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Anemia hemolítica autoimune

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bjh guideline

The diagnosis and management of primary autoimmune haemolytic anaemia

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Objetivos

- Orientação quanto ao diagnóstico, tratameto, investigação complememementar de pacientes com AHAI.

- Definir categorias de AHAI e avaliar responsividade de cada tipo ao tratamento.

Metodologia

- Revisão de literatura dos anos de janeiro de 1960 a outubro de 2015;
- Recomendações baseadas no GRADE.
- Grupo de trabalho baseado em especialistas do Reino Unido.

Revisão

- AHAI é causada pelo ataque imune contra células vermelhas;
- Incidência de 1/ 100 k/ ano;
- Pode afetar qualquer idade, mas é mais comum em pacientes mais velhos.

Revisão

- 65% são AHAI de anticorpos quentes;
- 29% são AHAI da doença de aglutininas frias;
- 1% de Hemoglobinuria paroxística a frio;
- 5% é mista.

Revisão

- 50% são idiopáticas;
- 50% são secundárias;
- Sintomas anêmicos são comuns; sinais de hemólise (icterícia, urina escura) estão presentes em 24% dos pacientes;
- Sempre avaliar sintomas da doença de base!

Revisão

- Acrocianose, Raynaud podem ocorrer em 40-90% dos pacientes com doença de aglutinina fria;
- Na criança a doença da aglutinina fria pode ser autolimitada.
- Hemoglobinúria paroxística a frio pode ser transiente, ocorrer após 1-2 semanas após IVAS. Hemólise pode ser perigosa (intravascular)

Table I. Classification of autoimmune haemolytic anaemia.

- Warm AIHA
  - Primary
  - Secondary
    - Neoplasia (CLL, Lymphoma, Solid organ)
    - Infection (e.g. Hepatitis C, HIV, CMV, VZV, Pneumococcal infection, Leishmaniasis, Tuberculosis)
    - Immune dysregulation
      - Connective tissue disorders (e.g. SLE, Sjögren syndrome, Scleroderma)
      - Ulcerative colitis, PBC, Sarcoidosis
      - Post transplantation
      - Immune deficiency syndromes (e.g. CVID)
- Cold AIHA
  - Cold Haemagglutinin Disease
    - Primary
    - Secondary
      - Malignancy (e.g. CLL, NHL, Solid organ)
      - Infection (e.g. Mycoplasma, Viral infections, including IM)
      - Autoimmune disease
      - Post-allogeneic HSCT
  - Paroxysmal Cold Haemoglobinuria
    - Primary
    - Secondary
      - Infection (e.g. Adenovirus, Influenza A, Syphilis, CMV, IM, VZV, Measles, Mumps, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *E. coli*)
- Mixed type AIHA
  - Primary
  - Secondary
    - Lymphoma, SLE, Infection

AIHA, autoimmune haemolytic anaemia; CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus; CVID, common variable immunodeficiency; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplantation; IM, infectious mononucleosis; NHL, non-Hodgkin lymphoma; PBC, primary biliary cirrhosis; SLE, systemic lupus erythematosus; VZV, varicella zoster virus.

Table II. Differential diagnosis of haemolytic anaemia.

- Hereditary
  - Membrane disorders (e.g. HS, HE)
  - Enzyme disorders (e.g. G6PD, PK deficiency)
  - Haemoglobinopathies (e.g. SCD, Unstable haemoglobins)
- Acquired
  - Immune
    - Autoimmune (e.g. Warm or cold AIHA)
    - Alloimmune (e.g. HDN, HTR, post-allogeneic HSCT)
    - Drug induced
  - Non-immune
    - Infection (e.g. Malaria, *Clostridium perfringens*)
    - Mechanical (e.g. Prosthetic heart valve)
    - PNH
    - TMA (e.g. TTP, HUS)
    - Hypersplenism
    - Oxidant substances (e.g. Dapsone, Arsine gas, Amyl nitrite)
    - DIC
    - Severe burns
    - Extracorporeal circuits
    - Renal failure

AIHA, autoimmune haemolytic anaemia; DIC, disseminated intravascular coagulation; G6PD, Glucose-6-phosphate dehydrogenase deficiency; HDN, haemolytic disease of the newborn; HE, hereditary elliptocytosis; HS, hereditary spherocytosis; HSCT, haematopoietic stem cell transplantation; HTR, haemolytic transfusion reaction; HUS, haemolytic uraemic syndrome; PK, pyruvate kinase; PNH, paroxysmal nocturnal haemoglobinuria; SCD, sickle cell disease; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

