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Practical guidance for the management of adults with Immune Thrombocytopenia during the COVID-19 pandemic
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This document aims to provide practical guidance for the assessment and management of patients with Immune Thrombocytopenia (ITP) during the COVID-19 pandemic. The intention is to support clinicians and, although recommendations have been provided, it is not a formal guideline. Nor is there sufficient evidence base to conclude that alternative approaches to treatment are incorrect. Instead, it is a consensus written by clinicians with an interest in ITP or coagulation disorders and reviewed by members of the UK ITP forum.

Background

The current COVID-19 pandemic, caused by a novel coronavirus (SARS-CoV-2), poses a number of dilemmas for the investigation of thrombocytopenia and the management of patients with ITP.

This includes consideration of the advantages and disadvantages of standard therapeutic options for new or relapsed acute ITP, and recognition of the challenge posed to the management of ITP patients because of both bleeding and thrombotic risks seen in patients hospitalised with COVID-19 infection. Furthermore, patients may be unclear about the extent of required self-isolation procedures or whether there are safety concerns with the coronavirus vaccine.

Thrombocytopenia and COVID-19

COVID-19 infection induces platelet activation, aggregation and immunomodulatory activity, which plays an important role in the immunothrombotic coagulopathy seen in patients with this disease. There is evidence that the platelets themselves can contain the SARS-2 virus despite absence of angiotensin-converting enzyme 2 (ACE2) receptors by which the virus usually gains entry into cells (Zaid *et al.,* 2020). In addition to direct viral-mediated injury (Kolb-Maurer *et al.,* 2003), damaged platelets release cytokines and antimicrobial peptides and interact with leucocytes leading to a hyperinflammatory reaction (Manne *et al.,* 2020). This cytokine storm contributes to the multi-organ damage seen in severe and critical COVID-19.

Whilst this platelet consumption would lead to thrombocytopenia, the platelet count is relatively preserved by increased thrombopoietin production from liver stimulation and megakaryocytes in the lung producing large amounts of platelets (Thachil, 2020). Mild thrombocytopenia is common (Guan *et al.,*) but a count below 100 x 10^9/l is unusual, only occurring in around 5% of hospitalised patients and 8% of those on ITU (Huang *et al.,* 2020). In end stage COVID-19 infection multi-organ failure may exacerbate thrombocytopenia and pooled results of nine studies involving 1779 COVID-19 positive patients revealed that the platelet count was lower in those with very severe disease ($p<0.001$) (Lippi *et al* 2020). Indeed the lower the platelet count the worse the prognosis. This was supported by a large single centre study from Wuhan involving 1476 consecutive patients with COVID-19, showing mortality increasing with progressively lower platelet counts (Yang *et al.*, 2020). This is perhaps not unexpected as other studies of critically ill patients show thrombocytopenia to be a marker of poor clinical outcome (Nijsten *et al.,* 2000). Huang et al found 20% of COVID-19 patients who died had a platelet count <100 x 10^9/l, compared with 1% of survivors ($p<0.0001$) (Huang *et al.,* 2020).

Outside the context of end-stage COVID-19 disease, a very low platelet count of <20 x 10^9/l, or a sudden fall in the platelet count >50% over 24-48 hours is likely to indicate an immune aetiology. Causes such as thrombotic thrombocytopenia purpura and atypical haemolytic uraemia syndrome should be considered if there is associated microangiopathic haemolytic anaemia (MAHA) and, in the former, an ADAMTS13 level <10%. Experience of testing COVID-19 patients without TTP, has found ADAMTS13 levels of 20-40%, typical of other inflammatory states, and not surprisingly lowest levels reflect greater severity of COVID-19 disease and higher mortality risk (Bazzan, *et al.,* 2020). Drug induced thrombocytopenia develops at a median of 14 days after the onset of a new drug or sooner if there has been previous exposure. Heparin induced thrombocytopenia (HIT) occurs between 5 and 10 days after the first exposure, or within 24 hours of recurrent exposure. Autoimmune thrombocytopenia is a diagnosis of exclusion, there being no confirmative test.

