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## Definition, diagnosis and treatment of immune thrombocytopenic purpura

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In this issue, Arnold and colleagues document by a systematic review of controlled studies that eradication of *H. pylori* infection increases the platelet count in patients with immune thrombocytopenic purpura (ITP).[1] This observation, together with data from a previous systematic review,[2] requires that we address two questions. 1) What is the role of *H. pylori* infection in the pathogenesis of ITP? 2) What is the role of eradication of *H. pylori* infection in the management of ITP? These questions require a discussion of the definition, diagnosis, and current treatment of ITP. This discussion focuses on adults, as *H. pylori* infection is rare in children and two current systematic reviews have only identified studies of ITP in adults.[1,2]

### Definition and diagnosis of immune thrombocytopenic purpura

ITP is defined as isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia.[3] This definition provides the basis for the initial patient evaluation. No specific criteria establish the diagnosis of ITP; the diagnosis relies on the exclusion of alternative disorders, such as the examples listed in Table 1. Exclusion of recognized alternative etiologies of thrombocytopenia was the basis for the original name for ITP, *idiopathic thrombocytopenic purpura*.[3] A current perspective has proposed the name *primary immune thrombocytopenia* for ITP, to distinguish ITP from identifiable alternative *secondary* etiologies.[4]

Should *H. pylori* infection be considered an alternative disorder, the same as HIV and hepatitis C infections? Does the diagnosis of *H. pylori* infection exclude the diagnosis of ITP? The current status of *H. pylori* infection, as indicated in Table 1, is uncertain. *H. pylori* infection may be an alternative, additional, or incidental unrelated disorder; all three possibilities are suggested by different studies. It is the inconsistency among current studies which has prevented broad acceptance of the association of *H. pylori* infection with ITP.

There are striking geographical disparities of both the frequency of *H. pylori* infection among patients with ITP and the frequency of platelet count responses following eradication of *H. pylori* infection, and these two frequencies correlate with each other.[1,2] In countries with a high prevalence of *H. pylori* infection and high platelet count response rates following eradication, such as Japan (where most studies of *H. pylori* eradication in ITP have been performed) and Italy, testing for *H. pylori* infection has been recommended as a standard diagnostic procedure in adults with suspected ITP and eradication therapy is recommended as the initial treatment in *H. pylori*-infected patients.[5,6] These studies suggest that thrombocytopenia associated with *H. pylori* infection may be an alternative disorder, similar to the thrombocytopenia associated with HIV and hepatitis C infections. In contrast, only three studies have been reported from the United States and Canada and they have all reported lower frequencies of both *H. pylori* infection and platelet count response rates following eradication treatment.[7-9] These data suggest that *H. pylori* infection may be merely an incidental observation, not excluding the diagnosis of ITP and not clinically important for management. In between these alternative interpretations are studies reporting partial platelet count responses, suggesting that *H. pylori* infection may contribute to the thrombocytopenia in ITP but is not the sole cause.[2] An explanation for the different platelet count response rates following *H. pylori* eradication may be the presence of different genotypes of *H. pylori* in different geographical regions.[6] For example, most *H. pylori* strains in Japan express the product of the cytotoxin-associated gene A (CagA); the frequency of CagA-positive strains of *H. pylori* in Western countries is lower.[2]

**Table 1. Evaluation of patients with suspected immune thrombocytopenic purpura: exclusion of alternative etiologies of thrombocytopenia.**

| Alternative Disorders | Comment |
|---|---|
| Pseudothrombocytopenia | The first alternative diagnosis that must always be excluded. Typically caused by EDTA-dependent platelet agglutinins. No clinical importance |
| Drug (herbal remedy, beverage, or food)-induced thrombocytopenia | This alternative diagnosis should be assumed in patients with recurrent episodes of acute thrombocytopenia |
| HIV infection | HIV infection may cause isolated thrombocytopenia; typically occurs in patients with advanced disease and resolves with effective antiretroviral treatment |
| Hepatitis C infection | Chronic hepatitis C infection may cause immune-mediated thrombocytopenia |
| Systemic lupus erythematosus, Lymphoproliferative disorders | May have immune-mediated thrombocytopenia comparable to ITP, but primary treatment is different |
| Myelodysplasia | Some patients with myelodysplasia may initially present with isolated thrombocytopenia |
| Thrombotic thrombocytopenia purpura | Patients with TTP commonly present with only thrombocytopenia and anemia, without neurological or other systemic symptoms; anemia may be mistakenly attributed to blood loss |
| Congenital/hereditary thrombocytopenia | An important consideration, especially in young patients, when there is no response to treatment of ITP |
| **Alternative, Additional, or Incidental Unrelated Disorder?** | **Comment** |
| *H. pylori* infection | In some patients, eradication of *H. pylori* infection appears to completely correct the thrombocytopenia and may therefore represent an alternative diagnosis. In some patients, *H. pylori* infection appears to be an additional disorder that worsens the thrombocytopenia in patients with ITP. In some patients, eradication of *H. pylori* infection appears to have no effect on the course of thrombocytopenia. |

