Haematological management of cyanotic congenital heart disease (CCHD).

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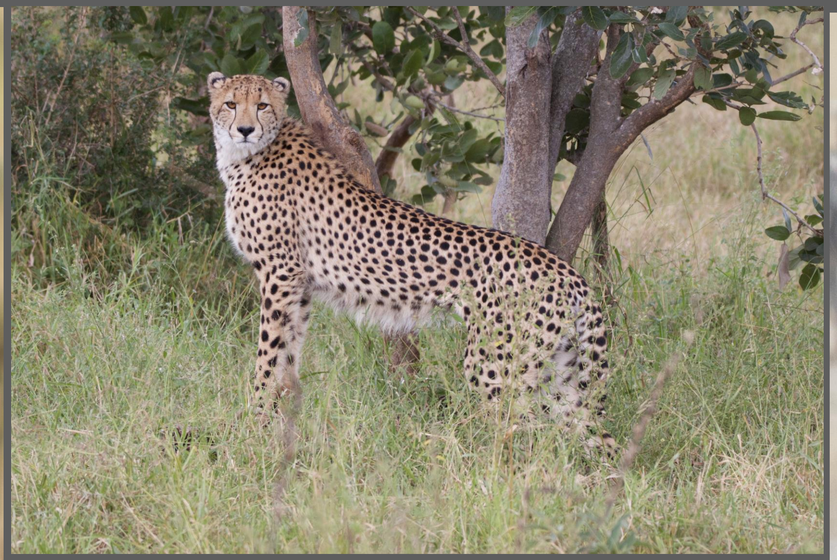
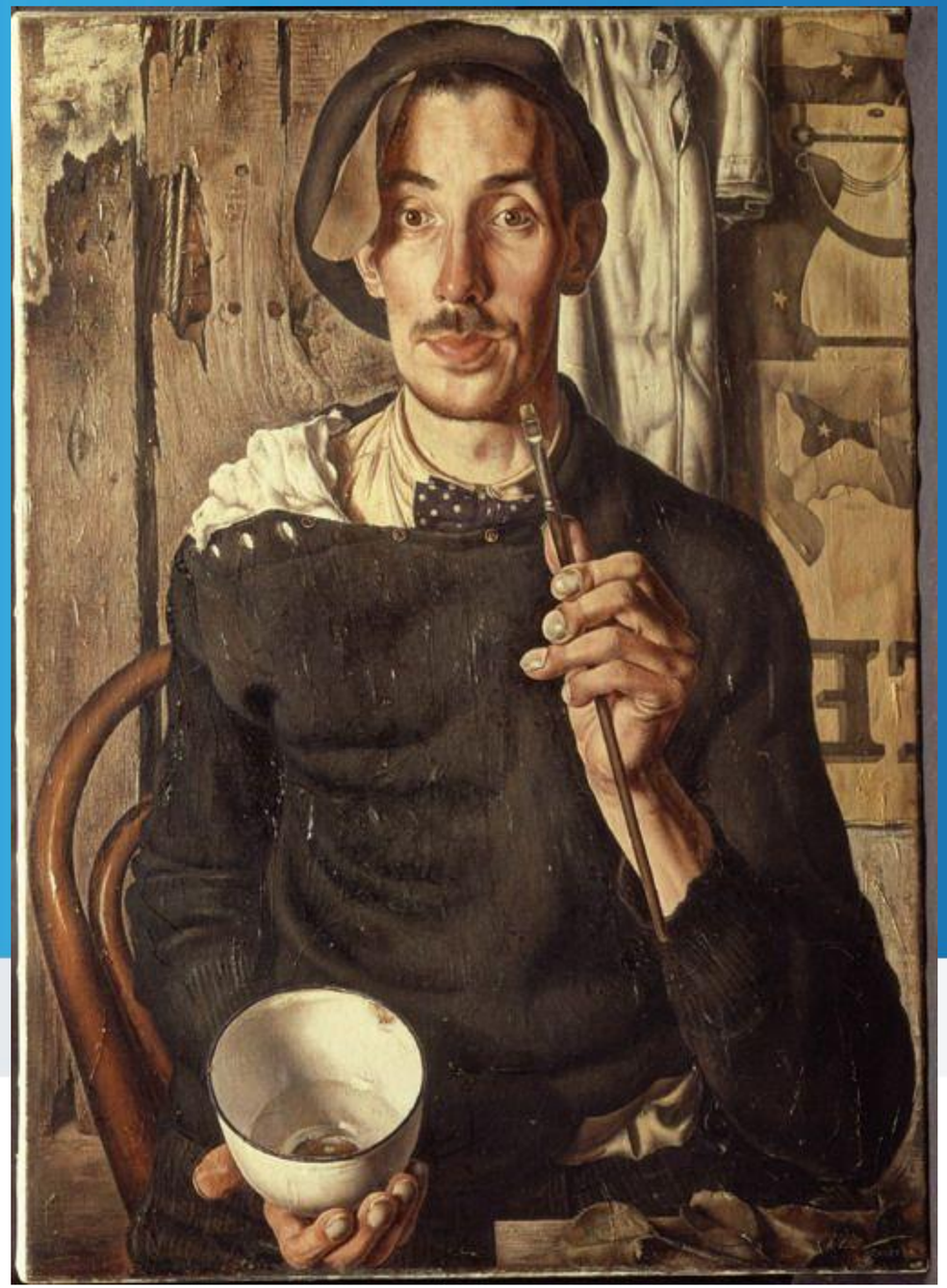
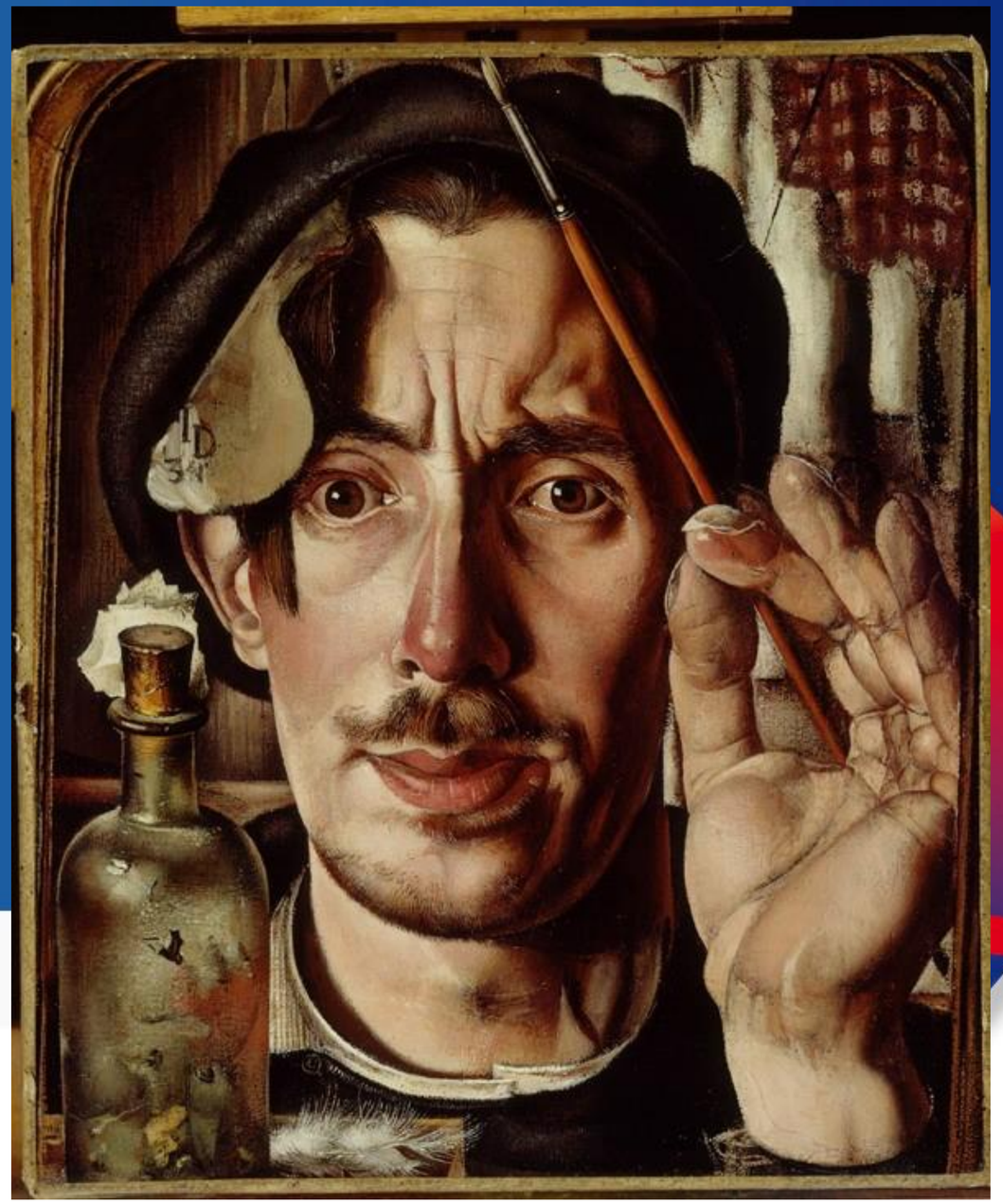
No disclosures





