APPENDIX 1: LITERATURE SEARCH STRATEGIES

Search Method

Databases searched were MEDLINE (1966 to December week 3 2007), Embase (1980 to 2007 week 50), Biosis previews (1990 to December 20, 2007), Econlit (searched Aug 2, 2006) and TRIP database (searched Aug 2, 2006). The following databases of The Cochrane Library were searched: CDSR, Central, HTA, and NHS EED (4th quarter 2007). Supplemental searching for epidemiology, standard care and emerging treatment for ITP was undertaken in MEDLINE (1950 to January Week 5 2007).

*CADTH IVIG - MEDLINE*

1. exp Purpura, Thrombocytopenic/
2. (thrombocytop$ adj2 purpur$).mp.
3. ((Idiopathic or immun$) adj2 thrombocytop$).mp.
4. ITP.mp.
5. or/1-4
6. Immunoglobulins, Intravenous/
7. (ivig or igiv or ivy or ivigg).mp.
8. (intravenous immunoglobulin$ or intravenous immune globulin$ or iveegam$ or gammaglobulin$ or gammadigm$ or gammimune$ or gammimmune$ or gammimmund$ or gammad$ or gammadg$ or sandoglobulin$).mp.
9. (intraglobulin$ or venoglobulin$ or polygam$ or gammonativ$ or intraglob$ or alphaglobin$ or endobulin$ or venimmune$ or (globulin adj N) or intravenous ig).mp.
10. (Intravenous antibod$ or iv immunoglobulin$).mp.
11. or/6-10
12. 5 and 11
13. limit 12 to animals
14. limit 12 to humans
15. 13 not (13 and 14)
16. 12 not 15
17. limit 16 to ("clinical prediction guides (sensitivity)" and (consensus development conference or consensus development conference, nih))
18. limit 16 to systematic reviews
19. limit 16 to meta analysis
20. limit 16 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial)
22. clinical trials/
23. (randomized or randomly or placebo).ab.
24. trial.ti.
25. or/21-24
26. "Value of Life"/
27. (ECONOMICS or COST or COSTS or COST-BENEFIT or PRICES or PRICING).ti,ab.
28. (EXPENDITURES or BUDGETS or QUALITY ADJUSTED LIFE YEARS or QUALITY-ADJUSTED LIFE YEARS or QALYS).ti,ab.
29. (WILLINGNESS TO PAY or VALUE OF LIFE or LIFE VALUE or ECONOMETRICS).ti,ab.
30. 16 and (or/26-29)
31. limit 16 to "costs (sensitivity)"
32. limit 16 to "economics (sensitivity)"
33. or/30-32
34. 16 and (or/17-20,25,33)
35. 16 not 34
36. limit 35 to english language
37. Or/34,36

**CADTH ITP IVIG - EMBASE**

1. Idiopathic thrombocytopenic purpura/
2. (thrombocytop$ adj2 purpur$).mp.
3. ((Idiopathic or immun$) adj2 thrombocytop$).mp.
4. ITP.mp.
5. or/1-4
6. Immunoglobulin/
7. (ivig or igiv or igv or ivigg).mp.
8. (intravenous immunoglobulin$ or intravenous immune globulin$ or iveegam$ or gammaglobulin$ or gamimmune$ or gammimune$ or gammimmune$ or gammaguard$ or gamaguard$ or gamagard$ or gammagard$ or sandoglobulin$).mp.
9. (intraglobulin$ or venoglobulin$ or polygam$ or gammonativ$ or intraglobin$ or alphaglobin$ or endobulin$ or venimmune$ or (globulin adj N) or intravenous ig).mp.
10. (Intravenous antibod$ or iv immunoglobulin$).mp.
11. or/6-10
12. 5 and 11
13. limit 12 to (amphibia or ape or bird or cat or cattle or chicken or dog or "ducks and geese" or fish or "frogs and toads" or goat or guinea pig or "hamsters and gerbils" or horse or monkey or mouse or "pigeons and doves" or "rabbits and hares" or rat or reptile or sheep or swine)
14. limit 12 to humans
15. 12 not (13 not 14)
16. evidence based medicine/ or consensus development/ or meta analysis/ or "systematic review"/ or practice guideline/ or clinical pathway/ or clinical protocol/ or good clinical practice/
17. exp clinical trial/
18. (randomized or randomly or placebo).ab.
19. trial.ti.
20. or/16-19
21. (ECONOMIC$ or COST or COSTS or COST-BENEFIT or PRICES or PRICING).ti,ab.
22. (EXPENDITURES or BUDGETS or QUALITY ADJUSTED LIFE YEARS or QUALITY-ADJUSTED LIFE YEARS or QALY$).ti,ab.
23. (WILLINGNESS TO PAY or VALUE OF LIFE or LIFE VALUE or ECONOMETRIC$).ti,ab.
24. COST BENEFIT ANALYSIS/ or COST UTILITY ANALYSIS/ or HEALTH CARE COST/ or QUALITY ADJUSTED LIFE YEAR/
25. ECONOMICS/ or ECONOMIC ASPECT/ or ECONOMIC EVALUATION/ or COST EFFECTIVENESS ANALYSIS/
26. or/21-25
27. 15 and (or/20,25)
28. 15 not 27
29. limit 28 to english language
30. or/27,29
CADTH ITP IVIG - CDSR & CENTRAL

1. exp Purpura, Thrombocytopenic/
2. (thrombocytopen$ adj2 purpur$).mp.
3. ((Idiopathic or immun$) adj2 thrombocytopen$).mp.
4. ITP.mp.
5. or/1-4
6. Immunoglobulins, Intravenous/
7. (ivig or igiv or igv or ivigg).mp.
8. (intravenous immunoglobulin$ or intravenous immune globulin$ or iveegam$ or gammaglobulin$ or gamimmune$ or gammimmune$ or gammaguard$ or gamaguard$ or gamagard$ or gammagard$ or sandoglobulin$).mp.
9. (intraglobulin$ or venoglobulin$ or polygam$ or gammonativ$ or intraglobin$ or alphaglobin$ or endobulin$ or venimmune$ or (globulin adj N) or intravenous ig).mp.
10. (Intravenous antibod$ or iv immunoglobulin$).mp.
11. or/6-10
12. 5 and 11
13. limit 12 to protocols
14. from 13 keep 70-72
15. 12 not 14

Cochrane HTA & NHS EED

#1 (ivig or igiv or igv or ivigg):ti,ab,kw in Technology Assessments and Economic Evaluations 1 edit delete
#2 (intravenous immunoglobulin* or intravenous immune globulin* or iveegam* or gammaglobulin* or gamimmune* or gamimmune* or gammimmune* or gammaguard* or gamaguard* or gamagard* or gammagard* or sandoglobulin* or intraglobulin* or venoglobulin* or polygam* or gammonativ* or intraglobin* or alphaglobin* or endobulin* or venimmune* or (globulin and N) or intravenous ig or Intravenous antibod* or iv immunoglobulin*):ti,ab,kw in Technology Assessments and Economic Evaluations 55 edit delete
#3 (#1 OR #2)

Biosis Previews - IVIG ITP

#5 606 (#1 or #2) and (#3 or #4)
DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes; Database=BIOSIS Previews; Timespan=1990-2006

#4 6,586 TS=(ivig or igiv or igv or ivigg or intravenous immunoglobulin* or intravenous immune globulin* or iveegam* or gammaglobulin* or gamimmune* or gamimmune* or gammimmune* or gammaguard* or gamaguard* or gamagard* or gammagard* or sandoglobulin* or intraglobulin* or venoglobulin* or polygam* or gammonativ* or intraglobin* or alphaglobin* or endobulin* or venimmune* or (globulin same N) or intravenous ig or Intravenous antibod* or iv immunoglobulin*)
#3 3,745 TS=(Intravenous Immunoglobulin*)
#2 6,765 TS=((Idiopathic or immun*) same thrombocytop*) or (thrombocytop* same purpur*) or ITP)

#1 691 DS=idiopathic Thrombocytopenic Purpura

**Econlit**

KW=((ivig or igiv or igv or ivigg or intravenous immunoglobulin* or intravenous immune globulin* or iveggam* or gammaglobulin* or gamimune* or gammimmune* or gammimmune* or gammaguard* or gamaguard* or gamagard* or gammagard* or sandoglobulin* or intraglobulin* or venoglobulin* or polygam* or gammonativ* or intraglobin* or alphaglobin* or endobulin* or venimmune* or (globulin same N) or intravenous ig or Intravenous antibod* or iv immunoglobulin*)

not (polygamy or polygamous))

TRIP database

intravenous immunoglobulin* or IVIG
Thrombocytopenic Purpura

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**CADTH ITP IVIG - epidemiology and major articles supplement**

**MEDLINE**

1. *Purpura, Thrombocytopenic, Idiopathic/ep
3. How I treat idiopathic thrombocytopenic purpura.ti.
4. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods.ti.
5. High risk of severe bleeding in aged patients with chronic idiopathic.ti.
6. Therapy for Adults with Refractory Chronic Immune Thrombocytopenic Purpura.ti.
12. or/1-11

**CADTH ITP IVIG - standard care supplement**

**MEDLINE**

1. exp Purpura, Thrombocytopenic/
2. (thrombocytop$ adj2 purpur$).mp.
3. ((Idiopathic or immun$) adj2 thrombocytop$).mp.
4. ITP.mp.
5. or/1-4
6. Immunoglobulins, Intravenous/
7. (ivig or igiv or igv or ivigg).mp.
8. (intravenous immunoglobulin$ or intravenous immune globulin$ or iveegam$ or gammaglobulin$ or gamimune$ or gammimmune$ or gammimmune$ or gammimmune$ or gammaguard$ or gamaguard$ or gamagard$ or gammagard$ or sandoglobulin$).mp.
9. (intraglobulin$ or venoglobulin$ or polygam$ or gammonativ$ or intraglobin$ or alphaglobin$ or endobulin$ or venimmune$ or (globulin adj N) or intravenous ig).mp.
10. (Intravenous antibod$ or iv immunoglobulin$).mp.
11. or/6-10
12. 5 and 11
13. limit 12 to animals
14. limit 12 to humans
15. 13 not (13 and 14)
16. 12 not 15
17. limit 16 to ("clinical prediction guides (sensitivity)" and (consensus development conference or consensus development conference, nih))
18. limit 16 to systematic reviews
19. limit 16 to meta analysis
20. limit 16 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial)
22. clinical trials/
23. (randomized or randomly or placebo).ab.
24. trial.ti.
25. or/21-24
26. "Value of Life"/
27. (ECONOMIC$ or COST or COSTS or COST-BENEFIT or PRICES$ or PRICING).ti,ab.
28. (EXPENDITURE$ or BUDGET$ or QUALITY ADJUSTED LIFE YEARS or QUALITY-ADJUSTED LIFE YEARS or QALY$).ti,ab.
29. (WILLINGNESS TO PAY or VALUE OF LIFE or LIFE VALUE or ECONOMETRIC$).ti,ab.
30. 16 and (or/26-29)
31. limit 16 to "costs (sensitivity)"
32. limit 16 to "economics (sensitivity)"
33. or/30-32
34. 16 and (or/17-20,25,33)
35. 16 not 34
36. limit 35 to english language
37. or/34,36
38. Splenectomy/
39. Rituximab.mp.
40. exp Adrenal Cortex Hormones/
41. or/38-40
42. 5 and 41
43. limit 42 to randomized controlled trial
44. 42 and (or/26-29)
45. limit 42 to "costs (sensitivity)"
46. limit 42 to "economics (sensitivity)"
47. or/43-46
APPENDIX 2: DATA ABSTRACTION AND QUALITY ASSESSMENT FORMS

