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ITP: Diagnosis including Secondary ITP, and Selection of Second Line Treatment
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This article summarizes our approach to the diagnosis, secondary ITP, and choice of second line options in patients with immune thrombocytopenic (ITP). We very briefly summarize first-line treatment and then utilize a case-based approach. We will first explore persistent-chronic ITP in a younger female. We consider many possibilities beyond primary ITP e.g., hypogammaglobulinemia, chronic infection, and anemia, and how to approach their diagnosis and management. The journey continues throughout pregnancy and post-partum and eventually includes fourth-line treatment after a late relapse. We then consider an older male, emphasizing differences in diagnostic considerations and management. The focus is on initiation and continuation of second line treatment, pros and cons of each option, and briefly the impact of treatment choices related to endemic presence of SARS-CoV-2. During review of potential second-line treatment options, we also briefly touch upon novel treatments. Finally, there is a short section on refractory disease drawn from our extensive review in Blood in February 2020(1). The clinical nature of the discussions replete with figures and tables and with interspersion of pearls regarding efficacy and toxicity at different ages and genders, will serve the reader in management of “typical” adult patients who develop persistent and chronic ITP.
ITP is a complicated disease because of its heterogeneity and lack of diagnostic markers making selection of treatment difficult. Perhaps the most straightforward part of management is at presentation of ITP. If the platelet count is very low and no other findings are present, the worldwide consensus treatment is steroids. Whether dexamethasone (dex), prednisone/prednisolone (pred) or IV methylprednisolone (MP) is used, the results are relatively predictable as to response rate and side effects. IV MP or dex increase the platelet counts faster and may have less side effects than do weeks of pred(2). Questions revolve around whether to add IV Immunoglobulin (IVIG), and/or platelet transfusion. While the latter is rarely appropriate if there is serious bleeding and/or the diagnosis is unclear, a medical-records-based analysis in the United States identified that as many as 25% of ITP patients receive platelet transfusion(3), far too often.

Management of ITP becomes more complicated if other findings arise, if patients do not respond to steroids, or if patients continue to require treatment. Both the ASH guidelines and the International Consensus reports heavily emphasized that continued steroid use beyond 6 weeks is to be avoided care(4, 5). Compliance with this strong recommendation entails earlier use of “second line” therapy in patients with ITP, a practice already gaining traction. However, the definition of “early” remains fluid; “early” can be at 1 month of steroid treatment to allow discontinuation of steroids. “Early” can also be in the first 3 months when ITP is “newly diagnosed(6). These ill-defined distinctions are one reason for substantial variation in management of ITP. Another is the uncertainty of diagnosis. A third, the focus of this discussion, is how to select second line treatment.

This review will focus on initiation of second line treatment reviewing the pros and cons of different agents utilizing a case-based approach by first exploring ITP in a young female and continue throughout a pregnancy. It will then outline diagnostic considerations and management in. an older male with particular attention to secondary ITP in both patients.

**Section I. Young female patient with ITP: Second Line Options**

**Patient History**
A 20-year-old female returns home from college. She notes heavier periods and easy bruising. Her internist sees that she appears pale and has visible petechiae on her arms. Complete blood counts show mild anemia (hemoglobin 10.2 g/dL) and thrombocytopenia with platelets 5 x 10^9/L. The internist sends her urgently to the emergency room concerned that she might possibly have leukemia. There is no hepatosplenomegaly or lymphadenopathy or other abnormal findings on physical examination.

Review of peripheral blood smear indicates absence of blasts or abnormalities of other cell lines although her mean corpuscular volume (MCV) is low (72 fL) and several of her very few platelets are large. She is diagnosed with ITP and receives prednisone 1mg/kg. Over the next few days, she has typical steroid-related side effects: feeling “a little crazy”, insomnia and abdominal pain. Her bruises and petechiae disappear, and her period ends. Her hematologist prescribes oral
iron supplements and changes her pred to dex 40 mg daily for four days. Her steroid-related side effects worsened during the four days on dex 40 mg; however, she soon felt better with no further petechiae, bruising, or menstrual bleeding noted.

Her platelet count normalized to 147 x 10^9/L and her hemoglobin improved to 11.2 g/dL. She began checking her counts monthly. The improved Complete Blood Count (CBC) with a nearly normal Mean Cell Volume (MCV) excludes marrow failure, and also thalassemia trait or microangiopathic hemolytic anemia. Similarly, the normal hemoglobin and neutrophil count does not suggest Evans’ syndrome. Her platelets remain normal range and her hemoglobin improves to the normal range. Next visit, her platelets have decreased to 80 x10^9/L. One month later, her platelets are 28 x10^9/L with continued normal hemoglobin and infrequent small bruises. With her platelets trending downward, second-line treatment for her ITP is considered.

There is less urgency to consider secondary ITP or a missed diagnosis since she has done well but at any change of management, it is good practice to re-evaluate. Below we consider some of the “what if” clinical scenarios for this young female.

What if the patient had been persistently anemic despite iron supplementation?
If the MCV is low, consider workup for underlying thalassemia trait or iron deficiency with the latter common in the setting of heavy menses. Iron replacement is not always straightforward; using oral replacement every other day may be equally effective as daily administration(7). Resorting to IV iron may be important especially if oral replacement does not correct iron status and/or there are signs of chronic inflammatory disease. If the MCV is high, marrow failure must be considered. There could also be pernicious anemia secondary to B12 deficiency or autoimmune hemolytic anemia, Evans’ Syndrome. Another possibility is microangiopathic anemia with thrombocytopenia, whether thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS). In these cases, there would likely be increased reticulocytosis. While individually each of these conditions is rare, having one of many rare conditions would not be as surprising.

If heavy menstrual bleeding persists, a progesterone-based approach is superior to an estrogen-based approach in women with ITP as it raises the platelet count (8). While estrogen-based therapies are more commonly used in general practice for heavy menstrual bleeding, they might worsen the ITP (9). In contrast, progestestational agents have previously been tried as treatment in ITP with good effect. Progesterone may be administered orally at 5-10 mg daily or medroxyprogesterone acetate (Depo-Provera) can be given IM once every 3 months but the latter may result in intermittent vaginal bleeding.

What if the ITP was part of a larger spectrum of autoimmune disease?
Her immunoglobulins were normal, so she does not have Common Variable Immunodeficiency (CVID) or IgA deficiency. Neither the diagnosis of CVID nor IgA deficiency require a history of infections; in fact, there may be a history of autoimmunity especially in a patient presenting with ITP, or allergy. Furthermore, diagnosis of CVID is often not made until after the age of 30 (10). The IgG level does not have to be very low in cases of CVID presenting as ITP which may account for the lack of infectious history in many of these patients. In cases of
CVID, and possibly systemic lupus erythematosus (SLE) with ITP, there may have been an episode of ITP years before treated with steroids with the patient having gone into remission for years without any medication (Charlotte Cunningham-Rundles, personal communication). Other immunodeficiency states are also associated with ITP, not all of which will include hypogammaglobulinemia (11).