Outcomes have improved due to better diagnostics and better treatment



disease

Which patients are we dealing with?

AortoPulmonary connections:

- PDA
- Central shunt
- MAPCAs

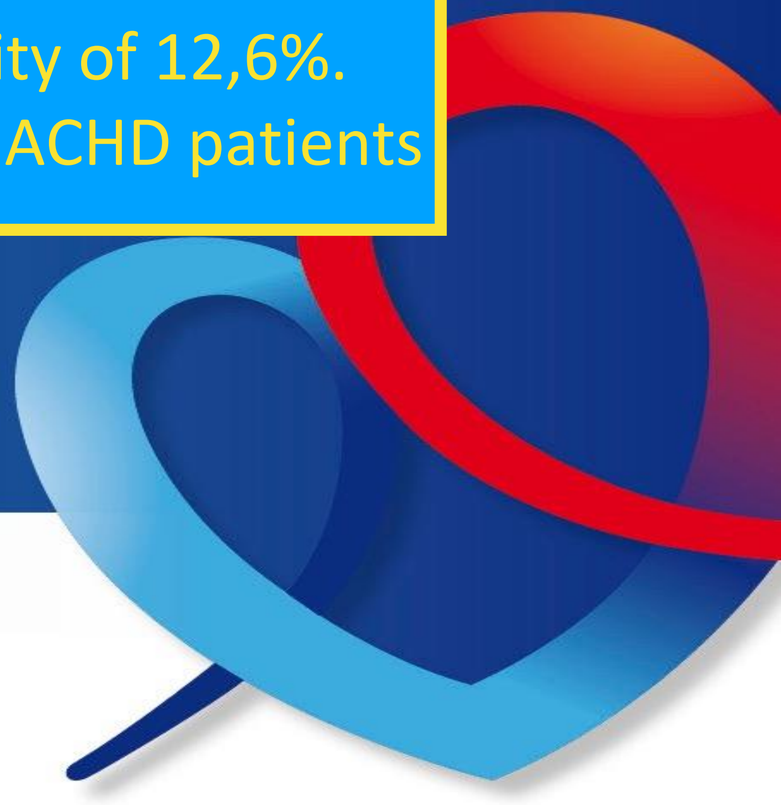
Shunt with normal or restricted pulmonary flow:

- Tetralogy of Fallot
- DORV/Taussig Bing anomaly
- Pulmonary atresia VSD MAPCAS
- Ebstein’s anomaly with ASD
- Univentricular heart with pulmonary outflow tract restriction

Pulmonary vascular disease due to a non restrictive shunt:

- Large non restrictive VSD
- Atrial shunt/ASD
- Univentricular heart without pulmonary outflow tract restriction
- Truncus arteriosus

5yr mortality of 12,6%.
Highest of all ACHD patients



Oechslin E. Heart 2015;101:485–494. doi:10.1136/heartjnl-2012-301685

Management of adults with cyanotic congenital heart disease

Hematological management of cyanotic congenital heart disease: objectives of discussion:

The Good: Physiology

The Bad Complications & The Ugly Uncertainties

1) RBC Erythrocytosis : Inverse relation with platelets
Hyperuricaemia
Viscosity
Phlebotomy
Iron deficiency

2) Risk of bleeding - contributes to iron deficiency
3) Risk of thrombosis - wisdom of anticoagulation
4) Decreased immunity - contributors
- risk of cerebral access related to hyperviscosity
- risk of infective endocarditis
5) Vascular bed dysfunction / Atherosclerosis

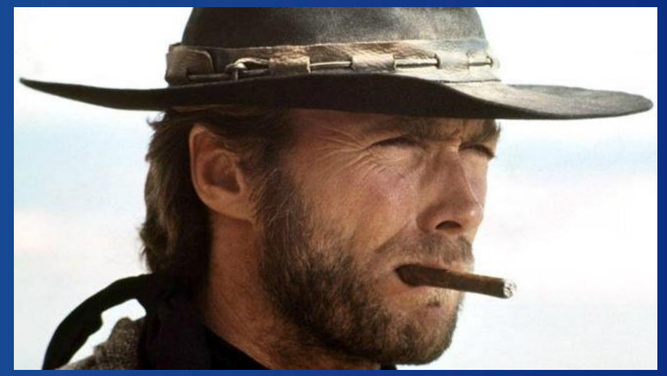
Hematological management of cyanotic congenital heart disease: objectives of discussion: Management

The Good Management Steps and Therapies

1) Risk reduction: Avoid destabilization of the equilibrium
   - Treatment if iron deficiency
   - Avoidance of dehydration
   - Avoidance of paradoxical embolism
   - Precise decisions on anticoagulation

2) Therapy: Hyperviscosity
   - Cerebrovascular complications
   - Thrombosis
   - Haemoptysis
   - Gout

Hematological management of cyanotic congenital heart disease: The Good Adaptations



- Despite severe hypoxaemia, adverse cardiac hemodynamics, pulmonary hypertension & poor exercise tolerance, patients have good Q of L & reasonable prognosis.
- CCHD patients have beneficial physiological adaptations of cardiac & skeletal muscle.
- Chronic cyanosis leads to increase EPO production & an isolated rise in RBC count enhancing oxygen delivery.
- 2,3 DPG curve rightward shift enhances oxygenation.
- Cardiac output increases.
- Compensated erythrocytosis leads to new equilibrium. Appropriate EPO levels in response to hypoxia.
- Iron metabolism is preserved & hyperviscocity symptoms are absent.