Publication
- Refid number, author, publication year
- Number of review-relevant studies that this report describes
- Publication type (full study report or abstract - exclude abstract) Companion papers, refid number and type (e.g. subgroup analysis, pharmacoeconomic analysis)
- Country in which the study was conducted Number of sites (multicenter or single center)
- Funding source and specify type of funding (government, industry, private or non-industry, hospital, other, not reported, can't tell)

Study design

Specify type of RCT
- RCT: parallel design
- RCT: cross-over design
- conditional (specify conditions and timing)
- complete crossover
- RCT: factorial design
- identify any problems with the research design e.g. inappropriateness of run-in and washout periods or its implementation:
- study duration, including follow-up observation, open-label extension phases

Population
- sample size (report total N and by arm)
  a) N screened if available:
  b) N enrolled
  c) N completing study
  d) N evaluable
- study inclusion criteria including platelet count at enrolment
- study exclusion criteria including any concurrent conditions or risk factors for adverse events associated with treatment medication
- age: mean/median age (SD; range) of study participants: note if all children or all adults (exclude exclusively neonatal populations as per screening)
- classify group as children (< 18 years of age); adults (≥ 18 years of age) or mixed population
- gender (% female)
- racial groups identified as participants
- concurrent conditions (ITP in association with other conditions e.g. Evans Syndrome, SLE were excluded in screening - confirm here); note if ITP in pregnant women
- baseline characteristics - specify any differences between groups
- prior treatment for ITP
• prior use of IVIg and note if response is part of selection criteria for the study

**ITP classification**
- Acute ITP (e.g. newly diagnosed and untreated)
- Chronic ITP (report mean duration of disease)
- Recurrent ITP (relapse after acute at > 6 months)
- Refractory ITP
- Mixed population (acute and chronic)

**ITP severity** - note bleeding (wet, dry purpura, significant bleeding); platelet count

**Intervention**
- IVIg - specify product name/manufacturer; dose and dosing regimen; interval before repeated infusion
- comparator - dose/dosing regimen
- mandated or allowed pre-medications (pre-infusion)

**Efficacy Outcomes (report per group)**
- overall mortality, N (%):
- mortality due to hemorrhage; treatment-related mortality:
- Incidence of hemorrhage/bleeding:
  a) intracranial hemorrhage
  b) other major bleeding episodes (define e.g., bleeding causing hemodynamic compromise, a drop in hemoglobin or requiring transfusion)
  c) recurrent bleeding (define)
  d) decrease in bleeding (define; observation period)
  e) minor bleeding (define)
- total serious adverse events (treatment or condition-related) e.g. intracranial hemorrhage; thrombosis; renal dysfunction
- for acute ITP populations, % of patients progressing to chronic ITP
- incidence of splenectomy
- quality of life measurements.
- platelet counts (\(10^9/L\)) (mean/SD (range), or median/range)
  a) Baseline counts and counts at specified time intervals post treatment or on treatment
  b) Time to platelet recovery post initiation of treatment: i.e. days to platelet count \(\geq 20\), \(\geq 50\), \(>150\) \((x 10^9)/L\)
  c) Observation period(s) (report all intervals): mean/SD, median/range platelet count for each period
  d) Duration of followup time with platelet count \(\geq 20\), 50 or 150 \((x 10^9)/L\) (and specify duration of followup)
  e) Number of patients (%) with a platelet count \(\geq 50 \times 10^9/L\) at 24, 48 and 72 h
  f) Number of patients (%) with a platelet count \(\geq 20 \times 10^9/L\) at 24, 48 h and 72 h
  g) Number of patients (%) with "partial remission or response" [definition and observation period]
  h) Number of patients with "complete remission or response" [definition and observation period]
Patients requiring additional treatment (or retreatment) (and definition of relapse or indication for re-treatment)

Adverse Events (AE)

- total number of patients experiencing one or more AE
- withdrawal due to adverse events (WDAE), N (%) per group
- serious adverse events (SAE), N (%) per group; specify details of each SAE (note some SAE recorded above as efficacy outcomes for ITP)
- specific AE reported, N (%) per group
  record all specific reported AE;
  also note if the following are reported:
  a) hypersensitivity reactions
  b) volume overload signs or symptoms
  c) fever
  d) headaches
  e) aseptic meningitis; CSF changes; meningismus
  f) nausea and/or vomiting
  g) renal dysfunction
  h) liver dysfunction (e.g., transaminase elevation)
  i) hemolysis or hemolytic anemia
  j) neutropenia or other cytopenia; other hematological abnormality:
  k) vascular thrombosis (specify details)
  l) cardiac events

Note any prespecified laboratory monitoring for AE (e.g. biochemical evidence of hemolysis)
Quality Assessment Forms:
Randomized controlled Trials (Jadad Scale\textsuperscript{38})

The Jadad instrument, as described in Jadad et al. 1996 is as follows:

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)? yes = 1 point; no = 0 points

For question 1, give one additional point if the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, etc.).

For question 1, deduct 1 point if the method to generate the sequence of randomization as described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)

2. Was the study described as double blind? yes = 1 point; no = 0 points

For question 2, give 1 additional point if the method of doubling blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.).

For question 2, deduct 1 point if the method of double blinding was described and it was inappropriate (e.g., comparison of tablet vs injection with no double dummy).

3. Was there a description of withdrawals and dropouts? yes = 1 point; no = 0 points

Total possible score = 5 points

Allocation Concealment (Schultz treatment allocation concealment questionnaire\textsuperscript{39}):
1 = yes; 0 = no

A: Adequate
- Sequentially numbered, opaque, sealed envelopes (SNOSE)
- Pharmacy controlled
- Numbered or ordered containers
- Central randomization - for example by telephone to a trials office or other method whose description contained elements convincing of concealment - for example a secure computer assisted method.

I: Inadequate
- Alternation
- Reference to case record numbers or to dates of birth

U: Unclear
- No mention of an allocation concealment approach at all
- An approach that does not fall into either adequate or inadequate allocation concealment
APPENDIX 3: QUOROM FLOW CHART

Stage 1

1577 citations from electronic search

907 reports excluded (L1)

Stage 2

670 potentially relevant reports were eligible for further assessment (full text)

593 reports excluded
- not potentially relevant (43)
  i.e. not a report on IgIV utilization patterns, or the efficacy/effectiveness and/or harms associated with IVIG treatment of acute or chronic ITP in children or adults
- non-English (33)
- potentially relevant (English language) reports but not an RCT (283)
- neonatal or antenatal treatment of thrombocytopenia of any cause in neonates (56)
- thrombocytopenia in association with a co-morbidity e.g. HIV; Evans syndrome; SLE; others (145)
- use of anti-D immunoglobulin without a polyclonal IgIV arm (23)
- unobtainable for review (9)

Continued on next page
Two hundred and forty two citations were identified from an update search using the same search strategies. However, all were excluded from data analysis, for the reasons of: no efficacy and/or harm outcomes data (78), not appropriate study design (15), and duplicate from the original search (149).

27 reports identified as potentially relevant to pharmacoeconomics review at L2, and will be evaluated in the economic review.

Stage 3

77 relevant reports further assessed (L3)

50 reports were identified as relevant RCTs for clinical review at L2

19 abstracts excluded

31 reports of 28 unique RCTs included in clinical review

* Two hundred and forty two citations were identified from an update search using the same search strategies. However, all were excluded from data analysis, for the reasons of: no efficacy and/or harm outcomes data (78), not appropriate study design (15), and duplicate from the original search (149).
APPENDIX 4: FIGURES SECONDARY OUTCOMES IN CHILDREN AND ADULTS WITH ITP

Figure 1. IvIg versus corticosteroid in acute ITP: proportions of children with platelet count ≥20×10^9/L at 24h

<table>
<thead>
<tr>
<th>Study of sub-category</th>
<th>MG</th>
<th>Steroids</th>
<th>RR (random)</th>
<th>Weight</th>
<th>RR (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchette 93</td>
<td>11/19</td>
<td>6/18</td>
<td>12.32</td>
<td>1.74 (0.81, 3.70)</td>
<td></td>
</tr>
<tr>
<td>Hamnute 94 (c)</td>
<td>57/65</td>
<td>11/25</td>
<td>24.01</td>
<td>1.90 (1.10, 3.28)</td>
<td></td>
</tr>
<tr>
<td>Ruski 35</td>
<td>17/23</td>
<td>11/20</td>
<td>33.21</td>
<td>1.94 (0.94, 2.49)</td>
<td></td>
</tr>
<tr>
<td>Ancora 02</td>
<td>10/42</td>
<td>10/31</td>
<td>27.47</td>
<td>1.47 (0.60, 3.48)</td>
<td></td>
</tr>
<tr>
<td>Dona 02</td>
<td>5/12</td>
<td>2/16</td>
<td>2.83</td>
<td>1.50 (0.58, 7.43)</td>
<td></td>
</tr>
<tr>
<td>Total (63%) CI</td>
<td>164</td>
<td>124</td>
<td>1.00 (1.15, 1.83)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 91 (MG), 43 (Steroids)
Test for heterogeneity: Chi² = 1.96, df = 4 (P = 0.90), I² = 6%
Test for overall effect: Z = 3.22 (P = 0.001)

Favours Steroids  Favours MG

Figure 2. IvIg versus corticosteroid in acute ITP: proportions of children with platelet count ≥20×10^9/L at 48h

<table>
<thead>
<tr>
<th>Study of sub-category</th>
<th>MG</th>
<th>Steroids</th>
<th>RR (random)</th>
<th>Weight</th>
<th>RR (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchette 93</td>
<td>16/18</td>
<td>12/18</td>
<td>20.59</td>
<td>1.42 (1.01, 2.00)</td>
<td></td>
</tr>
<tr>
<td>Hamnute 94 (c)</td>
<td>40/65</td>
<td>25/33</td>
<td>41.26</td>
<td>1.30 (1.01, 1.66)</td>
<td></td>
</tr>
<tr>
<td>Ancora 02</td>
<td>19/42</td>
<td>20/33</td>
<td>20.22</td>
<td>1.25 (0.89, 1.76)</td>
<td></td>
</tr>
<tr>
<td>Dona 02</td>
<td>8/12</td>
<td>8/12</td>
<td>7.51</td>
<td>1.00 (0.57, 1.76)</td>
<td></td>
</tr>
<tr>
<td>Enkara 03</td>
<td>10/22</td>
<td>10/22</td>
<td>19.14</td>
<td>1.90 (1.17, 3.09)</td>
<td></td>
</tr>
<tr>
<td>Total (63%) CI</td>
<td>164</td>
<td>126</td>
<td>1.00 (1.14, 1.56)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 105 (MG), 76 (Steroids)
Test for heterogeneity: Chi² = 3.32, df = 4 (P = 0.93), I² = 6%
Test for overall effect: Z = 1.70 (P = 0.089)

Favours Steroids  Favours MG
### Figure 3. IVIg versus corticosteroid in acute ITP: proportions of children with platelet count ≥20×10^9/L at 72h

