Universitätsklinikum Carl Gustav Carus
DIE DRESDNER.

Letaler Verlauf einer Hirnblutung bei einem Jugendlichen mit chronisch Immunthrombozytopenie

Dietrich T.[1], Brenner S.[2], Pargac K. N.[3], Stächele J.[1], Lohse J.[1], Knöfler R.[1]

Fallvorstellung – Tom 15 Jahre

8. LJ.

- Manifestation mit Petechien bei isolierter Thrombozytopenie (<2 GPt/L)
  - Prednisolon p.o.
  - Thrombozytenanstieg mit dauerhafter Normalisierung der Thrombozytenwerte

Fallvorstellung – Tom 15 Jahre

8. LJ.

- Manifestation mit Petechien bei isolierter Thrombozytopenie (<2 GPt/L)
  - Prednisolon p.o.
  - Thrombozytenanstieg mit dauerhafter Normalisierung der Thrombozytenwerte

12. LJ.

- 2 thrombozytopenische Episoden (4-6 GPt/L) mit Haut- und Schleimhautblutungen, Mikrohämaturie
  - Prednisolon p.o. und i.v. Immunglobulin G (IVIG)
  - Thrombozytenanstieg jeweils in Normbereich

Fallvorstellung – Tom 15 Jahre

8. LJ.

- Manifestation mit Petechien bei isolierter Thrombozytopenie (<2 GPt/L)
  - Prednisolon p.o.
  - Thrombozytenanstieg mit dauerhafter Normalisierung der Thrombozytenwerte

12. LJ.

- 2 thrombozytopenische Episoden (4-6 GPt/L) mit Haut- und Schleimhautblutungen, Mikrohämaturie
  - Prednisolon p.o. und i.v. Immunglobulin G (IVIG)
  - Thrombozytenanstieg jeweils in Normbereich

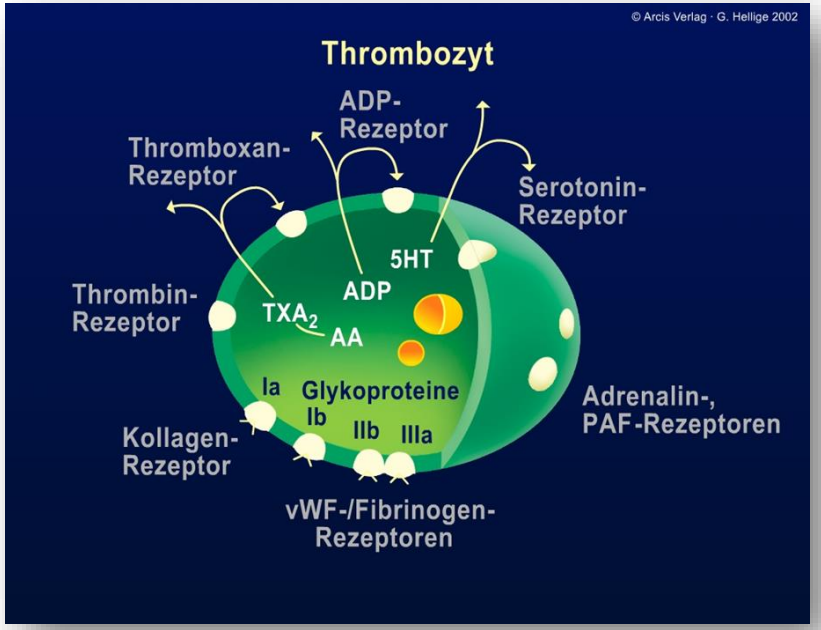
15. LJ.

- rezidivierende ausgeprägte Thrombozytopenien
  - Beginn Eltrombopag 25mg/d
  - Normalisierung der Thrombozytenwerte über 6 Monate.

- Unter Eltrombopag Infekt-assoziierter Thrombozytenabfall (4 GPt/l)
  - normalisierte Thrombozytenzahl innerhalb 1 Woche, Beibehaltung Eltrombopag-Dosis

Fallvorstellung – Tom 15 Jahre

- Im Verlauf: leichte Granulozytopenie (abs. 1,2 – 1,3 GPt/l [normal: 1,8 – 7,9 GPt/l])
- Nachweis granulozytärer und thrombozytärer Antikörper (gegen Glykoproteine IIB/IIIA und IbIX)



- Ausschluss von Willebrand-Erkrankung Typ 2B, thrombotisch-thrombozytopenische Purpura (TTP), Lupus erythematodes
- Immunol. Diagnostik (Immunglobuline, ANA, ANCA, dsDNA, Vit. B12, Lymphozytensubpopulation mit doppelt neg. T-Zellen) unauffällig

Fallvorstellung – Tom 15 Jahre

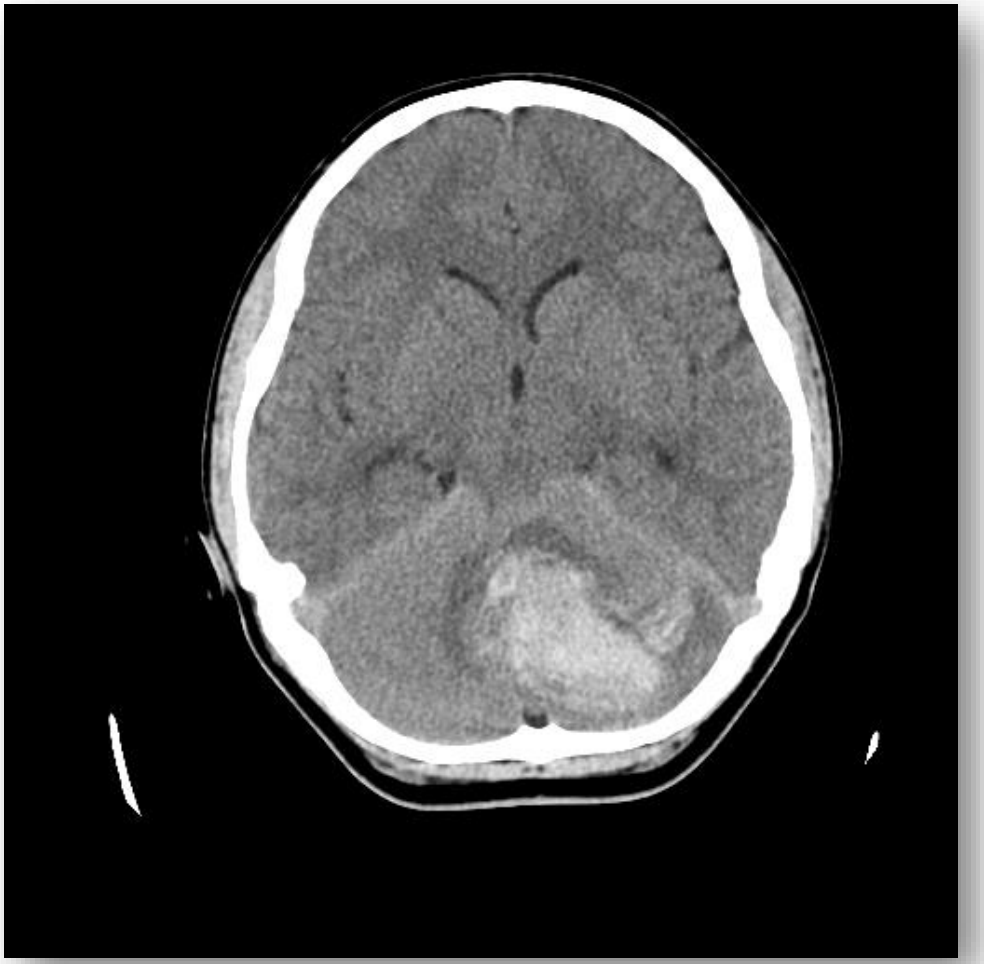
- erneut Thrombozytenabfall (5 GPt/L) mit Epistaxis und ausgeprägten Haut- und Mundschleimhautblutungen

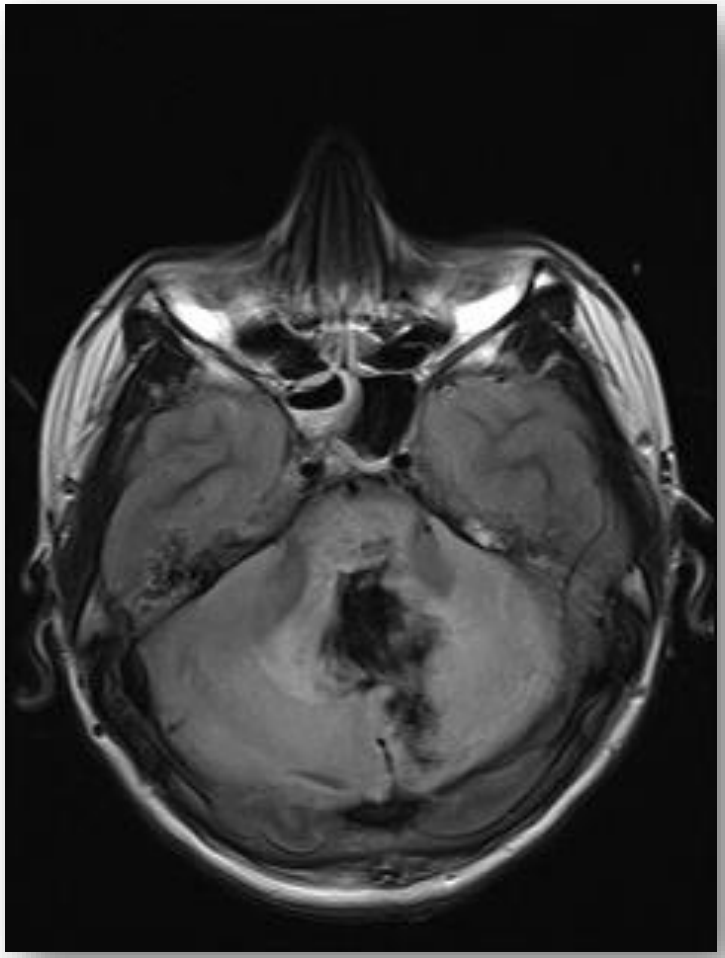
  - stationäre Aufnahme in externes Krankenhaus mit IVIG-Gabe über 5 Tage (kumulativ 2 g/kgKG) und Erhöhung Eltrombopag-Dosis auf 50 mg/d

