EBM

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Presenter : R1 紀乃宇

大綱

- 臨床情境
- 臨床問題和形成PICO
- 文獻搜尋
- 文獻評讀
- 臨床的建議

臨床情境-- *(Clinical Scenario）*

- 一位**60** 歲女性因出現全身性小血斑入院治療，沒有系統性疾病。入院期間血小板數量低下**(2000/uL)**，經排除其他可能原因後，推測其為**免疫性血小板缺乏紫斑症(Immune thrombocytopenic purpura)**，傳統第一線藥物治療 **(prednisolone、IVIG)** 治療無效後，依據治療**guideline,** 應該**splenectomy**。但聽說**血漿置換術 (plasma exchange)** 也是一種治療方式。病人問:**血漿置換術對我的疾病幫助有多大?** 我們該如何回答這一個問題呢?

ASH 2011 evidence-based practice guideline for ITP

ITP in the adult

*Blood.*2011;117(16):4190-4207

Treatment of fresh case

- Suggest
  - Treat newly diagnosed patients with platelet count <30x10^9/L(2C)
  - Longer courses of steroid are preferred than short courses of steroid or IVIG as first-line treatment (2B)
  - IVIG combined with steroid if more rapid increase in platelet count desired(2B)
  - IVIG or anti-D as first line if steroid contraindicated(2C)
  - IVIG dose : 1g/Kg as one-time dose, repeated higher doses if necessary (2B)

Br J Haematol 1999;107(4):716-719.

Treatment of unresponsive or relapse cases after initial steroid

- Recommend
  - Splenectomy for patients failing steroid (1B)
  - The only treatment for sustained remission off all treatment at 1 year and beyond in a high proportion of patients
  - Deferred for at least 6 months after diagnosis

Blood. 2010;115(2):168-186.

臨床問題及PICO (ASK)

- ***An answerable question:***

–血漿置換術 **(plasma exchange) 治療Immune thrombocytopenic purpura 是否有幫助？**

- ***PICO:***

Patient/ Problem	**Immune thrombocytopenic purpura**
Intervention	**Plasma exchange (plasmapheresis)**
Comparison	**prednisolone**
Outcome	**Treatment response (platelet count)**

Type of question: Therapy

Search Strategy (Acquire)

- **Keyword:**

  idiopathic thrombocytopenic purpura

  immune thrombocytopenic purpura

  plasma exchange

- **Data base:**

  Pub-Med, Medline

以Immune thrombocytopenia purpura 和plasma exchange 為關鍵字搜尋PubMed ，共出現133篇文獻，其中1篇Free Full Text，2篇Review。分析其中文獻，與我們主題相關只有9篇。

- Systemic lupus erythematosus presenting as thrombotic thrombocytopenia purpura: how close is close enough?
- Perez CA, Abdo N, Shrestha A, Santos ES.
- Case Report Med. 2011;2011:267508. Epub 2011 May 10.
- PMID: 21629797 [PubMed] Free PMC Article

- [The effect of plasmapheresis on the clinical and laboratory parameters of patients with idiopathic thrombocytopenic purpura].
- Kerimov AA, Kalinichenko LG, Guseĭnov TN, Babaeva LI.
- Klin Med (Mosk). 1991 Nov;69(11):67-9. Russian.
- PMID: 1808413 [PubMed - indexed for MEDLINE]

- Plasma exchange in idiopathic thrombocytopenic purpura.
- Williams C, Buskard N, Bussel J.
- Curr Stud Hematol Blood Transfus. 1990;(57):131-51. Review. No abstract available.
- PMID: 2272199 [PubMed - indexed for MEDLINE]

- [Immunocorrective treatment of idiopathic thrombocytopenic purpura by plasmapheresis].
- Kovaleva LG, Reshetnikova ME, Kalinin NN, Petrova VI, Iakovleva ON.
- Gematol Transfuziol. 1989 Feb;34(2):9-12. Russian.
- PMID: 2707565 [PubMed - indexed for MEDLINE]

