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REACTIVE TRHOMBOCYTOSIS IN CHILDREN

Ayu Hafsari, Nadirah Rasyid Ridha
Departemen Ilmu Kesehatan Anak, Fakultas Kedokteran, Universitas Hasanuddin Makassar, Indonesia
email: ayuhafsari144@gmail.com

Abstract

Thrombocytosis is a condition which the platelet count exceeds 450,000/mm3. Thrombocytosis was classified as: mild (450,000-700,000/mm3), moderate (700,000-900,000/mm3), severe (900,000-1,000,000/mm3) and extreme (>1,000,000/mm3). Functionally, thrombocytosis is divided into primary (essential) and secondary (reactive). The novelty of this study due to examining reactive thrombocytosis in children. The purpose of this study was to look at reactive thrombocytosis in children. Essential thrombocytosis is a myeloproliferative disorder due to monoclonal or polyclonal abnormalities of hematopoietic cells or biologic abnormalities of thrombopoietin (Tpo) in the primary regulation of megakaryopoiesis. Meanwhile, reactive thrombocytosis occurs temporarily due to stimulation of megakaryopoiesis with haematological or non-haematological abnormalities. Reactive thrombocytosis is an increase in thrombopoiesis due to reactive process due to infection, chronic inflammation, malignancy, and splenectomy surgery. Bacterial or viral infections are the most common cause (about 37-78%) at any age during childhood. Reactive thrombocytosis are asymptomatic and is usually found incidentally. Based on the guidelines the British Society for Haematology recommends three initial investigations: (1) Peripheral blood smear, (2) Inflammatory markers, and (3) Iron status. Management of reactive thrombocytosis by threated the main diseases, then platelet count returns to normal after the underlying disease is resolved. The overall prognosis depends on the underlying causative condition, approximately 8% of patients with acute infection examined have mild, transient thrombocytosis and show no infectious complications. However, these patients had an increased acute-phase response, prolonged length of stay, more bacteraemia and increased mortality although it only affected a minority of patients. This distinction between essential and reactive thrombocytosis is important because it implies evaluation, prognosis and treatment.

Keywords: Reactive Thrombocytosis; Secondary Thrombocytosis; Transient.

INTRODUCTION

Platelets are essential for maintaining the integrity of the vascular endothelium and controlling bleeding from small blood vessels by forming platelet plugs. The normal number of platelets ranges from 150,000-450,000/mm3. Platelets are sourced from megakaryocytes and are in circulation for 7-10 days mainly functioning as regulators of hemostasis and thrombosis (1) (2). Platelets are meaningless pieces of blood that originally originated from hematopoietic lines through megakaryocytes. Platelet production from megakaryocytes is a systematic and regular process that is thought to occur in the bone marrow. During its normal life cycle, platelet size decreases so that young platelets are larger than older platelets. Platelets at the end of their life span after full activation and are introduced into the formation of clots in blood vessels (3), they

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are removed from the blood vessels by neutrophils and macrophages then transported to the spleen for removal from the body (1).

Thrombocytosis is the number of platelets exceeding 2 standard deviations (SD) from the normal count of platelets by age or platelet count exceeding 450,000/mm3. This platelet count disorder can be caused by many things and is often found in daily clinical practice. Based on the underlying abnormality, thrombocytosis is divided into primary (essential) and secondary (reactive). Primary thrombocytosis is rarely found and is not typical in children due to limited identification of genetic mutations and clinical information. Primary thrombocytosis is a myeloproliferative disorder caused by monoclonal or polyclonal abnormalities of haematopoietic cells or biological abnormalities of thrombopoietin (Tpo) in the primary regulation of megakaryopoiesis. Secondary or reactive thrombocytosis generally occurs transiently due to stimulation of megakaryopoiesis associated with hematological or non-hematological abnormalities. This difference between primary and secondary thrombocytosis is important because it carries implications for evaluation, prognosis, and treatment (2) (4).

Secondary thrombocytosis is the most common cause in the adult and children population, consisting of 88-97% of cases of thrombocytosis in adults and almost 100% in the child population. Reactive thrombocytosis is based on medical coditions as diverse as the inflammatory process, where platelets are one of the acute phase reactions. This is more common in children, it can be caused by innate / adaptive immunity immunity or caused by children being infected more often. Other causes of thrombocytosis besides inflammation and infection include acute bleeding, iron deficiency anemia, or malignancy. After splenectomy, the platelet count will increase in the first week then return to normal after three months (5)(6)(7).

RESEARCH METHODS

Metode penelitian yang digunakan adalah metode *Systematic Review* (SR) merupakan metode *literature review* yang mengidentifikasi, menilai, dan menginterpretasi temuan-temuan pada suatu topik penelitian untuk menjawab pertanyaan

penelitian (*research question*) yang telah ditetapkan sebelumnya.

RESULTS AND DISCUSSION

Structure And Function Of Platelets

Platelets are derived from megakaryocytes, large cells first described in 1890 by Howell. Although the role of megakaryocytes in platelet formation proposed by Wright in 1906 was quickly acceptable, the place of platelet production has been the subject of debate for at least 100 years. Megakaryocytes of the bone marrow are the origin of platelet formation. The diameter of the matur platelets is 2-3 μm, which usually remains viable for 7-10 days. About 2/3 of the platelets circulate in the blood and 1/3 are deposited in the spleen. The normal platelet count is 150,000-450,000/mm3. Each megakaryocyte can produce 5,000-10,000 platelets. About 70% of the total platelets circulate in the circulation and another 30% in the spleen. An average healthy adult can produce 1011 platelets per day and old platelets are destroyed by phagocytosis in the spleen and liver (Kupffer cells) (8)(9)(10).

The formation of platelets from megakaryocytes involves a complicated process that transforms the cytoplasm into branched proplatelets with a length of 100 to 500 μm until individual platelets are formed. The process of proplatelet and platelet formation generally starts from one megakaryocyte location where 1 or more pseudopodia. Over a period of 4-10 hours, the process of pseudopodia continues to lengthen and become tapered into proplatelets with an average diameter of 2-4 μm. Proplatelets are randomly formed with several protrusions or swellings, each of which is similar in size to platelets, which gives them the appearance of beads connected by a thin cytoplasm (11).