At our patient’s age and gender, one would not be surprised if she had a positive ANA and was developing SLE. A study from France suggests that hydroxychloroquine may be considered in an ITP patient with a positive ANA (12). Nor would it be surprising if her thyroid testing was abnormal, as thyroid disorders in young women with ITP are usually autoimmune (13-16). In a young woman, there is a relatively high rate (as high as 5-10%) of abnormalities of thyroid function and this finding may be more frequent in women with ITP. The question remains if these conditions should be tested for in all patients or only if there are suggestive findings. If the patient is fatigued that would necessarily instigate an evaluation of underlying causes that would include hypothyroidism. Fatigue and depression are relatively common but poorly understood in ITP (17), thus requiring evaluation to be comprehensive.

What if the ITP is secondary to a subclinical viral infection?

Multiple viruses have been associated with ITP. In children, ITP is often thought to be a post-infectious sequela. There also may be underlying viral disease which is asymptomatic and thus elude detection. It remains unclear if all patients with ITP should be screened for hepatitis C and HIV; with the coronavirus pandemic, it might be appropriate to screen for SARS-CoV-2 (18). Treatment of these 3 viral infections would alter ITP management. For both hepatitis C and HIV, primary treatment for these 2 agents likely would increase the platelet count. However, if hepatitis C has progressed to cirrhosis, the platelet effects of antiviral treatment may be limited. Another viral infection that could be subclinical is CMV which might be revealed only by atypical lymphocytes and/or mildly elevated liver tests. CMV can worsen ITP in patients receiving immunosuppressive treatments because these agents will activate the CMV and thus worsen the ITP making it more resistant to treatment(19, 20). H pylori may “cause” ITP but only in certain places, eg Japan and Italy, is searching for it at diagnosis of ITP routine and is its eradication a uniformly effective approach to ITP (21).

What if she has an inherited thrombocytopenia (IT)?

As her bleeding resolved in parallel with the improvement of her platelet count, this suggests that our patient does not have platelet dysfunction as seen in Bernard-Soulier or Wiskott-Aldrich syndrome, nor does she have any syndromic features manifested consistent with an It. Review of her prior records reveals that she has had at least one prior normal platelet count. The stability of the counts after initial treatment excludes cyclic thrombocytopenia which is an often-forgotten form of inherited thrombocytopenia (22). There are very many forms of IT and new ones seem to be discovered regularly. Certain features should suggest an IT (23, 24): 1) presence of other family members with thrombocytopenia; 2) no past normal platelet count; 3) too many too large platelets on smear (not all IT have macrothrombocytes but most do); 4) features of a syndrome e.g. Thrombocytopenia Absent Radius Syndrome (TAR); 5) failure to
respond to ITP treatment such as IVIG and steroids: 6) bleeding out of proportion to the platelet count e.g., Bernard-Souillier, Wiskott-Aldrich Syndrome (WAS), RUNX-1; and 7) a relatively stable platelet count. In the absence of an apparent specific syndrome, whole exome screening may be helpful, however this approach is effective in less than half of such cases (25). Ideally this possibility would be explored in conjunction with an experienced geneticist. A primary reason to identify the specific diagnosis is not only for the platelets per se, but for the associated medical problems with it including propensity for autoimmunity, malignancy, or bone marrow aplasia.

**What if the ITP is secondary to other blood disorders?**

While chronic lymphocytic leukemia (CLL) and myelodysplastic syndrome (MDS) would be very unlikely at this young age, other clinical conditions could be present such as autoimmune lymphoproliferative syndrome (ALPS) and SLE. Which tests are performed to search for specific conditions, even if there are no specific symptoms or conditions suggesting a particular entity, remains undecided. We perform immunoglobulin levels and thyroid testing in our patients, certainly in this one. Ideally in the future there would be an established panel of testing for patients with putative ITP that would explore inherited thrombocytopenias, marrow failure, secondary ITP, other diagnoses that could resemble ITP such as MDS, and markers of the future course of the ITP, the degree of bleeding, and to which treatments the patient would respond best.

**Which Second Line Treatment is Optimal for a Young Female?**

There are numerous options that can be considered in this non-pregnant premenopausal female (table 1)

**Rituximab**

Rituximab and other (generic) anti-CD20s are monoclonal antibodies that exert immunosuppressive effects by depletion of B lymphocytes. This occurs uniformly in the blood and bone marrow but what happens to B cells in lymph nodes is not well-defined. Women under the age of 40 years with < 2-year history of ITP respond to rituximab with a high response and especially “cure” rate (26). If our patient and her hematologist opted for rituximab, she would receive four infusions of 375 mg/m2 weekly for 4 weeks. If there is a good response, close monitoring may not be needed. While studies have not determined the optimal dose, 375 mg/m2 x 4 weekly doses is the most common dose. If there is a good response, close monitoring may not be needed. While studies have not determined the optimal dose, 375 mg/m2 x 4 weekly doses is the most common dose. The addition of dex to the rituximab may provide extra “curative” effect via its anti-plasma cell effect, though this also increases the risk of hypogammaglobulinemia. It will reduce the first-infusion side effects of rituximab, and our patient could stop the dex after one or two cycles if she does not tolerate it well instead of completing 3 cycles.

It is prudent to check immunoglobulin levels to rule out CVID and a hepatitis B panel prior to starting rituximab. The risk of COVID and delayed vaccination are in addition to other potential side effects such as first infusion reactions, serum sickness, and even the very rare possibility of progressive multifocal leukoencephalopathy (PML). If the patient combines dex and ritux, there is a 10-20% possibility of developing hypogammaglobulinemia which may necessitate IVIG for a few months even in those who start out with normal Ig levels. Combining that with the issue of
being unable to receive a vaccination for COVID reduces the benefit/risk of rituximab treatment substantially despite the curative potential. If the coronavirus pandemic wanes, this may be less of a consideration. If treatment with rituximab is delayed too long in this woman, the chance of “cure” may be reduced.

Her immunoglobulin levels are normal and she does not have hepatitis B surface antigen, so the risks of aggravated hepatitis B and hypogammaglobulinemia are less substantial. For more information on rituximab (27).

The current COVID pandemic, either after vaccination and/or infection, affects ITP and may impact patients who are on second-line ITP options. Post infection or vaccination ITP treatment guidelines are summarized in table 2. This patient should be vaccinated for SARS-CoV-2 at least 5-8 weeks before initiating rituximab to have time to receive and fully respond to both doses of Moderna and Pfizer vaccines. It might be optimal to wait a little longer afterwards to sustain the vaccine effect. If the patient were not vaccinated prior to rituximab, she would be unable to be vaccinated for SARS-CoV-2 for at least six if not 12 months (28); this would also apply to a booster vaccination (Table 2). The vaccination might affect her platelet count although she is not in a high-risk group which includes those who had prior splenectomy and/or ≥5 lines of previous ITP treatment (29). Limited information is available in ITP patients undergoing rituximab therapy in regard to developing severe COVID infection. In CVID and especially agammaglobulinemia patients, the ability to clear the SARS-CoV2 virus may be limited, and a patient may remain PCR-positive for weeks or even months.

On the one hand, rituximab with dex sounds good because, after the four weekly infusions if she responds well, she can then be checked relatively infrequently afterward. On the other hand, the effects on response to COVID vaccination are clinically significant. There appears to have been a marked decrease in rituximab use in ITP since the onset of COVID.