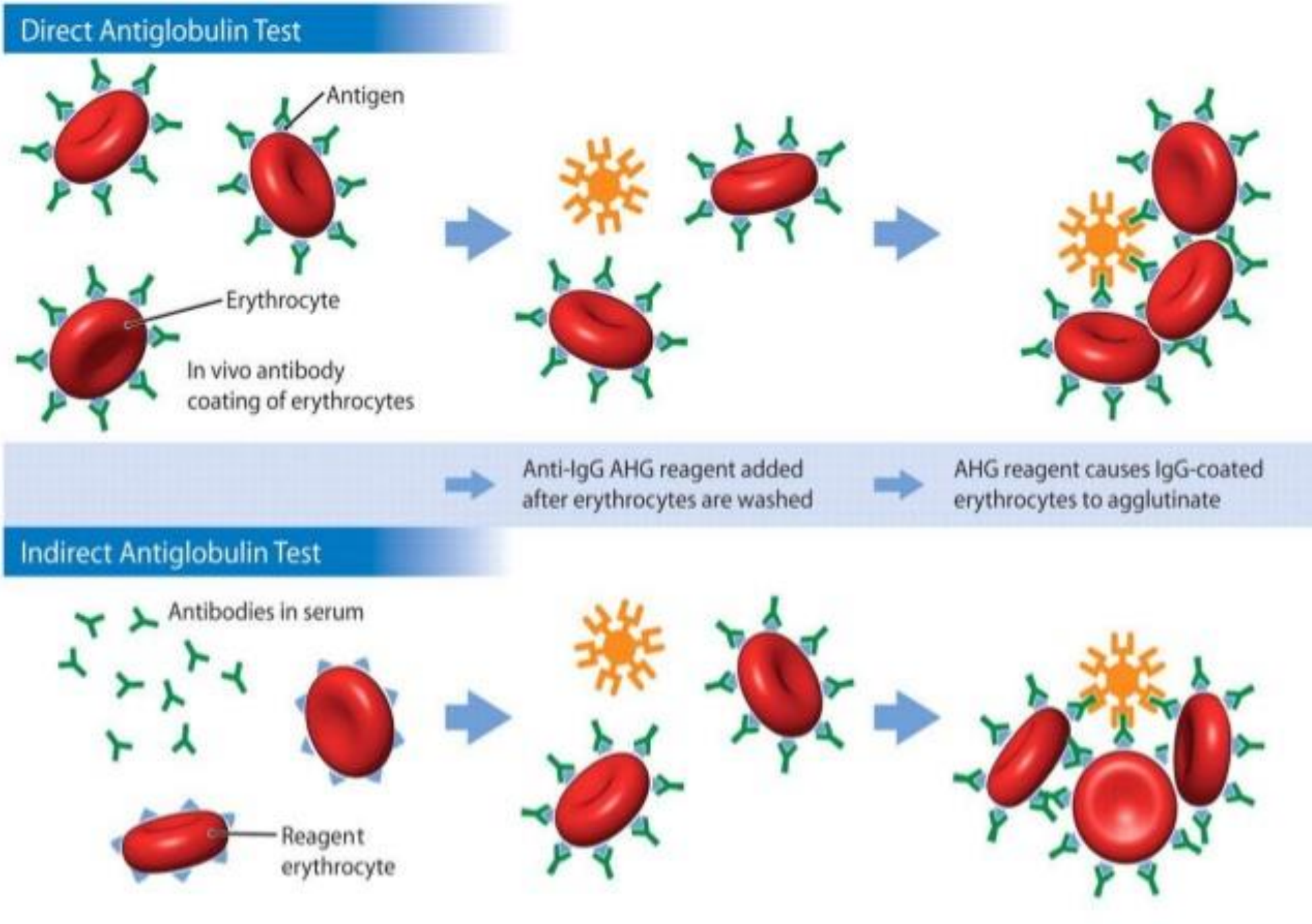
Table III. Investigations in patients presenting with autoimmune haemolytic anaemia (AIHA).