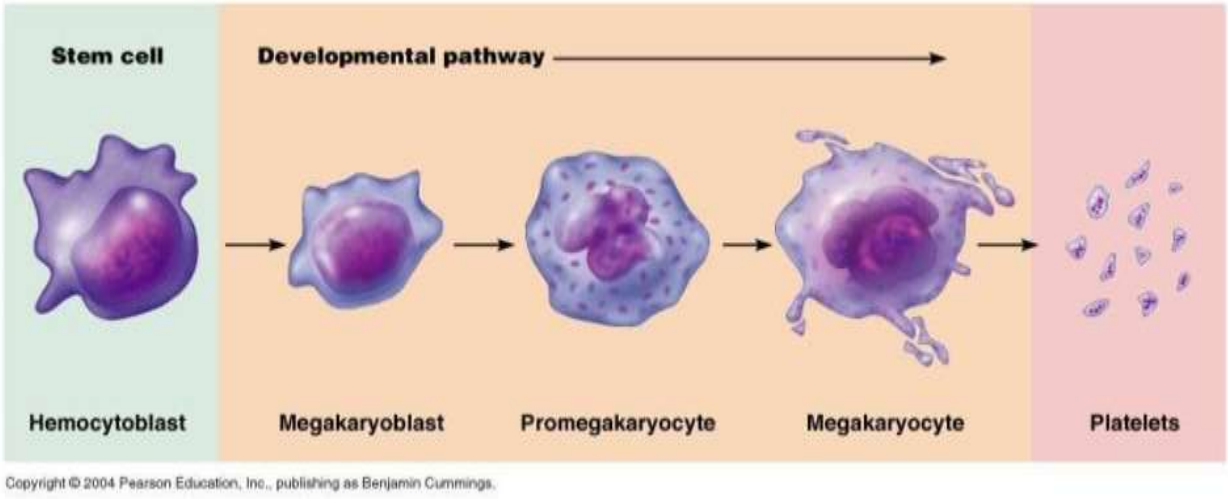

Figure 1. The process of thrombopoesis (quoted from (12))

Platelets that have an un-nucleated structure but have different mitochondria. The plasma membrane of platelets, consisting of a double layer of phospholipids, is the site of expression of various surface receptors and lipids that help in intracellular signaling. Mitochondria produce ATP and can also participate in the regulation of platelet activation responses (8)(9).

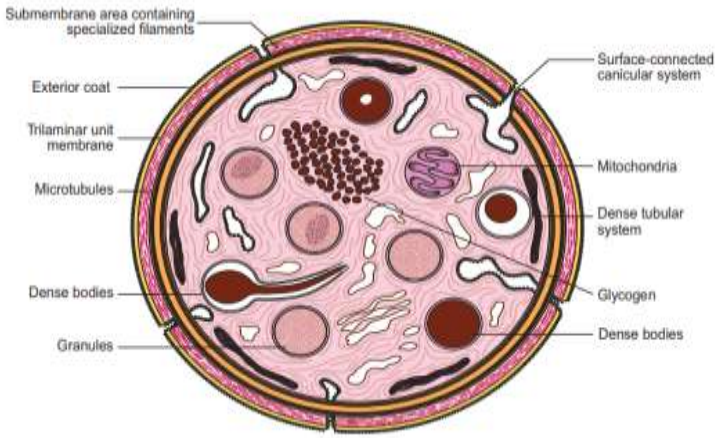

Figure 2. An ultrastructural feature diagram is observed on a thin section of a dispossessed platelet cut on the plane of the equator. (quoted from (13))

The components of the peripheral zone include the outer layer (EC), the membrane of the trilaminar unit (CM) and the submembrane area containing special filaments (SMF) that form the platelet wall and the channel channel of the canaliculi system (CS) connected to the surface. The inner matrix of platelets is a sol-gel zone containing microfilament actin, structural filaments, microtubule roving bands (MT) and glycogen (Gly). Formed elements are embedded in the sol-gel zone including mitochondria (M), granules (G) and Dense bodies (DB). Collectively, they form organelle zones. The membrane system includes the surface of the connected canalicular system (OCS) and the solid tubular system (DTS), which serves as a platelet sarcoplasmic reticulum.

Platelets play an important role in the process of hemostasis. The main function of platelets is to form mechanical plugs on normal hemostasis against vascular injuries. The process of transforming inactive platelets into an active form goes through three steps, namely in the form of adhesion, aggregation and secretion. Although the role of platelets is considered to be limited only to maintaining vascular hemostasis under normal conditions and causing occlusive thrombus in pathological conditions, another potential role for platelets has been studied that is independent of hemostasis or thrombosis. These roles include roles in immunity (8).

After the occurrence of vascular injury, platelets will be activated by the contact of platelets with collagen or vWF. Glycoprotein Ib (GP Ib) on platelet membranes binds von Willebrand (vWF) to initiate the adhesion process in exposed subendotel tissue. The interaction of those subendothelial components (collagen, vWF, fibronectin and laminin) allows platelets to bind to other receptor ligands resulting in static adhesions. After adhesion, platelets become more spherical and accentuate long pseudopodia-pseudopodia to strengthen interactions between adjacent platelets. Platelet aggregation is then achieved through a GP IIb-IIIa bond that binds fibrinogen. This aggregation can be stimulated by the administration of the antibiotic ristosetin, which will stimulate vWF to bind to Ib receptors. Platelet aggregation with ristosetin can be used as an

examination to see the interaction between GP Ib and vWF because aggregation will not occur when both are absent or have a disorder (8).

During the occurrence of platelet stimulation, solid granules and granules release the contents of their granules through an open canaliculi system. The ADP inside the granule will be secreted into the plasma and will improve the process of adhesion and platelet aggregation. Fibrinogen, vWF and coagulation factors will also improve the process of adhesion and platelet aggregation. Phospholipase is also active and will release arachidonic acid from the cell membrane. With the help of cyclooxygenase, arachidonic acid is metabolized into various forms of prostaglandins and thromboxane A2. ThromboxanE A2 is a potent stimulus for platelet aggregation. The coagulation factors secreted during the secretion phase interact not only with platelets but also with the intrinsic coagulation system. Coagulation factors in platelets include fibrinogen, vWF, factor V and factor XIII (8).

