La gestione della Piastrinopenia Immune (ITP) nel paziente anziano

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The elderly patient and frailty

Population ageing worldwide is rapidly accelerating from 461 million people aged over 65 years in 2004 to an estimated 2 billion people by 2050, which has profound implications for the planning and delivery of health and social care. Frailty is the most problematic expression of population ageing.

Frailty *is the most problematic expression of population ageing. It is a state of vulnerability to poor resolution of homoeostasis after a stressor event and is a consequence of cumulative decline in many physiological systems during a lifetime. This cumulative decline depletes homoeostatic reserves until minor stressor events trigger disproportionate changes in health status.*

Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet (London, England) 2013;381:752-762.

Epidemiology of ITP

- The incidence of ITP is 2.68-3.9 / 100,000 inhabitants per year.
- **It is a disease with two modal peaks, one in pediatric age and one in old age**. Incidence increases with age (from 1.94 to 4.62 / 100,000 over the age of 60 up to 9 over the age of 75).
- With the increase of age the prevalence between the two sexes tends to overturn.

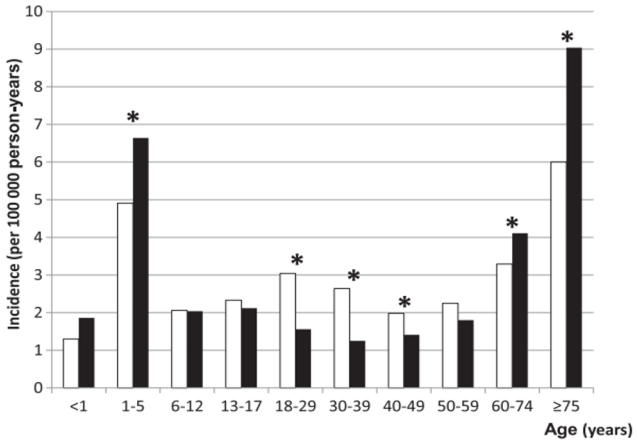


Figure 2. Incidence of ITP in France during the period from mid-2009 to mid-2011 by age and gender. Females, white bars; males, black bars. Stars indicate statistically significant differences among males and females (α = 5%).

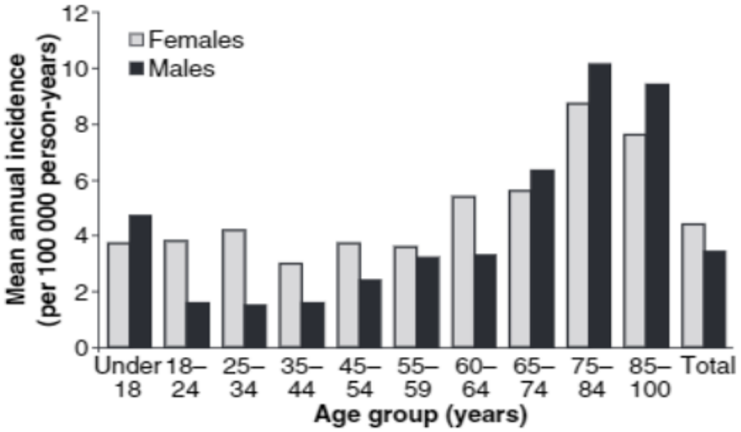


Fig 1. Average annual ITP incidence by age group and gender (n = 1145).

Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. Blood 1999;94:909-913.
Moulis G, Palmaro A, Montastruc JL, et al. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. Blood 2014;124:3308-3315.
Schoonen WM, Kucera G, Coalson J, et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. Br J Haematol 2009;145:235-244.

First: exclude MDS

- The 2011 ASH GLs did not suggest necessary bone marrow and cytogenetic evaluation, irrespective of age, for patients presenting with typical ITP. It should be considered when other hematological abnormalities are present or after refractoriness to the first line therapy (not addressed in 2019 ASH GLs).
- Thrombocytopenia complicates 40-65% of myelodysplastic syndromes
- MDS presents itself at diagnosis with isolated thrombocytopenia, in 10% of cases

Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011; Neunert C et al. Blood Advances 2019.
Kantarjian H, Giles F, List A, et al. The incidence and impact of thrombocytopenia in myelodysplastic syndromes. Cancer 2007.
Waisbren J, Dinner S, Altman J, et al. Disease characteristics and prognosis of myelodysplastic syndrome presenting with isolated thrombocytopenia. Int J Hematol 2017.