Cyanotic congenital heart disease (CCHD): focus on hypoxemia, secondary erythrocytosis, and coagulation alterations.
Zabala LM, Guzzetta NA.
Paediatr Anaesth. 2015 Oct;25(10):981-9. doi: 10.1111/pan.12705. Epub 2015 Jul 17. Review.

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disease: The Bad Effects on RBCs, Platelet function&Coagulation

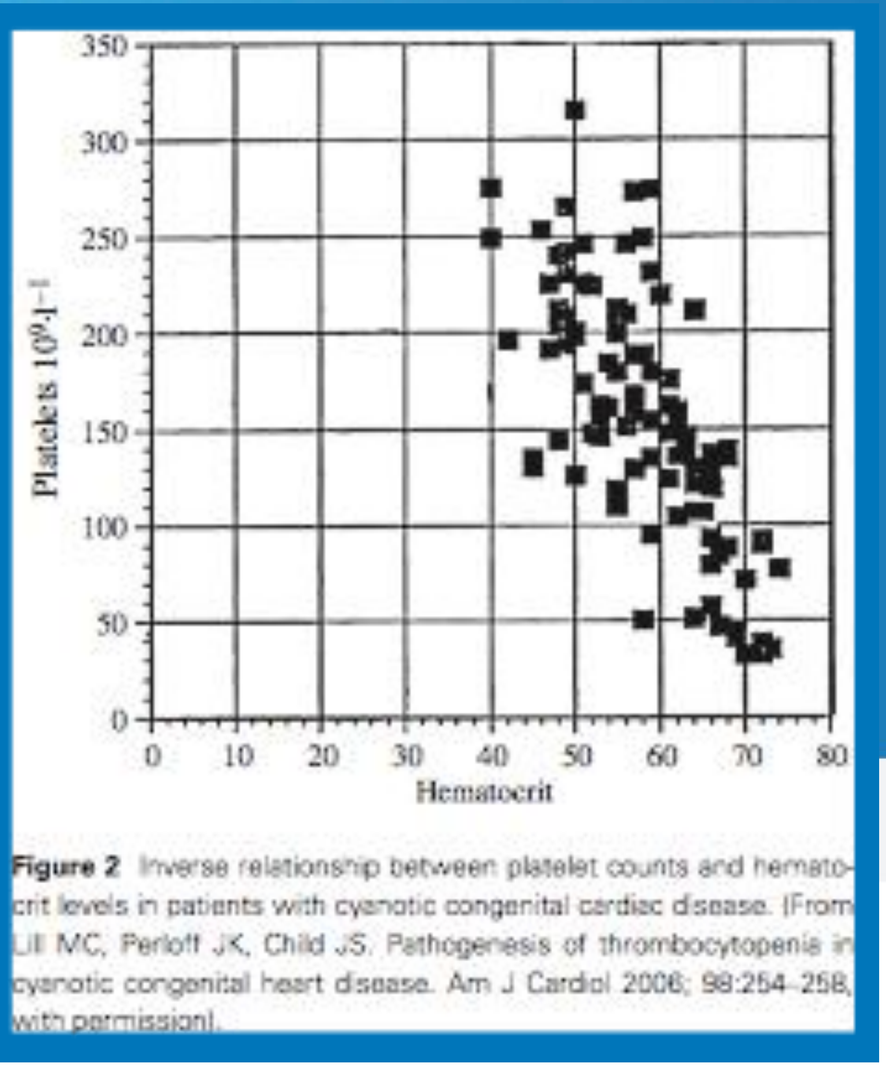

Figure 2 Inverse relationship between platelet counts and hematocrit levels in patients with cyanotic congenital cardiac disease. (From Lill MC, Perloff JK, Child JS. Pathogenesis of thrombocytopenia in cyanotic congenital heart disease. Am J Cardiol 2006; 98:254–258, with permission).

Inverse relationship between platelet count & haematocrit!

Thrombocytopenia in congenital heart disease patients.
Martínez-Quintana E, Rodríguez-González F.
Platelets. **2015**;26(5):432-6. doi: 10.3109/09537104.2014.925104. Epub 2014 Jun 23.