  - kein Anstieg der Thrombozytenzahl, jedoch rückläufige Blutungssymptomatik und daher Entlassung

- Am Morgen des Folgetages rezidivierendes Erbrechen und zunehmende Somnolenz

Schädel-CT





ausgeprägte intracerebrale Blutung infratentoriell mit Liquoraufstau

Fallvorstellung – Tom 15 Jahre

- Übernahme in unsere Klinik mit bereits bestehenden lichtstarren Pupillen
- sofortige operative Hämatomausräumung und Einlage externer Ventrikeldrainage
- initial nicht messbare Thrombozytenwerte
  - Transfusion von 36 TBK´s, Gabe Eltrombopag 75 mg/d, IVIG (0,3g/kgKG einmalig), Dexamethason (0,3 mg/kgKG/d über 1d), Methylprednisolon (1000mg/d über 2d)
  - nur über einige Stunden anhaltender Thrombozytenanstieg auf max. 113 GPT/L
- trotz neuroprotektiver und hirndrucksenkender Maßnahmen progrediente untere und obere Einklemmung
- Entscheid zur Beendigung der Therapie und Versterben des Patienten
- Auslöser der ICH wahrscheinlich intrakranieller Druckanstieg unter starkem Pressen beim Toilettengang

Intracranielle Hämorrhagie (ICH)

- Inzidenz ICH 0,19% - 0,78%

- Thrombozytenzahl:
  - 90% Thrombozytenzahl < 20 GPT/L
  - 75% Thrombozytenzahl < 10 GPT/L
  - 10 % Thrombozyten 35 – 60 GPT/L

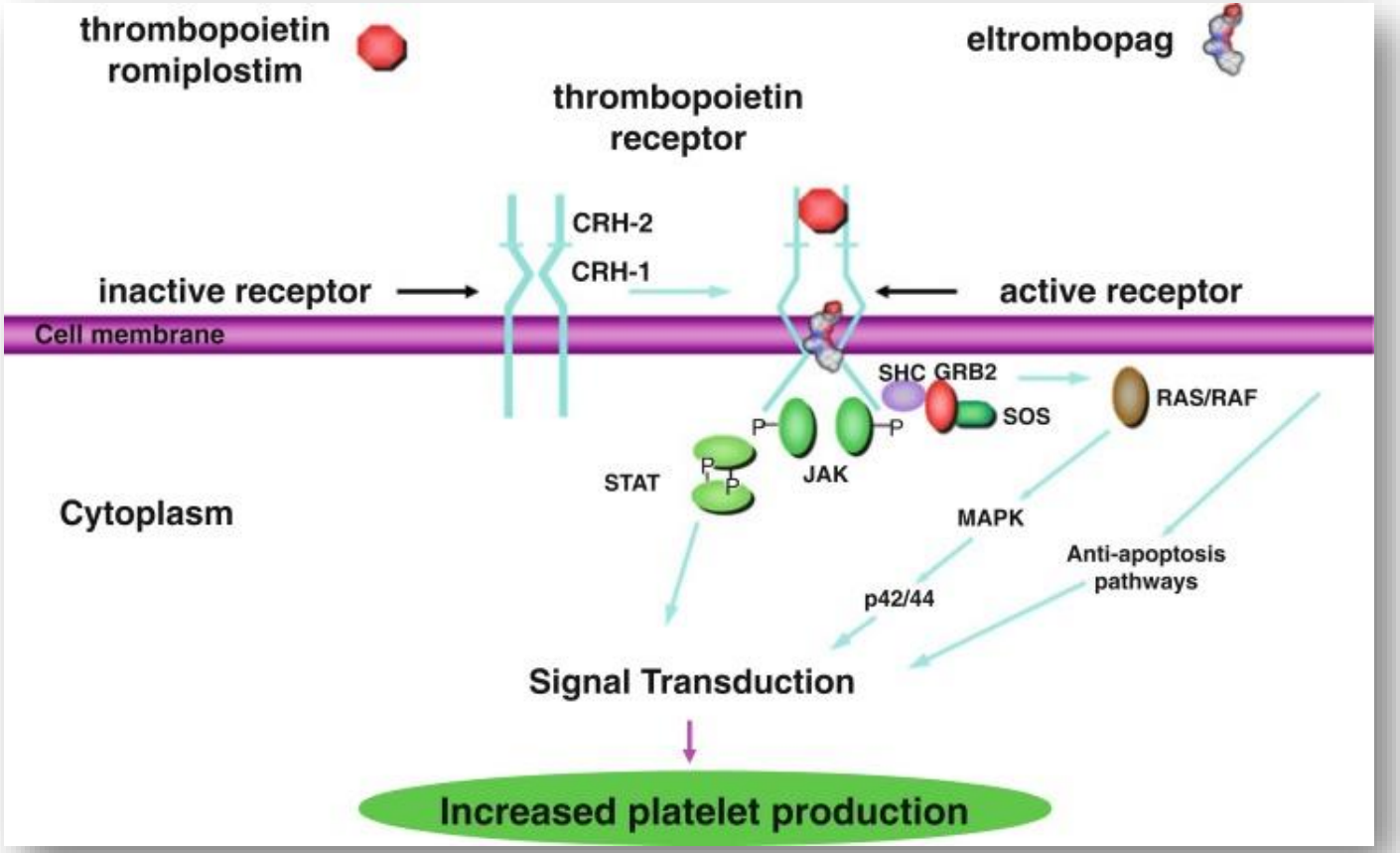
- Zeitpunkt:
  - 45% innerhalb 7 Tage nach Erstdiagnose (davon 55% ICH als Erstsymptom der ITP)
  - 25 % 1 Woche – 6 Monate nach ED
  - 30% mit chronischer ITP

- Kopftrauma (33%) und Hämaturie (22,5%) mit ICH assoziiert

- Mortalität 25%, neurologisches Defizit (33%)

Bethan Psaila et al. Intracranial hemorrhage (ICH) in children with immune thrombocytopenia (ITP): study of 40 cases. *Blood* 2009

Thrombopoetin-Rezeptoragonisten



Zulassung ab dem 1. Lebensjahr mit ITP >6 Monate und unzureichendem Ansprechen auf Glukokortikoide, IVIG oder Splenektomie

Angelica Maria Garzon et al. Use of Thrombopoietin Receptor Agonists in Childhood Immune Thrombocytopenia. *Front Pediatr.* 2015

Eltrombopag – Thrombozytenanstieg

	12–17 years		6–11 years		1–5 years		Total		Odds ratio (95% CI)	p value
	Eltrombopag (n=23)	Placebo (n=10)	Eltrombopag (n=26)	Placebo (n=13)	Eltrombopag (n=14)	Placebo (n=6)	Eltrombopag (n=63)	Placebo (n=29)		
Primary endpoint										
Responders	9 (39%)	1 (10%)	11 (42%)	0	5 (36%)	0	25 (40%)	1 (3%)	18·0 (2·3–140·9)	0·0004
95% CI	0·20–0·61	0·00–0·45	0·23–0·63	NA	0·13–0·65	NA			..	..
East Asian responders, n/N (%)	..	..	..	..	..	..	7/20 (35%)	0/10	NC	
Secondary endpoints										
Responders during weeks 1–12	..	..	..	..	..	..	..	..	25·3 (8·2–78·7)	<0·0001
Responders any time weeks 1–12	..	..	..	..	..	..	47 (75%)	6 (21%)	11·7 (4·0–34·5)	<0·0001
Responders any time weeks 1–6	15 (65%)	2 (20%)	17 (65%)	3 (23%)	7 (50%)	0	39 (62%)	5 (17%)	8·3 (2·7–25·1)	0·00018
Maximum continuous response (first 12 weeks)										<0·0001
Mean (SD), weeks	3·6 (3·2)	1·0 (2·5)	3·4 (3·0)	0·2 (0·4)	2·8 (3·5)	0·0 (0·0)	3·3 (3·1)*	0·4 (1·5)	..	..
Median (range), weeks	2·0 (0–10)	0·0 (0–8)	3·0 (0–11)	0·0 (0–1)	1·5 (0–12)	0·0 (0–0)	3·0 (0–12)	0·0 (0–8)	..	..
Rescue therapy needed	3 (13%)	2 (20%)	6 (23%)	3 (23%)	3 (21%)	2 (33%)	12 (19%)	7 (24%)	0·44 (0·2–0·9)	0·032

Data are n (%) unless otherwise indicated. Data for east Asian responders were not analysed by cohort. Data for the secondary endpoints responders at any time and responders at weeks 1–12 were only done for the treatment groups overall and not by cohort. NA=not available. NC=cannot be calculated. *Van Elteren stratified rank test.

