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Demography of Characteristic and Prognostic Variables in Newly Diagnosed Children with ImmuneThrombocytopenia Benghazi Children Hospital 2000-2008

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In the name of God most Gracious and most merciful

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Abbreviations

- Ab : Antibody
- ADP : Adenosine diphosphate
- Ag : Antigen
- ANC : Absolute Neutrophil Count
- APC : Antigen Presenting Cell
- ASH : American Society of Haematology
- ATP : Adenosine triphosphate
- BMA: Bone Marrow Aspiration
- C3 : Complement 3
- C4 : Complement 4
- CBC : Complete blood Count
- CD34: Clusters of Determinte34
- CD40:Clusters of Determinte40
- CD154 : Clusters of Determinte154
- CD52 : Clusters of Determinte52
- CD20 : Clusters of Determinte20
- Cs : Corticosteroids
- EDTA : Ethylene Diamine Tetra acetic Acid
- FcR : Fragmented cell Receptors
- FDA : Food Drug Administration
- GPIIb : glycoprotein IIb
- GPIIIa : glycoprotein IIIa
- H Pylori : Helicobacter Pylori

- HLA-DR: Human Leukocyte Antigen DR
- I.V : Intra venous route
- ICH : Intracranial Hemorrhage
- IFN : Interferon
- IgG : Immunoglobulin G
- IL10 : Inter Leukine10
- IL2 : Inter Leukine 2
- ITP : Idiopathic thrombocytopenic purpura
- IVIG : Intravenous Immunoglobulin
- MAIPA: Monoclonal Antibody Specific Immobilization of Platelet Antigen
- MGDF: Megakaryocyte Derived Growth Factor
- MHC II : Major Histocompatibility II
- MMR : Mumps Measles Rubella
- MP : Methyl Prednisolone
- MPV: Mean Platelet Volume
- PDGF: Platelet d Derived Growth Factor
- URTI : Upper Respiratory Tract Infection
- WBC : White Blood Count
- TPO : Thrombopoietin
- TCR : Thymus Cell Receptor
- Th cell : Thymus helper cells
- VWF : Von Will brand Factor

v Abstract

Background: Idiopathic thrombocytopenic purpura (ITP) in children is usually a benign and self-limiting disorder. It may follow a viral infection or immunization and caused by an inappropriate response of the immune system. The diagnosis relies on exclusion of other causes of thrombocytopenia.

Objective :To determine the epidemiological, clinical features for ITP children and risk factors for chronic immune thrombocytopenia.

Setting : The medical department and hematology clinic at Benghazi Children Hospital between January-2000 and December- 2008 .

Patients and methods : One hundred eighty two files were analyzed, of this files were excluded because data were incomplete, 20 of them involved in incidence of Benghazi city, 155 were analyzed for residence, age, sex, date of diagnosis, clinical and laboratory features at time of diagnosis, modality of treatment, result of treatment and outcome. The prediction for prognostic parameters for chronic ITP at diagnosis were studied, age, sex, type of bleeding, platelet count, Mean platelet Volume values and treatment.

Results: Most cases were from Benghazi 123(79.3%), the average annual estimated incidence in Benghazi city is 5.6/100,000/year. Eighty two(52.9%) male, male : female ratio 1.1:1, in acute ITP M:F ratio 1.3:1 , in chronic F: M ratio 2.6:1, mean age:5.4 years, range5 months-14 years, most of children with acute ITP were in the 1-4 years age group, most of cases in Spring and Summer, some of them 61 (39,4%) had history of upper respiratory tract infection 1 to 2 weeks before symptoms. One hundred fifty two (98%) presented with ecchymosis and petechiae, 26(16.8%) epistaxis, 14(9%)gum bleeding, 7(4.5%)haematuria, 3(1.9%)dark stool, 1(0.65%)rectal bleeding.

The mean platelet count was 26x10^9/L, rang (0-123), with mean platelet volume (MPV) was 9.7fl, 131 (84.5%) of children presented with platelet count under 50x10^9/L, 91 (58%) presented with platelet count under 20x10^9/L, 45(29%) with platelet count < 10 x10^9/L.

Twenty five(16%) of patients with platelet above 20x10^9/Lwithout mucosal bleeding were managed with observation, Intravenous immunoglobulin(IVIG) given to 85(54.8%) and steroid alone to 38 (24.5%) combined of steroids and IVIG given to 7(4.5%) patients with severe mucocutaneous bleeding, two patients received blood transfusion, one patient received platelet transfusion, two patients underwent splenectomy, one patient received anti CD20(Rituximab), no patient died , no patient had ICH.

One hundred thirty three(85.8%) have recovery within 6 months of diagnosis 22(14.2%) went to chronic ITP .

We found female patients, age more than 6years and MPV more than 8fL values are powerful predictors for chronic ITP, whereas platelet count at time of diagnosis, type of bleeding, history of upper respiratory tract infection and the drug treatment do not seem to alter the clinical course of the disease.

Conclusion : ITP is a generally benign disease in infancy and childhood. This study highlights the situations ITP in Libya and may help in establishing guidelines for the investigation and management of ITP in our children .The study finding are in line with other international reports . Certain characteristic of ITP in this series, such as seasonal variation viral infection, bacterial infection and post vaccine ITP to be defined in prospective studies.

Chapter I

Introduction

IMMUNE THROMBOCYTOPENIC PURPURA

Immune thrombocytopenic purpura (ITP) in children is usually a self limiting disorder,the American Society of Hematology in 1996 defined ITP as isolated thrombocytopenia with no clinically apparent associated conditions and no other cause of thrombocytopenia e.g human immunodeficiency virus infection, systemic lupus erythematous,lymphoproliferativedisorder,myelodysplasia,agammaglobulinemia, drug inducedthrombocytopenia,alloimmunethrombocytopeniaandcogenital/hereditary nonimmue thrombocytopenia**(George et al,1996) (Abdull Rehman, 2007)**.

The other terms used for ITP are idiopathic thrombocytopenic purpura, autoimmune hematologic disorder, and most recently immune thrombocytopenia, which nonetheless has a complex pathophysiology and clinical course **(Rodeghiero et al, 2009).** The definition of chronic ITP starts after the disease has been present for more than six months, children with ITP 75-90% have an acute transient bleeding episodes that resolve within a few days or within six months **(Ramosetal,1978)(Di Paola&Buchanan, 2002)**

(Dickerhoff& VonRuecker,2000)(Isam Haddadin, 2005).

ITP can be separated, pathophysiologically, into:

Primary ITP: no other disorder can be identified.

Secondary ITP: associated with various diseases, such as infections, autoimmune disorder, malignancies and certain drugs**(Andreas et al, 2010)**.

Recently, an international working group in October,2007 has suggested new definitions of the clinical phases of ITP based on time since diagnosis **:**

Newly diagnosed ITP, occurs within 3 months from diagnosis

Persistent ITP, occurs between 3 to 12 months from diagnosis

Chronic ITP, thrombocytopenia more than 12 months.

(Rodeghiero et al, 2009).

Although ITP is known to be caused by autoantiplatelet antibody, the aetiology of the autoimmune disease remain mysterious, numerous immunological studies have not yet clarified why certain people create antiplatelet antibodies and develop ITP, whereas the great majority do not, among patient who develop ITP certain patient have more benign course, whereas others refractory life threatening **(April et al, 2006)**.

v 1-1-Historical review

In 1735, Werlhof described a bleeding disorder which he called morbusmaculoushemorrhagicus**(Jones&Tocantins,1933)**.

In 1883, Krauss observed decreased platelets and in 1890 Hayem performed the first platelet count and found a low number of platelets in disease**(Imbach,2006).**

The first splenectomy in ITP was successfully performed in Prague in 1916 **(Kasnelson et al, 1916)**, subsequently splenectomy became the main treatment of chronic ITP despite a lack of knowledge, this concerning the pathophysiologic role of the splenic disorder.

Since 1950 there has been increasing clinical evidence for an immune pathogenic mechanism of ITP, in 1951Harrington etal, observed that newborns of mothers with chronic ITP often had a transient decrease in their platelet count,suggesting the transfer of a humeral antiplatelet factor from the mother to her baby, Harrington developed a classical transient ITP after self administration of plasma from a patient with ITP as did other volunteer later**(Harrington&Minnich,1951) (Harrington et al, 1953**).

Shulman *et al,* showed that the thrombocytopenic factor was associated with the 75 IgG fraction of ITP plasma and importantly that this factor bind to autologous as well as homologous platelets**(Shulman et al, 1965)**.

Since 1975, laboratory techniques have demonstrated elevated platelets associated IgG in the majority of patient with thrombocytopenia **(Dixon Rosse,1975)**

In 1980, Imbach et al observed that the intravenous administration of intact 75 IgG fractionated and pooled from single blood donors raises the platelet count in patient with acute and chronic ITP **(Imbach et al, 1981)**, two years later Salam*a etal*, described the use of anti-D immunoglobulin in ITP **(Salama et al, 1983)**.

In 1982 Van Leeuwen*etal*, provided the first evidence of autoantibodies in chronic ITP they reported that 32of 42 elutes from ITP platelets would bind to normal but not to thrombasthenic platelet,since the latter platelet are deficient in glycoprotein GPIIb and IIIa, they postulated that ITP patients have autoantibodies to one of these glycoproteins. **(Van leeuwen et al, 1982)**.

In1987 two assays were developed that can detect both platelet associated and free plasmic autoantibodies, the immunobead assay **(McMillan et al, 1987**) and the monoclonal antibody specific immobilization of platelet antigen (MAIPA) assay **(Kiefel et al, 1987)**.

In 1991 Semple and Freedman documented that chronic ITP was associated with a CD4T-helper cell defect in which peripheral blood T cell secrete interleukin IL-2 on stimulation with autologous platelets **(Semple& Freedman,1991)**.

In 2000-2001the role of phagocytosis and fc receptors in ITP was elucidated by the group of Ravetch**(Ravetch& Lanier, 2000)(Samuelson et al, 2001)**.

v 1-2-Incidence

ITP is diagnosed more frequently than any other form of destructive thrombocytopenia, in its acute form affects mostly children, while the chronic form is frequently seen in young adult by all studies.

