# L'anemia emolitica autoimmune: terapia front-line

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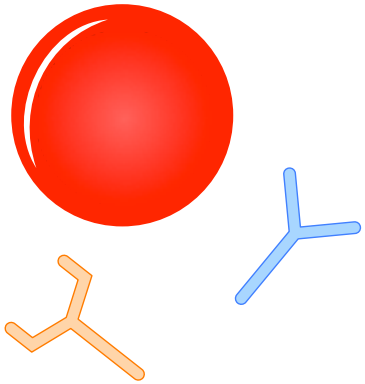
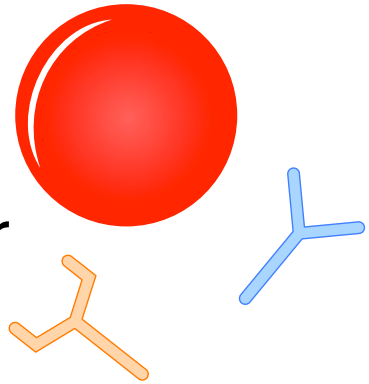
# Outline

1. General considerations
2. First-line treatment of Warm AIHA
3. First-line treatment of Cold AIHA
4. Concluding remarks

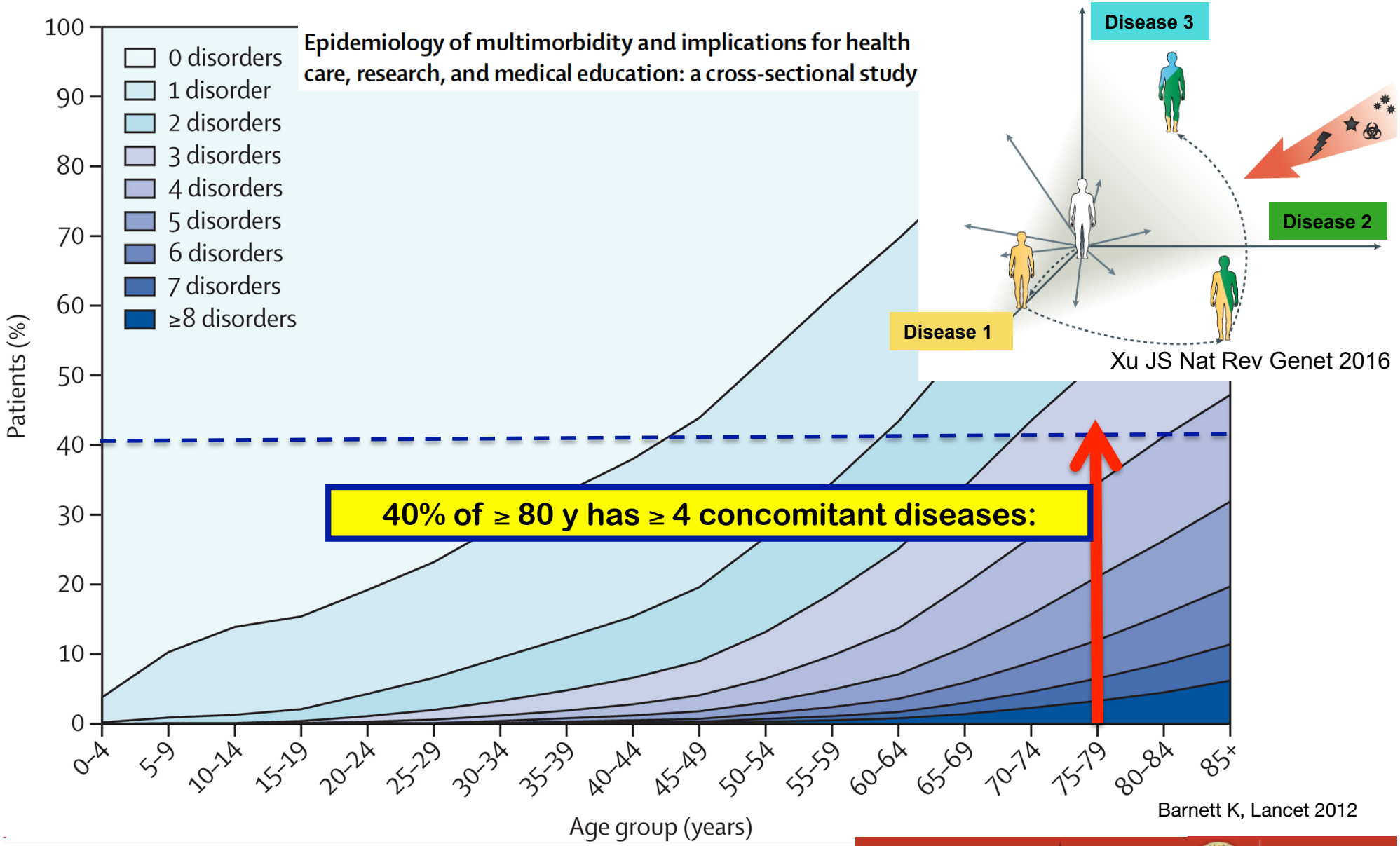


# AIHA therapy: general considerations

- Challenging/therapeutic dilemma.
- Lack of clinical trials and evidence-based standardized therapies (annual incidence 1-3:100.000 per year).
- Considerable clinical heterogeneity (including associated disorders).
- Chronic disorders
- Personalized approach depending on type of auto-Ab (warm, cold, mixed), whether AIHA is primary or secondary, patients features (age, comorbidities…)



# Multimorbidity







Xu JS Nat Rev Genet 2016

Barnett K, Lancet 2012

# AIHA therapy: reference papers

Review

## Treatment of autoimmune hemolytic anemias

Alberto Zanella and Wilma Barcellini

haematologica | 2014; 99(10)

How I Treat

blood

## How I treat autoimmune hemolytic anemia

Ronald S. Go,[1] Jeffrey L. Winters,[2] and Neil E. Kay[1]

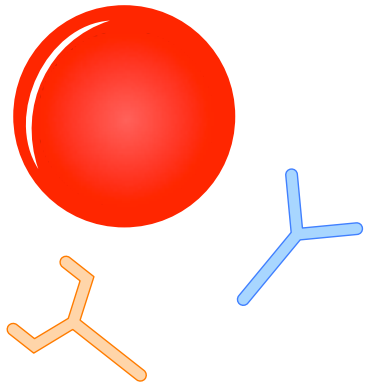
BLOOD, 1 JUNE 2017 • VOLUME 129, NUMBER 22

bjh guideline

## The diagnosis and management of primary autoimmune haemolytic anaemia

Quentin A. Hill,[1] Robert Stamps,[2] Edwin Massey,[3] John D. Grainger,[4] Drew Provan,[5] and Anita Hill[1] on behalf of the British Society for Haematology

