

Challenges for management of immune thrombocytopenia during COVID-19 pandemic

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It is almost 6 months since novel coronavirus disease 2019 (COVID-19) started as a local outbreak in Wuhan, China¹ For hematologists and patients suffering from hematological disorders, the COVID-19 pandemic has brought challenges with regard to the diagnosis, treatment, follow-up, office visits, and so on.^{2,3} We hereby discuss the current challenges for management of immune thrombocytopenia (ITP) during COVID-19 pandemic, based on our practical experience and interim expert recommendations suggested by the hematology societies.

1 | THROMBOCYTOPENIA IN CORONAVIRUS DISEASE 2019

Thrombocytopenia, in general, is one of the very commonly encountered laboratory anomalies in hematological practice. It is a challenging entity because of multiple reasons which can interplay to cause thrombocytopenia. Thrombocytopenia, and lymphopenia, has been found as common hematological abnormalities in patients with COVID-19, which has also been shown to be an indicator of poor outcome and survival.^{4,5} The prevalence of thrombocytopenia is extremely variable. Huang et al noted COVID-19 non-survivors (20%) to be more thrombocytopenic than survivors (1%).⁶ In most COVID-19 cases of thrombocytopenia, the platelet count does not fall below $100 \times 10^9/L$. Severe degree of thrombocytopenia ($<20 \times 10^9/L$, or a sudden drop $>50\%$ over 24–48 hours) narrows down the differentials to ITP, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, microangiopathic hemolytic anemia, heparin induced thrombocytopenia, or disseminated intravascular coagulation.^{7,8}

But before considering the diagnosis of ITP, it is important to evaluate patients with other treatable causes of thrombocytopenia.^{7,9} The approach to ITP is based on the clinical history, systemic examination, and a detailed hematological work up including a complete blood count, and peripheral smear examination. It is recommended to test patients for HCV and HIV to rule out this viral mediated thrombocytopenia. Guidelines do not recommend bone marrow examination in cases with isolated thrombocytopenia unless there is a concern for aplastic anemia, leukemia, or myelodysplastic syndrome.¹⁰ Other immune conditions like antiphospholipid syndrome (APLA) could present with thrombocytopenia.¹¹ Revised classification criteria for the APLA with clinical and lab criteria in making the diagnosis of APLA in such scenarios.

Based on the above-mentioned points, three scenarios could be expected for any hospitalized patient with COVID-19 and thrombocytopenia, (Figure 1):

- (1) Known ITP (chronic), who develops COVID-19.
- (2) New onset ITP (acute) and COVID-19 at the same time and for the first time.
- (3) Thrombocytopenia in patients with COVID-19 unrelated to ITP.

For evaluation of all these three categories, a review of previous records is crucial, as it might save a lot of time and prevent from ordering unnecessary investigation for the evaluation of thrombocytopenia while taking care of a patient with COVID-19. Also, it is important to note that the timing of thrombocytopenia in patients