Primary evaluation	
Haemolytic screen	
FBC, blood film, LDH, haptoglobin, bilirubin, DAT, reticulocyte count ± urine for haemosiderin or urine dipstick and microscopy	
Detection of underlying disorders (investigation of AIHA)	
Serum Igs and electrophoresis with immunofixation*	
HIV, HBV, HCV	
Anti-dsDNA, ANA	
CT chest, abdomen and pelvis	
Additional investigation in selected patients with AIHA	
Bone marrow examination:	CHAD, age ≥60, features in history, examination, FBC or film suggesting possible marrow infiltration
U&E, LFT, clotting, BP, urine dipstick:	If pregnant or thrombocytopenic, to exclude DIC or pregnancy-associated TMA
Infection screening:	Dependent on symptoms, travel history and age (see Table I)
Peripheral T-cell subsets, creatinine, LFT, clotting:	All children and if suspected Evans syndrome
Parvovirus, haematinics:	If reticulocytopenia
Additional serological investigation in selected patients with AIHA	
Direct agglutination test (DAggT)	If DAT positive for C3 ± IgG
Cold antibody titre	If DAggT positive
Monospecific DAT for IgM, G, A, C3	If DAT-negative AIHA suspected
Red cell eluate	If (monospecific) DAT- negative AIHA suspected
Donath-Landsteiner	If DAT is positive for C3 ± IgG and i)DAggT negative or insignificant CAs and ii)age <18 years or haemoglobinuria or cold associated symptoms or atypical serology
Cold autoagglutinin thermal amplitude	If clinical significance of cold autoagglutinin unclear

ANA, antinuclear antibody; BP, blood pressure; C3, complement component 3; CHAD, cold haemagglutinin disease; CT, computerised tomography; DaggT, direct agglutination test; DAT, direct antiglobulin test; DIC, disseminated intravascular coagulation; dsDNA, double-stranded DNA; EBV, Epstein Barr virus; FBC, full blood count; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; Igs, immunoglobulins; LDH, lactate dehydrogenase; LFT, liver function tests; TMA, thrombotic microangiopathy; U&E, urea and electrolytes.
*If a cold autoantibody suspected, keep sample at 37°C until serum has been separated.

Abordagem diagnóstica

- Três questões devem ser respondidas:
  - Existe hemólise?
  - A hemólise é autoimune?
    - Avaliação do TAD (TAD negativo vs TAD positivo)
  - Que tipo de AHAI é?
    - Quente
    - Doença da aglutinina fria
    - Hemoglobinuria paroxística a frio
    - Tipo misto


Direct Antiglobulin Test
Antigen
Erythrocyte
In vivo antibody coating of erythrocytes
Anti-IgG AHG reagent added after erythrocytes are washed
AHG reagent causes IgG-coated erythrocytes to agglutinate
Indirect Antiglobulin Test
Antibodies in serum
Reagent erythrocyte

TAD

- Deve ser pelo menos IgG/C3d;
- Se positivo, deve-se avaliar:
  - Transfusão recente nos últimos três meses;
  - Realizou transplante de órgãos/SCT;
  - Se criança, cuidado com DHRN;
  - Está em uso de droga?
  - Existe outra causa de hemólise?

TAD negativo

- Raramente pacientes com AHAI podem ter TAD negativo no tubo;
- TAD no gel é mais sensível;
- Teste de Donath-Landsteiner pode ser considerado em crianças com hematúria.
- TAD negativo AHAI geralmente causa anemia moderada e responde bem aos corticoides.

Tipo de AHAI

- Quente:
  - IgG (age melhor em 37°C);
  - TAD IgG 35%; IgG/C3d 56%; C3d 9%.

- Dça aglutinina fria:
  - IgM (age melhor em 4°C);
  - TAD C3d+ (21% IgG);
  - Aglutinação na distensão;

Tipo de AHAI

- Hemoglobinúria paroxística a frio:
  - IgG bifásico que se liga a hemácias em temperatura baixa e fixa complemento à medida que a temperatura sobe;
  - TAD C3+; Donath-Landsteiner positivo;
  - TAD negativo em alguns casos

- Misto:
  - IgG/IgM com amplitude térmica;

Table IV. Serological features of AIHA and cold agglutinins.

	Warm AIHA	Mixed AIHA	CAs	CHAD	PCH
Typical DAT	IgG or IgG + C3	IgG + C3	Negative	C3	C3
Antibody specificity	Usually a high incidence antigen. ~3% have specificity (e.g. anti-e, anti-E or anti-c)	Warm IgG usually lacks specificity. The cold antibody may be anti-I, anti-i or lack specificity	Usually anti-I	Usually anti-I (~90%), sometimes anti-i, rarely anti-Pr	Usually anti-P
Antibody titre (at 4°C)	Not applicable	Cold antibody may have a low titre (<1:64)	Usually <1:64	Usually >1:500 but can be less	Usually <1:64
Thermal amplitude	Bind optimally at 37°C	Usually ≥30°C	Usually <25°C	Usually ≥30°C	Usually <20°C

AIHA, autoimmune haemolytic anaemia; CAs, cold agglutinins; CHAD, cold haemagglutinin disease; DAT, direct antiglobulin test; PCH, paroxysmal cold haemoglobinuria.