Table 2: **Efficacy during the double-blind period**

John D Grainger et al. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. *Lancet 2015*

Eltrombopag – adverse events

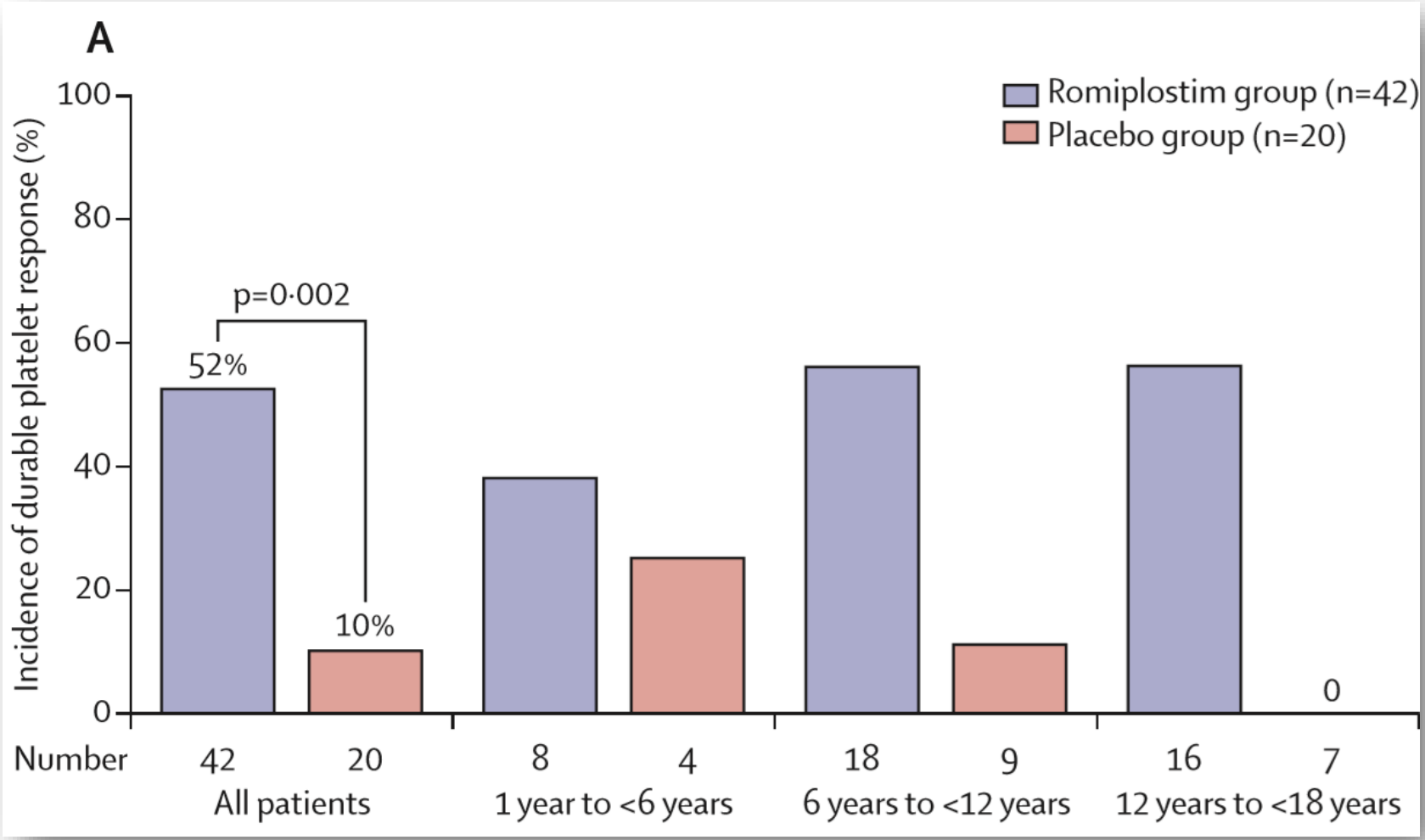
	Eltrombopag	Placebo
Double-blind period (baseline)		
Grades 1–4 (any bleeding)	45/63 (71%)	20/29 (69%)
Grades 2–4 (clinically significant)	16/63 (25%)	6/29 (21%)
Double-blind period (week 12)		
Grades 1–4 (any bleeding)	23/63 (37%)	16/29 (55%)
Grades 2–4 (clinically significant)	3/63 (5%)	2/29 (7%)
Open-label period (baseline)		
Grades 1–4 (any bleeding)	55/87 (63%)	..
Grades 2–4 (clinically significant)	17/87 (20%)	..
Open-label period (week 24)		
Grades 1–4 (any bleeding)	19/79 (24%)	..
Grades 2–4 (clinically significant)	5/79 (6%)	..

Data are n/N (%).

***Table* 3: Bleeding by WHO bleeding scale**

John D Grainger et al. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. *Lancet 2015*

Romiplostim - Thrombozytenanstieg



Michael D Tarantino et al. Romiplostim in children with immune thrombocytopenia: a phase 3, randomised, double-blind, placebo-controlled study. *Lancet 2016*

Romiplostim – adverse events

	Romiplostim group (N=42)	Placebo group (N=19)*
Most common (≥20% in romiplostim group)		
Contusion	21 (50%)	7 (37%)
Epistaxis	20 (48%)	10 (53%)
Headache	18 (43%)	11 (58%)
Upper respiratory tract infection	16 (38%)	5 (26%)
Petechiae	11 (26%)	6 (32%)
Mouth haemorrhage	11 (26%)	4 (21%)
Vomiting	11 (26%)	4 (21%)
Oropharyngeal pain	11 (26%)	1 (5%)
Diarrhoea	10 (24%)	3 (16%)
Nausea	9 (21%)	7 (37%)
Pyrexia	9 (21%)	2 (11%)
Serious adverse events	10 (24%)	1 (5%)
Epistaxis	2 (5%)	..
Headache	2 (5%)	..
Contusion	2 (5%)	..
Bronchiolitis	1 (2%)	..
Nausea	1 (2%)	..
Nephrotic syndrome	1 (2%)	..
Petechiae	1 (2%)	..
Petit mal epilepsy	1 (2%)	..
Pyrexia	1 (2%)	..
Thrombocytosis	1 (2%)	..
Urinary tract infection	1 (2%)	..
Vomiting	1 (2%)	..
Animal bite	..	1 (5%)
Haematuria	..	1 (5%)
All bleeding	35 (83%)	14 (74%)
Non-cutaneous bleeding	32 (76%)	13 (68%)

Most common bleeding adverse events†		
Contusion	21 (50%)	7 (37%)
Epistaxis	20 (48%)	10 (53%)
Petechiae	11 (26%)	6 (32%)
Mouth haemorrhage	11 (26%)	4 (21%)
Gingival bleeding	8 (19%)	4 (21%)

Data are n (%). *One patient randomised to placebo withdrew consent before receiving investigational product, hence N=19 (not 20). †20% or greater in either group.

Table 3: **Incidence of adverse events**

Michael D Tarantino et al. Romiplostim in children with immune thrombocytopenia: a phase 3, randomised, double-blind, placebo-controlled study. *Lancet 2016*

Zusammenfassung

- ✓ICH bei ITP selten, jedoch mit hoher Mortalität und schlechtem neurologischem outcome assoziiert
- ✓Romiplostim/Eltrombopag als innovative Therapie bei chronischer ITP (cITP), jedoch noch unklar, ob lebensbedrohliche Blutungen signifikant reduziert werden können
- ✓individuell angepasstes Management der chronischen ITP (cITP) weiterhin gerechtfertigt mit watch and wait Strategie bei leichter bis moderater Blutungsneigung
- ✓Identifizierung von Risikofaktoren und Entwicklung eines Risikoscores für Einschätzung der Blutungsgefährdung bei cITP sinnvoll

Fragen?