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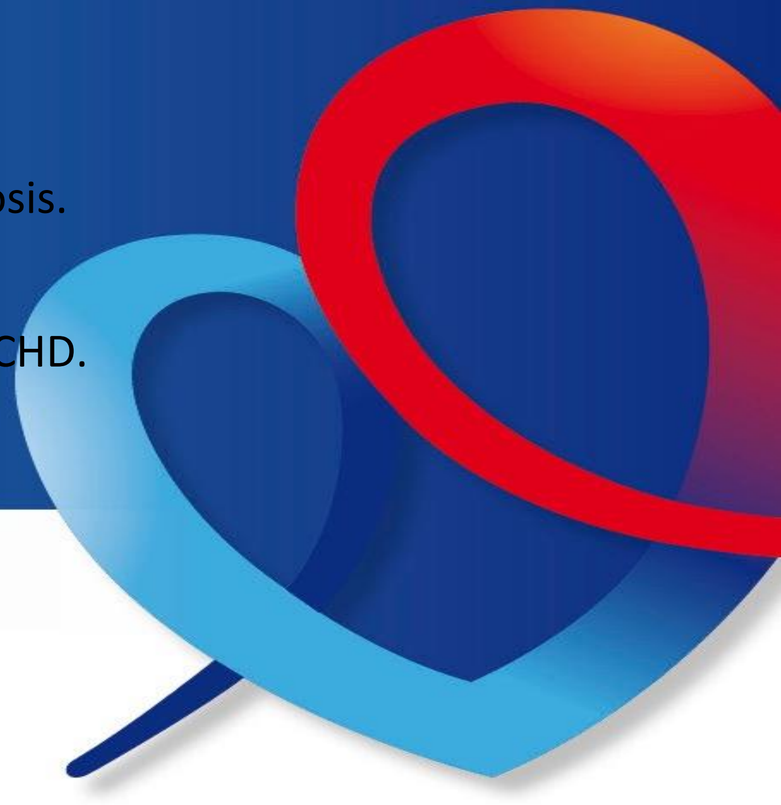
disease: The Bad Effects on RBCs, Platelet function&Coagulation

- In CCHD,the pulmonary circulation are bypassed by Right to Left shunt. Platelet production is dependent on fragmentation of megakaryocytes in lung vessels. Platelets ↓
- Large shunt = fewer platelets+bad prognosis.
- Additional theories suggest decreased megakaryocytic production, increased platelet destruction and increased platelet activation contribute to low platelet counts.
- Thrombocytopenia seems independent of hemoglobin and iron levels.

Hematological management of cyanotic congenital heart disease: The Bad Effects on RBCs, Platelet function.

- Decompensated erythrocytosis leads to persistent EPO secretion, iron depletion & eventual iron deficiency anemia.
- Iron deficient red cells are microcytic and less deformable, leading to hyperviscocity.
- Hyperuricaemia occurs due to ↑ RBC breakdown & ↓ renal breakdown.
- Gout seldom clinically problem.
- Thrombosis & infarction are devastating complications of decompensated erythrocytosis.
- Cerebral blood flow is inversely related to hematocrit & viscosity.
- AF, hypertension & microcytosis are the perfect storm leading to CVA in adults with CCHD.



3 Baumgartner H, Bonhoeffer P, De Groot NM, De Haan F, Deanfield JE, Galie N, et al. Task force on the management of grown-up congenital heart disease of the European Society of Cardiology (ESC). Association for European Paediatric Cardiology (AEPC). ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010; **31**:2915–2957.

4 Oechslin E, Mebus S, Schuler-Nesick I, Niwa K, Trindade PT, Eicken A, et al. The adult patient with Eisenmenger syndrome: a medical update after Dana Point. Part II: specific management and surgical aspects. *Curr Cardiol Rev* 2010; **6**:363–372.

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Hematological management of cyanotic congenital heart disease: The Bad Effects on Bleeding/Coagulation balance.

- Interplay of thrombocytopenia, shortened platelet survival, Von Willebrand factor deficiency & clotting factor deficiencies increases risk of bleeding.
- Bleeding contributes to iron deficiency.
- Despite low platelet counts the function of platelets seem preserved.
- Fibrinogen dysfunction inhibits normal clot formation.
- Chronic low grade DIC picture may contribute.

Hematological management of cyanotic congenital heart disease: The Bad Effects on Bleeding/Coagulation balance.

- Reduced Vit K dependent coagulation factors are likely the result of poor cardiac output, hypoxia, & hepatic congestion.
- Accelerated fibrinolysis adds to risk of bleeding.
- Thrombotic events frequent. Thrombus in PA in up to 30% of Eisenmenger patients.
- Hemoptysis is frequent & can be deadly.
- Bleeding events are the most common cause of “non cardiac“ death in CCHD.
- Bleeding events seem to occur at approx 2,6% per patient yr. Mostly hemoptysis, mostly minor.