*The table lists selected alternative etiologies of thrombocytopenia that should be considered in patients who are initially suspected to have ITP. The appropriate designation of* H. pylori *infection remains undetermined. It may be an alternative disorder, such as infection with HIV or hepatitis C; it may only be an additional disorder that can worsen thrombocytopenia in some patients with ITP; or, in some patients, it may be an incidental infection that is unassociated with thrombocytopenia and unrelated to ITP. Or perhaps all three possibilities are correct, each in different geographical locations or in different patients.*

### *Management of immune thrombocytopenic purpura*

Ideally, treatments for ITP should be effective, safe, tolerable, and inexpensive. Detection and eradication of *H. pylori* infection is safe, tolerable, and inexpensive. However, because effectiveness has not been consistent, there has not been broad acceptance of detection and eradication of *H. pylori* infection as part of the routine evaluation and management of patients with ITP. Figure 1 presents an oversimplified algorithm of current management, with *H. pylori* eradication remaining outside the boxes of the routine sequence of treatments.

The goal of treatment is to achieve a safe platelet count to prevent serious bleeding; a normal platelet count may provide confidence that the ITP has resolved, but is not the primary goal. Therefore, the initial management decision is to distinguish patients who need only observation from patients who require treatment. Multiple large cohort studies have supported the use of a platelet count of $30\times10^9$/L as a practical distinguishing definition (for example [10]). Although management decisions are traditionally based on the platelet count, these decisions must also consider the presence and severity of bleeding symptoms. When treatment is appropriate, corticosteroids have been the established initial agents for 50 years. Although prednisone (or prednisolone) at a daily dose of 1 mg/kg is commonly used, other regimens, such as a high dose of dexamethasone (40 mg) daily for four days may be more effective.[11] The principal problem of corticosteroids, from the patients' perspective, is that the treatment may become worse than the ITP itself, since side effects are often intolerable[12] and bleeding symptoms are often minimal. Therefore, it is appropriate to use corticosteroids for only a limited time.

At each successive step in the management of ITP, treatments may be more effective but also may have greater risk. Therefore, the indications for continued treatment must be more stringent and continued treatment must be a shared decision between the physician and patient. Following failure of initial corticosteroid treatment to achieve a durable, safe platelet count, splenectomy has been the traditional second treatment for many decades. More than two-thirds of patients have durable responses.[13] However, even with current laparoscopic procedures, risks of splenectomy remain, with clinically important complications in 10% of patients and death in 0.1%.[13] Longterm risks following splenectomy, such as sepsis and thrombotic disorders, are a rare but important concern. Recently rituximab has become an alternative second treatment for patients with ITP, although the rate and durability of responses appear to be less than with splenectomy.[14] A recent randomized clinical trial documented that a combination of four days of dexamethasone plus four weekly infusions of rituximab resulted in sustained safe platelet counts over $50\times10^9$/L at six months in 63% of patients, a significantly greater response than with dexamethasone alone (36% response).[15] This combination may be an appropri-

ate second treatment for patients with ITP. Although this clinical trial was performed in previously untreated patients,[15] rituximab is not appropriate for initial treatment of patients with ITP.

Patients who require further treatment after splenectomy are uncommon, representing less than 10% of all patients who are initially diagnosed with ITP.[16] Observation without treatment has been preferred for patients who are asymptomatic in spite of severe thrombocytopenia because further immunosuppressive treatments create greater risk for opportunistic infections, and one large case series documented that deaths from treatment-related infection exceeded deaths from ITP-related bleeding.[10] In 2008, two thrombopoietin (TPO)-mimetic agents, romiplostim and eltrombopag, were approved by the US FDA for treatment of chronic ITP in patients who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy; romiplostim was also approved by the EMEA for a more restricted indication, splenectomized adults who are refractory to other treatments. The TPO-mimetic agents do not modify the course of the disease; they only support the platelet count and must be continually administered.[17] Therefore, the most appropriate use of these agents is for patients who have severe and symptomatic thrombocytopenia following failure of treatments to achieve a durable, safe platelet count. For these patients, continuous treatment with TPO-mimetic agents is a remarkable and potentially life-saving measure. Not only can the platelet count be sustained at a safe level in approximately 85% of these patients,[18] but side effects of steroids and other immunosuppressive agents are avoided. These agents may not be appropriate for treatment earlier in the sequence of ITP management because of the requirement for continuous treatment and the expense.

