Idiopathic thrombocytopenic purpura: current therapeutical strategies and review of the literature on outcome after splenectomy

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**Abstract:** Immune thrombocytopenia (ITP) is an immune and hematological disease resulting in low platelet count and high risk of hemorrhagic events. Therapy is challenging and the therapeutic outcome depends on multivariate factors, mostly still unknown and specific per-patient. Therefore, treatment should be tailored to the patient. Large randomized trials about the management of ITP are very few, resulting in significant therapeutic controversies. Indications and outcomes of splenectomy have considerably changed in the last years, because of improvement in medical therapy, especially for monoclonal antibodies. Furthermore, there are contradictory outcomes especially after surgical treatments in the Literature. For this reason, several guidelines have been formulated and revised in the last years. Recently, the American Society of Hematology published the new guidelines just focused on the management of ITP. In this systematic review of the Literature, we analyze the state of art about medical and surgical management of ITP and the therapeutic outcomes reported in the Literature, comparing them with the results from our studies.

**Keywords:** Immune thrombocytopenia (ITP); laparoscopic splenectomy; autoimmune hematologic disease.

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**Introduction**

Immune thrombocytopenia (ITP) is a hematological disease where an autoimmune condition lead to low platelet count and high risk of hemorrhagic events.

ITP is challenging to treat and the therapeutic outcomes depend on multivariate factors, mostly still unknown and specific per-patient. Therefore, treatment should be tailored to the patient according to factors like the patient's age, life style, comorbidities, compliance and preferences (1,2).

Indications and outcomes of splenectomy for ITP have considerably changed in the last years, because of improvement in medical therapy, especially after the introduction of monoclonal antibodies (3). Despite new therapies to treat patients with ITP has been introduced in the last years, large randomized trials about the management of ITP are very few, resulting in therapeutic controversies. Furthermore, there are contradictory outcomes after medical and surgical treatments in the Literature. Therefore, it is very difficult to standardize the therapeutic process.

For this reason, several guidelines have been formulated and revised in the last years. Recently the American Society of Hematology (ASH) has published the new guidelines just focused on the management of ITP. In this systematic review of the Literature, we analyze the state of art about medical and surgical management of ITP and the therapeutic outcomes reported in the Literature, comparing them with the results from our studies.

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focused on the management of ITP (4).

In this systematic review of the Literature, we analyze the state of art and the novelties on medical and surgical management for ITP, comparing the outcomes reported in the Literature with the results from our studies. In performing our review of the literature, we inserted on PubMed the words: ‘current therapies AND idiopathic thrombocytopenic purpura’. We restricted the research to the papers lasting no more of 10 years.

Discussion

ITP is an autoimmune hematological disease where the destruction of opsonized platelets in the reticulo-endothelial system, mainly in the spleen, or the inhibition of platelet production (5-7), result in a low platelet count, which may lead to risk of spontaneous bleeding (5,8-12).

Primary ITP was defined by the International Working Group as a platelet count <100,000/µL in absence of other causes leading to thrombocytopenia (12). ITP is a relatively common hematological disorder that may affect people of all ages, with an incidence of 2–5/100,000 per year in the general population (12-17).

Spontaneous remission may happen in 5–11% of adult patients (18) within 3 months after diagnosis. Otherwise, ITP is persistent when lasts 3–12 months, and chronic ITP exceeds 12 months (4).

In 2019, the ASH revised the previous guidelines and formulated new ones focused on the management of ITP and based on updated systematic reviews of the Literature (4).

The aim of ITP treatment is to maintain a platelet count at a sufficient level to prevent bleeding events. The International Working Group in 2011 defined complete response when a platelet count >100,000/µL is achieved at 12 months with treatment (12). According to the new ASH guidelines, the therapeutic response is considered durable when a platelet count >30,000/µL is achieved, or if a doubling platelet count from the baseline is observed in symptomless patients 6 months after the therapy start. Early response occurs when a platelet count is ≥30,000/µL and at least doubling from the baseline at 1 week of therapy. Initial response is a platelet count ≥30,000/µL and at least doubling from the baseline at 1 month of therapy. Remission is defined by a persisting platelet count >100,000/µL at 12 months from the therapy start (4).

Steroid therapy and splenectomy are the most effective therapies for management of this disease. The cure rate of steroid therapy ranges from 64% to 88% (5,19-21).

In about 12–36% of patients relapse has been reported (5,22,23) and partial response has been observed in about 12% of cases (5,22).

