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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 thrombocytopenia, with a particular focus on 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 are often unclear about the extent of required self-isolation procedures.

Thrombocytopenia and COVID-19

Thrombocytopenia was described in 36% of patients hospitalised with COVID-19 in one of the early studies (Guan *et al.*, 2020), although subsequent researchers have confirmed this is usually mild. The hyper-inflammatory state and cytokine storm induced by the viral infection results in a prothrombotic state and likely endothelial and platelet activation occurs (Violi, 2020). Thrombocytopenia is usually multifactorial in critically ill patients. Its pathogenesis is likely to be more complex than the conventional model of platelet consumption associated with thrombin-mediated platelet activation, and the use of antibiotics, antivirals, heparin and other commonly used agents, as well as haemodialysis and extracorporeal membrane oxygenation (ECMO) may contribute in some cases. Furthermore, platelet production may be affected by direct viral insult to

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the bone marrow (Kolb-Mäurer *et al.*, 2003) or reduced effect of thrombopoietin (Assinger, 2014). 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 recent 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 $< 100 \times 10^9/l$, compared with 1% of survivors ($p < 0.0001$) (Huang *et al.*, 2020).

Despite the numerous potential causes of thrombocytopenia in COVID-19 positive patients, a count below $100 \times 10^9/l$ is unusual, only occurring in around 5% of hospitalised patients and 8% of those on ITU (Huang *et al.*, 2020). Postulated mechanisms for the relative preservation of platelet count are increased thrombopoietin production from liver stimulation and megakaryocytes in the lung producing large amounts of platelets (Thachil, 2020). Very low platelet counts of $< 20 \times 10^9/l$, or a sudden fall in the platelet count $> 50\%$ over 24-48 hours is likely to indicate an immune aetiology, although this can also occur in the pre-terminal stages of COVID-19. Immune 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. 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 $< 20 \times 10^9/l$, 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

Like all viral infections, COVID-19 may trigger a new presentation of ITP, as illustrated in a recently published case report (Zulfiqar, 2020), or it may cause relapse in an existing patient. The need to actively treat ITP is 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. Treatment decisions may differ depending on whether the patient is COVID-19 negative or positive.

First line therapy for COVID-19 negative patients

Standard 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 *et al.*, 2019).

There are few data to inform whether or not steroids pose a higher risk of the development of COVID-19 infection or worsening symptoms once infected. However, current guidance from the WHO is to avoid steroids if there are alternative treatment options (WHO 2020). In patients who are negative for COVID-19 infection, using thrombopoietin receptor agonists (TPO-RAs) as first line therapy may be the preferred option. This use is off-label and local funding may need to be sought through the COVID-19 Interim Measures scheme. 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, the treatment dilemma is even more pronounced. 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 standard treatment with steroids may be the preferred option for initial treatment. There is concern about potential higher risks of mortality and secondary infection, which were seen in a systematic review of observational studies of corticosteroids in patients with influenza; however, most of the included studies reported on patients receiving high steroid doses (>40mg methylprednisolone per day) and the evidence was judged as very low to low quality, owing to confounding by indication (Lansbury *et al.*, 2019). Another study that addressed this limitation by adjusting for time-varying confounders found no effect on mortality (Delaney *et al.*, 2016). Finally, a recent study of patients receiving corticosteroids for MERS used a similar statistical approach and found no effect of corticosteroids on mortality but delayed clearance of MERS-CoV from the lower respiratory tract (Arabi *et al.*, 2018).

Thus, whilst further evidence is awaited, steroids may be the better option for COVID-19 positive patients presenting with new or relapsed ITP; however the dose and duration of treatment should be kept to the minimum necessary. Starting doses of 20mg daily (regardless of patient's weight) may be considered in non-bleeding patients, and increasing after 3-5 days if no response. Long courses of steroids should be avoided, and the usual recommendation of tapering after 2 weeks should be adhered to.

Intravenous Immunoglobulin

Intravenous immunoglobulin (Ivlg) may be necessary if immediate elevation of the platelet count is required to control bleeding, although this cannot be relied upon as indicated in a recent case report of ITP occurring in the context of COVID-19 infection (Zulfiqar, 2020). Ivlg may also be used as second line treatment if there is failure to respond to steroids. However, administration requires hospital attendance, supply is short and whilst clinical complications are rare, they can be significant (Stiehm, 2013).

The role Ivlg may play in the management of patients with severe COVID-19 infection is unknown. A small retrospective study from Wuhan suggested that initiation of Ivlg 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). In the absence of adequate titres of neutralizing antibodies, standard Ivlg is unlikely to have a biologic effect on COVID-19. Preparations of anti-SARS-CoV-2 polyclonal and monoclonal antibodies are being developed but currently routine use of Ivlg from COVID-19 patients is not recommended (Alhazzani 2020).

Tranexamic acid

Tranexamic acid (TXA) inhibits fibrinolysis and while it is contraindicated in frank DIC, the COVID-19 associated coagulopathy (CAC) does not fulfil the ISTH criteria for DIC. However localised fibrin thrombi occur in the alveolar capillaries and small vessels in association with inflammation and alveolar damage (Fox *et al.*, 2020), and endogenous fibrinolysis breaking down the disseminated thrombi could theoretically aid recovery from this. 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 is being 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 thrombopag hepatotoxicity may be difficult.

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.

Intravenous immunoglobulin (1g/kg) may be necessary if immediate elevation of the platelet count is required to control bleeding. It may also be used as second line treatment if there is failure to respond to steroids.

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 to isolation procedures is crucial. The British Society for Rheumatology provides helpful guidance on shielding measures for patients on immunosuppressants (Figure 1).

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 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 self-isolation and shielding measures 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.

Venous and arterial thromboembolic complications have been identified in 31% of 182 patients with COVID-19 pneumonia in ITU (Klok *et al.*, 2020). Predominantly these were pulmonary emboli (81%), with at least two thirds involving more than just subsegmental arteries. Deep vein thrombosis was less frequent in this study, although has been shown to increase with duration of hospitalisation and be significantly higher in ITU patients compared with those not on ITU (Middeldorp *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.

LMWH also has anti-inflammatory and anti-platelet properties which may be of benefit in these patients but 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). 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 $\geq 30 \times 10^9/l$ and there are no haemorrhagic features.

ITP patients hospitalised with COVID-19 whose platelets are $<30 \times 10^9/l$ 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

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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.

They should be provided with information regarding self-isolation procedures and shielding (Figure 1), 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 self-isolation and shielding procedures and given contact arrangements for COVID-19 related symptoms or suspected ITP relapse.

Figure 1

Patients who should be shielding

The Government strongly advises people with serious underlying health conditions to follow shielding measures. Guidance from the British Society for Rheumatology suggests inclusion of the following immunosuppressant regimes

- Corticosteroids $\geq 20\text{mg}$ ($0,5\text{mg/kg}$) prednisolone, or equivalent, per day for > 4 weeks
- Corticosteroid dose of $\geq 5\text{mg}$ 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)

Shielding measures include

1. Staying in the home and receiving deliveries of food and medicines as necessary.
2. Strict avoidance of contact with someone who is displaying symptoms of COVID-19.
3. Avoiding gatherings, including friends and families in private places
4. Using remote technology for contact (phone, internet, social media).
5. Register for the Government helpline for vulnerable people
www.gov.uk/coronavirusextremely-vulnerable or call **0800 0288327**

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