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Challenges of Blood Disorders Admist COVID-19

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Abstract

In the outbreak of SARS CoV-2 pandemic, no one is spared from fear, worries and health concern of self and their family members. However, the challenge of difficult time has given way to several new prospects of dealing different issues. Our focus is on the blood disorders of public health importance and their basic requirements, which has now become an unmet need. Few vulnerable category of patients living with sickle cell disease, thalassemia and haemophilia are ignored admist COVID-19. It carries importance because the clinical features and their disease complications may either overlap or get aggravated with corona virus infection. An attempt is made for patients as well as health professionals to find the best possible measure to provide health services within the prevailing adversities.

Keywords: COVID-19 pandemic, Hemoglobinopathy, Sickle cell disease, Thalassemia, Bleeding disorder, Haemophilia, Intravascular coagulation

Introduction

Worldwide at every level, the focus is solely on COVID-19 pandemic and its variable impact on mass population. Several guidelines are followed with changing time. There are vulnerable group of patients with high risk for infection, either because of the disease itself or due to unavoidable frequent exposures for their health related issues. At risk population are those who can have fatal outcomes because of their associated co-morbidities or immuno-compromised state. They need to adopt all preventive measure and shield them self from getting infected. Here we discuss separately about three relevant health issues along with their pitfalls and the best possible solutions that can be adopted during this time period.

Sickle cell disease, Haemophilia and Thalassemia are genetically inherited blood disorders with public health importance. Hemoglobinopathy is broadly defined as mutational defect in haemoglobin gene. It may be qualitative (sickle cell disease)or quantitative (Thalassemia). If hemoglobinopathy get associated with severe SARS-CoV-2 infection, the condition may

trigger serious complications because heart, lung and coagulation system are worse affected. Children born with defective genes(inherited from parent) in their disease expression form, are the lifelong sufferers. The clinical presentation and their social aspect are different, so they need to be managed accordingly. Common for all, suffering needs timely management along with physical, mental and social support. The circumstances have re-enforced negligence at every sphere because of uncontrolled corona virus spread, fear from getting infected, high rate of mortality, non-availability of vaccine and absence of definite treatment. All these have led to interference in strategy of emergency management. Best possible way is the knowledge and awareness about these three diseases along with the principles of management among the patients, parents and the health professionals.

Concept on Corona Virus Infection

An overall visualization on Corona virus infection and its clinical presentation is briefly discussed here. Broadly, the viral infection has 2 phases of response. First phase of viral response may be followed by second phase of hyper-inflammation. The disease course of COVID-19 proceeds in three stages: asymptomatic features as stage 1, non-severe symptomatic as stage 2 and the severe respiratory inflammation as stage 3. Stage 2 is the transition between phase of viral response and hyper-inflammation. Not necessarily, an infected person will go through all the three stages of infection but it is variable to individual's immune status and co-morbid factors.

The clinical features of the corona virus disease manifestation is categorised as mild, moderate, severe and critical. Mild disease presents with minimal features with normal chest radiology. Moderate manifests with fever, cough, shortness of breath and imaging may show features of pneumonia. Severe disease manifest with respiratory distress with any of the criteria as increased respiratory rate, fall in oxygen saturation and chest radiography may have characteristic features of diffuse reticular ground glass opacity, predominant in perihilar, peripheral lung field. The respiratory failure with ventilator support, multi-organ failure and shock indicates the critical condition.

Haematological and biochemical investigations can help to monitor the progression or recovery from the disease. Complete blood cell count may be normal in early asymptomatic phase but with increasing severity of disease, it may manifest with lymphocytopenia. Thrombocytopenia is the marker for severe COVID-19 infection [2]. Other ancillary findings like low haemoglobin, low eosinophil count may be associated but are non-specific. Biochemical tests are more informative with hyper-inflammatory phase of the disease. The common inflammatory markers like ESR, CRP, Ferritin (can be done in the most of the district health centres) are usually increased.

COVID-19 is a pro-thrombotic disorder which predisposes to vascular thrombosis (arterial, venous and capillaries), lung vasculopathy stroke and myocardial infarction. In such cases, monitoring D-Dimer, fibrin, prothrombin test can eventually help[3,4]. However, these tests may not be available at most of the health centres. So the challenge remains for diagnosis and prevention of coagulopathy.