An average estimate of incidence of ITP in children in united states is 50 cases per 1,000,000/year**(Fogarty &segal, 2007)** ,North American studies report an estimated incidence of 7.2-9.5/100,000 children between 1and 14 years of age**(Philip, 2011)** and according to other studies in Denmark and England occurs in approximately10-40cases per1,000,000/year **(Michael, 2009)**.

In Qatar, the incidence was 72 cases per1,000,000/year **(Naima*et al,*2009)**another study in Kuwait showed a higher incidence of ITP in the world 125 cases per 1,000,000/year **(Mohamed Zaki et al, 1990**).

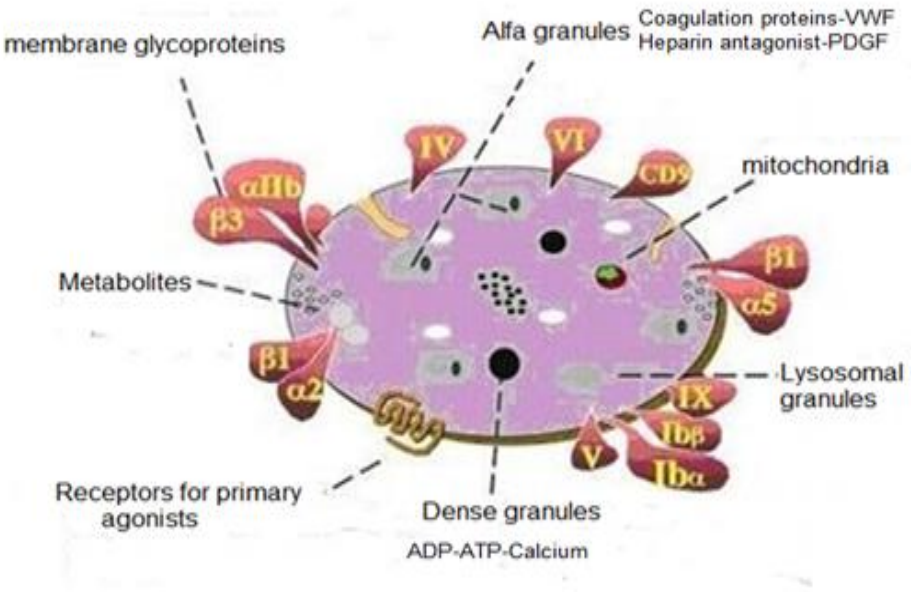
A **prospective** study documented a higher rate of acute ITP in boys than girls (54.8% vs 45.2%) on all continent worldwide(**Kuhne et al, 2001**).

The male/female ratio was highest in infant and decreased with age **(Kuhne *et al,* 2003)** another study was considered acute ITP in children is equally distributed between males (52%) and females (48%) with peak occurrence is between 2 and 4 years of age **(Ahn&Horstman, 2002)**(**Michael, 2009) (Naima et al, 2009)**.

Data from Maryland showed incidence of ITP in 1-4 years age group as 9.3, 6-11 years age group as 7.3 and 11-14 years as 4.1 per 100,000 people and there was a predominance of males in childhood ITP**(Segal *& power,* 2006**).

v 1-3-Pathophysiology

Platelets are small disc shaped cells without nucleus normally measuring 3x0.5µm in diameterwith a mean volume about 7-11fl, the mean platelet count in normal children is $250x10^9$/L, usuallyranging from 150-$400x10^9$/L, and the normal life span is 7-10 days**(A.V.Hoffbrandet al, 2006)**.Platelets are derived from the cytoplasm of megakaryocyte, primarily located in bone morrow, with membrane overlying glycocalyx and sub membrane structure, mediate response to platelet stimulation and express specific antigenic characteristic, major examples of these components include the surface and transmembrane glycoproteins, membrane adenylatecyclase,lipoproteins,surface glycoproteins variously serve as receptors, facilate platelet adhesion, contraction and determine expression of specific platelets antigen **(Denis et al, 1999)**.The composition of membrane system of platelet is thought to be different from external membrane of megakaryocyte, this finding could contribute to an explanation of paradox in ITP, patients have circulating antiplatelet antibodies and large number of marrow megakaryocyte.The platelet contains three types of storage granules : dense granules, alpha granules and lysosomes. The more frequent specific alpha granules contain a heparin antagonist , platelet derived growth factor(PDGF), fibrinogen, von willebrand factor and other clotting factors.Dense granules are less common and contain adenosine diphosphate(ADP), adenosine triphosphate(ATP), 5-hydroxytryptamine(5-HT) and calcium, lysosomes contain hydrolytic enzymes**(Figure1).**



Fig(1)Ultrastructure of platelet

htt://www.newjersysportsmedicin.com/treatment/platelet-rich-plasma.html

Thrombopoietin is the major regulator of platelet production and is constitutively produced by the liver and kidneys, the time interval from differentiation of the human stem cell to the production of platelets averages approximately 10 days **(A.V.Hoffbrand et al, 2006) .**

ITP is a heterogeneous disease with a complex pathogenesis,the pathogenesis of acute ITP is regarded as consequence of inappropriate immune recovery after an infection, circulating antigen or antibody may alter the platelet membrane, it has been proposed that acute ITP may be due to across reactive immune response directed against an infectious agent **(Kaplan et al, 1992)**,the pathogenesis of chronic ITP is attributed to autoantibodies directed against platelet constituents such as glycoproteins.

Mechanisms of pathogenesis

v Antibody mediated destruction

The most commonly identified antigenic targets of the platelet autoantibodies in ITP are GPIIb/IIIa and GPIb/IX, and a number of ITP patients have circulating or platelet bound antibodies directed to multiple platelet antigens**(Mc Millan,1987**) **(Mc Millan,1990) (Kiefel et al,1991)**. Assays for antiplatelet antibodies have not proven to be pathognomonic tests for a diagnosis of ITP, and their routine use has not been recommended by practice guidelines**(Provan et al, 2010) (George et al,1996)**.However, some glycoprotein specific antigen capture assays have demonstrated superior sensitivity and specificity and may be useful to support a diagnosis of ITP in cases with atypical presentation or clinical course**(Berchtold et al,1997**).The presence of antiplatelet glycoprotein antibodies has also been shown to correlate with a need for more intensive therapy**(Fabris et al, 2004)**.

v Platelet Phagocytosis The rapid destruction of platelets are due to either autoantibodies that bind via the antigenic site or immune complexes that bind via FcR on platelets, opsonized cells are rapidly removed by cells of mononuclear phagocytic system

(Figure2). Phagocytosis of platelets has been demonstrated by on vivo studies using blockade with monoclonal anti-FcR antibodies (**Clarkson et al, 1986**).Human macrophages express several Fc receptors that bind IgG specifically**(Crow etal,2001),**engagement of FcγRIIA on the surface of human macrophages by anti GPIIb/III coated platelets, triggers intracellular signaling through the tyrosine kinase, that leads to engulfment of the opsonized platelets **(Crow&Lazarus, 2003)**.However, the role of complement in pathogenesis of ITP is not yet clear, several studies have shown that ITP patients demonstrate elevated levels of platelet associated C3,C4 and C9, suggesting in vivo complement activation **(Kurata et al, 1985)**.In vitro studies show binding of C3and C4 followed by lying after incubation of platelet with plasma and fresh serum **(Tsubakio et al,1985) (Meli et al, 2005)**.Some of the effects of IVIG may occur by reducing C3 and C4 deposition on platelets **(Nomura et al, 1993)**.

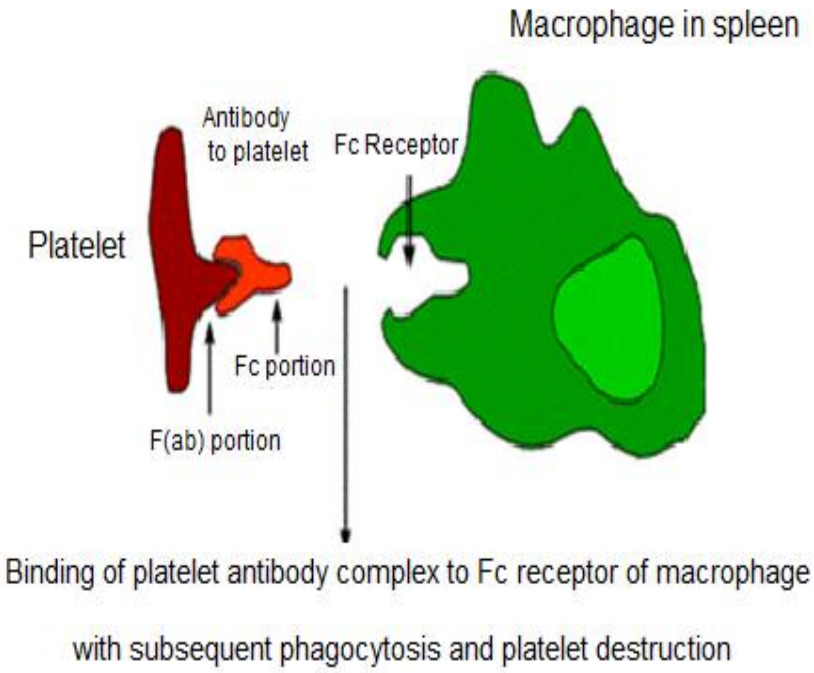


Figure2: Mechanism of platelet destruction in ITP patients http://www.medscape.org/viewarticle/4209046

- **Cellular Activity** ITP is primarily mediated by IgG autoantibodies, the production of these autoantibodies are regulated by the influence of Thymus Lymphocytes Cell (T Cell),B Lymphocytes Cell(B Cell) and Antigen Presenting Cells

(APC) **(Bussel, 2002)**.platelet proteins are cleaved to peptides by an APC and expressed on the APC cell surface via Major Histocompatibility Cells (MHC class II molecules) **(Figure 3)**.The Thymus Cell Receptor (TCR) of the T cell can then bind the peptide MHC complex and signal activation that upregulatesCD154(CD40 ligand) to interact with CD40on APC and cause additional costimulatory interactions to occur, the activated T cell produces

cytokines that promote B cell differentiation and antibody production **(Figure 3)**. Ongoing interaction between T cells and B cells through CD40-CD40L (CD154) isnecessary to maintain active platelet autoimmunity **(Diana, 2006)**.The CD40-CD154 axis is an attractive therapeutic target for patients with refractory chronic ITP, and monoclonal antibodies against CD154 have undergone clinical trials in ITP (**Kuwanaet al, 2003)**.It has been recently reported that platelets themselves express CD154 and may thus play a more active role in the autoimmune process than simply bearing antigens and accepting a fate of destruction. **(Solanilla et al, 2005)**.