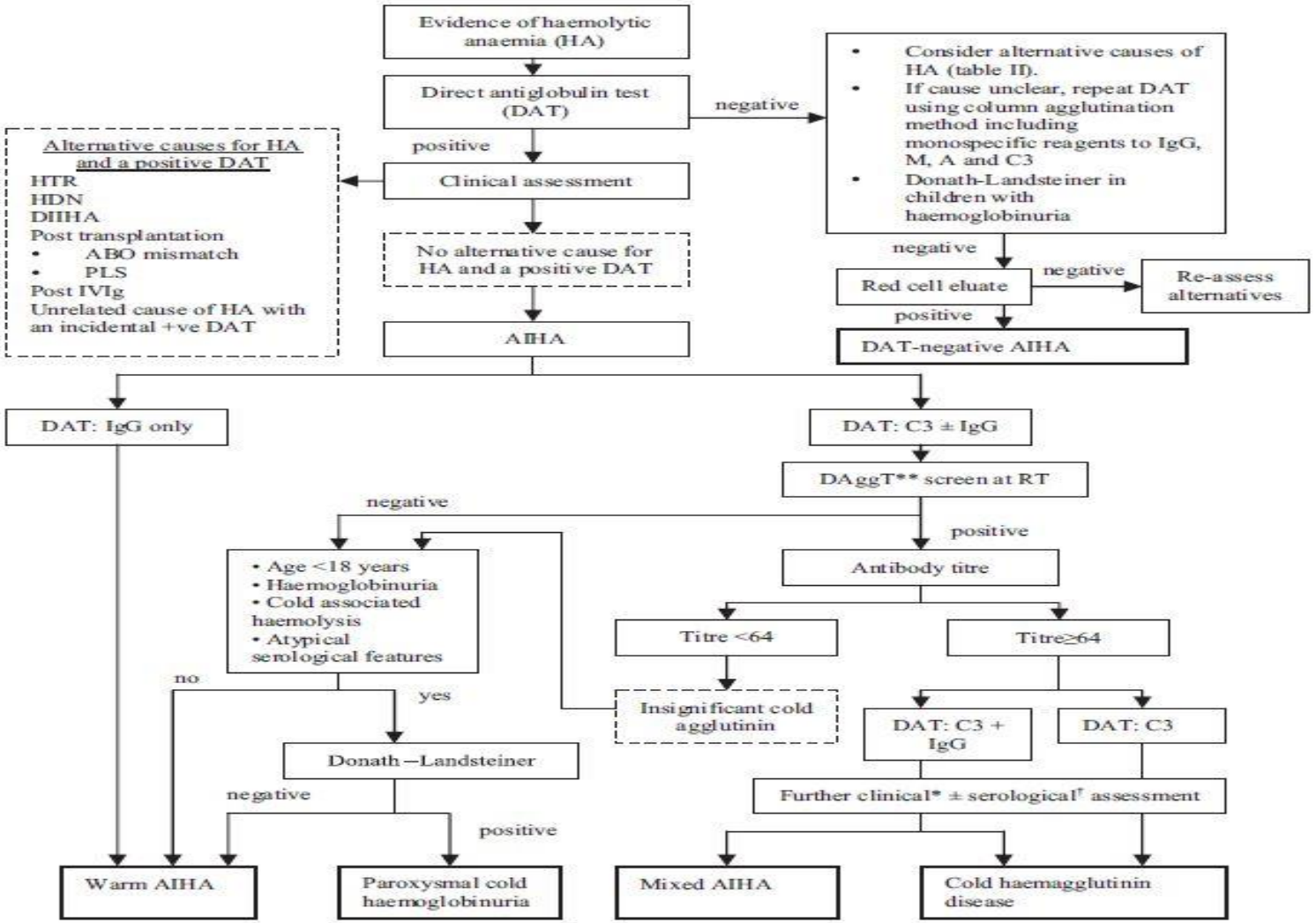
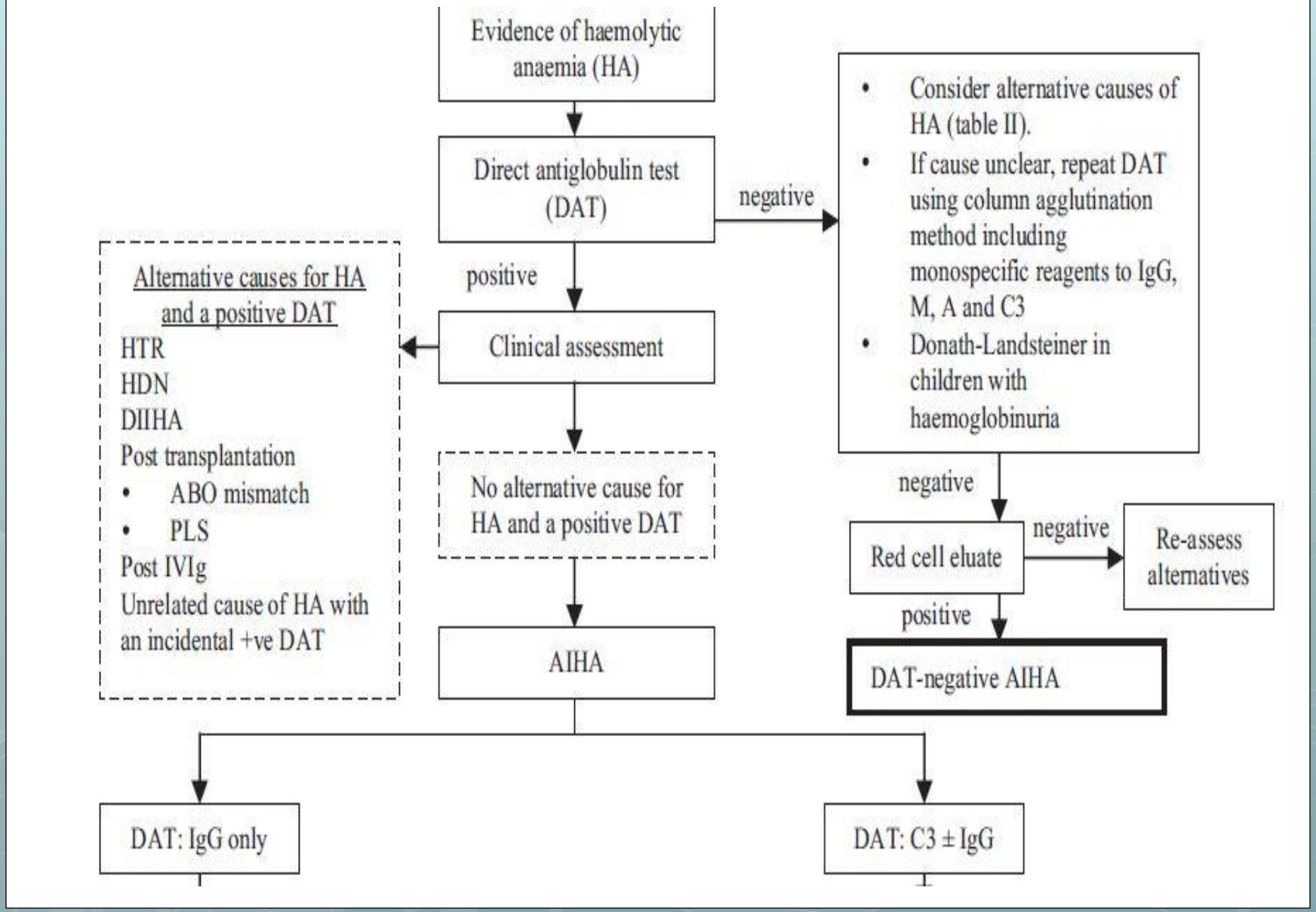
