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An Update on Pathogenesis, Diagnosis and Treatment of COVID-19-Related Cytokine Storm

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A B S T R A C T

CoronaVirus Disease 2019 (COVID-19) is a viral infection caused by the Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), which is globally influential and has killed more than 6 million patients until today. Hyper-secretion of pro-inflammatory cytokines triggered by the viral infection that cannot be eliminated by the immune system and an ongoing hyper-inflammatory state primarily in the lung seem to be the major causes of death. The mechanisms proposed to explain the pathogenesis of the cytokine storm associated with COVID-19 included poor viral clearance and persistent robust cytokine response despite inadequate antiviral immunity. The diagnosis can be made easily by clinical features, imaging techniques, and nasopharyngeal PCR. The diagnosis of this hyper-inflammatory state in a patient with COVID-19 can be made with rapid deterioration in clinical features, and laboratory findings including abnormally high serum CRP, ferritin and D-dimer levels, and rapidly progressive pulmonary radiological findings.
In addition to the anti-viral and supportive treatments, corticosteroids, IL-1, or IL-6 receptor blockers are frequently used to suppress the increased cytokine response.

INTRODUCTION

CoronaVirus Disease 2019 (COVID-19) is a viral infection caused by Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), which has affected the whole world and has killed more than 6 million patients to date (1,2). Excessive secretion of pro-Inflamatory cytokines triggered by a viral Infection which cannot be sufficiently eliminated by the immune system and ongoing hyper-Inflamatory state, particularly in the lungs, seem to be the main causes of death (3-6). There has been a rapid development in the diagnostic methods of COVID-19, and the diagnosis can be made easily by clinical features, imaging techniques, and nasopharyngeal PCR (7). The diagnosis of this hyper-Inflamatory state developing in the course of COVID-19 can be made based on clinical features, abnormally high serum ferritin, CRP, and D-dimer levels, and rapidly progressive pulmonary radiological findings (5,6).

In addition to the antiviral and supportive treatments developed for COVID-19, corticosteroids, IL-6 or IL-1 receptor blockers are frequently used to suppress the increased cytokine response (4,8).

In this article, we have reviewed the latest developments in the pathogenesis, diagnosis, and management of cytokine storm that occurs in the course of COVID-19.

Evidence Acquisition

There are many publications on COVID-19 and hundreds of new articles are added to the literature every day. Most of them are repeated articles on similar topics. For convenience, we planned to select those that were published in 2022. So, we searched the articles published during the last six months to reach to most recent evidence on COVID-19 and cytokine storm. We carried out a PubMed search using the keywords of "COVID-19", "Cytokine Storm", "Macrophage Activation Syndrome", "IL-1 blockage" and "IL-6 blockage" from 01

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January to 01 July 2022 and selected original articles, reviews, and meta-analyses written in English with full text available.

RESULTS

As a result of the PubMed search, 309 articles were reached. After reading their titles or abstracts, 32 were selected. In addition, 20 key manuscripts covering this subject in previous years were also used. This review was written using these articles.

The review was outlined as follows: Initially, we discussed the general features of COVID-19 Infection, followed by pathogenesis and immunologic features of COVID-19 Infection, cytokine storm secondary to COVID-19 Infection, and finally the diagnosis and management of these immunologic complications.

COVID-19 Infection

COVID-19 is a clinical syndrome caused by a mutational RNA virus called Severe Acute Respiratory Syndrome CoronaVirus2 (SARS-CoV-2). It was first identified in China in December 2019 and then rapidly spread Worldwide and was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020. SARS-CoV-2 is a beta virus, like two other coronaviruses, Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV) and the Middle East Respiratory Syndrome Corona Virus (MERS-CoV), which have caused fatal Infections in humans during the last 20 years (1).

SARS-CoV-2 spreads through the inhalation or direct contact with saliva or respiratory droplets that are thrown out when an infected person sneezes, coughs, or even talks (1, 8).