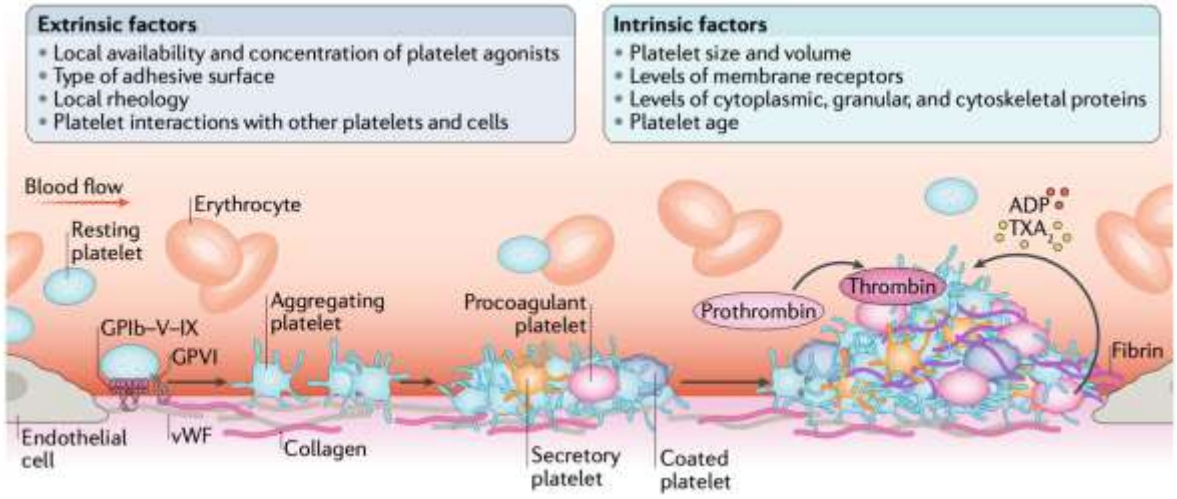

Figure 3. Factors affecting platelet heterogeneity in thrombus (quoted from (14))

Platelets have recently been shown to express Toll-like receptors (TLRs). Furthermore, the pattern of TLR expression was observed to differ by gender. It will be interesting to see how the potential role of platelets in immunity is described in future studies and if platelets play an important role in innate immunity to bacteria, viruses,

or even tumors. To this end, a recent study showed that platelets show the ability to autophagy, However, their role in autophagia in circulation is still unclear. Another related function of the platelets that have recently been proposed is their ability to sample the blood environment. This environmental sampling can be used to hold foreign viruses or bacteria into other immune cells. Finally, platelets are known to release microparticles in a regulated way in the blood. Since more than 95% of microparticles are thought to come from platelets, it is possible that these particles containing genetic material (miRNA, mRNA, etc.), enzymes, proteins, and small molecules, can alter or modulate the functioning of other cells within the blood vessels. This latest study significantly expands the potential role for platelets in the body beyond acting as "bandages" at the site of injury in the endothelium to prevent blood loss. Current and future foci of platelets will help explain their role in regulating physiological and pathophysiological processes (1).

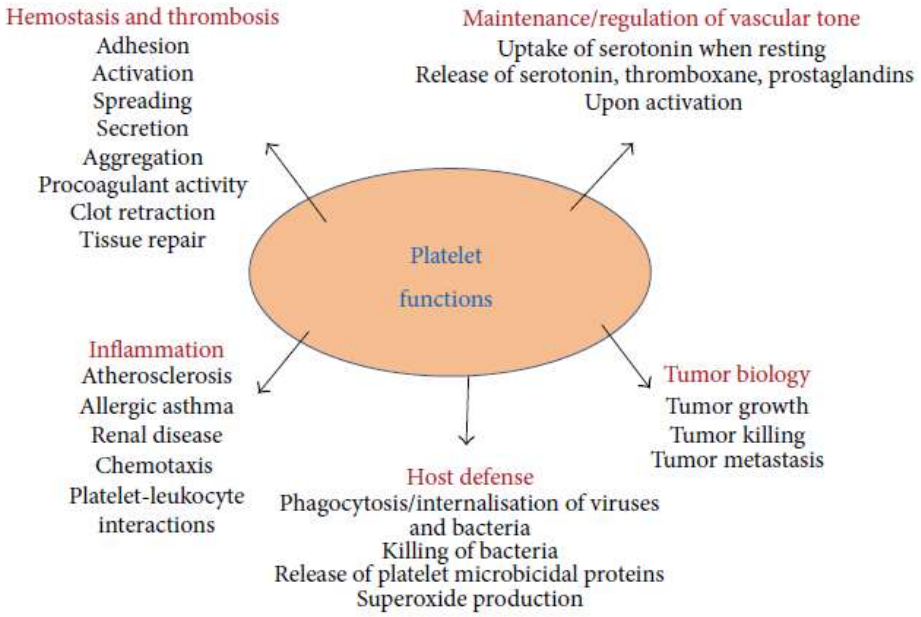

Figure 4. Platelet multifunctionality (quoted from Harrison, 2005).

Reactive Thrombocytosis

Definition

Reactive thrombocytosis is the number of platelets exceeding 2 standard deviations (SD) from the normal calculation of platelets by age, generally occurring temporarily (transiently) due to stimulation of megakaryopoiesis associated with hematological or non-hematological abnormalities. Classification of thrombocytosis: mild (450,000-700,000/mm3), moderate (700,000-900,000/mm3), severe (900,000-1,000,000/mm3), extreme thrombocytosis (>1,000,000/mm3). Thrombocytosis can be considered physiological thrombocytosis up to the age of six. The maximum cut point of thrombocytosis is 650,000/mm3 at the age of two months which will then decrease gradually until adulthood. Based on the underlying abnormality, thrombocytosis is divided into primary (essential) and secondary (reactive) (2)(15).

Tabel 1. Karakteristik dari trombositosis primer dan sekunder pada anak[2]

Kriteria	Trombositosis primer	Trombositosis sekunder
Usia	Jarang pada usia anak	Terbanyak 11 tahun
Insiden per tahun	1/1000.000 anak	> 600/100.000 anak
Lama trombositosis	Bulan, tahun, menetap	Hari, minggu, bulan, sementara
Splenomegali Demam Kelainan perdarahan/trombosis	Selalu Tidak ada Monoclonal TE: sering Familiar thrombocytopenia jarang	Jarang Selalu Sangat jarang
Laboratorium	BT memanjang, PT dan PTT meningkat pada 20%, anti-phospolipid antibodies	Peningkatan VWF, fibrinogen proinflammatory cytokines dan C-reactive protein bila disebabkan infeksi
Jumlah trombosit Morfologi trombosit Fungsi trombosit	Terbanyak >1.000.000mm3 Besar atau kecil, dismorfik Abnormal	<800.000 mm3 Besar, morfologi normal Normal
Bone marrow	Jumlah megakariosit meningkat dengan morfologi abnormal	Jumlah megakariosit meningkat dengan morfologi normal
Mekanisme patogenik	Defek klonal dalam hematopoietik atau progenitor megakariopoietik berkurang ekspresi c-mpl, dan atau hiperreaktif pada Tpo	Produksi Tpo meningkat, atau pelepasan factor pertumbuhan megakariopoietik terutama IL-6

One of the types of thrombocytosis is Spurious thrombocytosis. This condition is often categorized as reactive thrombocytosis because it is often related with the process of occurrence of reactive thrombocytosis. Characteristic of Spurious thrombocytosis is a nonplatelet structure in peripheral blood that is calculated as a platelet on an automatic counting device. Variations in structure include cryoglobulin crystals, cytoplasmic fragments resembling platelets. Peripheral blood evaluation is a simple method to confirm variations in such structures (16).