Symptoms of COVID-19 may vary in severity, from mild to serious clinical features, those may include fever, tiredness, and dry cough, shortness of breath, sore throat, headache, myalgia (muscle pain) or arthralgia (joint pain), chills, vomiting, and nasal congestion. Diarrhea, haemoptysis (coughing up blood

from the respiratory tract), and conjunctival congestion can occur but are less frequent symptoms . The evident cause of increasing mortality in COVID-19 infection can be either due to lung infection, Pulmonary vasculopathy or consequence of deranged coagulation that results in thrombosis.

COVID-19 and Hemoglobinopathy

COVID-19 is a novel virus infection caused by Severe Acute Respiratory Syndrome corona virus-2 (SARS CoV-2). At its outbreak, it was declared as pandemic by world health organization (WHO)in December 2019. Thalassemia and Sickle cell disorders are the hemoglobinopathies, those belong to one among high risk category in COVID-19 pandemic, as declared by Centres for Disease Control and Prevention (CDC) [1]. Certain clinical conditions may mimic or overlap symptom clinically as COVID-19 features.

Comparatively, patients with Sickle cell disease have increased risk of lung infections than those in Thalassaemia [5]. Common in both is the increased susceptibility to viral or bacterial infections, which can worsen their physical condition. A splenectomised Thalassemia patient is equivalent to functional hyposplenism in Sickle cell disease [5]. Both the diseases are also vulnerable to infection due to compromised immunity and can trigger serious, life threatening sepsis because a virus infected patient may develop secondary bacterial infections.

Sickle Cell Disease (SCD)

It is a haematological disorder, where the red blood cells have the tendency to undergo configurational change from flexible biconcave disc to stiff sickle shape cells. The process of sickling is enhanced mostly with fever, infection, dehydration and acidosis [5]. Few of the physiological conditions as pregnancy, stress , exercise and anxiety can also precipitate the sickling process . This depends on the percentage of sickle cell fraction in the blood of an individual. The narrow blood vessels get occluded due to sickle shaped red blood cells and painful crisis occurs due to the reduced oxygenation of the tissue. Therefore, Sickle cell is a disorder of high morbidity and mortality [6].

Basic requirements

Painful episodes are the commonest manifestation in sickle cell disease. These are also known as Sickle cell crisis, which needs immediate interventionand supportive care. Infection enhances the crisis; therefore, if there is fever or suspicion of infection, it should be quickly managed with oral anti-pyretic, antibiotics, IV/Oral analgesics and IV fluid at their local health centres.

As a part of complication in Sickle cell disease, there is increased risk of stroke, acute chest syndrome, organ failure and bone damage which is a mimic of COVID-19. At times, it can be life threatening. Fear of corona infection has influenced the delay in quick hospitalization and overall management from both aspects of patient and health professionals. Instead of emergency management, the focus is more on acquiring a negative report for COVID-19.

Sickle cell disease and COVID 19

Patient of Sickle cell disease are prone for pneumonia or acute chest syndrome as a part of the disease complication but the symptoms overlap significantly with respiratory features of COVID-19.[7]This can be differentiated by radio-imaging of chest. A localized lesion/ opacity is consistent with pneumonia whereas COVID-19 is consistent with diffuse ground glass appearance. Further COVID-19antigen RT-PCR test (nasal and throat swab), stool culture, blood and sputum culture can delineate the underlying pathogen which can guide the management further. Acute chest

syndrome (ACS) is often managed by blood transfusion, analgesics and hydration.

Pitfalls and possible solutions

Frequent painful crisis and complications are dealt with simple/top up/ exchange blood transfusion. For immediate management, it is opted with an intent of dilution or decreasing the concentration of Sickle cells in the circulation. In this crucial time of pandemic, there is severe shortage of blood.

For long term management, hydroxyurea should be added because it increases the level of HbF and reduces HbS aggregation [7]. But widespread non-availability, knowledge about the drug and it's monitoring is the major barrier for its usage at peripheral health sectors.

It is high time for the patients to understand their disease and take care of themselves to avoid the inciting factors like dehydration, infection, anxiety that may exacerbate sickle process.

Thalassemia

It is an inherited blood disorder, where the patient manifest with low haemoglobin due to genetic defect. They are unable to produce adequate blood and are clinically characterised with symptoms of anaemia like easy fatiguability, weakness, reduced appetite, breathlessness and bone pain.

Basic requirements

Blood transfusion is the mainstay of treatment along with medications like iron chelators, folvite, calcium and zinc supplementation. They depend on regular blood transfusion once or twice in a month for their survival.

