Piastrinopenie

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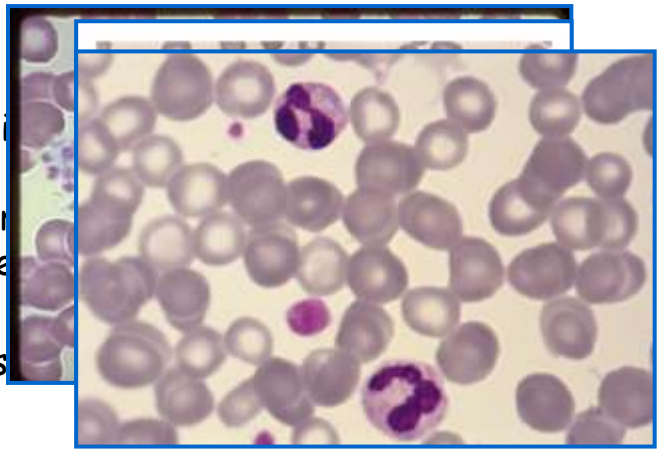
Piastrinopenia o Trombocitopenia
Definizione

Condizioni caratterizzate da un numero di piastrine inferiori a 150.000/mmc

Le manifestazioni emorragiche non compaiono di solito per valori superiori a 50.000/mmc, anche se tale limite è variabile da soggetto a soggetto

Pseudo trombocitopenia



•Preli

•Aggr
•Sate

•Pres

Piastrinopenia

- Ridotta produzione
- Aumentata distruzione
- Sequestrazione

Piastrinopenia

- Ridotta produzione
- Aumentata distruzione
- Sequestrazione
  - Ipersplenismo di varia origine

Piastrinopenia

- Ridotta produzione
  - Farmaci mielotossici
  - Pancitopenia
    - Leucemia
    - Tumori solidi
    - Aplasia midollare acquisita
    - Anemia di Fanconi
    - Osteopetrosi
  - Piastrino-penie, -patie congenite
- Aumentata distruzione
- Sequestrazione

Piastrinopenie, -patie congenite

Depongono per piastrinopenia congenita

- **Familiarità** (frequente trasmissione AD) per piastrinopenia, patologia renale, sordità, cataratta, dismorfismi, sindromi mielodisplastiche
- Sintomi emorragici assenti o poco presenti
- Piastrinopenia presente in tutti gli emocromi precedenti
- **Trombocitopenia isolata** con conte normali di GR e GB

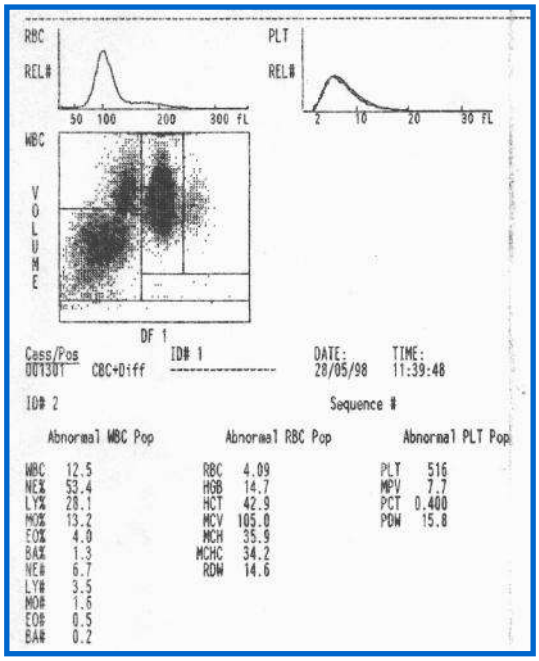
Non depongono per piastrinopenia congenita

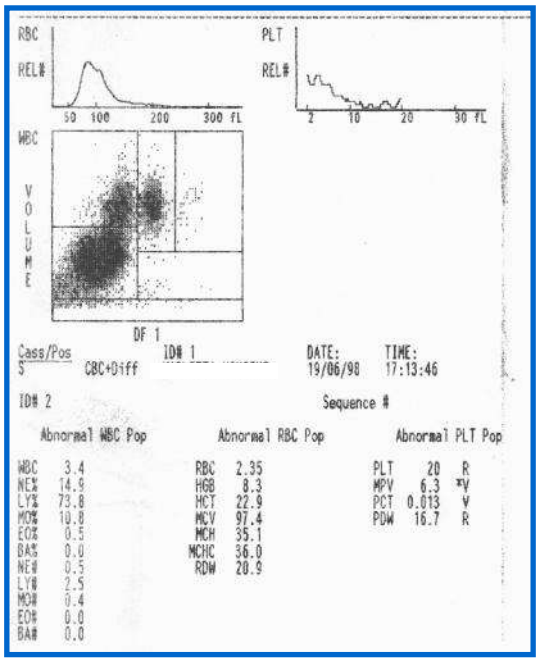
- Febbre, infezioni ricorrenti, perdita di peso, astenia, dolore osseo o articolare, rash cutaneo (patologia neoplastica, aplasia midollare, patologia immune sistemica)
- Assunzione di farmaci
- **Disponibilità di precedente conteggio piastrinico nella norma**
- **Alterazioni della serie rossa e/o bianca**

MPV

Mean platelet volume

- E' la media del volume piastrinico
- Il valore normale è compreso tra 7.0 e 11.0 fl
- Permette di classificare le piastrinopenie in base alle dimensioni delle piastrine


RBC
REL#
50 100 200 300 fL
PLT
REL#
2 10 20 30 fL
WBC
VOLUME
DF 1
Cass/Pos
001301
CBC+Diff
ID# 1
DATE:
28/05/98
TIME:
11:39:48
ID# 2
Sequence #
Abnormal WBC Pop
Abnormal RBC Pop
Abnormal PLT Pop
WBC 12.5
NE% 53.4
LY% 28.1
MO% 13.2
EO% 4.0
BA% 1.3
NE# 6.7
LY# 3.5
MO# 1.6
EO# 0.5
BA# 0.2
RBC 4.09
HGB 14.7
HCT 42.9
MCV 105.0
MCH 35.9
MCHC 34.2
RDW 14.6
PLT 516
MPV 7.7
PCT 0.400
PDW 15.8


RBC
REL#
50 100 200 300 fL
PLT
REL#
2 10 20 30 fL
WBC
VOLUME
DF 1
Cass/Pos
S
CBC+Diff
ID# 1
DATE:
19/06/98
TIME:
17:13:46
ID# 2
Sequence #
Abnormal WBC Pop
Abnormal RBC Pop
Abnormal PLT Pop
WBC 3.4
NE% 14.9
LY% 73.8
MO% 10.8
EO% 0.5
BA% 0.0
NE# 0.5
LY# 2.5
MO# 0.4
EO# 0.0
BA# 0.0
RBC 2.35
HGB 8.3
HCT 22.9
MCV 97.4
MCH 35.1
MCHC 36.0
RDW 20.9
PLT 20 R
MPV 6.3 *V
PCT 0.013 V
PDW 16.7 R

Platelet diameters in inherited thrombocytopenias: analysis of 376 patients with all known disorders

Patrizia Noris,[1] Ginevra Biino,[2] Alessandro Pecci,[1] Elisa Civaschi,[1] Anna Savoia,[3,4] Marco Seri,[5] Federica Melazzini,[1] Giuseppe Loffredo,[6] Giovanna Russo,[7] Valeria Bozzi,[1] Lucia Dora Notarangelo,[8] Paolo Gresele,[9] Paula G. Heller,[10] Nuria Pujol-Moix,[11] Shinji Kunishima,[12] Marco Cattaneo,[13] James Bussel,[14] Erica De Candia,[15] Claudia Cagioni,[1] Ugo Ramenghi,[16] Serena Barozzi,[1] Fabrizio Fabris,[17] and Carlo L. Balduini[1]

