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Interesting case

Polycythemia & bleeding disorder

دکتربابک عبدالکریمی

هماتولوژیست آنکولوژیست کودکان

پاییز ۱۴۰۰

Etiology

Go to:

Classification

Spurious Polycythemia

This occurs due to volume contraction rather than an increase in true RBC mass.

Causes include:

- Severe dehydration due to isolated fluid loss: potentially seen in diarrhea and severe vomiting
- Gaisbock syndrome: Usually seen amongst obese, hypertensive males. Consumption of cigarettes, excessive alcohol, and use of diuretics are contributory.[3]

True Polycythemia

Further stratified based on serum erythropoietin (EPO) levels as follows:

Low serum EPO levels (Primary polycythemia)

- Polycythemia vera
- Primary familial and congenital polycythemia

High serum EPO levels (Secondary polycythemia)

- High altitude
- Respiratory disorders: Chronic obstructive pulmonary disease (COPD), Pickwickian syndrome
- Cyanotic heart diseases with right-to-left shunts
- Renal disorders: Renal cysts, cancer, renal artery stenosis, Bartter syndrome, focal sclerosing glomerulonephritis

- Elevated carboxyhemoglobin: usually seen in smokers
- Hemoglobinopathies: High-affinity hemoglobins such as Hb Yakima, methemoglobinemia
- EPO-secreting tumors: sources include hepatomas, uterine leiomyomas, and cerebellar hemangiomas
- Iatrogenic causes: Including erythropoietin administration, anabolic steroids, and testosterone replacement therapy

History and Physical

Go to:

History

Common presenting symptoms, usually non-specific, include fatigue, headache, dizziness, transient blurring of vision, amaurosis fugax, and other symptoms suggestive of transient ischemic attacks (TIAs).

Infrequently, patients may complain of pruritus after a warm water shower, particularly over the back.

A history of epistaxis, gastrointestinal (GI) bleed, or easy bruising may be forthcoming.

Peptic ulcer disease commonly coexists, and patients may present with non-specific abdominal pain. Left hypochondrial pain and early satiety should arouse the suspicion of splenomegaly.

Rarely, patients may present with a history of unexplained thrombotic complications, such as Budd-Chiari syndrome or digital infarcts.

It is vital to try and elicit etiology-specific history such as a history of smoking, an extended stay at high altitudes, congenital cardiac disease, among others. Significant family history may be elicited in patients with hemoglobinopathies.

Physical Examination

Abnormal facial ruddiness may be prominent.

Cyanosis and clubbing, along with the presence of a murmur on auscultation, provide strong evidence favoring a congenital cyanotic heart disease.

Nicotine staining of the nails and teeth provides presumptive evidence of smoking, even in a non-forthcoming patient.

The presence of morbid obesity could raise the possibility of Pickwickian syndrome; whereas, a barrel chest could suggest an obstructive lung disease.

Examination of the abdomen may lead to finding a palpable spleen or eliciting the bruit of renal arterial stenosis.

Treatment / Management

Go to:

The treatment of secondary polycythemia is directed at correcting the cause.

For polycythemia vera, available treatment modalities include:

Phlebotomy

Phlebotomy was established as the backbone of therapy, primarily based on the trial conducted by the Polycythemia Vera Study Group (PVSG). The study found that, compared to the use of chlorambucil or radioactive phosphorous, treatment with phlebotomy alone was associated with longer median survival.[7]

The rationale behind repeated phlebotomies was that cytoreduction would reduce hyperviscosity. Additionally, it would induce a state of iron deficiency that would help retard red-cell proliferation.

In practice, weekly sessions are conducted, during which approximately 500 mL of blood is removed, provided the hemodynamic status permits this.

This is continued weekly until a target hematocrit of under 45% is obtained. This target was determined based on the findings of the CYTO-PV trial conducted in Italy. Investigators observed significantly lower rates of cardiovascular deaths and major thrombotic episodes in patients kept under this threshold.[8]

For secondary polycythemias, phlebotomy is usually reserved for the following conditions:[9]

- Chronic lung diseases
- Cyanotic heart diseases
- Post-renal transplant patients with hypertension and erythrocytosis, not responding to optimal doses of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs)

Hydroxyurea

Hydroxyurea is usually considered second-line therapy. Evidence of benefit came from, among others, a study by the Polycythemia Vera Study Group (PVSG)[10] that showed lower rates of thrombosis compared to a historical cohort treated with phlebotomy alone. Despite theoretical concerns, studies[11] have not found a significant association between the use of hydroxyurea and an increased risk of leukemic transformation. Indications for use include:

- Poor venous access
- High phlebotomy requirement
- When phlebotomy is not possible due to logistic reasons
- Severe thrombocytosis
- Intractable pruritus

The standard daily doses range from 500 to 1500 mg per day.