British Journal of Haematology, 2017, **176**, 395–411



**GRADE for practice guidelines**

| Grade of recommendation* | Clarity of risk/benefit | Quality of supporting evidence | Implications |
|---|---|---|---|
| 1A<br>Strong recommendation<br>High quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. | Strong recommendation, can apply to most patients in most circumstances without reservation |
| 1B<br>Strong recommendation<br>Moderate quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate. | Strong recommendation, likely to apply to most patients |
| 1C<br>Strong recommendation<br>Low quality evidence | Benefits appear to outweigh risk and burdens, or vice versa | Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain. | Relatively strong recommendation; might change when higher quality evidence becomes available |
| 2A<br>Weak recommendation<br>High quality evidence | Benefits closely balanced with risks and burdens | Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. | Weak recommendation, best action may differ depending on circumstances or patients or societal values |
| 2B<br>Weak recommendation<br>Moderate quality evidence | Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks and burdens | Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate. | Weak recommendation, alternative approaches likely to be better for some patients under some circumstances |
| 2C<br>Weak recommendation<br>Low quality evidence | Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens | Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain. | Very weak recommendation; other alternatives may be equally reasonable |

* GRADE can be implemented with either three or four levels of quality of evidence. UpToDate implements three levels and uses numbers and letters to represent strength of recommendation and quality of evidence respectively.

# GRADE

*Primary warm AIHA - first line treatment: Recommendations*

- First line therapy is prednisolone 1 mg/kg/day (1B)

*Treatment of primary CHAD: Recommendations*

- Patients should be advised to avoid cold exposure where possible (1C)
- Indications for treatment: symptomatic anaemia, severe circulatory symptoms or transfusion dependence (1C)
- First line treatment: rituximab, or if clonality has been demonstrated, the addition of fludarabine may be considered (1B)

*Osteoporosis prevention: Recommendations*

- All patients should receive oral calcium and vitamin D supplements while taking corticosteroids (1A)

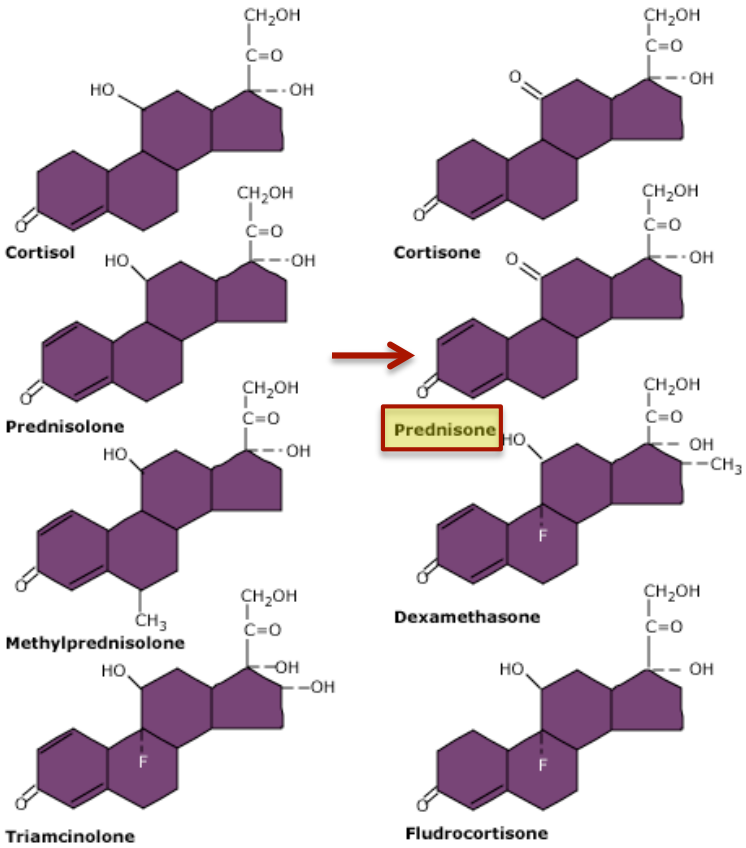
# Drugs associated with immune hemolytic anemia or positive DAT

| | | |
|---|---|---|
| Aceclofenac | Diethylstilbestrol | p-aminosalicylic acid |
| Acetaminophen | Diphenylhydantoin | Penicillin G |
| Aminopyrine/pyramidon | Dipyrone | Phenacetin |
| Amoxicillin | Erythromycin | Piperacillin |
| Amphotericin B | Etodolac | Probenecid |
| Ampicillin | Fenoprofen | Procainamide |
| Antazoline | Fludarabine | Propyphenazone |
| Butizide | Fluorescein | Quinidine |
| Carbenicillin | Fluoroquinolones (eg, temafloxacin) | Quinine |
| Carbimazole | | Ranitidine |
| Carboplatin | Fluorouracil | Rifampicin |
| Carbromal | Glafenine | Sodium pentothal/thiopental |
| Catergen/cyanidanol | Hydralazine | Stibophen |
| Cefamandole | Hydrochlorothiazide | Streptokinase |
| Cefazolin | 9-hydroxy-methyl-ellipticinium | Streptomycin |
| Cefixime | Ibuprofen | Sulbactam sodium |
| Cefotaxime | Indene derivatives (eg, sulindac) | Sulindac |
| Cefotetan | Insulin | Sulfonamides |
| Cefoxitin | Interferon | Sulfasalazine |
| Ceftazidime | Interleukin-2 | Sulfonylurea derivatives |
| Ceftizoxime | Isoniazid | (eg, chlorpropamide and tolbutamide) |
| Ceftriaxone | Latamoxef | Suprofen |
| Cephalexin | Levodopa | Tazobactam sodium |
| Cephaloridine | Mefenamic acid | Teicoplanin |
| Cephalothin | Mefloquine | Temafloxacin |
| Chlordiazepoxide | | |

Think of this possibility and withdraw the drug ASAP

Schrier SL, UpToDate (accessed May 2018)