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>IVIg</th>
<th>Steroids</th>
<th>RR (random)</th>
<th>Weight</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchette 93</td>
<td>18/39</td>
<td>15/18</td>
<td></td>
<td>19.52</td>
<td>1.14 (0.96, 1.43)</td>
</tr>
<tr>
<td>Blanchette 94 (c)</td>
<td>66/69</td>
<td>51/39</td>
<td></td>
<td>27.66</td>
<td>1.20 (1.02, 1.42)</td>
</tr>
<tr>
<td>Aronsco 02</td>
<td>45/42</td>
<td>25/33</td>
<td></td>
<td>24.73</td>
<td>1.28 (1.04, 1.58)</td>
</tr>
<tr>
<td>Duht 02</td>
<td>11/12</td>
<td>11/12</td>
<td></td>
<td>18.04</td>
<td>1.00 (0.79, 1.27)</td>
</tr>
</tbody>
</table>

Total (95% CI) 142/104
Total events: 196 (IVIg), 83 (Steroids)
Tests for heterogeneity: Q = 2.89, df = 3 (P = 0.44), I² = 6%
Test for overall effect: Z = 2.48 (P = 0.003)

### Figure 4. IVIg versus corticosteroid in acute ITP: proportions of children with platelet count ≥20×10^9/L at 6 months

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>IVIg</th>
<th>Steroids</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchette 93</td>
<td>2/19</td>
<td>5/18</td>
<td>13.77 0.58 (0.08, 1.71)</td>
</tr>
<tr>
<td>Blanchette 94 (c)</td>
<td>11/69</td>
<td>4/39</td>
<td>26.88 1.35 (0.62, 4.61)</td>
</tr>
<tr>
<td>Tapanema 90</td>
<td>7/52</td>
<td>23/57</td>
<td>53.22 0.83 (0.39, 1.41)</td>
</tr>
<tr>
<td>Ozczyoja 93</td>
<td>2/6</td>
<td>1/10</td>
<td>6.46   2.60 (0.27, 22.06)</td>
</tr>
</tbody>
</table>

Total (95% CI) 128/154
Total events: 224 (IVIg), 33 (Steroids)
Tests for heterogeneity: Q = 3.10, df = 3 (P = 0.38), I² = 32%
Test for overall effect: Z = 0.29 (P = 0.77)
Figure 5. IVIg versus anti-D in acute ITP: proportions of children with platelet count ≥20×10⁹/L at 24h

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>IVIg nM</th>
<th>Anti-D nN</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchette 94</td>
<td>37/68</td>
<td>10/38</td>
<td>3.79 [1.14, 1.62]</td>
<td>62.12</td>
<td>1.27 [0.98, 1.66]</td>
</tr>
<tr>
<td>Tartinita 06</td>
<td>27/55</td>
<td>40/66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>104</td>
<td>104</td>
<td>1.32 [0.92, 1.92]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Q = 2.35, df = 1 (P = 0.10), I² = 62%
Test for overall effect: Z = 1.63 (P = 0.10)

Figure 6. Higher versus lower dose IVIg in acute ITP: proportions of children with platelet count ≥20×10⁹/L at 48h

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>IVIg higher dose nM</th>
<th>IVIg lower dose nN</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchette 94</td>
<td>25/36</td>
<td>51/33</td>
<td>0.96 [0.86, 1.16]</td>
<td>68.76</td>
<td>0.96 [0.86, 1.16]</td>
</tr>
<tr>
<td>Teariner 57</td>
<td>4/5</td>
<td>3/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>39</td>
<td>38</td>
<td>0.55 [0.86, 1.24]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Q = 2.14, df = 1 (P = 0.11), I² = 6%
Test for overall effect: Z = 1.34 (P = 0.18)
Figure 7. Higher versus lower dose IvIg in acute ITP: proportions of children with platelet count $\geq 20 \times 10^9/L$ at 72h

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>IVIg higher dose n/N</th>
<th>IVIg lower dose n/N</th>
<th>RR (random)</th>
<th>Weight %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchette 94</td>
<td>32/34</td>
<td>34/34</td>
<td>75.56</td>
<td>67.58</td>
<td>0.97 [0.88, 1.07]</td>
</tr>
<tr>
<td>Benesch 63</td>
<td>15/17</td>
<td>13/17</td>
<td>24.44</td>
<td>10.52</td>
<td>1.15 [0.84, 1.58]</td>
</tr>
<tr>
<td>Total (56% CI)</td>
<td>51/52</td>
<td></td>
<td></td>
<td>100.00</td>
<td>1.01 [0.84, 1.21]</td>
</tr>
</tbody>
</table>

Data for heterogeneity: Chisq = 1.52, df = 1 (P = 0.21), P = 37.1%

Test for overall effect: Z = 0.12 (P = 0.90)
# APPENDIX 5: TABLES

Table 1: Acute Childhood ITP - Trial Characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Design</th>
<th>Population (Total N Randomized)</th>
<th>Platelet Count Inclusion Criterion</th>
<th>IVIG dose (N)</th>
<th>Comparators &amp; (N)</th>
<th>Efficacy Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancona et al., 2002&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Parallel, 2 arms</td>
<td>Newly diagnosed children, age 6mo-15y (77)</td>
<td>&lt;20 with purpura (but no major bleeds)</td>
<td>1g/kg/d×2 [last dose only if plt. count&lt;50] (42)</td>
<td>30mg/kg/d×3 [last dose only if plt. count&lt;50] (35)</td>
<td>Plt. counts</td>
<td>Serious bleeding</td>
</tr>
<tr>
<td>Albayrak et al., 1994&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Parallel, response-conditional crossover, 3 arms</td>
<td>Children, age 2mo-17y, (57)</td>
<td>&lt;25</td>
<td>0.5g/kg/d×5d (19)</td>
<td>Oral MP 30mg/kg/d×7d (19) Oral MP 50mg/kg/d×7d (19)</td>
<td>Plt. counts</td>
<td>Crossover (IVIG to MP-30 and both MP to IVIG) when and if counts &lt;50</td>
</tr>
<tr>
<td>Blanchette et al., 1993&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Parallel, 3 arms</td>
<td>Children, age 6mo-18y, without major bleeding (56)</td>
<td>≤20</td>
<td>1g/kg/d×2d (21)</td>
<td>OP 4mg/kg/d×7d tapering off gradually over 21ds (18) &amp; No tx or expectant therapy (17)</td>
<td>Plt. counts</td>
<td></td>
</tr>
<tr>
<td>Duru et al., 2002&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Parallel, response-conditional crossover, 2 arms</td>
<td>Children whose parents could not be persuaded conservative management, or who needed urgent tx, age 2mo-15y (24)</td>
<td>&lt;20 with or without wet purpura</td>
<td>0.8g/kg/d×2d (12)</td>
<td>Oral MP 30mg/kg/d×3 followed by 20mg/kg/d×4 (23)</td>
<td>Plt. counts</td>
<td>Conditional crossover if and when plt. count was &lt;20 either as a non-response or relapse</td>
</tr>
</tbody>
</table>

Note: All plt. counts are \( \times 10^9/L \)
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Design</th>
<th>Population (Total N Randomized)</th>
<th>Platelet Count Inclusion Criterion</th>
<th>IVIG dose (N)</th>
<th>Comparator(s) &amp; (N)</th>
<th>Efficacy Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erduran et al., 2003&lt;sup&gt;3&lt;/sup&gt;&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Parallel, response-conditional crossover, 2 arms</td>
<td>Children, age 1-13y (46)</td>
<td>&lt;20</td>
<td>1g/kg/d×2d (23)</td>
<td>Oral MP 30mg/kg/d×3d followed by 20mg/kg/d×4d (23)</td>
<td>Plt. counts</td>
<td>Conditional crossover if and when plt. count was &lt;20</td>
</tr>
<tr>
<td>Fujisawa et al., 2000&lt;sup&gt;3&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Parallel, 4 arms</td>
<td>Untreated children, age 1mo-14y (119)</td>
<td>&lt;10 or 10-29 with wet purpura</td>
<td>1g/kg/d×1d [± on d 4 if plt. &lt;30] (32)</td>
<td>OP 2mg/kg/d for 2wks, tapering off by d21 (29) &amp; IVMP 5mg/kg/d×5d (31) &amp; IV MP 30mg/kg/d×3d (27)</td>
<td>Plt. counts Incidence of major bleeding and prolonged bleeding</td>
<td>Additional tx when count of less than 30 with wet purpura within 28d</td>
</tr>
<tr>
<td>Heegaard et al., 1999&lt;sup&gt;3&lt;/sup&gt;&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Subgroup analysis of Rosthoj et al., 1996&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Untreated children positive for parvovirus B19 specific DNA (6)</td>
<td>1g/kg/d×2d (3)</td>
<td>IV MP 30mg/kg/d×2d (3)</td>
<td>Plt. counts</td>
<td>Post hoc one tailed superiority analysis</td>
<td></td>
</tr>
<tr>
<td>Imbach et al., 1984&lt;sup&gt;4&lt;/sup&gt;&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Parallel, response-conditional crossover, 2 arms Interim evaluation</td>
<td>Untreated children, Age criterion NR (80 – not all evaluable)</td>
<td>&lt;30</td>
<td>0.4g/kg/d×5d (30)</td>
<td>OP 60mg/m²/d ×21d (33)</td>
<td>Plt. counts</td>
<td>Crossover within first 7ds in non-responders, within next 14ds after first relapse, and after 21ds following second relapse</td>
</tr>
<tr>
<td>Imbach et al., 1985&lt;sup&gt;4&lt;/sup&gt;&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Parallel, response-conditional crossover, 2 arms</td>
<td>Untreated children, age ≤15y (108)</td>
<td>&lt;30</td>
<td>0.4g/kg/d×5d (55)</td>
<td>OP 60mg/m²/d ×21d (53)</td>
<td>Plt. counts</td>
<td>Parallel retreatment in those who relapsed after 3&lt;sup&gt;rd&lt;/sup&gt; wk Crossover tx in those who did not respond at all in the 1&lt;sup&gt;st&lt;/sup&gt; wk or relapsed (counts&lt;30) in 2&lt;sup&gt;nd&lt;/sup&gt; or 3&lt;sup&gt;rd&lt;/sup&gt; wk or had 2&lt;sup&gt;nd&lt;/sup&gt; relapse after 3&lt;sup&gt;rd&lt;/sup&gt; wk</td>
</tr>
</tbody>
</table>

Note: All plt. counts are ×10<sup>9</sup>/L
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Design</th>
<th>Population (Total N Randomized)</th>
<th>Platelet Count Inclusion Criterion</th>
<th>IVIG dose (N)</th>
<th>Comparator(s) &amp; (N)</th>
<th>Efficacy Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imbach, 1985</td>
<td>Parallel, response- conditional crossover, 2 arms</td>
<td>Acute ITP children, age criterion NR (45 – not all were evaluable)</td>
<td>NR</td>
<td>0.4g/kg/d×5d (15)</td>
<td>OP 60mg/m²/d×21d (14)</td>
<td>Plt. counts</td>
<td>Within 21d crossover when counts &lt;100 or relapse (&lt;20 after initial increase &gt;100); and in second relapse after 21d</td>
</tr>
<tr>
<td>Khalifa et al., 1993</td>
<td>Parallel, 3 arms</td>
<td>Children, age 2-14y (30)</td>
<td>&lt;10</td>
<td>0.4g/kg/d×5d (10)</td>
<td>IV MP 10mg/kg/d×5d (10) &amp; OP 2mg/kg/d×4wk (10)</td>
<td>Plt. counts</td>
<td></td>
</tr>
<tr>
<td>Ozsoylu et al., 1993</td>
<td>Parallel, 2 arms</td>
<td>Untreated children, age 2mo-11y (20)</td>
<td>&lt;50</td>
<td>0.4g/kg/d×5d (10)</td>
<td>Oral MP 30 and 20mg/kg/d for 3 and 4ds, respectively (10)</td>
<td>Plt. counts</td>
<td></td>
</tr>
<tr>
<td>Rosthoj et al., 1996</td>
<td>Parallel, response- conditional crossover, 2 arms</td>
<td>Untreated children, age 6mo-15y (43)</td>
<td>&lt;20 with purpura but without IgA, ICH, or major transfusion requiring haemorrhage</td>
<td>1g/kg/d ×2d (23)</td>
<td>IV MP 30mg/kg/d×2d (20)</td>
<td>Plt. counts</td>
<td>Both txs given after 3d of observation period to those without increase in plt. counts, Rescue cross-over tx of poor responders on d4 &amp; d5 – one tailed superiority analysis, Additionally, a d5 onwards crossover of symptomatic pts who relapsed (plt. &lt;20) – 2 tailed analysis accounting for carryover and period effects as per Hills and Armitage</td>
</tr>
</tbody>
</table>