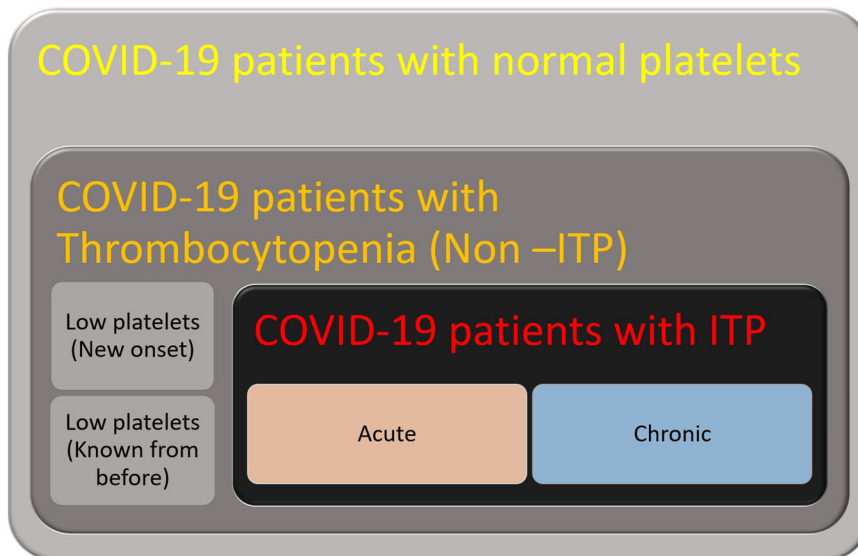


FIGURE 1 Descriptive figure suggesting the broader categories of scenarios possible in a patient with coronavirus disease 2019 (COVID-19). ITP, immune thrombocytopenia

with COVID-19 can be remarkably variable and patients with COVID-19 can rarely present in the form of acute ITP or relapse.⁹

While approaching a suspected case of ITP, it is important to look for other common causes of thrombocytopenia and determining if ITP is primary versus secondary.

As the universal bearing of COVID-19 grows daily, the International ITP Coalition remains devoted to the health and safety of the patients with ITP. The Platelet Disorder Support Association, American Society of Hematology (ASH), British Society of Hematology (BSH) and other international hematology societies are working relentlessly to ensure that constant updates and developments made readily available in the form of interim guidance to the treating physicians and hematologists worldwide.¹²⁻¹⁴

2 | ITP IN COVID-19

Like any viral illness, severe acute respiratory syndrome coronavirus 2 could potentially trigger a new event of ITP. Recently, Zulfiqar et al reported a case of newly diagnosed ITP in a 65-year-old female with COVID-19 that required a sequential trial of multiple drugs, including intravenous immunoglobulin (IVIG), prednisolone, and eltrombopag for complete recovery.¹⁵

The consensus is that if required, non-immunosuppressant treatment modalities should be considered above the immunosuppressant treatment strategies, while managing ITP during the COVID-19 pandemic. The commonly used non-immunosuppressant is IVIG and TPO analogs like romiplostim and eltrombopag. Both ASH and BSH have given the interim recommendations for managing patients with ITP in COVID-19 (Table 1). BSH precisely mentions about the differential approach to acute ITP in COVID-19 positive and COVID-19 negative patients. BSH recommends considering steroids over thrombopoietin receptor agonists (TPO-RAs) in COVID-19 positive cases and using TPO-RAs (off label) as the first line in COVID-19 negative patients.

COVID-19 positive patients are at increased risk of the thromboembolic phenomenon and hence steroids are preferred over TPO agents. Use of steroids and TPO-RAs is based on the risk of increased mortality and superadded infection associated with steroids (in high doses) versus increased thrombotic potential while using TPO-RAs.⁶

We believe that every patient with ITP brings his or her own challenge and due to lack of enough evidence, management should be based on the combination of available data, additional experience, and interim recommendations given by hematology societies (figure 2).

3 | NEW ACUTE/RELAPSED CHRONIC ITP WITH POSITIVE COVID-19

TPO-RAs are associated with increased thrombotic potential, hence there is always a risk of promoting thromboembolic episodes in patients with COVID-19. Recent recommendation published in the *British Journal of Hematology* hence proposed steroids as a preferred first-line therapy than TPO-RAs. Steroids are not risk-free and there are concerns of increased mortality and secondary infection at higher doses (>40 mg methylprednisolone/day). Hence, the BSH recommended that steroid dose and duration should be kept to the minimum with an initial dose of 20 mg daily followed by a tapering trial after 2 weeks. Both BSH and ASH recommend using IVIG as a bridging therapy for dangerously low platelet counts of less than 10 to $30 \times 10^9/L$, while waiting for the response of steroids or TPO-RAs. The use of platelet transfusion should be restricted only for major bleeding.