Fever, sore throat, widespread muscle pain, loss of taste and smell, cough, and dyspnea were the most common complaints, especially in Infections with wild type. It frequently causes hospitalization and intensive care unit admission due to lung involvement (1,9). High serum CRP, ferritin, and D-dimer levels, tendency to monocytosis rather than lymphocytosis, hepatic dysfunction, thrombotic tendency, very high cytokine levels, disseminated intravascular coagulation (DIC), and progressively increasing radiological pneumonic infiltrates are typical laboratory and radiological features of COVID-19. While mortality rate of 10-20% was reported with wild-type SARS-CoV-2, virulence was decreased in the variants that developed over time, resulting in less severe disease course. Latest variants like Omicron and its subtypes were notable with having higher contagiousness, however they caused milder disease course, less severe complications and decreased mortality rate (10,11).

Pathogenesis and Immunologic Features of COVID-19 Infection

Most of the clinical and laboratory findings mentioned above for COVID-19 are similar to those seen in SARS-CoV and MERS-CoV Infections. These viruses carry some structural similarities, similar to the clinical diseases they cause. Spike glycoproteins located on the surface of the virus bind to the angiotensin-converting enzyme-2 (ACE-2) receptors, allowing the virus to enter the host cell. There are resemblances between the spike glycoproteins of SARS-CoV and SARS-CoV-2, which are the most immunogenic portions of coronaviruses (12). SARS-CoV-2 has 79.5% and 50% genome-wide sequence identity with SARS-CoV and MERS-CoV, respectively. More importantly, the spike protein of SARS-CoV-2 has a 10-20 times higher affinity for the ACE-2 receptors (13,12). The clinical and antigenic similarities suggest that their pathogenesis may be similar (8,14). In addition to ACE-2, transmembrane protease serine 2 (TMPRSS2) and endosomal cysteine proteases, cathepsin B and L (CatB/L) are also involved in the pathogenesis of SARS-CoV Infection (12). The ACE receptor is most commonly found on the surface of the upper and lower respiratory tract cells, especially on type-2 pneumocytes. Stimulation of the ACE receptor by the S1 domain of the SARS-CoV-2 virus down-regulates ACE-2 which causes compensatory production of high amounts of angiotensin-2 by ACE-1 activity, causing increased permeability in the lungs. For these reasons, the Infection causes severe damage in the lungs.

Under normal conditions, when the immune system encounters foreign antigens such as viruses, antigen-presenting cells process these antigens and then present them to both natural killer (NK) and CD8 positive cytotoxic T cells, as usual, via major tissue compatibility (MHC) antigens (5, 6,). At the beginning of this process, the foreign antigenic threat, which is called pathogen-associated molecular patterns (PAMPs), or Damage or death-associated molecular patterns (DAMPs), activate structures named Pattern Recognition Receptors (PRRs), which are mostly found on the cell surface or cytosol. For viruses, viral nucleic acids play a role as PAMP. There are four main PRRs families: Toll-like receptors (TLR); Nucleotide-binding oligomerization domain-like receptors (NLR); C-type lectin receptors (CLR) and RIG-1-like receptors (RLR) (14-16) Activation of these molecules triggers the Inflamatory reaction by activating the mitogen-activated protein kinases (MAPK) and nuclear factor of kappa light polypeptide gene enhancer in B-cells (NF-κB) pathways. This Inflamatory response is mediated by activation of both innate and adaptive immunity and increased production of many pro-Inflamatory cytokines including TNF-α, interferon-γ (IFN-γ), IL-1, IL-6 and IL-18 (5, 6, 14, 15).

During normal immune response, anti-Inflamatory mechanisms of the immune system prevent further activation of the Inflamatory process and over-secretion of cytokines, which may be harmful for the body. So, virus-infected cells are destroyed by activation of NK cells and CD8-positive cytolytic T cells using the perforin-mediated secretion of granulysin. Finally, after the end of antigenic stimulation, antigen-presenting cells and related cytotoxic T cells go to apoptosis, which results in preventing further immune activation and cytokine secretion (17-19) But, in some patients, these control mechanisms are inadequate, and prolonged hyper-Inflamatory state called as “cytokine storm” may develop, causing thrombotic tendency, multi-organ failure, and sometimes death due to un-controlled activation of the macrophage-monocyte system, secretion of pro-Inflamatory cytokines, chemokines and matrix metalloproteinases (MMP) such as TNF, IFN-γ, IL-1, IL-18, IL-6, IL-33, CCL5, CXCL8, and CXCL-10 (Fig. 1) (5, 6, 14, 18, 20, 21).