Doses are adjusted to target platelet counts below 500,000/mcL. However, it is necessary to adjust doses such that the absolute neutrophil count remains above 2000/microliters.

Ruxolitinib

The *JAK2* inhibitor ruxolitinib is used when patients are intolerant or unresponsive to hydroxyurea.

Evidence supporting the use of Ruxolitinib in myeloproliferative disorders came from the COMFORT trials. The COMFORT-I study compared the efficacy of Ruxolitinib with placebo therapy, whereas COMFORT-II compared it with "best available therapy." Both trials showed a significant reduction in splenomegaly, improvement in symptoms, and better survival.[12][13]

However, despite this enhanced benefit, the use of ruxolitinib was associated with increased risks of anemia, often dose-limiting, and thrombocytopenia.

Hypouricemic Agents

Agents such as allopurinol and febuxostat may be required in cases with significant hyperuricemia. Recent studies indicate that, between them, allopurinol may be a safer alternative with respect to all-cause and cardiovascular mortality.[14]

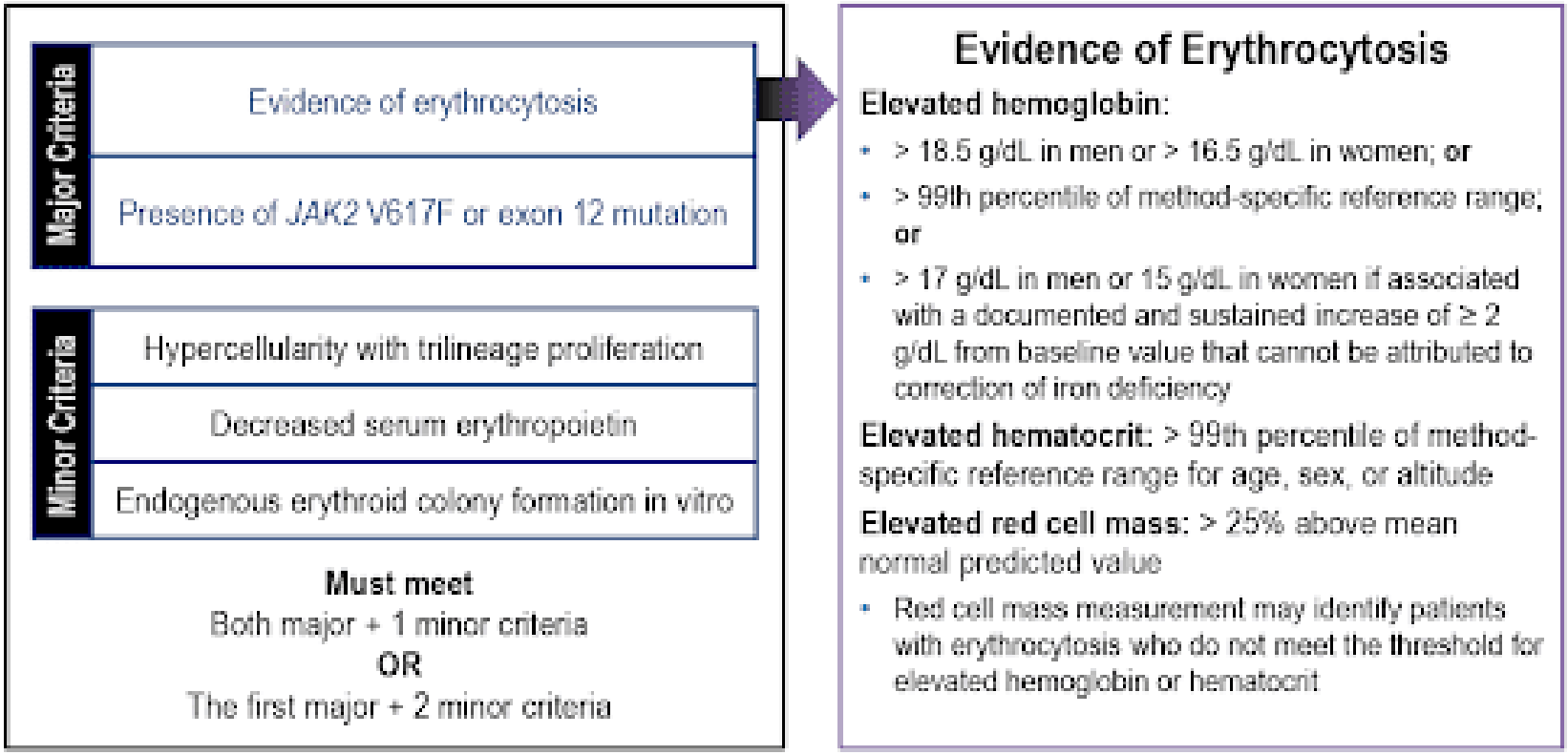
Management of Pruritus

Depending on the severity of pruritus and the clinical response to therapy, therapeutic modalities available for symptomatic relief include antihistamines[15] and selective serotonin reuptake inhibitors (SSRIs).[16]

Management of Polycythemia Vera in Pregnancy [17]