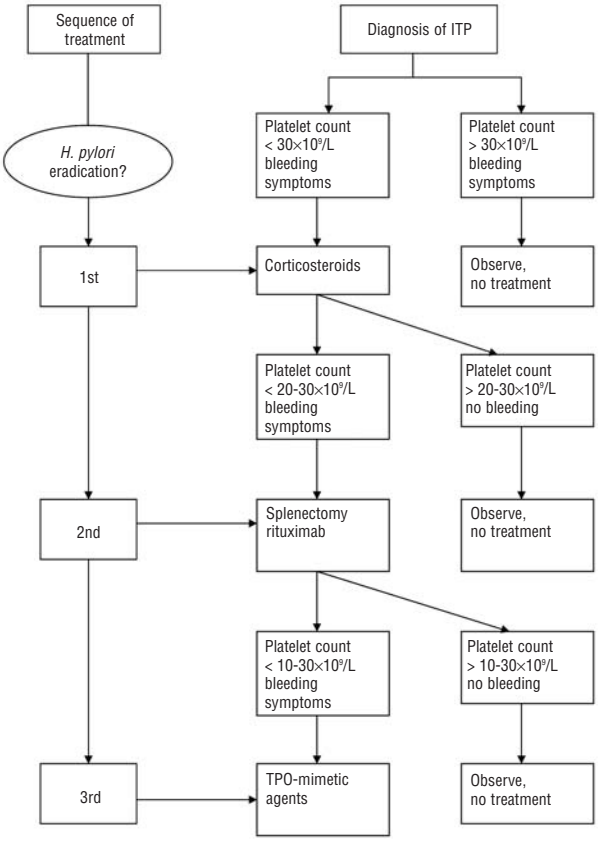


**Figure 1. Sequence of management of patients with ITP – 2009. An oversimplified approach to management is outlined as three consecutive steps. Initial corticosteroid treatment should be limited in duration to avoid intolerable side effects. For patients who fail to respond to corticosteroid treatment, the indications for further treatment become more stringent, as the treatments involve more risk. Both splenectomy and rituximab are frequently used as second treatment options, with one following the other if there is no response. TPO-mimetic agents may become established as third treatment options, because of the risks of infection with more intensive and prolonged use of immunosuppressive agents. At this time, eradication of *H. pylori* infection is "outside the boxes" of conventional treatment. If it is demonstrated to be effective in certain groups of patients with suspected ITP, it could become a first option treatment because of its safety, tolerability, and low cost.**

## *Role of* H. pylori *eradication in the management of immune thrombocytopenic purpura*

Although current treatment options are more effective than even just one year ago,[17] there remains substantial room for improvement. Current treatments may be effective, but they are all either poorly tolerated, have important risks, or are extremely expensive. Because detection and eradication of *H. pylori* infection are well tolerated, safe, and inexpensive, it has been proposed as a routine step in the initial evaluation and management of patients with ITP.[2] This may be appropriate now in locations where the frequency of *H. pylori* infection is high. Although it may also be reasonable to consider *H. pylori* eradication in patients with ITP in all countries, enthusiasm has been limited by the low frequency of *H. pylori* infection and the low platelet count response rates to *H. pylori* eradication in countries such as the United States and Canada.

The most important results of the current reviews of *H. pylori* infection and ITP[1,2] will be to increase awareness and stimulate further investigation of the relationship between *H. pylori* infection and ITP. The inconsistencies emphasized by these reviews[2] provide a perfect clinical research question for international collaborations, with the goal to resolve the geographical disparities and to determine if *H. pylori* detection and eradication are appropriate initial measures for all patients with ITP, or only for some patients with ITP, or perhaps for all patients with ITP but only in some geographical regions. With greater understanding, *H. pylori* detection and eradication may then be moved "into the boxes" of appropriate management for patients with ITP.

## Conflicts of interest

*Dr. George has served as a consultant Amgen, Inc., Thousand Oaks, CA and has received research support from Amgen for the development of romiplostim.*

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## α1-antitrypsin and the maintenance of hemostatic balance


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Serine protease inhibitors, known as serpins, belong to a superfamily of proteins that are the quintessential regulators of extracellular peptidase pathways.[1] Serpins prevent the deleterious effects of excessive peptide bond hydrolysis. The principal determinant of serpin specificity appears to be the P1 residue localized within the substrate recognition sequence of the reactive center loop.[2] A serine protease and its specific serpin form a tight inactive complex after cleavage of a scissile bond between P1 and P1' residues. Antithrombin is the principal serpin involved in the regulation of blood clotting proteinases but it differs from other serpins in having several multiple target proteinases such as thrombin, factor Xa, factor IXa, factor XIa and factor XIIa. Its importance as a major regulator of thrombin generation is well demonstrated since the initial publication of antithrombin deficiency.[3] Alpha1-antitrypsin has major homology with antithrombin, but its major substrate is the leucocyte elastase, with accessory inhibitory activity toward trypsin, chymotrypsin and activated protein C. P1-P1' residues in antithrombin are constituted of the Arg 393-Ser 394 residues when this bound is Met 358-Ser 359 in α1-antitrypsin.

In 1978, Lewis *et al.* described the first report of α1-antitrypsin Pittsburgh (Met 358 to Arg mutation) as a variant causing severe hemorrhagic disease in a young boy born in 1966 who died at the age of 14 of a huge hematoma of his leg and abdomen in 1981, after more than 50 severe bleeding episodes during his short life.[4,5] We described, in 1992, a second case of α1-antitrypsin Pittsburgh in a 15 year-old boy during a routine preoperative laboratory investigation before an operation.[6,7] We have been following this case since 1990 and he is now 35 years-old. He has had an uneventful life except for one bleeding episode of the right buttock after a minor trauma that required surgery due to compression of the sciatic nerve.[7] Since then he has never experienced new bleeding episodes. In this issue of the journal, Hua