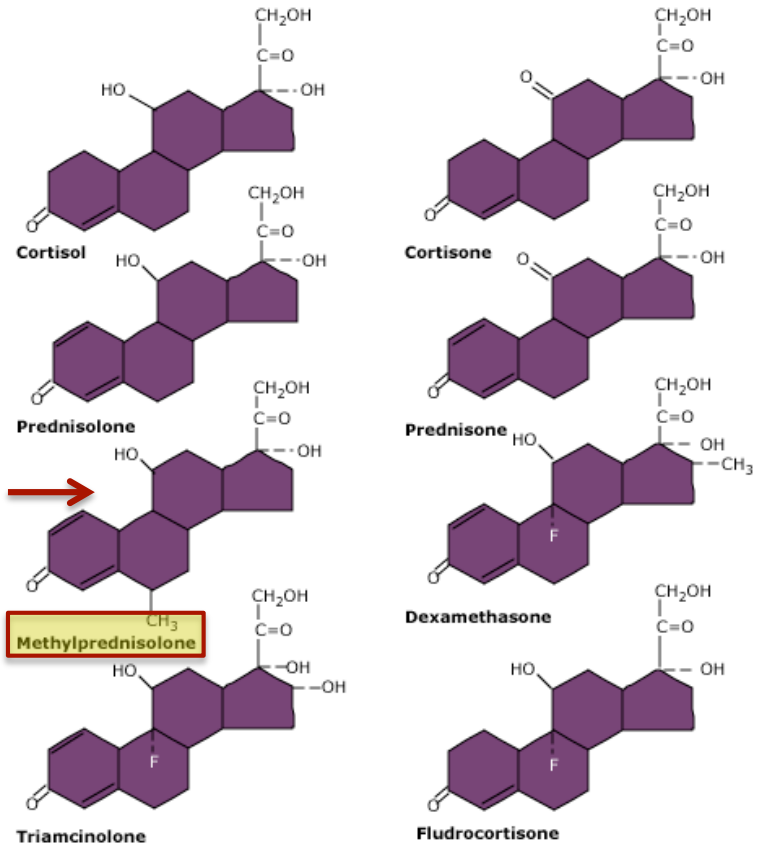
# Warm AIHA Front-line therapy: corticosteroids




## Starting dose

- ✓ **Prednisone**: most reports and experts use **1.0-1.5 mg/kg per day (Grade 1B)** or a flat dose of 60-100 mg/daily.
- ✓ Most responses occur during the second week. No or minimal response in the third week = ineffectiveness.

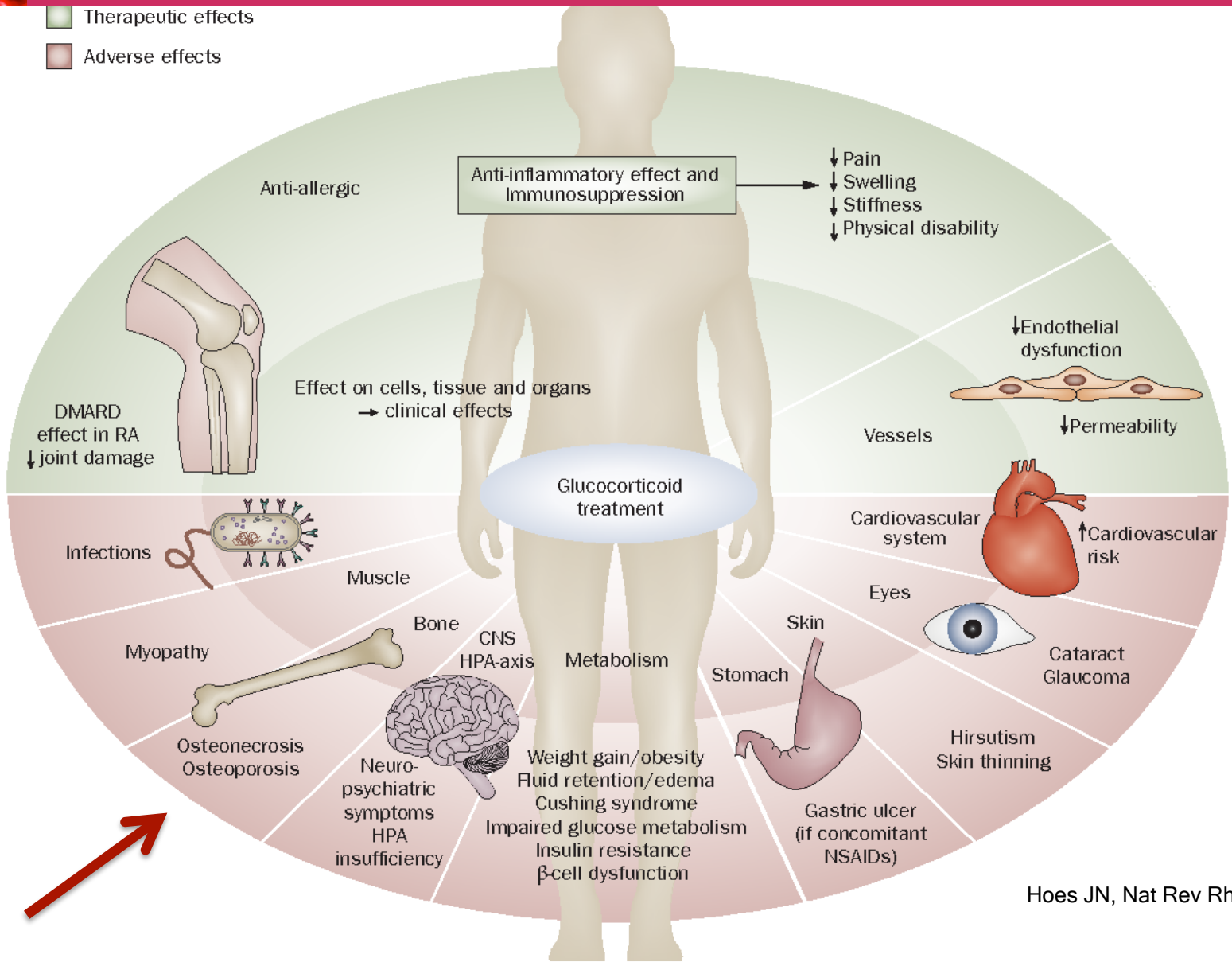
# W-AHIA: High-dose I.V. Methyl-Prednisolone




100-200 mg/day for 10-14 days
or
**250-1000 mg/day for 1-3 days**

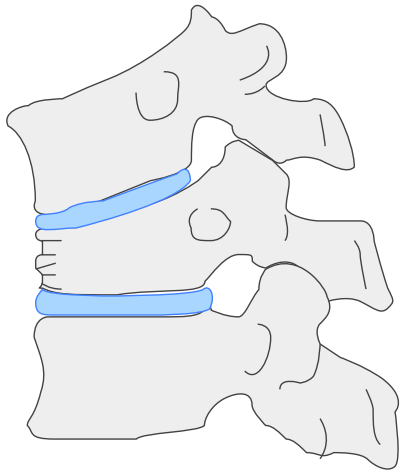
Used in:
- Severe anemia with rapid hemolysis
- Evans' syndrome
.