Second: exclude drug-related thrombocytopenia

Table I. Drug-induced immune thrombocytopenia.

Drugs identified by both clinical data from published case reports and identification of drug-dependent, platelet-reactive antibodies (Reese *et al*, 2010)	Drugs selected because of ≥5 published reports with definite or probable evidence for a causal relationship to thrombocytopenia (George & Aster, 2009)	Drugs more frequently associated with immune thrombocytopenia in the Berlin Case–Control Surveillance Study (Garbe *et al*, 2012)
Abciximab	Abciximab	Abciximab
Acetaminophen	Acetaminophen	Amlodipine
Amiodarone	Carbamezapine	Cotrimoxazole
Ampicillin	Chlorpropamide	Digitalis glycosides
Carbamazepine	Cimetidine	Drospirenone/ethinyestradiol
Cotrimoxazole	Cotrimoxazole	Gentamicin
Eptifibatide	Danazol	Moxonidine
Ethambutol	Diclofenac	Tirofiban
Haloperidol	Efalizumab	Triamterne/hydrochlorothiazide
Ibuprofen	Eptifibatide	
Irinotecan	Gold	
Naproxen	Hydrochlorothiazide	
Oxaliplatin	Interferon-α	
Phenytoin	Methyldopa	
Piperacillin	Nalidixic Acid	
Quinidine	Quinidine	
Quinine	Quinine	
Ranitidine	Ranitidine	
Rifampin	Rifampin	
Simvastatin	Tirofiban	
Sulfisoxazole	Vancomycin	
Tirofiban		
Valproic acid		
Vancomycin		

Mahevas M, Michel M, Godeau B. How we manage immune thrombocytopenia in the elderly. Br J Haematol 2016
Reese JA, Li X, Hauben M, et al. Identifying drugs that cause acute thrombocytopenia: an analysis using 3 distinct methods. Blood 2010

Older age and bleedings

Subgroup Analysis of the Odds of Hemorrhage in 117 Patients With ITP

Category	No. of Patients	Total Person-Years of Observation	No. of Events	Person-Time Incidence Rates	Odds Ratio	*P* Value
Age (y)						
<40	54	257	1	0.4	1.0*	—
40-60	32	177	2	1.1	2.8	NS
>60	31	67	7	10.4	28.9	<.010
Previous hemorrhagic events						
No	111	468	4	0.8	1.0*	
Yes	6	33	6	18.2	27.5	<.0005
Hypertension						
No	99	432	8	1.8	1.0*	
Yes	18	69	2	2.9	1.6	NS
Overt coexistent organic lesion						
No	96	409	7	1.7	1.0*	
Yes	21	92	3	3.3	1.9	NS

Abbreviation: NS, not significant.
*Reference category.

Age (in addition to any previous haemorrhagic events) increases the bleeding risk in patients with ITP.
Neither arterial hypertension nor elevated CCI determines an increased bleeding risk.

TABLE III. Factors Associated with a Significant Bleeding by Multivariate Analysis

Variable	aOR	95% CI	*P* value
Group			
Controls	1		0.009
Elderly	3.46	1.36–8.78	
Platelet count at diagnosis ($\times 10^9$/L)	0.89	0.85–0.94	<0.001
Hypertension[a]			
Absent	1		
Present	0.81	0.30–2.19	0.68
Comorbidity included into the Charlson comorbidity index[a]			
No comorbidity	1		
At least one comorbidity	0.96	0.37–2.45	0.94

Cortelazzo S, Finazzi G, Buelli M, et al. High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura. Blood 1991;77:31-33.

Older age and bleedings

Severe hemorrhagic events such as GI and CNS bleeding are more common in elderly patients with ITP.