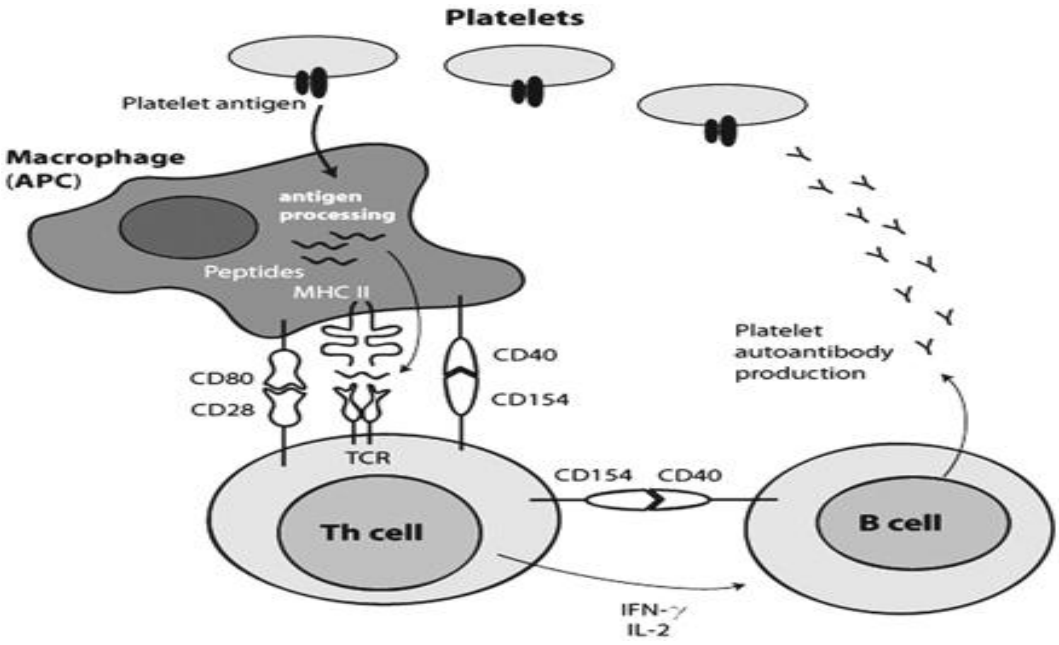


Figure (3)Emergence of antiplatelet autoantibodies

htt;//asheducationbook.hematologylibrary.org/content/2006/1/402

Recently Olsson e tal, have documented evidence for direct Tcell mediated cytotoxicity against platelets in chronic ITP**(Olsson et al, 2003)**.

Enhanced serum level of HLA-DR molecules have been detected in chronic ITP **(Boshkov et al, 1992) (Santoso et al, 1993),** increased activation of T cells, increased serum level of of interleukin2 (IL2), interferonγ**(** IFNγ)**(Semple et al, 1991) (Garcia et al, 1995**), increased production of specific autoantibodies **(Nagata, 1997) (Hengartner, 2000)**.

v Impaired Megakaryopoiesis

It was demonstrated in 1980s that sera of patients with ITP actually inhibit megakaryocyte growth in culture, supporting the concept of suboptimal platelet production as a contributing factor to thrombocytopenia **(Heyns et al, 1986) (Ballem et al,1987)**.

Circulating and tissue bound Thrombopoietin (TPO) or Megakaryocyte Derived Growth Factor (MDGF) levels in ITP are normal or only slightly increased in ITP, in contrast to the elevated levels found with thrombocytopenia dueto bone marrow failure**(Mukai et al, 1996) (Schrezenmeier et al, 1998)(Nomura et al, 2002)**.

Chang et al, 2002 studied TPO driven megakaryocyte growth in vitro in the presence of anti glycoproteins antibody positive plasma from children with ITP and found that antiplatelet antibodies particularly anti-GPIb interfered with megakaryocyte proliferation**(Figure4).**

Experiments using $CD34^+$ human hematopoietic stem cells in culture and plasma from adults with chronic ITP also inhibited megakaryocyte production. **(McMillan et al, 2003)**.

Growth factor stimulation of megakaryopoiesis might be expected to increase the platelets count in patients with ITP**(Diana, 2006)**.

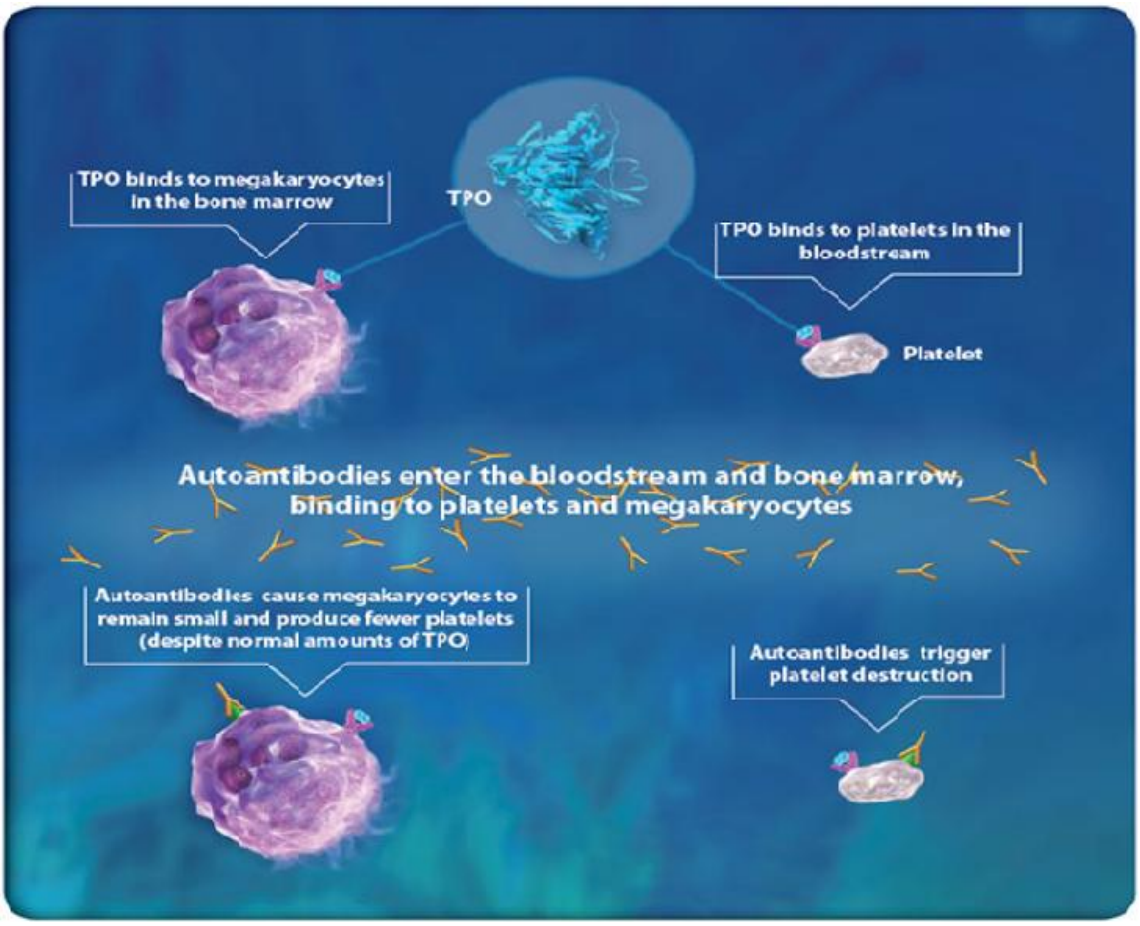


Figure (4)

TPO binding to platelets and to megakaryocytes

TPO bound platelets are tagged with autoantibodies

by B cells are subsequently destroyed by spleen

http://www.itpvillage.com/html/hcp/library-the-platelet-dossieraspxg

v 1-4- Genetics and ITP

There is emerging evidence that genetics can play a major role in the development and clinical outcome of this disease, high number of ITP patient with a positive family history indicating the likely existence of a genetic susceptibility for ITP disease.

Rischewski *et al,* 2006, studied whole blood gene expression profile in five ITP patients and five control samples, using DNA micro arrays that contained 24,473 unique putative genes , it was found that 176 cDNA were strongly correlated with ITP (**Sood*et al,* 2006**).

The Fc gamma RIIIa-158V were significantly over represented in Children with ITP versus the control subjects, the same statistical difference was noted with the combined Fc gamma RIIa-131H and Fc gamma RIIa-158V allelic gene frequencies **(Carcao*et al,* 2003**).

Another suggested that the IL-4 intron 3 and IL-10 polymorphisms contribute to the susceptibility of developing childhood chronic idiopathic thrombocytopenic purpura **(Wu KH et al, 2005)**.

Idiopathic thrombocytopenic purpura unlike other autoimmune diseases, a series of studies have demonstrated only a weak association with HLA B8,DR3 in patients with chronic ITP **(Stanworth et al, 2002)**.

HLA types have only been clearly linked to the development or clinical course of ITP in genetically homogenous population, such as the Japanese **(Nomora et al, 1998)**.

Nonetheless, immune recognition as result of HLA may be critical in development of autoimmunity in heterogeneous population as well (**Nichola&James, 2006**).

v 1-5-Clinical features

The classical clinical features Include a previously well child with sudden onset of excessive bruising petechiae and or mucous membrane bleeding**(Figures 5,6).**

1-4 weeks following a viral infection or an immunization, 60.2% of cases viral infection preceding the disease in children 1-10 years of age, both genders are equally affected **(Kuhne et al, 2003**)and according to researchers in UK, one every 22,3000 MMR vaccines will result in ITP .