While the ASH guidelines of 2011 outlined that there is limited evidence for treatment recommendation based on platelet count in ITP patients (12), new guidelines suggest the use of corticosteroids rather than observation in adults with new diagnosis of ITP and a platelet count <30,000/µL who are asymptomatic or have minor mucocutaneous bleeding (4). This indication does not significantly differ from the ASH guidelines of 1996, where treatment for newly diagnosed ITP should be indicated for patients with a platelet count <30,000/µL or in patients with a platelet count <50,000/µL with significant bleeding or risk of bleeding (24).

The recent ASH guidelines recommend the use of corticosteroids rather than rituximab plus corticosteroids for initial therapy in adults with newly diagnosed ITP, preferably administering a short course (<6 weeks) than a prolonged course (>6 weeks) of prednisone (4).

In corticosteroid-dependent adults or in non-responders to corticosteroids with ITP lasting ≥3 months, the new ASH guidelines suggest the use of a thrombopoietin receptor agonist (eltrombopag or romiplostim) rather than of rituximab or splenectomy (4,25).

Eltrombopag and romiplostim are safe and effective, even if they lead to an increased risk of thrombosis, and long-term toxicity is unknown. Rituximab has to be used in non-immunocompromised patients, but long-term remission rate is low. Also other drugs, such as dapsone and danazol, are safe and effective, and are preferred for treating elderly patients (26). Data from the Literature report that intravenous immunoglobulins and thrombopoietin receptor agonists, rituximab or immunosuppressors arise temporary benefit (26,27). A good strategy for management of patients with severe disease is obtained combining an immunosuppressant therapy with a thrombopoietin-receptor agonist may be (28).

Discordant opinions about the indication for splenectomy and the timing of surgery have been present over time. In fact, in 1996, ASH guideline panelsists (24) considered indications to splenectomy when the platelet count is <10,000/µL after 6 weeks or <30,000/µL after 3 months from diagnosis with or without bleeding. In the same consensus conference, the panelists considered splenectomy to be inappropriate in symptomless patients diagnosed from 6 months with a platelet count >50,000/µL and low hemorrhagic risk. In 2003, the British Committee
for Standards in Haematology guideline recommended splenectomy when the platelet count is <30,000/µL in cases refractory to medical treatment (29). Other authors (30) recommended early splenectomy in patients who do not respond quickly to initial glucocorticoid treatment. However, in a review of most series reported in the Literature, splenectomy was postponed later than 6 months from diagnosis (31). The latest ASH guideline suggests splenectomy instead of thrombopoietin-receptor agonists in adults with ITP lasting ≥3 months who are corticosteroid-dependent or have no response to corticosteroids (4).

The percentage of patients who need splenectomy ranges from 20% to 45% according to large series (32,33).

Although it is the second-line therapy in disease refractory to the medical treatment (34), splenectomy appears to be a long effect therapy (27), since the site of platelet destruction is removed.

As reported in the Literature, a complete response after splenectomy has the longer response (53%) and the higher rate of remission (68.8%) (5,6,21,22,35,36). The initial relapse rate may decline over time (22,37) with 15% relapse rate within the first year as reported in several studies (5,21-23,38) and two-thirds of patients remaining asymptomatic 10 years after surgery (37,39).

Despite the high response rate of splenectomy, the number of post-surgical failures remains significant and the knowledge of predictive factors for response to splenectomy could help selecting patients who will benefit from surgery. Several studies (23,32,35,40) have tried to correlate the response to splenectomy in ITP patients to some hypothetic predictive factors. Age and sex, length of the disease, time interval between diagnosis and surgery, length and response to the preoperative corticosteroid therapy have been often considered as predictive factors for response to splenectomy. In most studies, a better response to splenectomy was observed in patients older than 50 years (26,41), with higher preoperative platelet count (42,43) and complete or partial preoperative response to steroid therapy (22,35,42,44), with short length of disease (5) and with a temporary increase in platelet count after high-dose antibody therapy. On the other hand, other investigators could not demonstrate that age and sex (22,38,40,45), length of the disease (43), time between diagnosis and splenectomy (22,46), response to medical treatment (16,22) and preoperative platelet count (22,43,45,47) could predict the success of splenectomy. Other studies related positively the response to splenectomy to patients’ age less than 40 years (42-44) and lower preoperative platelet count (48).