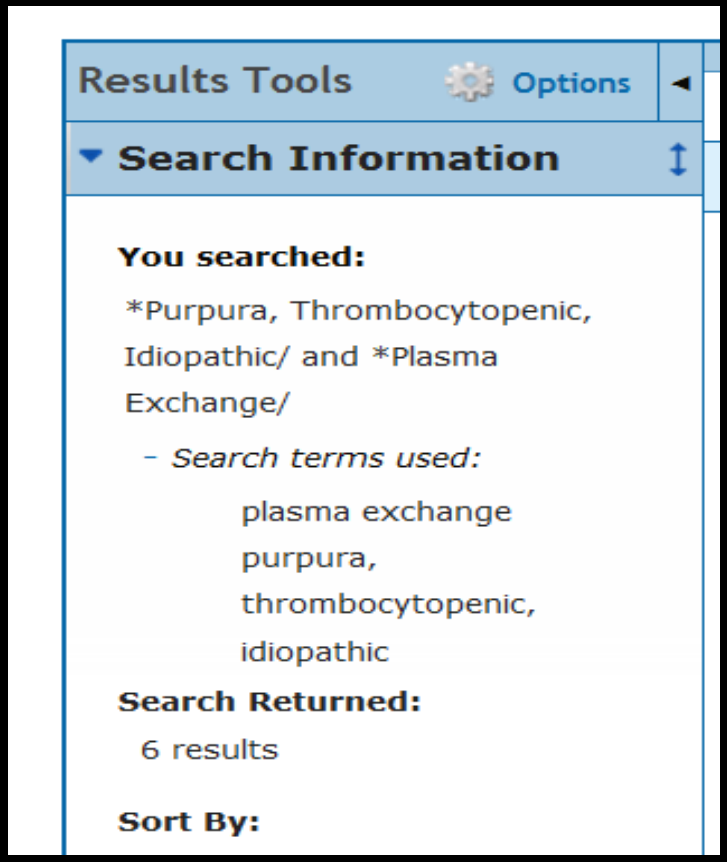
- Plasmapheresis for idiopathic thrombocytopenic purpura unresponsive to intravenous immunoglobulin.
- Pettersson T, Riska H, Nordström D, Honkanen E.
- Eur J Haematol. 1987 Jul;39(1):92-3. No abstract available.
- PMID: 3653382 [PubMed - indexed for MEDLINE]

- Idiopathic (autoimmune) thrombocytopenic purpura with a complement-fixing autoantibody and response to plasma exchange.
- Szatkowski NS, Aster RH.
- Scand J Haematol. 1985 Nov;35(5):525-30.
- PMID: 4089531 [PubMed - indexed for MEDLINE]
- Related citations

- Intensive plasma exchange therapy in ten patients with idiopathic thrombocytopenic purpura.
- Blanchette VS, Hogan VA, McCombie NE, Drouin J, Bormanis JD, Taylor R, Rock GA.
- Transfusion. 1984 Sep-Oct;24(5):388-94.
- PMID: 6435294 [PubMed - indexed for MEDLINE]

- One-year follow-up of plasma exchange therapy in 14 patients with idiopathic thrombocytopenic purpura.
- Marder VJ, Nusbacher J, Anderson FW.
- Transfusion. 1981 May-Jun;21(3):291-8.
- PMID: 7195085 [PubMed - indexed for MEDLINE]

- Plasma exchange in the treatment of fulminant idiopathic (autoimmune) thrombocytopenic purpura.
- Branda RF, Tate DY, McCullough JJ, Jacob HS.
- Lancet. 1978 Apr 1;1(8066):688-90.
- PMID: 76226 [PubMed - indexed for MEDLINE]



以Idiopathic thrombocytopenia purpura 和plasma exchange 為關鍵字搜尋Medline ，共出現6篇文獻，其中1篇Free Full Text，2篇Review。分析其中文獻，與我們主題相關有3篇。 我們選取治療型態、PICO相符、臨床情境與病人最符合之文獻1984年RCT文獻1篇。

[Inefficacy of plasma perfusion in thrombotic thrombocytopenic purpura and early relapse after plasmapheresis]. [Spanish]

Bergua JM. Santos A. Gracia A. Garcia Blanco MJ.