Unlike BSH that expressed its concerns over thrombotic side-effects of TPO agents, ASH suggests that those chronic ITP patients with newly identified COVID-19, who are already on TPO agents in the case of relapse to either increase the dose or to add a second TPO agent.⁹

TABLE 1 Various scenarios of ITP with COVID-19 and their management

Scenario	Recommendations	Society
New onset acute or relapsed chronic ITP COVID-19 positive.	Consider steroids >TPO-RAs (because of concerns of increased thrombosis with TPO-RAs) non-bleeding patients <ul style="list-style-type: none"> Starting dose: 20 mg once daily (irrespective of patient weight) Dose increment: by 1 mg/kg after 3-5 d in case of no response Tapering protocol: after 2 wk, slowly if there has been good response, rapidly if there is no response. Bleeding patients <ul style="list-style-type: none"> In addition to steroids, consider using IVIG (1 g/kg) and platelet transfusions. Tranexamic acid, except in patients with frank DIC. Caution: Minimum possible dose and duration of steroids is recommended-risk of high mortality and superadded infection with higher doses (>40 mg/day) based on previous studies	BSH
New onset acute or relapsed chronic ITP without COVID-19 symptoms or COVID-19 negative test	TPO-RAs may be preferred as first line treatment >steroids(because of the concerns of the steroids causing immunosuppression and predisposition to COVID-19) caution: <ul style="list-style-type: none"> Challenge will be an off-label use as TPO-RAs are usually 2nd line agents, hence procurement may be a concern. TPO-RAs might take 10-14 d before an effect, hence bridging with IVIG or platelet transfusions might be needed on case to case basis. 	BSH
Chronic ITP patients already on TPO-RAs (hospitalized for COVID-19)	-Trial of dose increment of TPO agent or a addition of second one (eg, add romiplostim to eltrombopag or avatrombopag or add eltrombopag or avatrombopag to romiplostim)	ASH
Chronic stable ITP without COVID-19 symptoms	<ul style="list-style-type: none"> BSH Patients should remain on their current medication, even if this includes steroids and immunosuppressants. <ul style="list-style-type: none"> ASH -If on low doses of immunosuppressive drugs: No modification if they are stable.-If on higher doses of corticosteroids or immunosuppressive drugs: Use of TPO agents and/or IVIG could allow for tapering and possibly discontinuation of these medications. <ul style="list-style-type: none"> Avoid rituximab as it can decrease formation of de novo antibodies, hence reduced immunity against COVID-19 (Both ASH and BSH) 	
Splenectomised patients	<ul style="list-style-type: none"> No data to suggest that splenectomized patients are more vulnerable to COVID-19 To continue prophylactic antibiotics Up to date with their pneumococcal, haemophilus influenza and meningitis vaccinations 	(Both ASH and BSH)
Thromboprophylaxis in patients with ITP hospitalized for COVID-19	<ul style="list-style-type: none"> <30 × 10⁹/L: Intermittent pneumatic compression alone until their platelet count recovers. ≥30 × 10⁹/L and there are no hemorrhagic features: LMWH thromboprophylaxis 	BSH

Note: Synopsis of BSH and ASH recommendations.

Abbreviations: ASH, American Society of Hematology; BSH, British Society of Hematology; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; LMWH, low-molecular-weight heparin; TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonist.

4 | NEW ACUTE/RELAPSED CHRONIC ITP WITHOUT COVID-19 SYMPTOMS OR NEGATIVE COVID-19 TEST

This category includes patients who have newly detected or relapsed chronic ITP without any COVID-19 related concerns or were found to be COVID-19 negative upon testing. BSH recommends TPO-RAs (off label) as the first line over steroids. The idea of not using steroids in COVID-19 negative patients is to keep their immune system active against acquiring COVID-19.⁷ The challenge of TPO-RAs would be a

delayed onset of action (10-14 days) that might require using IVIG or platelet transfusions as needed.