Risk factors

Iron overload can cause diabetes, hypothyroidism, adrenal insufficiency, heart failure, intravascular thrombosis, venous ulcer, which in itself will be a cause for increased mortality in COVID-19 infection.[8]

Dependency on Blood transfusion since childhood make them prone to various transfusion transmitted infection like Hepatitis B/C or HIV. Majority donot follow any vaccination module.

Post splenectomy patients are immuno-compromised and to some extent, those on hydroxyurea.

Thalassemia and COVID-19

Blood banks are facing tremendous blood scarcity due to unwilling voluntary donors, dwelling in the fear of corona infection.[9] This has become the crisis of the hour and an unmet need. Patients on regular transfusion are getting blood transfusion at a haemoglobin level of 4-6 gm/dl.

Severe anaemia, features of breathlessness, infections or ill health features may manifest with overlapping symptoms as COVID-19. Must identify them and address the clinical issue on emergency basis.

Intravascular coagulation may be accentuated with super-imposed corona virus infection. If suspicion arises, investigation and prophylactic anticoagulation have to be adopted with physician advice.

Immuno-compromised patients need to be very careful with exposure to infection by adopting sanitization measures, hand hygiene, minimize outside exposure and maintaining proper social distancing in the outdoor.

All transfusion dependent thalassaemic should follow vaccination module.

Splenectomised patients to adopt Pneumococcal vaccination in every 5 years and annual vaccination for haemophilus Influenza along with prophylactic antibiotic coverage with penicillin or erythromycin is required.

Infection like Hepatitis B, Hepatitis C and HIV to be monitored and those with already known infections for any, should follow the treatments.

Those on iron chelators should not discontinue it, unless advised.

Other transfusion dependent thalassemia intermediates, heterozygous Thalassaemic with sickle or haemoglobin E should adhere to Hydroxyurea .

Pitfall in Social Participation and Possible solution

Blood donation from non-remunerated voluntary donors are the first step to suffice their basic need. Blood banks and hospitals cannot help these patients if healthy people do not come forward for donating blood. During this COVID-19 pandemic, all are moving in an uncertain situation but it does not mean to forget social responsibilities for this section of people, who depend on general population.

Small blood camps should be frequently organised by following norms of guidelines like maintaining social distance, personal hygiene and adopting protective measures. The best way to avoid gathering in camps is to encourage individual donors to donate blood in blood banks where they take all precautionary measures.

Haemophili

It is an inherited bleeding disorder which is characterised by deficiency of clotting factors, most commonly are Factor VIII deficiency (Haemophilia A) followed by Factor IX (Haemophilia B). It can clinically manifest with spontaneous episode of internal bleeds or trauma induced bleeds that may occur at any site of the body. Most common site are joints, more often in knee followed by ankle. Repeated joint bleed damages the cartilage and bone, which ultimately leads to crippling arthropathy. But bleeds can be life threatening, when it occurs in brain, throat, gastro-intestinal, intra-abdominal, urinary tract etc.

Modality of treatment

Infusion of clotting factor concentrates within two hours of acute bleed is the crucial step in management . Simultaneously pain and swelling are supported by other ancillary protocol of rest for at least 24-48 hrs, local application of ice, medications for pain management and anti-fibrinolytic agent for clot stabilization.

Resources

Factor concentrates is available at few government hospital. Cryoprecipitate or plasma are also used as an alternative substitution product. But most of the blood banks do not have component separator to prepare cryoprecipitate. Therefore, they have to travel in search of resources.

Haemophilia and COVID-19

This category of patients are high risk group, especially the elderly haemophiliacs with chronic diseases[10]. Unlike general population, they too suffer same as others but bleeding complications can add on to it.

Infection with Corona virus may cause systemic inflammatory response in the form of DIC(disseminated intravascular coagulation) with decreased platelets, increased consumption of all coagulation factors. The investigation shows prolonged screening tests (PT and aPTT), decreased level of fibrinogen and other clotting factors. The condition may exacerbate bleed in haemophilia [11]. If severe infection in COVID-19 is diagnosed, prophylaxis with factor replacement therapy should be continued. In such case, close monitoring for bleeding and thrombosis should be done in the individuals as the infection progresses. Anticoagulants (e.g. low molecular weight heparin, LMWH) are being recommended as part of treatment protocols for patients with elevated D-dimers and

severe infection. Use of anticoagulants should be accompanied by factor replacement therapy[11].

A thrombotic event if recorded in a haemophilia patient, detailed monitoring is important with COVID-19 status, laboratory investigation, imaging, dose of replacement therapy.