Sangre. 40(5):439-40, 1995 Oct.

[Case Reports. Letter] UI: 8553186

Plasma exchange in idiopathic thrombocytopenic purpura. [Review] [58 refs]

Williams C. Buskard N. Bussel J.

Current Studies in Hematology & Blood Transfusion. (57):131-51, 1990.

[Journal Article. Review] UI: 2272199

Intensive plasma exchange therapy in ten patients with idiopathic thrombocytopenic purpura.

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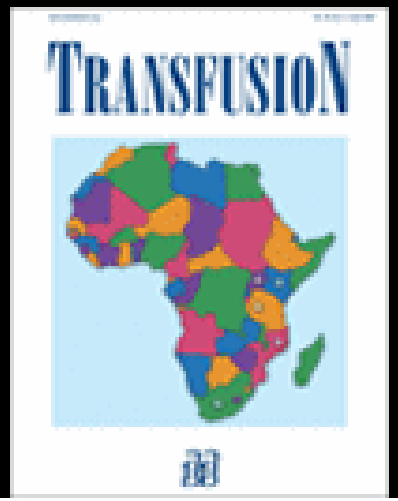
Transfusion. 24(5):388-94, 1984 Sep-Oct.

[Journal Article] UI: 6435294

- The Canadian Experience Using Plasma Exchange for Immune Thrombocytopenic Purpura

Transfusion. 24(5):388-94, 1984 Sep-Oct.



此篇文獻納入理由

★ 最符合臨床問題
★ 最佳研究設計
★ 有全文可供評讀
★ 臨床納入人數最多

Inclusion Criteria:

➔ 23 patients collected for 20 years:

- ✓ ITP of less than 6 months duration
- ✓ With no or only a partial response to prednisone (minimum dosage 1 mg/kg/day)
- ✓ Be over 18 years of age
- ✓ Platelet count of <100 * 109/L
- ✓ No prior treatment with immunosuppressive agents other than prednisone.