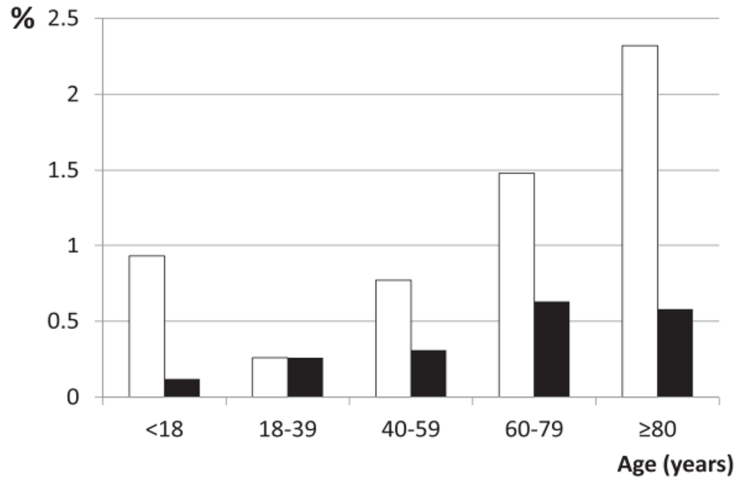
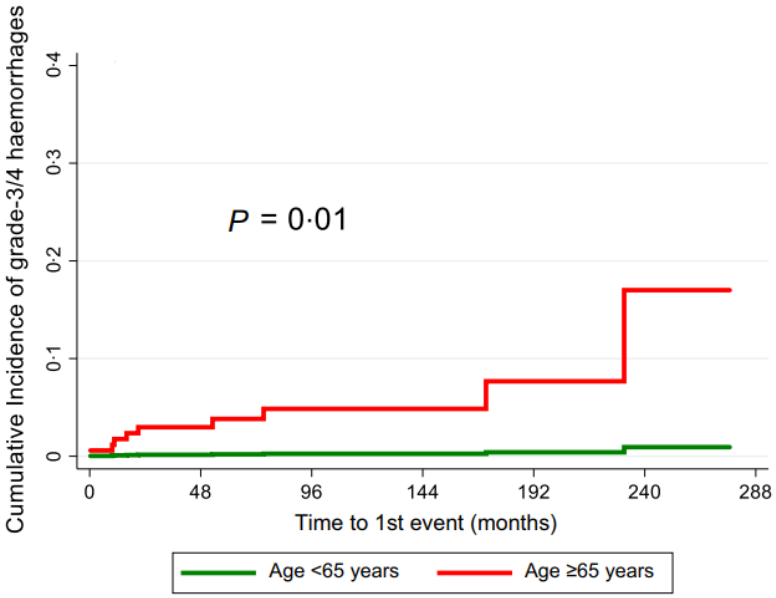


Figure 6. Percentages of incident ITP patients with gastrointestinal (white bars) and CNS (black bars) bleeding by age. Linear testing for an increasing relation between age and severe bleeding at diagnosis was significant for gastrointestinal bleeding among adults ($P = .003$) and for CNS bleeding in the whole population ($P = .02$).



Moulis G, Palmaro A, Montastruc JL, et al. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. Blood 2014;
Palandri F, Catani L, Auteri G, et al.. Understanding how older age drives decision-making and outcome in Immune Thrombocytopenia. A single centre study on 465 adult patients. BJH 2018.

Older age and thrombosis (a population-based study)

Table 3 Incidence rates (IRs) among men per 1000 person-years and 95% confidence intervals (CIs) for first deep-vein thrombosis alone (DVT) and pulmonary embolism with or without DVT (PE ± DVT) in Nord-Trøndelag County (n = 93 857) in 1995–2001

		DVT alone			PE ± DVT		
Age groups (years)	Person-years	n	IR	95% CI	n	IR	95% CI
60–64	14 893	17	1.14	0.71–1.84	11	0.74	0.41–1.33
65–69	14 181	23	1.62	1.08–2.44	12	0.85	0.48–1.49
70–74	14 045	26	1.85	1.26–2.72	22	1.57	1.03–2.38
75–79	11 620	41	3.53	2.60–4.79	17	1.46	0.91–2.35
80–84	7243	27	3.73	2.56–5.44	18	2.49	1.57–3.94

Table 4 Incidence rates (IRs) among women per 1000 person-years and 95% confidence intervals (CIs) for first deep-vein thrombosis alone (DVT) and pulmonary embolism with or without DVT (PE ± DVT) in Nord-Trøndelag County (n = 93 857) in 1995–2001

