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Title: **Treatment options for patients with continued severe ITP after failure of steroids and splenectomy.**

Authors: **James N. George, M.D.**, Oklahoma City, **George Buchanan M.D.** Dallas

This essay focuses on patients who continue to have very low platelet counts and persistent bleeding problems following splenectomy. This problem is most common in adults. Prolonged and symptomatic very low platelet counts are uncommon in children with ITP. After failure of splenectomy to provide a stable, safe platelet count, there is no clear sequence of appropriate treatments. It seems that every hematologist has their own idea of what treatment to try next, and then what treatment to explore after the previous treatment fails. There is no evidence from medical research that one treatment is better than another after failed splenectomy. This uncertainty creates a confusing and disturbing situation for both patients and their doctors, and suggests that careful consideration must be given to observation alone, with no specific drug treatment. Since all treatments have potentially serious side effects and none will predictably increase the platelet count, avoiding further drug treatment may be the best course to follow unless serious bleeding occurs, even for patients with very low platelet counts. When medication is required, the key consideration is to minimize side effects.

Most current drug treatments for ITP suppress the patient's immune production of antibodies against their own platelets. But of course this immune suppression also increases the risk for serious infection, because the patient's ability to make antibodies against viruses, bacteria, and other infectious agents is also suppressed. One new and currently popular immune suppressive drug is rituximab. Rituximab is one of a new class of drugs described as "biologic agents". It was initially produced as a mouse antibody that reacts against cells of the human immune system. Then, through molecular engineering, most pieces of the mouse antibody are replaced by human protein sequences, leaving only the tiny fraction of mouse protein required to react with the human immune cells. Rituximab has been remarkably effective in the treatment of malignant lymphomas, cancers of the immune system. Rituximab has also been effective in many autoimmune diseases, not only ITP but also lupus and rheumatoid arthritis. Although patients may have severe allergic reactions to the initial intravenous rituximab infusion, subsequent side effects are uncommon. The typical treatment consists of four intravenous infusions at one week intervals. About one-third to half of patients with severe and persistent ITP will respond to rituximab.

Other immune suppressive drugs used in ITP are less specific and more toxic. Many are also used as chemotherapy for malignant lymphoma and other forms of cancer. These agents include cyclophosphamide (cytoxan) and vincristine. Other drugs, used primarily as immune suppressants for patients who have received organ transplants, have also been effective in some patients with ITP, though responses occur in fewer than half of patients and the side effects may be serious. These agents include azathioprine (imuran), cyclosporine, and mycophenolate mofetil.

A novel approach to treatment of chronic ITP is to stimulate platelet production by the bone marrow rather than suppress the immune system in an attempt to decrease the rapid platelet destruction. Many hematologists thought that this approach would not work, since they assumed that platelet production in ITP is already operating at a maximum rate. However, the recent purification of thrombopoietin, the hormone that regulates platelet production, has opened a new way to treat ITP. Research on patients with ITP is currently being conducted in Europe and the United States using a modified version of the thrombopoietin hormone. It appears to have no serious side effect; while it increases platelet production. In normal volunteers, tiny doses of this hormone can increase platelet counts to over 1,000,000/L. Preliminary results have documented that patients with ITP, in whom other treatments have failed, can also respond with an increase in their platelet counts. Continuing research to completely understand the possible risks of this treatment, and how the doses should be adjusted, will require several more years. But if this research is successful, then persons with ITP may be able to give themselves injections of this hormone (under their skin, the same way that patients with diabetes give themselves insulin injections) every week or two to maintain platelets at a safe level and avoid the need for immune suppression treatment. The most important message for ITP sufferers is that there is much active and productive research directed at improving their lives.