# Glucocorticoids side-effects




Hoes JN, Nat Rev Rheumatol 2010

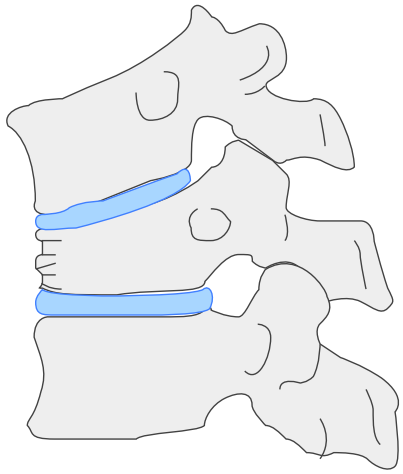
# Glucocorticoid-induced osteoporosis



Glucocorticoid-induced compression fracture

- ✓ Increased risk of fracture reported with prednisone equivalent doses as low as **2.5 to 7.5 mg daily**.
- ✓ Glucocorticoid-induced bone loss should be treated **aggressively**, particularly in pts. already at high risk (older age, prior fragility fracture).

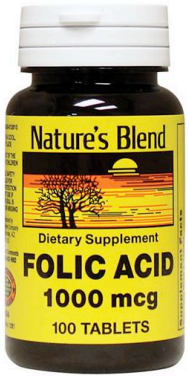
# Glucocorticoid-induced osteoporosis: guidelines

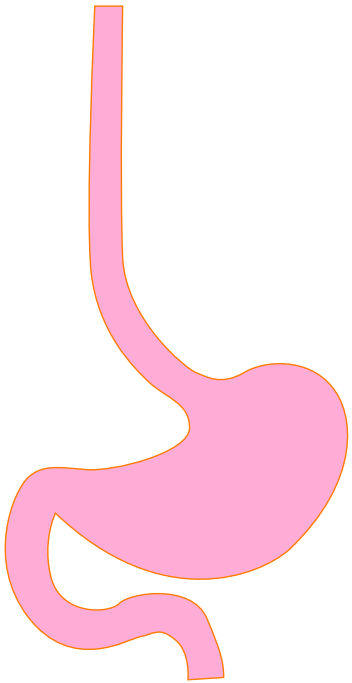


Glucocorticoid-induced compression fracture

- ✓ All patients receiving any dose of glucocorticoid therapy with an anticipated duration of ≥3 months should receive calcium (e.g. **1200 mg of elemental Ca daily**) and **vitamin D** supplementation (e.g. **800 IU daily**) (**Grade 1A**).
- ✓ For men ≥50 years and postmenopausal women, **oral bisphosphonate** (e.g. **alendronate 70 mg weekly**) is recommended (alternative: IV zolendronic acid).
- ✓ The choice regarding this therapy should be individualized in premenopausal women and younger men.

# Prevention of other corticosteroid AEs



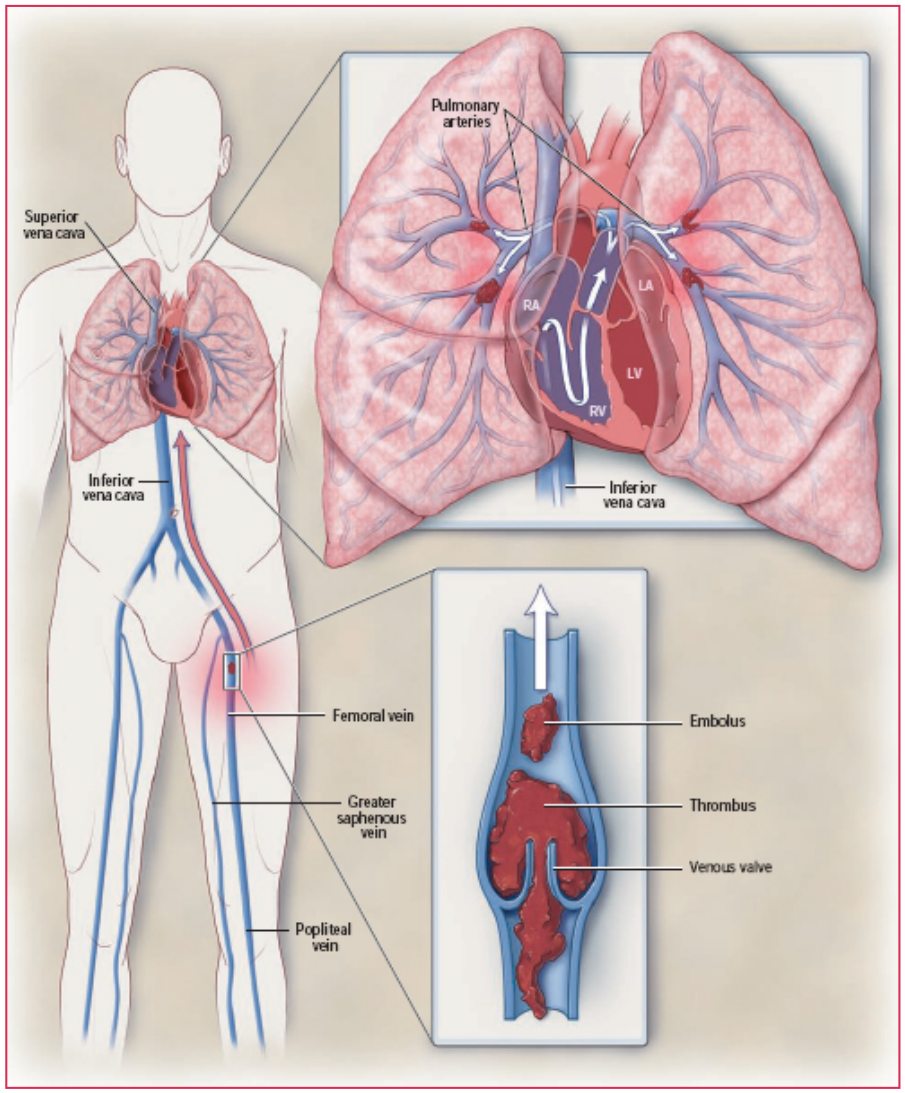



**Folic acid** supplementation (e.g. **1 mg/day**) (**Grade 1B**).

Patients at increased risk for peptic ulcer disease e.g. concomitant thrombocytopenia, prior history peptic ulcer disease, concurrent use of NSAIDs, anticoagulant or antiplatelet drugs and age ≥60 y, should receive a **proton pump inhibitor** (**Grade 2C**).

Hill QA, Brit J Haematol 2017

# AIHA and VTE




important cause of morbidity and mortality in AIHA, esp. when hemolysis is active (≈ 20%).