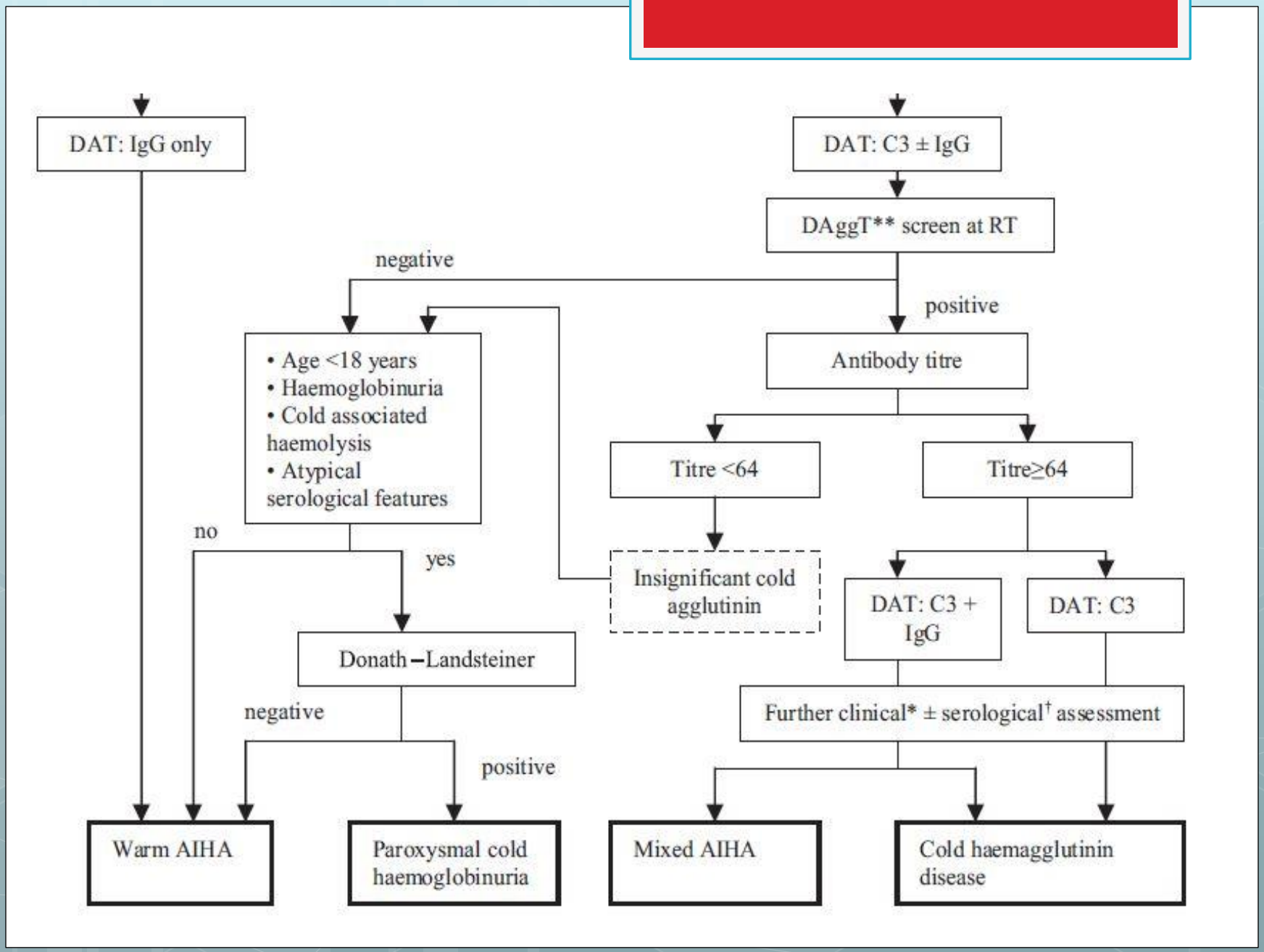