Note: All plt. counts are ×10⁹/L
Table 1. (continued) Acute Childhood ITP - Trial Characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Design</th>
<th>Population (Total N Randomized)</th>
<th>Platelet Count Inclusion Criterion</th>
<th>IVIG dose (N)</th>
<th>Comparators &amp; (N)</th>
<th>Efficacy Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchette et al., 1994&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Parallel, 4 arms</td>
<td>Untreated children, age 6mo-17y (146)</td>
<td>≤20</td>
<td>1g/kg/d×2d (34) &amp; IVIG 0.8g/kg/d×1d (35)</td>
<td>Anti-D 25μg/kg/d×2d (38) &amp; OP 4mg/kg/d with tapering over 21d (39)</td>
<td>Plt. counts</td>
<td>Separate randomisations on rhesus positive and negatives – latter not randomised to anti-D Retreatment was administered to non-responders at an unspecified time</td>
</tr>
<tr>
<td>Tarantino et al., 2006&lt;sup&gt;82&lt;/sup&gt;</td>
<td>Parallel, 3 arms</td>
<td>Untreated rhesus positive children without severe ongoing haemorrhage and with haemoglobin ≥6.3mmol/L, age 1-18y (105)</td>
<td>&lt;20</td>
<td>0.8g/kg/d×1d (35)</td>
<td>Anti-D 75μg/kg/d×1d (35) &amp; Anti-D 50μg/kg/d×1d (35)</td>
<td>Plt. counts</td>
<td>Premedicated before infusions with diphenhydramine &amp; acetaminophen Retreatment after 72h if counts &lt;20 or new/worsened bleeding regardless of counts</td>
</tr>
</tbody>
</table>

Note: All plt. counts are ×10⁹/L
### Table 1. (continued) Acute Childhood ITP - Trial Characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Design</th>
<th>Population (Total N Randomized)</th>
<th>Platelet Count Inclusion Criterion</th>
<th>IVIG dose (N)</th>
<th>Comparators &amp; (N)</th>
<th>Efficacy Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burdach et al., 1986</td>
<td>Parallel, 2 arms</td>
<td>Untreated children with ITP of &lt;3mo duration, and with wet purpura or large ecchymoses. Age eligibility criterion NR (20)</td>
<td>≤30</td>
<td>7S (with Fc portion) 400mg/kg/d×5d [half life: 16d] (10)</td>
<td>IVIG 5S (Fc partially removed) 400mg/kg/d×5d [half life: 24h] (10)</td>
<td>Plt. counts</td>
<td>Mean (SD) age: IVIG 7S 6.5 (6.6); IVIG 5S 7.0 (3.7)</td>
</tr>
<tr>
<td>Benesch et al., 2003</td>
<td>Parallel, 2 arms</td>
<td>Untreated children, all with dry purpura and infrequent wet purpura, age 6mo-18y (34)</td>
<td>&lt;20</td>
<td>1g/kg/d×2d (17)</td>
<td>IVIG 0.3g/kg/d×2d (17)</td>
<td>Plt. counts</td>
<td>Nonresponders (counts &lt;20) in lower dose group were given 2 additional higher IVIG doses of 0.7g/kg/d on d5 and 6</td>
</tr>
<tr>
<td>Warrier et al., 1997</td>
<td>Parallel, 2 arms</td>
<td>Children, age 4mo-5y (12)</td>
<td>&lt;30 or ≤75 plus bleeding</td>
<td>0.5g/kg/d×2d (6)</td>
<td>IVIG 0.25g/kg/d×2d (6)</td>
<td>Plt. counts</td>
<td>One of 2 trials in this report that randomised acute ITP children Infusions premedicated with acetaminophen, diphenhydramine, and ondansetron. Booster doses of IVIG given within 10d to non-responders and also within 3mo for reversion to thrombocytopenia &lt;30</td>
</tr>
</tbody>
</table>

**Note:** All plt. counts are ×10⁹/L

ITP – Idiopathic (immune) thrombocytopenic purpura; IVIG – Intravenous immunoglobulin; d – Days(s); mo – Month(s); wk – Week(s); y – year; plt. – platelet; vs. – Versus; NR – Not reported; OP – oral prednisone; IV – Intravenous; MP – methylprednisolone; NS – Not significant; S – significant; ICH – Intracranial haemorrhage; tx- treatment; pt – patient
Table 2. Acute Childhood ITP - Results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Jadad AC</th>
<th>All Haemorrhage reported</th>
<th>Time to platelet count &gt; 20 &amp; 50 &amp; other platelet related endpoints</th>
<th>LFUP/Excluded from analysis</th>
<th>WDAE SAE</th>
<th>Specific AE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IVIG vs. IV MP (Observation period: 4wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ancona et al., 2002[^56^]</td>
<td>1 Unclear</td>
<td></td>
<td>Mean increase in counts was higher with IVIG at 24, 48, &amp; 72h [S]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>IVIG appears to be more effective in improving plt. counts in the first wk of tx Harms of txs were not examined Four pts on IVIG and 3 on IV MP received extra tx than that indicated in protocol Groups differed at baseline in % of pts with active bleeding (14% vs. 34%), female representation (40% vs. 86%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Serious bleeding: 0 vs. 0</td>
<td>Mean increase in counts was higher with IVIG at 24, 48, &amp; 72h [S]</td>
<td>% Pts with counts ≥10; 20; &amp; 50 at 24h: 62 vs. 40; 55 vs. 37; 21 vs. 9</td>
<td>% Pts with counts ≥10; 20; &amp; 50 at 48h: 90 vs. 74; 71 vs. 57; 61 vs. 28</td>
<td>% Pts with counts ≥10; 20; &amp; 50 at 72h: 95 vs. 83; 95 vs. 74; 79 vs. 69</td>
</tr>
<tr>
<td>Benesch et al., 2003[^55^]</td>
<td>1 Unclear</td>
<td></td>
<td>IVIG 1g/kg vs. IVIG 0.3g/kg (Observation period: 1y)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Higher dose IVIG increases plt. count more than lower dose in the first few d of tx, but is likelier to be associated with AE Primary outcome and plt. counts before d 5 were not confounded by non-randomised, IVIG retreatment in lower dose group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% Pts with 72h counts &gt;20: 88 vs. 77 -NS Median (range) counts on d2: 4 &amp; 7 were not different between groups, but d3 counts were: 103 (0-188) vs. 50 (0-143)</td>
<td>% Pts with counts &gt;20: 88 vs. 77 -NS Median (range) counts on d2: 4 &amp; 7 were not different between groups, but d3 counts were: 103 (0-188) vs. 50 (0-143)</td>
<td>% Pts with counts &lt;20: 12 vs. 24</td>
<td>% Retreated: 35 vs. 41 - NS Chronicity: 18 vs. 29 - NS</td>
<td>Total drug related AE were significantly more with higher dose: 41% vs. 12%</td>
</tr>
</tbody>
</table>

Note: All plt. counts are ×10⁹/L
### Table 2- (continued)- Acute Childhood ITP- Results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Jadad AC</th>
<th>All Haemorrhage reported</th>
<th>Time to platelet count &gt; 20 &amp; 50 &amp; other platelet related endpoints</th>
<th>LFUP/ Excluded from analysis</th>
<th>WDAE/ SAE/ TAE</th>
<th>Specific AE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanchette et al., 1994</td>
<td>2 Adequate</td>
<td>IVIG 1g/kg vs. IVIG 0.8g/kg vs. anti-D vs. OP</td>
<td>(Observation period: 6mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR</td>
<td>Median d with counts &lt;20 (range): 2 (1-30) vs. 1 (1-6) vs. 2 (1-28) vs. 2 (1-16) [S difference found in both IVIG vs. anti-D]</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median d with counts &lt;50 (range): 2 (1-14) vs. 2 (1-37) vs. 2.5 (1-68) vs. 3 (1-82) [S difference found in both IVIG vs. anti-D, and OP vs. anti-D]</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR</td>
<td>Rates of AEs: 16% vs. 18% vs. 3% vs. 0</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D7-14 fall in haemoglobin: 12% vs. 6% vs. 24% vs. 0 (statistical significance not provided)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean weight gain was 6% with OP vs. 2% with IVIG 1g/kg vs. 1% with IVIG 0.8g/kg vs. 1% with anti-D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time to plt. count ≤20: both IVIG bx proved superior to anti-D, the difference between IVIG 0.8g/kg and anti-D remained [S] after adjustment for multiple comparisons.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time to plt. count ≥50: IVIG appears to be superior to anti-D, the difference between IVIG 0.8g/kg and anti-D remained [S] after adjustment for multiple comparisons.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Side effects should be considered in a risk-benefit assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Retreatment frequencies were similar in the 4 groups – 26% vs. 32% vs. 32% vs. 15% [NS].</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: All plt. counts are $\times 10^9$/L
### Table 2- (continued)- Acute Childhood ITP- Results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Jadad AC</th>
<th>All Haemorrhage reported</th>
<th>Time to platelet count &gt; 20 &amp; 50 &amp; other platelet related endpoints</th>
<th>LFUP/ Excluded from analysis</th>
<th>WDAE SAE TAE</th>
<th>Specific AE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parallel, no Crossover Trials</strong></td>
<td></td>
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</tr>
<tr>
<td>Blanchette et al., 1993⁵⁴</td>
<td>2 Adequate</td>
<td>NR</td>
<td>IVIG vs. OP vs. expectant tx (Observation period: 6mo)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Of drug related AE, 75% with IVIG had one or more symptoms of nausea, vomiting, fever and headache Mean weight gain was 3.6% with OP; 6% on OP had transient glycosuria, epigastric discomfort, and behavioural change IVIG and OP m be more efficacious than no tx in rapidly increasing plt. counts above 20 IVIG appears to be superior to OP in limiting d with plt. count &lt;50 Side effects should be considered in a risk-benefit assessment Retreatment frequencies were similar in the three groups – 18% to 25%.</td>
</tr>
<tr>
<td>Burdach et al., 1986⁶⁰</td>
<td>1 Unclear</td>
<td>NR</td>
<td>IVIG 7S vs. IVIG 5S (Observation period: 9d)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Drug related AE: Chills and tachycardia (n=1) vs. 0 AE IVIG 7S appears to be more efficacious in inducing short-term plt. increment in acute ITP Acute ITP diagnostic criteria were not comprehensive to exclude secondary causes</td>
</tr>
</tbody>
</table>