Other Immunomodulating Agents
Previously, immunomodulating agents were widely used second-line treatments, but drawbacks include the need to wait 1-3 months for the platelet count to increase, side effects (depending on the agent) such as hepatic toxicity, and the need to take these medications consistently long-term (5). If a single agent is used, the risk of infection despite the immunosuppression seems very small, but for these agents, efficacy is < 50%. This group is lumped together as if all agents are the same; it potentially includes mycophenolate mofetil (MMF), danazol, dapsone, azathioprine, cyclosporine, and cyclophosphamide.

Recently, a randomized controlled trial of steroids with or without MMF within 1 week of diagnosis of ITP demonstrated a higher “cure” rate in the combination arm (30). One surprise was that quality of life was significantly lower on the combination arm despite a better platelet response. Another surprise was that more than 50% of patients on the steroid alone arm were cured despite a low rate of dex usage and that 27% of the patients were over 65 years of age. The study nonetheless highlighted the potential advantage of earlier use of second line treatment.

There are at least twenty studies of danazol, almost all of which demonstrated a positive effect on platelet counts; it induces facial hair and acne and may have hepatic toxicity. Dapsone,
beyond an immunosuppressive effect, induces hemolysis which mimics IV anti-D; in patients with G6PD, hemolysis can be severe. Azathioprine has a long-standing history of use in ITP and a contributing safety base in pregnancy in patients taking it following kidney transplantation; it may have hepatic toxicity in 1%. We reported its combination with danazol with good results in 13 of 17 difficult patients(31). Cyclosporine repolarizes cell membranes which shuts down cell membrane pumps that extrude therapeutic agents from the cell. This may reinstate the effect of certain treatments e.g., steroids. Finally, cyclophosphamide can be given IV or PO. The best results appear to occur when using it IV with 2-3 infusions (32). Mechanistic information supporting the use of cyclophosphamide is that it has anti-plasma cell effects and that it spares megakaryocytes and platelets. There are well-known substantial side effects with cyclophosphamide: hematuria, bladder fibrosis, immunosuppression, and nausea and vomiting.

**Thrombopoietin receptor agonists (TPO-RA)**

Another option for second line therapy would be a thrombopoietin receptor agonist (TPO-RA). The primary advantages are the high response rate and low likelihood of induction of malignancy or other irreversible toxicity. The primary toxicity is development of venous and arterial thrombosis. If this young woman were on birth control, there may be an added risk for thrombosis.

There are three TPO agents currently available in the United States and Western Europe: romiplostim (33), eltrombopag (34) and avatrombopag (35); their efficacy and toxicity is outlined in a recent review, including discussion of class effects such as headache, myalgia, and thrombosis (36). The mechanisms of effect of these agents differ in where they bind to the TPO-receptor, in RNA upregulation of transcription factors by romiplostim and eltrombopag (37), and by the essential role of intracellular iron chelation by eltrombopag (38). The clinical importance of these mechanistic differences is “confirmed” by “switch studies” in which one of romiplostim or eltrombopag was effective when the other was not (39, 40). Recent studies demonstrated that switching from one of these two TPO agents to avatrombopag was also often effective (29, 41). Toxicity and efficacy do not substantially differentiate the 3 agents although one article suggests that romiplostim maintains efficacy at higher endogenous TPO levels than does eltrombopag(29) and eltrombopag is thought to have higher rates of transaminitis(34, 36).

**Eltrombopag.** Eltrombopag is an oral TPO-RA which requires a very empty stomach ideally two hours before and after taking it which is intimately related to its requirement to chelate intracellular iron as an integral part of its mechanism of effect(38). If eltrombopag has chelated calcium or iron during ingestion, it cannot chelate intracellular iron and thus will be ineffective. Eltrombopag requires monitoring of liver function tests (LFTs), as hepatotoxicity is considered common (1-10%) and 3% of adults and children cannot tolerate eltrombopag for this reason (36).

**Romiplostim.** Because romiplostim is injected subcutaneously weekly, there are no questions of absorption or compliance. There may be more cycling of the platelet count as compared to the oral TPO agents, likely because of its weekly instead of daily administration. As with all the TPO agents, making small changes in dosing will limit the likelihood of cycling. Development of antibodies to romiplostim, neutralizing and non-neutralizing, is more common in children than
adults (44); however, these antibodies have surprisingly little effect on clinical efficacy for reasons that are not clear. Myalgia may be more common with romiplostim. As of this writing, romiplostim can be patient self-injected in Europe but not the United States.

Avatrombopag. Avatrombopag, a second oral TPO-RA, has the least data describing its use. It is taken once daily using only tablets of 20 mg with dose ranges from 20 mg by mouth once a week to 40 mg (2 tablets) daily. There is very limited long term usage data. In one study, avatrombopag was associated with a 16.5% incidence of thrombosis but this likely was an artifact of small patient numbers (42). Two recent studies testified to its effect in patients not responding to romiplostim and/or eltrombopag (29, 41). It is recommended to be taken with food so that absorption will be more consistent.

The use of a TPO agent would have much to recommend it for this young woman (43, 44). There is no reason to suspect that it adversely impacts the clinical course of COVID if an infection were to occur although there may be an additive risk of thrombosis (29). In the COVID pandemic, the oral agents would be preferred over romiplostim to lessen SARS-CoV2 exposure secondary to weekly attendance at an outpatient department. Local laboratory counts and virtual visits lessen this risk for patients; home nursing visits for injections would do the same.

Fostamatinib
Fostamatinib is a first-in-class orally-active spleen tyrosine kinase (Syk) inhibitor indicated for treatment of ITP. The primary studies underestimated its efficacy; the trial population had more than 8 years median duration of ITP and 47% of patients had failed a TPO agent (45, 46). While the starting dose is 100 mg bid, 89% of responders increased to 150mg twice daily. Long-term use and in vitro experiments have suggested that fostamatinib is anti-thrombotic but not pro-hemorrhagic because blocking Syk reduces signaling via the C-type lectin-like type II transmembrane receptor (CLEC2) and (glycoprotein VI) GPVI pathways. These two pathways have less redundancy in thrombosis than in control of bleeding. Fostamatinib also is thought to be anti-inflammatory and potentially useful in COVID, independent of any platelet effects (47). On the other hand, of all approved second-line agents for ITP, it may be the least tolerable. It increases blood pressure in most recipients and there are relatively frequent GI effects either nausea with very occasional vomiting or development of diarrhea; 5% of patients may develop transaminitis. There has not been evidence of increased infection frequency or severity even though Syk is in macrophages as well as B cells and other cells.

Splenectomy
The ASH guidelines and International Consensus report recommend splenectomy be delayed at least 1 year from ITP diagnosis, since the rate of resolution of ITP within the first 1-3 years of disease appears substantial even in adults (4, 5). Laparoscopic splenectomy is infrequently complicated by peri-operative problems; response rates are initially 80% which relapse reduces to 60%. Late relapse beyond 2 years post-splenectomy is very uncommon. Whether delaying splenectomy reduces its efficacy is a concern; a recent study from France(48) suggests that efficacy is maintained, and some patients responded better to TPO agents after splenectomy.