Thromboprophylaxis with **LMWH** recommended for in-patients with an acute exacerbation of haemolysis (**Grade 1C**) and should be considered in ambulatory pts. during exacerbations (Hb <8.5 g/dl) (**Grade 2C**)

Hill QA, Brit J Haematol 2017

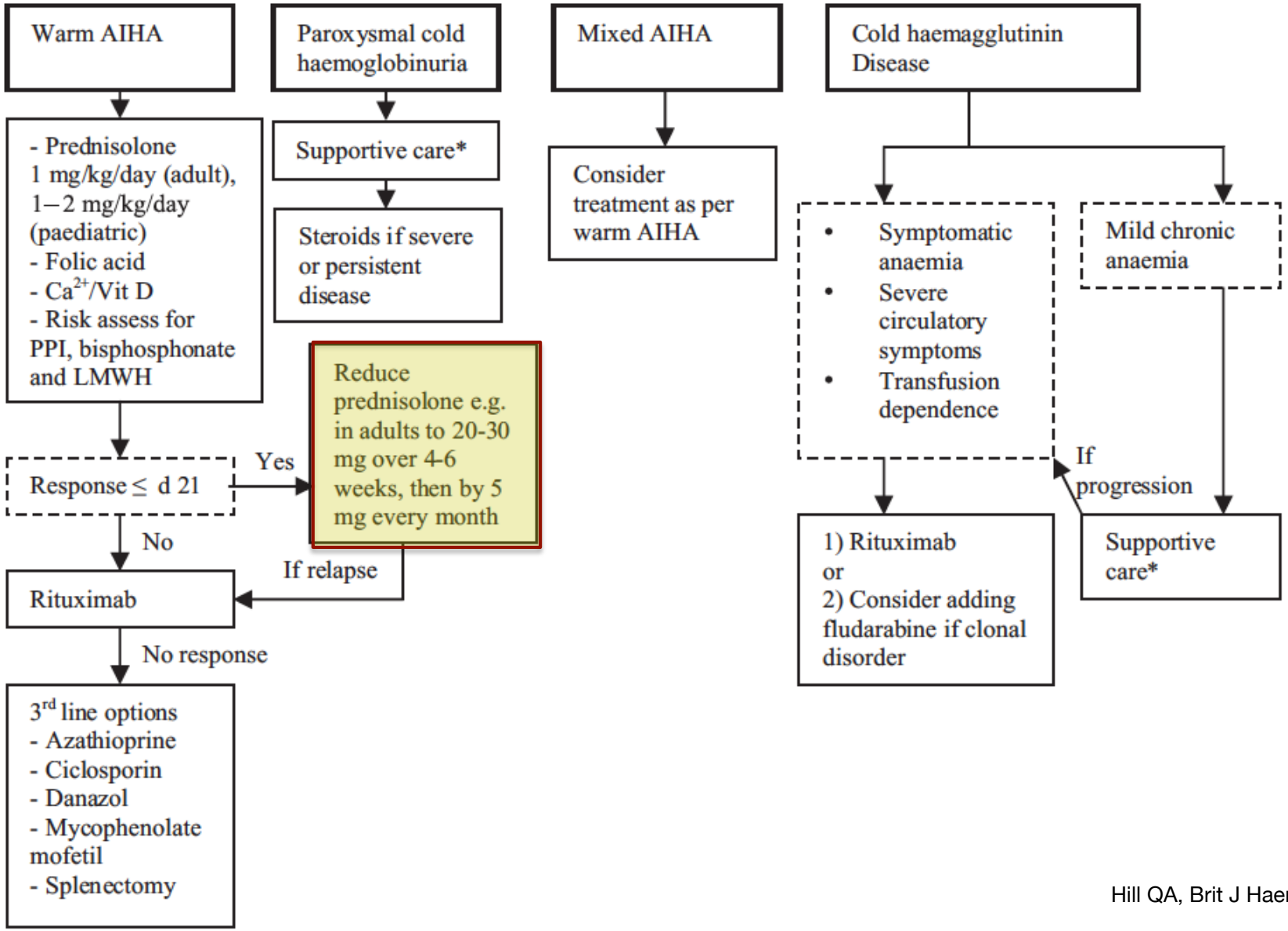
# Prednisone tapering (slow!)

- ✓ The starting dose is maintained for at least 2 weeks (1-3) and until achievement of hemoglobin >12 (10) g/dL.

- ✓ Tapering: by 20 mg (10-15) every week until a dose of 20 (20-30) mg daily is reached, followed by a slower taper (e.g. 5 mg every 1-2 week over 4 to 8 weeks). Some Authors suggest even slower tapering (e.g. when 15 mg/die is reached, 2.5 mg every 2 weeks until withdrawal).

- ✓ Minimum 3-4 months at low dose (≤10 mg/day). Discontinuation within 6 months = increased relapse and shorter duration of remission.