Definition Immunthrombozytopenie (ITP)

- Primäre ITP:

Autoimmunerkrankung mit **isolierter Thrombozytopenie** im **peripheren Blut < 100 GPT/L ohne zugrundeliegende andere Erkrankung**, welche mit Thrombozytopenie assoziiert sein kann

- Sekundäre ITP: alle Formen der immun-vermittelten Thrombozytopenien mit Ausnahme der primärem ITP

Francesco Rodeghier et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2010

Klassifikation Immunthrombozytopenie (ITP)

Klassifikation	Definition
Neu diagnostizierte ITP	Innerhalb der ersten 3 Monate nach Erstdiagnose
Persistierende ITP	4-12 Monate nach Erstdiagnose
Chronische ITP	>12 Monate nach Erstdiagnose
Schwere ITP	Blutungszeichen mit Therapie-Notwendigkeit bei ED, Auftreten neuer Blutungen mit Notwendigkeit Dosiserhöhung/Therapieänderung

Rodeghier et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Francesco *Blood* 2010

Blutungsscore – modifizierter Buchanan-Score

Grad	Risikoeinschätzung	Blutungszeichen
0	Keine	Keine frischen Blutungszeichen
1	Geringfügig	Wenige Petechien (<100) und /oder < 5 kleine Hämatome (<3cm Durchmesser), Keine Schleimhautblutungen
2	Mild	Viele Petechien und >5 große Hämatome (Durchmesser >3cm)
3 a	Moderat niedriges Risiko	Mundschleimhautblutungen, Blutkrusten in den Nasenlöchern, milde Epistaxis, Dauer <5min
3b	Moderat hohes Risiko	Epistaxis >5 min, Makrohämaturie, rektale Blutungen, schmerzhafte Mundschleimhautblutungen, signifikante Menorrhagie
4	Schwer	Schleimhautblutungen oder Blutungen innerer Organe (Gehirn, Lunge, Muskulatur, Gelenke), mit Notwendigkeit zur umgehenden medizinischen Versorgung oder Intervention
5	Lebensbedrohlich	Nachgewiesene intrakranielle Blutung oder lebensbedrohliche, tödliche Blutung jeder Lokalisation.

Schoettler ML, Graham D, Tao W, et al. Increasing observation rates in low-risk pediatric immune thrombocytopenia using a standardized clinical assessment and management plan (SCAMP(R)). *Pediatric blood & cancer 2017*

Definition

Primary ITP	Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count $<100 \times 10^9$/L) in the absence of other causes or disorders that may be associated with thrombocytopenia. The diagnosis of primary ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy. The main clinical problem of primary ITP is an increased risk of bleeding, although bleeding symptoms may not always be present.
Secondary ITP	All forms of immune-mediated thrombocytopenia except primary ITP*

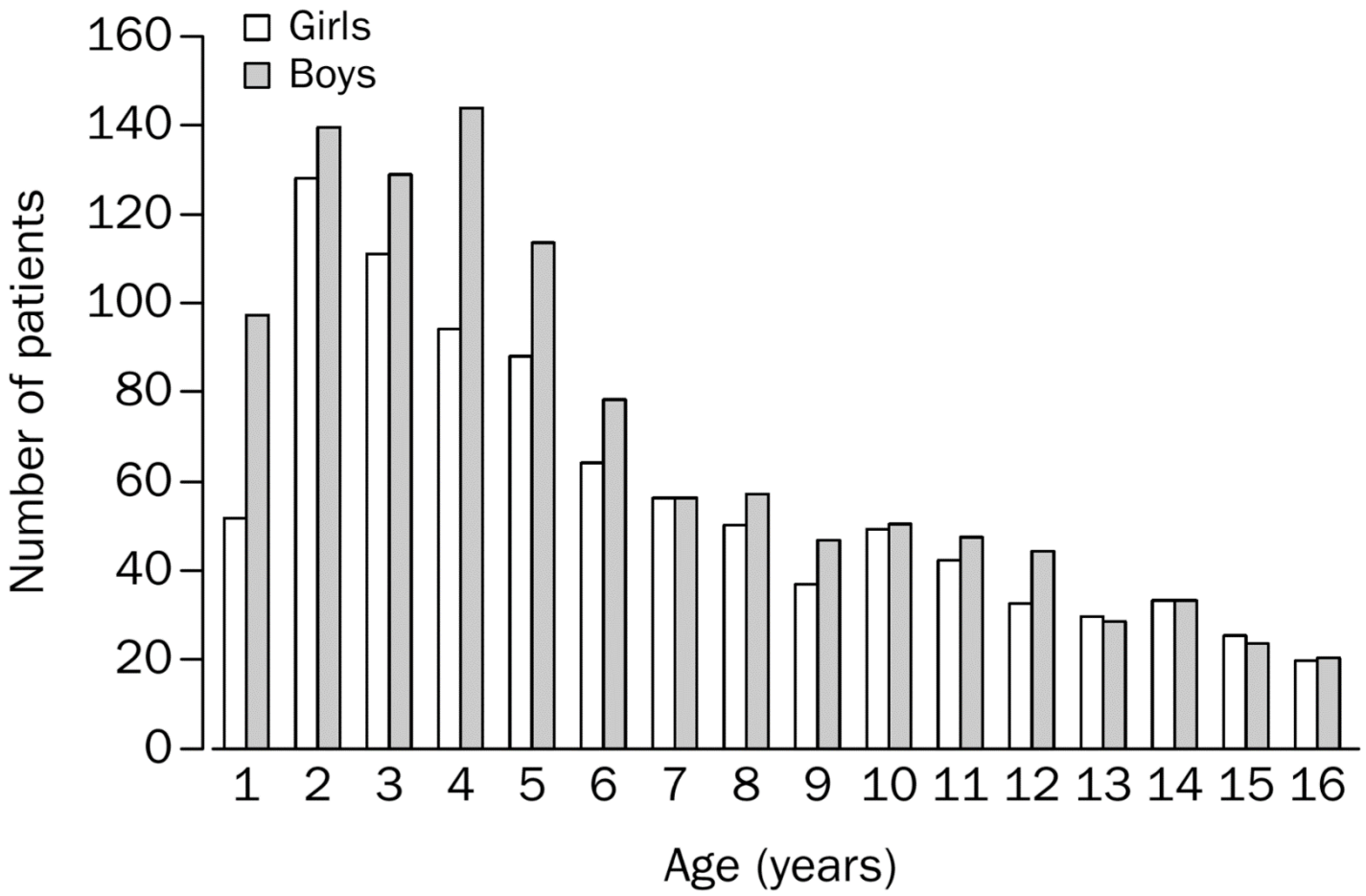
Blood 2010 Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Francesco Rodeghier et al

Krankheitsstadien

Phases of the disease	Newly diagnosed ITP: within 3 months from diagnosis Persistent ITP: between 3 to 12 months from diagnosis. Includes patients not reaching spontaneous remission or not maintaining complete response off therapy. Chronic ITP: lasting for more than 12 months Severe ITP: Presence of bleeding symptoms at presentation sufficient to mandate treatment, or occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose

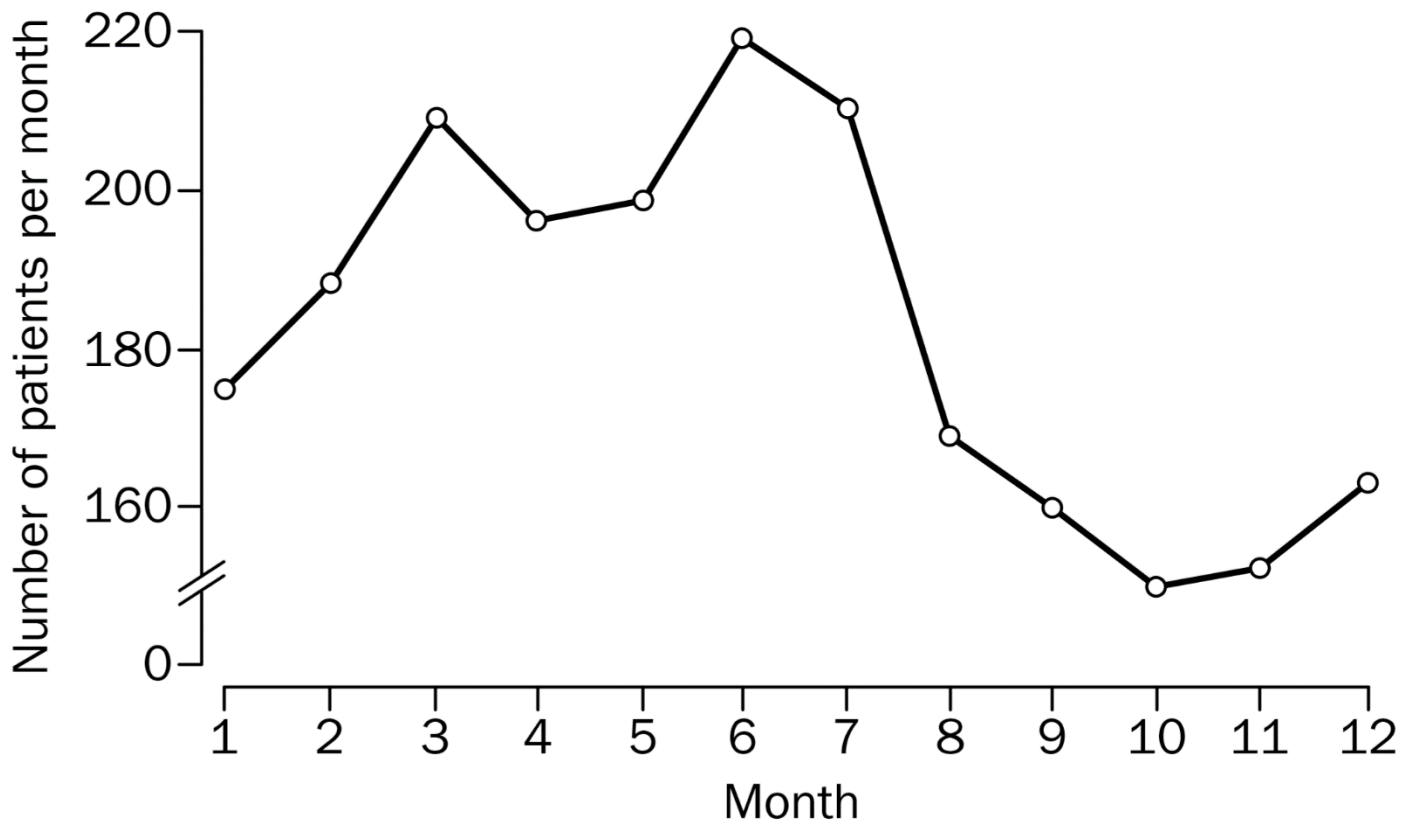
Blood 2010 Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Francesco Rodeghier et al