There are long-term risks of adverse effects of splenectomy which are clinically significant, including not only overwhelming sepsis but also thrombosis especially stroke. The risk of sepsis
is based on less efficient blood stream phagocytosis and exacerbated by low antibacterial antibody levels. Pneumococci are a more frequent cause of post-splenectomy sepsis than all other infections combined(49); following splenectomy, individuals also have an elevated risk of encapsulated Gram-negative pathogens, i.e., *Capnocytophaga canimorsus* and *Bordetella holmesii*, and also intraerythrocytic parasites, i.e. malaria and *Babesia*, as noted in a recent review of post-splenectomy infections(50).

Providing patients appropriate and timely immunizations for pneumococci, *Hemophilus influenzae* B, and meningococcus, antibiotic prophylaxis, education, and prompt treatment of infection mitigates this risk(51); when to repeat pneumococcal and other vaccinations remains unclear. While vaccination appears more effective if given at least 2 weeks prior to splenectomy, vaccination can be administered post splenectomy if there is not time pre-splenectomy or if vaccination would likely be ineffective if the patient is receiving high dose immunosuppression or recent rituximab.

Thrombosis post-splenectomy was not initially appreciated. Population studies using a Danish registry identified it as a risk, particularly risk of stroke, with confirmation in other populations, e.g. the Nurses’ Health study(52). Splenectomy for hemolytic anemias has been complicated by pulmonary hypertension, with mitigation by partial splenectomy and reduction in the use of splenectomy. While partial splenectomy may “hit the sweet spot” by reducing RBC phagocytosis but maintaining enough phagocytosis to prevent pulmonary hypertension and sepsis. The apparent absence of pulmonary hypertension after splenectomy for ITP, suggests that partial splenectomy, like splenic embolization and radiation, is very rarely if ever used.

**How we treated the young woman with refractory ITP**

As this woman could not taper her prednisone successfully, still has bleeding, and has a count < 20 x 10⁹/L, she meets criteria to receive a second-line treatment. After the considerations provided above and with her primary ITP, she opted for a TPO agent which was based on her fear of COVID and need for vaccination and being in her first year of her disease. She chose to reserve rituximab, fostamatinib and immunosuppressives. She took a TPO agent for a year and then was gradually able to discontinue it. She maintained a platelet count of 60-90 x10⁹/L on no treatment for several years without manifestations of bleeding. She is not troubled by fatigue or heavy menstrual bleeding.

**Section II. The young female became pregnant: ITP in Pregnancy**

Years later, our patient becomes pregnant.

**What are treatment considerations for our patient during pregnancy?**

As ITP is common in women of reproductive age, it is not surprising that it may complicate the course of pregnancy. For pregnant women with known ITP, management changes throughout the course of pregnancy (53). **Figure 1** reviews treatment options available during each trimester, leading up to delivery and post-partum. In the first trimester of pregnancy, platelet counts may spontaneously increase apparently because of the increased progesterational hormones in the first trimester (54). For this reason, relatively few women with ITP require treatment in the first trimester which is fortunate from a teratogenic point of view. In the first trimester, risk of cleft palate from steroid use appears to be small.
In the second and especially third trimester, platelet counts decrease even in healthy women without ITP resulting in “gestational” thrombocytopenia (GTP)(55). Three large series suggest the prevalence of GTP at the end of pregnancy is between 6.6% and 11.6%(56-60). This has been attributed to increased volume of distribution in the later stages of pregnancy as well as “consumption”. Recently, work from China presented at 2021 EHA hypothesized that very high estradiol levels towards the end of pregnancy inhibit platelet production(61). While requiring confirmation, this hypothesis fits both platelet counts falling and cases of ITP in pregnancy becoming progressively more difficult to treat with steroids and IVIG. Fortunately, there is rarely clinically significant bleeding in pregnant women with ITP unless the platelet counts become very low; one exception may be subchorionic hematomas.

Tranexamic acid can be used after delivery to reduce blood loss after delivery and thus reduce blood transfusion requirements. Risk of postpartum thrombosis seems very low, although PE have been reported in two cases (62).

**Steroids in Pregnancy**

The standard treatments for ITP during pregnancy are steroids and IVIG (Table 3) which are the most widely used and felt to be the safest. The pred recommendation for ITP in pregnancy, because of the limited duration of anticipated treatment, is relatively low dose prednisone (e.g., 10-20 mg daily) based on targeting a platelet threshold of 20-30 x 10^9/L. Pred often exacerbates physiologic changes of pregnancy e.g., hyperglycemia, hypertension, and fluid retention; dex is avoided because of its fetal effects. If this lower pred dose is successful, it avoids the risks of long-term high dose steroids for the mother. Little to no prednisone enters the fetus because of placental Beta-11-hydroxylase(63).

**IVIG in Pregnancy**

IVIG is effective; however, it must be given often e.g., biweekly so that steroids are the recommended treatment. One study suggests that both steroids and IVIG are slightly less effective in pregnant women(64). Overall, whether efficacy of IVIG and pred in pregnancy is maintained becomes more important later in pregnancy. Difficult patients require higher and higher doses of prednisone and more and more frequent IVIG dosing as pregnancy progresses.

Treatment of fetal and neonatal alloimmune thrombocytopenia provides safety information. ‘Aggressive intrapartum treatment’ exceeds that of ITP by including IVIG 1-2 g/kg/week and prednisone 0.5 mg/kg/day for many weeks. The apparent safety of these very high doses helps to assuage concerns regarding their use in ITP (65).

Even with less severe ITP, preparing for safe delivery often requires intervention to undergo epidural anesthesia, for which platelets are often “required” to be > 80 x 10^9/L. For spinal anesthesia, the requirements may not be as strict and are more variable than they are for epidural anesthesia. Even in a patient who responds well to IVIG and pred combination treatment, a platelet count of 80 x 10^9/L or higher is often achieved for only 2-5 days. If these are relied upon, scheduling elective delivery is crucial so that administration of IVIG can be timed to achieve its optimal effect. The patient could either undergo a Caesarian section or have her membranes
ruptured so she enters labor at the desired time. Depending, an amniocentesis may be required to assess fetal lung maturity.

**Rituximab in Pregnancy**

In one study of 231 pregnancies with maternal rituximab exposure for treatment of autoimmune cytopenias and other autoimmune disease, few neonatal infections were seen among exposed neonates (66). Hypogammaglobulinemia will not be present at birth if the mother does not herself have low IgG levels; however, it may manifest at 2 to 4 months of age if there is persistent absence of infant B cells. Women are encouraged to avoid pregnancy for >4-6 months after rituximab exposure to prevent transmission of rituximab to the fetus (66). As shown in Figure 1, we believe that rituximab can be used in patients who do not respond well to steroids and IVIG.

**Intravenous anti-D, Azathioprine, Cyclosporine, and Splenectomy in Pregnancy**

Eight patients were treated with IV anti-D (Winrho) with reasonable efficacy and fetal safety (67); no cases of neonatal anemia or hyperbilirubinemia were seen. Azathioprine has been extensively used in women who had undergone renal transplantation and became pregnant (68). The registry of these patients suggested that azathioprine is relatively safe during pregnancy, but azathioprine takes 1-3 months to increase the platelet count. Infants of mothers taking azathioprine are noted to have increased prematurity rate, lower birth weight, and intrauterine growth restriction (IUGR); no malformation risks were seen. Immune impairment was reported in some exposed infants (69). The effects of cyclosporine in pregnant women with ITP appear to be like that of azathioprine: reasonably effective, slow in onset, and with limited fetal risk. The cyclosporine experience is also in women post transplantation (70); mycophenolate is contraindicated in pregnancy (71). Splenectomy, if required, is recommended to be performed in the second trimester because the risk to the fetus is less than in the first trimester and the size of the uterus will be less obstructive than in the third trimester. Experience consists of isolated case reports.