The standard therapeutic measures of phlebotomy and low-dose aspirin are appropriate in most cases. Certain high-risk women may require the addition of pegylated interferon (IFN)-alpha.

Polycythemia Vera
2008 WHO Diagnostic Criteria



WHO: World Health Organization

Thiele J, et al. In: Swerdlow S, Campo E, Harris N, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008:40-43.

Classic treatment of PV:

- busulfan (Myleran)
- chlorambucil (Leukeran)
- hydroxyurea (Hydrea)
- interferon alfa (Intron A)
- ruxolitinib (Jakafi)

New treatment option in PV:

- **Selective serotonin reuptake inhibitors(SSRI):**
- These are typically used for depression, but they may also help reduce **itchiness**.

- **JAK2 inhibitors:**
- These help block a mutated *JAK2* gene from producing too many blood cells.

- **Imatinib mesylate:**
- help decrease **spleen size** and **reduce the number of phlebotomies** a person needs.

- **Givinostat:**
- This is a **histone deacetylase** medication that helps prevent abnormal cell growth. It may be a **second line** of treatment for people whose bodies do not tolerate first-line treatments well.
- **Peginterferon alfa-2a (Pegasys):**
- This is a JAK2 inhibitor targeting the *JAK2* gene.
- **Idasanutlin:**

This is an MDM2 inhibitor that blocks certain protein interactions.

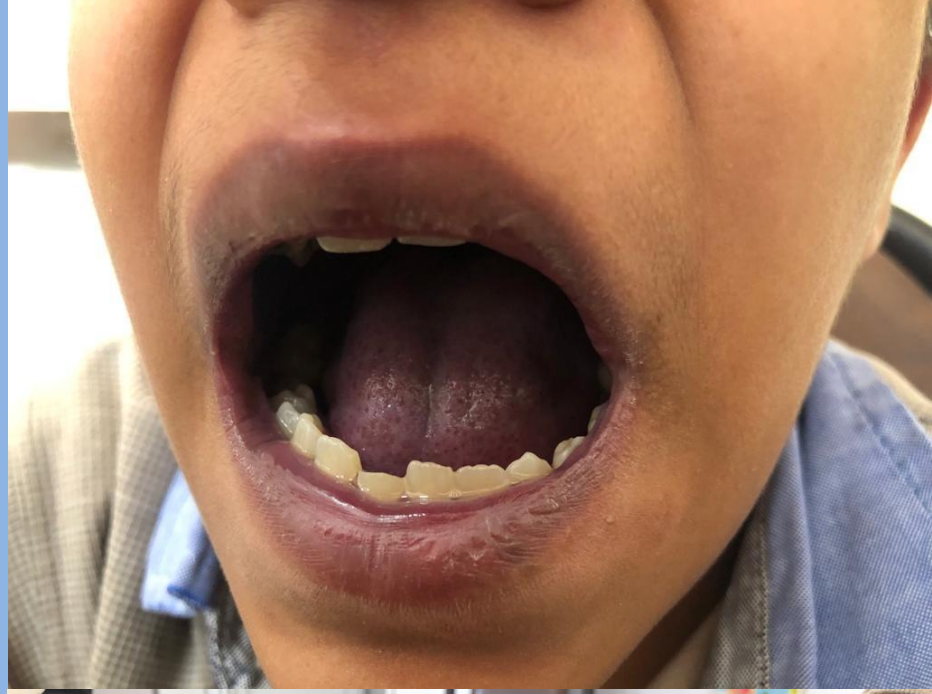
- Another recent study, called the PTG-300 Polycythemia Vera Study, is looking at the medication **PTG-300**. control the number of red blood cells in the body.

