

# Speculations of Immunotherapy in COVID-19 Patients with Practical Applications During Childhood and Pregnancy

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## ABSTARCT

The rapid spread of novel coronavirus disease (COVID19) throughout the world without available specific treatment or vaccine necessitates alternative options to contain the disease. Historically, children and pregnant women were considered high-risk population of infectious diseases but rarely have been spotlighted nowadays in the regular COVID-19 updates, may be due to low global rates of incidence, morbidity, and mortality. However, complications did occur in these subjects affected by COVID-19. We aimed to explore the latest updates of immunotherapeutic perspectives of COVID-19 patients in general population and some added details regarding pediatric and obstetrical practice.

Immune system boosting strategy is one of the recently emerging issues allowing the body defense mechanism to produce virus-neutralizing antibodies to counteract the viral impacts on multiple organ damage. Measles vaccination (which is universally used for children in many countries, but contraindicated during pregnancy) could urge the body to produce these antibodies which may apply their effects through cross-reactivity of measles vaccine and COVID-19 antigenic proteins. In addition, intravenous immunoglobulin and convalescent plasma could have such neutralizing antibody effect leading to clinical improvement and viral elimination. Pediatric and obstetrical experience has appeared in previous publications.

Human monoclonal antibodies are the future promising approach to treat and prevent COVID-19 with the use of tocilizumab in recent studies. Pediatric data are still in progress while no pregnancy ongoing trials are planned up to date.

The better understanding of the host antiviral response may pave the way to develop immunotherapeutic plans against COVID-19 in the near upcoming days.

## Keywords:

Convalescent plasma, Coronavirus, immunoglobulin, monoclonal antibody, vaccination

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## INTRODUCTION

The world now is in the middle of novel coronavirus disease (COVID-19) pandemic, and all scientific, educational, social, economic, and even political global efforts are directed to control over this disease that changed the way we live in our planet.<sup>[1]</sup>

There are ongoing works to closely identify the viral structure and its contagious and damaging ability to understand immunological and systemic complications caused by COVID-19.<sup>[2]</sup>

The disease heavily hit all parts of the world with different severity where it was more aggressive in United States and Europe, and even it was largely distributed in Asia and Africa. Up to the

time of preparing this report, more than 14,007,791 confirmed cases and 597,105 deaths all around the world. Elevated death rates in the developed countries when calculated per one million population could be due to presence of large sector of the community with high age, chronic illnesses that affect cardiopulmonary health, and immune dysregulation.<sup>[3,4]</sup>

There are four major protein parts within the COVID-19 structure are blamed to cause human cell invasion and intracellular replication, spike (S), envelop (E), membrane (M), and nucleocapsid (N) proteins. There are more than 140 sites of mutation identified in COVID-19 structure, but protein N, and S have been encoded

by genes resistant to mutation which could be the base step in vaccine trials that have focused on antibodies effect.<sup>[5]</sup>

Children have COVID-19 incidence three times lower than older subjects (1.3% versus 3.5%). This has drawn the attention of scientists especially when they found children being less susceptible to the disease and related mortality. So, it was suggested that certain adaptation and unique behavior of pediatric immune system may lead to negligible opportunities of cytokine storm.<sup>[6,7]</sup>

During pregnancy, there is a physiological disturbance of the natural balance of T-lymphocytes specifically helper cells type 1 and 2, with T-helper lymphocytes 2 predominance. This mechanism will put the pregnant lady into a position of increased vulnerability to viral infections including COVID-19. In addition, antibody production against attacking viruses would be suppressed throughout pregnancy until beyond delivery. Evidently, serological diagnosis of COVID-19 would be affected.<sup>[8,9]</sup>

Cytokine storm syndrome is the most dangerous sequelae of COVID-19, mostly affecting people with other risk factors like diabetes, smoking, hypertension, obesity, and previous pulmonary illness. There is a rapid and fatal immune activation triggered by lung infiltration of inflammatory cells and T- helper lymphocytes immunoreaction leading to wide release of cytokines into the circulation. The management constitutes of administration of immunosuppressive medications and intensive cardiorespiratory support.<sup>[10,11]</sup>

While scientists worldwide are racing against time to have a better understanding of COVID-19 mechanism of action to find out the best guidelines of fighting the disease, health authorities for the time being suggest practical recommendations based on expert opinions and uncontrolled case series due to the deficiency of long-term controlled trials with acceptable scientific designs. Accordingly, cohort studies based on emerging hypotheses are used to offer current plans of management and prevention of COVID-19. Some of these studies may have ethical violation issues and they are in need to follow the standards of research reporting.<sup>[12,13]</sup>

Up to date, because of the absence of effective antiviral therapies and approved vaccines, the

available response to this pandemic may concentrate on supporting the immune system with special focus on virus-neutralizing humoral immunity. Given the low global rate of COVID-19 morbidity and mortality in children and pregnant women, they have only a small share of COVID-19 released data. This may be challenging to pediatricians and obstetricians during routine daily practice.<sup>[14]</sup>

In this article review, we will have a speculated overview of COVID-19 immune therapy and antibody role in general population with special focus on the current practice during childhood and pregnancy.