(*Blood* 2014;124(6):e4-e10)

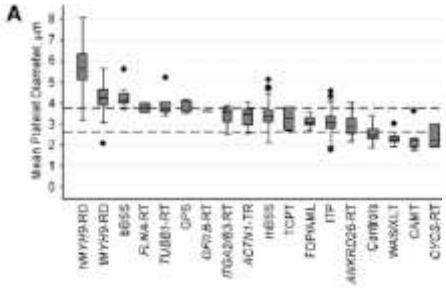


Table 5. Classification of ITs according to MPDs and the percentage of large platelets

ITs	MPD (µm)	Large platelets (%)	
With giant platelets	>4	PDLCR >50%	hMYH9-RD sBSS uMYH9-RD
With large platelets	>3.2	PDLCR >20%	TUBB1-RT GPS *FLNA*-RT *GFI1b*-RT mBSS *ITGA2B/B3*-RT *ACTN1*-RT
With normal or slightly increased platelet size	>2.6	And/or PDLCR >5%	FDP-AML TCPT XLTT *ANKRD26*-RT CTRUS VWDP
With normal or slightly decreased platelet size	<2.6	And/or SDCR >5%	TAR CAMT *CYCS*-RT XLT/WAS

Lo striscio

- **Allestimento curato** del vetrino al momento del prelievo
- Lettura da parte di personale con **specifiche competenze** (medico o biologo con esperienza di ematologia)
- Disponibilità di **tempo**


The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Volume 353:498-507 August 4, 2005 Number 5

Diagnosis from the Blood Smear

Barbara J. Bain, F.R.A.C.P., F.R.C.Path.

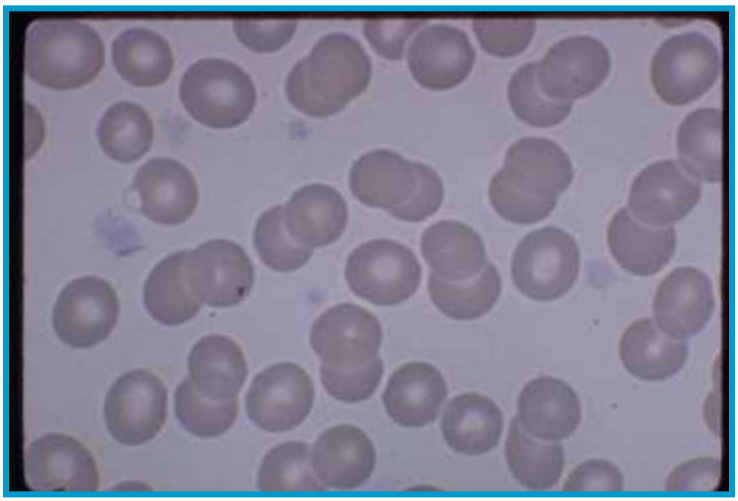
Lo striscio

Indicazioni cliniche
Caratteristiche che suggeriscono
- Anemia
- Ittero
- Emoglobinopatie
- **Trombocitopenia**
- Leucemie/linfomi
- C.I.D.
- Malattie infettive riconoscibili al vetrino
- Mononucleosi e altre malattie virali

Indicazioni di laboratorio

Morfologia piastrinica

Piastrine piccole	S. Wiskott Aldrich
Piastrine grandi	Porpora trombocitopenica idiopatica
Piastrine giganti	S. di May-Hegglin, S. Bernard Soulier,
Piastrine grigie	S. delle piastrine grigie (deficit α granuli)



Piastrinopenie, -patie congenite

Sebbene rare, tutte queste forma vanno sospettate e riconosciute, al fine del corretto inquadramento diagnostico

La diagnosi consente di

- fornire le informazioni corrette al paziente, al fine di evitare lunghi ed invasivi esami diagnostici e, soprattutto, terapie incongrue
- fornire informazioni sul possibile esito a lungo termine e dare consigli su come affrontare eventuali situazioni che richiedono una ottimale funzione piastrinica (interventi chirurgici)
- offrire una consulenza genetica per il soggetto e tutta la famiglia
- identificare altri soggetti familiari affetti

Piastrinopenia

Ridotta produzione

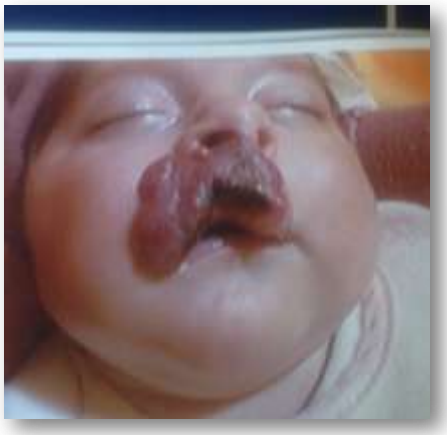
Aumentata distruzione

Sequestrazione

Immuno-mediata
- Piastrinopenia idiopatica (PTI)
- Post-virale
- LES e altre malattie autoimmuni
- Iso-immune neonatale

Non immuno-mediata
- Sindrome uremico emolitica
- CID
- Sindrome di Kasabach-Merritt
- Farmaci

Sindrome di Kasabach Merrit



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Trombocito-Penia immune (ITP)

Patogenesi

Autoimmunitaria: ↓ vita media delle piastrine (poche ore invece dei normali 9-13 giorni)

Incidenza

4-10 casi/100.000 bambini

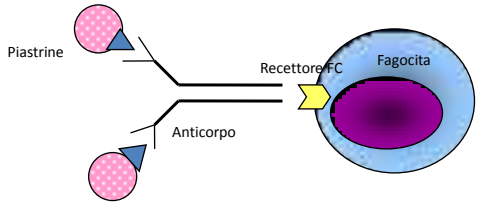
Esordio

Brusco, con comparsa di manifestazioni emorragiche, talvolta post-infettiva o post-vaccinale

Presentazione clinica

Emorragie cutanee (ecchimosi, petecchie)
Emorragie mucose (epistassi, gengivorragia)
Assenza di altri sintomi e/o segni

Trombocitopenia Immune



Accelerata distruzione piastrinica immuno-mediata

Trombocitopenia immune (ITP)

Esami di laboratorio

Piastrinopenia (PLT 5.000-50.000/mmc) isolata
Esclusione di una **pseudotrombocitopenia**
Anticorpi anti piastrine

Diagnosi

Si basa sul reperto di **numerosi megacariociti** nell'aspirato midollare e sull'**esclusione di cause note** di trombocitopenia (infezioni, LES etc)

Trombocitopenia Immune

- Nuove definizioni
- E' sempre necessario eseguire l'aspirato midollare?
- Indicazioni al trattamento delle ITP
- Quali farmaci utilizzare
- Strategie di seconda linea
- Helicobacter pylori
- Qualità di vita

Nuove definizioni


blood

Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group

The panel decided to avoid the term "idiopathic," preferring "immune," to emphasize the immune-mediated mechanism of the disease and to choose "primary" (as opposed to idiopathic) to indicate the absence of any obvious initiating and/or underlying cause. The term "purpura" was felt inappropriate, because bleeding symptoms are absent or minimal in a large proportion of cases.[17,18]

I — Immune

T — ThrombocytoPenia

P — Purpura

Nuove definizioni

Primary ITP	Primary ITP is an autoimmune disorder characterised by isolated thrombocytopenia (peripheral blood platelet count < 100 × 10⁹/L) in the absence of other causes or disorders that may be associated with thrombocytopenia. The
Secondary ITP	All forms of immune-mediated thrombocytopenia except primary ITP*