**TPO-RA in Pregnancy**

A major recent development affecting ITP in pregnancy is the use of TPO agents. Three sets of evidence for use of TPO agents in pregnancy exist beyond scattered case reports. One study used recombinant human TPO (rhTPO, available in China) agent and evaluated 33 pregnancies in 31 women with ITP in pregnancy who did not respond to or relapsed after initial response to prednisone (72). Seventy percent of women responded to rhTPO with an increase in the maternal platelet count and no overt maternal toxicity. Importantly, newborns followed until one year of age did not have any identified side effects of rhTPO treatment. A follow up compilation of ITP cases explored 13 pregnancies in 12 women with one pair of twins (73). Usage was divided equally between eltrombopag and romiplostim and both agents appeared effective and safe. Third, a safety surveillance program report of use of romiplostim in 186 women with ITP who received romiplostim during pregnancy indicated that in over 50 pregnancies with pregnancy outcomes and in over 50 pregnancies with birth outcomes romiplostim appeared safe (74). There were 12 births with thrombocytopenia requiring treatment, consistent with the maternal ITP; all were discharged home with 8 having their thrombocytopenia resolved pre-discharge. Although limited by incomplete information, 75 women were exposed to romiplostim in the first trimester because of having been treated with romiplostim at the time they became pregnant. From the >
150 pregnancies for which any data were available, five infants had (1 each): CMV, unilateral inguinal hernia, single umbilical artery with no other findings reported, a child normal at birth whom at age 2 was identified as autistic; and one infant with trisomy 8 whose mother received only 1 dose of romiplostim in the third trimester.

In summary, TPO agents in pregnancy in 3 reports of 3 different agents appear to be safe as a class with no information available for avatrombopag, very limited information for eltrombopag, and considerable safety but little efficacy information for romiplostim. While efficacy is likely preserved in the mother, whether transplacental passage of these agents increases the neonatal platelet count is unknown. Our conclusion is that a TPO agent should only be used when the benefit outweighs the risk. However, if a TPO agent is considered in the third trimester, the available data strongly suggest that romiplostim is safe for the fetus. (figure 1, table 2).

After scheduled vaginal delivery, our patient does well as does her baby. She breastfeeds but her newborn has persistent thrombocytopenia with counts down to 30 x 10⁹/L. She is prompted to stop breast feeding and, upon so doing, the infant’s platelet count rapidly increases to normal. The mother also has her platelet count return to its pre-pregnancy level and all treatment can be stopped.

**Section III: Second Line Treatment of ITP for an Older Male Patient**

What if instead of a young woman in her early 20s, our patient is a 63-year-old male? He is generally healthy but slightly overweight and had his gall bladder removed without incident 6 years ago. He has taken daily losartan, atorvastatin, and a baby aspirin for several years. Upon presentation with bruises, petechiae and profuse bleeding from his gums when he brushes his teeth, he is told to stop his aspirin. He is given dexamethasone 40mg/day x 4 days and IVIG 1 grsm/kg x 1 because of the aspirin. His platelets increase dramatically within 2 days.

What diagnostic considerations are important here? First, as with the young woman, ITP must be distinguished from other thrombocytopenias; these are common in the elderly but different from those in a young woman. Autoimmune diseases like SLE are much less likely as are inherited thrombocytopenias. CVID is possible at any age but in addition to serum immunoglobulins, serum protein electrophoresis to look for monoclonal proteins is appropriate. Other congenital immunodeficiency diseases are less likely, but lymphoproliferative diseases are more common. Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin Lymphoma (NHL) both are B-cell diseases associated with ITP. The smear may have too many small mature-looking lymphocytes; if T and B cell studies are performed, they would reveal too many B cells. Clonal Hematopoiesis of Indeterminate Potential (CHIP) might occur but it is not clear what CHIP would portend assuming the clonal cells do not reflect an overt malignancy. Preliminary information suggest that clonal T cell populations may mediate refractoriness(75). Ultrasound and/or CT scans to look for malignancy may be indicated.

An important cause of thrombocytopenia in elderly patients is MDS which would require a bone marrow examination. Typically, the marrow will be x, but marrow cells will be undergoing apoptosis and not producing mature blood cells and reveal dyspoiesis. Diagnostics have
improved remarkably as has clinical discrimination of different subtypes of MDS. Nonetheless, cases of MDS early in their evolution may be difficult to distinguish from “difficult” ITP(76).

Drug-induced thrombocytopenia is a possibility since older patients may be taking more medications. Limited laboratory testing is available to demonstrate that thrombocytopenia is drug induced. Diagnosis generally relies on recognizing medications likely to cause thrombocytopenia; one approach is to change medications if any are newly initiated. Viral infections could also occur in this population e.g., hepatitis C, CMV.

Patients over the age of 60 are thought to have a higher likelihood of fatal and non-fatal serious bleeding compared to younger patients(77-79); recent studies of intracranial hemorrhage have supported earlier findings demonstrating a higher risk in those above 60 years of age. Thus, it may be appropriate to pursue an aggressive approach in this patient such as the addition of IVIG to steroids.

**Which Second Line Treatment is optimal for a 63-year-old male?**

*Rituximab in an Older Male*
In this case of ITP, the older man has a reasonable likelihood of a response but, even if he responds well, it will very likely last only 6-12 months. The chance of a long-term (> 1 year) response is low. Furthermore, as discussed, after rituximab the patient would be unable to be vaccinated against SARS-CoV-2, which is important since this 63 year is in a high-risk group and would benefit from boosters. As indicated, there is a 10-20% possibility of developing significant hypogammaglobulinemia when dex with rituximab is used(26). A good initial response followed by the expected relapse would allow rituximab to be reused, but it remains unlikely to lead to cure(80) and the probability of occurrence of hypogammaglobulinemia is thought to increase with repeated use.

*Splenectomy in an Older Male*
Splenectomy is used even less in this age group, since efficacy is lower, and the risk of side effects is higher. Older patients with ITP have less successful results of splenectomy, but there is no clear age at which this effect occurs(81). In addition, there may be a higher risk of peri-surgical complications and post-splenectomy thrombosis in this older patient. One could take a risk-based approach to splenectomy for this 63-year-old by considering the co-morbidities and proceeding if he has few to no comorbidities.

*TPO-RA in an Older Male*
Another second-line therapy is a TPO-RA. The primary advantages remain the high response rate and the low likelihood that there will be major side effects although venous and arterial thrombosis would be the primary concerns in this older man. It is important to fully assess the risk of thrombosis looking at risk factors such as obesity, family history, and personal history (53). Using TPO agents would be similar in both patients and is described in the package inserts and a recent review(36).