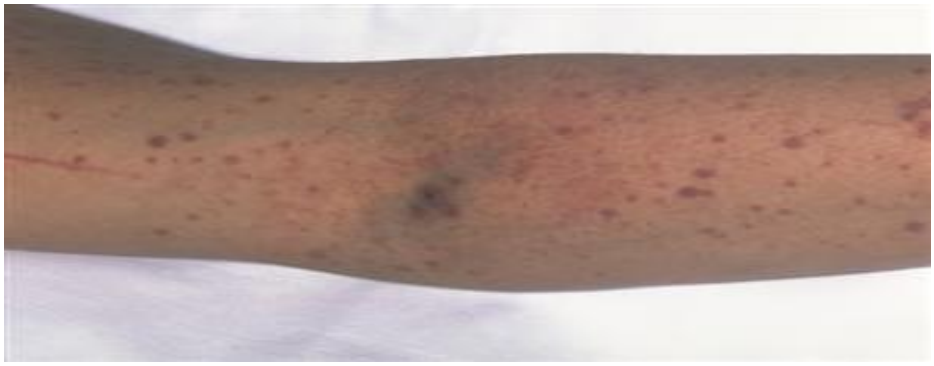
Fever; lethargy; weight loss; bone pains; joint pains; pallor; lymphadenopathy ;hepatomegaly and splenomegaly are characteristically absent, splenomegaly is rare.

ITP classified according to the severity of the disease:

Mild ITP : symptoms ranging from no bleeding to few petechiae and some bruises without mucosal hemorrhage.

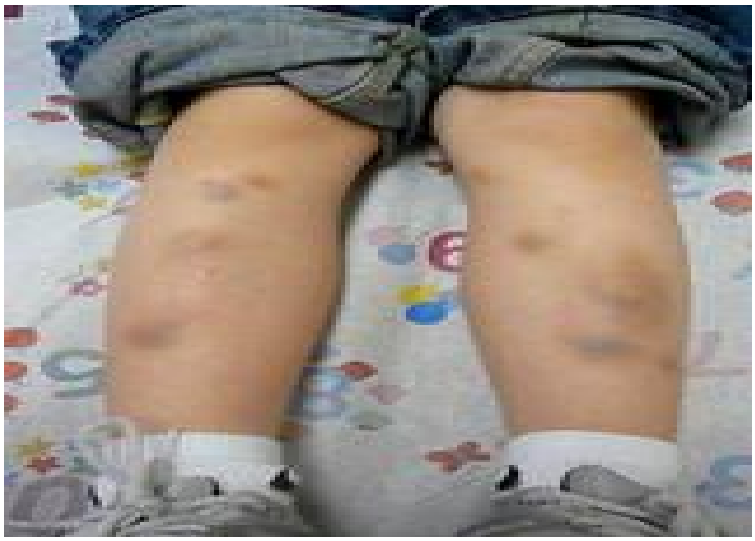
Moderate ITP: clinical picture with more petechiae bruising and mucosal hemorrhage.

Severe ITP: clinical picture with sever cutaneous and mucosal bleeding symptoms with at least one of the following features : retinal hemorrhage, intracranial hemorrhage other sever internal hemorrhage; hemorrhagic shock; and life threating bleeding(**De Mattiaet al, 2000**).



F.g(5)Extensive bruising on upper limb of ITP patients

http://dx.doi.org/10.1016/0002-9343(83)90881-1,



Fig(6)Extensive bruising on lower limb of ITP patients

Photo@ vincetIannell About.com

Intracranial hemorrhage (ICH) is extremely rare, the incidence as reported by recent studies is (0.2-0.8%) from 13months to 16 years, the majority of ICH events do not occur during the first few days after diagnosis but later in course of the disease.

Butros & Bussel, reviewed 75 published cases of ICH with ITP from 1954 to 1998, sixty-two cases ranged from 6 months to 20 years of age, ICH in 72% of cases occurred within six months of diagnosis, but only 7(10%) occurred within three days of diagnosis, the platelet count was less than $10x10^9$/L in 71.4% of cases **(Butros & Bussel, 2003)**.

In some studies on ITP, no case with life threatening hemorrhage was found**(Dickerhoff**&**Von Ruecker2000)** as in a study occurred in Germany from Oct 1995 to Sep 1997(**Sutor et al, 2001**).

In some cases precipitating causes like arteriovenous malformation, head injuries or aspirin treatment were identified **(Lilleyman, 1994)** and hemorrhage more than petechiae and bruises **(Philip, 2011)**.

No correlation with either the severity of bleeding symptoms or the platelet count at the onset of ICH, it occurred in children even on treatment(**Iyori et al, 2000) (Butros & Bussel 2003**).

However, recent studies reported 25% of ICH cases were occurred at presentation, 90% of ICH cases occurred with platelet count <20 $x10^9$/L,75% with platelet count<10 $x10^9$/L, 70% had prior treatment**(Philip, 2011)**.

v 1-6-Investigations

The diagnosis depends upon the exclusion of other causes of thrombocytopenia, a pseudothrombocytopenia due to in vitro platelet agglutination in the presence of EDTA ought to be ruled out from the true thrombocytopenia, complete blood count(CBC) and examination of peripheral blood smear are essential for the diagnosis.

The Complete Blood Count demonstrates isolated thrombocytopenia, some children may be anemic due to blood loss, approximately 10% of children have transient absolute neutropenia **(Catherine &Manno, 2005).**

- Platelets may be normal or large in size but consistently giant platelets are absent, there should be normal red blood cell morphology normal white blood count and morphology.
- The features which are not consistent with diagnosis of ITP include predominant giant platelets, polychromatophilia, macrocytosis and nucleated red blood cells, some children may have increased number of normal or atypical lymphocytes on peripheral smear reflecting a recent viral illness.
- Thrombocytopenia (<100 $x10^9$/L) without morphologic evidence for dysplasia in the peripheral blood film and presence of any of three or more increased platelet associated anti-GPIIb/IIIa antibody level, elevated percentage of reticulated platelets, normal or slightly increased plasma thrombopoietin level<300pg/ml (**Beng& Tee, 2000**).

- There is general consensus that bone marrow aspiration is not indicated in a typical case, but it should be done if there is any doubt about diagnosis or steroids are given for treatment **(Halperin&Doyl, 1988) (Calpin*et a*l, 1998**) or infants with Down syndrome home thrombocytopenia of the following laboratory finding : absence of anemia, normal leukocyte count, may herald the development of megakaryoblastic leukemia, the purpose of bone marrow investigation is to exclude the other causes of thrombocytopenia (**Zipursky*et al,* 1992**).
- **Other investigations:** the antiplatelet antibodies assays, flow cytometry have no value in the diagnosis or prognosis of the disease (**Taub et al, 1995) (Romero et al, 2000**), antinuclear antibody, direct antiglobulin antibody test, level of platelet associated C3,C4,C9.Coombs test in anemic patient to rule out Evans syndrome.

  Mean platelet volume (**MPV**)are also not included in the routine workup of establishing the diagnosis but recent studies considered that as prognostic factors in newly diagnosis children with ITP (**Shahid *et al,* 2004**).

  Screen patients with ITP for helicobacter pylori(H.Pylori) particularly in those population with high background prevalence of H.pylori infection (**Roberto Stasi & Drew Provan, 2008**).

  Computed tomography scanning and magnetic resonance imaging are relatively benign and useful noninvasive imaging promptly performed when the medical history or physical findings suggest serious internal bleeding .

v 1-7-Differential diagnosis

- A clear history of acute onset of purpura in an otherwise well child , together with careful examination and blood film is essential to exclude other diagnosis acute leukemia, aplastic anemia and myelodysplastic syndromes rarely present with a low platelet count alone.
- Congenital thrombocytopenia may be missed if not considered in the differential diagnosis, the following are the reasons to suspect congenital thrombocytopenia**:**

  Family history of thrombocytopenia, lack of platelet response to ITP therapies including intravenous immunoglobulin, intravenous anti-D and steroids to more than $30x10^9$/L from baselinewill rule out ITP, while $<10x10^9$/L peak increase is compatible with congenital thrombocytopenia or with a diagnosis of refractory ITP, numbers in between are ambiguous. Diagnostic features of congenital thrombocytopenia on smear such as abnormal size of platelet(small,large,gaint), absence of platelet alpha granules or Dohle like bodies or microcytosis, bleeding out of proportion to platelet count, onset at birth, associated clinical features such as absent radii, mental retardation, renal failure, hearing loss, cataracts or the development of leukemia, Persistence of a stable level of thrombocytopenia for years**(Cines *et al*, 2004)**.
- History of drug administration e.g heparin ,quinidine or quinine, cephalosporins, rifampicin, antiepileptic drugs should also be elicited to rule out drug induced thrombocytopenia.
- Children with lymph proliferative disorders may present as thrombocytopenia but they are usually sick looking with recurrent upper and lower respiratory tract infection, possibly gastro esophageal reflux, and failure to thrive, Family history is often positive.

- VonWillibrond disease type 2b is also characterized by abnormal bleeding tendency due to rapid clearance of platelets and VonWillibrond factor, so the diagnosis is based on demonstrating thrombocytopenia with low von Willibrond factor.
- Disseminated intravascular coagulation frequently accompanies a severe systemic disease process and is characterized by thrombocytopenia, prolonged prothrombin, partial thromboplastin, thrombin time due to consumption coagulopathy, there may be associated microangiopathic hemolytic anemia.
- Thrombotic thrombocytopenia is very rare in children and is pentad of fever, microangiopathic anaemia,thrombocytopenia, abnormal renal function and central nervous system changes.
- Hemolytic U History of drug administration e.g heparin ,quinidine or quinine, cephalosporins, rifampicin, antiepileptic drugs should also be elicited to rule out drug induced thrombocytopenia.
- Older children , particularly those having a chronic course should be investigated for signs and symptoms of systemic lupus or antiphospholipid syndromes**(Abdul Rehman, 2007)**.

v 1-8-Treatment of ITP

The emphasis is focused to treat or forestall bleeding without excess drug induced toxicity or burden to the patient. the problem with all these treatment is that they do not treat the underlying disorder, only the low count , so relapse is common and they do not change the prognosis, there is substantial discrepancy among published guidelines and among clinician who like to over treat the disease.