# Therapeutic pathways in AHIA: summary




Hill QA, Brit J Haematol 2017

# Therapeutic pathways in AHIA: summary

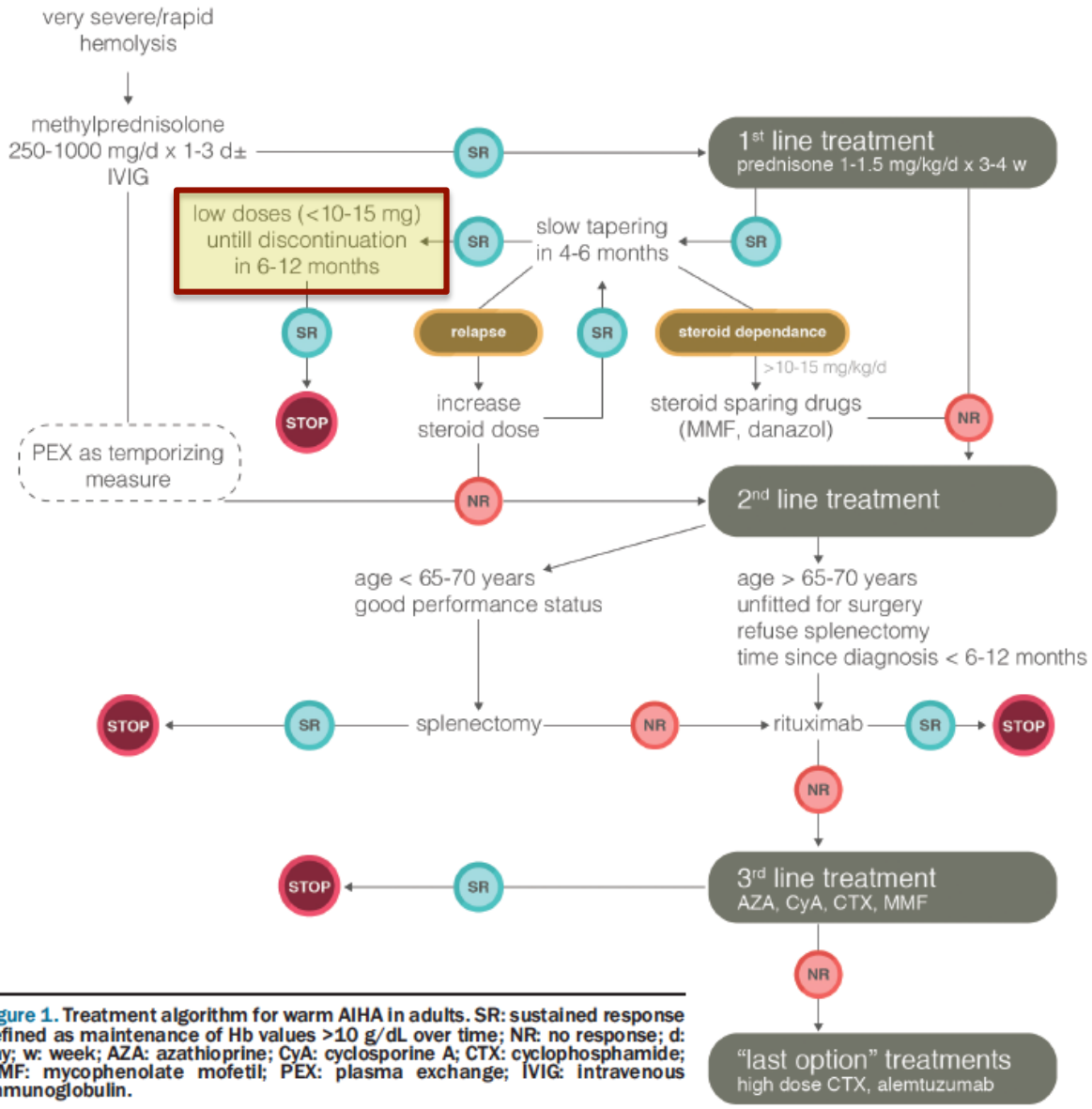


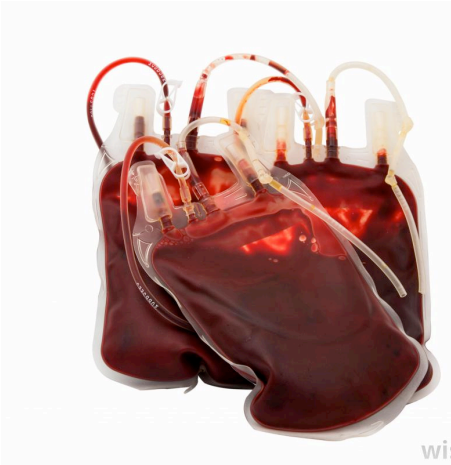

**Figure 1.** Treatment algorithm for warm AIHA in adults. SR: sustained response defined as maintenance of Hb values >10 g/dL over time; NR: no response; d: day; w: week; AZA: azathioprine; CyA: cyclosporine A; CTX: cyclophosphamide; MMF: mycophenolate mofetil; PEX: plasma exchange; IVIG: intravenous immunoglobulin.

Zanella A, Haematologica 2016

# First-line corticosteroids in WAHIA: expected outcome

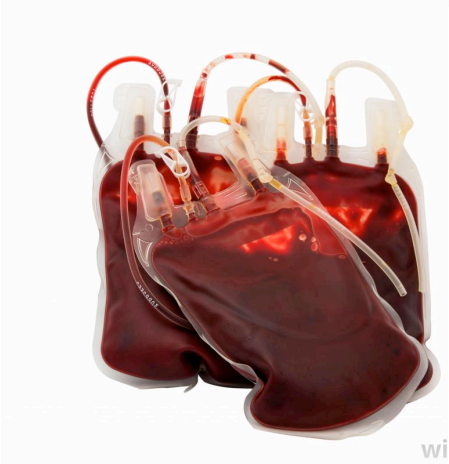
- ✓ Response rate: 70-85% of patients.
- ✓ Only ≈1/3 remain in long-term remission after discontinuation (chronic disease!).
- ✓ ≈50% require maintenance doses.
- ✓ ≈20-30% need additional second-line therapies.
- ✓ Estimated **cure** with steroids alone: **<20% of patients**.
- ✓ Note: unresponsiveness should prompt diagnostic re-evaluation (e.g. AIHA associated with malignant tumors are often steroid-refractory).

# AIHA supportive therapy – RBC transfusion - 1



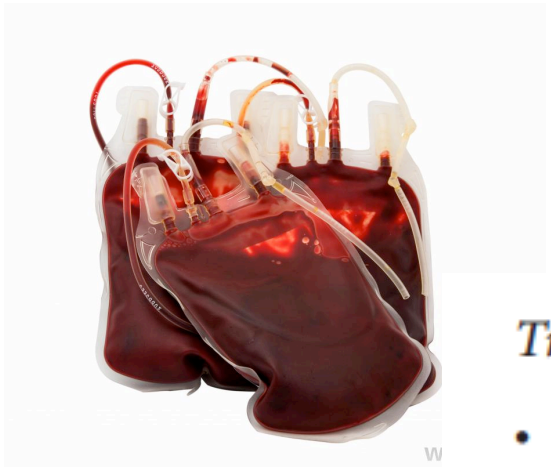
- ✓ Often required in severe cases to maintain acceptable Hb until specific treatments become effective.
- ✓ Criteria: not only Hb! Consider patient's clinical status, comorbidities, acuteness/rapidity of progression, signs of severe hemolysis (e.g. hemoglobinuria).
- ✓ Do not deny to critical patients, even if no truly compatible units can be found.