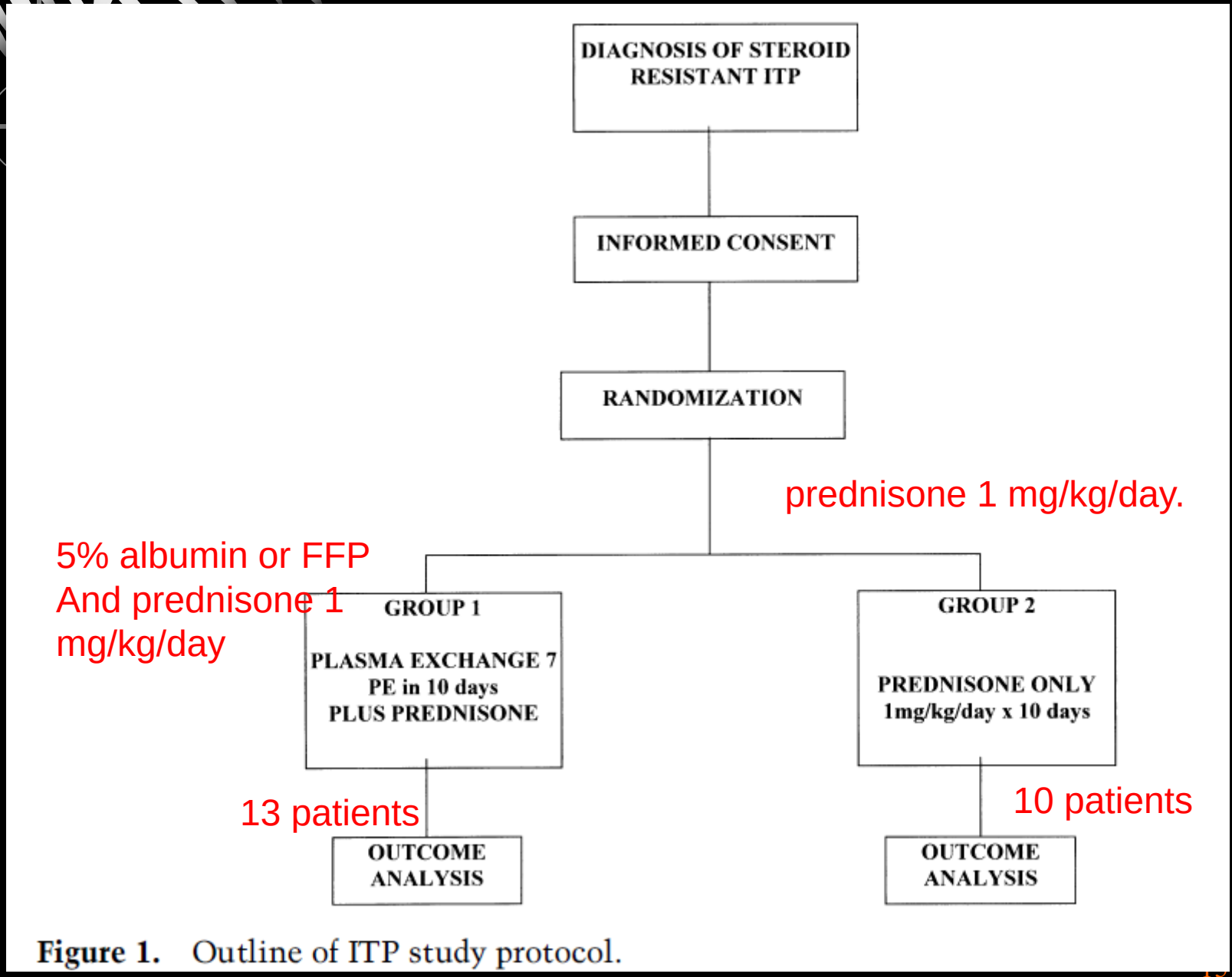


Figure 1. Outline of ITP study protocol.

Transfusion. 24(5):388-94, 1984 Sep-Oct.

Table 1. Patient Outcome At End of Treatment*

Treatment	Response	Partial response	Failure	Total
PE and prednisone	8	3	2	13
Prednisone only	4	0	6	10
Total	12	3	8	23

*Treatment period was 7 out of 10 days for PE and 10 days for prednisone.

. **Complete response** (platelet count >100*10^9/L on day 11)

. **Partial response** (platelet count on day 11 >50*10^9/L and at least twice the platelet count before therapy started)

.**Treatment failure**

➔**Treatment response: 11/13 VS 4/10** ($p < 0.05$)

➔**Complete respones: 8/13 vs 4/10** ($p > 0.05$)

Transfusion. 24(5):388-94, 1984 Sep-Oct.

End point

Table 2. Patient Outcome At 6 Month Follow-up

Treatment	Response	Partial response	Failure	Total
PE and prednisone	8	3	1	12
Prednisone only	3	3	1	7
Total	11	6	2	19

Transfusion. 24(5):388-94, 1984 Sep-Oct.

What question did the systematic review addressed (PICO) 想要回答什麼問題？

☐ 是	☐ 否	☐ 不清楚

評論：

- [P]:A patient has Immune thrombocytopenic purpura
- [I]:Treatment with Plasma exchange (plasmapheresis)
- [C]:Prednisolone treatment only
- [O]:Treatment response (platelet count)