In a child with reactive thrombocytosis, no thromboembolic complications or bleeding were found. There is no evidence of prophylactic efficacy with anticoagulants or platelet aggregation inhibitors although platelet counts > 1,000,000/mm^3.(2)

Epidemiology

The incidence rate in children is not known for certain but it is estimated to be around 3-15% in children who are hospitalized, while for children who are on road treatment it is estimated to be around 1.5%. Occurs most often in neonates, especially premature ones, as well as infants up to 2 years of age and less in children over 2 years of age. This is due to the high levels of thrombopoietin in newborns especially premature babies and megakaryocytic precursors that are more sensitive to thrombopoietin. Thrombocytosis is more common in boys (61.2%) than girls (38.8%). In children, moderate reactive thrombocytosis is about 6-8%, while extremes are below 2-3%. (2)(17)

The incidence of reactive thrombocytosis depends on the underlying disease. The incidence of reactive thrombocytosis caused by post-splenectomy is 75 – 82%. In patients with iron deficiency anemia about 31% (17).

Etiology

Reactive thrombocytosis is caused by an increase in thrombopoesis due to reactive processes that occur due to the presence of infections, chronic inflammation, malignancy, as well as splenectomy surgery. Bacterial or viral infections are the most common cause (about 37-78%) at any age during childhood. In this group, respiratory infections reach 60-80%, followed by infections of the

gastrointestinal tract and urinary tract. No link was found between thrombocytosis and the prognosis or antibiotic treatment of the infection.(18)(19)

Tabel 2. Penyebab trombositosis reaktif pada anak

Infeksi (Saluran napas, gastrointestinal, sistem saraf pusat, otol, dan lainnya
Anemia defisiensi besi, anemia hemolitik
Perdarahan
Gangguan jaringan konektif (*Juvenile rheumatoid arthritis*, *Wegener's granulomatosis*, Poliartritis nodosa, dan lainnya)
Kawasaki's disease I
Inflammatory bowel diseases
Langerhans cell histiocytosis
Keganasan (Tumor solid seperti hepatoblastoma, karsinoma hepatoseluler, neuroblastoma, jarang pada leukemia limfoblastik akut)
Obat-obatan (adrenalin, kortikosteroid, miconazole, antibiotic, haloperidol, narkotika)
Trauma, luka bakar
Olah raga intens
Splenektomi (pembedahan atau fungsional cth. *Sickle cell anemia*)

Pathomechanism

In the bone marrow, stem cells turn into very large cells called megakaryocytes. Thrombopoetin is a key hormone in the regulation of the differentiation and proliferation of megakaryosites. Megakaryosites form cell fragments known as platelets and each megakaryocyte can produce between 5,000 to 10,000 platelets. The pathophysiology of secondary thrombocytosis may be different, depending on the cause of thrombocytosis. Thrombocytosis is triggered by overproduction of thrombopoietin, interleukin-6, other cytokines or catecholamines in inflammatory, infectious, or neoplastic conditions or in stressful situations (2).

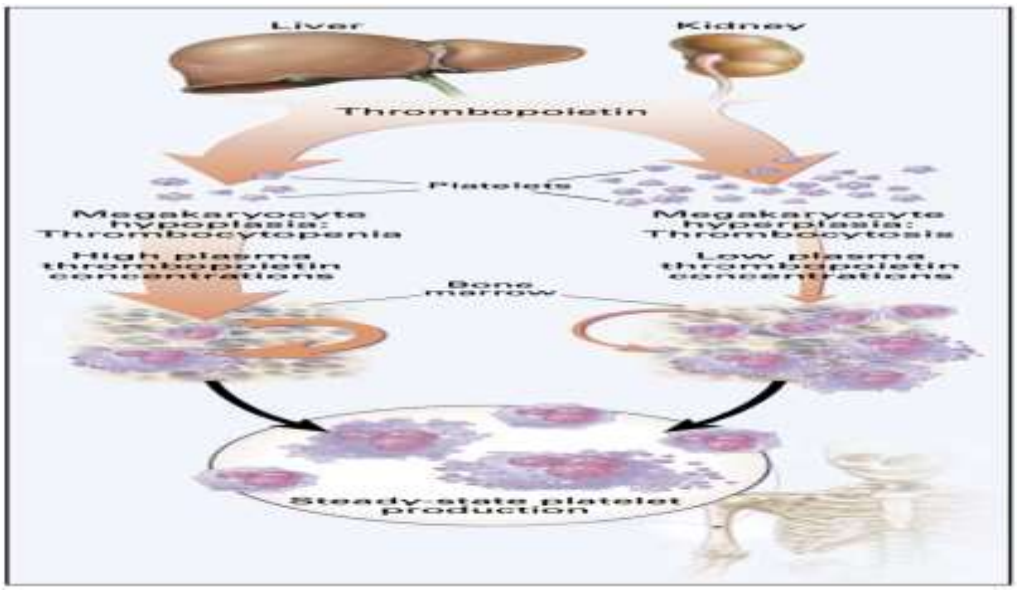

Figure 5. Thrombopoietin Regulatory Model. (quoted from Wood. AJ, 2015)

The liver and kidneys produce thrombopoietin constitutively and release it into the circulation. Platelets have receptors for thrombopoietin and excrete them from the plasma. In the state of thrombocytopenia (indicated in the pathway on the left), a small amount of the released thrombopoietin is metabolized, and the resulting high concentration of plasma thrombopoietin stimulates the hypoplastic marrow. In addition, the marrow stroma produces thrombopoietin during thrombocytopenia (curved arrow, left). High concentrations of plasma thrombopoietin help restore megakaryosites and platelet production. On the contrary, during thrombocytosis (indicated on the path on the right), a high platelet count removes most of the thrombopoietin from circulation, and the production of marrow stromal cells almost stops; as a result, a small amount of thrombopoietin is left to work on many megakaryocytes in the marrow (curved arrow, right), allowing it to return to stable platelet production.