# AIHA supportive therapy – RBC transfusion - 2



- ✓ ABO- and RhD-matched RBCs can be safely administered if alloantibodies are reasonably excluded (previous transfusion and/or pregnancy history).
- ✓ In less urgent cases, extended phenotyping to select compatible RBC units (complex procedures).
- ✓ Limit the amount of blood transfused (avoid volume overload in elderly and hemoglobinuria).
- ✓ Administer RBCs units (leuko-depleted) slowly, when possible, not exceeding 1 mL/kg/h

# AIHA: supportive therapy – RBCs transfusion



*Transfusion: Recommendations*

- If anaemia is life threatening in the time required for full compatibility testing, transfuse with ABO, Rh and K matched red cells (1C)
- Consider the use of a blood warmer for transfusion in patients with cold AIHA (CHAD, mixed AIHA and PCH) (2C)

Hill QA, Brit J Haematol 2017

# RBCs transfusion – general guidelines

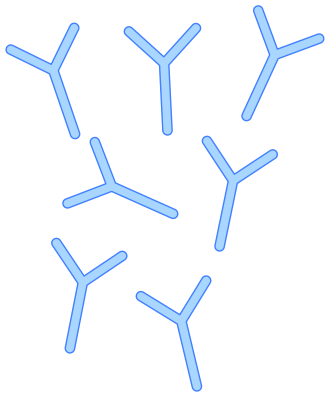
## Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB*

(for hemodynamically stable patients without active bleeding)

| Hb level | recommendation |
|---|---|
| <6 g/dl | Transfusion *recommended*, except in exceptional circumstances. |
| 6 to 7 g/dl | Transfusion *generally likely* to be indicated. |
| 7 to 8 g/dl | Transfusion should be *considered* in postoperative surgical patients, including those with stable cardiovascular disease, after evaluating the patient's clinical status. |
| 8 to 10 g/dl | Transfusion *generally not indicated*, but should be considered for some populations (e.g., those with symptomatic anemia, ongoing bleeding, acute coronary syndrome) |
| >10 g/dl | Transfusion generally *not indicated* except in exceptional circumstances |

Carson JL, Ann Intern Med 2016

# Options in WAHIA (emergency situation)



## IVIG

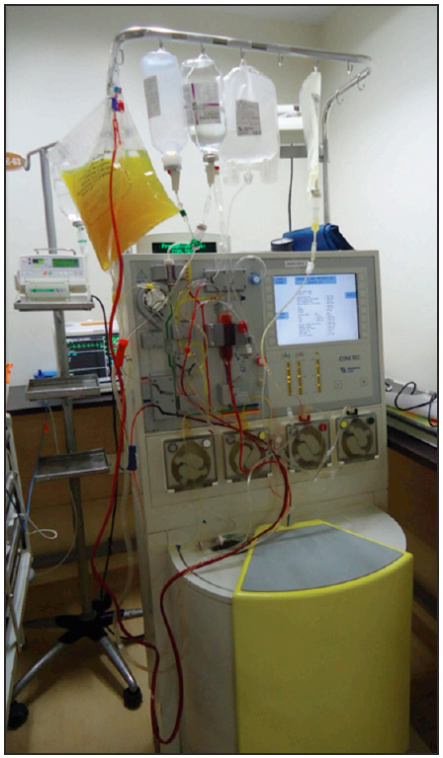
*Immunoglobulins.* Evidence from case series suggests that 40% of patients respond to IVIg 0·4–0·5 g/kg/day for 5 days and most responders maintained their Hb for ≥3 weeks (Flores *et al*, 1993). Response was predicted by low pre-treatment Hb; and IVIg is accepted in the UK Department of Health guidelines as a short term treatment when the Hb is <60 g/l (but higher in patients with co-morbidities) or as a temporising measure prior to splenectomy (Wimperis *et al*, 2011).

"Consider if severe or life-threatening anemia occur (Grade 2C)"

Hill QA, Brit J Haematol 2017

# Options in WAHIA (emergency situation)

## Plasma-Exchange

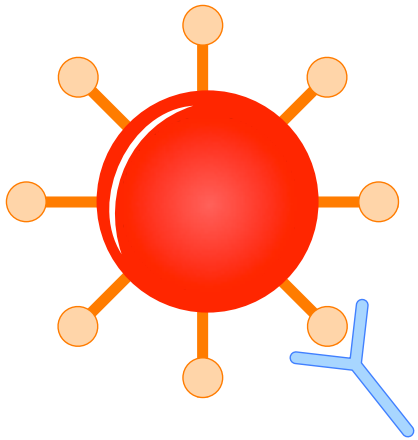


*Plasma exchange.* The evidence for plasma exchange is largely limited to case reports and any benefit is temporary. Plasma exchange has been used in patients with severe haemolysis while attempting control with other therapies, such as immunosuppression (Von Baeyer, 2003; Szczepiorkowski *et al*, 2010).

"Consider if severe or life-threatening anemia occur (Grade 2C)"

Hill QA, Brit J Haematol 2017

# AIHA monitoring



With initiation of therapy, it is best to monitor restoration of the hemoglobin and reticulocyte levels over the first several weeks of therapy.

Monitoring the DAT is routine, but even if the result remains positive, this may not reflect a lack of disease control.

# Reticulocyte production index

## Calculator: Reticulocyte Production Index (RPI) in adults

**RPI = (Hct / 45) * Retic / Maturation**

**Input:**

**Hct** [ ] %

**Retic** [ ] %

**Results:**

**RPI** [ ] %

**Decimal precision** 1

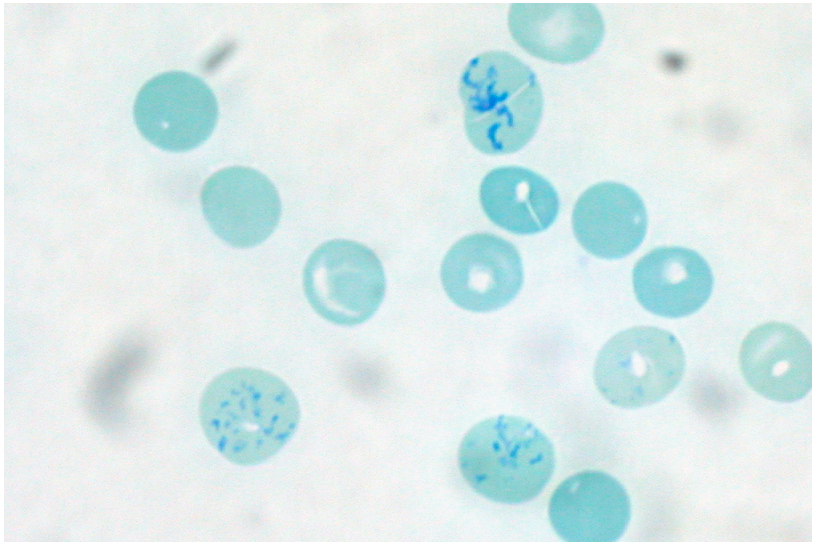
Reset form

**Notes**

- The **Maturation** term represents the maturation time of red blood cells (in days) at various levels of anemia.
- **Maturation** = 1.0 for **Hct** >=40%.
- **Maturation** = 1.5 for **Hct** 30 to 39.9%.
- **Maturation** = 2.0 for **Hct** 20 to 29.9%.
- **Maturation** = 2.5 for **Hct** <20%.
- An **RPI** >3 shows a normal marrow response to anemia. An **RPI** <2 is an inadequate response to anemia.