Note: All plt. counts are ×10⁹/L
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<th>Specific AE</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Fujisawa et al., 2000</td>
<td>Adequate</td>
<td>Reduction in haemorrhage (in those with gross bleeding at baseline): 1/1 vs. 2/2 vs. 2/2</td>
<td>Median (range) d to raise counts ≥50: 2 (1-24) vs. 4 (2-84) vs. 3 (1-42) vs. 3 (1-42) [Only IVIG significantly different from OP]</td>
<td>NR</td>
<td>NR</td>
<td>Incidence of drug related AE (%): 9 vs. 10 vs. 13 vs. 4 [NS]</td>
<td>IVIG appears to offer faster early plt. recovery than OP and IVMP Possible inclusion of neonatal alloimmune or autoimmune thrombocytopenia Second infusion of IVIG on d4 was not administered in 94% of pts Also, it is unclear how comprehensively other causes of thrombocytopenia were excluded</td>
</tr>
</tbody>
</table>

Note: All plt. counts are ×10⁹/L
Table 2- (continued)- Acute Childhood ITP- Results

<table>
<thead>
<tr>
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<th>Specific AE</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Parallel, no Crossover Trials</td>
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<td></td>
</tr>
<tr>
<td>Khalifa et al., 1993&lt;sup&gt;51&lt;/sup&gt;</td>
<td>1</td>
<td>Unclear</td>
<td>Mean (SD) counts on d1; 3; 5; &amp; 14: 18.4 (5.1) vs. 22.6 (5.2) vs. 7.4 (2.1); 50 (10.7) vs. 60 (12.9) vs. 10 (4.3); 160 (36) vs. 180 (27) vs. 40 (8.7); and 210 (33) vs. 240 (48) vs. 80 (14.8) [S difference between IVIG vs. OP and IV MP vs. OP for all ds]</td>
<td>IVIG vs. IV MP vs. OP (Observation period: 2 wk)</td>
<td>NR</td>
<td>NR</td>
<td>One non-fatal ICH in OP group</td>
</tr>
<tr>
<td>Ozsoylu et al., 1993&lt;sup&gt;59&lt;/sup&gt;</td>
<td>1</td>
<td>Unclear</td>
<td>Pt % with: d3 count &gt;50: 80 vs. 80 d3 count &gt;150: 60 vs. 60 d7 count &gt;150: 90 vs. 80 wk 2/3/4 count &gt;150: 90/80/60 vs. 50/44/70 3mo count &gt;150: 55 vs. 70 6mo count &gt;150: 75 vs. 90</td>
<td>IVIG vs. corticosteroids (Observation period: 6 mo)</td>
<td>NR</td>
<td>NR</td>
<td>No AE with steroid vs. fever and chills in 30% of pts on IVIG</td>
</tr>
</tbody>
</table>

Note: All plt. counts are ×10<sup>9</sup>/L
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<th>Author, Year</th>
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<th>Specific AE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarantino et al., 2006</td>
<td>2</td>
<td>Unclear</td>
<td>% Pts with counts ≥20 at 24h: 77 vs. 72 vs. 50 [S for IVIG vs. anti-D 50; and anti-D 75 vs. anti-D 50] No [S] difference in % pts with counts ≥20 at 48h, 72h and 7d d7 IVIG and antiD-50 associated with S lower mean and median counts than anti-D-75 Pts with wet purpura tended to respond worse to tx</td>
<td>Four pts excluded from analysis: 0 vs. 3 (received 100μg/kg) vs. 1 (diagnosed acute lymphocytic leukaemia)</td>
<td>WDAE 4 [3 in anti-D-75 received higher dose and experienced substantial decline in haemoglobin. One pt in anti-D-50 was found to have acute lymphocytic leukaemia] NR</td>
<td>d7 mean haemoglobin decreased by 0.5 vs. 1.9 vs. 1.6g/dL [NS] Approximate % with headache: 35 vs. 35 vs. 25 [NS] Approximate % of pts with fever 13 vs. 17 vs. 2.5 Approximate % of pts with chills 13 vs. 27 vs. 6; 1 pt had ICH in anti-D-75 group</td>
<td>IVIG and anti-D-75 appear to be superior to anti-D-50 in increasing platelet counts above 20 by 24h. Efficacy analyses after 72h are confounded by non-randomised retreatment of some pts in each group – overall 48% were retreated Lack of blinding could bias interpretation of harms Apparently there was no allocation concealment (“randomization and tx were not blinded”),</td>
</tr>
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</table>

Note: All plt. counts are ×10^9/L
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<th>Specific AE</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Warrier et al., 1997</td>
<td>2</td>
<td>Unclear</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Number of AEs per 100 infusions: 14 vs. 14 SAEs were not reported by tx arm Results are indeterminate for of both (surrogate) efficacy and infusion related AEs Despite premedication, incidence of infusion related AE appears to be remarkable Thrombocytopenia of 3-6mo duration was considered chronic</td>
</tr>
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<th>Specific AE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albayrak et al., 1994</td>
<td>2</td>
<td>Unclear</td>
<td>IVIG vs. oral MP-30 vs. oral MP-50 (Observation period: up to 11mo)</td>
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<td>Parallel trials with response-conditional crossover</td>
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<td></td>
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<td></td>
<td>No S differences between groups in terms of responses or plt. counts</td>
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<td></td>
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<td>In a 30d follow up proportion of pts with counts &lt;100 responding to crossover tx: 4/4 vs. 0/1 vs. 4/5</td>
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<td>By 11mos of follow up, chronicity persisted in 1 IVIG and 1 MP-50 pt</td>
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<td></td>
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<td>1 withdrawal from HDMP-30 because of hepatitis A</td>
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<td>1 HDMP-50 pt had ICH and convulsions</td>
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<td></td>
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<td>NR</td>
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<td></td>
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<td></td>
<td>ICH: 0 vs. 0 vs. 1</td>
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<td></td>
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<td></td>
<td>Indeterminate efficacy Neonatal and alloimmune thrombocytopenia was not specifically excluded Response conditional crossover tx was non-randomised and confounded overall results besides introducing carryover and tx period effect</td>
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</tbody>
</table>

Note: All plt. counts are ×10⁹/L
### Table 2- (continued)- Acute Childhood ITP- Results

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<tr>
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<th>Specific AE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duru et al., 2002&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Unclear</td>
<td>NR</td>
<td>IVIG vs. oral MP (Observation period: 30 d, but also report chronicity data)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Drug related AE IVIG (n): 4 headache; 2 nausea &amp; vomiting; 1 fever and rash MDMP (n): all with weight gain (0.8-2.6 kg); 7 with gastric discomfort; 1 hyperglycaemia; 1 hypertension</td>
</tr>
<tr>
<td>Heegaard et al., 1999&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Adequate</td>
<td>NR</td>
<td>IVIG vs. IV MP as first line tx followed by tx crossover (Observation period: 6mo) - subgroup analysis of Rosthoj et al., 1996&lt;sup&gt;44&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>IVIG given as first line vs. second line tx was not found superior in effecting incremental platelet response – type II error is likely</td>
</tr>
</tbody>
</table>

Note: All plt. counts are ×10<sup>9</sup>/L
Table 2- (continued)- Acute Childhood ITP- Results

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<th>Specific AE</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Erduran et al., 2003</td>
<td>2</td>
<td>Unclear</td>
<td>IVIG vs. oral MP (Observation period: short term -14d and longer term &gt;6mo)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Weight gain &amp; mild cushingoid appearance in all in steroid group Gastric discomfort in 10%; hypertension in 10% &amp; behavioural changes in 15% of steroid group Headache, fever and vomiting in 23% of IVIG pts</td>
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### Table 2- (continued)- Acute Childhood ITP- Results

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<th>Specific AE</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Imbach et al., 1984</td>
<td>1 Unclear</td>
<td>NR</td>
<td>Mean Ages: 5.8 vs. 5 Over 60d of observation, of those not requiring additional tx children on IVIG had more ds with normal counts [p-value NR] Of those requiring crossover (approx. 1/3 of pts), initial IVIG group required fewer courses of retreatment (p-value NR)</td>
<td>17 (details NR)</td>
<td>NR NR</td>
<td>NR</td>
<td>7 reports of headache and 2 of vomiting associated with IVIG. AE in steroid group were observed im most pts (details NR)</td>
</tr>
<tr>
<td>Imbach, 1985</td>
<td>1 Unclear</td>
<td>NR</td>
<td>D with normal counts were more with IVIG Normal counts over 50d period (n): 11 vs. 6 Chronicity in a 6 mo or more observation period (n): 0 vs. 3</td>
<td>Sixteen cases were not yet evaluable</td>
<td>NR NR</td>
<td>NR</td>
<td>Indeterminate efficacy of one intervention vs. another Incomplete and preliminary results Crossover, non-randomised additional tx introduced confounding, tx period and carryover effect</td>
</tr>
</tbody>
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<th>Specific AE</th>
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<tbody>
<tr>
<td>Imbach et al., 1985⁴⁹</td>
<td>3 Unclear</td>
<td>NR</td>
<td>% Pts attaining counts ≥100: 83% vs. 77%</td>
<td>1 NR</td>
<td>NR</td>
<td>Infusion related AE due to 3% of infusions in 22% of exposed pts -- vomiting, fever, vertigo and headache. Steroid related AE in 77% of exposed -- Cushing, increase in body weight, acne etc.</td>
<td>Indeterminate efficacy of one intervention vs. another Crossover, non-randomised additional tx and carryover and tx-period effects confound analysis</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>% Pts attaining counts &gt; 30, 100 and 150 was significantly greater for IVIG on d60 and 120</td>
<td>Withdrawals (n): 4 in IVIG (2 had baseline counts &gt;30, 1 had AE, and 1 was amegakaryocytic) vs. 1 in OP who received both txs</td>
<td>Other missing data (n=9): Lack of compliance - 3 IVIG vs. 2 OP; Early death – 1 IVIG LFUP: 0 vs. 3 OP</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>Subgroup analysis: IVIG better only in pts who did not respond to, or relapsed thereafter, the initial tx</td>
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<td>% Pts requiring additional tx: 34 vs. 43</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Chronicity at 6mo and 1y: 32% vs. 43 % and 17% vs. 23 %</td>
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<tbody>
<tr>
<td>Rosthoj et al., 1996&lt;sup&gt;44&lt;/sup&gt;</td>
<td>1 Adequate</td>
<td>N/A</td>
<td>IVIG vs. IV MP (Observation period: 6mo)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>A 2d course of high dose IVIG is superior to IV methylprednisolone pulse therapy in raising plt. count &gt;50 by d4</td>
</tr>
</tbody>
</table>

Note: All plt. counts are \( \times 10^9/L \)