Thrombocytosis is a consequence of three mechanisms namely:(20)

a. Lengthening of the life span of platelets of more than 10 days
b. Decreased or no platelet pooling due to hyposplenism or post-splenectomy
c. Increased platelet production

In reactive thrombocytosis, the mechanism that plays the most role is increased platelet production which is associated with increased levels of Thrombopoietic growth factors including Thrombopoietin (Tpo) and interleukin-6 (IL-6). In rare cases of familial thrombocytosis, a Tpo gene mutation occurs, which causes excessive production of Tpo and the mutase of the Tpo receptor gene will cause activation.(20)

Interleukin-6 plays a major role in the pathogenesis of reactive thrombocytosis, due to its prominent role in the response to the acute phase of inflammatory and neoplastic diseases. IL-6 stimulates megakaryopoiesis both directly and indirectly by stimulating the production of Tpo in the liver.(20)

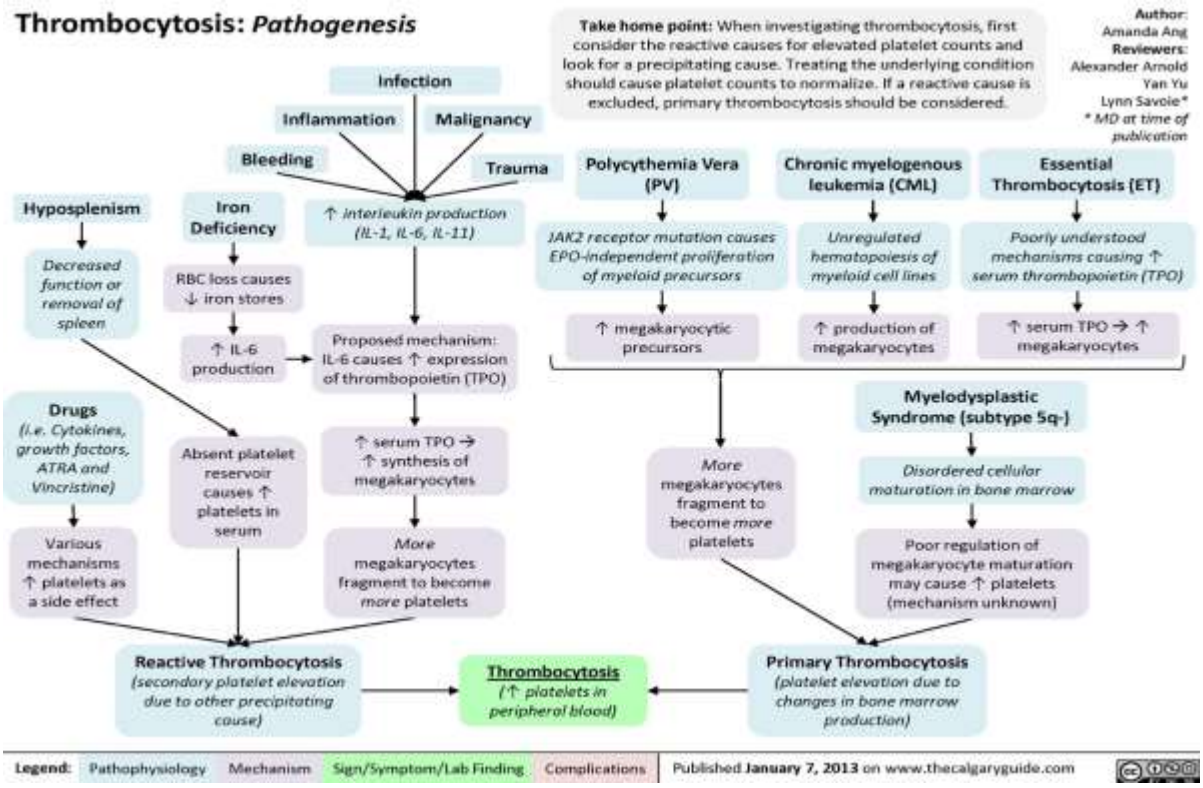

Figure 6. Pathogenesis of various causes of Thrombocytosis quoted from (21))

a) Thrombocytosis in infectious and inflammatory

The most common infection associated with thrombocytosis is pneumonia. Vlacha and Feketea described 102 children treated with a diagnosis of lower respiratory tract infection; 49 of these children (average age 31 months) there was an increase in platelet count by more than 500,000/mm^3.(22)

Platelets have a clear role in the inflammatory response and immune regulation, this is based on the characteristics of platelets, among others, being able to bind to pathogenic bacteria, secrete various cytokines and immunoregulator chemokines, and express receptors for various immune effects and regulatory functions. One of the basic mechanisms of secondary thrombocytosis is the upregulation of TPO expression thereby increasing TPO levels. Hepatic mRNA TPO expression increases as a result of inflammation. Interleukin-6 (IL-6) is elevated in various inflammatory conditions and is associated with increased plasma TPO levels and mRNA TPO expression.(6)(23)

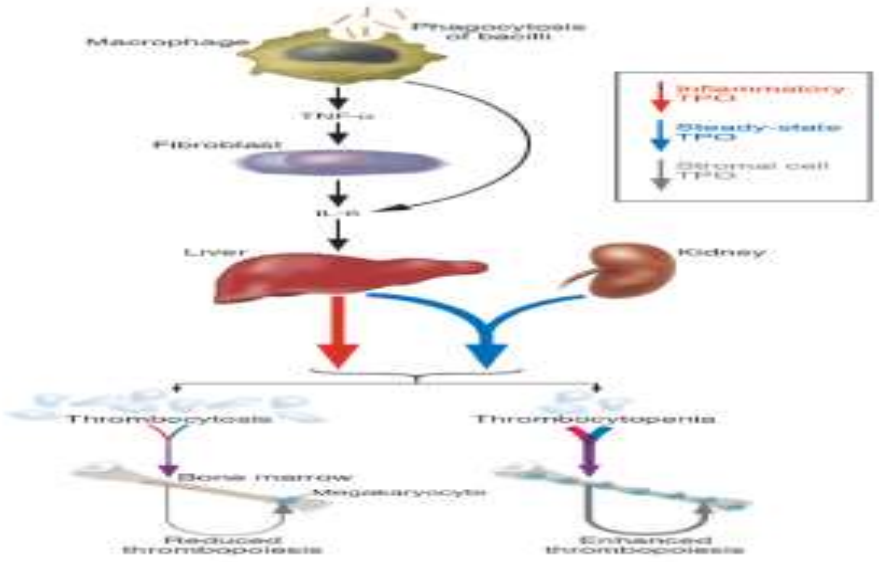

Figure 7. Regulation of thrombopoietin levels.