Eziologia

- Primitiva (assenza di cause apparenti)
- Secondaria

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

Fase della malattia

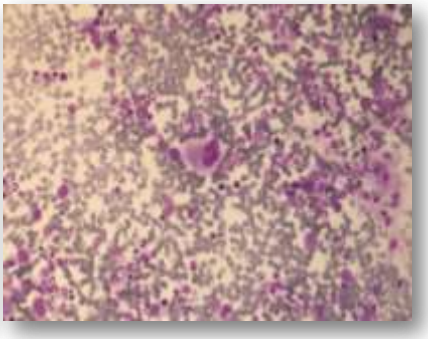
- Nuova diagnosi (0-3 mesi dalla diagnosi)
- Persistente (3-12 mesi dalla diagnosi)
- Cronica (> 12 mesi dalla diagnosi)

	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

Manifestazioni cliniche

- Severa (persistenza di sanguinamento)

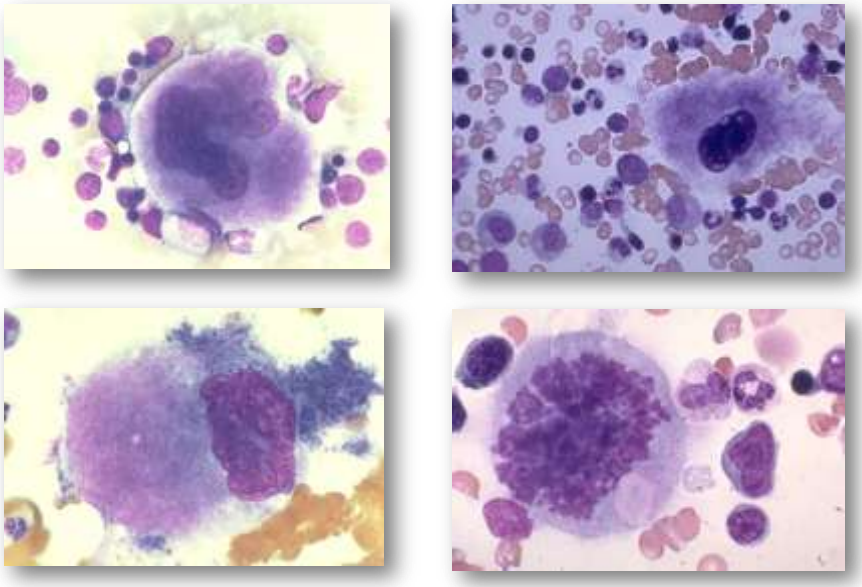
Aspirato midollare: sempre necessario ?



Piastrinopenia

Ridotta produzione

Aumentata distruzione → Assenza metaplasia, infiltrazione estrinseca



Linee guida: ITP acuta

Haematologica 2000; 85:420-424
decision making and problem solving

Hemostasis & Thrombosis

Acute childhood idiopathic thrombocytopenic purpura: AIEOP consensus guidelines for diagnosis and treatment

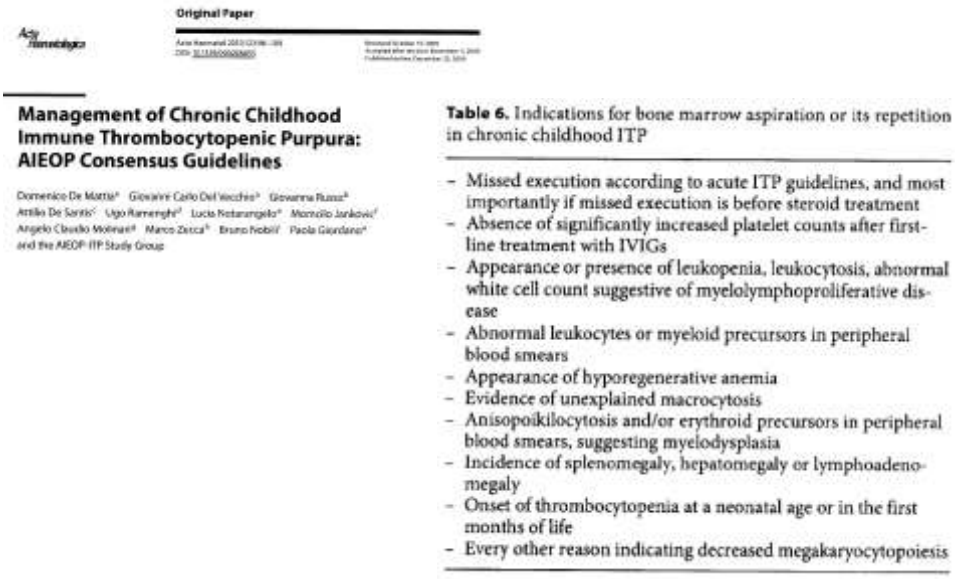
Domenico De Matta,* Domenico Del Principe,* Giovanni Carlo Del Vecchio,* Momcilo Jankovic,# Alberto Arrighini,§ Paola Giordano,* Adriana Menichelli,* Piergiorgio Mori,^ Marco Zecca,@ Andrea Pession&# and The AIEOP ITP Study Group§§

*Dipartimento di Biomedicina dell'Età Evolutiva, Università di Bari; *Dipartimento Sanità Pubblica, Clinica Pediatrica, Università Tor Vergata di Roma; #Clinica Pediatrica, Ospedale San Gerardo, Università di Milano; §Clinica Pediatrica, Università di Brescia; ^Dipartimento di Ematu-Oncologia, Ospedale Pediatrico G. Gaslini; @Dipartimento di Scienze Pediatriche, Università di Pavia; &Clinica Pediatrica, Università di Bologna, Italy

§§Francesco Schettini (Bari), Giuseppe Masera (Monza), Pierantonio Macchia (Pisa), Giovanni Amendola (Napoli), Maria Baligan (Bologna), Carlo Barone (Roma), Pierfranco Biondi (Cagliari), Caterina Borgna (Ferrara), Silvana Croce (Perugia), Raffaella De Santis (San Giovanni Rotondo), Leonardo Felici (Ancona), Mariangela Lafranchi (Brescia), Giacomo Mancuso (Palermo), Fausta Massolo (Modena), Luigi Nespoli (Varese), Bruno Nobili (Napoli), Ugo Ramenghi (Torino), Giovanna Rosso (Catania), Fabio Tucci (Firenze)

Bone marrow aspiration: this is not unanimously recommended (strength of recommendation 5.5 – D) in all cases at diagnosis. It is appropriate before starting glucocorticoid treatment for the first time (strenght of recommendation 8.9 – B).

Linee guida: ITP cronica



Original Paper

Management of Chronic Childhood Immune Thrombocytopenic Purpura: AIEOP Consensus Guidelines

Domenico De Mattia[a] Giovanni Carlo Del Vecchio[b] Giovanna Russo[b] Attilio De Santis[c] Ugo Ramenghi[d] Lucia Notarangelo[e] Momcilo Jankovic[f] Angelo Claudio Molinari[g] Marco Zecca[h] Bruno Nobili[i] Paola Giordano[a] and the AIEOP ITP Study Group

Table 6. Indications for bone marrow aspiration or its repetition in chronic childhood ITP

- Missed execution according to acute ITP guidelines, and most importantly if missed execution is before steroid treatment
- Absence of significantly increased platelet counts after first-line treatment with IVIGs
- Appearance or presence of leukopenia, leukocytosis, abnormal white cell count suggestive of myelolymphoproliferative disease
- Abnormal leukocytes or myeloid precursors in peripheral blood smears
- Appearance of hyporegenerative anemia
- Evidence of unexplained macrocytosis
- Anisopoikilocytosis and/or erythroid precursors in peripheral blood smears, suggesting myelodysplasia
- Incidence of splenomegaly, hepatomegaly or lymphoadenomegaly
- Onset of thrombocytopenia at a neonatal age or in the first months of life
- Every other reason indicating decreased megakaryocytopoiesis

Diagnosi differenziale

Depongono per ITP

- Esordio acuto dei sintomi
- Recente infezione virale o vaccinazione con virus vivo attenuato
- **Trombocitopenia isolata** con conte normali di GR e GB
- Disponibilità di precedente conteggio piastrinico nella norma