Recommendation

Significant thrombocytopenia is uncommon in COVID-19 positive patients until end stage disease.

Very low platelet counts of <20 x 10^9/l, or a sudden fall in the platelet count >50% over 24-48 hours may indicate an immune aetiology.

Other causes of immune thrombocytopenia, such as HIT, MAHA and drugs, should be considered before a diagnosis of ITP is made.

Management of new/relapsed ITP

ITP per se does not pose increased risk of COVID-19 infection or worsening disease but like all viral infections, COVID-19 may trigger a new presentation of ITP, as illustrated in published case reports (Zulfiqar, 2020), or it may cause relapse in an existing patient. The indications for treatment remain unchanged from current consensus guidelines (Provan *et al.,* 2019) however, the additional potential burden of treatment in the context of the COVID-19 pandemic (for example greater hospital contact and immunosuppression and/or thrombotic risk) need to be carefully balanced against the risks of bleeding from ITP. The need for treatment should be case-based and depend on severity of thrombocytopenia (platelet count <20 x10^9/L), bleeding manifestations, bleeding risk, comorbidities and other medications such as anticoagulants. However the choice of treatment may differ depending on whether the patient is COVID-19 negative or positive.

Recommendation

ITP per se does not pose increased risk of COVID-19 infection or worsening disease and indications for treatment of ITP are no different during the pandemic. The need for treatment should be case-based and depend on severity of thrombocytopenia (platelet count <20 x10^9/L), bleeding manifestations, bleeding risk, comorbidities and other medications such as anticoagulants.

Choice of treatment may differ depending whether the patient is COVID-19 negative or positive.

First line therapy for COVID-19 negative patients

Usual first line therapy for the management of new or relapsed acute ITP is prednisolone, given at a dose of 1mg/kg (max 80mg) for 2 weeks and thereafter tapered off, slowly if there is a good response, or rapidly if treatment is ineffective (Provan D *et al.,* 2019). However during the COVID-19 pandemic, current guidance from the WHO is to avoid steroids if there are alternative treatment options (WHO 2020); there is concern that the immunosuppression will increase risk of COVID-19 infection and lead to more severe disease. Evidence with coronaviruses has shown steroids to delay clearance of the virus from the lower respiratory tract (Arabi *et al.,* 2018), and the recent RECOVERY trial showed that, whilst patients on ventilation derived significant benefit from dexamethasone, patients with less severe COVID-19 disease who received dexamethasone had a tendency to worse outcomes (Horby *et al.,* 2020).

Therefore, during the pandemic, thrombopoietin receptor agonists (TPO-RAs) are preferred as first line therapy for ITP in patients who are negative for COVID-19 infection as they are not immunosuppressive. Although this use is off-label there is growing evidence of the benefit of early use of TPO RAs in ITP (Arnold, *et al.,* 2020, Kuter, *et al.,* 2019, Lozano, *et al.,* 2020, Newland, *et al.,* 2016) and increasing experience amongst experts in the field. The practice has been endorsed by NHS England (NHSE 2020). One should be mindful that TPO-RAs can take 7-14 days before an effect is seen and if urgent platelet elevation is needed, intravenous immunoglobulin may be required.

First line therapy for COVID-19 positive patients

For patients who are COVID-19 positive, a concern with the use of TPO-RAs for initial treatment is the increased thrombotic potential, which might exacerbate thromboembolic risk in a patient with COVID-19. A recent in vitro study of samples from 26 patients showed that those with ITP (not in the context of COVID-19) had increased microvesicle-associated thrombin generation two weeks after initiation of TPO-RA treatment compared with controls and pre-treatment levels (Garabet *et al.,* 2020).