Sufficient amounts are regulated by the c-Mpl receptor which regulates hormone uptake and digestion. In inflammatory conditions, IL-6 is released by macrophages and stimulates TNF-α and circulates to the liver to increase thrombopietin production (24).

b) Thrombocytosis in Iron Deficiency Anemia

Iron deficiency is the most frequent cause of reactive thrombocytosis. The pathophysiology of thrombocytosis in iron deficiency anemia, although it is not fully understood. Rayko Evstatiev et al, mentioned the occurrence of thrombocytosis does not seem to be due to an increase in cytokines (IL-6, IL-11, and TPO). The level of these cytokines is similar to that of iron-deficient patients without thrombocytosis, and no changes have been observed in the fulfillment of iron. Thrombocytosis is due to the presence of stimulation of platelet production by an increase in the concentration of erythropoietin, which occurs in patients with ADB. (7)(25) (26).

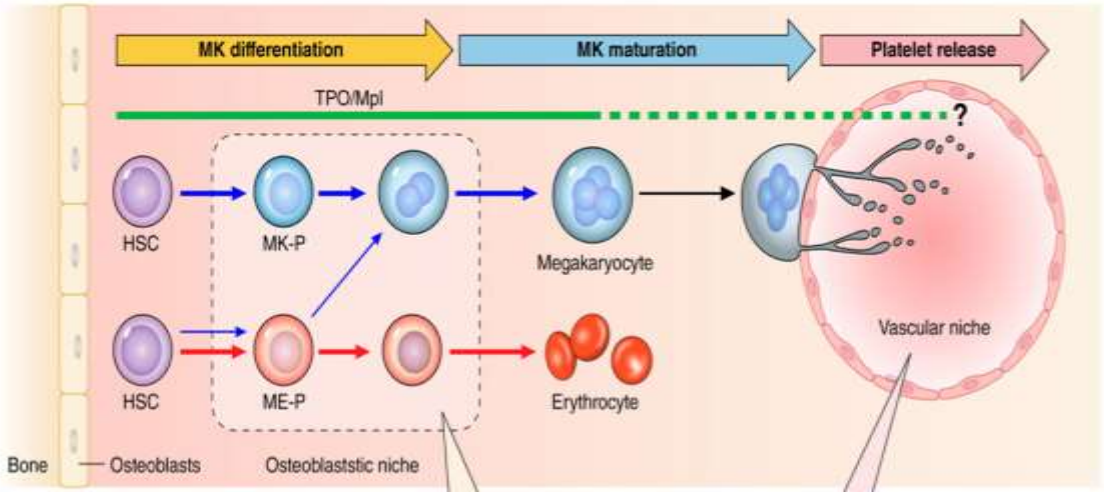

Figure 8. Pathways of erythropoesis and thrombopoesis (quoted from Eto.K, 2016)

c) Thrombocytosis in hyposensitism (post-splenectomy)

Lien is the main place of platelet destruction so thrombocytosis is often found in patients with hyposplenism or post-splenectomy. Post-splenectomy reactive thrombocytosis has an incidence of about 75% to 82%. Platelet counts will increase

and peak at one to three weeks and return to normal numbers in a matter of weeks, months, and sparsely in a matter of years (27).

d) Thrombosistosis due to drugs

Medications are a rare cause of reactive thrombocytosis. Many studies have found that LMWHs (Low Molecular Weight Heparins) and neonatal drugs withdrawal syndrome are the most frequent causes of reactive thrombocytosis. Thrombocytosis in neonatal drugs withdrawal syndrome is suspected to rebound megakaryopoeisis after suppressing fetal Tpo production due to intrauterine exposure to methadone, hydratoin, or psychopharmaceutical drugs. Epinephrine can increase platelets but rarely reaches the threshold of thrombocytosis. Antibiotics can cause platelet increases but sometimes overlap with acute-phase reactants caused by infections. The mechanism of thrombocytosis by gemcitabine is still less pronounced, considered the rebound effect of chemotherapy that compresses the bone marrow (19).

Corticosteroids have the effect of transient thrombocytosis by releasing platelets stored in the lien into the circulation. In ITP patients, megakaryopoiesis accelerates in response to the destruction of immune system-mediated platelets, so that, during treatment, platelet overproduction occurs as a compensatory mechanism (28).

Symptoms of the clinic

Reactive thrombocytosis has no physically visible or perceived symptoms, usually found incidentally. Symptoms of the underlying condition usually predominate. However, there is no clear correlation between symptoms and platelet count. Therefore, it is necessary to check the blood regularly to find out the number of platelets from the spinal cord. The high number of platelets can be an indication of thrombocytosis (29).

The risk of thromboembolism complications is low and rare in reactive thrombocytosis, even in patients with extreme reactive thrombocytosis, unless it is triggered by an underlying condition such as malignancy or atherosclerosis (7).

Diagnosis

Anamnesis and a thorough examination should identify the most

common reactive causes of thrombocytosis: underlying infections, chronic diseases, malignancies, anemia, previous splenectomies, or recent operations. The British Society for Hematology guidelines for the investigation of thrombocytosis recommend three preliminary investigations: (29)

Peripheral blood smear

In reactive thrombocytosis caused by infection or inflammation, platelet size is usually normal, while in thrombocytosis due to myeloproliferative abnormalities (essential thrombosistosis, polycythemia vera, or chronic myelocytic leukemia) platelet sizes are usually large (>4 nm) and there are some giant platelets (30).

Careful clinicalopathological correlation often identifies the cause of secondary thrombocytosis, and a bone marrow biopsy is usually not required. However, if a bone marrow evaluation is performed, a bone marrow biopsy often shows normal cellularity (7)

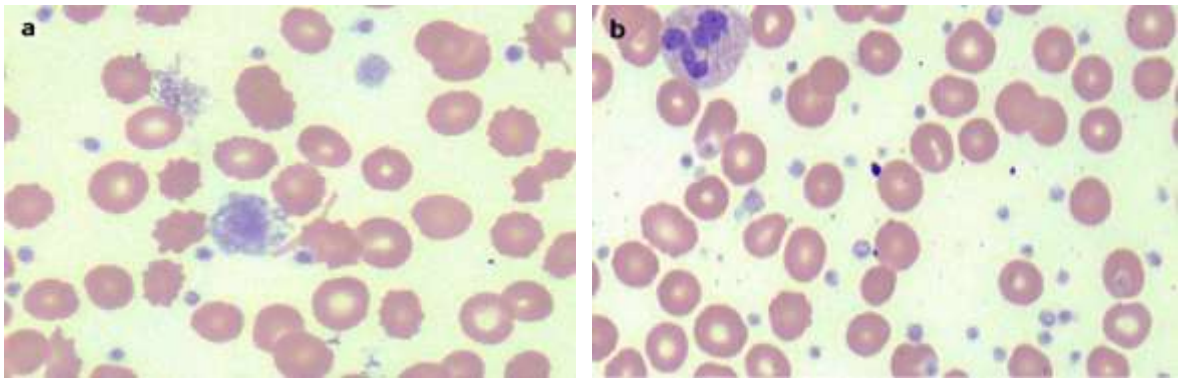

Figure 9. Peripheral blood smears (a) Very large platelets in myeloproliferative neoplasms, (b) Platelets appear normal in reactive platelets