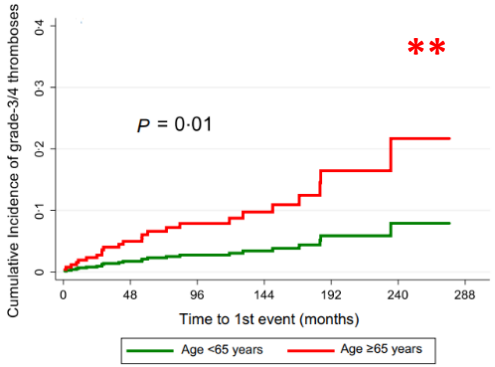
		DVT alone			PE ± DVT		
Age groups (years)	Person-years	n	IR	95% CI	n	IR	95% CI
60–64	15 050	14	0.93	0.55–1.57	6	0.40	0.18–0.89
65–69	15 013	17	1.13	0.70–1.82	15	1.00	0.60–1.66
70–74	15 857	23	1.45	0.96–2.18	11	0.69	0.38–1.25
75–79	14 954	44	2.94	2.19–3.95	25	1.67	1.13–2.47
80–84	11 727	45	3.84	2.87–5.14	24	2.05	1.37–3.05
≥85	9726	46	4.73	3.54–6.31	26	2.67	1.82–3.93

Thrombotic events are more frequent with increasing age and the number of cardiovascular risk factors.

Naess IA, Christiansen SC, Romundstad P, et al. Incidence and mortality of venous thrombosis: a population-based study. Journal of thrombosis and haemostasis : JTH 2007;5:692-699.

Elderly ITP pts and thrombosis

- Elderly patients with ITP have a greater tendency to develop thrombotic events.
- Thrombotic events occur > 20 times more frequently in patients over 60 than under 40.
- G3-4 thromboses are more frequent in elderly in comparison to younger ITP patients.



* **Table 3** Age-stratified number of thromboembolic events and incidence rate per 100 patient-years

Age (years)	All events $n = 43$	Venous events $n = 15$	Arterial events $n = 28$
< 40 years ($n = 322$)			
Event number (%)	3 (0.93)	2 (0.62)	1 (0.31)
Incidence rate (95% CI)	0.2 (0.08–0.73)	0.16 (0.04–0.63)	0.08 (0.01–0.56)
40–60 years ($n = 285$)			
Event number (%)	8 (2.80)	5 (1.75)	3 (1.05)
Incidence rate (95% CI)	0.67 (0.33–1.34)	0.33 (0.12–0.89)	0.25 (0.08–076)
> 60 years ($n = 379$)			
Event number (%)	32 (8.40)	8 (2.10)	24 (6.30)
Incidence rate (95% CI)	2.47 (1.75–3.50)	0.68 (0.36–1.32)	1.76 (1.17–2.65)
All ages ($n = 986$)			
Event number (%)	43 (4.36)	15 (1.52)	28 (2.83)
Incidence rate (95% CI)	1.14 (0.84–1.54)	0.39 (0.23–0.65)	0.71 (0.49–1.04)

* **Ruggeri M**, Tosetto A, Palandri F, et al. Thrombotic risk in patients with primary immune thrombocytopenia is only mildly increased and explained by personal and treatment-related risk factors. Journal of thrombosis and haemostasis : JTH 2014.

** **Palandri F**, Catani L, Auteri G, et al. Understanding how older age drives decision-making and outcome in Immune Thrombocytopenia. A single centre study on 465 adult patients. BJH 2018.