If romiplostim is chosen, we would initiate treatment with 3 micrograms/kg/week and increase by 2 mics/kg/week until the platelets rise over 30-50 x 10^9/L. In more practical terms, this could
mean whole vials of 250 and 500 micrograms which are almost universally available; if smaller and larger vial sizes are/become available this would allow more precise weight-based dosing. If a sufficient platelet count is achieved, it is important not to change romiplostim doses too quickly, i.e., not more than 1 mic/kg/week. This minimizes cycling of counts and prevents counts from going too high or falling too low. If the count goes very high (this is true for all 3 agents), do not hold the dose. Go down 1 microgram/kg (or equivalent); several days of aspirin can be given if there is concern of thrombosis.

If eltrombopag is chosen, dosing starts at 50 mg by mouth daily; lower doses might be required in East Asian patients. If the count did not increase sufficiently within 1-2 weeks, increase the dose to 75 mg daily. If the count increases too much, decrease to 25 mg daily. The maximum change would be 25 mg/daily once a week. If none of the doses allow for a stable count of 50-100,000, then alternating doses might be preferred e.g., 50 mg on odd days and 75 mg on even days. As discussed, eltrombopag must be taken on an empty stomach. In our experience, the best approach is to eat dinner and then not eat after the end of dinner with eltrombopag taken with water at bedtime, at least 2 hours after dinner. If this gentleman urinates every night, this could be a time to take eltrombopag.

If taking avatrombopag, he would start with 20 mg daily. The dose could be adjusted to as high as 40mg daily or as low as 20mg one day per week. As stated, avatrombopag has only one size tablet of 20mg. It is taken once daily and has no dietary restrictions. As with the other agents, dose changes should be limited in magnitude and not more often than weekly.

With all three agents, it is not clear how/when to taper and attempt to discontinue treatment. A recent study demonstrated >50% successful discontinuation by requiring at least 2-3 months of stable TPO agent dosing, no bleeding, and a count > 100 x 10^9/L (82). Patients were on romiplostim a median of 12 months before tapering; administered doses were higher than normal to obtain stable counts > 100 x 10^9/L. The study tapered at two weekly intervals for a total of not more than 2 months of tapering. It remains unclear how often a patient who has required a TPO agent for 2 or more years will be able to discontinue treatment; other studies have suggested an approximately 20-25% rate of successful discontinuation in the first year.

**Fostamatinib in an Older Male**
If this patient were at particular risk of thrombosis, fostamatinib might be a particularly good option. Otherwise, in general practice, it is usually reserved for failure of response to TPO agents.

With many options for second-line agents, there are variable treatment courses depending on individual responses, relapses and potential complications with each agent as demonstrated in Figure 2.

**Section IV: Third Line Therapy and Beyond**
What happens if the TPO agent used in both patients had not worked or at least couldn’t be tapered?
a) In this case, the count remained less than $20 \times 10^9/L$ and the young woman had heavy menses, bruising and nosebleeds. The now 26-year-old woman opted for rituximab. She had a long-term response but unfortunately relapsed after 4 years. She considered repeating the rituximab and undergoing splenectomy but opted to try a different TPO agent since she was not planning a repeat pregnancy in the immediate future. Previously she used eltrombopag so now she tried avatrombopag. On 20 mg a day dose she was able to maintain an adequate count and is very slowly tapering her dose. This choice was consistent with evidence that not responding well to one TPO-RA does not preclude good response to another.

b) Given continued bruising and minor nosebleeds, the older man was afraid of major bleeding; he also felt very tired even though he was not anemic. The now 64-year-old man opted to try rituximab since his avatrombopag did not work well for him. He received the standard dose of rituximab with dexamethasone. He responded to a platelet count of $60 \times 10^9/L$ by 6 weeks after initiating treatment; however, his count started to fall monthly down to $30 \times 10^9/L$. He and his doctor decided to initiate MMF and he began with 500 mg twice daily and then increased to 1000 mg twice a day. He tolerated it well and his platelets remain around 40-50 $\times 10^9/L$.

Thus, both patients needed treatment. Some patients with low (not very low) counts who have no bleeding or other issues e.g., need for anticoagulants or fatigue, may not require treatment; avoiding treatment is always optimal if this does not jeopardize quality of life.

What if none of the obvious options (TPO agents, rituximab, splenectomy) helped and no single treatment, including fostamatinib and MMF, was effective?

It is difficult to predict what approach will be effective in these “refractory” patients. If a patient has been on too low a dose or for too short a period, it may not be clear that a given medication will not be helpful.

The approach to a difficult patient such as these examples is discussed at great length in our review of refractory ITP and in a recent review(1, 83). The major principles are:

a) Spend time reconfirming the diagnosis; reconsider all options if response to treatments of ITP is absent or very limited.

b) Unless one was performed recently, do a complete bone marrow examination with aspirate, biopsy, flow cytometry, and cytogenetics.

c) If a treatment is ineffective, continue the treatment and add another treatment initiating combination therapy. In our opinion, this is preferable to discontinuing the ineffective treatment and starting another one.

d) If indeed the case is refractory ITP, combination approaches are often better than single treatments. Including treatments with different mechanisms of effect of the treatments are useful; however, there are situations in which two agents targeting the same mechanism are effective such as combining IVIG and IV anti-D(31).
e) In combination treatments, it would be ideal to a) not use maximum doses and b) to select agents with differing toxicities. If an adverse event requiring a change in treatment occurs, it is then easier to choose the agent to stop and/or replace.

f) In our review of published reports(1), a TPO agent was often a crucial component of combination treatments.

In difficult patients, the inability to define the pathogenesis in most cases makes the treatment selection blind. Fortunately, multiply refractory patients for whom no treatment seems to bring their count up at all are very rare. More commonly at least one treatment will transiently increase the platelet count. This minimizes the chance of serious bleeding and creates an approach for ongoing management, although continued steroid overuse must be avoided.

**Section V: Agents Currently Under Study**
What are the experimental agents which are likely to be available in the future?

*FcRn inhibitors*
Their putative mechanism of effect is reduction of antiplatelet IgG levels by inhibition of “normal” IgG recycling. IgG levels fall dramatically with FcRn inhibition, and it is thought that the IgG anti-platelet antibody levels fall at least as much resulting in less platelet destruction and greater platelet production. Efgartigimod and rozanolixizumab had phase 2 studies published in 2020 both demonstrating more than 50% acute platelet response(84, 85). Both agents have ongoing phase 3 trials which, like many studies, were slowed by the COVID pandemic. Since FcRn inhibition does not lower IgA and IgM levels nor affect T cell or macrophage function, trials have not been complicated by development of infections despite achieving very low IgG levels. Nonetheless, there is concern that IgG levels < 200 mg/dl (LLN 639 mg/dl) may be dangerous. With 1 FcRn inhibitor, albumin levels were lowered, and cholesterol increased; FcRn also recycles albumin.

Active studies of FcRn inhibitors include treatment of myasthenia gravis, pemphigus vulgaris, Hemolytic disease of the fetus and newborn, and antibody-mediated neurologic diseases. The phase 3 studies administer FcRn inhibitors weekly by subcutaneous administration with the goal of eventual home administration.