(quoted from (29))

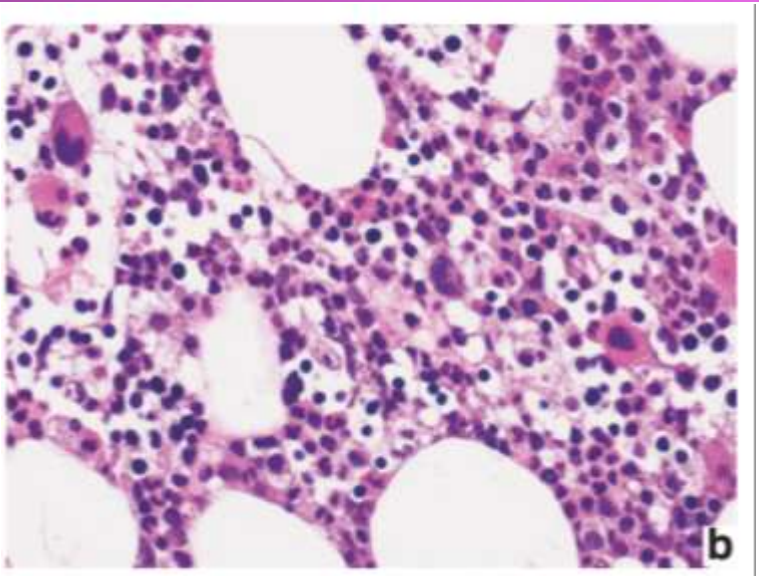

Figure 10. Bone marrow aspiration results show normocular.

(quoted from (7))

Inflammatory markers

Elevated inflammatory markers such as c-reactive proteins or erythrocyte sedimentation rates favor the diagnosis of reactive thrombocytosis, although normal values do not rule out inflammation or malignancy. Similarly, increased levels do not rule out possible clonal causes (29).

Iron status

Iron deficiency anemia (ADB), causing microcytic anemia, occurs at about 2% to 5%. It is a potentially treatable cause of reactive thrombocytosis. Low serum ferritin confirms ADB with a specificity close to 100%. However, the interpretation of iron studies can be complicated by concomitant inflammation that increases ferritin levels; another way to determine iron status may be required. If ADB has been confirmed, the management is carried out according to standard guidelines (29).

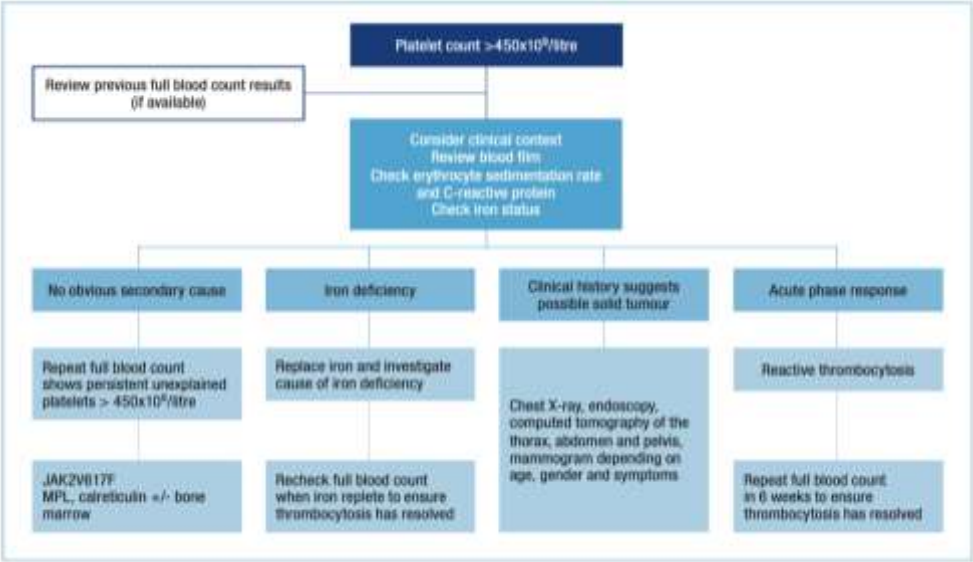

Figure 11. Algorithm in the investigation of patients with thrombocytosis (31)

Governance

The management of reactive thrombocytosis is to address the main causes. Platelet counts usually return to normal after the underlying disease is resolved. In recurrent thrombosistosis with platelet levels of >1,000,000/mm3 can be considered a low dose of aspirin 65 mg /day to curate platelet aggregation and platelet count, to minimize stroke or thrombosis (2).

Blood re-examination can be requested based on clinical assessment to check for any improvement or persistent thrombocytosis. If the cause is suspected to be reactive thrombocytosis, retesting should be carried out to ensure the thrombocytosis has been resolved after proper management. There is no standard definition for "persistent thrombocytosis", but for practical purposes it can be defined that thrombocytosis occurs for more than three months from the initial assessment (29).

Anagrelide is the latest approved platelet-lowering agent in patients with essential thrombocytosis. Research conducted by Harrison et al on the administration of hydroxyurea combined with aspirin compared to anagrelide and aspirin, showed that hydroxyurea is better than anagrelide in reducing the risk of arteriole thrombosis, bleeding and myelofibrosis transformation. However, hydroxurea has a higher risk of venous thrombosis than anagrelide. But the use of

hydroxyurea should be monitored for the transformation of leukemia (27).

Reactive thrombocytosis in children does not justify general prophylaxis with anticoagulants or inhibitors of platelet aggregation, even if the platelet count >1,000,000/mm3. There is no evidence of prophylactic efficacy against thromboembolic complications in asymptomatic children with reactive thrombosistosis. Individually adjusted thrombosis prophylaxis should be considered if there are additional thrombotic risk factors. Treatment should be targeted at the underlying disease (e.g. iron deficiency) not at platelet count. It is indicated only if thrombosis occurs repeatedly, a reduction in platelet aggregation and platelet count can be given (19).