This is also the main pathogenic mechanism for "Hemophagocytic LymphoHistiocytosis (HLH)", which often develops due to a defect in lymphocyte cytolytic activity caused by genetic problems. HLH may also develop secondary to various conditions. Whatever the cause is, HLH is characterized with the inability of NK and cytolytic CD8 T cells to lyse infected and activated antigen-presenting cells (17, 18). Primary HLH is frequently diagnosed in childhood and also it may be familial. It is caused by various mutations and has a genetic inheritance. Secondary HLH may develop in the presence of an underlying disease. In other words, secondary HLH frequently

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occurs secondary to malignancies, Infections, autoimmune/autoInflamatory diseases, or various medications (22, 23). Among the rheumatologic diseases, this disorder is mostly seen in the course of juvenile and adult onset Still's diseases and is generally called "Macrophage Activation Syndrome" (MAS). Virus Infections such as EBV, CMV, Herpes Viruses, and HIV are well known to cause secondary HLH. Since the beginning of 2020, SARS-CoV-2 has also been added to this list (18).

COVID-19-Associated Cytokine Storm

Numerous cases of adult-onset respiratory distress syndrome (ARDS) have been reported in the early stages of COVID-19, accompanied with very high serum levels of pro-Inflamatory cytokines, more than expected in viral Infections (9). Although there is no consensus, different terms and names were used for this hyper-Inflamatory state, such as "MAS due to COVID-19", "hyper-inflammation seen in the course of COVID-19", and "COVID-19-associated cytokine storm". We prefer to use the term "COVID-19-associated cytokine storm".