### **Cross-reactivity of immune response:**

In many countries, measles vaccine is given universally to all children. The association between COVID-19 and measles vaccine and other antiviral vaccinations (like mumps and rubella) was suggested by some reports and preprints hypothesizing a possible cross-resistance.<sup>[15,16]</sup>

The production of antibodies to HIV-1 proteins in individuals vaccinated with measles, mumps, and rubella, or post-measles infection was the main observation made by previous studies and this may explain some of mild or asymptomatic COVID-19 pediatric cases with low deaths in countries with mandatory national vaccination program.<sup>[17,18]</sup>

The assumed structural similarities and cross-reactivity between measles and COVID-19 glycoproteins has practical application on the medical ground supporting the use HIV protease inhibitory drugs like ritonavir and lopinavir that found to be effective in some studies involving COVID-19 patients, and even with other comorbidities including human immune deficiency virus (HIV) and hepatitis C virus.<sup>[19-21]</sup>

On the other hand, during COVID-19 era, some scientists recommend to vaccinate healthy children against influenza and pneumococcal pneumonia in an attempt to protect them from community-acquired pneumonia, and for patients with autoimmune diseases before the administration of immunosuppressive drugs.<sup>[22,23]</sup>

Surprisingly, the hypothesis of cross-reactivity to COVID-19 in subjects vaccinated with influenza

and pneumococcal pneumonia vaccines was adopted by no previous papers.

Pregnancy by itself is considered a state of low immunity and therefore, live attenuated vaccines such as measles, mumps, and rubella were contraindicated.<sup>[24]</sup>

Moreover, about one fourth of pregnant women are serologically not immune against measles. The application of measles vaccine should be avoided during pregnancy as it might cause congenital malformations also.<sup>[24,25]</sup>

#### **Bacillus Calmette-Guérin (BCG) vaccination:**

An increasing amount of studies hypothesized the protective role of BCG vaccination against COVID-19. Multiple vaccination strategy was claimed by many preprints and published papers to provide what is called a trained immunity phenomenon which is safe and effective in patients with type 1 diabetes and other autoimmune diseases through a non-specific immune activation to fight against COVID-19 and other viruses, though this idea was put under suspicion by other workers.<sup>[26-28]</sup>

The differences in mortality rates of COVID-19 among different countries has supported the assumption of BCG protection in areas where BCG vaccine was universal and mandatory. There are two ongoing trials to investigate the hypothesized protection effects of BCG, both are now in phase three. We hope to update our knowledge as soon as the results of these trials will be released.<sup>[29,30]</sup>

These trials are named as BCG-CORONA (Reducing Health Care Workers Absenteeism in COVID-19 Pandemic Through BCG Vaccine), and BRACE trial (BCG Vaccination to Protect Healthcare Workers Against COVID-19). They have recruited 5170 participants over 6 and 12 months, respectively to test the non-specific beneficial effects of BCG vaccination on COVID-19 incidence and severity. Nevertheless, the exposure of participants to coronavirus may raise an ethical concern.

During pregnancy, BCG vaccination is contraindicated as pregnancy represents a state of virtual immune deficiency state including cellular response. Again, BCG vaccination could not be an adapted approach during pregnancy unlike children and general adult population.<sup>[31]</sup>

#### **Intravenous immunoglobulin:**

Currently marketed intravenous immunoglobulin (IVIG) forms have antibodies that showed in-vitro reaction with antigens of COVID-19 and other viruses. These forms involve proteins gathered from thousands of healthy recovered donors after exposure representing a large pool of immunoglobulins (proteins) to inactivate the targeted pathogen (COVID-19). Some experts from Wuhan, China assumed that IVIG could be effective against severe COVID-19 cases when they used high doses (25 g/kg) for five days in combination with antiviral medications (ritonavir and lopinavir) and steroids (methylprednisolone).<sup>[32,33]</sup>

Pediatric use of IVIG for severe COVID-19 cases was reported in China. However, World Health Organization (WHO) has not recommended IVIG or a specific therapeutic agent in children yet until the final results of ongoing clinical trials are released. Pediatricians could be challenged by the absence of official recommendations and they may depend on scattered available experiences. [<sup>34,35]</sup>

The use of IVIG during pregnancy is encouraged in the Chinese experience for COVID-19 infected pregnant women. Also, IVIG for management of reproductive problems were endorsed by a recent American research for women during COVID-19 pandemic.<sup>[36,37]</sup>

#### **Convalescent plasma:**

The concept of virus-neutralizing antibody effects was said by many scientific published materials and based upon collection of IgG antibodies from recently recovered COVID-19 patients who appeared to have confirmed high IgG levels in their plasma (more than 1: 160).<sup>[38]</sup>

The only known limitation is to restrict the plasma donation locally due to the presence of several COVID-19 viral strains across different geographical areas. Donated plasma containing IgG antibodies could provide a passive immunity through cytotoxic and phagocytic properties which was proved to support patients with moderate and severe COVID-19 illness when combined with antivirals.<sup>[38]</sup>