Altersverteilung ITP



Thomas Kühne et al. for the Intercontinental Childhood ITP Study Group. Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study; *Lancet* 2001

Saisonales Auftreten ITP



Lancet 2001 Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study; Thomas Kühne, Paul Imbach, Paula H B Bolton-Maggs, Willi Berchtold, Victor Blanchette, George R Buchanan, for the Intercontinental Childhood ITP Study Group

Therapieansprechen

Table 2. Proposed criteria for assessing response to ITP treatments

Quality of response*†

- CR: platelet count ≥ 100 × 10^9/L and absence of bleeding
- R: platelet count ≥ 30 × 10^9/L and at least 2-fold increase the baseline count and absence of bleeding
- Time to response: time from starting treatment to time of achievement of CR or R‡
- NR: platelet count < 30 × 10^9/L or less than 2-fold increase of baseline platelet count or bleeding
- Loss of CR or R: platelet count below 100 × 10^9/L or bleeding (from CR) or below 30 × 10^9/L or less than 2-fold increase of baseline platelet count or bleeding (from R)

Timing of assessment of response to ITP treatments

- Variable, depends on the type of treatment (see Table 3)

Duration of response§

- Measured from the achievement of CR or R to loss of CR or R
- Measured as the proportion of the cumulative time spent in CR or R during the period under examination as well as the total time observed from which the proportion is derived

Corticosteroid-dependence

- The need for ongoing or repeated doses administration of corticosteroids for at least 2 months to maintain a platelet count at or above 30 × 10^9/L and/or to avoid bleeding (patients with corticosteroid dependence are considered nonresponders)

Supplemental outcomes (whenever possible)

- Bleeding symptoms measured by a validated scale (requires additional studies)
- Health-related quality of life assessment measured by a validated instrument (requires additional studies)

Blood 2010 Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Francesco Rodeghier et al

Therapie der akuten Blutung

Grad	Blutungstyp	Therapieempfehlung
0-2 (Niedrig)	Keine Blutungen oder ausschließlich Hautblutungen	Beobachtung
3a (Moderat-niedrig)	Mundschleimhautblutungen, Blutkrusten in den Nasenlöchern, milde Epistaxis, Dauer <5min	Keine generelle Empfehlung möglich, individualisierte Therapieentscheidung
3b (Moderat-hoch)	Epistaxis >5 min, Makrohämaturie, rektale Blutungen, schmerzhafte Mundschleimhautblutungen, signifikante Menorrhagie	Prednison oder äquivalentes Glukokortikoid oder/ und IVIG Ggf. zusätzlich Tranexamsäure 3 x 20-25 mg/kg/d p.o.
4 (Hoch)	Schleimhautblutungen oder Blutungen innerer Organe (Lunge, Muskulatur, Gelenke), mit Notwendigkeit zur umgehenden medizinischen Versorgung oder Intervention	Prednison oder äquivalentes Glukokortikoid und IVIG Ggf. zusätzlich Tranexamsäure 3 x 20- 25 mg/kg/d p.o.
5 (Lebens-bedrohlich)	Nachgewiesene intrakranielle Blutung oder lebensbedrohliche Blutung jeder Lokalisation.	Gleichzeitige Gabe von: (1) Thrombozytenkonzentraten, wiederholte Transfusionen, höhere Dosierungen wegen verkürzter Halbwertzeit. (2) Methylprednisolon 30 mg/kg i.v. (max. 1 g) an 3 aufeinanderfolgenden Tagen. (3) IVIG 0.8- 1g/kg/d an 2 aufeinanderfolgenden Tagen (4) Ggf. Tranexamsäure 3 x 20-25 mg/kg/d p.o. oder 3 x 10-15mg/kg/d i.v. in 3 ED Als Ultima Ratio operative Verfahren: Notfallsplenektomie, bei zerebralen Blutungen ggf. Entlastungskraniotomie.

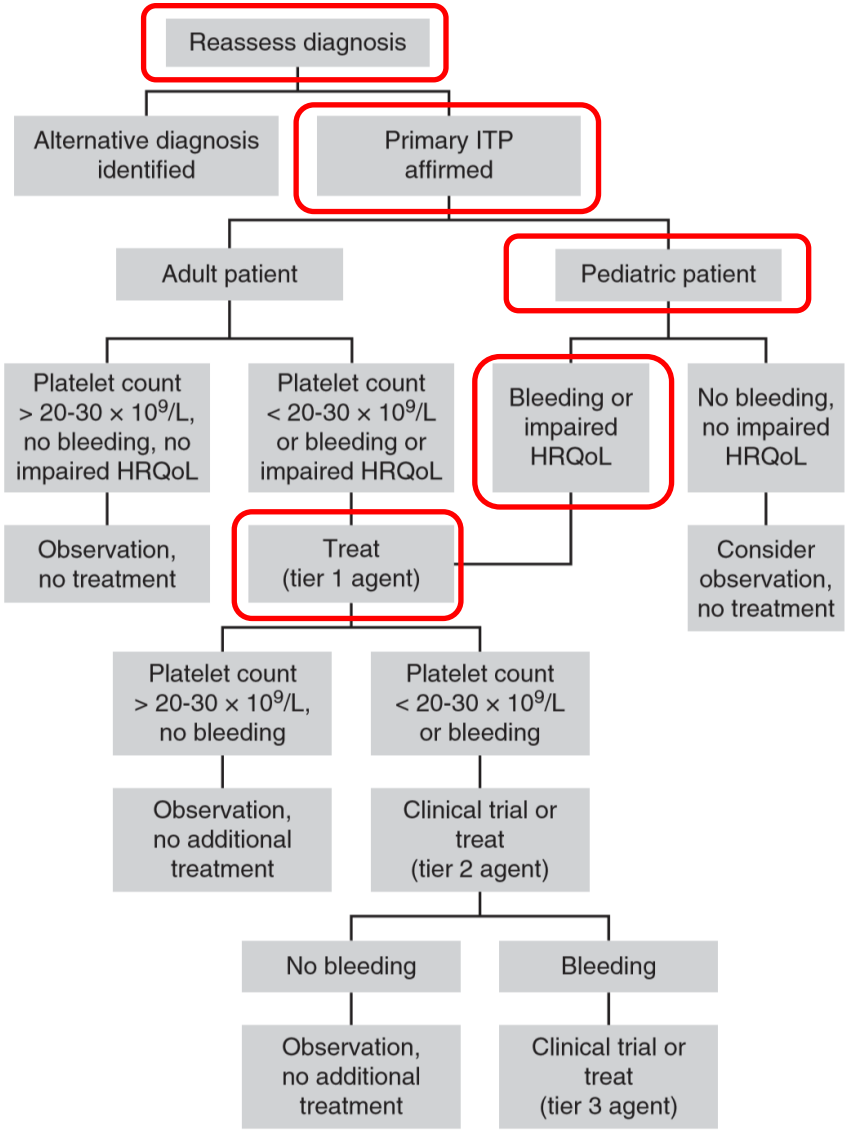
Therapie der akuten Blutung

Table 9. First-line/initial treatment in children with ITP

Recommended management strategy	Approximate response rate	Approximate time to platelet recovery	Toxicities	Sustained response
IV anti-D 50-75 μg/kg	50%-77% achieve a platelet response depending on dose	≥ 50% respond within 24 h	Headache, fever, chills (less common than with IVIg) Hemolysis, renal failure (very rare in absence of comorbidity)	Similar to IVIg although longer responses have been described with repeated dosing
IVIg single dose of 0.8-1 g/kg on d 1	Effective in more than 80% of patients	1-2 d	Side effects include headache (which can be severe), fever	Similar to corticosteroids. One-third of patients fall below acceptable platelet counts after 2-6 wk
Prednisone conventional dose 1-2 mg/kg/d for a maximum of 14 d; 4 mg/kg/d for 3-4 d	Up to three-fourths (≤ 75%) of patients will respond, depending on dose	2-7 d	Transient mood changes, gastritis, and weight gain. Caution in presence of active infection (especially varicella) or GI bleeding	No curative benefit known
Watch and wait	Approximately two-thirds of children will improve spontaneously within 6 mo	Days to ~ 6 mo	Preventable hemorrhage occurs, activity restriction, anxiety	Spontaneous remissions are generally durable