ITP – Idiopathic (immune) thrombocytopenic purpura; LFUP – lost of follow-up; WDAE – withdrawl due to adverse events; IVIG – Intravenous immunoglobulin; d – Days(s); mo – Month(s); wk – Week(s); y – year; AC – Allocation concealment; vs. – versus; NR – Not reported; AE – Adverse event; SAE – Serious adverse event; TAE – total adverse event; OP – oral prednisone; IV – Intravenous; MP – methylprednisolone; NS – Not significant; S – significant; ICH – Intracranial haemorrhage; pt – patient; tx – treatment; plt – platelet
# Table 3- Chronic Childhood ITP- Trial Characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Design</th>
<th>Population (Total N randomised)</th>
<th>Platelet count inclusion criterion</th>
<th>IVIG dose (N randomised)</th>
<th>Comparator(s) &amp; (N randomised)</th>
<th>Efficacy Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>El Alfy et al., 2006</strong>&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Protocol 1 (1994-1998): parallel, response conditional crossover – 2 arms</td>
<td>Children [&lt;16y of age] with chronic ITP (16)</td>
<td>Either counts &lt;10 or &lt;100 with severe bleeding</td>
<td>0.8 g/kg as single dose (8)</td>
<td>IV HDMP 10mg/kg/d × 3d</td>
<td>Severe bleeding episodes, splenectomy, and platelet counts</td>
<td>In case of steroid induced gastrointestinal bleed, pt reassigned to IVIG</td>
</tr>
<tr>
<td><strong>El Alfy et al., 2006</strong>&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Protocol 2 (1999-2003): parallel, response conditional crossover – 3 arms</td>
<td>Children [&lt;16y of age] with chronic ITP (22)</td>
<td>Either counts &lt;10 or &lt;100 with severe bleeding</td>
<td>0.25 g/kg/d×2d (7) 4-6wk cycles (maximum 12 cycles)</td>
<td>Anti-D 50μg/kg/d as single dose (8) &amp; Oral MP 4mg/kg/d×4d (7) Both txs in 4-6wk cycles (maximum 12 cycles)</td>
<td>Severe bleeding episodes, splenectomy, and platelet counts</td>
<td>In case of steroid induced gastrointestinal bleed, pt reassigned to IVIG or anti-D</td>
</tr>
<tr>
<td>Hedlund-Treutiger, 2003&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Parallel, response conditional crossover – 2 arms</td>
<td>Non splenectomised children with chronic ITP [3-17y] (23)</td>
<td>&lt;30 or &lt;50 with bleeding within last 2 mo</td>
<td>0.8 g/kg, once [or to be repeated on d3 when counts &lt;30] every 4 wks up to maximum 6 cycles as long as counts are less than 30] (8)</td>
<td>Oral dexamethasone 0.6 mg/kg/d×4d every 4 wks for 6 cycles (15)</td>
<td>Platelet counts</td>
<td>After 4 mos, refractory pts offered crossover to alternative tx and cycles started all over again</td>
</tr>
</tbody>
</table>

Note: All plt. counts are ×10<sup>9</sup>/L
Table 3- (continued) Chronic Childhood ITP - Trial Characteristics

<table>
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<tr>
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<th>Platelet count inclusion criterion</th>
<th>IVIG dose (N randomised)</th>
<th>Comparator(s) &amp; (N randomised)</th>
<th>Efficacy Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>El Alfy et al., 2006&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Parallel, 2 arm</td>
<td>Chronic ITP [18 mo-16y] in non-splenectomised pts responsive to prior tx of steroid and immunosuppressive agents (34)</td>
<td>&lt;30</td>
<td>0.25 g/kg/d × 2d (16)</td>
<td>Intravenous anti-D 50 μg/kg × once (18)</td>
<td>Splenectomy, haemorrhage and platelet counts</td>
<td>Additional doses of anti-D were administered every 3-4 wks to a subgroup representing 67% of anti-D group – it is not clear why this was undertaken. Thus results pertaining to this phase of the study are not considered</td>
</tr>
</tbody>
</table>

Note: All plt. counts are ×10⁹/L

ITP – Idiopathic (immune) thrombocytopenic purpura; IVIG – Intravenous immunoglobulin; d – Days(s); mo – Month(s); wk – Week(s); plt. – Platelet; vs. – Versus; NR – Not reported; OP – oral prednisone; IV – Intravenous; MP – methylprednisolone; NS – Not significant; S – significant; ICH – Intracranial haemorrhage; tx – treatment
## Table 4- Chronic Childhood ITP- Results

<table>
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<tr>
<th>Author, Year</th>
<th>Jadad AC</th>
<th>Splenectomy rates &amp; other endpoints</th>
<th>Time to platelet count &gt; 20 &amp; 50 &amp; other platelet related endpoints</th>
<th>LFUP/Withdrawals Exclusion from analysis</th>
<th>WDAE SAE TAE</th>
<th>Specific AE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>El Alfy et al., 2006 (protocol 1)¹⁸</td>
<td>1 Unclear</td>
<td>IVIG vs. IV MP (Observation period: 30mo)</td>
<td>% With counts &gt; 100 for 3mo: 37.5 vs. 25 Mean (SD) wks with counts &lt; 10: 11.2 (1.9) vs. 14.3 (2.4)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Both efficacy and harms data cannot be meaningfully interpreted given incomplete reporting of tx discontinuations, substantial non-randomised reassignments and crossover Trial reports lacked inferential statistics</td>
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Table 4- (continued)- Chronic Childhood ITP- Results

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<th>Specific AE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>El Alfy et al., 2006 (protocol 2)¹⁸</td>
<td>1 Unclear</td>
<td>18 Splenectomy: 1 vs. 2 vs. 1 Mean (SD) number of severe bleeding episodes &amp; ds per pt: 9.4 (1.2) vs. 10.1 (0.9) vs. 8.9 (1.3) &amp; 4.9 (0.6) vs. 4.9 (0.8) vs. 5.1 (0.7)</td>
<td>% With counts &gt;100 for 3mo: 29 vs. 29 vs. 37.5 Mean (SD) wks with counts &lt;10: 13.7 (2.3) vs. 15.1 (0.26) vs. 12.9 (2.1)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>IVIG vs. OP vs. anti-D (Observation period: 30 mo)</td>
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</tbody>
</table>

Note: All plt. counts are $\times 10^9$/L

IVIG and steroid AE data are reported combined across two separate randomisations No intravascular haemolysis. Extravascular haemolysis NR IVIG AEs: aseptic meningitis Steroid AEs: hypertension and hyperglycaemia

Both efficacy and harms data cannot be meaningfully interpreted given incomplete reporting of tx discontinuations, substantial non-randomised reassignments and crossover Trial reports lacked inferential statistics
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Jadad AC</th>
<th>Splenectomy rates &amp; other endpoints</th>
<th>Time to platelet count &gt; 20 &amp; 50 &amp; other platelet related endpoints</th>
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<tbody>
<tr>
<td>Hedlund-Treutiger, 2003¹⁰</td>
<td>2</td>
<td>Unclear</td>
<td>Crossover n: 5 vs. 3 Total n receiving IVIG vs. dexamethasone: 11 vs. 20 Short-term increase ≥30 in counts on d3 of cycle 1 of: 100% vs. 75% Longer term responses (PR+CR; PR; and CR) (%): 9 vs. 25; 0 vs. 10; and 9 vs. 15 5ys follow-up sustained CR: 1/1 vs. 1/3</td>
<td>Dropouts: 3 vs. 6 (either AE or lack of response)</td>
<td>NR NR NR</td>
<td>Pts with at least one drug rebated AE: 91% vs. 95% Common side effects IVIG (%): Headache 70; dyspepsia/nausea 30; fever 30 Common side effects of dexamethasone (%): psychiatric symptoms 84; increased appetite 58, dyspepsia 58, headache 47, facial flush 26, Cushing syndrome 21, and fever 21</td>
<td>Results are indeterminate for efficacy superiority because both efficacy and harms data are confounded by this non-randomised crossover tx exposure</td>
</tr>
</tbody>
</table>

Note: All platelet counts are $\times 10^9$/L
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<tbody>
<tr>
<td>El Alfy et al., 2006(^{25})</td>
<td>1 Unclear</td>
<td>Mild bleeding during trial: 18.7% vs. 11.1% &amp; Serious bleeding during trial: 0 vs. 0</td>
<td>Counts &gt;50, or doubling of baseline counts, on d3 &amp; d7: 37.5% vs. 33.3% &amp; 75% vs. 66.6% (NS) &amp; Platelet responses up to 4 wks were not significantly different</td>
<td>NR</td>
<td>NR</td>
<td>In the anti-D group, haemoglobin dropped by a mean of 0.5±0.3 mmol/L in 61% of anti-D group &amp; All these pts returned to baseline haemoglobin in 3-4 wks post infusion</td>
<td>Unclear randomisation – “all pts on anti-D were rhesus positive”. Further, groups differed in terms of bleeding tendency at baseline &amp; Given questionable randomisation and lack of statistical significance, relative efficacy remains indeterminate</td>
</tr>
</tbody>
</table>

Note: All platelet counts are \( \times 10^{11} / L \)

ITP – Idiopathic (immune) thrombocytopenic purpura; AC – allocation concealment; LFUP – lost of follow-up; WADE – withdrawal due to adverse events; SAE – serious adverse event; TAE – total adverse event; IVIG – Intravenous immunoglobulin; d – Days(s); mo – Month(s); wk – Week(s); y – year; plt. – Platelet; vs. – Versus; NR – Not reported; OP – oral prednisone; IV – Intravenous; MP – methylprednisolone; NS – Not significant; S – significant; ICH – Intracranial haemorrhage; CR – complete remission (normal platelet counts); PR – partial remission; pt – patient; tx - treatment
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Design</th>
<th>Population (Total N randomised)</th>
<th>Platelet count inclusion criterion</th>
<th>IVIG dose (N randomised)</th>
<th>Comparator(s) &amp; (N randomised)</th>
<th>Efficacy Outcomes</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Godeau et al., 2002&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Parallel, 2 arm factorial design (addition of OP &amp; placebo from d 4-21)</td>
<td>Previously untreated adults [16-75y] with no life threatening haemorrhage (116)</td>
<td>&lt;20</td>
<td>IVIG 0.7g/kg/d×3d (56)</td>
<td>IV MP 15mg/kg/d×3d (60)</td>
<td>Mortality, life threatening haemorrhage, and plt. counts</td>
<td>No evidence of tx interaction in the four groups – data from for relevant tx groups are abstracted</td>
</tr>
<tr>
<td>Jacobs et al., 1989 (preliminary report)&lt;sup&gt;46&lt;/sup&gt;, Jacobs et al., 1994 (final report)&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Parallel, 3 arm</td>
<td>Previously untreated adults [15-66y] with or without SLE but with wet and/or dry purpura - largely Xhosa and Malay population (43)</td>
<td>NR (Also, baseline counts NR)</td>
<td>IVIG 0.4g/kg/d×5d (13)</td>
<td>Tapering dose of 1mg/kg/d of oral prednisone (17) &amp; IVIG 0.4g/kg/d×5d PLUS tapering dose of 1mg/kg/d of oral prednisone (13)</td>
<td>Splenectomy rates, mortality (only preliminary report), and plt. counts</td>
<td>Splenectomy in non-responders, those requiring (high OP doses, and relapsing pts</td>
</tr>
<tr>
<td>Colovic et al., 2000&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Parallel, 2 arms</td>
<td>Adults [mean age 39.7±12.1y] with chronic ITP (24)</td>
<td>Approx. 20</td>
<td>Novel IVIG 1g/kg/d×2d (15)</td>
<td>Novel IVIG 0.4g/kg/d×5d (9)</td>
<td>Haemorrhage and plt. counts</td>
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</table>