Elderly and Very Elderly ITP pts and thrombosis

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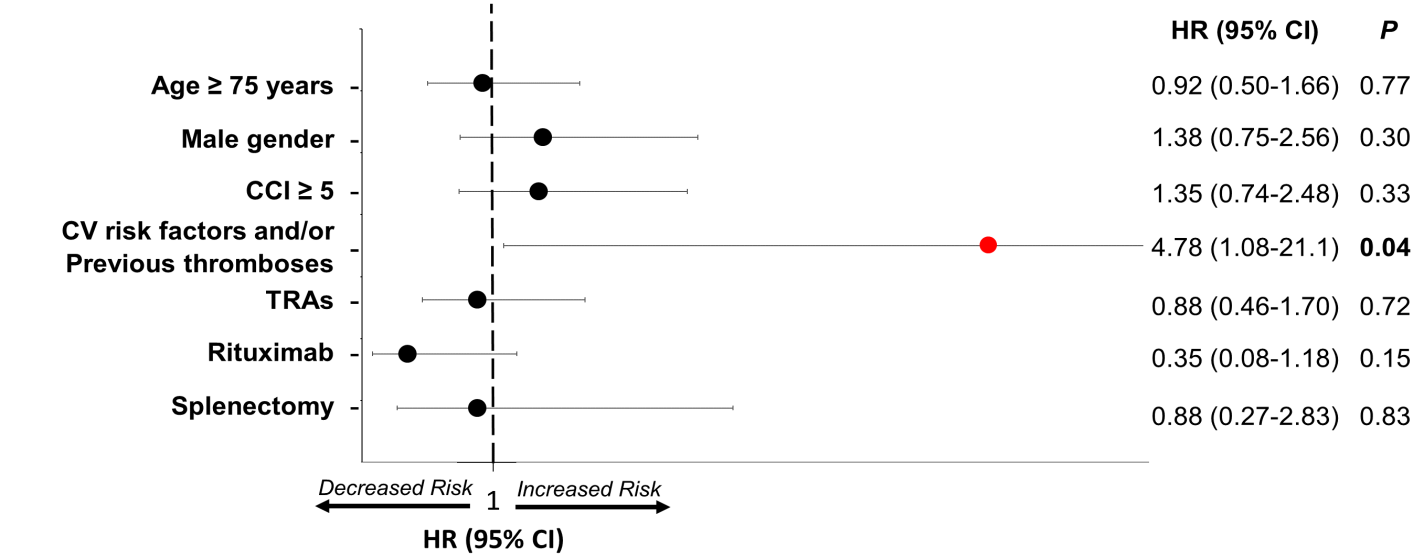
- 49 thromboses in 43/451 (9.5%) pts over 60 yrs old were observed during follow-up.
- Incidence rate of thrombosis was 1.7 (grade≥3: 0.9x100pts/yr).
- Cardiovascular risk factors and/or previous thromboses were found to significantly predict thromboses.
- The TRAs don't seem to impact negatively



ITP: Older age and clinical outcome

- Patients with ITP have a relative risk of 4.5 to be hospitalized for an infection within one year from diagnosis (4.8 in over 60s).
- **Elderly patients with cITP are admitted more frequently due to intracranial bleeding, compared to younger cITP patients and to elderly patients without cITP**
- **Elderly patients with ITP have also a greater risk of death (All-cause 5-year cumulative mortality)**

The 5-y hematologic malignancies-related mortality was 3.3% in patients with cITP and 0.4% in comparison cohort.
5-y infection-related mortality was 4.2% in patients with cITP and 0.7% in comparison cohort.
5-y hemorrhage-related mortality was 2.5% in patients with cITP and 0.3% in comparison cohort members.

225 pts were ≤ 60 yrs old

182 pts were ≥ 60 yrs old

Table 5. All-cause 5-year cumulative mortality and mortality rate ratio among 407 patients with cITP and 4069 members of the general population in Denmark

	No. of cITP deaths	Five-year mortality in patients with cITP, % (95% CI)	Five-year mortality in the comparison cohort, % (95% CI)	Crude MRR (95% CI)	Adjusted MRR (95% CI)*
All-cause mortality	87	24.3 (20.1-29.2)	14.3 (13.1-15.6)	1.9 (1.5-2.4)	2.3 (1.8-3.0)
Age at cITP diagnosis, y					
≤ 60	11	5.6 (3.1-9.9)	1.7 (1.2-2.4)	3.6 (1.8-7.2)	3.8 (1.9-7.7)
> 60	76	47.1 (39.5-55.4)	30.1 (27.8-32.6)	1.9 (1.5-2.5)	2.2 (1.7-2.9)
Sex					
Female	47	20.4 (15.7-26.3)	12.2 (10.9-13.7)	1.9 (1.4-2.6)	2.3 (1.7-3.2)
Male	40	31.4 (23.8-40.6)	18.1 (15.9-20.4)	2.0 (1.4-2.8)	2.4 (1.7-3.4)
Year of cITP diagnosis					
1996-2001	31	18.6 (13.5-25.4)	11.5 (10.1-13.2)	1.7 (1.2-2.5)	2.0 (1.3-2.9)
2002-2007	56	29.7 (23.0-37.7)	17.3 (15.4-19.4)	2.1 (1.6-2.8)	2.6 (1.9-3.5)
Comorbidity score					
0	26	11.9 (8.2-17.1)	4.9 (4.0-5.9)	2.8 (1.8-4.3)	3.0 (1.9-4.7)
≥ 1	61	44.9 (36.6-54.2)	29.9 (27.3-32.6)	1.8 (1.4-2.4)	2.1 (1.6-2.8)

cITP indicates chronic immune thrombocytopenia; CI, confidence interval; and MRR, mortality rate ratio.
*Adjusted for age (≤ 60 years and > 60 years), sex, calendar year, and level of comorbidity.