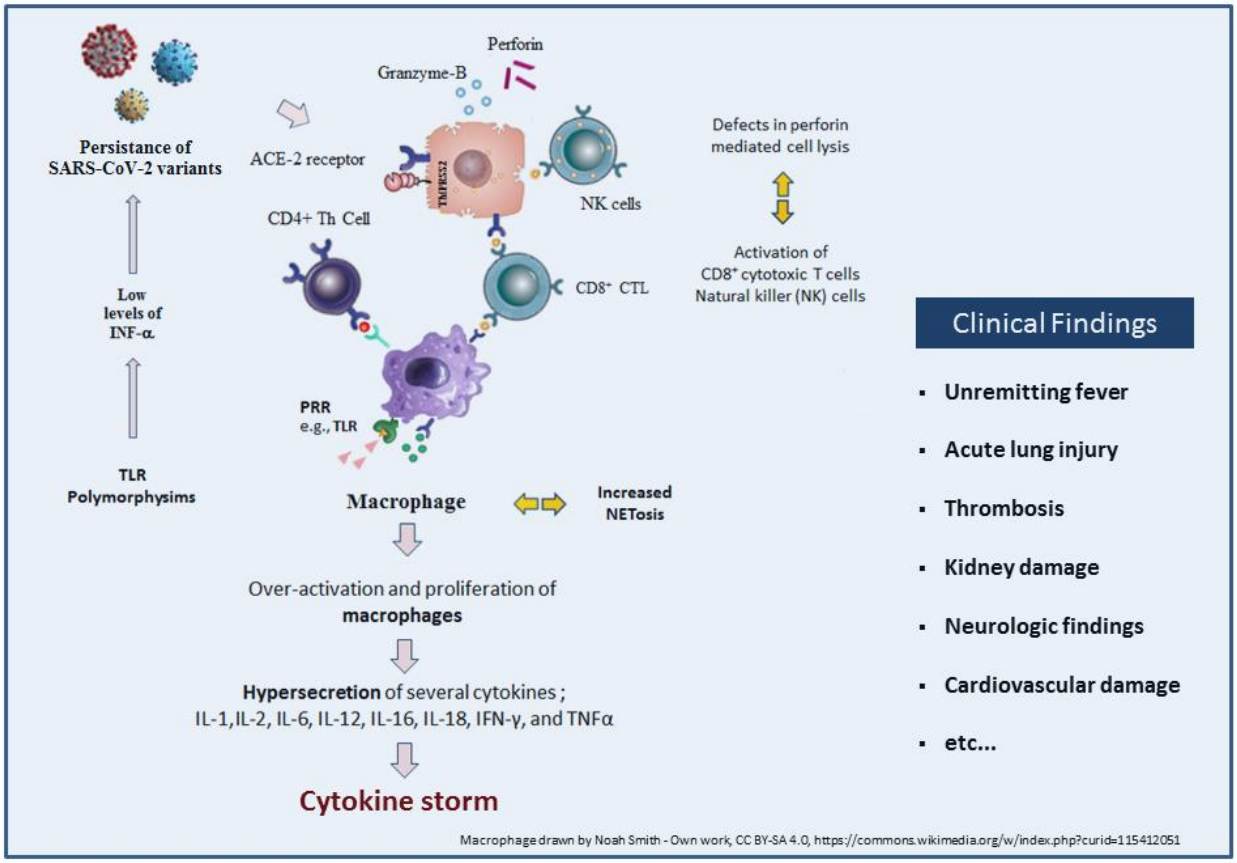


Fig. 1. Pathogenesis and clinical findings in COVID-19 induced cytokine storm.

Cytokine storm, which is the most important cause of death in COVID-19 patients, develops especially in the older patients having co-morbid diseases such as hypertension, diabetes mellitus, and chronic lung diseases (4,5,12,24). It has also been reported that COVID-19 is more severe in patients taking drugs such as rituximab (RTX) and corticosteroids (25).

Many mechanisms have been proposed in the pathogenesis of the COVID-19-related cytokine storm. Poor viral clearance and persistent intensive cytokine production despite inadequate anti-viral immunity appear to be the main mechanisms underlying the pathogenesis (Fig. 1).

Viral Factors

The SARS-CoV and MERS-CoV viruses develop strategies such as double membranes to escape from the immune system and cause defective viral clearance. This mechanism may also apply to SARS-CoV-2. The spike protein of SARS-CoV-2 has a 10-20 times higher affinity for the ACE-2 receptors, as mentioned above. In addition, SAR-COV-2 antigen persistence in the vascular bed may also play a role in prolonged immune activation (12, 13, 18, 26).

Immunogenetic Factors

When type I interferons, which are very important for the antiviral immune response, are not secreted as much as necessary, a sufficient anti-viral immune response cannot be generated. IFN-γ levels were also found to be lower in the serum of some patients with severe COVID-19. Both TLR3 and IRF3 gene polymorphisms may be responsible for this condition. However, these polymorphisms could be demonstrated in only up to 3.5% of the patients. There may be other genetic factors. Antibodies to IFN have been shown in some patients. Interestingly, TLR4, which plays a role in

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antibacterial immunity, can also trigger IFN-γ activation and formation of neutrophil extracellular traps (NETS) and support antiviral response (27, 28). Increased NETOsis may also contribute to the immunopathogenesis of COVID-19 (29). Toll-like receptors, which have important roles in the recognition of self and non-self antigens, have important roles in the pathogenesis of SARS-CoV-2 and the complication of cytokine storm. Some TLR gene polymorphisms such as TLR7 have been reported to play a role in the development of severe COVID-19 disease. However, such polymorphisms are rare. Interestingly, it has been claimed that TLR blockers may work in the treatment of cytokine storms (28).

Defects in lymphocyte cytolytic activity which are major causes of primary HLH, have only minor role in the pathogenesis of COVID-19-associated cytokine storm.

Ben Moftah et al suggested that ADAM-19 and MMP-9 play role in the shedding of ACE-2, and may lead to the development of other pathogenic mechanisms in a patient with COVID-19-associated cytokine storm. They also suggested that targeting these enzymes may be a therapeutic approach (24).

Many pro-Inflamatory cytokines, such as IL-6, which are elevated in the course of COVID-19 also activate the JAK-STAT pathway and may contribute to many clinical features, including thrombotic manifestations in the course of COVID-19 (30).