Systematic review of trials looking at clinical thromboembolic events has found higher rates in patients on TPO-RAs compared with controls (Catala-Lopez *et al.*, 2012) and a long-term clinical study of eltrombopag showed 6% of patients developed arterial or venous thrombosis (Wong *et al.,* 2017). There are similar findings with romiplostim but direct comparison with placebo, showed no increase in thrombotic risk (Cines *et al.,* 2017, Kuter *et al.,* 2019), however, as expected, risk of thrombosis increases with age (Kuter *et al.,* 2019).

Additionally, hepatobiliary events have been found to occur in 15% of patients on eltrombopag (Wong *et al.,* 2017) and the drug carries a black box warning for risk for hepatotoxicity. Although clinically significant liver injury has reported to be uncommon in COVID-19 (Bangash *et al.,* 2020), liver enzymes are usually elevated and the required monitoring of liver function tests throughout treatment with eltrombopag (Promacta®, 2018, Revolade, 2018), would be complicated.

Although there are no data on the use of TPO-RAs in COVID-19 positive patients, the risk of hepatotoxicity and potential for increased thrombosis would prompt caution with their use in this setting and, whilst further evidence is awaited, intravenous immunoglobulin may be the better first-line option for patients presenting with new or relapsed ITP during hospitalisation with COVID-19. The exception is those requiring supplementary oxygen or ventilatory support for COVID-19 infection, where dexamethasone 6mg daily for 10 days has been shown to reduce mortality (Horby, *et al.,* 2020).

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIg) may be the preferred option for patients with new or relapsed ITP, who are hospitalised with COVID-19 but not requiring supplementary oxygen or ventilation, as steroids may

worsen the course of their disease and TPO RAs may potentially increase thrombotic risk. The role IVIg may play in the management of patients with severe COVID-19 infection is unknown. A small retrospective study from Wuhan suggested that initiation of IVIg as adjuvant treatment for COVID-19 pneumonia within 48 hours of admission to intensive care may reduce the use of mechanical ventilation and promote earlier recovery of patients (Xie *et al.,* 2020).

For COVID positive ITP patients requiring treatment but who either fail to respond to IVIg alone, or need ongoing therapy, additional treatment with steroids or TPO RAs may need to be considered depending on the individual risk/benefit balance at the time.

In the outpatient setting, IVIg may be necessary if immediate elevation of the platelet count is required to control bleeding. However, administration requires hospital attendance, supply is short and whilst clinical complications are rare, they can be significant (Stiehm, 2013).

Tranexamic acid

Tranexamic acid (TXA), a fibrinolytic inhibitor, is helpful for ITP patients with bleeding. However in those infected with COVID-19 the inhibition of fibrinolysis may theoretically impair recovery from the associated microvascular thrombosis. Therefore, in a bleeding patient with COVID-19 disease, judgement should be made regarding the balance of risks associated with bleeding and thrombosis. If tranexamic acid is used, the duration of treatment should be kept to the minimum necessary. For oral bleeding, tranexamic acid mouthwashes can be given to rinse and spit out.

Interestingly, a recent report in Physiological Reviews proposed that the endogenous protease plasmin acts on COVID-19 virus by cleaving a newly inserted furin site in the S protein portion of the virus resulting in increased infectivity and virulence (Ji *et al.,* 2020). Blunting of this response with tranexamic acid has been postulated to reduce infectivity of the virus and an exploratory, randomised, placebo-controlled, double-blind Phase 2 clinical trial has been established (Ness, 2020).