Explanation of the clinical course of ITP to the parents of affected child is necessary, it is important to temporarily restrict motor activities ,to avoid contact sports , to avoid some procedures (e.g dental extraction) and do not use certain drugs like aspirin and ibuprofen which may worsen bleeding symptoms, it is advised to present to the hospital in the event of accidents.

Treatment is certainly indicated for troublesome bleeding or platelet count below $20x10^9$/L,but still differing opinion concern whether therapy is required in any or all children who present with profound thrombocytopenia(<10-$20x10^9$/L) without extensive bleeding.

The guidelines for ITP treatment also differ, the most comprehensive ITP practice guidelines are those of the American Society of Hematology (ASH**)** published in 1996and the British Committee for Standards in Haematology published in 2003.

There is criticism over the ASH guidelines which recommend that children with ITP and presented with a platelet count less than $10x10^9$ /L be given treatment, regardless of whether there is any bleeding (**Tarantino &Buchanan, 2004**).

The British guidelines suggest that only patients who have significant mucosal or more serious bleeding should receive treatment (first-line being steroids) and that intravenous immunoglobulin (IVIG) and platelet transfusions should be reserved for life-threatening bleeding only**(Table1)**.

Table(1)Comparison of national treatment guidelines for childhood immune thrombocytopenia

Guidelines	Platelet $<20x10^9$/L	Platelet $>20x10^0$/L $<30x10^9$/L	Platelet $>30x10^9$/L	Life threatening Hemorrhage
1)-American Society of Hematology	$<10x10^9$/Land any Clinical bleeding treat with CS or IVIG $<20x10^9$/L with Dry purpura: observe or Cs or IVIG $<20x10^9$/L with wet purpura: treat with Cs or IVIG	dry purpura: observe or Cs or IVIG wet purpura : treat with Cs or IVIG	dry purpura : observe wet purpura : treat with Cs or IVIG	treat with multi modalities I.V Cs , IVIG, platelet transfusion
2)-British Committee for Standards in Hematology	Treat mucous membrane bleeding and more extensive Symptoms with high dose prednisolone for short course (i.g 4days) Lower dose Cs (1-2mg/kg/day)for 14 days Reserve IVIG for life threatening hemorrhage			treat with multi modalities I.V Cs , IVIG, platelet transfusion

1)-George et al,1996 IVIG: Intravenous 2)-British Committee for Standards in Hematology,2004 Cs: Corticosteroids

v 1-8-1-Treatment of acute ITP

The 3 main modalities of treatment of acute ITP in children are shown in (**Table2)**

Table(2) Comparison of acute immune thrombocytopenic purpura (ITP) treatment regimens in children.

Treatment Response	Prednisone (4 mg/k/day 1-7) max 60 mg	IVIG (1-2 g/kg)	Anti-D Immunoglobulin (75 µ/kg)
Response> 20,000 at 48 hours	60-70% of patients	70-80% of patients	77% of patients
Common side effects	Weight gain, irritability, hypertension, stomach pain, hyperglycemia	Post-infusion, vomiting, allergi reaction, headache	Hemoysis, chills, fever
Rare but severe reactions	Gasticulcer,reflux bleeding, hypertension induced ICH	Anaphylaxis, aseptic meningitis renal failure	Massive hemolysis with associated back pain myalgia, anemia
Duration of intial response (days	Wide range of response afte 30 days of weaning from initia dose to 0	21-72 days with platelet coun greater than 20,000/mm3	21-48 days based on the 75 µ/kg dose

Diane J. Nugent .Immune Thrombocytopenic Purpura of Childhood. American Society of Hematology Hematology book;2006;97-103.

- **1-8-1-1)-Immunoglobulin**

IVIG is a product manufacture from pooled human plasma and typically contains more than 95% unmodified immunoglobulin G (IgG) which has intact Fc-dependent effectors functions and only trace amounts of immunoglobulin A (IgA) or immunoglobulin M.

IgG may be involved in occupying the Fc receptors on reticuloendothelial cells, resulting in survival of the opsonized platelets**(Bussel, 2000)**.

Another mechanism of action may be the presence of anti idiotypic antibodies in the pooled IgG preparation, which bind to circulating autoantibodies rendering them ineffective for platelet opsonins and may also IVIG suppress the B-cells that produce the offending autoantibodies **(Hoyle et al, 1986)**.

Some effects of IVIG may occur by reducing C3 and C4 deposition on platelets **(Nomura et al, 1993)**.

Recent studies of mouse models of ITP have lead to the hypothesis that the IgG molecules does this by upregulatingFcRIIb, the inhibitory FcRIIb on phagocytes(Philip, 2011) .

Treatment with IVIG resulted in quicker and more extensive increase in platelets counts compared with patient treated with corticosteroid**(Imbach et al, 1985)(Blanchetteet al, 1993) (Warrier& *Lusher,* 1990)** based on these finding,American society of hematology panel recommends the use of IVIG in preference to corticosteroids for the treatment of children with ITP**(George et al, 1996)**.

The recommended regimen is 0.8g/kg for two days, In very severe cases , a total dose of 2g/kg divided in 2-5 days can be used, achieves the same results as the dose of 400mg/kg for 5consecutive days but costs less, is more convenient and may have fewer side effects(**Blanchetteet al, 1993)**.

In randomized study showed that IVIG (1g/kg/dose,1- 2 days) was effective in 80% of cases while methylprednisolone 30mg/kg/dose for 2-3 days) was effective in 60% of cases in increasing platelets count>$50x10^9$/L within 48 hours, but without any difference at one week or later, no serious bleeding was noted in either of the treatment group (**Anconaet al, 2002)**.

Meta-analysis showed that children treated with corticosteroids were 26% less likely to have a platelets count >$20x10^9$/L after 48 hours of therapy when compared with who treated with IVIG (**Beck et al,2005)** but another randomized study reported that platelet counts increased more rapidly after IVIG (1g/kg/dayx2days) as compared with 0.8g/kg/day for 2days dose (**Benesch*et al*, 2003**).

Adverse effects of IVIG are common (15% to 75%) but generally mild, most of the adverse reactions are primarily related to infusion rate activation of complement and anaphylactic reactions to a component of product (**Wordell, 1991**) these include flu-like reactions like low grade fever, chills, muscle aches,fatigue and backache , rare complications include aseptic meningitis, alloimmune hemolysis, hepatitis C infection, renal failure and anaphylaxis .

However , no hepatitis C infection has been reported with viral inactivated products **(Marilyn, 2005)**.

In randomized study noted that neutropenia (ANC<1500/µl) developed in 18% of cases treated with IVIG , which was likely to be a transient condition **(Niebanck*et al*,2005**) . Anotherstudy reported that 34% of cases treated with IVIG had transient neurological complications manifested by severheadache , nausea , and rarely , aseptic meningitis. (**Kattamis et al, 1997**).

Retrospective study showed that a short course of prednisone (2mg/kg/day during and for 3 days of IVIG therapy) decreased incidence and severity of neurological complications of IVIG **(Jayabose*et al*, 1999)**.

- **1-8-1-2)-Steroids**

Steroids when compared with placebo, corticosteroid administration was associated with an earlier rise in platelet count as compared to when no therapy was administrated**(George et al, 1996) (Buchanan &Holtkamp,1984**) a short course of high dose corticosteroids, using either an oral or intravenous preparation, results in a clinically significant to be multifactorial.

They can increase vascular stability and platelet survival, an effect attributed to both decreased production of anti-platelet antibodies and decreased clearance of opsonized platelet**(Schultz et al,1998)**.

The dose regimens include oral glucocorticoid 2mg/kg/day or 60mg/m^2/day of prednisone for 14 days, followed by a tapering down dose and discontinuation on day 21**(Buchanan et al, 1984**)or 4mg/kg/day followed by a 50% reduction in the dose in the second week and then by a tapering down dose and discontinuation on day21**(Blanchetteet al, 1993)**.

Other regimens include intravenous glucocorticoid as15-30mg/kg of methylpredisolone administered over 30-60 minute bolus injection for three days with max dose of 1g/day, platelet count recovery achieved by using high dose parenteral glucocorticoid was faster than that obtained by oral glucocorticoids and as rapid as that with IVIG**(Van Hoff&Ritchey,1988)(Ozsoylu et al, 1989)**.

Other study randomized showed that IVIG (0.5g/kg/day for 5consecutive-days), mega dose methylprednisolone (administered MP 30mg/kg/day for 7days orally administered or MP 50mg/kg/day orally for 7 days) were equally effective **(Albayraket al, 1994)**.

Duru et al, 2002 studied IVIG, mega dose MP or no therapy and showed that platelet counts at three days after starting therapy were significantly higher in both IVIG and megadose MP groups than in the no therapy group ($p<0.01$), but there was no difference between the three groups at 10 and 30 days after initiation of therapy.

Erduran et al, 2004 used IVIG , mega dose methyl prednisolone, the mean time of achievement of platelets count above $20x10^9$/L was 4.1 and 2.9 days ($P<0.05$) and above $50x10^9$/L was 5.0 and 5.2days ($P>0.05$) respectively, no significant differences were observed on days 30, 60, 90, 120, 180.

Corticosteroids still the treatment of choice in many developing countries due to high cost of IVIG **(Di Paola &Buchanan,2002)**, short courses utilized in childhood ITP are not commonly associated with the side effects of weight gain, gastritis, sleep disturbance, growth retardation hypertension ,cataracts, pseudotumorcerebri, avascular necrosis and hyperglycemia, careful monitoring is still needed (**Kumar et al, 2005**).

ASH, 2011recommended that, for pediatric patients requiring treatment, a single dose of IVIG(0.8 to 1g/kg) or a short course of corticosteroids be used as first line treatment and IVIG can be used if a more rapid increase in the platelet count is desired**(Cindy et al, 2011)**.