Six et al suggested that COVID-19 is an endotheliopathy, based on the findings that the SARS-CoV-2 virus infects the endothelium, especially the respiratory tract, and causes endothelial damage. Moreover, Infection of the endothelium may also cause distant spread, induction of the secretion of pro-Inflamatory cytokines, and intravascular thrombus formation (31). They suggested that therapies for improving endothelial dysfunction, such as antioxidants and ACE inhibitors, may be useful in the treatment of COVID-19.

Diagnosis of Cytokine Storm Associated COVID-19

The diagnosis of COVID-19 can be easily made by clinical signs, radiological evidence of viral pneumonia, and PCR testing for COVID-19. In addition, early diagnosis of cytokine storm is particularly important; delay of diagnosis may cause poor outcomes. Unfortunately, there are no specific clinical findings or laboratory tests for quickly and correctly diagnosing this life-threatening condition. The criteria proposed for HLH and MAS are not acceptable for COVID-19-associated cytokine storms (7, 18).

Recently, Caricchio *et al*. suggested a preliminary set of criteria for predicting COVID-19-associated cytokine storm (32). Although these preliminary criteria may be useful for patients whose general condition deteriorates rapidly, we think it is too early to use them as widely applicable general diagnostic criteria, and further studies are needed. In our opinion, COVID-19-associated cytokine storm should be taken into account in a patient with a confirmed diagnosis of COVID-19, if rapid deterioration in general condition develops in the presence of persistent fever lasting more than three days associated with a progressive increase of the serum CRP, ferritin, and D-dimer levels. This practical approach is accepted by many authors. In the case of cytokine storm, diagnostic and management principles should be guided by a committee consisting of at least one rheumatologist with training in internal medicine, a hematologist, a clinical immunologist, and specialists in chest disease, infectious disease, and intensive care.

Management of COVID-19-associated Cytokine Storm

Since the beginning of 2020, very important developments have been seen in the treatment of COVID-19 and cytokine storms, which are among the major causes of death in the world. First of all, the spread of the Infection has been brought under control, thanks to the preventive measures taken worldwide and the vaccination studies implemented all over the world since the end of 2020. Also, although the last variant, the Omicron variant, is more contagious, its potential to cause severe disease is reduced, especially in fully vaccinated people (2, 7, 10).

Among all the developments, including preventive measures, since the beginning of the epidemic, the two most important developments are noticeable. The first is the development of effective vaccines in the prevention of COVID-19, and the other is the development of anti-viral therapeutics that are effective in its treatment (33-35.) Most of the current COVID-19 vaccines are effective in preventing the disease and allowing milder disease course. Among anti-viral agents, ritonavir-assisted nirmatrelvir (Paxlovid, i.e. nirmatrelvir-ritonavir) and molnupiravir (Lagevrio) are currently under emergency use authorization in the United States of America (USA). These two drugs have been accepted for the treatment of mild to moderate COVID19 patients who are not currently hospitalized but are at high risk of developing a serious illness. Nirmatrelvir-ritonavir and molnupiravir are approved for use within first five days of the onset of COVID-19 symptoms. These anti-viral agents may be administered to all patients at 65 years of age or older. On the other hand, patients at 12 years of age or older may receive these anti-viral agents, only in the presence of a co-morbidity that increases the risk of serious consequences of COVID-19, including malignancy, heart disease, diabetes mellitus, and obesity (33).

Numerous studies of monoclonal anti-SARS-CoV-2 antibodies have been conducted for prophylactic and therapeutic purposes, and two of them (bamlanivimab plus etesevimab and casirivimab plus imdevimab) have been approved by the FDA for post-exposure prophylaxis of individuals who are at high risk of progression. For pre-exposure use, tixagevimab plus cilgavimab have been approved (36).

Despite the above-mentioned preventive and antiviral treatments, some patients develop further complications such as ARDS and cytokine storm, which are major causes of death. Treatment of COVID-19-associated cytokine storm includes treatments targeting the underlying mechanisms. The critical point is that an early diagnosis should be made and the treatment should be started on time. Since the beginning of the epidemic, numerous medications have been tried in the treatment of cytokine storms. However, those with positive evidence of efficacy are only corticosteroids and some anti-cytokine agents (6, 37-39). In addition, it is critical to initiate anticoagulant therapy for some patients who are at risk for thrombosis due to hypercoagulability.