RPI >3 = normal marrow response to anemia. RPI <2 inadequate response to anemia

# Insufficient reticulocytosis



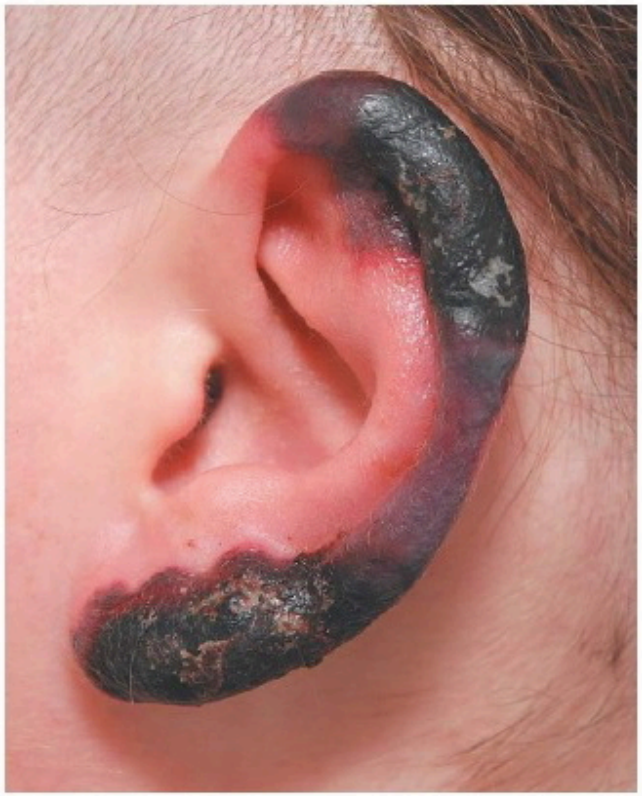
Insufficient reticulocytosis may occur in children and in adults with very severe hemolysis.

Recognition of this phenomenon has generated data indicating that the use of **erythropoietin** may be useful in managing situations like this and refractory AIHA.

# Cold AIHA: when to treat

IMAGES IN CLINICAL MEDICINE

Cutaneous Necrosis Associated with Cold Agglutinins



Pts. with symptomatic anemia, transfusion dependence, and/or disabling circulatory symptoms.

Non-severe asymptomatic forms require only protection against exposure to cold and occasional transfusions in winter.

RBCs transfusions can safely be given, with appropriate precautions (the patient and the extremities should be kept warm, use of an in-line blood warmer recommended).

Avoid infusion of cold liquids.

# Cold AIHA: First-line treatment

Corticosteroids not recommended/discouraged (effective in only 14-35%, unacceptably high doses required to maintain remission).

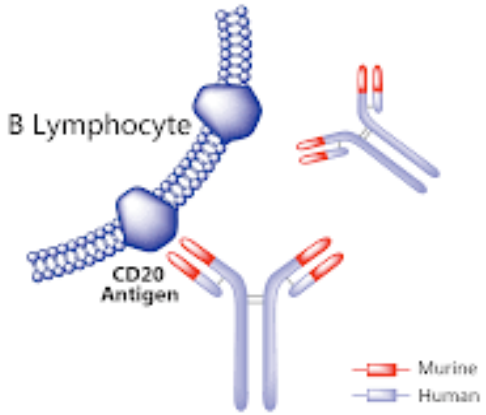
Rituximab now recommended as the first-line treatment (Grade 1B). Effective in ≈60-80%.

Median time to response 1-2 months (generally observed following a $2^{nd}/3^{rd}$ course, in relapsed cases).

Complete/sustained remissions uncommon (response duration is generally 1 year).

Combination with oral fludarabine (40 mg/m$^2$ on days 1-5) suggested for cases refractory to 1-2 courses of R alone.

# Rituximab




375 mg/m$^2$ weekly for a median of 4 weeks*

**Warm AIHA**

2 years disease free survival: 72%

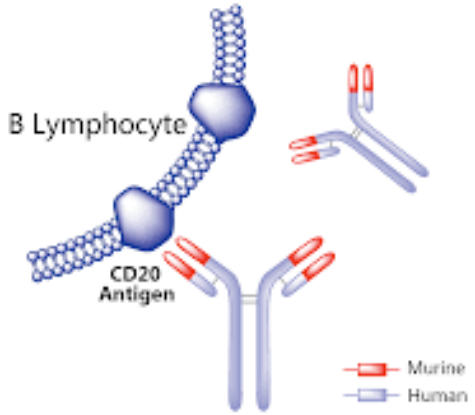
**Cold AIHA**

2 years disease free survival: 56%

Effective in both idiopathic/secondary forms, in Evans' syndrome.

*low-dose schedule: (100 mg fixed dose/weekly for 4 weeks)

# Rituximab – precautions




well tolerated; no SAEs in most patients, infusion-related side effects.

Relatively good safety profile (infections in ≈7%): rare cases of progressive multifocal encephalopathy, hepatitis B reactivation and other viral infections.

To prevent hepatitis B reactivation antiviral prophylaxis is now recommended (even after prolonged steroid therapy).

# Paroxysmal Cold Hemoglobinuria (PCH)

Acute intravascular hemolysis by the Donath-Landsteiner biphasic hemolysin (binds to RBCs at low temperatures and causes complement-mediated hemolysis at 37°C).

Most Ab are IgG directed against the P blood group system.

In the past, PCH mainly associated with syphilis.
Now usually follows viral and bacterial infections, including Mycoplasma pneumonia.

PCH is usually self-resolving. The few severe cases may require transfusions and steroid treatment, whose effectiveness is difficult to evaluate because of the transient nature of the hemolysis.

# Take-home messages

- ✓ AIHA represent a heterogeneous group of rare disorders, mostly chronic, sometimes with severe or life-threatening onset/exacerbation that can be extremely challenging.

- ✓ Treatment is largely based on expert consensus because of scarcity of evidence-based data available.

- ✓ Guidelines are useful tools that must be known by every hematologist. However, especially in the elderly patient with multimorbidity, clinical judgment and a certain degree of flexibility is required to “personalize” the approach to the individual patient.

# The Verona Interdisciplinary group on anemia and iron disorders

Fabiana Busti,Annalisa Castagna, Giorgio Gandini, Giacomo Marchi, Oliviero Olivieri, Monica Rizzi, Alice Vianello, Acaynne Lira Zidanes, Luciano Xumerle.

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EuroBloodNet European Reference Networks

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- Clara Camaschella, HSR, Milan
- Paolo Arosio, University of Brescia
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- Elizabeta Nemeth and Tom Ganz, UCLA
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