• 1-8-1-3)- Anti-D immunoglobulin

Anti-D immunoglobulin also known as IV(Rh)D, although the effect of anti-D on platelet count is generally not as long-lived as that of IVIG many practitioners prefer its ease of administration (IV-push) but American Society of Hematology practice guideline was not recommended by 1996.

Mechanism of action is said to be that RBC antibody complexes bind to macrophage Fc receptors and interfere with platelet destruction, therapy causing a rise in platelet count within two days**(Philip, 2011).**

In a randomized study found that single 75µg/kg/dose of anti-D was better in raising the platelet count than standard- dose anti-D (50µg/kg/dose) and was as effective as IVIG (0.8g/kg) with an acceptable safety profile**(Tarantino et al, 2006)**.

Adverse events include headache, nausea, chills and fever, as reported sixteen percent of patients developed hemolysis with a mean hemoglobin drop of 0.8g/dl seven days after treatment with anti-D immunoglobulin**(Gaineet al, 2000)**, reported case of irreversible encephalopathy 28 hours following an I.V infusion of anti-D for ITP**(Christopher *et al* 2004)**,the Food Drug Administration (FDA), received 120 reports worldwide of acute renal failure which may be irreversible (**Scheinfeld et al, 2005)**.

Administration of anti-Rh(D) globulin to Rh-positive patients resulted in significant increase in platelet counts $>20x10^9$/L, uncontrolled studies have demonstrated that anti-Rh(D) may increase the platelet count in approximately 80% of Rh positive children (**Becker etal, 1986) (Borgna et al,1994)** however uncontrolled clinical study showed that was less effective in comparison with IVIG or corticosteroids, whereas another reported that approximately70% of patients have an initial response to 75µg/kg/ within 1 day**(Philip,2011)**, it can only be used in Rh-D positive patients who have not undergone splenectomy **(Christopher et al 2004)**.

v 1-8-2-Treatment of chronic ITP

If the episodes persistent beyond the six months from the onset of original disease usually involves repeated administration of one of the standard treatment (IVIG-steroids-Anti-D) and treatments drugs should be alternated, the goal is to give child time to improve one year after diagnosis and defer splenectomy and other recent options .

• 1-8-2-1)-Splenectomy

Guidelines from the American society of hematology(ASH) and practical guidelines in United Kingdome recommended the splenectomy be considered for children who have had ITP for at least a year with symptomatic sever thrombocytopenia as reported (**Eden&Lilleyman, 1992) (Cindy et al, 2011)**.

Recent studies document decline in rates of splenectomy in16 reports (277childern in total) 72% of patients with ITP achieved a remission following surgical splenectomy**(Bussel etal, 1983) (Aronis et al, 2004) (Wang et al, 2006)**.

Elective splenectomy in children with chronic ITP is only recommended if platelet counts remain $< 10x10^9/L$ in the absence of treatment (IVIG, corticosteroids, anti-D) for more than 14 days or in instances of sever and repetitive hemorrhage.

It is paramount that children immunized against Homophiles influenza, pneumococci meningococci prior to splenectomy **(Lortan, 1993)**.

Adverse effects : The important late effect of splenectomy is the increased risk of fatal bacterial infections, particularly in children below 5 years of age, a fatality rate of 1 in 300-1000 patient/years has been calculated.However recent article showed that patients with ITP who have a poor response to IVIG are unlikely to have a good or an excellent response to surgical splenectomy (**Mark et al,1999)**.The difficulty is therefore to decide whether the adverse effects of splenectomy outweigh its potential benefits since spontaneous recovery from ITP has been observed many years after diagnosis.

The ASH 2011, consider that persistent of sever thrombocytopenia after splenectomy as refractory ITP **(Cindy et al, 2011) (April et al, 2006),** whereas the others define refractory ITP to patients who fail to maintain platelet count above $30x10^9$/L after six to twelve months of standard therapy **(Diana, 2006) (Imbach, 2006)**.

The 1996 ASH guideline noted that numerous agents have been used in small numbers of children and adolescents with chronic or persistent ITP who failed to response to more conventional therapy.

- **1-8-2-2)-Vinca alkaloids**

The use of vinca alkaloids in ITP is based on the observation that the administration of vincristine and vinblastine can cause lymphocytopenia and suppression of antibody production, the increase in platelet after treatment with vincristine or vinblastine lasts 1-3 weeks in two-thirds of patients.

The recommended dose of vincristine is 1-1.5mg/m^2 intravenously (maximum single dose 2mg) every 1-2 weeks, combination with oral corticosteroid 1-2mg/kg daily for 3 days may enhance the effect for vinblastine the recommended dosage is 6mg/m^2intravenously every 1-2weeks.

Adverse effects include neuropathy, constipation, leucopenia and fever,the infusion of vinblastine-loaded platelets has not shown convincing results**(Kelton etal, 1981) (Manoharan 1986**).

- **1-8-2-3)-Azathioprine**

An immunosuppressive drug, was the first compound reported to be effective in chronic ITP refractory to glucocorticoid treatment and splenectomy.

50-70% of patients may achieve an improvement , continuous treatment for 4 months appears to be necessary before a patient is considered unresponsive, the recommended dose is 50-300mg/m^2 by mouth daily **(Bouroncle& Doan, 1966)**.

- **1-8-2-4)-Cyclophosphamide**

Patients treated with Cyclophosphamide, 60-80% will respond with an increase in plateletcount,althoughof similar therapeutic potency to Azathioprine.
cyclophosphamidehas more severe side effects, the recommended dose is 3-8mg/kg by mouth daily . Adverse effects are leucopenia, alopecia, infertility, teratogenicity and urinary bladder hemorrhage **(Srichaikul et al, 1980)**.

- **1-8-2-5)-Cyclic high dose methylprednisolone**

Methylprednisolone(20-30mg/kg I.V) or dexamethasone(1mg/kg orally) can be given on three to four consecutive days every 4 weeks for 4 months. However both the adverse effects and response rates of these high dose corticosteroid regimens are disappointing in children **(Nugent et al, 1994)**.

- **1-8-2-6)-Danazol**

An androgenic steroid with minimal virilizing effects, was suggested for the treatment of ITP because one of the documented side effects is thrombocytosis.

There is a broad range of response to Danazol in patient with ITP (10-80%), the usual recommended dose is 100-150mg/m^2 orally three times daily.

Adverse effects include weight gain headache, hair loss, liver dysfunction, myalgia, amenorrhea, some virilization and even thrombocytopenia **(Mazzucconi e*t al*,1987)**.

- **1-8-2-7)-Plasma exchange and Protein A immunoadsorption**

Physical measures to improve antiplatelet antibodies, in 20-30% of patients with chronic ITP.

Plasma exchange may transiently result in a response, according to study of effect plasma exchange in acute ITP in Canada from 1980 to 1997 indicate increased the length of time before splenectomy but did not alter the need for splenectomy, short term benefits of plasma exchange were accomplished with no increase in morbidity or mortality which confirms that plasma exchange is a safe procedure in patients with ITP .

Marder et al, 1981 reported using protein A immunoadsorption to remove antiplatelet antibodies, another study showed 16 of 72 patients demonstrated a sustained platelet increase , this extracorporeal treatment is required daily for 3-5 days **(Synder et al, 1992)**.

- **1-8-2-8)-Ascorbic acid (vitamin c)**

Although a response rate of 15% has been reported the role of ascorbic acid in the treatment of ITP remains to be determined, the recommended dose is 1-1.5g/m^2 by mouth daily **(Jubelireret al, 1993)**.

- **1-8-3-Platelet transfusion**

Platelet transfusion has little benefit in ITP, since platelet autoantigens are public antigens and are present on all normal platelet count, although exceptions can occur, is usually unsucceful in producing a long term platelet count increase**(AbdullRehman2007)**, but are required for rare emergency situations including intracranial hemorrhage, internal bleeding and emergency surgery, platelet survival is short, some hemostatic activity is usually obtained **(Philip, 2011).**

- **1-8-4-Recent treatment options**

New therapeutic development have the main goal of influencing the altered immune response associated with ITP .

1-8-4-1-Treatment influencing the T-cell immune response

- **1-8-4-1-1)-Cyclosporine**

In child with normal renal function, Cyclosporine causes a dose-dependnet increase in platelet count, the dose should be adjusted according to the serum level and with the aim of achieving a safe thrombocyte count, in this way low dose Cyclosporin with less adverse effects may be possible, in one study the long term response rate was 11 of 20 patients (five complete response, six partial responses)**(Kappers&vant' Veer,2001) (Emilia *et al,* 2002)**.

- **1-8-4-1-2)-Cytotoxic T-lymphocyte Associated Antigen-4 Immunoglobulin(CTLA-4-Ig)**

CTLA-4-Ig a fusion protein between CTLA-4 and the immunoglobulin Fc portion, aims to block Tcell stimulation and down regulate cytokine production, this treatment was succefully used in patients with psoriasis, such a drug may also be effective in other autoimmune disorders driven by dysregulated T cell, including ITP, but no data are yet available**(Abram et al, 1999)**.

1-8-4-2-Treatment influencing the B-cells immune response

- ### 3-8-5-2-1-Anti-CD20 monoclonal antibody(Rituximab)

The human /mouse anti-B-cells monoclonal antibody rituximab is a k immunoglobulin with murine light and heavy chain variable sequences and human constant sequence, the chimeric molecule binds to the CD20 antigen on B cells and mediates its lysis by immune effector cells was approved by the United State, Food Drug Administration in 1997 for treatment of B cell non Hodgkins lymphoma.

However researchers are experimenting with a new use of rituximab in treatment of chronic ITP and Evans syndrome. Ten centers across the United State are using rituximab to treat children and teenagers with chronic ITP, initial results are encouraging, three to four courses of rituximab (375mg/m^2/week , IV for 4 weeks), approximately two-thirds of patients had an increase in platelet count and some had long-lasting response (>6months).

Adverse effects during treatment were transient, mild and comprised fever, chill, headache, dizziness, asthenia, nausea, vomiting and hypotension No infections were noted (**Reffet al, 1994) (Stasi et al, 2001)**.

