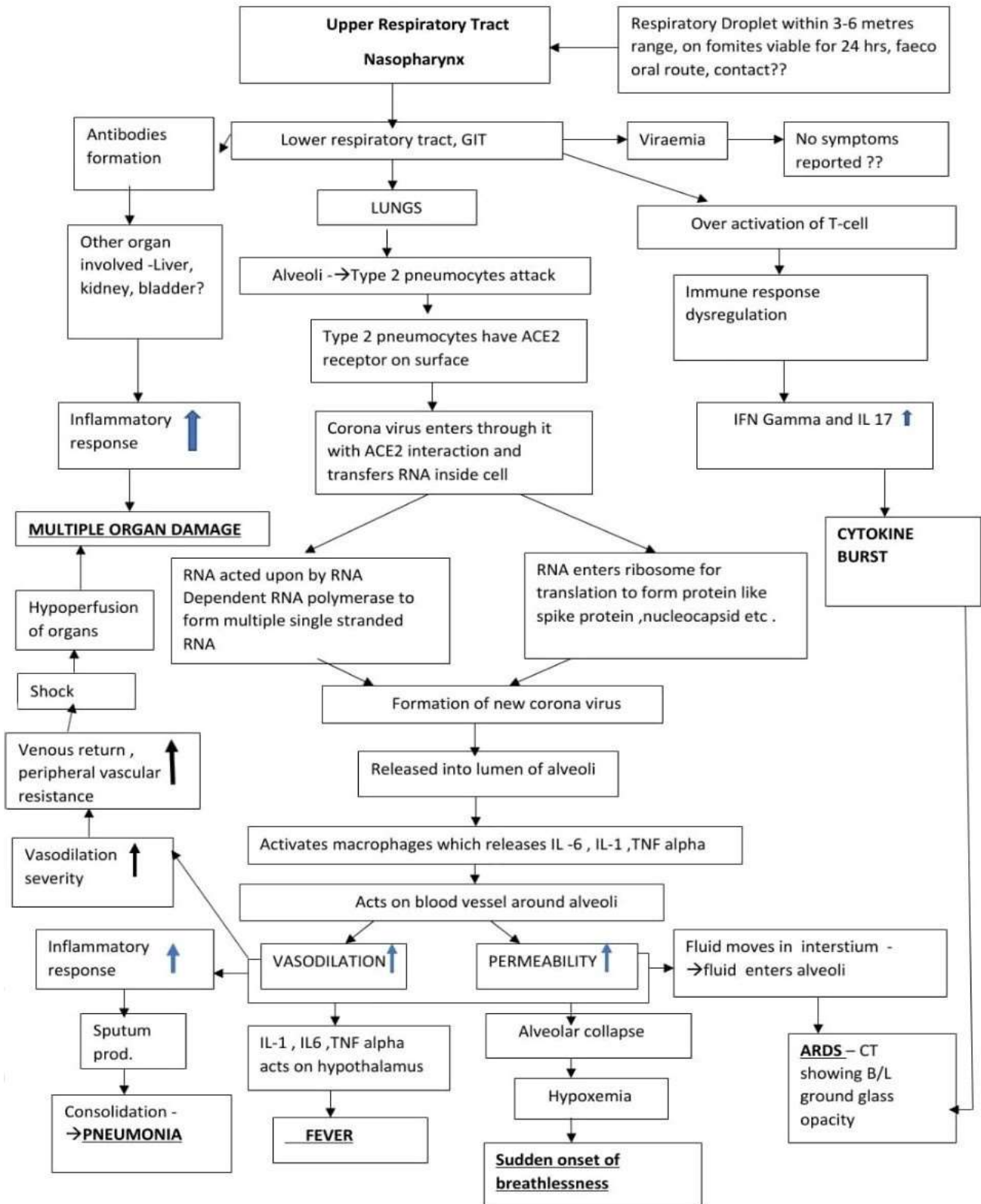


Figure 1: Pathogenesis of SARS CoV -2.

PRACTICAL CLINICAL IMPLICATIONS

The scientific community has been indecisive about the actual threat that viraemia poses to blood donation. On one

hand, till date, there has been no reported case of transfusion-induced infection of SARS-CoV-2. Further, no study on respiratory viruses has shown transmission by blood or blood products. With the existing guidelines,

anyone with symptoms of active respiratory tract illness is automatically deferred from blood donation.²¹ Screening donors for SARS-CoV RNA was not recommended by WHO and American association of blood banks (AABB) during the 2003 outbreak as the viral load was not considered to be significant enough to pose a risk, and no cases of transfusion-transmission were reported.^{22,23,24} Similarly, blood transfusion during the current pandemic has been deemed fairly safe. With the lack of evidence suggesting transfusion-transmission, AABB, Food drug administration (FDA), and CDC have not recommended any changes in blood transfusion guidelines specific to the COVID-19 pandemic.²²

On the other hand, the presence of viral RNA in plasma/serum of asymptomatic infected persons poses a theoretical risk. Studies following the 2003 outbreak showed evidence of SARS-CoV in plasma of the patients.³⁻⁹ After the SARS-CoV and MERS-CoV outbreaks, studies investigated pathogen inactivation/reduction technologies (PRTs) to eliminate the potential risk of transmission via transfusion.²⁵⁻²⁹ However, the cost associated with them is a major limitation. WHO's interim guidance regarding COVID-19 states that the risk of transmission through transfusion of blood and components is likely minimal, but several precautionary measures have also been suggested in view of the potential risks.³⁰

This urgently necessitates that we explore the infectiousness of the viral particles in the blood further to decide whether to employ radical changes as necessary in the transfusion guidelines. This includes screening to filter out the symptomatic and asymptomatic patients and the widespread installation of PRTs. Currently, with the dearth of evidence of any risk, it would not be wise to turn away donors due to fear of asymptomatic infection. Employing costly PRTs is also unnecessary as the threat of infective particle seems hypothetical at best.