Hematological management of cyanotic congenital heart disease:

The Bad Effects on Bleeding/Coagulation balance.

- No clear relation between bleeding or thrombosis and platelet count.
- CCHD patient have a point of balance between thrombogenicity and bleeding liability.
- Raised fibrinogen & raised factor VIII/ VonWillebrand factor complex due to chronic disease. Also raised PF4, P selectin and E selectin. This leads to platelet and endothelial activation.
- These increases compensate for the bleeding risk of low platelet numbers, and may lead to thrombogenicity.
- Thrombosis relatively common….perhaps 1% risk per patient yr.
- Despite risk of paradoxical stroke, PE's and CVA uncommon at 0.06% and 0.12% per patient yr.

3 Baumgartner H, Bonhoeffer P, De Groot NM, De Haan F, Deanfield JE, Gatzoulis N, *et al*. Task force on the management of grown-up congenital heart disease of the European Society of Cardiology (ESC). Association for European Paediatric Cardiology (AEPC). ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010; **31**:2915–2957

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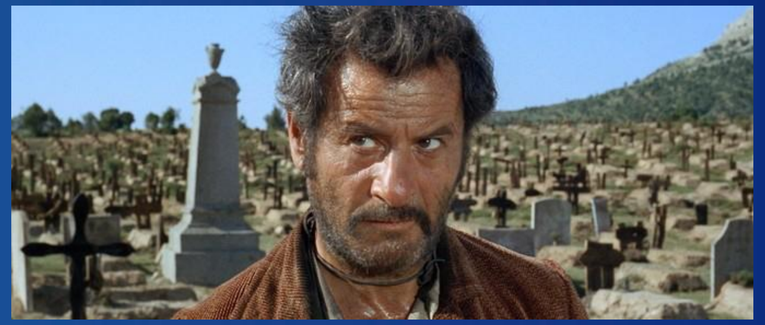
Hematological management of cyanotic congenital heart disease: The Ugly: Is it better to anticoagulate?

- Anti coagulation strategies in patients with idiopathic PAH are proven.
- This can not be extrapolated to Eisenmenger patients.
- Eisenmenger patients do worse when anti coagulated!
- No survival benefit, 16% risk of severe bleeding.
- Anecdotal best practice is to anticoagulate Eisenmenger patients only if thromboembolism is proven, or other clear indications such as valve prosthesis are present.

Does anticoagulation in **Eisenmenger** syndrome impact long-term survival?
Sandoval J, Santos LE, Córdova J, Pulido T, Gutiérrez G, Bautista E, Martinez Guerra ML, Peña H, Broberg CS.
Congenit Heart Dis. 2012 May-Jun;7(3):268-76. doi: 10.1111/j.1747-0803.2012.00633.x. Epub 2012 Feb 23.

Hematological management of cyanotic congenital heart disease: The Ugly: Is it better to anticoagulate?



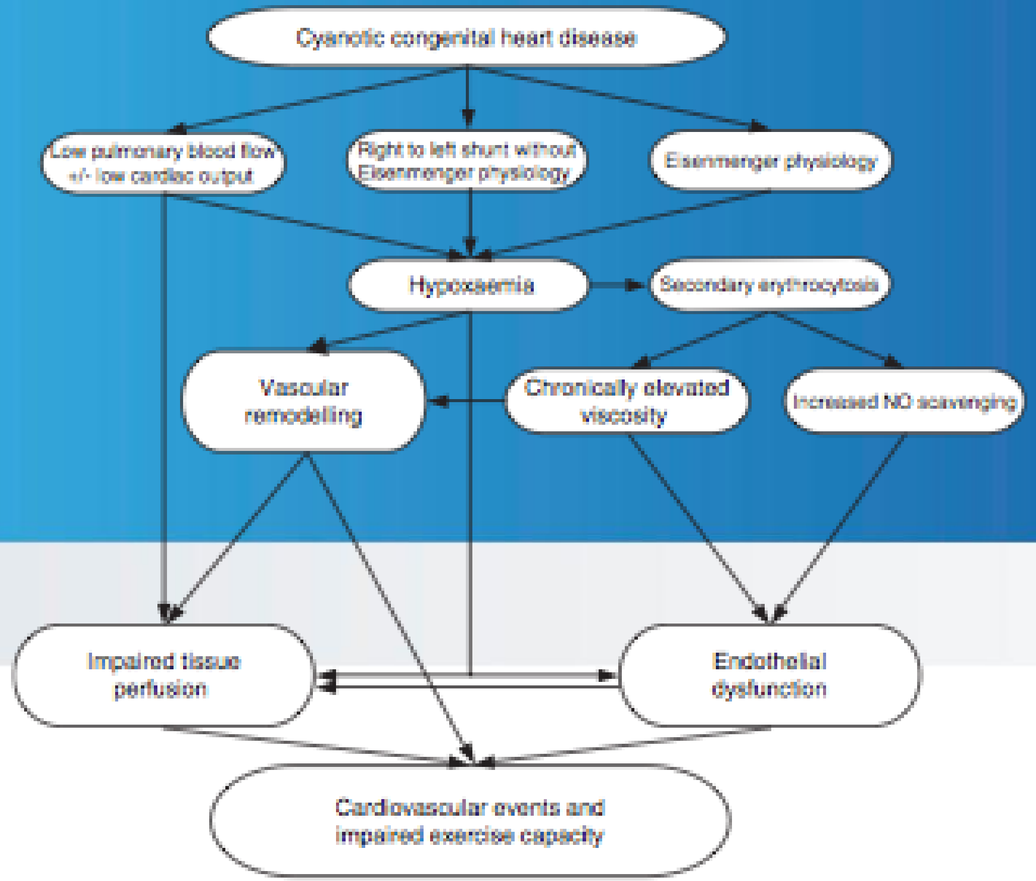
- Anti coagulation strategies in patients after Fontan operation is a vastly different story!
- Guidelines not so clear!
- My feeling is to anticoagulant the Fontan patient with arrhythmia, end organ damage or proven thrombosis.
- Always consider anticoagulation benefit vs risk at each follow up.