Non depongono per ITP

- Febbre, infezioni ricorrenti, perdita di peso, astenia, dolore osseo o articolare, rash cutaneo (patologia neoplastica, aplasia midollare, patologia immune sistemica)
- Assunzione di farmaci
- Familiarità per piastrinopenia, patologia renale, sordità, cataratta, dismorfismi, sindromi mielodisplastiche (piastrinopatia congenita)
- Segni e sintomi di immunodeficienza
- **Alterazioni della serie rossa e/o bianca**

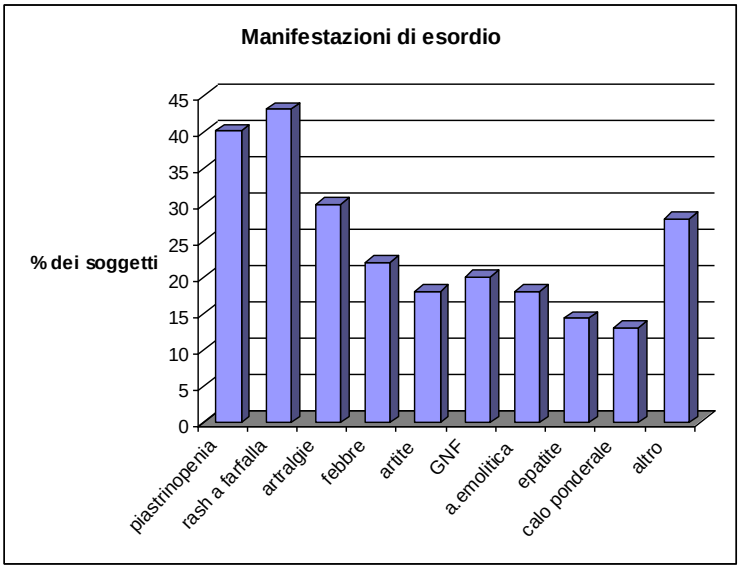
Diagnosi ITP secondaria

Nel 14% dei bambini diagnosticati come ITP, è stata trovata un'altra causa di piastrinopenia

- Trombocitopenie familiari
- Lupus Eritematoso Sistemico
- Ipersplenismo
- Trombocitopenia neonatale alloimmune
- Wiskott Aldrich Syndrome
- Infezione
- Sindrome da Immuno Deficienza Comune Variabile

Bryant & Watts 2011

LES – Sintomi all'esordio



CVID – Sintomi all'esordio

Pz con ID in terapia sostitutiva - Catania

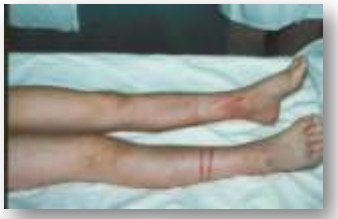
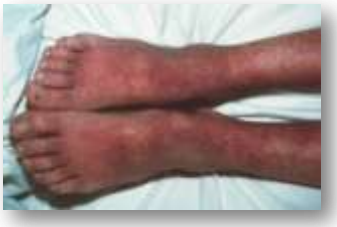
N. pazienti	17
M/F	12/5
Età	4-35 anni
Diagnosi	
CVID	9
XLA	5
Iper IgM	2
OMA	1
Terapia con Ig e.v.	5–30 g/4 sett
Efficacia (infezioni gravi)	Ottima
Efficacia (funzionalità polmonare)	Buona-ottima
Compliance	Ottima
Qualità di vita	Buona

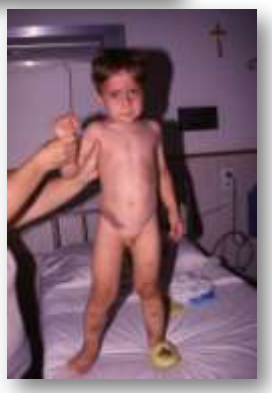
3/9 pazienti sono stati diagnosticati e trattati come ITP per 9-24 mesi prima di ottenere la diagnosi definitiva di CVID

ITP: quando trattare?

- Entità della **trombocitopenia**
- Gravità delle **manifestazioni emorragiche**
- Presenza di **altre manifestazioni**
- Presenza di **altri fattori di rischio** emorragico
- **Qualità di vita**

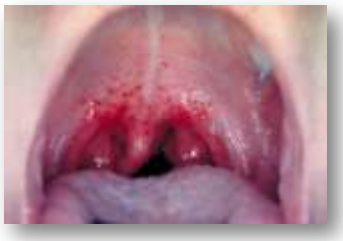
Emorragie cutanee



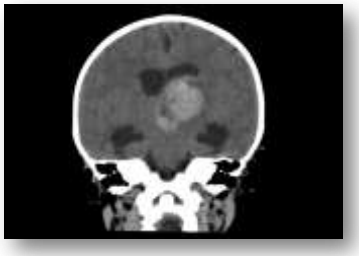
Emorragie mucose

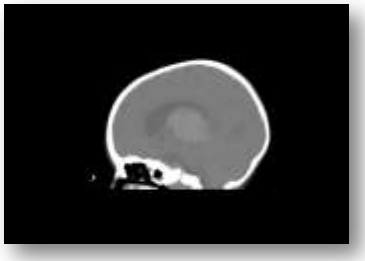


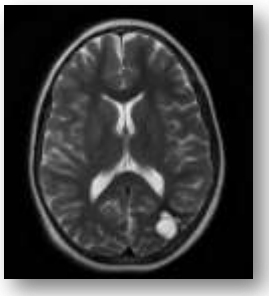



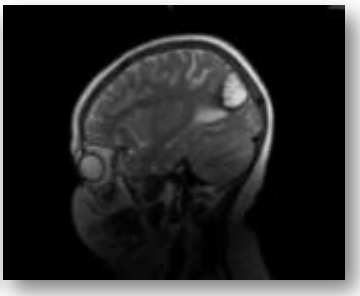
Emorragie interne: ICH

ITP acuta









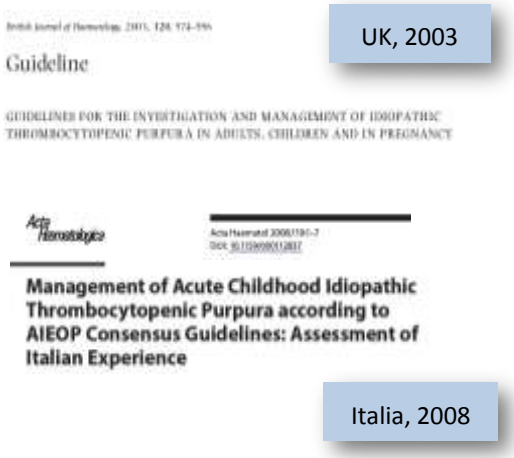
ITP cronica

Gravità delle manifestazioni cliniche

Tipo A	**Silente**	Nessuna manifestazione emorragica
	Lieve	Ecchimosi e petecchie Epistassi occasionali Nessuna limitazione delle attività quotidiane
Tipo B	**Moderata**	Manifestazioni cutanee più gravi ed estese Emorragie mucose Epistassi prolungate e/o frequenti
Tipo C	**Grave**	Emorragie (epistassi, melena, e/o menorragia, ICH) che richiedono ricovero Qualità di vita scadente

Linee-guida AIEOP, Haematologica 2000

Le linee guida



Guideline

GUIDELINES FOR THE INVESTIGATION AND MANAGEMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA IN ADULTS, CHILDREN AND IN PREGNANCY