5 | CHRONIC ITP WITH STABLE COUNTS WITHOUT COVID-19 SYMPTOMS

Chronic ITP patients with stable platelet counts should be extremely cautious during the COVID-19 pandemic. BSH recommends continuing steroids and immunosuppressants in general, while ASH

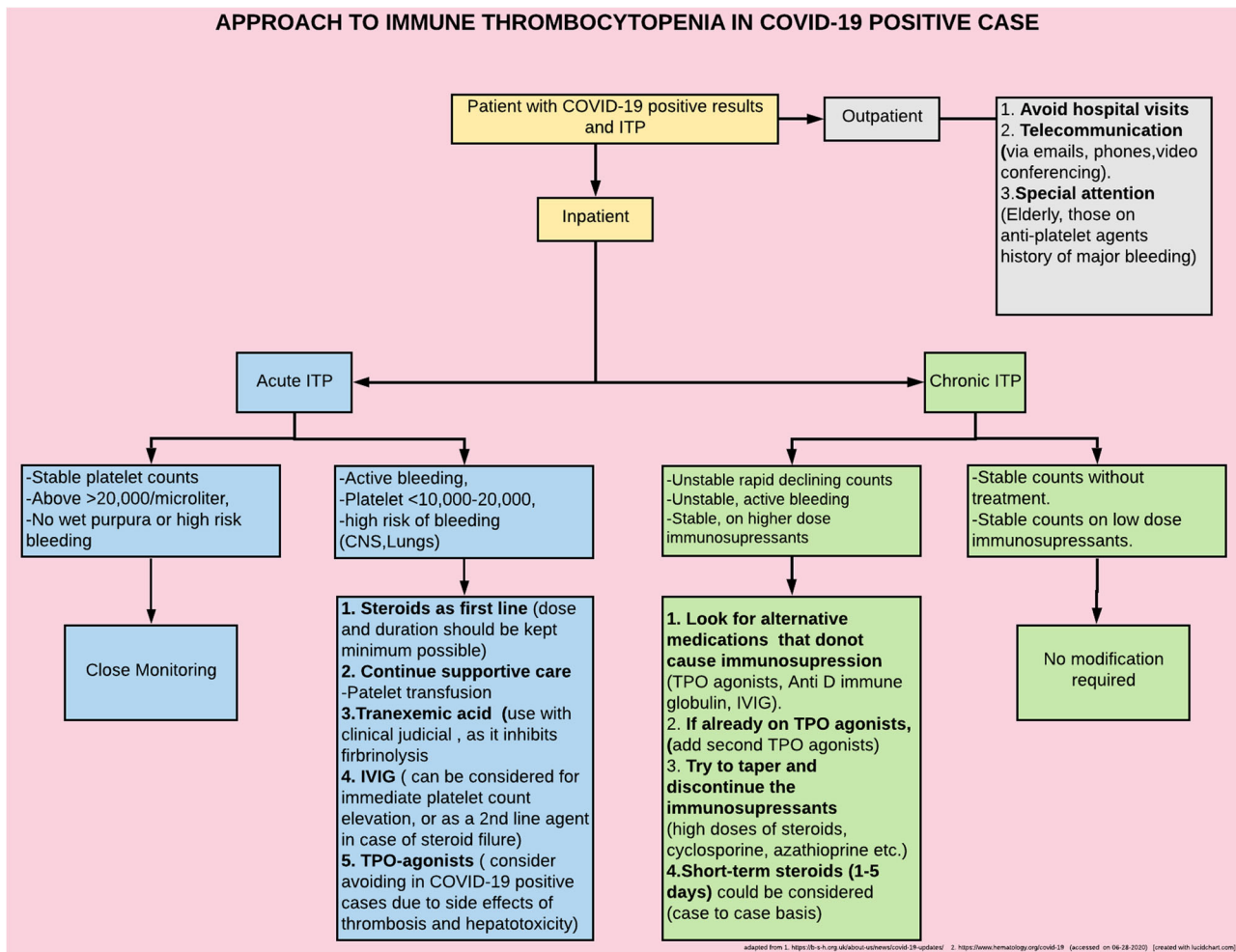


FIGURE 2 Proposed flowchart to approach ITP patients with COVID-19 (based on interim recommendations by American society of hematology and British society of hematology). CNS, central nervous system; COVID-19, coronavirus disease 2019; ITP, immune thrombocytopenia; TPO, thrombopoietin