Case Presentation:

پسر ۱۱ ساله بیمارشناخته شده single ventricle ترمیم شده (cyantic heart disease +right to left shunt)که به دلیل اپیستاکسی شدید ومکرروتستهای انعقادی مختل از ۳ ماه قبل ازمراجعه به درمانگاه هماتولوژی کودکان ارجاع شد درسابقه ازبدو تولد سابقه بیماری خونریزی دهنده نداشته است.دربررسی اولیه:

PT=18 PTT=60

BT=5



آزمایش

بیمارستان امام خمینی(ره) الشتر

تهران

تاریخ چاپ : 1400/07/30 19:49

واحد آزمایشگاه تلفن:

نام و نام خانوادگی : امیرمحمد حسنوند شماره پرونده : EMR_C01-0007-054984 تاریخ درخواست : 1400/07/30 17:57

شماره پیمار 7-03046 نام پدر :حسن رضا جنس و سن : مذکر 13سال بخش : اورژانس سرپایی نوع مراجعه : بالینی

Hematology

Test	Result		Unit	Normal Ranges
WBC	4.8		10^3/uL	Adult(18-49)Female:3.9-11.7 Adult(18-49)Male :3.7-9.7
RBC	9.53	H	10^6/uL	Adult Female : 3.85-5.16 Adult Male: 4.54-5.78
Hgb	21.6	H	g/dL	Adult Female : 12-15 Adult Male:13.3-17.2
HCt	72.5	H	%	Adult Female: 34.8-45 Adult Male: 38.9-50.9
M.C.V	76.1	L	fL	Adult Female :78.5-96.4 Adult male : 81.2-94
M.C.H	22.7	L	pg	Adult female : 26.4-33.2 Adult male: 27.1-32.5
M.C.H.C	29.8	L	g/dL	Adult Female : 31.8-35.9 Adult Male :32.5-36.7
Platelets	80*		10^3/uL	Adult Female: 172-440 Adult Male: 174-373

Rechecked

تعداد کل صفحه : 4 صفحه 3 شماره پرونده : EMR_C01-0007-054984 بیمار: امیرمحمد حسنوند بخش درخواستی: اورژانس سرپایی

بخش انتقالی:

شماره نظام پزشکی:

این برگه بدون مهر و امضاء فاقد اعتبار است

بیمارستان امام خمینی(ره)الشتر
دکتر مهرجو ابراهی
متخصص تصاویر وقت آسیب شناسی
۱۲۹۷۵۳

آزمایشگاه تشخیص طبی سازمان انتقال خون ایران

تهران - بزرگراه شیخ فضل اله نوری - ورودی همت - جنب برج میلاد

تلفن: ۸۸۶۱۰۰۱۱ - ۸۲۰۵۲۲۷۰ - ۸۲۰۵۲۲۷۱

شماره پذیرش: 10-634 تاریخ پذیرش: 1397/10/09 تاریخ جوابدهی: 1397/10/11

نام مراجعه کننده: آقای امیر محمد حسنوند سن: 10 سال پزشک معالج: جناب آقای دکتر ضیائی

Coagulation

Test		Result	Unit	Reference Interval
aPTT patient	***H***	***53.4***		***28 - 37***
aPTT .control		31.8	Sec	
Mixed aPTT		35.6	Sec	
P.T. (Patient)	***H***	***16.1***	***Sec***	***9.7 - 11.7***
PT Control.		11.3	Sec	
Mixed PT		12.6	Sec	
INR.	**H**	**1.49**		1 - 1.3
Fibrinogen *		329	mg%	200 - 400
Factor II *	**L**	**55**	%	67 - 107
Factor V *	**L**	**54**	%	63 - 116
Factor VII *	**L**	**25**	%	52 - 120
Factor X *	**L**	**31**	%	55 - 101

It is recommended to repeat Vit-K dependent coagulation factor tests .