Immunosuppressant drugs

There is concern that patients on immunosuppressant drugs may be at high risk of developing COVID-19 and/or the disease becoming more severe. However, unlike common viral agents such as adenovirus, rhinovirus, norovirus, influenza, and respiratory syncytial virus, coronaviruses have not been shown to cause a more severe disease in immunosuppressed patients (D'Antiga, 2020). Preliminary experience with patients on disease modifying agents for chronic arthritis and other immune-mediated inflammatory disease, is that they do not seem to be at increased risk of respiratory or life-threatening complications from COVID-19 than the general population (Monti, 2020, Haberman, 2020). Perhaps this is not unsurprising as the severe complications caused by this family of viruses are driven by the aberrant inflammatory and cytokine response perpetuated by the host immune system. Rituximab is responsible for long-lasting B-cell depletion and potentially severe infectious events and the impact of the drug on infection risk of COVID-19 is not clear. Furthermore it can decrease formation of de novo antibodies. Until further information becomes available, it may be prudent to avoid immunosuppressant agents and rituximab in new or relapsed patients during the COVID-19 pandemic if possible.

Platelet transfusions

Platelet transfusions are not usually necessary or helpful and should not be routinely offered to thrombocytopenic COVID-19 patients with no bleeding. They may exacerbate a prothrombotic state in

COVID-19 positive patients with coagulopathy and in patients with immune thrombocytopenia they are likely to be consumed too quickly to be of value. Platelet transfusions should only be given if it is considered that haemorrhage is life-threatening or in a critical site such as the eyes.

Recommendation

There is little evidence to inform the optimal management of a patient presenting with new or relapsed acute ITP.

In patients who are negative for COVID-19, TPO-RAs may be preferred as first line treatment, to avoid corticosteroids which may increase risk of COVID-19 infection during the pandemic.

In patients who are positive for COVID-19, TPO-RAs may potentially increase the thrombotic complications and identifying eltrombopag hepatotoxicity may be difficult.

Intravenous immunoglobulin (1g/kg) may be the preferred first-line option in ITP patients hospitalised with COVID-19 but not requiring supplementary oxygen or ventilation. IVIg may also be necessary if immediate elevation of the platelet count is required to control bleeding.

If steroids are used as first line therapy, the dose and duration should be kept to the minimum necessary. A starting dose of 20mg daily may be considered in non-bleeding patients, with increase to 1mg/kg after 3-5 days if there has been no response.

Steroid doses should be tapered after 2 weeks – slowly if there has been good response, rapidly if there is no response.

Patients with severe COVID-19 infection requiring supplementary oxygen or mechanical ventilation are likely to be on dexamethasone. If additional steroids are required for the ITP this should be in discussion with the ITU team.

Tranexamic acid in COVID-19 infected patients should be used as required for the management of bleeding in ITP patients, but avoided in those with frank DIC.

Platelet transfusions should only be given if bleeding is thought to be life threatening, or at a critical site.

Management of chronic ITP

Management of patients with chronic stable ITP should not alter because of the pandemic; patients should remain on their current medication, even if this includes steroids and immunosuppressants. However attention should be paid to COVID-19 prevention measures and self-isolation as appropriate. The British Society for Rheumatology provides helpful guidance on risk stratifying patients on immunosuppressants to identify those who are clinically extremely vulnerable (CEV) (Table 2).

Patients with splenectomy are probably not at increased risk of COVID-19 infection but are susceptible to bacterial infections and must be vigilant with their prophylactic antibiotics during this time and up to date with their pneumococcal, haemophilus influenza and meningitis vaccinations.

ITP patients not requiring treatment in the last 12 months, or on non-immunosuppressive agents such as TPO-RAs, are not considered to be at increased risk of COVID-19 infection and should comply with COVID-19 prevention and self-isolation measures as for all individuals in the UK.

Recommendation

Patients with chronic ITP should remain on their usual treatment.

They should be vigilant with COVID-19 prevention measures and self-isolation as appropriate.

Splenectomised patients should be stringent with their antibiotic prophylaxis and up to date with vaccinations.

Regular patient contact should be maintained, and appointments conducted by telephone or online platforms.