- ### 1-8-4-2-2- Anti-CD52 monoclonal antibody (alemtuzumab)

Anti-CD52 antigen is present on lymphocytes and monocytes, monoclonal antibody directed against CD52 is effective in clearing B lymphocytes, of 21childern and adult with hemolytic anaemia, pure red cell aplasia, ITP or Even syndrome, 15 showed a response to treatment with alemtuzumab, some patients had a sustained response.

Adverse effects during treatment included fever and chill, serious adverse effects can potentially occur with alemtuzumab such as profound lymphocytopenia (with potential for opportunistic infection) intravenous hemolysis, systemic venous thrombosis, or thrombotic thrombocytopenic purpura **(Hale, 1995)**.

- **1-8-4-2-3-Interferonα(IFN-α)**

Uncontrolled studies with IFN-αshowed a response rate of 25% in children and adult with chronic ITP, however it may not be feasible to conduct the essential controlled trails needed to establish the efficacy of IFNα in ITP because, a difficult mode of application (300.000 units IM, three times weekly for 4 weeks) and is expensive **(Hrstkovaet al, 2002)**.

- **1-8-5--Helicobacter pylori eradication**

Researchers in Japan and Italy have found possible connection between H.pylori infection and ITP,some patients given antibiotics (triple therapy), a combination of amoxicillin, clarithromycin and a proton pump inhibitor for 1 to 2 weeks to eradicate the bacterial infection have had their platelet count increase dramatically **(Emilia et al, 2001)** **(Roberto Stasi& Drew Provan, 2008).**

v 1-8-6-Investigational new drugs

Several promising drugs are in clinical trials which increase platelets counts in persons with ITP by increasing in number of platelets produced and released by bone marrow .

- **1-8-6-1-Thrombopoietin Receptor Agonist**

TPO and TPO mimetic have been effective in a small number of patients, this is consistent with the known physiology, relatively low TPO level despite sever thrombocytopenia in ITP. Inadequate low TPO levels are associated with insufficient proliferation and differentiation of megakaryocytes, decreased proplatelet formation, subsequent platelet release .

As it would appear that the hard core group that is the most difficult to treat may be those who are not making platelets, TPO might be especially useful .

An abstract reporting on a Thrombopoietic peptides drugs has confirmed substantial short term efficacy of this approved approach in refractory patients **(Bussel et al, 2006)**.

- **1-8-6-1-1-Romiplostim**

Romiplostim is a thrombopoiesis stimulating protein, was approved by the US food and drug administration in august 2008 that increase platelet count in acute and chronic ITP without repots of significant toxicity**(Kuteret al, 2008) (Jamaliet al, 2009)**.

- **1-8-6-1-2-Promacta /Revolade (eltrombopag)**

Promacta is significantly raised platelets count and lowered the bleeding risk in clinical trials for short term treatment of patients with chronic ITP (**Bussel et al, 2007**) (**Ricel, 2009**).

v 1-8-7-Other options

- ***Recombinant* factor VII**

There is promising role of recombinant factor VII in the management of refractory sever hemorrhage both in acute as well as chronic ITP **(Culic 2003)(Wrobelet al,2006).**

- **Autologous hematologic stem cell transplantation**

Autologous hematologic stem cell transplantationhas been performed in 12 adults patients with partial remission **(Huhnet al,1999)**.

v 1-9-Prognosis of ITP

ITP has a favorable prognosis in children,75-90% of cases in most studies showing complete remission within six months irrespective of treatment given .

Persistent thrombocytopenia more than six months in only 10-25% of cases,**(Shahid et al, 2004**), chronic course which also had a high rate of remission over time, up to 80%. (**Imbach et al, 2006) (Philip, 2011)**.

At time of diagnosis, it is not possible to predict the course of disease, some studies of children demonstrate that platelets count $>20x10^9$/L and age over 10 years at diagnosis are significant predictors of chronic ITP **(Glanz etal,2008) (ElAlfyet al, 2010)**.

Univariate analysis, a low admission platelet counts $<10x10^9$/L,low admission MPV < 8 fl, history of viral infection predict for a favorable outcome while age and sex did not correlate with remission,whereas in multivariate analysis, low admission MPV and a history of a viral illness were independent factors of course of disease **(Shahid et al , 2004)**.

Chapter II

Aims of the study

Aims of the study

- To view the demography of ITP at Benghazi Children hospital between January-2000 to December-20008.

- To determine the prognostic variables in (newly diagnosed)children with Immune thrombocytopenia.

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Chapter III

Patients and Methods

Patients and Methods

All files of children were admitted with ITP, in Benghazi children hospital from January 2000 to November 2008 (no=182) were reviewed in this retrospective study, of these 27 patients were excluded because data were incomplete for the presenting symptoms and follow up, 20 of them involved in incidence of ITP at Benghazi city.

All patients were diagnosed and treated in general medical department and followed up in hematology clinic in Benghazi children hospital.

Benghazi children hospital is the only referral admitting hospital in Benghazi city and eastern part of Libya.

All patients were from the eastern region of Libya.

Medical records for 155 patients were reviewed and analyzed for residence, age, sex, date of diagnosis, clinical and laboratory features at time of diagnosis, modality of treatment, result of treatment and outcome.

The diagnosis of ITP was based on exclusion of other causes of thrombocytopenia by detailed history, physical examination, complete platelet count with blood smears and bone marrow examination for selected cases,blood count were done by counter analyzer.

Most children were treated with IVIG in a dose of 400mg /kg for 5days or 800mg/kg for 2 days or IV 30mg/kg methylprednisolone for 3days, oral prednisolone 1-2 mg /kg for 2 weeks, children with platelet count $>20x10^9$/L were not given any treatment unless they had a major bleeding symptom .

After discontinuation of therapy, patients were followed up at intervals of weeks to years, persistent thrombocytopenia more than six month after diagnosis was defined as chronic immune thrombocytopenic purpura.

The prognostic of the following values parameters at diagnosis were studied ,age, sex, type of bleeding, platelet count and mean platelet volume (MPV) values and type of treatment

- **Design of study**: Case- control study (retrospective).

- **Statistical analysis**: Data were analyzed using SPSS program , and results were shown as mean standard deviation , x^2, t test were used statistical analysis, and $P<0.05$ was accepted as significant .

Chapter IV

Result

Results

PatientpopulationOne hundred eighty two children were newly diagnosed in Benghazi children hospital in 9years(2000-2008),they constitute 1.8/1000 children per year of the general admitted cases in same hospital, of these 27 patients were excluded because data were incomplete for presenting symptoms and follow up, they only involved in incidence.

Benghazi children hospital is the only referral admitting hospital in Benghazi and eastern part of Libya, the population of Benghazi city is 749060 and (262022-295204) for children 0-15 years, which makes the average of estimated annual incidence of ITP in 9 years is 5.61/100.000 children (range2.83-8.13 per100,000) **(figure7)**,even if few cases were not admitted or treated in private hospital, it would only further increases the incidence in Benghazi city.

All patients with acute ITP were diagnosed and treated in general medical pediatric departments.

Most of cases were from Benghazi 123(79.3%) **(figure8)**.

Clinical and laboratory features

Among the 155 patients, 82(52.9%) male,73(47%)female. M:F ratio1.1:1, in acute ITP M: F ratio was 1.3:1, in chronic F:M ratio was 2.6:1.

Mean age was 5.4years (range 5months -14years) **(figure9&Table3)**.

Most cases of acute ITP 91(59%) are presented in Spring and Summer **(figure10)**.

The clinical features of studied case are shown in **(Table4&Table5).**

Sixty one(39.4%) children had history of upper respiratory tract infection (URTI)1week to 2 weeks before their symptoms.

Majority of patients152(98.7%) presented with ecchymosis and petechiae, 26(16.4%) epistaxis, 14(9%)gum bleeding,7(4.5%)hematuria, 3(1.9%)dark stool,1(0.65%)rectal bleeding,1(0.65%)accidental and 1 (0.65) with fever.

The laboratory findings are shown in**(Table6)** the mean platelet count was $26x10^9$/L, range (0-123),131(84.5%)of children presented with platelet count under 50×10^9/L, 91 (58.6%) presented with platelet count under $20x10^9$/L, 45(29%) with platelet count below$10x10^9$/L

Mean platelet volume (MPV) values was available in 81 patients with range from 5.9 to 21.2 fl with MPV value was 9.7fl, the correlation between the platelet count and MPV valuesshown in **(figure11)**.

WBC count were normal in most ofcases,39(25%) with Hb level below10g/dl, ESR was reported in 56 patients,10(17.8%)above 20mm/hr, bone marrow examination was performed in 108(69%) cases.

Response to treatment and outcomee

All children were managed in the Benghazi Children Hospital**,** twenty five (16%) patients with platelet above $20x10^9$/L without mucosal bleeding were managed with observation.

IVIG represented the first drug of choice for treatment of our patients 85(54.2%) and 38(24.5%) of our patients treated with steroid alone where IVIG was not available to theme, 7(4.5%) with severe mucocutaneous bleeding received combined therapy of steroids and IVIG **(figure12)**,we found15(9.6%) received treatment, although their platelet count $>30x10^9$/L, two patient received platelet transfusion and one patients received blood transfusion, no patient had intracranial hemorrhage(ICH)and no deaths.

Splenectomy was carried out in two chronic patients, one cured and one not improved. One patient received (anti CD20 Rituximab) as three courses but with no improvement .

One hundred thirty three (85.8 %) of children have recovery within 6 months of diagnosis with recurrence episodes within 3 months of initial one,22(14.2%) went to chronic ITP**(figure13)**.

Prognostic factors In this study we found statistically female patients more prone to develop chronic ITP with female to male ratio 2.6:1 and (P=0.009),patients age more than 6years have significant risk for chronic ITP with (P=0.000), **(figure14)** and those with MPV > 8 fl is powerful predictor for chronic ITP with (P=0.000),also there is difference in platelet counts between acute and chronic ITP **(figure15)** but statistically considered insignificant predictor of chronic ITP (P=0.216),also no significant different in prognosis between the type of bleeding neither wet nor dry at presentation with (P=0.503), statistically the history of URTI independent prognostic factor (P=0.210)**(Table7)**.