An ample amount of research is proceeding to investigate the vertical transmission of SARS-CoV-2 in the infants of COVID-19 positive mothers. Table 3 gives a summary of the studies done on infants of mothers infected in the third trimester so far. Only one of the studies showed positivity in a meagre 9% of the newborns, it is to be noted that in these cases the infection was probably not due to perinatal transmission.³² No other neonate in any of the other studies was found to be positive. Thus, vertical or perinatal transmission in all probability is non-existent. This suggests the redundancy of the common practice of first-day testing in newborns born to mothers infected in the third trimester. Delivery by caesarean section in the absence of any other indication and testing of umbilical blood need not be done for babies of COVID-19 positive mothers. In view of the severe lack of resources around the world, these practices put a greater strain on the already overworked and understaffed healthcare sector and must be stopped immediately until there is newfound proof.

Table 3: Presence of COVID-19 infection in infants born to COVID-19 positive mothers.

Author ³¹⁻³⁵	Sample size (number of COVID-19 positive mothers)	Infants tested positive (%)
Chen et al	4	None
Zeng et al	33	9
Khan et al	3	None
Alzamora et al	1	None
Zeng et al	6	None

Little is known about the effects on the foetuses of pregnant women who are infected during conceiving or the first trimester. Past studies on epidemic viruses like Zika virus have shown deadly effects including microcephaly in the foetuses of the mothers infected in the first trimester.³⁶ There have been studies showing adverse outcomes in foetuses of SARS-CoV and MERS-CoV positive mothers too, including growth retardation.³⁷ In the coming months, as more data is collected on such mothers for SARS-CoV-2, we might be able to add to our current knowledge on the effects on pregnant women and their foetuses, and further explore whether viraemia has a potential role to play in the outcome of these pregnancies. Prospective studies must be carried out from the first-trimester itself instead of solely carrying out studies in the third trimester in infected mothers. Ramped up screening measures since the beginning to detect all possible adverse outcomes in the foetus are necessary. The outcomes of these pregnancies and complications found in the newborn must also be recorded.

The presence of viraemia can also be a gateway for the virus to other bodily secretions. Various studies have shown the definite presence of feco-oral transmission and viral RNA in the faeces.³⁸ Although Angiotensin converting enzyme-2 (ACE-2) receptors are expressed in the testis and male reproductive system, no study has shown the presence of the virus in semen in males.^{39,40} As for females, there is a lack of ACE-2 expression in the vaginal and cervical tissues. RT-PCR of vaginal swabs has tested negative in the available studies.⁴¹ Thus the possibilities of sexual transmission of COVID-19 are highly unlikely. It must be noted here that certain sexual behaviours could possibly still lead to spread of infection due to feco-oral transmission. There have been isolated case reports showing viral RNA in breast milk.⁴² Thus, breastfeeding by a mother having active disease should not be recommended unless it is proven to be non-infective as this puts the baby at great risk. Virus particles have also been isolated from urine, saliva, conjunctival secretions and tears.⁴³⁻⁴⁵

CONCLUSION

Much research has already been done on the SARS-CoV-2 in a short span of time, justifiably so considering the magnitude of the havoc created by it across the globe. The quest to know about its structure, pathogenesis, infectivity, sources of transmission still has major gaps that need to be filled. One such controversial subject has been the presence of viraemia in infected individuals and its implications. There has been substantial evidence to show that viral RNA has been found in the serum of a large proportion of infected individuals. However, to date, there is a paucity of literature that proves infectiousness via blood. This significance if proved would possibly open up newer modes of transmission and a revamp of the current guidelines regarding precautionary measures against the Novel Coronavirus. This could be in the form of newfound proof regarding the existence of vertical transmission and necessary screening protocol in appropriate trimesters. Similarly, its presence in other bodily fluids could open up the possibility of exploring routes of sexual transmission, and protection against the same will have to be advised. All current guidelines regarding blood donation will have to be updated if there is a proven significant risk of this being a potential source of infection. It is necessary that we correlate the levels of viraemia with the presence or absence of symptoms in the individual as well. If present in both symptomatic, as well as asymptomatic individuals, more stringent screening methods, would need to be put into place. This will in turn need greater resource allocation and improved technology as well. We need to explore the possibility of risk to health care workers from sources apart from a droplet infection. If the bloodborne infection is proven, we will have to find out if our current protective equipment would suffice.

As the presence of viraemia is found to be insignificant and negligible to cause any major changes to our current understanding of the virus and its spread, we might consider changing our related strategies. For example, precautionary Caesarean sections need not be performed, newborns of COVID-infected mothers need not be tested on the first day, if all safety precautions are in place. Any changes in blood donation guidelines seem unnecessary and a waste of resources. The ongoing pandemic has been showing a huge rise in the number of worldwide cases with each passing day, and studies throughout the world have shown a decrease in the precautionary habits practiced by individuals and opening up of lockdowns in densely populated countries like India. Thus, it is necessary to do further research on these burning questions as they could play a role in the shaping of the future course of this pandemic.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Soni A, Arickatt TM, Bhalerao A, Kondekar S. Covidaemia and its implications. *Int J Contemp Pediatr* 2020;7:2409-15.