Fig 1. Diagnostic pathway for AIHA. AIHA, autoimmune haemolytic anaemia; CHAD, cold haemagglutinin disease; DAggT, direct agglutination test; DAT, direct antiglobulin test; DIIHA, drug-induced immune haemolytic anaemia; HA, haemolytic anaemia; HDN, haemolytic disease of the newborn; HTR, haemolytic transfusion reaction; IVIg, intravenous immunoglobulin; PLS, passenger lymphocyte syndrome; RT, room temperature. *The final diagnosis of CHAD or mixed AIHA is based on the overall clinical picture, including supportive serological findings. †For example the thermal amplitude. **Saline suspended red cells and patient's serum at room temperature for 30–60 min.


Evidence of haemolytic anaemia (HA)
Direct antiglobulin test (DAT)
negative
positive
Clinical assessment
Alternative causes for HA and a positive DAT
HTR
HDN
DIIHA
Post transplantation
• ABO mismatch
• PLS
Post IVIg
Unrelated cause of HA with an incidental +ve DAT
No alternative cause for HA and a positive DAT
AIHA
DAT: IgG only
DAT: C3 ± IgG
• Consider alternative causes of HA (table II).
• If cause unclear, repeat DAT using column agglutination method including monospecific reagents to IgG, M, A and C3
• Donath-Landsteiner in children with haemoglobinuria
negative
Red cell eluate
negative
Re-assess alternatives
positive
DAT-negative AIHA