Corticosteroids: Suppression of excessive inflammation, through the timely administration of corticosteroids in the early stage of cytokine storm, can effectively prevent the development of ARDS and preserve the patient's organ functions. Severe and critical clinical condition, persistent fever (>39 °C), acute hypoxemia and respiratory failure, involvement of more than 50% of the lungs within 48 hours according to thorax CT scan findings, need for mechanical ventilation, and the presence of progressively increasing serum CRP and ferritin levels require corticosteroid therapy. On the other hand,

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initiation of corticosteroids is not necessary for every COVID-19 patient; it may cause an increase in viremia and may be harmful, especially in the early phases of the disease (6, 32). In addition, patients with long-term corticosteroid use for other reasons may experience life-threating COVID-19 course (40,25).

Cytokine Inhibition: The studies conducted in the early days of the epidemic showed that serum levels of pro-Inflamatory cytokines such as IL-1, IL-6, and TNF-α were quite high, especially in patients with poor outcomes. Inhibition of these cytokines was reported to contribute positively to the outcome of these patients (9). Moreover, disease outcome was found better than expected in patients with rheumatic diseases using biologic treatments (25).

Inhibition of IL-6, IL-1, TNF-α, as well as the inhibition of the JAK/STAT pathway constitute the mostly studied anti-cytokine treatments (30, 38, 41- 46).

The rheumatologists are familiar with IL-1 blockade and IL-6 blockade, since these treatments are also used for the treatment of some systemic Inflamatory rheumatic diseases. IL-1 receptor blocker, Kineret, can be preferred, because it has a short half-life, can be administered intravenously or subcutaneously, and can also be used during pregnancy (6). Cavalli et al. claimed that they benefited more from IL-6 blockade if the initial CRP values were very high, but in general, IL-1 blockade started in the early phase of the disease showed better results (47). The success of anti-cytokine treatment depends upon correct timing and appropriate patient selection.

TNF-α blockade is an important target in the management of cytokine storms due to the high serum level of TNF-α, in the course of cytokine storms and its interactions with SARS-CoV-2 and ACE-2. Numerous studies have shown that TNF blockers currently in use in the market may be useful in the treatment of cytokine storms (36, 45).

Inhibition of the JAK/STAT pathway, another step involved in release of some cytokines, was also found to be beneficial in the treatment of cytokine storms (46).

Although some studies have shown decreases in CRP levels and the severity of COVID-19, colchicine is thought to be ineffective in the COVID-19 cytokine storm (6, 48).

It has been suggested that caspase inhibitors may also work in severe COVID-19 cases, especially based upon their roles in the IL-1 pathway, apoptosis, and pyroptosis (49).

The role of interferons in normal antiviral defense has already been mentioned. Interestingly, SARS-CoV-2 weakens the antiviral defense by impairing the release of type 1 interferons. IFN-based therapies have been found useful in increasing antiviral immunity (27).

A combination of anthelmintic drug ivermectin with doxycycline, whose efficacy alone is controversial, has been claimed to be effective in suppressing cytokine storms (50). Remdesivir, a broad-spectrum anti-viral agent, increases recovery rates in moderate-to-severe COVID-19 patients who are not mechanically ventilated (51).

Therapeutic plasma exchange, convalescent plasma, and intravenous immunoglobulin may be useful in selected cases.

Thrombosis prophylaxis and treatment are of vital importance due to the high tendency for thrombosis that develops for many reasons.

Antifibrotic agents have been found to be useful in the treatment of pulmonary fibrosis, which is an important complication after severe COVID-19 (52).

CONCLUSION

Although nowadays, COVID-19 generally causes a milder Infection, thanks to preventive measures, vaccinations, and recent variants, it still continues to cause deaths, especially in elderly men, and in patients with additional co-morbidities such as diabetes and ischemic heart disease. In addition to anti-viral treatments, supportive measures and treatment of complications are vital. ARDS and cytokine storms seem to be the most important causes of death. Early recognition of these life-threatening conditions and the use of corticosteroids and, if necessary, cytokine blockers on time can be life-saving. Venous thrombosis prophylaxis is another life-saving step.

CONFLICT OF INTERESTS

The authos declare that they have no conflict of interest.

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