Note: All platelet counts are ×10<sup>9</sup>/L
Table 5- (continued) Adult ITP- Trial Characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Design</th>
<th>Population (Total N randomised)</th>
<th>Platelet count inclusion criterion</th>
<th>IVIG dose (N randomised)</th>
<th>Comparator(s) &amp; (N randomised)</th>
<th>Efficacy Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Godeau et al., 1993\textsuperscript{66}</td>
<td>Parallel, 2 arms</td>
<td>Non-splenectomised chronic ITP adults without life threatening haemorrhage [19-84y] (20)</td>
<td>&lt;50</td>
<td>IVIG 0.5g/kg/d×2d</td>
<td>IVIG 1g/kg/d×2d</td>
<td>Plt. counts</td>
<td>Booster IVIG tx when counts below 50</td>
</tr>
<tr>
<td>Godeau et al., 1999\textsuperscript{67}</td>
<td>Parallel, 2 arms</td>
<td>Adults [mean age 46y] with ITP of more [84% pts] or &lt;6 mos duration [16% pts], and no life threatening haemorrhage (40)</td>
<td>&lt;50</td>
<td>IVIG 0.5g/kg/d×1d (20) 5 pts had ITP for less than 6mo</td>
<td>IVIG 1g/kg/d×1d (20) 1 pt had ITP for &lt;6mo</td>
<td>Plt. counts</td>
<td>Reinfusion on d4 and 5 in nonresponders</td>
</tr>
<tr>
<td>Borte et al., 2004\textsuperscript{64}</td>
<td>Parallel, 2 arms</td>
<td>Adults [16-83y] with chronic ITP (33)</td>
<td>&lt;20</td>
<td>IVIG-F10 0.4g/kg/d×5d (16)</td>
<td>IVIG-regular 0.4g/kg/d×5d (17)</td>
<td>Haemorrhage and plt. counts</td>
<td>4 pts had prior splenectomy</td>
</tr>
<tr>
<td>Wolf et al., 2003\textsuperscript{63}</td>
<td>Parallel, 2 arms</td>
<td>Adults [17-91y] with chronic ITP (27)</td>
<td>&lt;20</td>
<td>IVIG-N 0.4g/kg/d×5d (16)</td>
<td>IVIG-regular 0.4g/kg/d×5d (11)</td>
<td>Haemorrhage and plt. counts</td>
<td></td>
</tr>
</tbody>
</table>

Note: All platelet counts are \texttimes 10^9/L

ITP – Idiopathic (immune) thrombocytopenic purpura; N - number; IVIG – Intravenous immunoglobulin; d – Days(s); mo – Month(s); wk – Week(s); y – year; plt. – Platelet; vs. – Versus; NR – Not reported; OP – oral prednisone; IV – Intravenous; MP – methylprednisolone; NS – Not significant; S – significant; ICH – Intracranial haemorrhage; pt – patient; tx - treatment
Table 6- Adult ITP- Results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Jadad AC</th>
<th>Splenectomy rates &amp; other endpoints</th>
<th>Time to platelet count &gt; 20 &amp; 50 &amp; other platelet related endpoints</th>
<th>LFUP/ Withdrawals Exclusion from analysis</th>
<th>WDAE SAE TAE</th>
<th>Specific AE</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Godeau, 2002</td>
<td>3 Adequate</td>
<td>NR</td>
<td>IVIG vs. IVMP (Observation period: 1y)</td>
<td>NR</td>
<td>4 vs. 0</td>
<td>IVIG: Headache, fever, convulsion, and venous thromboembolism HDMP: Diabetes mellitus, and arterial hypertension</td>
<td>Study stopped after an interim analysis on 100 pts</td>
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<td>Median number of ds with counts &gt;50 and &gt;20 were significantly higher with IVIG S higher median counts on d2 through d5 with IVIG S higher % of pts with counts &gt;50 on d2 through d5 with IVIG: 7, 41, 76 and 79 vs. 2, 33, 60 and 60 No mortality or life threatening haemorrhage Failure: 64% vs. 60% Pts with counts between 50-100: 7% vs. 3% Pts with normal counts: 29% vs. 37%</td>
<td>44% were lost to long term follow up of 12mos duration</td>
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</table>

Note: All platelet counts are ×10⁹/L
Table 6- (continued)- Adult ITP- Results

<table>
<thead>
<tr>
<th>Author, Year</th>
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<th>Splenectomy rates &amp; other endpoints</th>
<th>Time to platelet count &gt; 20 &amp; 50 &amp; other platelet related endpoints</th>
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<th>Specific AE</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Jacobs et al., 1994&lt;sup&gt;46&lt;/sup&gt; Final report</td>
<td>2 Unclear</td>
<td>IVIG vs. OP vs. IVIG + OP (Observation period: 2-3y)</td>
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<tr>
<td>Jacobs et al., 1989&lt;sup&gt;45&lt;/sup&gt;; Preliminary report of Jacobs et al.&lt;sup&gt;46&lt;/sup&gt;</td>
<td></td>
<td>Splenectomy: 62% vs. 71% vs. 92% Mortality (preliminary report only): 0 vs. 0</td>
<td>Initial complete remission: 39% vs. 71% vs. 77% [S difference between IVIG and dual therapy] Time to achieve peak counts - NS</td>
<td>One late LFUP in OP group</td>
<td>NR</td>
<td>1 Cerebro-vascular accident (tx assignment NR) reported in preliminary report</td>
<td>NR</td>
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<td>IVIG plus oral prednisone in tx of adult ITP could be more effective in terms of complete reversal of thrombocytopenia than IVIG alone in mildly symptomatic adult pts with recent onset immune mediated thrombocytopenia (not necessarily of idiopathic origin)</td>
</tr>
</tbody>
</table>

Note: All platelet counts are $\times 10^9$/L
Table 6- (continued)- Adult ITP- Results

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<th>Author, Year</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Colovic et al., 200368</td>
<td>1 Unclear</td>
<td>NR</td>
<td>% pts with counts ≥50: 93.3% vs. 88.9% Mean (SD) ds to counts ≥50: 4.4 (2.8) vs. 2.9 (0.6) Mean (SD) ds with counts ≥50: 17.6 (8.0) vs. 23.6 (6.3). % pts with overall regression of haemorrhages: 100% vs. 77.8% Mortality: 0 vs. 0</td>
<td>NR</td>
<td>0 vs. 0 0 vs. 0 Total AE: 27 vs. 11 Pts with AE: 66.7% vs. 55.6%</td>
<td>Headache; fever; nausea; and haemolysis (N): 5 vs. 4; 5 vs. 1; 2 vs. 1; 3 vs. 0</td>
<td>Indeterminate relative efficacy Type II error is a possibility Authors reported observed a trend in favour of the 5d group on platelet response and a trend was observed in favour of the 2d group on haemorrhagic response</td>
</tr>
</tbody>
</table>

Note: All platelet counts are $\times 10^9$/L
Table 6- (continued)- Adult ITP- Results

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<tbody>
<tr>
<td>Godeau et al., 199366</td>
<td>2</td>
<td>Unclear</td>
<td>IVIG-0.5g/kg vs. IVIG-1.0g/kg (Observation period: NR)</td>
<td>0 vs. 1</td>
<td>NR</td>
<td>AE not reported by tx AEs included headaches, chills, abdominal pain, vomiting, myalgia and rash 1 IgA deficient pt experienced severe infusion intolerance as fever and pyrexia with higher dose</td>
<td>Indeterminate efficacy for lack of statistical significance Type II error cannot be excluded</td>
</tr>
</tbody>
</table>

Note: All platelet counts are $\times 10^9$/L
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<th>Splenectomy rates &amp; other endpoints</th>
<th>Time to platelet count &gt; 20 &amp; 50×10⁹/L &amp; other platelet related endpoints</th>
<th>LFUP/Withdrawals Exclusion from analysis</th>
<th>WDAE SAE TAE</th>
<th>Specific AE</th>
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<tbody>
<tr>
<td>Godeau et al., 1999⁶⁷</td>
<td>2</td>
<td>Unclear</td>
<td>IVIG-0.5g/kg vs. IVIG-1.0g/kg (Observation period: approx. 3wk)</td>
<td></td>
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<td>Higher dose IVIG appears to be more efficacious than lower dose in short-term boosting of plt. count in pts at risk of immediate bleeding</td>
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<td></td>
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<td>Responders: counts &gt;80 (and with at least twice the baseline increase) after 72h</td>
<td>d³ responders: 24% vs. 61% [S] d4 responders: 24% vs. 67% [S] d8 responders: 88% vs. 78%</td>
<td>1 vs. 2 (protocol violations)</td>
<td>NR</td>
<td>NR</td>
<td>Two group A pts developed transient intolerance to infusion [changes in blood pressure, chills, vomiting and headache]</td>
</tr>
</tbody>
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Note: All platelet counts are $\times 10^9$/L.
Table 6- (continued)- Adult ITP- Results

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<td>Regular IVIG vs. modified IVIG (n=2)</td>
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<tr>
<td>Borte et al., 200464</td>
<td>2</td>
<td>Unclear</td>
<td>IVIG-F10 vs. IVIG-regular (Observation period: 30d for efficacy and 6mo for viral markers)</td>
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<td>Author, Year</td>
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<td>Splenectomy rates &amp; other endpoints</td>
<td>Time to platelet count &gt; 20 &amp; 50 &amp; other platelet related endpoints</td>
<td>LFUP/Withdrawals Exclusion from analysis</td>
<td>WDAE SAE TAE</td>
<td>Specific AE</td>
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<td>Wolf et al., 2003[63]</td>
<td>3</td>
<td>Unclear</td>
<td>IVIG-N vs. IVIG-regular (Observation period: up to 35d for efficacy and 6mo for viral markers)</td>
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<td>Pts with counts ≥50 within 29d: 75% vs. 100%</td>
<td>Mean (range) time to counts &gt;50: 5d (1-22) vs. 4d (1-8)</td>
<td>Mean (range) duration of counts &gt;50: 10 (1-29) vs. 18 (2-29)</td>
<td>Persistent (mild) bleeding, according to physician’s assessment and pt’s diary by d6 and 29, N= 1 vs. 2</td>
<td>1 (acute renal failure) vs. 0</td>
<td>Total reported AE: 75 vs. 48 %of pts with AE: 81 vs. 82</td>
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ITP – Idiopathic (immune) thrombocytopenic purpura; AC – allocation concealment; LFUP – lost of follow-up; WDAE – withdrawl due to adverse events; SAE – serious adverse event; TAE – total adverse event; IVIG – Intravenous immunoglobulin; d – Days(s); mo – Month(s); wk – Week(s); plt. – Platelet; vs. – Versus; NR – Not reported; OP – oral prednisone; IV – Intravenous; MP – methylprednisolone; NS – Not significant; S – significant; ICH – Intracranial haemorrhage; pt – patient
Table 7. ITP in Mixed Populations - Results

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<th>Splenectomy rates &amp; other endpoints</th>
<th>Time to platelet count &gt; 20 &amp; 50 &amp; other platelet related endpoints</th>
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<td>Bussel et al., 2004&lt;sup&gt;49&lt;/sup&gt;</td>
<td>3 Adequate</td>
<td>IVIG-C vs. IVIG-S/D (Observation period: 3-6mo)</td>
<td>% pts: With ecchymosis – 40 vs. 47 Who had splenectomy beyond d7 – 6 vs. 12</td>
<td>NR NR</td>
<td>%f pts with headache, fever, vomiting and rash: 50, 10, 13 &amp; 6 vs. 49, 10, 16 &amp; 0 No clinically S haemolysis in either group HAV, HCV, HBV, HIV, parvovirus B19 markers negative up to 3-6mos post infusion</td>
<td>IVIG-C could be at least as safe and efficacious as IVIG-S/D in ITP. Whether non-inferior safety and efficacy are age or chronicity dependent was not investigated. However, conclusions are based on per protocol analysis in the face of 17% missing data and additional non-randomised tx</td>
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<td>Warrier et al., 1997&lt;sup&gt;50&lt;/sup&gt;</td>
<td>2 Unclear</td>
<td>IVIG 0.4g/kg vs. IVIG 1.0g/kg (Observation period: 3 mo)</td>
<td>Pts with definite acute ITP: 4 vs. 5 % responders: 100 vs. 100 Secondary efficacy outcome data is reported mixed across 2 trials</td>
<td>0 vs. 1 0 vs. 1</td>
<td>Aseptic meningitis: 0 vs. 1</td>
<td>Results are indeterminate for both efficacy and infusion related AEs Despite premedication, incidence of infusion related AE appears to be high Thrombocytopenia of &gt;3mos duration was considered chronic, so it is not clear how many pts had disease &gt;6 mos duration</td>
<td></td>
</tr>
</tbody>
</table>