Haemophilia management in COVID-19 TIME

It has almost the risk same as general population but are categorized in vulnerable group because of unavoidable repeated exposures due to multiple hospital visits and adopted means of public transport. Factors are not available within their local reach out and majority have to travel a long distance for it. All attempts should be made to minimize the exposure through the underlying measures. The challenge of adverse situations will help the patients and their guardians to educate themselves.

Home therapy and Self infusion of factor concentrates should be encouraged with the patient and their parents. Those who know self-infusion must be issued at least one demand dose of factor concentrate for home. For this, government health officials need to understand and formulate the principle of empty vials replacement against issue of factor concentrate.

Bleeding episode in patient with severe haemophilia to be managed at home by self (teen ager, adolescent, young adults) or their parents by weighing out the risk of bleed management at home versus hospital visit.

If bleed is in joint, the factor should infused within 2 hours. Concerned doctor should at least mention two demand doses. One for joint bleed and another for serious site that may be life threatening.

In hospital, the concentrates should be available at casualty/ emergency triage. Every staff need to learn the mode of administration and should be educated about its pros and cons.

Highly active children or patient with target joint may bleed very frequently. A schedule of prophylaxis should be made by physician and home therapy to be implemented on monthly basis.

Ancillary method for joint bleeding beside factor concentrates, a protocol of "PRICE" (Protection, Rest, Ice, Compression, Elevation) should be adopted along with some pain relieving medications like analgesics (acetaminophen) and clot stabilizing antifibrinolytics agent (Aminocaproic acid, Tranexamic acid). The above mentioned medicines along with factor concentrate (at least one or two demand dose) must be kept in the home.

First aid for minor cuts and pressure bandage, ice pack for minor bruise and **Botroclot** topical solution can be used to control **bleed** in small wounds and **dental bleeds**.

Elderly haemophiliacs with chronic medical conditions should take extra precautions for co-morbid conditions like hypertension, diabetes, asthma, cardiovascular disease, obesity, HIV and those on steroids or other powerful immunosuppressant drugs etc. They should take measures to keep their blood pressure and sugar level in check and follow general guidelines[11].

For economical well off patient or people with insurance coverage can opt for Emicizumab (non-factor), a newer drug with patient support programme. It can be given to Haemophilia A patients with or without inhibitor and can be self-infused subcutaneously instead of intravenous infusion of factor concentrate. It is given as weekly/ biweekly or as monthly prophylaxis to attend zero bleed [12]. This can make them free from all anxiety of virus exposure and repeated anticipated bleeding events. Use of APCC should be avoided, if anyone gets bleed in between prophylaxis of Emicizumab.

Pitfalls and its solution of all three cases

1. Denial and ignorance about the disease are the biggest fallout of the service at public health sector. Patients, parents and health professionals need to enrich their knowledge. Webinars have given the opportunity to all for acquiring knowledge.

2. Fear factor of getting infected remains same for the patients as well as the care givers. But non-hostile behaviour and misconduct adds on to the apprehension and anxiety on top of patient's suffering. Guidelines to manage the adversities are to be followed.

3.Adequate self-protective measures should be the modality of self-care while delivering health service.

4. Telecommunication can help the patient and local health professionals at remote places to sought out help and interact with the referral doctors to manage the cases locally or in critical situation, can be sent to tertiary centres with supportive initial stabilization.

The all above mentioned notes are the protective measures to avoid crowds , non-essential travel and to stay safe at home. Therefore, patients should consult their healthcare providers if they manifest with any COVID-19 like symptoms.

Current Scenario

The major attention of the nation and the Government is towards treatment and prevention of COVID-19. The unplanned sudden re-enforcement of lockdown, weak health infra-structure in remote areas, ignorance of knowledge about these diseases and fear of COVID infection, all this has led to greater health risk. Many small cities and villages do not have blood transfusion centres. Public and community health centres need to follow guidelines. Many general hospitals have been converted into COVID hospitals and more health care staffs are diverted, which had negative impact on general public health service.

Conclusion

Anxiety, depression, loneliness, apprehension of isolation, quarantine, social ill treatment and death is the negative aspect of COVID-19 time. It is time to change our thoughts. Patients should understand their disease process and improve their knowledge to tackle it. Health professionals and care givers should equip themselves and follow preventive measures without neglecting their primary goal of patient cares. At individual level, social participation should be encouraged along with safety measures rather than running away from it. Telemedicine as an alternative or if hospital care mandatory, should be adopted at the earliest.

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