Drew Provan et al. International consensus report on the investigation and management of primary immunethrombocytopenia. *Blood* 2009

Chronische Therapie



Adam Cuker and Cindy E. Neunert. How I treat refractory immune thrombocytopenia. *Blood* 2016

Therapie der chronischen ITP

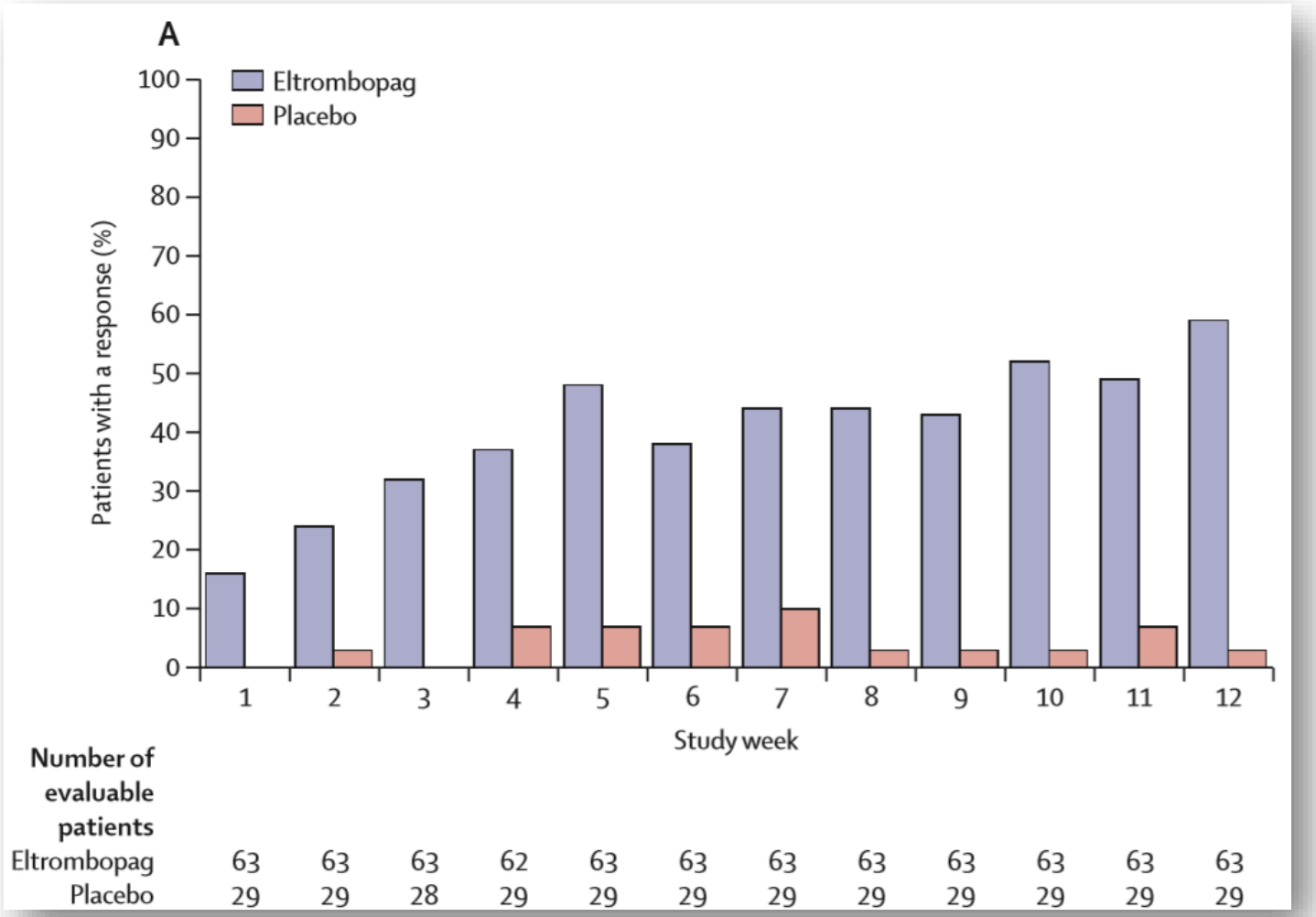
Table 2. Tier 1 treatment options

Drug	Dose	Response rate*	Time to response (wk)	Selected toxicities
Low-dose prednisone	≤5 mg orally once per day	<10%	N/A†	Weight gain, hyperglycemia, hypertension, osteoporosis, cataracts
Rituximab	375 mg/m^2 IV once per week × 4 (lower doses may be effective)	60% overall, 40% complete, 20%-25% at 5 y	1-8	Infusion reactions, serum sickness, HBV reactivation, PML (rare)
Romiplostim	1-10 μg/kg SC once per week	80% overall, 40%-50% persistent	1-4	Reticulin fibrosis, rebound thrombocytopenia, thrombosis
Eltrombopag	25-75 mg orally once per day	80% overall, 40%-50% persistent	1-2	Reticulin fibrosis, rebound thrombocytopenia, thrombosis, hepatotoxicity

HBV, hepatitis B virus; IV, intravenous; N/A, not applicable; PML, progressive multifocal leukoencephalopathy; SC, subcutaneous.
*Studies vary in their definition of response.
†In patients who are responding to intermediate or high doses of prednisone, we taper to low-dose prednisone. We do not start low-dose prednisone de novo.

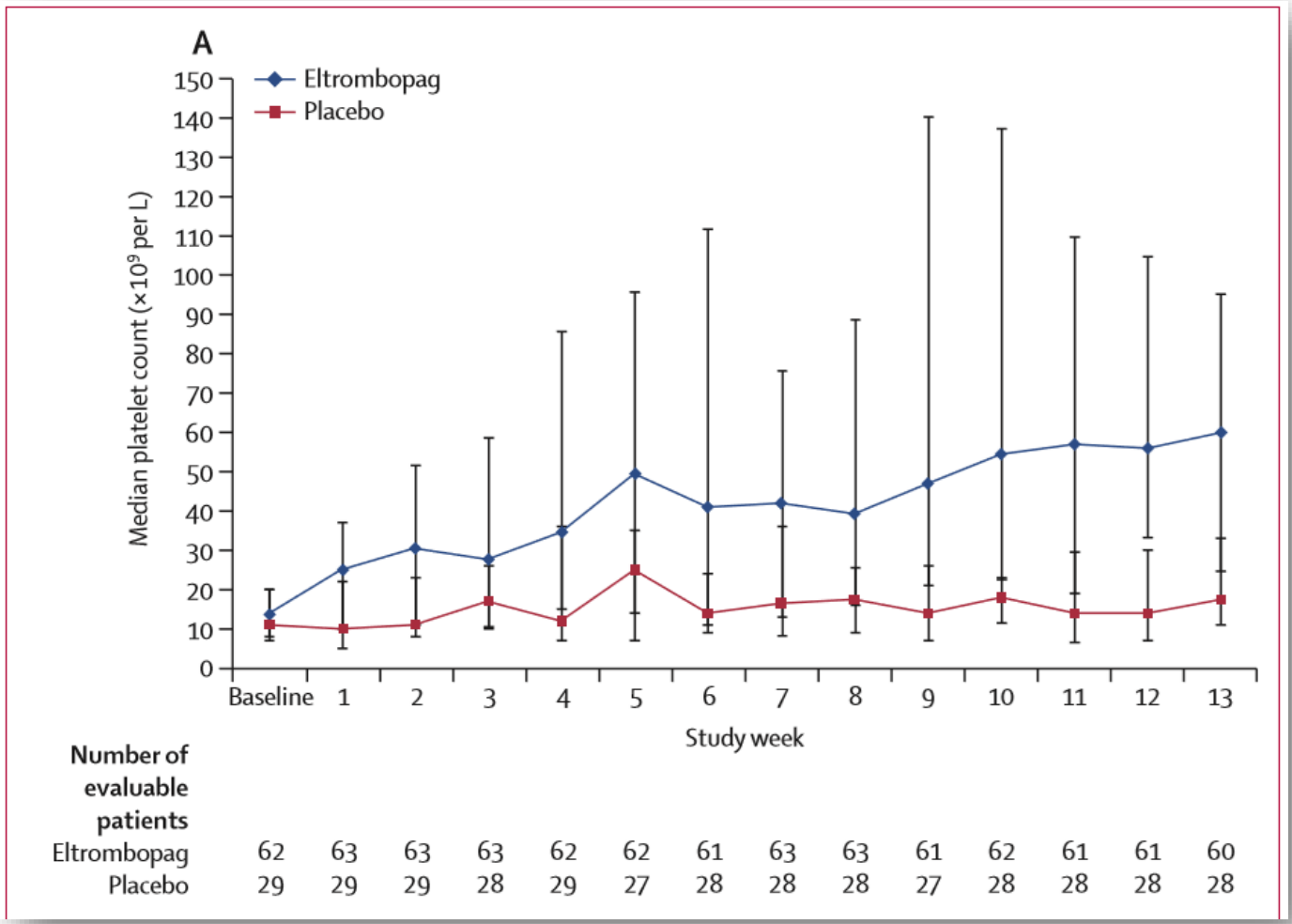
Adam Cuker and Cindy E. Neunert. How I treat refractory immune thrombocytopenia. *Blood* 2016