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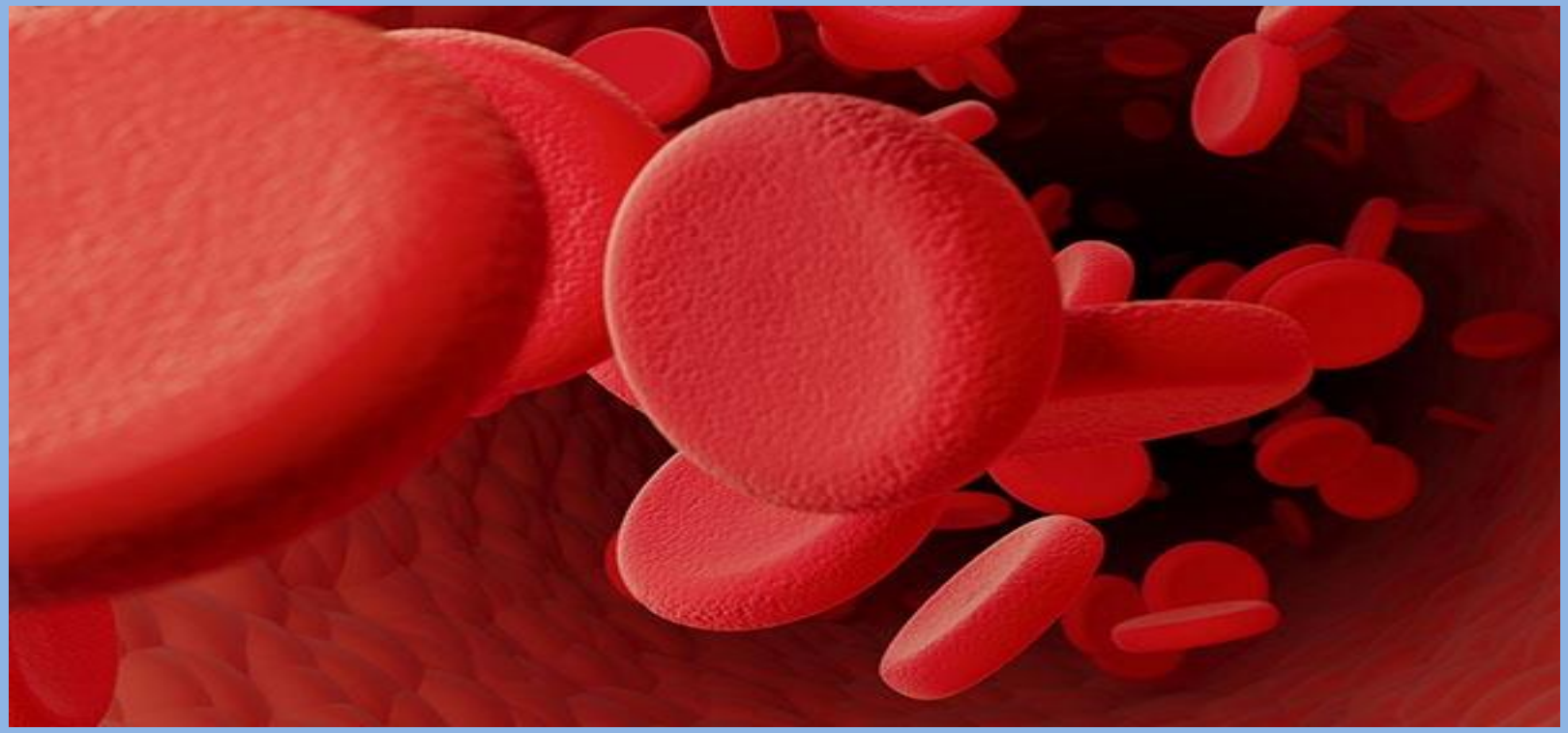
F IX *	**L**	**53**	%	63 - 89

H=High L=Low

- ***Acquired Coagulopathy in congenital cyanotic heart***



Etiology of BLEEDING DISORDER
Cyanotic Congenital Heart Disease

- ***1.Polycythemia***
-

  2.Thrombocytopenia
  3.Platelet function abnormalities
  4.DIC
  5.Decreased production of coagulation factors
  6.Impaired liver function
  7.Vitamin K deficiency
  8.Primary fibrinolysis