*Adjusted for age (≤ 60 y and > 60 y), sex, calendar year, and level of comorbidity.

Norgaard M, Jensen AO, Engebjerg MC, et al. Long-term clinical outcomes of patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. Blood 2011.

We treat a patient, not his platelet count ...

=> goals of therapy in ITP patient:

....To achieve a durable response....

Allow the patient to reach a "safe" platelet count

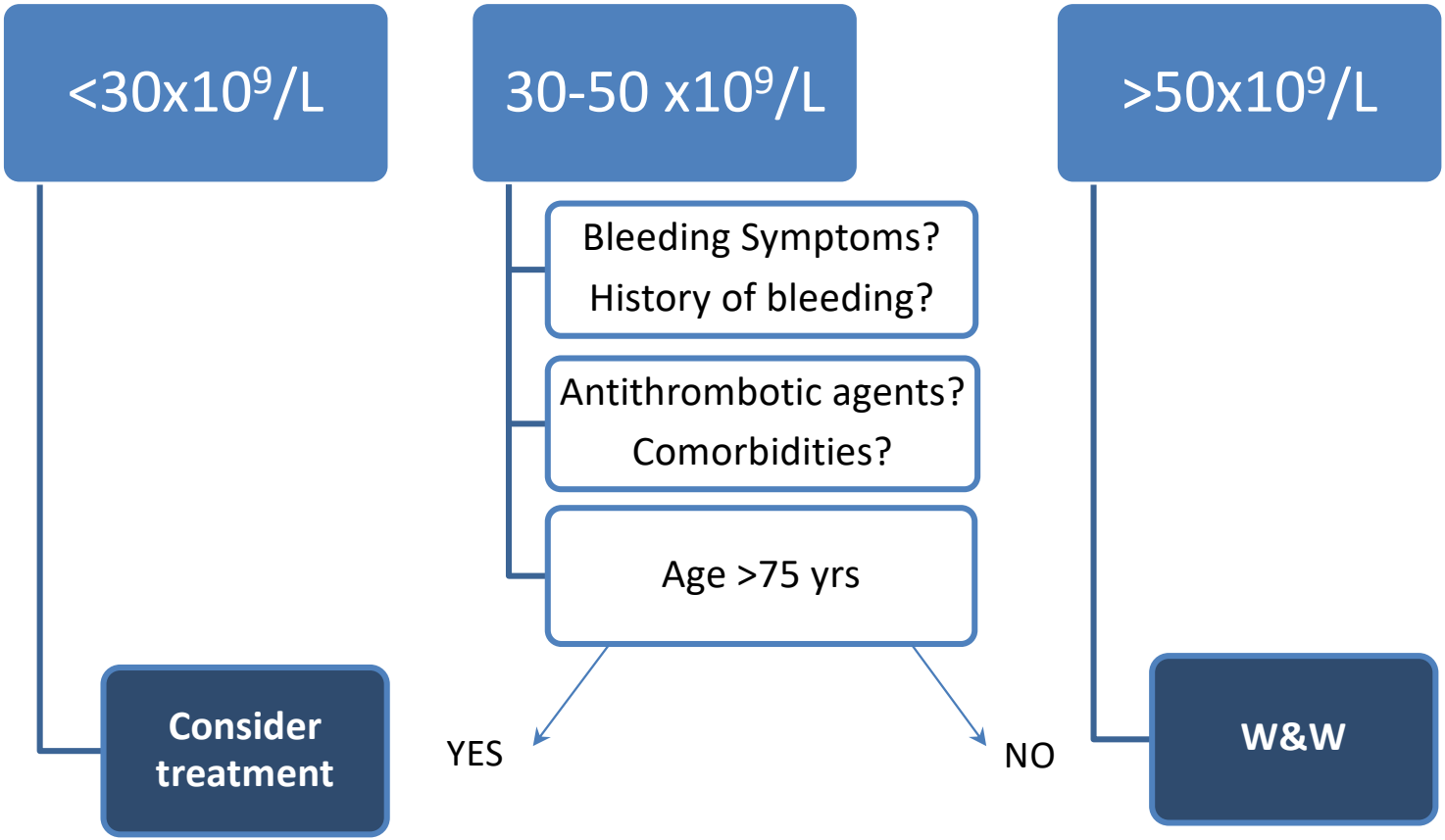
Avoid bleeding

Avoid potentially toxic therapies

We should evaluate which of these objectives can be achieved in the elderly patients