Eltrombopag - Thrombozytenanstieg



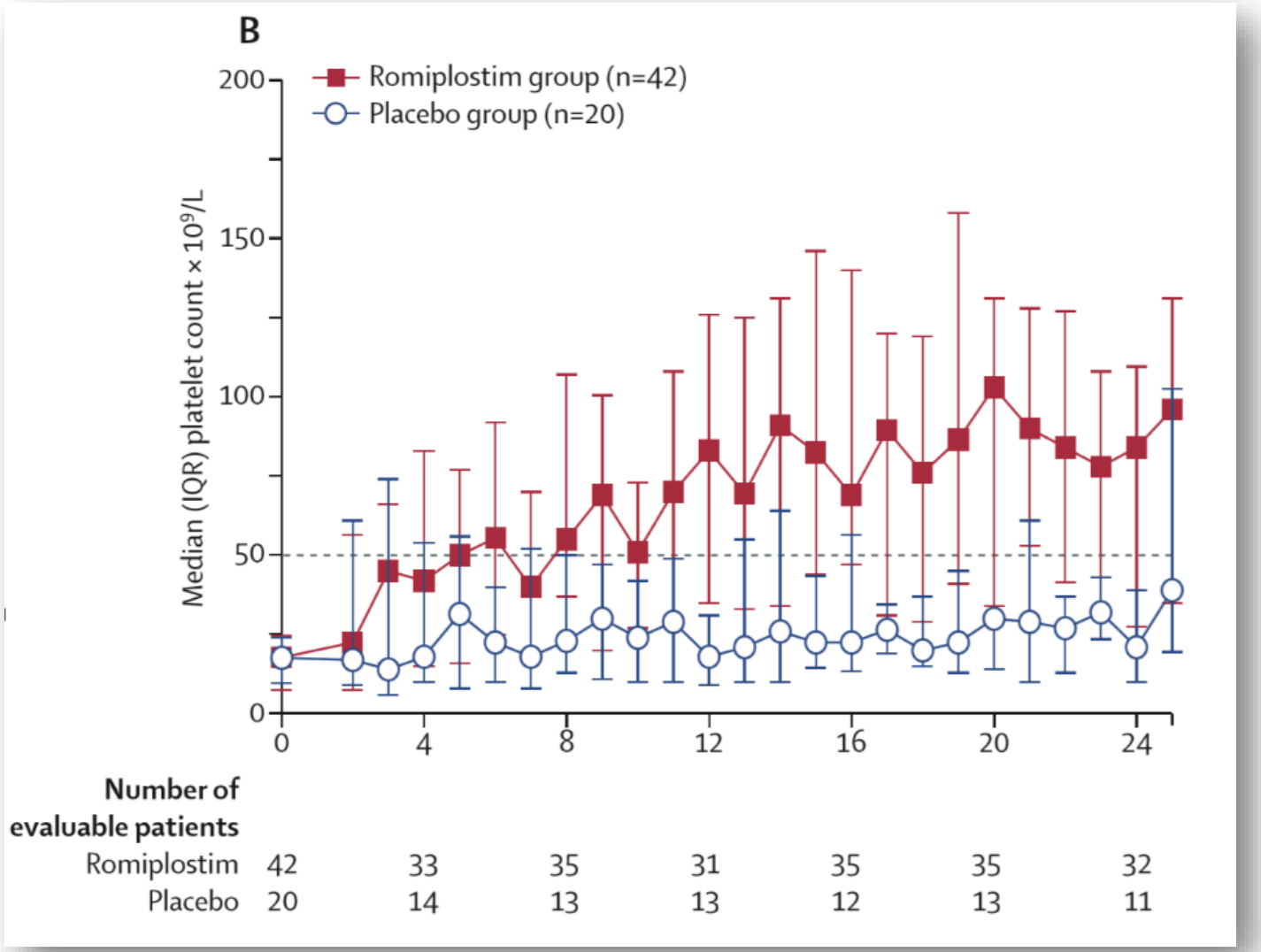
John D Grainger et al. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. *Lancet 2015*

Eltrombopag - Thrombozytenanstieg



John D Grainger et al. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. *Lancet 2015*

Romiplostim - Thrombozytenanstieg



Michael D Tarantino et al. Romiplostim in children with immune thrombocytopenia: a phase 3, randomised, double-blind, placebo-controlled study. *Lancet 2016*

Therapie der chronischen ITP

Table 10. Treatment options in children with persistent or chronic ITP

Recommended treatment strategy	Approximate response rate	Approximate time to response	Toxicities	Sustained response
Dexamethasone 28 mg/m^2/d	Up to 80% achieve a platelet response (study in adults and children)	3 d	Sleeplessness, behavioral changes, hypertension, anxiety, gastric distress, cataract, bronchial pneumonia, fatigue, pain	Responses are of short duration unless cycles are repeated
HDMP 30 mg/kg/d for 3 d followed by 20 mg/kg/d for 4 d	At least as effective as IVIg; 60%-100% of patients achieve platelet response	2-7 d	Worse side-effect profile compared with prednisone	
Rituximab 100 mg or 375 mg/m^2/wk for 4 wk	31%-79% response rates reported (CR/PR/MR)	Within a few weeks	Generally well tolerated. Side effects mild and easily resolved: serum sickness, maculopapular rash, arthralgia, low-grade fever, malaise, pruritus, urticaria, and throat tightness	63% achieved a CR lasting 4 to 30 mo; however, this is variable in literature
Single or combination regimens: cyclosporin A, azathioprine, prednisone, IVIg, anti-D, vinca alkaloids, and danazol	Approximately 70% of patients achieve platelet response	Days to months	Cytotoxic agents: usual side effects of monotherapies apply, consideration of carcinogenesis required	Individual responses vary
Splenectomy	60%-70% long-term response	24 h	Postsplenectomy complications include sepsis	80% of responders maintain platelet response over 4 y

Blood 2009 International consensus report on the investigation and management of primary immunethrombocytopenia Drew Provan et al.

Therapie der chronischen ITP

Table 3. Tier 2 treatment options

Drug	Dose	Response rate (%)*	Time to response	Selected toxicities
6-mercaptopurine	50-75 mg/m^2 orally once per day	83	Not reported	Hepatotoxicity, neutropenia, infection, pancreatitis
Azathioprine	1-2 mg/kg orally once per day (maximum 150 mg/d)	40-60	3-6 mo	Hepatotoxicity, neutropenia, infection, pancreatitis
Cyclosporin A	5-6 mg/kg/d orally divided into 2 doses per day (titrate to blood levels of 100-200 ng/mL)	30-60	3-4 wk	Nephrotoxicity, hypertension, tremor, parathesias, gingival hyperplasia
Cyclophosphamide	0.3-1.0 g/m^2 IV repeated once every 2 to 4 weeks × 1 to 3 doses; 50-200 mg orally once per day; after response has been achieved, dose can be tapered to 50 mg	24-85	1-16 wk	Neutropenia, nausea/vomiting, infertility, secondary malignancy
Danazol	50-800 mg/d orally divided into 2 to 4 doses per day	10-70	3-6 mo	Hepatotoxicity, virilization, amenorrhea
Dapsone	75-100 mg orally once per day	40-75	3 wk	Hemolysis (in patients with G6PD deficiency), rash, nausea, methemoglobinuria
Mycophenolate mofetil	250-1000 mg orally twice per day	11-80	4-6 wk	Headache, diarrhea, nausea, anorexia, infection
Vinca alkaloids	Vincristine: 1 to 2 mg IV once per week × 3 weeks Vinblastine: 10 mg IV once per week × 3 weeks	10-75	5-7 d	Peripheral neuropathy, vesication at infusion site, constipation, fever, neutropenia

G6PD, glucose 6-phosphate dehydrogenase.
*Studies vary in their definition of response.

Blood 2016 How I treat refractory immune thrombocytopenia. Adam Cuker and Cindy E. Neunert

Therapie der chronischen ITP

Table 4. Tier 3 treatment options

Treatment	Reference	Dose	Response rate (%)	Selected toxicities
ATRA	86	10 mg orally 3 times per day	29	Retinoic acid syndrome, flu-like symptoms, musculoskeletal pain, nausea/vomiting, peripheral neuropathy
Autologous HSCT	87	Cyclophosphamide 50 mg/kg IV once per day × 4 days (conditioning)	43	Neutropenic fever, infection
Colchicine	88	1.2 g orally once per day	21	Agranulocytosis, neuritis, diarrhea, nausea/vomiting
Interferon α	89-92	Various	0-36	Neutropenia, fever, influenza-like symptoms, hepatotoxicity
Plasma exchange	93-95	One plasma volume exchange once per day × 1 to 8 days	29-80	Hypocalcemia, anaphylactoid reactions
Protein A immunoadsorption	96	Average of 6 treatments (0.25 to 2.0 L plasma per treatment) over 2 to 3 weeks	21	Hypersensitivity reactions, pain, nausea/vomiting Cardiopulmonary complications
Vitamin C	97-100	2 g orally once per day	0-82	Dsypepsia, nausea/vomiting

ATRA, all-trans retinoic acid; HSCT, hematopoietic stem cell transplant

Blood 2016 How I treat refractory immune thrombocytopenia. Adam Cuker and Cindy E. Neunert