Alsaied T, Alsidawi S, Allen CC, Faircloth J, Palumbo JS, Veldtman GR. Strategies for thromboprophylaxis in Fontan circulation: a meta-analysis. *Heart*. 2015;101:1731–1737. doi: 10.1136/heartjnl-2015-307930.

Potter BJ, Leong-Sit P, Fernandes SM, Feifer A, Mayer JE Jr, Triedman JK, Walsh EP, Landzberg MJ, Khairy P. Effect of aspirin and warfarin therapy on thromboembolic events in patients with univentricular hearts and Fontan palliation. *Int J Cardiol*. 2013;168:3940–3943. doi: 10.1016/j. ijcard.2013.06.058.

Hematological management of cyanotic congenital heart disease: The Ugly Uncertainties.

Cyanosis related vascular dysfunction.



- High bilirubin, low iron, and low platelets lead to lower cholesterol levels and thus lower atherosclerosis risk.

- Potential target for medication.

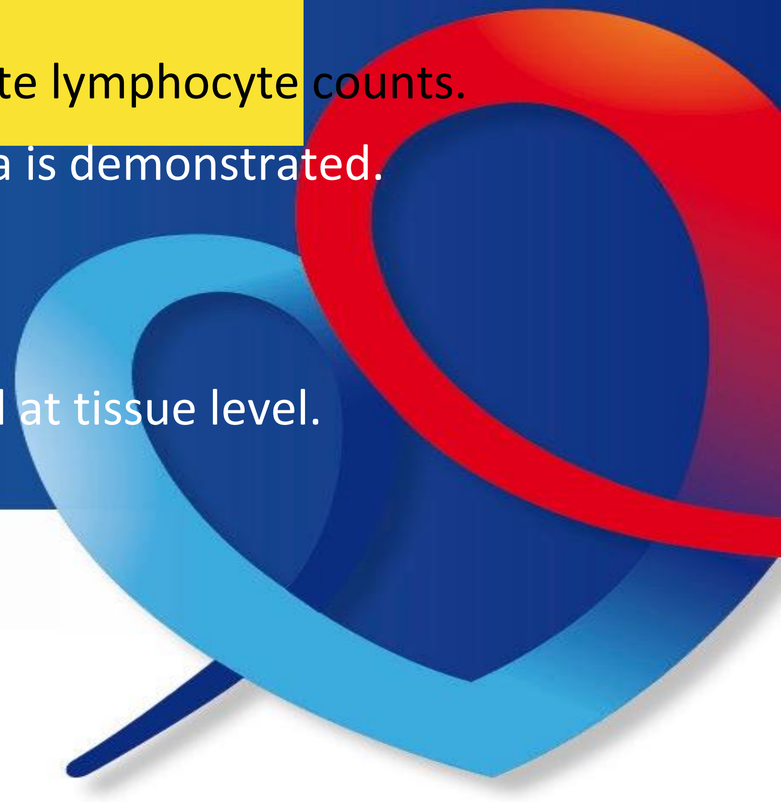
Cyanotic congenital heart disease and atherosclerosis.
Tarp JB, Jensen AS, Engstrøm T, Holstein-Rathlou NH, Søndergaard L.

Chronic cyanosis and vascular function: implications for patients with cyanotic congenital heart disease.
Cordina RL, **Celermajer** DS.
Cardiol Young. 2010 Jun;20(3):242-53. doi: 10.1017/S1047951110000466. Epub 2010 Apr 26. Review.