START THERAPY

Mahèvas M, Michel M and Godeau B, BJH 2016



THERAPY

PROS

SOLUTIONS
AND
COMPROMISE

CONS

Elderly ITP patients: treatment options and their pros and cons

Therapy	Pros	Cons
Steroids	Initial effectiveness in 70-80% of cases; Quick platelet count increase; Effective even at lower doses than conventional ones	Low rate of durable/off therapy response; Negative impact on QoL; Toxicity on bone, carbohydrate metabolism, etc.
HDIg	Quick platelet count increase Effective in about 80% of patients	Toxicity; AE rare but can occur in frail patients
Rituximab	Less effective in elderly patients	Higher risk of fatal infectious complication in elderly patients
Other immunesuppressive agents	Effective in 30-40% of cases, relatively easy to manage	Slow to act; Risk of infectious complication Drug interactions (Azathioprine) Toxicity (CyA, MMF)
Splenectomy	Effective, relative safe, potentially able to guarantee a lasting remission	Less effective (initial response and relapse) and more days of hospitalization in comparison to younger pts (< 60 or < 65 yrs);
TPO-ra	Comparable response rates in comparison to younger patients (durable response in about 60%); possibility to obtain therapy off response; No risk of infection	In this context they may have poor manageability; Comorbidity and thrombotic risk factors should be considered Safety profile not completely defined

Understanding how older age drives decision-making and outcome in Immune Thrombocytopenia. A single centre study on 465 adult patients

Palandri F. BJH 2018

ITP in the elderly: age of pts (>65 vs <65 yrs) and response to treatments

- The percentage of elderly pts **(>65yrs**) in drug-dependent response was significantly higher compared to younger group **(<65yrs**) (32.5% vs 14.8%,P< 0.001)
- The CR rate was significantly lower in the elderly pts (61.3% vs 76.6%, P= 0.006)

Management of elderly patients with immune thrombocytopenia: Real-world evidence from 451 patients older than 60 years

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- The outcome of **very elderly** (**VE**: age ≥75yrs) pts is overall comparable to **elderly** (**E**: age 60-74yrs) pts.
- This is despite, or probably thanks to, a differentiated therapeutic strategy for VE pts, which uses lower doses of corticosteroids as front-line treatment, reduces the use of potentially more toxic therapies such as RTX and splenectomy, and integrates the use of TRAs in the therapeutic algorithm.
- **Comorbidities and cardiovascular risk factors are crucial determinants of outcome in elderly ITP pts.**
- TRAs don't appear to negatively impact on thrombotic risk (**even in VE pts**)
- Careful evaluations of comorbid conditions and implementation of age-adapted treatment strategies should be further explored in this setting.

CONCLUSIONS

- **The elderly ITP patient is frail and has more comorbidities and an increased thrombotic, hemorrhagic and infectious risk.**
- Like all cases of ITP, treatment should be started when the patient is exposed to a significant bleeding risk (bleedings may occur more frequently in elderly in comparison to younger patients).
- Compared to younger patients, treatment may also be necessary for a higher platelet count (antithrombotic prophylaxis)
- The percentage of elderly pts (>65yrs) in drug-dependent response is significantly higher compared to younger group (<65yrs)
- The CR rate was significantly lower in the elderly pts
- No significant difference in terms of outcome between elderly e very elderly patients
- **Steroid** can be used in the elderly, but adverse effects must be carefully monitored (e.g blood pressure, blood glucose, BMD, vit. D). Lower dosage may be considered.
- **Splenectomy** can be performed in elderly "fit“ patients, however may be less effective with respect to **younger** pts and it is burdened by a greater risk of relapse, early and late complications.
- **Rituximab** appears to be more effective in **young** female pts, with a shorter response duration and a greater incidence of G3-4 infections in **older** pts.
- **TPOras** have comparable response rates in younger and elderly patients, but have some limits (require assistance from caregivers or food restrictions, several laboratoristic controls, not yet conclusive safety profile). **More data are needed concerning their safety.**

GRAZIE!!!.....a:

Francesca Palandri
Giuseppe Auteri
Emanuele Sutto
Christian Di Pietro
Daniela Bartoletti
Federica D'ambrosio
Stefania Giaquinta