所取樣本是否有臨床代表性，是否與我的病人差不多

☐ 是	☐ 否	☐ 不清楚

評論：**eligible for entry,**

The patient should have below criteria

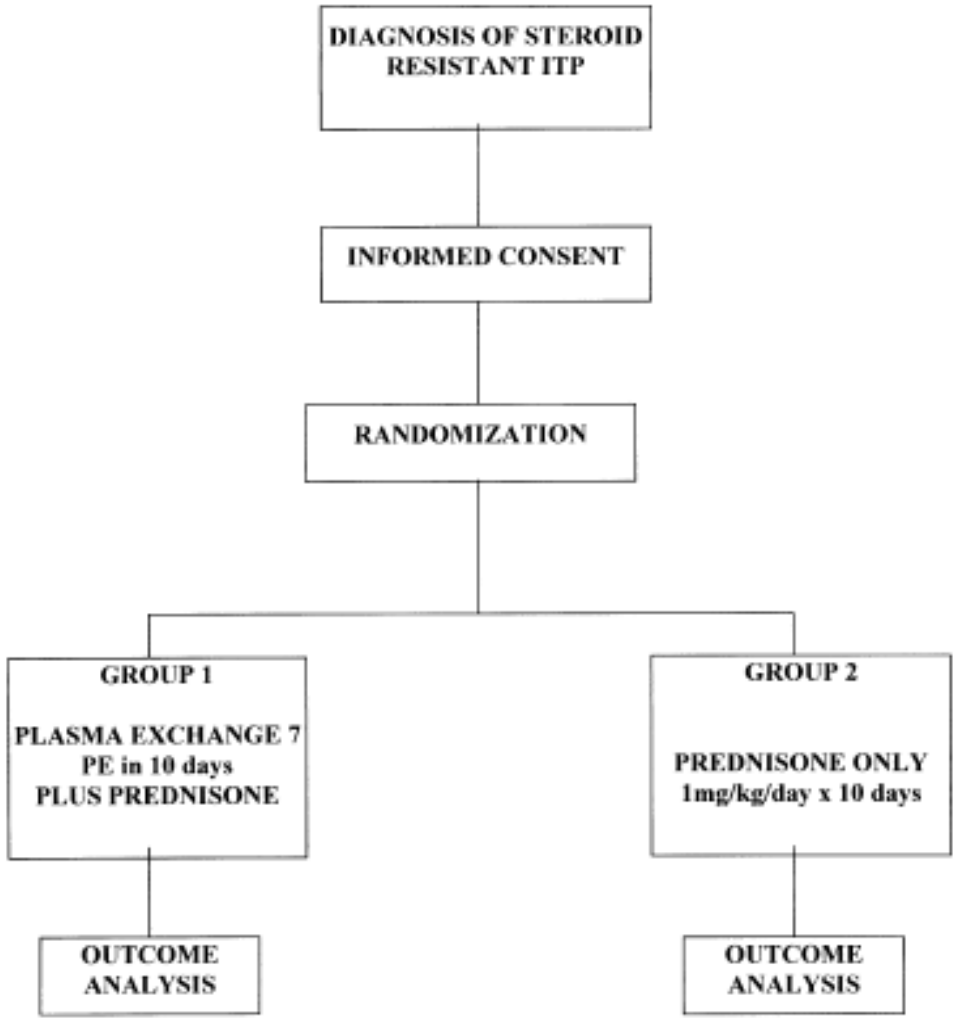
- ✓ITP of less than 6 months duration
- ✓With no or only a partial response to prednisone (minimum dosage 1 mg/kg/day)
- ✓Be over 18 years of age
- ✓Platelet count of <100 * 109/L
- ✓No prior treatment with immunosuppressive agents other than prednisone.

分組是否有隨機盲法分組

☐是	■ 否	☐ 不清楚

評論：

Only randomization, not a double-blind trial



失去追蹤個案數是否過多？5/20% rule

□是	■否	□ 不清楚
評論：		

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4 of 23 → < 5/20 % rule

I & C是否清楚描述並且是可行的

☐ 是	☐ 否	☐ 不清楚
評論： 確實比較 **prednisolone only** 與 **prednisolone** 加上 **plasma exchange** 的效果		

測量方式是否客觀，有無雙盲

■ 是	□ 否	□ 不清楚

評論：

Monitoring was done daily during treatment
monthly for 4 months and finally at 6 months post entry.