PATHOPHYSIOLOGY OF BLEEDING DISORDERS

- 1.lowered **prothrombin levels** are **the principal hemostatic defects** and are related to the severity of polycythemia

  2.(HCT>= 59% with hemoglobin 19 g/dL) +patient's age >=45 years)----→ A **shortened half-life of platelets** (80 hours with 80 to 130 hours as normal time) also has been

- 3.The resultant **vascular stasis** makes these patients lead to *DIC*.

localized intravascular coagulation(LIC)

- The degree of abnormality observed in these Cases did not suggest severe **DIC** but was consistent with either low-grade or **localized intravascular coagulation(LIC)** .

  It has been suggested that the **pulmonary microvasculature** is the ***major area*** of LIC.

- The **liver cell hypoxia** & **marrow reserve** determine the ***day-to-day balance*** between ***production & consumption*** of coagulation factors and their plasma levels.

- IC:
- 1.LIC----→localized+compensated response
- 2.DIC---→disseminated+uncompensated response

Heparin response

- The **increase in factor levels after *heparin administration(Heparin response) is*** evidence of ***significant LIC/DIC*** does take place in these patients.
- **heparinization should not be used routinely** and should be administered only in patients with **definite evidence of DIC**.
- ***Critical point:***
- The **polycythemia** reduces the **amount of plasma *(RBC mass / plasma)*** so that the amount of anticoagulant in the collection tube ***must be appropriately reduced***.
- ***Clinical & paraclinic matching is necessary.***

Correct blood sample:

Blood samples normally are collected with the usuall ratio of **1** part of anticoagulant to **9** parts of blood**.(1/9)**

The volume of blood added to **0.25 mL** of 3.8% **Na3 citrate** for coagulation tests can be calculated according to the following formula

Na 3 citrate volume(mL)=2.25 x (100 - normal hcrt/ 100 - patient's hct)

- Trisodium citrate is infused into the **arterial blood path to chelate calcium**, decrease ionized calcium, and **prevent activation of the coagulation cascade** while blood is circulated in the extracorporeal circuit.

Excessive Bleeding mechanisms in Congenital Heart Disease

- 1.**Hemodilution** **(increased HCT/plasma ratio)**
- **2.Delayed hepatic maturation** secondary to **poor organ perfusion**(decreased levels of coagulation factors compared with normal)
-

3.Secondary Vitamin K deficiency:

- 1.impaired synthesis (weak liver function) :

- 2.impaired absorption (weak intestine function)
- A. incomplete
- B. complete
- can lead to impaired activity of factors **II, VII, IX, and X.**
- (**likely resistant to vitamin K therapy)**.

treatment:

- **1.FFP/concentrated factor(**even **IM vitamin K** had no effect)
- **2.A:oral vit k**
- 2.B.IM Vit K (5- 8 mg of vitamin K1 daily for 2 days) but not with **oral of vitamin K**

Treatment of primary fibrinolysis (shortened euglobulin lysis time):

- 1.**antifibrinolytic**, in the **preoperative treatment** of **primary fibrinolysis** in CCHD **(FDP,D-Deimer)**

- **Other factor deficiency association with CCHD:**
- 1.VIII deficiency
- 2.von Willebrand factor
- 3.factor XII deficiency
-

Treatment strategy for presented patient:

- ***1.ASA***
- ***2.Hydroxiurea***
- ***3.phelebotomy(every months/far from health center)/partial exchange(N/S or FFP)***
- ***DIC prophylaxis***
- ***4.oral vit K (phytonadion)+vit k(IM) monthly(2 days)***
- ***5.Ferrosulfate(prophylactic dose)***

منابع:

- 1.Ali Ghasemi1, Mohsen Horri2,*Yaser Salahshour **Coagulation Abnormalities in Pediatric Patients with CongenitalHeart Disease: A Literature Review.** International Journal of Pediatrics, Vol.2, N.2-2, Serial No.5, Apr 2014

- 2.Deepak K. Tempe, Sanjula Virmani. **Coagulation Abnormalities in Patients With Cyanotic Congenital Heart Disease.** *Journal of Cardiothoracic and Vascular Anesthesia,* Vol 16, No 6 (December), 2002: pp 752-765

- 3. https://www.medicalnewstoday.com/articles/latest-treatments-for-polycythemia-vera