Intracranielle Hämorrhagie

- Fallserie 1987 – 2000 USA: 120 Kinder mit primärer ITP: 40 Kinder <17J. mit ICH und ITP, 80 Kontrollpat. mit Thrombozytenzahl <30 GPT/L

- Inzidenz ICH 0,19% - 0,78%; 90% Thrombozytenzahl < 20 GPT/L; 75% Thrombozytenzahl < 10 GPT/L; 10 % Thrombozyten 35 – 60 GPT/L

- 45% der Kinder (18/40) entwickelten ICH innerhalb 7 Tage nach Erstdiagnose, von denen 55% (10/18) ICH als Erstsymptom der ITP; 25 % 1 Woche – 6 Monate nach ED, 30% (12/40) mit chronischer ITP

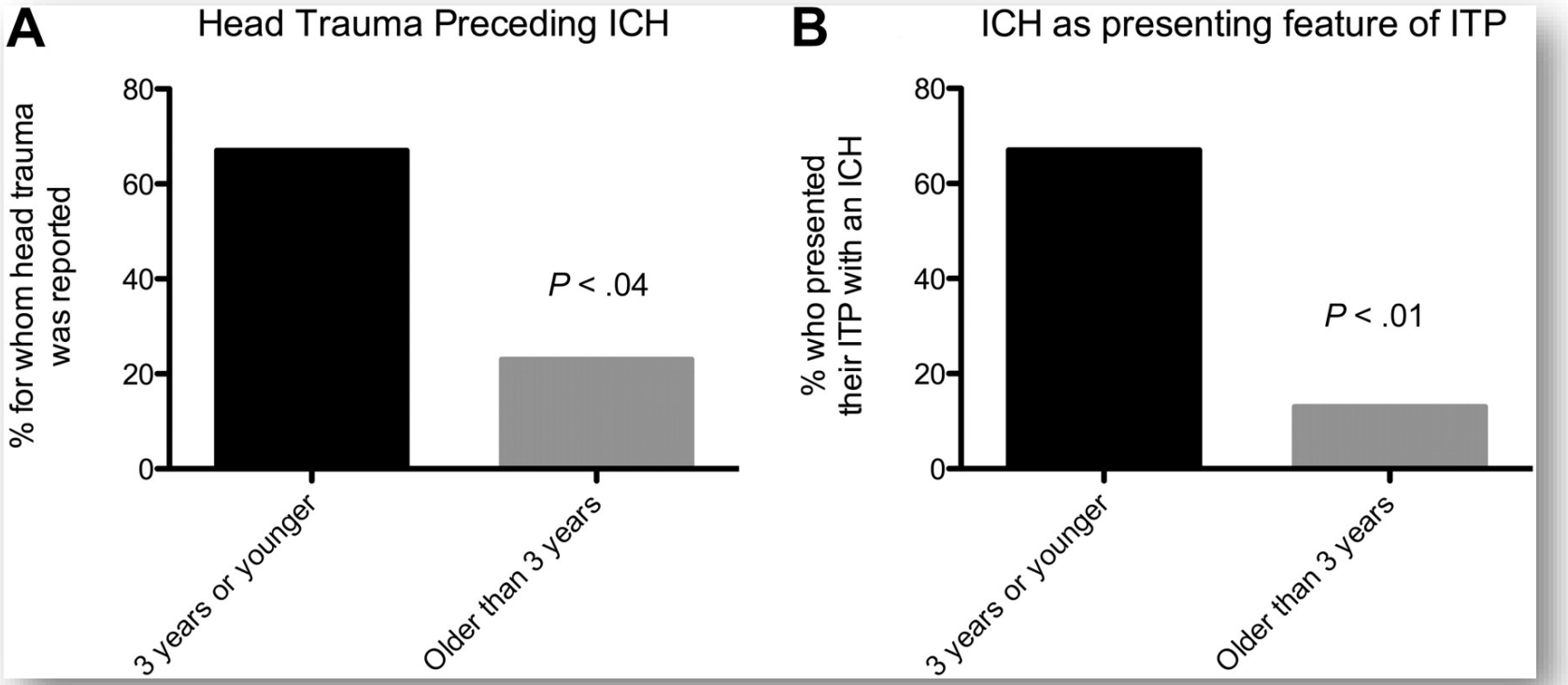
- Kopftrauma (33%) und Hämaturie (22,5%) mit ICH assoziiert, zstl. Ekchymosen, Petechien

- Mortalität 25% (10/40), neurologisches Defizit 10/30 (33%) (4 Hemiparese, 4 Hirnnervenausfälle, 1 kognitives Defizit, 1 Epilepsie, 1 Sprachstörungen)

- RF ICH: Thrombozyten < 10-20 GPT/L, NSAR, Kopftrauma, SLE, cerebrale Arterio-venöse Malformation

Blood 2009 Intracranial hemorrhage (ICH) in children with immune thrombocytopenia (ITP): study of 40 cases. Bethan Psaila et al.

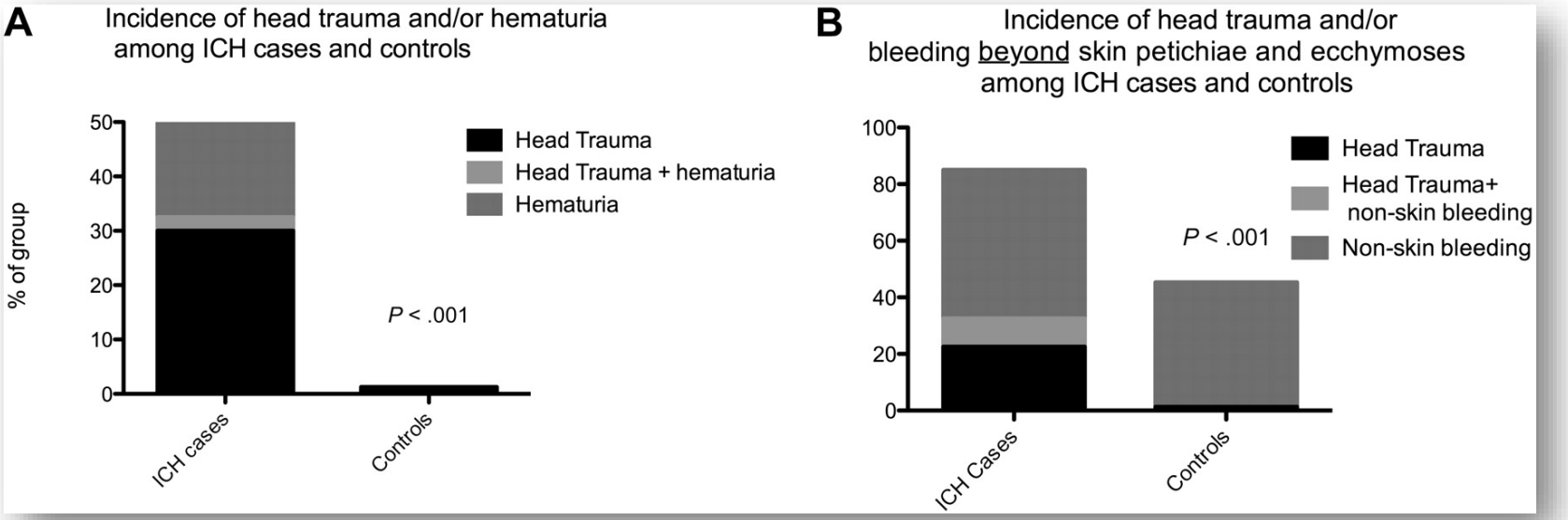
Intracranielle Hämorrhagie



Younger patients were significantly more likely to have head trauma preceding their ICH and to have an ICH as the presenting feature of their ITP.
(A) Head trauma preceding ICH. (B) ICH as presenting feature of ITP.

Blood 2009 Intracranial hemorrhage (ICH) in children with immune thrombocytopenia (ITP): study of 40 cases. Bethan Psaila et al.

Intracranielle Hämorrhagie



Combination of the risk factors of head trauma and bleeding to identify patients with ICH.
(A) Incidence of head trauma and/or hematuria among patients with ICH and control subjects.

Blood 2009 Intracranial hemorrhage (ICH) in children with immune thrombocytopenia (ITP): study of 40 cases. Bethan Psaila et al.

Risikofaktoren für chronischen Verlauf

- Risikofaktoren:
  - Weibliches Geschlecht (OR 1.17)
  - Höheres Alter (≥11J.) bei Erstdiagnose (OR 2.47)
  - Schleichender Beginn (OR 11.27)
  - Keine vorhergehende Infektion oder Impfung (OR 3.08)
  - mild bleeding
  - Höhere Thrombozytenzahl (≥ 20 GPT/L) bei ED (OR 2.15)
  - Vorhandensein antinucleärer Antikörper (OR 2.87)
  - Therapie-Kombination aus Methylprednisolon und IVIG (OR 2.67)

- Protektiv:
  - Schleimhautblutung bei ED (OR 0.39)
  - Alleinige IVIG-Therapie (OR0.71)

Blood 2014 Clinical and laboratory predictors of chronic immune thrombocytopenia in children: a systematic review and meta-analysis. Katja M. et al.