Hematological management of cyanotic congenital heart disease: The Ugly Complications and Uncertainties.

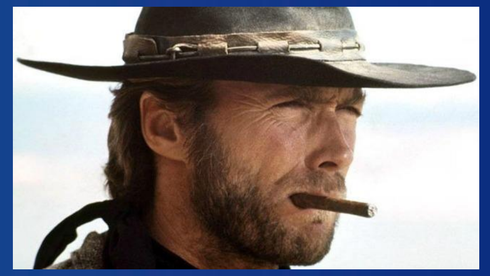
Immunosuppression

- CCHD patient certainly have risk of infective endocarditis and brain abcess.
- Do survivors of Fontan Procedure have immune deficiency?
- Surgical thymectomy, thoracic duct manipulation & PLE contribute to low absolute lymphocyte counts.
- T-cell lymphopenia with low CD 4+ and CD8+ counts & hypogammaglobulinaemia is demonstrated.
- Clinical effect is delayed clearance of cutaneous viral infections.
- Systemic opportunistic infections were not seen despite lab abnormalities.
- Theory is that lymphatic recirculation is defective, but T cell function is preserved at tissue level.



Risk Factors and **Clinical Significance** of Lymphopenia in Survivors of the **Fontan Procedure** for Single-Ventricle Congenital Cardiac Disease.
Morsheimer MM, Rychik J, Forbes L, Dodds K, Goldberg DJ, Sullivan K, Heimall JR.
J Allergy Clin Immunol Pract. 2016 May-Jun;4(3):491-6. doi: 10.1016/j.jaip.2015.11.034. Epub 2016 Feb 18.

Hematological management of cyanotic congenital heart disease: The Good Treatments for Hyperviscocity.



- Phlebotomy is exclusively used for hyperviscocity symptoms or pre operative autologous blood donation.

- Always rehydrate patients well.
- Consider cerebral access with appropriate imaging.

- No specific target hematocrit.

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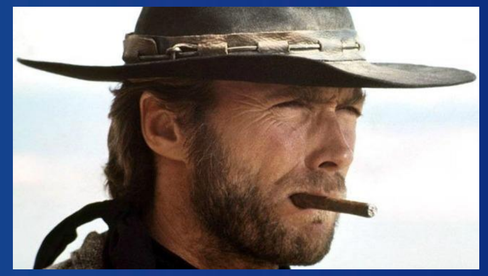
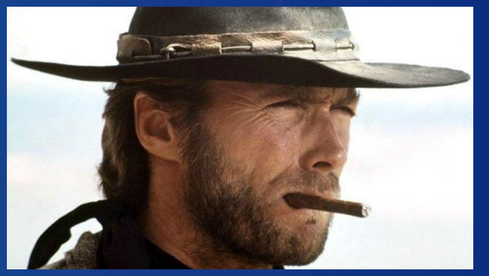
heart disease: The Good Treatments for Hyperuricaemia & Gout.



- Is it really gout? HPOA vs Periostitis vs Gout.
- Colchicine
- Allopurinol
- Rasburicase

Hematological management of cyanotic congenital heart disease: The Good Treatments for Iron Deficiency



- Iron supplementation is recommended especially for those with a inappropriately low Hb for severity of hypoxia.
- Perhaps as much as 45% of patients are iron deficient.
- Increased erythropoiesis, phlebotomy & bleeding contribute to iron deficiency.
- Age, kidney impairment, growth requirements & menorrhagia worsen iron loss.
- Iron replacement makes as much difference in 6MW test as Bosentan treatment. (BREATHE-5)
- No real data on type or duration of iron supplementation treatment
- Benefit of iron supplementation is more than risk.

Diagnosis and Management of Noncardiac Complications in Adults With Congenital Heart Disease: A Scientific **Statement** From the American Heart Association.
Lui GK, et al.
Circulation. **2017** Nov 14;136(20):e348-e392. Epub **2017** Oct 9. Review.

Int J Cardiol. 2008 Jun 23;127(1):27-32. Epub 2007 Jul 20.
Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: results of the BREATHE-5 open-label extension study.
Gatzoulis MA1, Beghetti M, Galiè N, Granton J, Berger RM, Lauer A, Chiossi E, Landzberg M; BREATHE-5 Investigators.

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Hematological management of cyanotic congenital heart disease: Take home message

- Hematological system contributes to adaptations and complications in CCHD.
- Challenges include are erythrocytosis, iron deficiency, anemia, hyperviscocity, hemorrhage,thrombosis and hyperuricaemia.
- Risk reduction and prevention strategies avoid destabilization of the equilibrium.
- ACHD clinic systems are imperative!

The Good: “There are two kinds of people in the world: those with guns and those that dig.
You dig?”

The Good: “There are two kinds of people in the world: those with hematological complications of cyanotic congenital heart disease, and those who complain.
You complain?”