*BTK inhibitors*
The most widely used BTK inhibitor is ibrutinib for CLL and NHL with excellent results in treating these entities; anecdotally, several thrombocytopenic patients with CLL had substantial platelet improvements. Thus, it was natural to think of FcRn inhibition for B cell diseases like ITP. However, Ibrutinib was found to lead to 1% or so serious bleeding subsequently suggested to be caused by inhibition of collagen-platelet interactions. Newer BTK inhibitors, e.g., rilzabrutinib, designed to allow normal platelet function for patients with ITP, have been effective in ITP in phase 2 trials with a 50% response seen at the top dose, 400 mg twice a day(86). As was seen in trials with fostamatinib and FcRn inhibitors, the patients have been those with long-term, heavily pretreated histories. It is highly likely that BTK inhibitors will inhibit response to COVID vaccination.
**Complement inhibitors**
Studies of complement pathway inhibitors in ITP would have begun years ago if the cost of the Alexion anti-C5 monoclonal antibody (eculizumab) was not so enormous. Early results of C1S inhibition are impressive but still preliminary. This agent has yielded good results in cold agglutinin disease demonstrating its biologic effect on the complement system translating to clinical hematological efficacy.

It remains uncertain whether, and if so where, any or all these agents, will ultimately have a major role in management of ITP. On the one hand, they could be more effective and less toxic than currently used agents and have unique areas of efficacy based on their unique mechanisms of effect. On the other hand, they might be redundant, have toxicities, and not provide substantial additional value.

**Conclusions**

*What would we have liked to have been able to offer our two ITP patients?*
First, it would have been nice to have been able to predict their course including many factors: risk of bleeding, likelihood of chronicity, which treatments would be most effective, and which most toxic.

Second, it would be nice to have a curative but non-toxic treatment to offer. We discussed the use of rituximab in a younger woman as there is good likelihood of cure in this age and gender. But in other patients, there is very little likelihood of cure and in her case, vaccination for SARS-CoV-2 was a problem. This leaves splenectomy which is remarkably effective; recent work suggests that it remains effective even in patients who have had TPO agents(48). Why are patients so unwilling to undergo splenectomy? Perhaps the primary reasons are the inability to know whether a patient will get better on their own, whether the splenectomy will be successful, and the irreversibility of it. Furthermore, post-splenectomy risks of sepsis and of thrombosis continue lifelong. In the future, use of combinations of agents (dex and rituximab, steroids and MMF, dex and eltrombopag, or others) within 1 week of diagnosis may provide a higher level of cure and justify the extra expense and higher risks of these interventions.

Finally, it would provide more rationality to treatment selection if there were randomized, controlled trials to compare agents and regimens. To date, all the randomized controlled double-blinded trials of second line agents have involved comparison of a treatment to placebo. No trials comparing one second line agent to another exist that we are aware of although recently, Chinese hematologists have compared a given agent to the same agent plus a second agent. Examples include rituximab with and without TPO, and Dexamethasone with and without eltrombopag. More of these studies are urgently needed.

In summary, it is not possible to have a one size fits all approach to ITP. Rather we have tried to emphasize that individualizing treatment is important and should include shared decision making. The optimal choices vary with gender and age and there is an impact of the pandemic as well. As additional information is accrued, management in certain situations may be clarified but there is a long way to go to achieve for ITP what we all take for granted in the evidence-based management of leukemia(87).
Table 1: Comparing Second Line Options in Non-Pregnant Premenopausal Females

<table>
<thead>
<tr>
<th>Treatment options</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| Rituximab                          | High likelihood of good response both short and especially long term (>50%) | o Risk of first infusion reaction which can be mitigated by steroids  
  o Unable to be vaccinated for COVID for 6-12 months 
  o Very rare risk of PML(45) 
  o Risk of hypogammaglobulinemia with Ritux + Dex 10-20% with possible need for short-term IgG-replacement IVIG |
| TPO-RA:                           |                                     |                                                                      |
| Eltrombopag                        | Very high response rate (70-80%)     | o Risk of thrombosis (increased with OCPs, underlying APLA, other prothrombotic causes) which usually occurs in 1st yr of use 
  o Pain from headache-myalgia occur 
  o Abnormal liver function especially for eltrombopag which also needs very strict ingestion on empty stomach |
| Romiplostim                        |                                     |                                                                      |
| Avatrombopag                       |                                     |                                                                      |
| Splenectomy                        | High long-term response rate (60-70%)| o Risk of perioperative bleeding, VTE, intracellular infection, sepsis  
  o Need to vaccinate at least 15 days prior to surgery(88) 
  o Revaccination schedule unknown |
| Fostamatinib                       | Overall response 43% in first 12 weeks on treatment, time to response 15 days(47) | o Side effects: hypertension, nausea-diarrhea, dizziness, ALT increases  
  o Clinically meaningful responses in patients that failed splenectomy, TPO-Ras and/or rituximab(45) |
| Immunomodulating agents:           | Many years of usage in some cases e.g., azathioprine, cyclosporine, dapsone, cytoxan | o Usually, slow responses which can take 1-3 months without predictability  
  o Various individual toxicities: 
    o Cyclosporine - neuro and renal 
    o Azathioprine and danazol - liver abnormalities 
    o Danazol - facial hair and acne 
    o MMF headache, GI 
    o Dapsone - hemolysis |

PML: Progressive Multifocal Leuкоencephalopathy  
OCP: Oral Contraceptive Pills  
APLA: Anti-PhosphoLipid Antibody
<table>
<thead>
<tr>
<th>Second line option</th>
<th>COVID Infection</th>
<th>SARS-CoV-2 vaccination prior to initiation of ITP 2\textsuperscript{nd} line treatment</th>
<th>SARS-CoV-2 vaccination after ITP 2\textsuperscript{nd} line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rituximab</strong></td>
<td>Limited information on effects of rituximab during active COVID infection[(89)]</td>
<td>Vaccinations should be given prior to starting rituximab e.g. Moderna given minimum 5 weeks prior, Pfizer given minimum 6 weeks prior</td>
<td>If not vaccinated prior to start on rituximab, need to wait to be vaccinated until 6-12 months after completion of last rituximab dose[(28)]</td>
</tr>
<tr>
<td><strong>TPO-Agents</strong></td>
<td>Risk of thrombosis[(29)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fostamatinib</strong></td>
<td>Potentially useful in COVID infections independent of platelet function[(47)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immunomodulating agents</strong></td>
<td>May be good candidates for administration of anti-SARS-Cov2 antibodies via convalescent plasma or engineered monoclonal antibodies[(44)]</td>
<td>Vaccination is recommended at least two to four weeks prior to starting immunosuppressive agents[(44)]</td>
<td>If the patient is receiving or has received immunosuppressive therapy, consider vaccination six months after the patient has been taken off therapy to increase the likelihood of developing immunity[(44)]</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Antibodies (44)</td>
<td></td>
<td></td>
</tr>
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<td>-------------</td>
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<td></td>
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</tr>
<tr>
<td>*Recommend screening for COVID infection prior</td>
<td>Urgent administration of IV antibiotics is mandatory until bacterial cultures are documented as negative, even if the fever is attributed to proven or suspected SARS-Cov-2 infection (44)</td>
<td>Vaccination is recommended at least two to four weeks prior to the planned splenectomy (44)</td>
<td>Splenectomized persons and those who received 5 or more prior lines of therapy were at highest risk of ITP exacerbation (29)</td>
</tr>
</tbody>
</table>
Table 3: ITP Treatment Options and Considerations During Pregnancy