Samples for this specialized testing were frozen and shipped
to the referral laboratories at 1 month intervals.

此測量方式不需要雙盲

測量結果的時間點是否合乎邏輯

■ 是	☐ 否	☐ 不清楚
評論： Monitoring was done daily during treatment, and D11 monthly for 4 months and finally at 6 months post entry.		

追蹤是否夠久

☐ 是	☐否	☐ 不清楚

評論：
追蹤6個月，屬於急性期治療效果

Reviewers‘ conclusions (Appraise)

- Plasma exchange 對於急性期;且對於steroid 治療無反應的病人，可以考慮同時治療，在6個月內treatment response 較高。

臨床應用(Clinical practice)與現況分析: (Apply)

- 即使文獻對於plasma exchange 在急性期的ITP 有支持性的文獻(許多都是case report)，但最新版的ASH 2011 治療ITP guideline 仍沒有將其納入治療選項。

Thanks for your attention !!

Phases of ITP

- Newly-diagnosed ITP: within three months of diagnosis
- Persistent ITP: 3 to 12 months from diagnosis. Patients not reaching spontaneous remission or not maintaining complete response off-therapy
- Chronic ITP: lasting for more than 12 months

- Rodeghiero F et al. *Blood* 2009;113:2386–2393

Consensus Report Recommendations: Overview of Management Options

Clinical situation	Therapy option	
First line (initial treatment for newly diagnosed ITP)	Anti-D Corticosteroids: dexamethasone, methylprednisolone, prednis(ol)one Intravenous immunoglobulin	
Second line*	Azathioprine Cyclosporin A Cyclophosphamide Danazol Dapsone	Mycophenolate mofetil Rituximab Splenectomy Thrombopoietin mimetic agents Vinca alkaloids
Treatment for refractory ITP (patients failing first- and second-line therapies)	**Category A: treatment options with sufficient data** Thrombopoietin-receptor agonists **Category B: treatment options with minimal data and considered to have potential for considerable toxicity** Campath-1H Combination of first- and second-line therapies Combination chemotherapy Hemopoietic stem cell transplantation	

Rodeghiero Fetal.*Blood*2009;113:2386–2393

Diagnosis

- Recommend
  - Check HCV and HIV (1B)
- Suggest
  - Further investigation if abnormalities other than thrombocytopenia (including IDA) in the blood count or smear (2C)
  - Bone marrow examination not necessary irrespective of age with typical ITP(2C)
- Insufficient evidence to recommend routine check anti-platelet Ab , APA, ANA, TPO levels

***Blood.*2011;117(16):4190-4207**

Treatment of unresponsive or relapse cases after initial steroid

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  - The only treatment for sustained remission off all treatment at 1 year and beyond in a high proportion of patients
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- Against further treatment in asymptomatic patients after splenectomy with platelet count >30x10^9/L (1C)

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  - IVIG combined with steroid if more rapid increase in platelet count desired(2B)
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  - IVIG dose : 1g/Kg as one-time dose, repeated higher doses if necessary (2B)

Br J Haematol 1999;107(4):716-719.

Table 1. Univariate Analysis of Clinical and Laboratory Variables Associated with the Outcome at Six Months among the 106 Patients with an Initial Response.*

Variable	Sustained Response at 6 Mo	Relapse within 6 Mo	P Value
Age (yr)	46.7±18.2	45.8±18.5	0.80
Sex (no.)			0.31
Female	33	40	
Male	20	13	
Platelet count (per mm³)			
Pretreatment	12,300±11,600	13,500±11,800	0.63
Day 3	46,700±16,500	42,100±23,400	0.34
Day 10	132,600±41,900	84,700±37,000	<0.001
3 Mo	185,100±73,400	59,100±57,500	<0.001

-Plt at D10<90X10^ 9/L->70% relapse
-36% required additional treatment
-42% had plt >50X10^ 9/L at 6 months

N Engl J Med 2003;349(9):831-836.

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