Note: All platelet counts are ×10<sup>9</sup>/L

ITP – Idiopathic (immune) thrombocytopenic purpura; AC – allocation concealment; LFUP – lost of follow-up; WDAE – withdraw due to adverse events; SAE – serious adverse event; TAE – total adverse event; IVIG – Intravenous immunoglobulin; pt – patient; tx – treatment; AE – adverse events; N – number; NR – not reported;
APPENDIX 6: REFERENCE LIST – EXCLUDED STUDIES

Level II


Not relevant to this review


Welch Jennifer C, Vora Ajay J. Non-interventionist management of children with acute immune...
RCTs excluded on the basis that they were studies on neonatal or antenatal thrombocytopenia


Farley N, Griffiths E, Sinor L et al. Neonatal alloimmune thrombocytopenia due to anti-HLA antibody responding to intravenous immunoglobulin. Transfusion (Bethesda) 1996;36(9 SUPPL.):


RCTs excluded on the basis they reported exclusively on Evans Syndrome (thrombocytopenia in association with hemolytic anemia)


Thrombocytopenia exclusively in association with HIV


Bussel J, Kauffman C, Woloski B. Neither response to IVIG nor to IV anti-D predicts the response to subsequent splenectomy in ITP. Blood 1997;90(10 SUPPL. 1 PART 1):


Rarick M U, Burian P, de Guzman N et al. Intravenous immune globulin use in patients with


Thrombocytopenia exclusively in association with systemic lupus erythematosus


Thrombocytopenia exclusively in association with other co-morbidities


Garcia B, Connelly E A, Newbury R et al. Pityriasis lichenoides and idiopathic thrombocytopenic purpura


Michel M, Chanet V, Galicier L et al. Autoimmune thrombocytopenic purpura and common variable immunodeficiency: analysis of 21 cases and review of the literature. [Review] [27 refs]. Medicine


Soriano Andres O, Ahn Yeon S, Horstman Lawrence L et al. Overlapping Syndrome of ITP and TTP: Case
Reports and Delineation of the Syndrome. Blood 2002;100(11):


Reports on the use of anti-D immunoglobulin exclusively


Bussel J. Lack of adverse effect of solvent-detergent treatment of IVIG: Comparison of Winrho and Winrho-SD in ITP. Blood 1993;82(10 SUPPL. 1):


Gaines A R. Disseminated intravascular coagulation associated with acute hemoglobinemia or hemoglobinuria following Rh(0)(D) immune globulin intravenous administration for immune thrombocytopenic purpura. Blood 2005;106(5):1532-1537.

Gaines A R. Acute onset hemoglobinemia and/or hemoglobinuria and sequelae following Rh(o)(D) immune globulin intravenous administration in immune thrombocytopenic purpura patients. [Review] [35 refs]. Blood 2000;95(8):2523-2529.


Novoa Maria V, Bussel James B. Safety and efficacy of intravenous (IV) anti-D treatment in pregnant women with immune thrombocytopenic purpura (ITP). Blood 2001;98(11 Part 1):


Zunich K, Harkonen W, Woloski M et al. RH-o(D) immune globulin intravenous in patients with ITP and history of prior treatment with intravenous immune globulin and/or corticosteroids. Blood 1994;84(10 SUPPL. 1):
Experimental studies (non-randomized)


Kurlander R J, Rosse W F. Efficacy of a 2-day schedule for administering intravenous immunoglobulin (IGIV) in treating adults with ITP. Blood 68(5 Suppl 1):112a


Cohort (prospective cohort, retrospective cohort, controlled before after study or time series)


Khellaft Mehdi, Michel Marc, Bierling Phillipe et al. Is the use of a haemorrhagic score (HS) more effective than platelet count to determine the treatment for patients with severe autoimmune thrombocytopenic purpura (AITP)? Blood 2003;102(11):


Tarantino Michael D, McFall Rebecca E. Immune thrombocytopenic purpura (ITP) in children: Outcome after treatment with IVIg, anti-D and
splenectomy. Blood 1999;94(10 SUPPL. 1 PART 1):


**Nested case-control**
no report found

**Cross-sectional**
no report found

**Case-control**
no report found

**Case series (observational or experimental uncontrolled before-after or time series studies)**


Immune globulin intravenous products: Risks identified. WHO Drug Information 1999;13(3):174


Aronis Sophie, Platokouki Helen, Avgieri Maria et al. Chronic ITP in children, a usually bening disease which may remit over the years. Blood 2003;102(11):


Beardsley D, Warrier I, Valdez L et al. Possible associated between recent silent viral infection and symptoms of aseptic meningitis following intravenous immunoglobulin (IGIV) therapy. Blood 1995;86(10 SUPPL. 1):


Brenner B. Clinical experience with Octagam, a solvent detergent (SD) virus inactivated intravenous gammaglobulin. Clinical & Experimental Rheumatology 1996;14 Suppl 15S115-S119.


Bussel J, Nass R. Etiology of headache after infusion of intravenous gammaglobulin (IVIG) for ITP. Blood 1995;86(10 SUPPL. 1):


Boruchov Donna M, Bussel James B, Driscoll Catherine M. Combination Therapy for Patients with Refractory ITP. Blood 2002;100(11):


Bussel J, Nass R. Etiology of headache after infusion of intravenous gammaglobulin (IVIG) for ITP. Blood 1995;86(10 SUPPL. 1):


Elalfy Mohsen, Saleh Khalifa, Ahmed S. 28 Years Experience in Childhood Immune Thrombocytopenic Purpura (ITP). Blood 2002;100(11):


Galatiuc C, Koehler M, Mirro J et al. Effects of IVIG therapy on NK cell function, phenotype and proliferation of PBL from patients with acute or chronic ITP. Blood 1995;86(10 SUPPL. 1):


Kuehne T, Spitz C, Imbach P. Is aseptic meningitis a sign of efficacy or an adverse effect of intravenous immunoglobulin therapy in severe immune thrombocytopenic purpura?. *Blood* 1996;88(10 SUPPL. 1 PART 1-2):


Michel Marc, Kreidel Felix, Chapman E et al. The number of large platelets but not the mean platelet volume (MPV) predicts the response to intravenous immunoglobulins (IVIG) and to anti-D in patients with immune thrombocytopenic purpura (ITP). Blood 2003;102(11):87b-88b.


Morfini M, Vannucchi A M, Grossi A et al. Direct evidence that high dose intravenous gammaglobulin blocks splenic and hepatic sequestration of 51Cr-labeled platelets in ITP. Thrombosis & Haemostasis 1985;54(2):554


Mouzaki A, Theodoropoulou M, Orphanos V et al. Cytokine gene expression in idiopathic thrombocytopenic purpura (ITP) before and after intravenous immunoglobulin G (IVIg) administration. Preliminary results. Blood 1997;90(10 SUPPL. 1 PART 2):


Ri-Sultan Muhammad, Ishaq. Intravenous immunoglobulin (IVIG) a life saving therapy for hemorrhage control in patients with idiopathic thrombocytopenic purpura (ITP) before surgery, labor and delivery which otherwise is not responding to other measures. J Allergy Clin Immunol 2002;109(1 Supplement):


Saba Hussain I. Efficacy of intraglobin F. (Biotest's gammaglobulin) in the intermittent infusion regimen for the management of ITP (immune thrombocytopenic purpura). Blood 1995;86(10 SUPPL. 1):


Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. [Review] [71 refs]. Haematologica 1993;78(6 Suppl 2):35-40.


Zeller B, Helgestad J, Hellebostad M et al. Immune thrombocytopenic purpura in childhood in Norway: a prospective, population-based registration. Pediatric...


Systematic review or meta-analysis

No records excluded.

Narrative review (some were excluded at level I; also includes commentaries)


Careful use of intravenous immunoglobulin therapy minimises adverse reactions. Drugs & Therapy Perspectives 2000;16(6):9-12.


Non-english publications


Petrov V, Yakunina L, Plahuta T et al. Acute pediatric thrombocytopenic purpura, associated with anti-rubella vaccination. *Pediatriya (Moscow)*


Viktorov O. Adverse reactions of gamimune (5% human Immunoglobulin for i.v. administration) manufactured by "Bayer" (Biological Products, Berkeley, Ca, USA). *Farmatsevtychnyi Zhurnal (Kiev)* 1998;0(6):93-94.


Unobtainable reports


Level III

Abstract or conference proceeding only (i.e. not a full study report)


Bussel James B, Hanna Kim. Intravenous immunoglobulin manufactured using a novel caprylate and chromatography-based method (IGIV-C, Gamunex (R)) was safe and well tolerated when administered at an increased maximum rate in patients with idiopathic thrombocytopenic purpura (ITP). Blood 2004;104(11, Part 1).


Bussel James B, Hanna Kim, IGIV C. Safety of Rapid Infusion of a New IGIV (IGIV-C, 10%) in Patients with Chronic ITP. Blood 2002;100(11).

Bussel James, Heddle Nancy, Richards Carl et al. MCP-1, IL-10, IL-6 and TNFalpha levels in patients with ITP before and after IV anti-D and IVIG treatments. Blood 1999;94(10 SUPPL. 1 PART 1):


O'Brien Sarah H, Ritchey A, Smith Kenneth J. Treatment of acute childhood idiopathic


Wehmeier A, Zahner J, Schneider W. Safety and efficacy of 10% intravenous immunoglobulin (IGIV) compared to 5% IGIV in the treatment of adult autoimmune thrombocytopenic purpura - a pilot study. Onkologie 1994;17(Suppl 2):163


**RCT does not report on relevant outcomes (e.g. reports pharmacodynamic parameters only)**

No report excluded.

**RCT with no numerical data for IVIg treatment.**

APPENDIX 7: INFORMATION REQUESTED FROM BAXTER AND TALECRIS

Requested Information

- Any long-term clinical outcome studies (observational or randomized controlled trials with placebo or active comparator) that evaluate the intermittent use of IVIG in patients who have chronic ITP. Long-term is defined as greater than six months.
- Randomized trials of any length that compare the use of polyclonal intravenous immunoglobulin to an active comparator in acute or chronic ITP. Active comparator includes the following: corticosteroids, other immunosuppressants in monotherapy or combination; plasma exchange; anti-D immunoglobulin etc.
- Cost effectiveness studies on intravenous immunoglobulin for ITP (acute or chronic ITP, children or adults, ITP in pregnancy).
- Any dose response data in patients with acute or chronic ITP.
- Any economic evaluation material that could be used to develop an economic model ie. any cost outcomes.
- Projected utilization for the specific indication of ITP.
- A list of ongoing or planned trials on the use of IVIG in patients with ITP.

Requested Information – General Information

- Any serious adverse event data pertaining to the use of polyclonal intravenous immunoglobulin for any indication.
- A list of ongoing or planned trials that analyze adverse events associated with the use of IVIG for any indication.
- Current price of IVIG and price fluctuation over last 5 years