CONCLUSION

Thrombocytosis is a condition of platelet count abnormalities that we often encounter in daily practice both inpatient and outpatient. Secondary thrombocytosis is the most common type and is usually identified in routine laboratory results and has symptoms that are asymptomatic. Patients with acute infections mostly develop mild thrombostosis and are temporary, as well as show no complications. However, patients may experience an increase in acute phase response, a lengthening of hospitalization, and more bacteremia. Secondary thrombocytosis (reactive thrombocytosis) is treated by curing the underlying causative condition.

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REFERENCES

1. Holinstat, M. Normal platelet function. Cancer and Metastasis Reviews. 2017;
2. Lubis. B. Trombositosis. Buku Ajar Hematologi Onkologi Anak. Edisi Revisi. Jakarta: Hal: 183-7. 2018;
3. Aswad Y. Darah Pendierita Hipertensi Di Panti Wirda Ilomata Effect of Considered Imagination on Blood Pressure Hypertension Patients at Wirda Ilomata retirement home. 2019;1(1):7–12.
4. Rokkam VR KR. Secondary

Thrombocytosis. [Updated 2021 Aug 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. 2022;

5. Kaufman RM AK. Abnormalities of Platelets and Platelet Support. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003. Available from: https://www.ncbi.nlm.nih.gov/books/NBK12971/. 2003;
6. Kucine N, Chastain KM, Mahler MB BJ. Primary thrombocytosis in children. Haematologica. 2014;99(4):620-628. doi:10.3324/haematol.2013.092684. 2014;
7. Thakral, B., Wang, S.A. Thrombocytosis, in: Diagnosis of Blood and Bone Marrow Disorders. Springer International Publishing, pp. 225–242. 2018;
8. Arbi. F. Gangguan Fungsi Trombosit. Buku Ajar Hematologi Onkologi Anak. Edisi Revisi. Jakarta: 2018. Hal: 173-5. 2018.
9. Ghoshal, K., Bhattacharyya, M. Overview of platelet physiology: Its hemostatic and nonhemostatic role in disease pathogenesis. The Scientific World Journal. 2014;
10. Lefrançais, E., Looney, M.R. Platelet biogenesis in the lung circulation. Physiology. 2019;
11. Patel SR, Hartwig JH IJJ. The biogenesis of platelets from megakaryocyte Mathur, A., Samaranayake, S., Storrar, N.P.F., Vickers, M.A., 2019. The BMJ 366. 2019;
12. Tallitsch RB, Frederic M MJT. Human anatomy(5th ed.). San Francisco: Pearson/Benjamin Cummings. p. 529. ISBN 978-0-8053-7211-3.
13. White JG. Disorders Affecting Megakaryocytes and Platelets. Inherited Conditions. Second Edition. Elsevier Ltd; 2011. doi:10.1016/B978-0-7020-3147-2.00032-8. 2011;
14. van der Meijden, P.E.J., Heemskerk, J.W.M. Platelet biology and functions: new concepts and clinical

perspectives. Nature Reviews Cardiology. 2019;

15. Stockklausner C, Duffert CM, Cario H, Knöfler R, Streif W KA. Thrombocytosis in children and adolescents—classification, diagnostic approach, and clinical management. Ann Hematol. 2021;100(7):1647-1665. 2021;
16. Bleeker, J.S., Hogan, W.J. Thrombosis 2011, 1–16. 2011.
17. Jaishankar D SP. Secondary Thrombocytosis [internet]. Medsape. 2020. [Cited 19th March 2022]. Available from https://emedicine.medscape.com/article/206811-overview#a2. 2022;
18. Mantadakis, E., Tsalkidis, A., & Chatzimichael A. Thrombocytosis in childhood. Indian pediatrics, 45(8), 669–677. 2008.
19. Dame, C., Sutor, A.H. Primary and secondary thrombocytosis in childhood. British Journal of Haematology. 2005;
20. Scharf, R.E. Do we need antiplatelet therapy in thrombocytosis? Contra: Proposal for an individualized risk-adapted treatment. Hamostaseologie. 2016;
21. Ang A AA. Pathogenesis of Thrombocytosis. The Calgary Guide to Understanding Disease. [Internet]. Calgaryguide. 2013. [Cited 19th March 2022]. Available from https://calgaryguide.ucalgary.ca/pathogenesis-of-thrombocytosis/. 2022;
22. Inoue S. Pediatric Thrombocytosis [internet]. Medscape. [Cited 19th March 2022]. Available from https://emedicine.medscape.com/article/206811-overview. 2020;
23. Chen, Y., Zhong, H., Zhao, Y., Luo, X., Gao, W. Role of platelet biomarkers in inflammatory response. Biomarker Research. 2020;
24. Kaushansky, K. The molecular mechanisms that control thrombopoiesis. Journal of Clinical Investigation. 2005;
25. Evstatiev, R., Bukaty, A., Jimenez, K., Kulnigg-Dabsch, S., Surman, L., Schmid, W., Eferl, R., Lippert, K., Scheiber-Mojdehkar, B., Michael Kvasnicka, H., Khare, V., Gasche, C. American Journal of Hematology 89,

524–529. 2014.

26. Akkermans, M.D., Uijterschout, L., Vloemans, J., Teunisse, P.P., Hudig, F., Bubbers, S., Verbruggen, S., Veldhorst, M., de Leeuw, T.G., van Goudoever, J.B., Brus, F. Pediatric Hematology and Oncology 32, 624–632. 2015.
27. Khan, P., Nair, R., Olivares, J., Tingle, L., Li, Z. Baylor University Medical Center Proceedings 22, 294–294. 2009;
28. Sarangi R, Pradhan S, Dhanawat A, Patanayak R BG. Thrombocytosis in children: Clinico-hematological profile from a single centre in Eastern India. J Lab Physicians. 2018;10(01):034-037. doi:10.4103/jlp.jlp_90_17. 2018;
29. Mathur, A., Samaranayake, S., Storrar, N.P.F., Vickers, M.A. The BMJ 366. 2019;
30. Gunawan.S. Intepretasi Darah Tepi. Buku Ajar Hematologi Onkologi Anak. Edisi Revisi. Jakarta: 2018. Hal: 439-40. 2018;
31. Appleby. N. Clinical and laboratory assessment of a patient with thrombocytosis. British Journal of Hospital Medicine 2017 78:10, 558-564. 2017;