UK, 2003

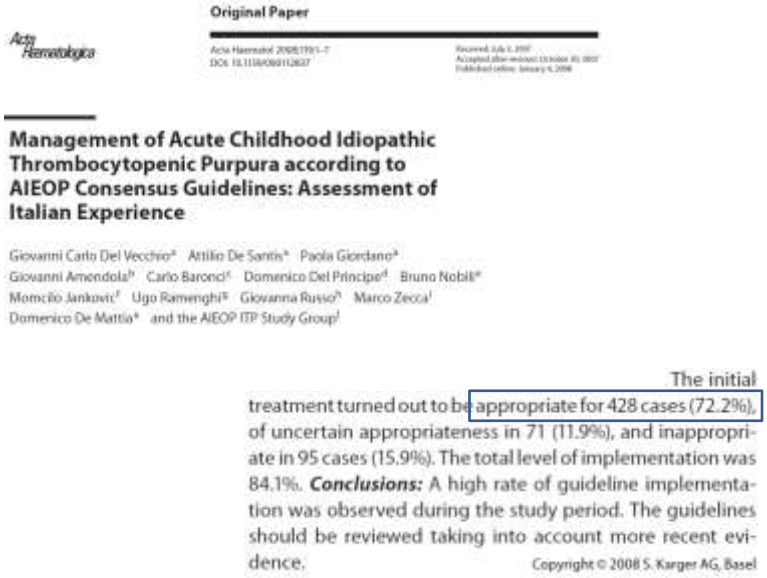
Acta Haematologica

Management of Acute Childhood Idiopathic Thrombocytopenic Purpura according to AIEOP Consensus Guidelines: Assessment of Italian Experience

Italia, 2008

1. La decisione se trattare o meno deve essere guidata dal dato clinico e non dalla conta piastrinica
2. E' opportuno trattare solo i bambini sintomatici (diatesi emorragica mucosa)
3. Il trattamento è finalizzato solo alla prevenzione delle emorragie gravi e potenzialmente fatali
4. L'efficacia della terapia è valutata in termini di incremento del valore piastrinico

La pratica clinica



Original Paper

Acta Haematologica

Management of Acute Childhood Idiopathic Thrombocytopenic Purpura according to AIEOP Consensus Guidelines: Assessment of Italian Experience

Giovanni Carlo Del Vecchio[a] Attilio De Santis[a] Paola Giordano[a] Giovanni Amendola[b] Carlo Baronci[c] Domenico Del Principe[d] Bruno Nobili[e] Momcilo Jankovic[f] Ugo Ramenghi[g] Giovanna Russo[h] Marco Zecca[i] Domenico De Mattia[a] and the AIEOP ITP Study Group[j]

The initial treatment turned out to be appropriate for 428 cases (72.2%), of uncertain appropriateness in 71 (11.9%), and inappropriate in 95 cases (15.9%). The total level of implementation was 84.1%. ***Conclusions:*** A high rate of guideline implementation was observed during the study period. The guidelines should be reviewed taking into account more recent evidence.

Si tratta di meno?

bjh review

A review of the management of childhood immune thrombocytopenia: how can we provide an evidence-based approach?

Nichola Cooper
Department of Haematology, Hammersmith Hospital, Imperial College, London, UK

*61% treatment rates in 1995, 38% treatment in 2003.
**Lower treatment rates in the period 1999–2003.

Country	Reference	Review period (years)	Patients (n)	Treatment rates	Morbidity
USA	Kime *et al* (2013)	2 (2008–2010)	2314	72%	ICH 0·6%
Nordic countries	Rosthoj *et al* (2012)	5	96		ICH 1%
UK	Grainger *et al* (2012)	5	225	16%*	ICH 0·5%
Japan	Shirahata *et al* (2009)	5	986	64%	
South Africa	Paling and Stefan (2008)	10	106	81%	ICH 3%
Italy	Del Vecchio *et al* (2008)		609	75%	
Canada	Belletrutti *et al* (2007)	10 (1994–2003)	198	90%**	ICH 0%

Estrema variabilità nei diversi paesi

E' aumentata l'incidenza della ICH ?

bjh review

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Uguale incidenza di emorragia intracranica (0-3%)

E' aumentato il numero di pazienti cronici?

Does treatment of newly diagnosed idiopathic thrombocytopenic purpura reduce morbidity?

Iris Treutiger, Jukka Rajantie, Bernward Zeller, Jan-Inge Henter, Göran Elinder, Steen Rosthøj, for the NOPHO ITP Study Group

Arch Dis Child 2007;92:704–707. doi: 10.1136/adc.2006.096442

	More than two-thirds treated, %	One- to two-thirds treated, %	Less than one-third treated, %
Initial treatment rates	89	57	14
Day 15 platelet count > 20 × 10^9/l	67	67	52
Day 15 platelet count > 150 × 10^9/l	38	29	29
Chronic ITP	27	22	25
Disease-related events in 6 months	23	22	19

Astenia

22% astenia in concomitanza con abbassamento PLTS

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DOI: 10.3109/08880010903026767

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Letter to the Editor

FATIGUE AS MARKER OF THROMBOCYTOPENIA IN CHILDHOOD IDIOPATHIC THROMBOCYTOPENIC PURPURA

Julie Blatt, MD, Brent Weston, MD, and Stuart Gold, MD *Division of Pediatric Hematology Oncology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA*

Patients with ITP are said to be normal apart from bleeding. Review of clinic notes for 27 children seen January–October, 2008 showed that 6 (22%) had a history of fatigue which resolved with improvement of platelet counts. While preliminary, our experience suggests that fatigue can be striking in children with ITP.

Astenia

bjh correspondence

Health-related lifestyle in adults and children with primary immune thrombocytopenia (ITP)

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Table 1. Health-related lifestyle survey summary results.

	Positive response %				
		Adults $N = 696$		Children $N = 94$	
Question	Total $N = 790$	Male $N = 199$	Female $N = 497$	Male $N = 51$	Female $N = 43$
Have you ever been unable to go to work or school because of tiredness and fatigue?†	12·5	10·6	14·3	6·1	10·0

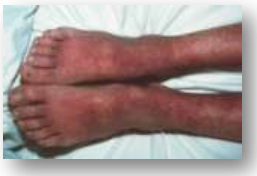
Qualità di vita: la prospettiva dei pazienti

bjh correspondence © 2010 Blackwell Publishing Ltd, *British Journal of Haematology*, **151**, 189–206

Health-related lifestyle in adults and children with primary immune thrombocytopenia (ITP)

	Positive response %				
		Adults $N = 696$		Children $N = 94$	
Question	Total $N = 790$	Male $N = 199$	Female $N = 487$	Male $N = 51$	Female $N = 43$
Do you try to hide your bruises?	307	32	155	10·0	14·6
	756	190	475	50	41
Are people ever suspicious that the bruises are a result of physical violence?	57	16	74	5·9	10·0
	750	191	468	49	40
I get bothered because I cannot do the activities I like?	318	101	199	23·9	22·5

Il nuovo approccio alla terapia

Chi	Diatesi emorragica	Astenia	Ridotta qualità di vita
	 +	 +	
Obiettivo	Prevenzione emorragie gravi	Aumento performances	Aumento qualità di vita
Outcome	Aumento PLTs	Nuove misure di outcome	Nuove misure di outcome

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ITP-QoL Questionnaire for Children with Immune Thrombocytopenia: Italian Version validation's

Paola Giordano, MD,[1] Giuseppe Lassandro, MD,[1] Fiorina Giona, MD,[2] Momcilo Jankovic, MD,[3] Margherita Nardi, MD,[4] Bruno Nobili, MD,[5] Lucia Dora Notarangelo, MD,[6] Giovanna Russo, MD,[7] and Sylvia von Mackensen, PhD[8]

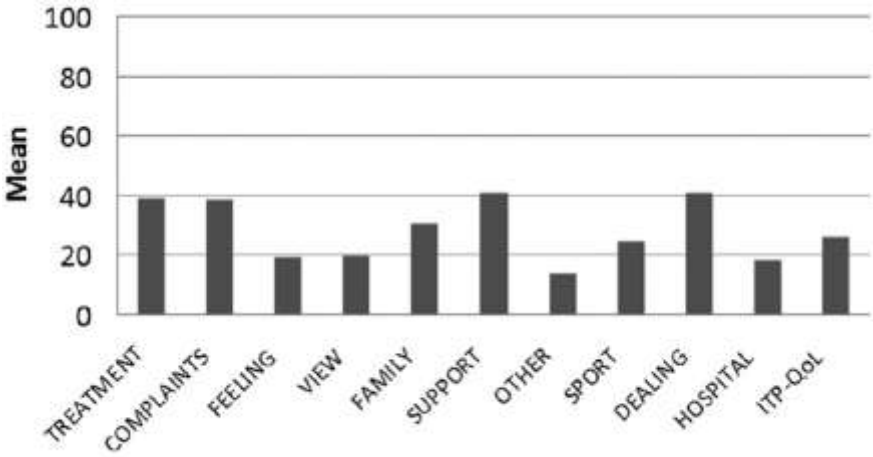


FIGURE 1 HRQoL profile in Italian children aged 8–16 years with ITP (ITP-QoL).