The amount and duration of convalescent plasma therapy may depend on the viral load and severity of COVID-19 infection. It could be used

in prevention and/ or treatment even in small amounts. People with chronic diseases, health care providers, and healthy individuals who have had a recent contact with known COVID-19 patients could get benefit from emergency administration of convalescent plasma. Convalescent plasma containing IgG antibodies could be stored for a long period, but because of the possible viral mutations over time which may change viral major characteristics, it is usually recommended to utilize donated plasma as soon as possible. Moreover, it is encouraged to provide such plasma before reaching the severe stage of illness<sup>[39]</sup>

Although convalescent serum has not been yet approved by WHO because all the available published case series are without matched controls, convalescent plasma has an increased administration frequency throughout the globe, but we should put in mind suspected adverse events like lung injury, anaphylaxis, and hemolysis.<sup>[40]</sup>

A fresh Polish publication has declared the first pediatric case of convalescent plasma administration due to COVID-19 severe case associated with aplastic anemia in a six-year-old girl. Antivirals and immunomodulation therapy were tried without benefits until convalescent plasma was introduced. Unfortunately, the little girl still has aplastic anemia although overall improvement and recovery from COVID-19 was achieved.<sup>[41]</sup>

There are several ongoing randomized clinical trials regarding the safety and efficacy of convalescent plasma, in many of which a state of pregnancy is included, while other published studies from Unites States and Italy have confirmed its benefit.<sup>[42-44]</sup>

#### **Monoclonal antibodies (mAbs):**

They represent the main class of biotherapeutics of passive immunity against viruses. Specific human mAbs function is to block coronavirus entry to human cells through the interaction with specific receptors called angiotensin-converting enzyme 2 (ACE2). As of the similar properties detected between Severe Acute respiratory syndrome coronavirus (SARS-CoV) that caused a previous outbreak and COVID-19 (which is also called as Severe Acute respiratory syndrome coronavirus 2 (SARS-CoV-2), several reports

have suggested the use of SARS-CoV mAbs to treat patients with SARS-CoV-2 (COVID-19) trying to block and / or neutralize the viral effects.<sup>[45]</sup>

It is a very complicated and sophisticated task to localize and standardize mAbs from B-lymphocytes of COVID-19 recovered subjects due to the wide variability of receptor proteins which in turn may lead to irreproducible outcomes.<sup>[46]</sup>

High IgG antibody titers were reported against novel coronavirus surface antigen (S) in most of recovered individuals when trying to clone mAbs.<sup>[47]</sup>

Recent works have identified certain human mAbs against COVID-19 including B38, H4, and 47D11 where a clinical improvement has been observed in involved patients. The current evidence for these reports is promising and presents mAbs as a potential future approach to treat and prevent COVID-19.<sup>[48]</sup>

An ongoing Chinese trial using a mAb named tocilizumab to severely affected COVID-19 children with high interleukin-6 levels shows encouraging results. Tocilizumab has the Food and Drug Administration (FDA) approval to treat rheumatoid arthritis since many years ago.<sup>[49]</sup>

Up to date, there are no ongoing studies testing the use of mAbs during pregnancy. Data are limited regarding tocilizumab use during pregnancy though some case series from Germany, Japan, and another multi-national study were published investigating the use of tocilizumab for rheumatoid arthritis in pregnant women during early pregnancy (first trimester) resulted in increased rates of abortions and preterm delivery.<sup>[50-53]</sup>

Congenital malformations and abortion could not be ruled out when using tocilizumab during pregnancy. An animal study has revealed a potential fetal risk when tocilizumab used for Cynomolgus monkeys during pregnancy and organogenesis.<sup>[55]</sup>

#### **Conclusion:**

The current COVID-19 pandemic is one of the worst scenarios that humans ever face throughout history. Usual well-known protective measures including social distance, appropriate hygiene, and personal protective equipment could have the potential ability to save lives of population with

high-risks like elderly, health care workers, and individuals with chronic illnesses or immunosuppressive state. There is a recognized sector of the community that is less spotlighted but carrying high-vulnerability of getting viral infections and related complications including children and pregnant women. Limited highly-qualified data are available to discuss COVID-19 management and prevention strategies in children and pregnant women.

Measles and BCG vaccinated individuals have less mortality and favorable outcomes when catching COVID-19 infection. This may encourage regular vaccination to promote community immune activation drills, especially for high-risk population.

Passive immunity is another management option in moderate and severe COVID-19 cases including IVIG, convalescent plasma, and mAbs. Convalescent plasma could be given as a protective measure in apparently healthy individuals having contact with COVID-19 patients, or it may be given emergently to exert virus-neutralizing effects before the viral-induced multiple organ damage becomes evident. A promising hope is recently related to mAbs role in the management of COVID-19 patients. Pediatric and obstetrical use of IVIG and convalescent plasma has appeared in some previous papers, but mAbs use has limited published data during childhood and pregnancy.

#### Conflict of interest:

The authors declare no conflict of interest.

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