<table>
<thead>
<tr>
<th>Treatments (Drug category)</th>
<th>Dosing FDA category ( )</th>
<th>Considerations for mother</th>
<th>Risks to fetus</th>
<th>Evidence for use in pregnancy/ Effect on lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone (Steroid)</td>
<td>10-20 mg daily can increase if necessary to 1mg/kg (C)</td>
<td>Usually the 1&lt;sup&gt;st&lt;/sup&gt; agent to use diabetes, weight gain, acne, hypertension, osteoporosis,</td>
<td>Very low risk of cleft palate from steroid use in 1&lt;sup&gt;st&lt;/sup&gt; trimester(53).</td>
<td>Very low concentrations in maternal milk and without biological effect(90)</td>
</tr>
<tr>
<td>Dexamethasone (Steroid)</td>
<td>High dose, 40 mg per day x 4 days (C)</td>
<td>Low cost, ease of administration</td>
<td>Dexamethasone can cross the placenta. Slight increased risk of premature rupture of fetal membranes and abruptio placentae.</td>
<td>50% response(64)</td>
</tr>
<tr>
<td>IVIG (intravenous Immunoglobulin)</td>
<td>Standard dose 400-1000 mg/Kg/day for 1-5 days</td>
<td>Can be given 1&lt;sup&gt;st&lt;/sup&gt; line, Initially high response but often decreases with repeated use -Aggravates fluid retention and hypertension -Can be used to increase pltS initially while awaiting low dose pred -Can be used for delivery but needs to be scheduled (timed rupture of membranes) -Can worsen pregnancy-associated headache, malaise, infusion reactions, aseptic meningitis, fluid overload</td>
<td></td>
<td>Very low concentrations in maternal milk and without biological effect(90)</td>
</tr>
<tr>
<td>Rituximab (Monoclonal antibody)</td>
<td>375 mg IV/ weekly x 4 (C)</td>
<td>Use only for very severe cases(5)</td>
<td>Can cross placenta like any IgG, Risk of B-cell depletion in neonate, perinatal and neonatal immunosuppression and subsequent infection</td>
<td>40-60% response within 1-8 weeks(66)</td>
</tr>
<tr>
<td>anti-RhoD (Blood Group RhoD antibody)</td>
<td>Can be used in refractory cases</td>
<td>Risk of hemolysis and</td>
<td>Risk of neonatal jaundice, anemia, and direct antiglobulin test positivity</td>
<td>&gt;70% of cases Case series (n=8)(67)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Dosing</td>
<td>Description</td>
<td>Contraindications/Effects</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
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<tr>
<td>IV 50-75 μg/kg (C)</td>
<td></td>
<td>anemia. Less expensive, shorter infusion time than IVIG</td>
<td>Given routinely for hemolytic disease of the fetus and newborn (HDFN) prophylaxis but at 1/10th the ITP dose</td>
<td></td>
</tr>
<tr>
<td>Azathioprine (Immunomodulator)</td>
<td>Variable dosing (D)</td>
<td>Increased risk of preterm birth</td>
<td>Can cross placenta, noted to have increased prematurity rate, lower birth weight, IUGR. No malformation risks across several studies. Immune impairment reported in some exposed infants (69)</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (Immunomodulator)</td>
<td>Variable dosing (C)</td>
<td>for refractory cases, No significant toxicity to mother or fetus when used in pregnancy for inflammatory bowel disease, possible increased risk of preterm birth</td>
<td>Increased risk of IUGR (70)</td>
<td></td>
</tr>
<tr>
<td>Romiplostim (TPO-RA)</td>
<td>(Not assigned)</td>
<td>Risk of maternal thrombocytosis Increased risk of VTE</td>
<td>Case reports with safety data in women with ITP in pregnancy(73)</td>
<td></td>
</tr>
<tr>
<td>Eltrombopag (TPO-RA)</td>
<td>Start at 25-50 mg PO daily and increase as needed (C)</td>
<td>Very limited requires a very empty stomach (ideally 2 hours before and after taking it), elevated liver enzymes</td>
<td>Case reports in pregnancy</td>
<td></td>
</tr>
<tr>
<td>rhTPO</td>
<td>(FDA not assigned, available in China)</td>
<td>No overt maternal toxicity</td>
<td>Case reports in pregnancy</td>
<td></td>
</tr>
<tr>
<td>Splenectomy (N/A)</td>
<td>For refractory ITP or if significant toxicity with other therapies</td>
<td>Risk of perioperative bleeding, VTE, opportunistic infection, miscarriage, preterm labor and preterm premature rupture of membranes</td>
<td>Risks to fetus least in 2nd trimester. Minimal data Transplacental passage of circulating maternal antiplatelet antibodies and the risk of neonatal thrombocytopenia are 88% response rate Few complications in 2nd trimester when least risky to fetus and uterine size may not complicate procedure(92)</td>
<td></td>
</tr>
<tr>
<td>Vaccination Requirement</td>
<td>Condition</td>
<td>Tranexamic Acid (B, post-partum setting only)</td>
<td></td>
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<tr>
<td>Need to be vaccinated at least 15 days prior to surgery(53)</td>
<td>not affected by splenectomy</td>
<td>Can reduce the amount of blood loss after delivery, reduces blood transfusion requirements. Low risk of post-partum thrombosis, PE reported in two cases(62). Used only post-partum. Avoid antepartum due to potential risk clotting off placenta</td>
<td></td>
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</tr>
</tbody>
</table>

Note on FDA pregnancy categories: (prior to 2015)

B - Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

C - Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

D - There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.


Figure Names & Legends

Figure 1: ITP treatment Options During Pregnancy, Leading Up to Delivery, and Post-Partum

Figure 2: Second Line ITP Treatment Options and Possible Treatment Courses
**1st trimester**
Treat if symptomatic with bleeding if platelets <20-30 x 10⁹/L
- Corticosteroids
- IVIG
- Platelet transfusion if clinically significant bleeding
- Immunosuppressants
- Azathioprine
- Cyclosporine

**2nd trimester**
Treat if symptomatic with bleeding if platelets <20-30 x 10⁹/L
- Corticosteroids
- IVIG
- Consider:
  - TPO-RA
  - Rituximab
  - Cyclosporine
  - Azathioprine
- If necessary:
  - Splenectomy

**3rd trimester**
Treat if symptomatic with bleeding if platelets <20-30 x 10⁹/L
- Corticosteroids
- IVIG
- TPO-RA*
- Rituximab
* TPO-RA work faster and have a higher response rate than rituximab if choosing TPO-RA, romiplostim has by far the most safety data

**Postpartum**
Close follow-up until return to pre-pregnancy state
- Can add tranexamic acid
- Platelet transfusion for delivery

**Leading up to delivery**
Treatment goal >50 x 10⁹/L for delivery to avoid major bleeding, but usually >80 x 10⁹/L for epidural anesthesia
- Corticosteroids
- IVIG
- Rituximab
- Consider TPO-RA

**Lactation**
- Specific consideration for ITP treatments during lactation
- Slow taper of steroids until return to pre-pregnancy levels in post-partum setting