Thrombotic risk associated with ITP

ITP is associated with a mild elevation in thrombotic risk, with a cumulative incidence of 3.2% for arterial (95% CI, 2.0–5.0) and 1.4% (95% CI, 0.8–2.5) for venous thrombosis at 5 years (Ruggeri *et al.,* 2014). Risk may be slightly heightened by treatment-related factors such as splenectomy and TPO RAs and is higher where there are associated antiphospholipid antibodies. It is unknown how this combines with the hypercoagulable state associated with COVID-19 and whether the increment in thrombotic risk is negligible or synergistic. Circulating megakaryocytes are found in ITP and in COVID-19 and have been proposed to play a role in triggering thrombosis in these conditions (Thachil *et al.,* 2020).

Systematic review and meta-analyses of studies evaluating the incidence of venous thromboembolic events in patients with COVID-19 has shown an overall incidence of 21% (Malas *et al*., 2020). In patients with COVID-19 pneumonia in ITU, venous and arterial thromboembolic complications have been identified in 31% of 182 patients (Klok *et al.,* 2020). Predominantly these were described as pulmonary emboli (PE) (81%), with at least two thirds involving more than just subsegmental arteries. The rates of PE are recognised to be confounded by the counting of in situ microvascular thrombosis (known as immunothrombosis) a recognised expression of acute respiratory distress syndrome) (Desborough *et al.,* 2020).
Deep vein thrombosis is less frequent, although has been shown to increase with duration of hospitalisation and be significantly higher in ITU patients compared with those not on ITU (Middledorp *et al,* 2020). Low molecular weight heparin (LMWH) has been shown to reduce mortality in patients with COVID-19 associated coagulopathy (Tang *et al,* 2020), however in both of the above studies, the patients had been taking prophylactic LMWH, raising the question whether doses should be increased in patients with more severe disease. Use and dose of LMWH needs to be balanced against the bleeding risk which is seen in some patients with severe COVID-19 infection, even without thrombocytopenia (Wang *et al.,* 2020). Indeed the anticoagulant arm of REMAP CAP which compared therapeutic heparin with standard of care, has paused due to concerns of the data monitoring committee, of futility and possible increased rates of major bleeding in those on therapeutic heparin.
LMWH may need to be avoided if platelets are $<30 \times 10^{9}$/l (Hunt, *et al.* 2020) and intermittent pneumatic compression should be used. The LMWH should be recommenced once the platelet count can be raised above this threshold. Regular assessment of both bleeding and thrombotic risk is essential throughout the course of the hospital stay and upon discharge.

Recommendation

One should be mindful of a potential further increase in thrombotic risk in patients with COVID-19 from ITP or its treatment.

ITP patients hospitalised with COVID-19 should receive weight-based LMWH thromboprophylaxis provided platelets are >=30 x 10^9/l and there are no haemorrhagic features.

ITP patients hospitalised with COVID-19 whose platelets are <30 x 10^9/l in whom LMWH is considered unsafe, should have intermittent pneumatic compression until LMWH can be restarted.

Regular assessment of both bleeding and thrombotic risk should be made throughout the course of the hospital stay and on discharge.

Patient information

This is an anxious time for everyone and not least for those with autoimmune diseases. Contact with patients is important and reassurance that services will continue as normal but that outpatient appointments will be conducted by telephone or online face-to-face platforms wherever possible. Arrangements for blood tests and safe pick-up or delivery of medications should be made clear.

Patients should be provided with information regarding their risk stratification and whether they are considered clinically extremely vulnerable (Table 2). They should receive advice on COVID-19 protective measures and self-isolation as appropriate, maintaining mental well-being, and who to contact if they are feeling unwell with fever and cough or are having difficulty breathing.

They should also be made aware that COVID-19 infection, like all viral infections, may cause a relapse of their ITP and informed who to contact if they think their platelet count has dropped or if they experience bleeding or unusual bruising.

Recommendation

Hospital attendance should be kept to the minimum necessary, with outpatient appointments conducted by telephone or online face to face platforms where possible.

Patients should be provided with information regarding protective measures and requirement for self-isolation as appropriate, and given contact arrangements for COVID-19 related symptoms or suspected ITP relapse. Those who are considered clinically extremely vulnerable should be identified.