recommendation varies based on whether the patient is on low dose versus high dose of immunosuppressants.^{12,13} ASH recommends smaller doses of steroids/immunosuppressants need not be changed, but recommends to consider tapering and possibly discontinuation of high doses by using alternative medications like TPO-RAs and/or IVIG.

6 | CLOSING THE KNOWLEDGE GAP OF PATIENTS WITH ITP DURING COVID-19 PANDEMIC

Patients with ITP may have some concerns about their risk to acquire COVID-19 or should they change or adjust ITP medications? It is particularly important to address these concerns because the COVID-19 pandemic is likely to sustain for at least a few months, if not years. British Society for Rheumatology suggested following

patients to be more vulnerable as compared with the others to COVID-19:

- Patients on corticosteroids ≥ 20 mg/day (0.5 mg/kg), prednisolone (or equivalent) for more than 4 weeks.
- Patients on corticosteroid dose of ≥ 5 mg/day prednisolone (or equivalent) for more than 4 weeks AND at least one other immunosuppressive medication or rituximab within the last 1 year.¹⁶
- Patients taking a combination of two immunosuppressants, including rituximab within the last 12 months AND an additional co-morbidity.

Patients should be encouraged to utilize the resources like telemedicine to reach out to their respective ITP clinics for immediate questions regarding their disease. Every attempt should be made to avoid unnecessary hospital visits and educating patients with proper resources could be a key factor to reduce their anxiety and motivate


Facts over Fear: Information for ITP patients regarding COVID-19 impact on their disease

Educate yourself: Impact on COVID-19 on ITP

- ⊕ SARS-CoV-2 infection can trigger episode of ITP.
- ⊕ ITP on its own doesnot predispose you to COVID-19.
- ⊕ Certain ITP drugs can reduced your immunity to fight.
- ⊕ If you are on following ITP drugs, it might reduce your immunity:
 - * Steroids, Cellsept, Azathioprine, Cyclosporine, Vincristine, Rituximab,
- ⊕ Following drugs doesnot effect your immune system:
 - * TPO agonists (Romiplostim, Eltrombopag)
 - * Intravenous Immunoglobulin
- ⊕ If you had splenectomy for ITP then:
 - * Take antibiotic prophylaxis (as per guidelines)
 - * Be Uptodate with Vaccination

Do's and Don't's for ITP patients during COVID-19

- ⊕ Donot change any ITP medication wiithout consulting your doctor.
- ⊕ If you are on immunosuppresents for ITP, be extra-diligent and seek urgent medical attention if develop COVID-19 like symptoms.
- ⊕ If your platelet count is <30,000/mm³ and/or having any bleeding symptoms , please call your doctor (donot visit urgent care unless active bleeding).
- ⊕ Many ITP consultations can be done over telemedicine, please maximise use of them than direct visits.
- ⊕ Keep yourself educated with latest and official updates:
 - * WHO, CDC (official websites)
 - * www.hematology.org/COVID-19 (ASH)
 - * bsh.org.uk/about-us/news/covid-19-updates



Regularly Sanitise
Hand Wash
Stay Hydrated
Avoid travel
Avoid gathering
Social distancing
Use televisits
Avoid direct visits
Donot panic, be informed

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FIGURE 3 Description of patient information (based on BSH/ASH) regarding ITP in COVID-19. ASH, American Society of Hematology; BSH, British Society of Hematology; COVID-19, coronavirus disease 2019; ITP, immune thrombocytopenia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TPO, thrombopoietin

them to keep following all the hygiene practices and social distancing (Figure 3).

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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