DAT: IgG only
DAT: C3 ± IgG
DAggT** screen at RT
negative
positive
• Age <18 years
• Haemoglobinuria
• Cold associated haemolysis
• Atypical serological features
Antibody titre
Titre <64
Titre≥64
no
yes
Insignificant cold agglutinin
DAT: C3 + IgG
DAT: C3
Donath–Landsteiner
Further clinical* ± serological† assessment
negative
positive
Warm AIHA
Paroxysmal cold haemoglobinuria
Mixed AIHA
Cold haemagglutinin disease

Tratamento

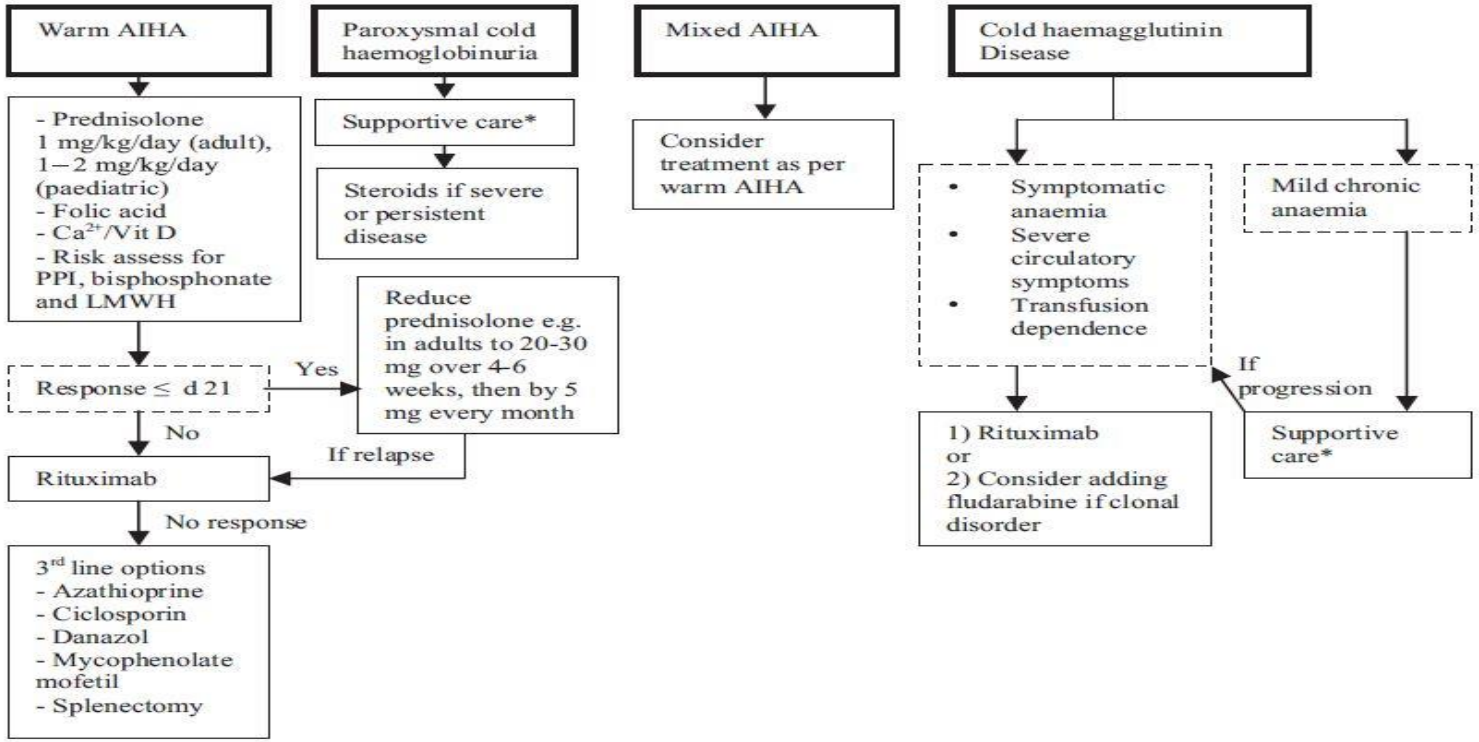
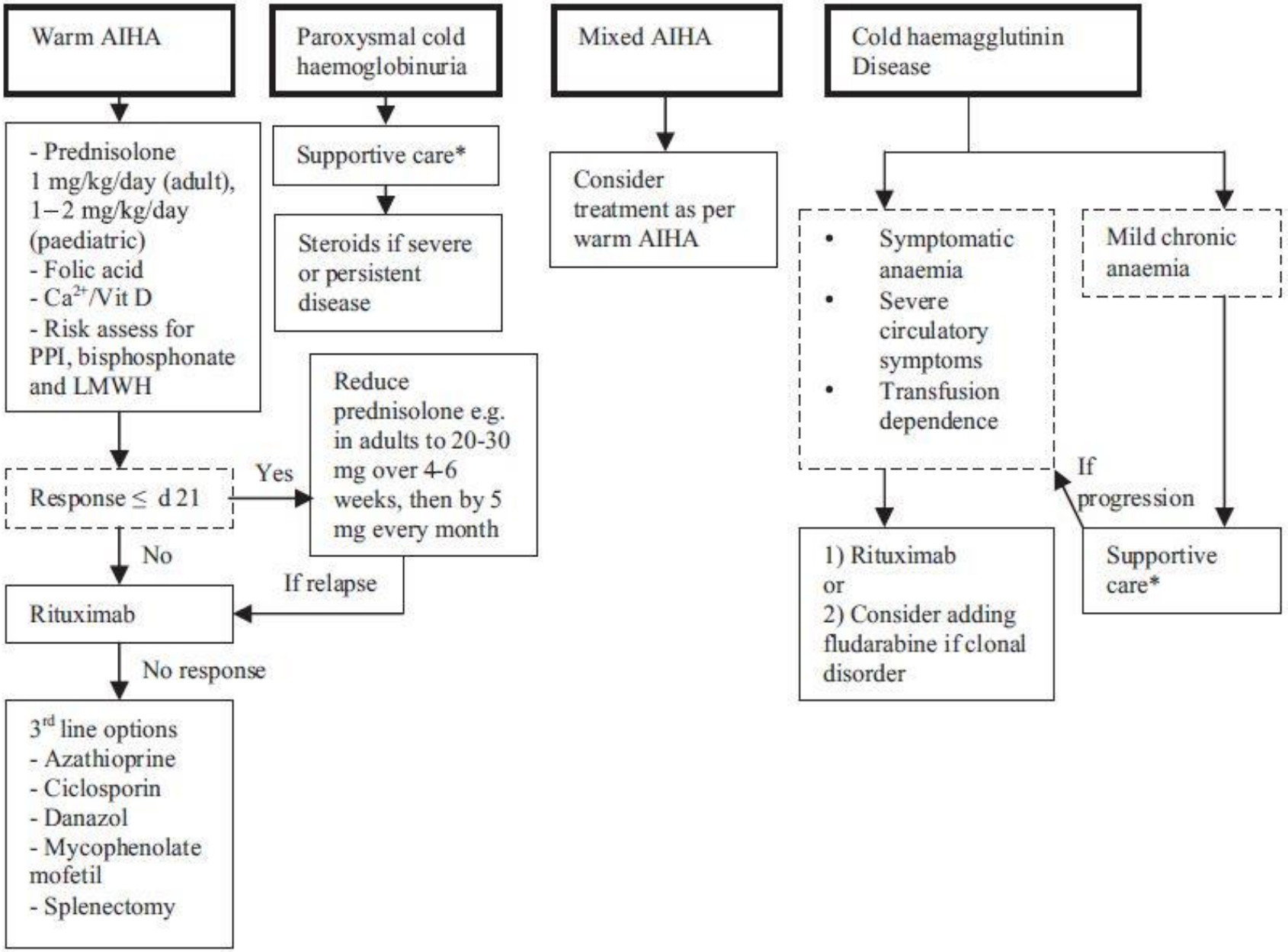


Fig 2. Therapeutic pathway for primary AIHA. Ca^{2+}/Vit D, Calcium/Vitamin D; ≤day 21, within 21 days; FBC, full blood count; LMWH, low molecular weight heparin; PPI, proton pump inhibitor. *keep warm, avoid active cooling, folic acid, monitor FBC +/− transfusion



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Na gestação

- TAD deve ser avaliado sempre;
- USG para morfologia fetal na sem20 para avaliar anemia fetal;
- Neonatologista deve estar ciente dos riscos de anemia e hiperbilirrubinemia;
- Cuidado com trombose na AHAI;
- 1ªlinha=> pred; 2ªlinha=>IgIV/aza;

Na gestação

- Avaliar TAD do RN; se TAD+ ou icterícia no RN=> rotina de avaliação e tratamento de hemólise no RN!

- seguimento por 6 semanas sem anemia ocorrer!