COVID-19 vaccine

ITP has been reported after vaccination for different viruses, possibly explained by molecular mimicry, or induced by adjuvants. Agents include measles-mumps-rubella (MMR), Haemophilus influenza, hepatitis B virus, human papilloma virus, varicella-zoster, diphteria-tetanus-acellular pertussis (DTap), polio, and pneumococcus (David et al., 2020). The COVID-19 vaccine trials have not reported this and whilst it remains a possibility, the risks are outweighed by the benefits of receiving the vaccine.

Patients who have received rituximab in the previous two years, or those on immunosuppressants, may not mount a full immune response to the vaccine, however, any immunity gained would be beneficial and the consensus is that patients should receive the vaccine when offered. None of the vaccines are considered live vaccines and although they have not been formally tested in patients on immunosuppressants there is no reason to think there will be safety concerns in this setting. All the evidence so far suggests the COVID-19 vaccines are very safe.

One should be mindful of the need to sustain pressure at the injection site for at least 5 minutes to avoid muscle haematoma. Ideally a platelet count of >30 x10^9/L is required but a lower platelet count should not

preclude it. It is of note also that epistaxis has been caused by the COVID-19 nasal PCR swab and avoidance or caution should be taken in patients with low platelet counts or a lateral flow test offered instead.

Once vaccinated, individuals should continue to follow government guidance around COVID-19 prevention measures such as social distancing and wearing masks.

Recommendation

COVID-19 vaccines are safe and are recommended for all patients with ITP with or without treatment.

The immune response to the COVID-19 vaccine may be reduced in patients following rituximab or immunosuppressants, but vaccination is advised as any immunity obtained will be beneficial.

Pressure at the intramuscular injection site should be sustained for at least 5 minutes in those with a low platelet count to avoid muscle haematoma.

Caution is advised with COVID-19 PCR test for patients with thrombocytopenia, as nasal swab may induce epistaxis.

Table 1: Practical recommendation for first line therapy for patients with newly diagnosed or relapsed ITP who need treatment

COVID-19 status	**Recommendation**
Negative	**Thrombopoeitin receptor agonists**
Positive	**Intravenous Immunoglobulin**
Requiring supplemental oxygen or ventilation	**Corticosteroids**

Table 2: Identification of those who are considered clinically extremely vulnerable

All individuals should follow the tier restriction guidance and stay up to date with Government advice.

Clinically extremely vulnerable (CEV) patients are strongly advised to pay particular attention to COVID-19 protective measures.

Clinically extremely vulnerable patients

Guidance from the British Society for Rheumatology suggests inclusion of the following immunosuppressant regimes in the CEV group:

- Corticosteroids ≥20mg (0,5mg/kg) prednisolone, or equivalent, per day for > 4 weeks
- Corticosteroid dose of ≥5mg prednisolone (or equivalent) per day for >4 weeks plus at least one other immunosuppressive medication (e.g. azathioprine, mycophenolate, ciclosporin) or rituximab within the last 12 months.
- A combination of 2 immunosuppressive medications including rituximab within the last 12 months plus an additional co-morbidity (age >70, Diabetes Mellitus, any pre-existing lung disease, renal impairment, any history of Ischaemic Heart Disease or hypertension).
- Splenectomy with ongoing immunosuppressive agents. (Authors' added guidance)

Summary of general COVID-19 protective measures:

1. Maintain strict social distancing (2 meters), wash or sanitise hands regularly, avoid touching face
2. Keep number of social interactions as low as possible
3. Avoid mixing with people who are not in the same household or support bubble
4. Maintain good ventilation and airflow indoors when mixing with people
5. Work from home wherever possible
6. Avoid travelling in peak hours
7. Receive deliveries of food and medicines as necessary.
8. Strict avoidance of contact with someone who is displaying symptoms of COVID-19.
9. Avoid gatherings, including friends and families in private places
10. Use remote technology for contact (phone, internet, social media).

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