Only a few studies have addressed the response to splenectomy in relation to the preoperative platelet count. Radaelli et al. (22) in a series of 65 adult patients who underwent splenectomy for ITP, did not find any relationship between response to splenectomy and preoperative platelet count. Balagué et al. (45) could not demonstrate that preoperative platelet count was a predictive factor of response to splenectomy in their univariate and multivariate statistical analysis on 103 ITP patients treated by splenectomy, since there was not a significant difference in the response comparing patients respectively with preoperative platelet counts less or more than 20,000/µL. Duperier et al. (23) observed a positive response to splenectomy in patients with a preoperative platelet count >70,000/µL in their study on 67 patients. In their univariate analysis, a statistical difference in outcome between two groups of patients respectively with more or less than 70,000/µL platelet was observed; younger patients and higher preoperative platelet count seemed to be correlated to a successful response to splenectomy. Patients with higher preoperative platelet count usually respond to splenectomy (43). In our series of two homogeneous groups of patients respectively with platelet count ≤ and >30,000/µL, a greater increase of platelet count after laparoscopic open surgery was recorded in patients with a lower preoperative platelet count. This result suggests that a low threshold of preoperative platelet count is an important indication for splenectomy in ITP patients. In our study, a higher increase in postoperative percent platelet count with a stable positive response can be found in patients with a preoperative platelet count ≤30,000/µL (49). In one of our previous studies comparing laparoscopic and open splenectomies groups for ITP (50), we observed that the greater increase of postoperative platelet count in patients with a lower preoperative platelet count seemed not to be related to the type of surgery. Explanations for this result are not known.

We hypothesized that a short diagnosis-to-surgery interval could be a factor influencing a good response to splenectomy, but some studies (5,22) did not demonstrate it. In our study (50), the better response to the laparoscopic removal of the spleen occurred in patients with the longer diagnosis-to-splenectomy interval. This result was not found in our open group. According to us, splenectomy should be better performed without increasing the morbidity, in patients who are not responding to medical treatment when the preoperative platelet count is ≤30,000/µL. In fact, laparoscopic surgery seems to correlate to hematological
benefits, since it reduces the need for platelets transfusion, and lower the perioperative blood loss and complications than open surgery (7,51,52).

Results after laparoscopic splenectomy in ITP patients have been reported only by a few studies in the Literature. Long-term remission rates ranged from 67.9% to 72% at 5 years after surgery (23,53-59). Data are still controversial when comparing the laparoscopic approach to the open approach. Shimomatsuya et al. (55) considered operating time, length of hospital stay, blood loss, and platelet count response and observed a minor blood loss during open splenectomy than laparoscopic splenectomy, without significant difference in the pre- and post-operative platelet count. Lozano-Salazar et al. (56) compared two groups of 26 and 22 ITP patients each, who respectively underwent open and laparoscopic splenectomy. Response rates were similar in both groups. Watson et al. (53) reported two groups of 47 patients and 13 patients each affected by ITP and operated respectively with open and laparoscopic splenectomy. The need of blood and platelet transfusions were reduced in the laparoscopic group. Long-term remission of platelet count was similar for the two techniques. Delaitre et al. (20) reported a relapse of ITP in 2 patients of the laparoscopic group and in 4 patients of the open group while comparing two groups of 28 patients each. Vecchio et al. (50) compared the results out of a laparoscopic and an open group of 20 patients each affected by ITP and observed a lesser amount of intraoperative blood loss in the laparoscopic group than in the open group. Need for platelet transfusion was lower in the laparoscopic group. Long-term results in platelet count were similar in both the open and the laparoscopic splenectomy groups. A positive response was observed in 80% of patients in the laparoscopic group and in 85% of patients in the open splenectomy group at 1 year after surgery. No statistical difference was observed in both the open and the laparoscopic groups when relating the rate of increase of the postoperative platelet count to age, sex, and length of preoperative therapy.

| Table 1 Factors with positive correlation for ITP response to splenectomy |
|---------------------------------|------------------|
| **Factors**                     | **Authors**      |
| Age (years)                     |                  |
| >50 years                       | Lucchini (26), Palandri (41) |
| <40 years                       | Guan (42), Kwiatkowska (43), Nyilas (44) |
| Pre-operative platelet count    |                  |
| Higher                          | Palandri (41), Guan (42), Kwiatkowska (43), Duperier (23) |
| Lower                           | Li (48), Vecchio (49) |
| No correlation                  | Radaelli (22), Balagué (45), Shimomatsuya (55) |
| Response to steroid therapy     | Radaelli (22), Elezović (35), Guan (42), Nyilas (44) |
| Length of disease               |                  |
| Short                           | Shojaiefard (5)  |
| Long                            | Vecchio (50)     |
| Surgical procedure              |                  |
| Open                            | –                |
| Laparoscopic                    | Delaitre (20)    |
| No correlation                  | Vecchio (50), Watson (53), Lozano-Salazar (56) |

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Footnote

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