Terapie disponibili per la ITP

Tutti i trattamenti che vengono utilizzati routinariamente sono capaci di incrementare, più rapidamente rispetto all'osservazione, la conta piastrinica, e sono utili per trattare o prevenire le manifestazioni emorragiche. Tuttavia, tutti hanno effetti collaterali significativi e **nessuno cura eziologicamente la ITP o ne aumenta la probabilità di guarigione**

ITP – Opzioni terapeutiche

Terapia	Efficacia	Rapidità di azione	Facilità di impiego	Effetti indesiderati	Costo
Vigile attesa	+ +	+	?	?	++
Prednisone x os 2 mg/kg/d 2-3 sett	+ + + +	+ +	+ + + +	+ + + +	+
Metilprednisolone e.v 15-30 mg/kg 2-3 gg	+ + +	+ + +	+	+ / + +	+ +
Ig ev 0.8-2 gr	+ + + +	+ + + +	+	+ +	+ + +
Splenectomia	+ +	+ + + +	-	+ +	+ + +

Nuovi scenari terapeutici

ITP di nuova diagnosi diatesi emorragica

ITP persistente/cronica diatesi emorragica e/o sintomi cognitivi e/o riduzione qualità di vita

- Farmaci di primo livello
- Farmaci di secondo livello
- Splenectomia
- Terapia di supporto (a. tranexamico, estroprogestinici)

ITP cronica

- Pazienti **refrattari** alle terapie convenzionali
- Pazienti **dipendenti** dalle terapie convenzionali
- Pazienti con **qualità di vita scadente** (limitazioni motorie, sociali, effetti collaterali, ospedalizzazione etc)

Original Paper

Acta Haematologica

Management of Chronic Childhood Immune Thrombocytopenic Purpura: AIEOP Consensus Guidelines

Domenico De Mattia[a] Giovanni Carlo Del Vecchio[a] Giovanna Russo[b] Attilio De Santis[c] Ugo Ramenghi[d] Lucia Notarangelo[e] Momcilo Jankovic[f] Angelo Claudio Molinari[g] Marco Zecca[h] Bruno Nobili[i] Paola Giordano[a] and the AIEOP-ITP Study Group

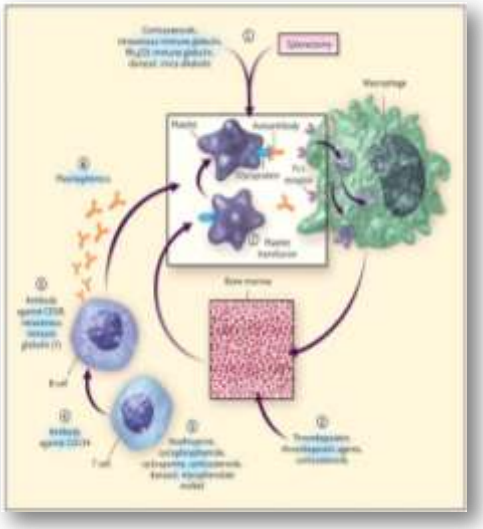
Table 7. Therapeutic strategies in chronic childhood ITP

Strategy	Drugs and recommended doses
A Emergency[a]	IVIGs, 0.8 g/kg IV methylprednisolone, 15–30 mg/kg/day for 3 days IV anti-D IGs, 50 μg/kg
B Maintenance	observation/suggestions IV anti-D IGs every 3–5 weeks IVIGs every 3–4 weeks
C Remission	splenectomy

[a] In well-selected cases, it is possible to combine treatments and add platelet transfusion.

Acta Haematol 2010;123:96–109

Le opzioni terapeutiche



Farmaci di primo livello

- IVIG ev
- Steroidi per os/ev
- Ig anti D

Farmaci di secondo livello

- Terapia combinata (IVIG + steroidi)
- Rituximab
- Agonisti del recettore della TPO
- Immunosoppressori

Splenectomia

Terapia combinata

ORIGINAL ARTICLE

Efficacy of combined intravenous immunoglobulins and steroids in children with primary immune thrombocytopenia and persistent bleeding symptoms

Emilia Parodi[1,2], Paola Giordano[2], Elisa Rivetti[2], Maria Teresa Giraudo[4], Giulia Ansaldi[1], Mirella Davitto[5], Anna Mondino[5], Piero Farruggia[5], Giovanni Amendola[6], Sofia M.R. Matarese[7], Francesca Rossi[7], Giovanna Russo[8], Ugo Ramenghi[1]

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since 1956
www.bloodtransfusion.it

Blood Transfus DOI 10.2450/2014.0185-13

Terapia combinata: risultati

Background. The aim of this study was to investigate the effect of the combined administration of intravenous immunoglobulins and steroids as a second-line therapy in 34 children with primary immune thrombocytopenia and persistent, symptomatic bleeding.

Materials and methods. Combined therapy (intravenous immunoglobulins 0.4 g/kg daily on days 1 and 2, and methylprednisolone 20 mg/kg daily on days 1-3) was administered to 12 patients with newly diagnosed ITP who did not respond to the administration of a single therapy (either intravenous immunoglobulins or steroids) and to 22 children with persistent and chronic disease who required frequent administrations (i.e. more frequently than every 30 days) of either immunoglobulins or steroids (at the same standard dosages) in order to control active bleeding.

Results. A response (i.e. platelet count $>50\times10^9$/L and remission of active bleeding) was observed in 8/12 (67%) patients with newly diagnosed ITP. The clinical presentation of responders and non-responders did not differ apparently. Patients in the chronic/persistent phase of disease had a significantly longer median period of remission from symptoms compared with the previous longest period of remission ($p=0.016$). The treatment was well tolerated.

Discussion. Our data suggest that the combined approach described is a well-tolerated therapeutic option for children with primary immune thrombocytopenia and persistent bleeding symptoms that can be used in both emergency and/or maintenance settings.

IVIG 0,4g/kg giorno 1 e 2

m-PDN 20 mg/kg giorno 1, 2, 3

12 pz con ITP di nuova diagnosi

Risposta in 8/12 (67%)

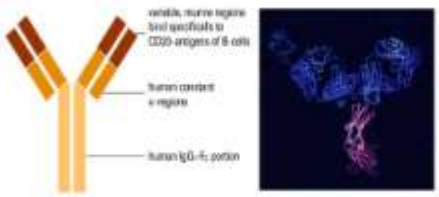
22 pz con ITP

persistente/cronica

Periodo di remissione

significativamente > 30 giorni

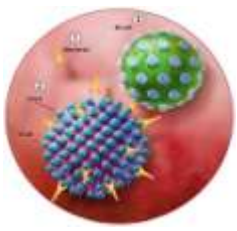
Rituximab



Il rituximab (anticorpo monoclonale anti CD20) è un anticorpo monoclonale chimerico, umano e murino

Il dominio Fab del rituximab si lega all'antigene transmembranico CD20 normalmente espresso sui linfociti pre-B e sui linfociti B maturi.

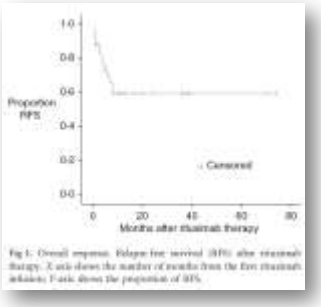
Il legame con il CD20 determina lisi cellulare ed induce l'apoptosi dei linfociti B con conseguente blocco della produzione di autoanticorpi



Rituximab – Studio cooperativo AIEOP

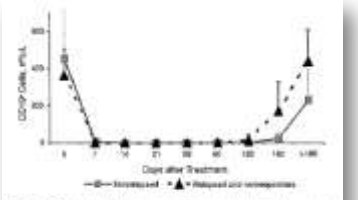
Efficacia

Br J Haematol 2008



Effetti collaterali

Int J Hematol 2006



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PLoS one

Rituximab for Children with Immune Thrombocytopenia: A Systematic Review

Yi Liang[1,2], Lingli Zhang[1]*, Ju Gao[3], Die Hu[1,2], Yuan Ai[3]

1 Department of Pharmacy, West China Second University Hospital, Sichuan University, Chengdu, China, 2 West China School of Pharmacy, Sichuan University, Chengdu, China, 3 Department of Pediatric Hematology and Oncology, West China Second University Hospital, Sichuan University, Chengdu, China

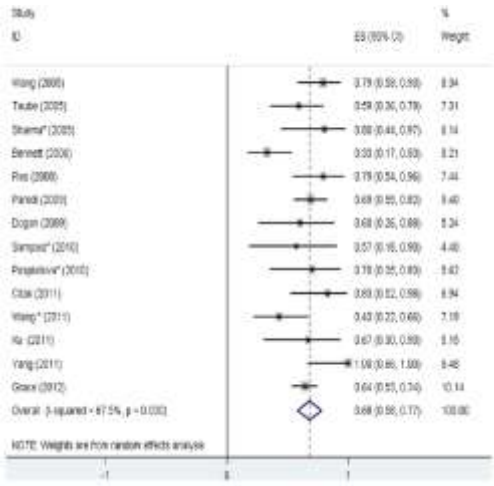
May 2012 | Volume 7 | Issue 5 | e36698

Rituximab – casistica review

Study	Country	Primary ITP, n	secondary ITP, n	Age, y	Splenectomized, n	ITP duration, mo	Platelet Count before rituximab treatment, $\times 10^9$/L	Previous treatment	Study design	Dosage of rituximab, mg/m^2/dose/ week	Doses, n
Taube (2005) [14]	Germany	23	None	3.8 (2.5–15.2)[a]	2	44 (14–103)	5 (2–27)	IVIG, SI, Anti-D, Sp	Case series	ⓘ	1
Wong (2000) [17]	USA	24	None	12.5 (2–19)	4	23 (6–120)	< 30	Sp, IVIG, SI, Anti-D, Dex, Az, VCR	Case series	ⓘ	4
Bennett (2006) [18]	USA	36	6 (ES associated)	11.2 (2.6–18.3)[c]	7	8.6 (1–121	1–27	SI,IVIG, Sp, Anti-D	Case series	ⓘ	4
Bader-Meunier (2007) [19]	France	None	11 (ES associated)	7.7 (0.7–15)	6	1 (0.2–8.3)	NR	IVIG, CSA, Az, Cyc, Sp, VCR, Dex	Case series	ⓘ	1–4
Ries (2008) [20]	USA	19	None	11 (3.8–18.4)	NR						
Dogan (2009) [21]	Turkey	18	None	2.5–13	0						
Kumar (2009) [22]	Canada	None	6 (SLE associated)	14 (8–18)	0						
Parodi (2009) [23]	Italy	49	None	10.7 (1.2–17.7)	3						
Ries (2009) [24]	USA	None	6 (ALPS associated)	10 (1–19)	3						
Cizak (2011) [25]	Turkey	13	None	6 (4–14)[a]	NR	36 (14–96)	8 (2–28)	SI, IVIG	Case series	ⓘ	4
Xu (2011) [26]	China	9	None	6.8 (5–13)	2	16 (8–29)	14 (3–21)	SI, Sp	Case series	ⓘ	4
Yang (2011) [27]	China	9	None	8	NR	12 (2–22	10–28	SI, IVIG, VCR, CSA	Case series	ⓘ	4
Grace (2012) [28]	USA/Canada	61	19[d]	7.5 (IQR 4.8, 12)[a]	NR	NR	14–40[a]	SI, IVIG	Longitudinal, observational, cohort	NR	NR
Sharma (2005)* [29]	India	16	None	9 (4–18)	6	NR	< 30	SI, CSA Cyc, VCR, IVIG Sp	Case series	ⓘ	4
Kim (2009)* [30]	South Korea	11	None	6.5 (0.5–15.4)	1	NR	13.7 (1–48)	IVIG SI Sp	Case series	ⓘ	4
Pospisilova (2010)* [31]	Czech Republic	18	None	4–18	NR	NR	NR	SI, VIG, AZ, anti-D	Case series	ⓘ	3–4
Sampaio (2010)* [32]	Portugal	7	None	4–18	1	27 (4–72)	NR	SI, VIG	Case series	NR	NR
Wang (2011)* [33]	China	21	None	NR	NR	NR	NR	NR	Case series	ⓘ, ⓘ	1–4

323 pazienti in età pediatrica

Rituximab – efficacia review



Complete Response

(PLTs > 100 x10 9/L)

39%

Response

(PLTs > 30 x 10 9/L)

68%

Durata mediana risposta

12.8 mesi

Rituximab – effetti collaterali review

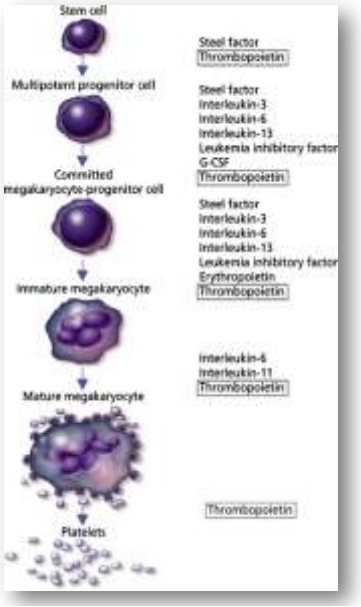
108 eventi avversi in 91 pazienti

91/108 (84%) di grado lieve/moderato

Eventi avversi di grado 3-4
- Infezione SNC
- Varicella
- Malattia di siero
- Polmonite
- Alterazioni sostanza bianca RM
- Immunodeficienza comune variabile
- Neutropenia
- Reazione immediata da ipersensibilità

Nessun decesso

Trombopoietina



La trombopoietina endogena, sintetizzata a livello epatico, regola la produzione piastrinica incrementando il numero, la ploidia e la maturazione dei precursori megacariocitari.

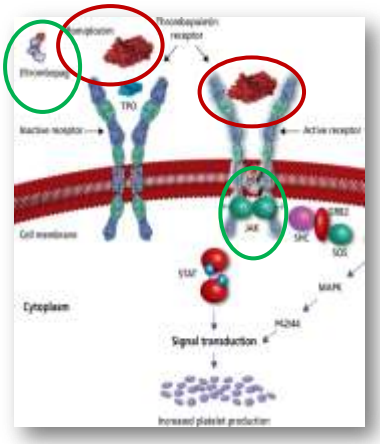
Il legame con il suo recettore sui megacariociti determina un aumento del numero delle cellule attraverso un meccanismo di inibizione dell'apoptosi

Nella ITP i precursori e i megacariociti sono in numero aumentato ma il legame con autoanticorpi IgG ne induce la apoptosi

Agonisti del recettore della TPO

ROMIPLOSTIM
- Agonista peptidico del recettore della TPO (4 catene)
- Non omologie con TPO endogeno, non immunogenico
- Compete con la TPO endogena
- **Somministrato s.c. 1 v/sett**

ELTROMBOPAG
- Agonista del recettore della TPO non peptidico
- Non omologie on TPO endogeno, non immunogenico
- Lega il dominio transmembrana (non compete con TPO)
- **Somministrato per os con T/2 di 24-40 ore**
- **Interferenza con cationi polivalenti (calcio, alluminio…)**



Agonisti TPO - Efficacia

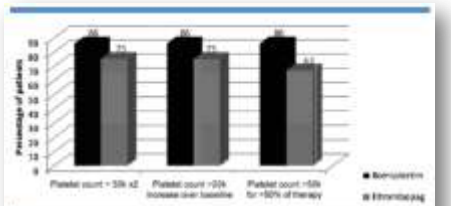


Figure 1. Efficacy end points for romiplostim and eltrombopag. Percent age of patients taking either romiplostim or eltrombopag who attained the 3 primary efficacy end points (end points taken from the first pediatric romiplostim study[11]). More than two-thirds of patients achieved each of the 6 responses.

Conclusion Retrospective analysis of off-study use of TPO agents in children with mainly chronic ITP showed increases in platelet counts in more than 4 of 5 children. The long-term use of TPO agents, up to 53 months, without tachyphylaxis supports their efficacy. These agents appear safe, effective, and tolerable in children with chronic ITP. (*J Pediatr 2014;165:600-5*).

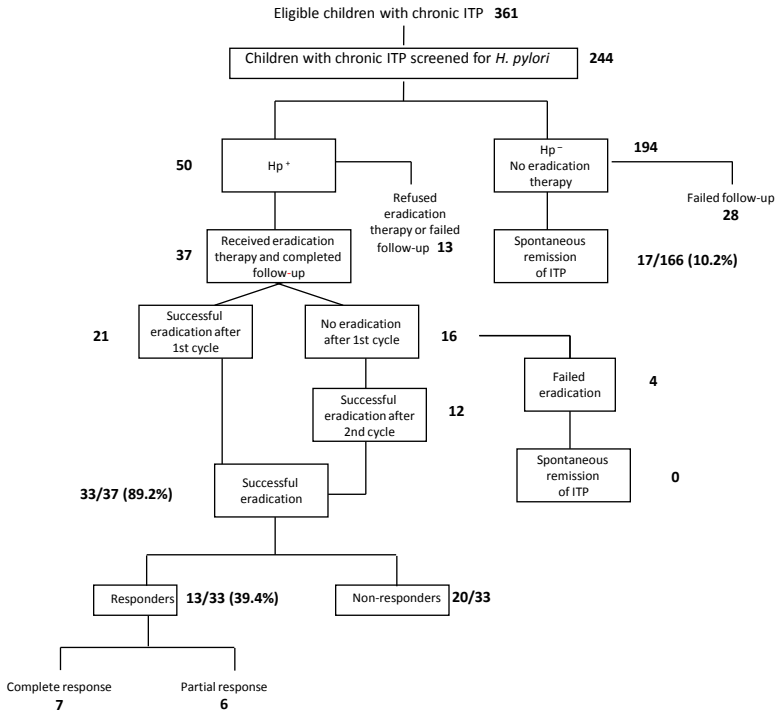
Infezione da Helicobacter pylori

Pediatr Blood Cancer © 2010 Wiley-Liss, Inc.

Effect of Eradication of *Helicobacter pylori* in Children With Chronic Immune Thrombocytopenia: A Prospective, Controlled, Multicenter Study

Giovanna Russo, MD,[1,*] Vito Miraglia, MD,[1] Francesca Branciforte, MD,[1] Sofia Maria Rosaria Matarese, MD,[2] Marco Zecca, MD,[3] Gianni Bisogno, MD,[4] Emilia Parodi, MD,[5] Giovanni Amendola, MD,[6] Paola Giordano, MD,[7] Momcilo Jankovic, MD,[8] Annalisa Corti, MD,[9] Margherita Nardi, MD,[10] Piero Farruggia, MD,[11] Laura Battisti, MD,[12] Carlo Baronci, MD,[13] Giovanni Palazzi, MD,[14] Fabio Tucci, MD,[15] Stefania Ceppi, MD,[16] Bruno Nobili, MD,[2] Ugo Ramenghi, MD,[5] Domenico De Mattia, MD,[7] and Lucia Notarangelo, MD[9] the AIEOP-ITP Study Group

Even if a causative role for *H. pylori* infection cannot be demonstrated, the availability of a safe, tolerable, and inexpensive method for detecting and treating *H. pylori* suggests that it may be appropriate to investigate and eradicate *H. pylori* infection in cITP children.



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Giovanna Russo, MD,[1,*] Vito Miraglia, MD,[1] Francesca Branciforte, MD,[1] Sofia Maria Rosaria Matarese, MD,[2] Marco Zecca, MD,[3] Gianni Bisogno, MD,[4] Emilia Parodi, MD,[5] Giovanni Amendola, MD,[6] Paola Giordano, MD,[7] Momcilo Jankovic, MD,[8] Annalisa Corti, MD,[9] Margherita Nardi, MD,[10] Piero Farruggia, MD,[11] Laura Battisti, MD,[12] Carlo Baronci, MD,[13] Giovanni Palazzi, MD,[14] Fabio Tucci, MD,[15] Stefania Ceppi, MD,[16] Bruno Nobili, MD,[2] Ugo Ramenghi, MD,[5] Domenico De Mattia, MD,[7] and Lucia Notarangelo, MD[9] the AIEOP-ITP Study Group

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The 2011 American Society of Hematology (ASH) guidelines (Neunert *et al.* 2011) do not recommend investigating for *H. pylori*, due to lack of evidence base. However, diagnosing and treating *H. pylori* is easy, has few adverse effects (if any) and, if responsive, may allow children to avoid other prolonged therapy. Further analysis is warranted.

Cooper N, BJH2014

Pediatr Blood Cancer 2006;47:742–745

Splenectomy in Children With Chronic ITP: Long-Term Efficacy and Relation Between its Outcome and Responses to Previous Treatments

TABLE I. Patient Characteristics

Mean age at diagnosis (years)	8 ± 3.9
Mean age at splenectomy (years)	11.3 ± 4.2
Mean duration of follow-up (months)	47 ± 36
Number of subjects with platelet count constantly above 50 × 109/L after splenectomy	68 (75%)
Number of subjects with improvement of social and sport activity after splenectomy	79 (88%)

Infections

There were 10 infectious episodes (0.028 patient/year) during the follow-up. One 10-year-old boy, splenectomized 6 years earlier, died 2 hr after admission for profound asthenia and fever of undetermined etiology. No difference in infection incidence was observed between patients who did or did not receive antibiotic prophylaxis.

Pediatr Blood Cancer 2006

C'è indicazione alla trasfusione di piastrine?

Le trasfusioni i piastrine hanno scarso beneficio visto che gli allergeni piastrinica sono presenti in tutte le piastrine.

In caso di rischio emorragico per la vita si infondono 2 - 4 U/m2 ogni 6-8 ore o 0,5 – 1 U/m2 per ora

Conclusioni

Al momento non sono disponibili linee guida che definiscano la priorità di una opzione terapeutica rispetto alle altre

Ciascun farmaco presenta un profilo di efficacia e sicurezza unico, in alcuni casi non ancora completamente definito

Numerose sono le variabili che devono essere prese in considerazione al fine di identificare il trattamento più idoneo per ciascun paziente

Take-home message

Qualunque decisione terapeutica deve essere condivisa con i piccoli pazienti e con le loro famiglie, con l'obiettivo di migliorarne globalmente la qualità della vita