Our chronic cases received many trial of steroids and IVIG as single or combined therapy at beginning of illness and statistically by t test(-10.724) considered the type of drug treatment does not seem to alter the clinical outcome of the disease but it may shorten the period of profound thrombocytopenia.

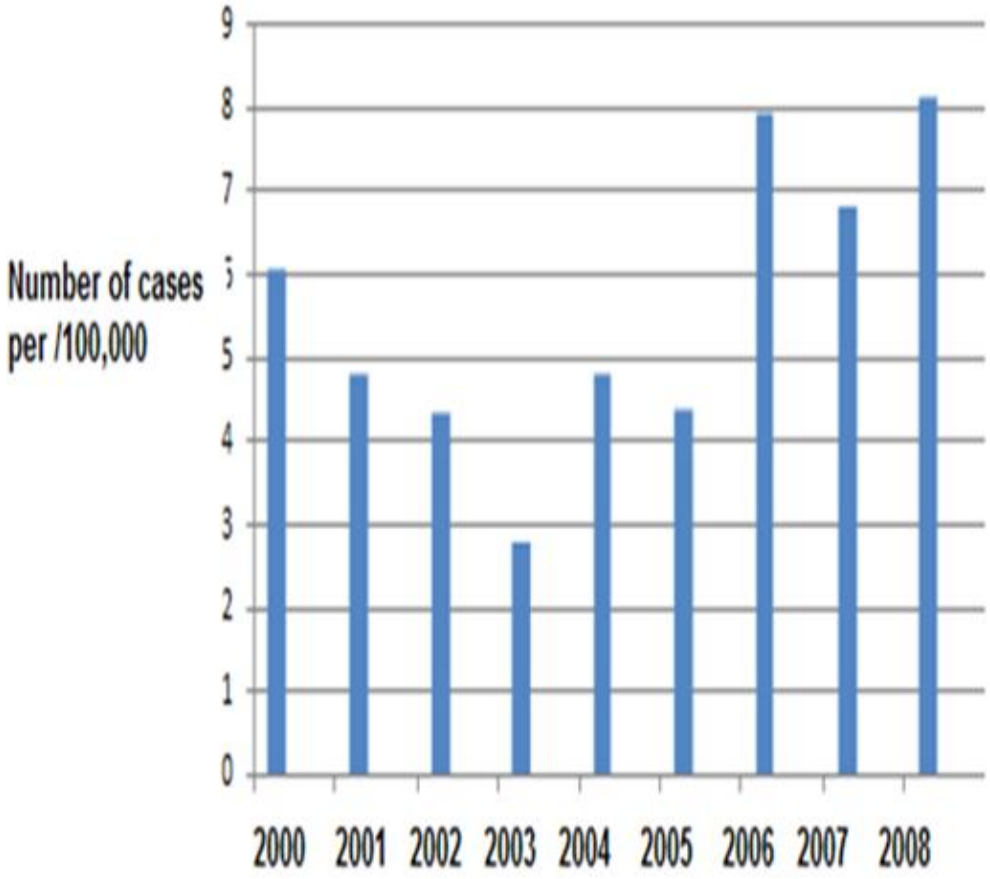

Fig 7. Annual incidence of ITP in Benghazi city (5.6/100,000 children)

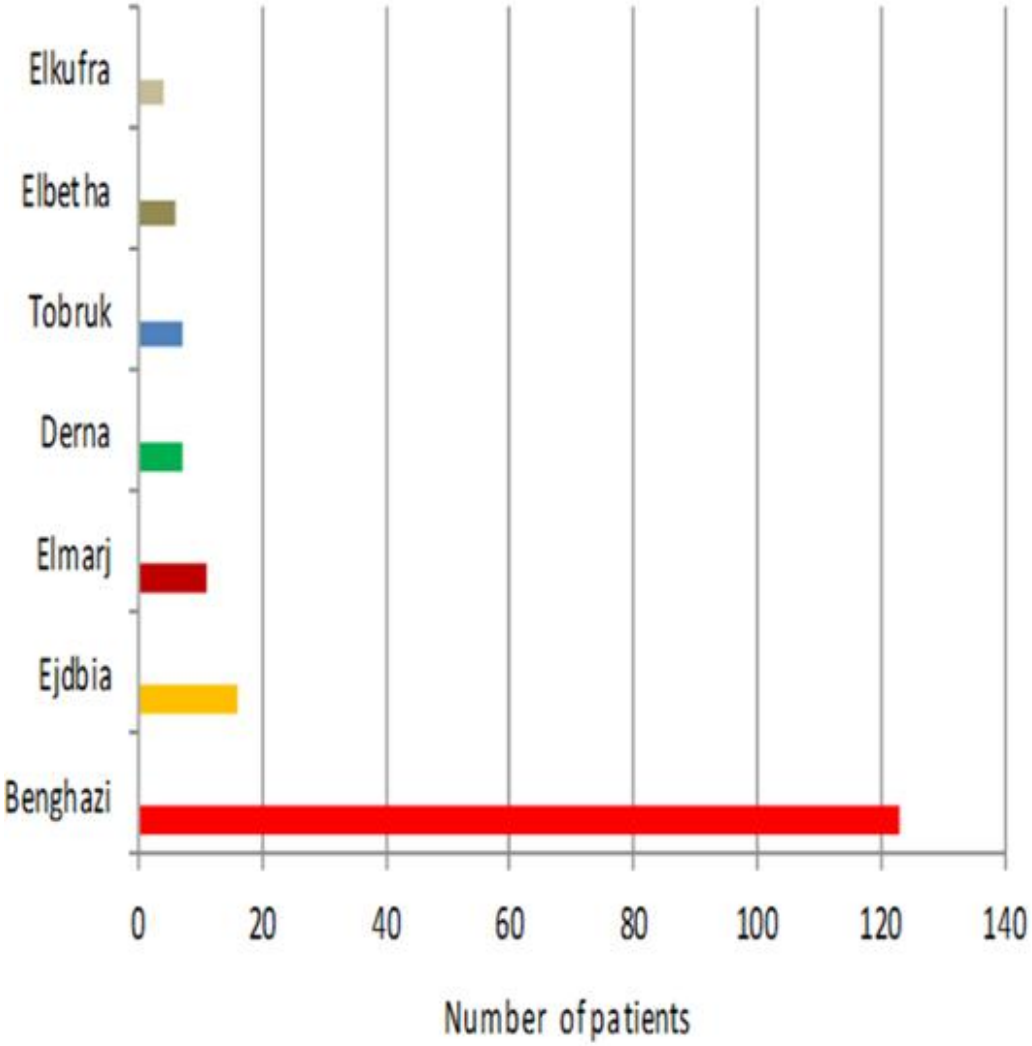

Fig.8 Distribution according to residence

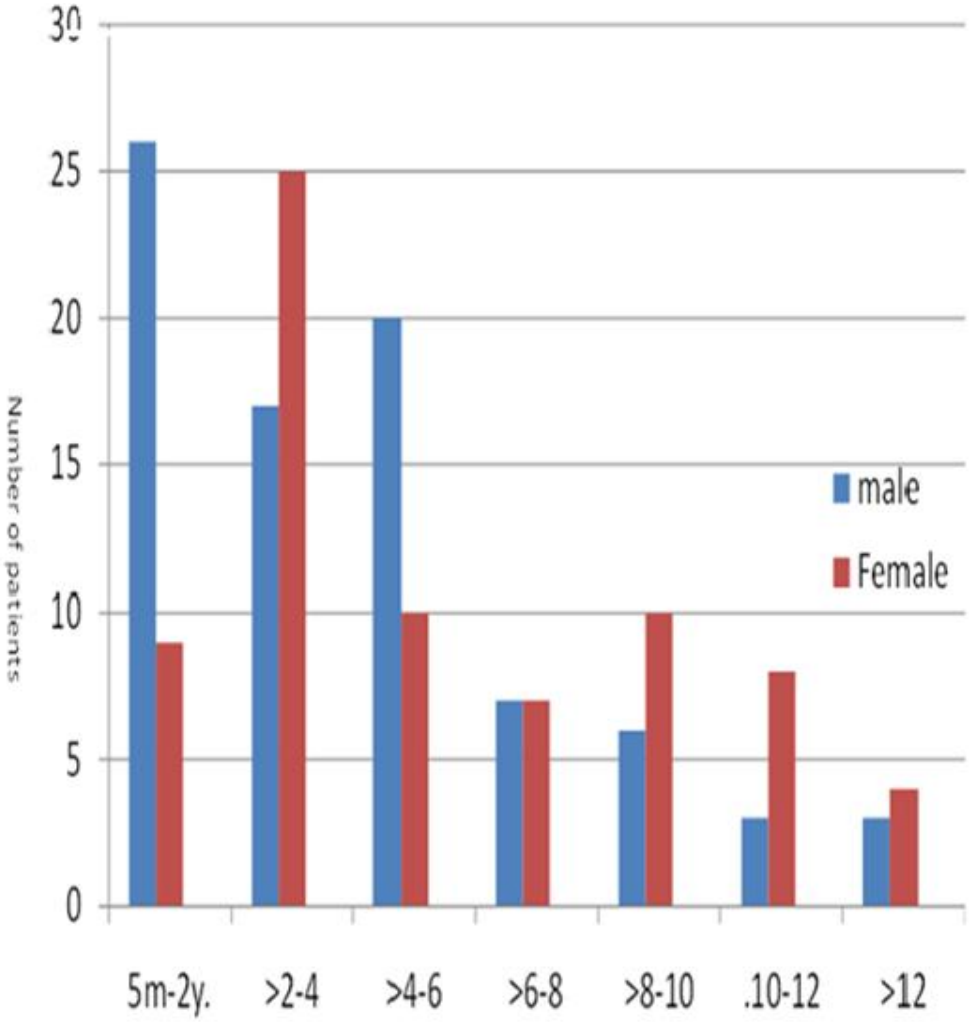

Fig.9 Age by years and sex distribution of ITP

Table 3 : Distribution of 155 patients according to some demographic characters

Demographic characters	Number of cases	%
Age		
5m-2	35	23
>2-4	42	27
>4-6	30	19
>6-8	14	9
>8-10	16	10
>10-12	11	7
>12-14	7	4
sex		
Male	82	53
female	73	47

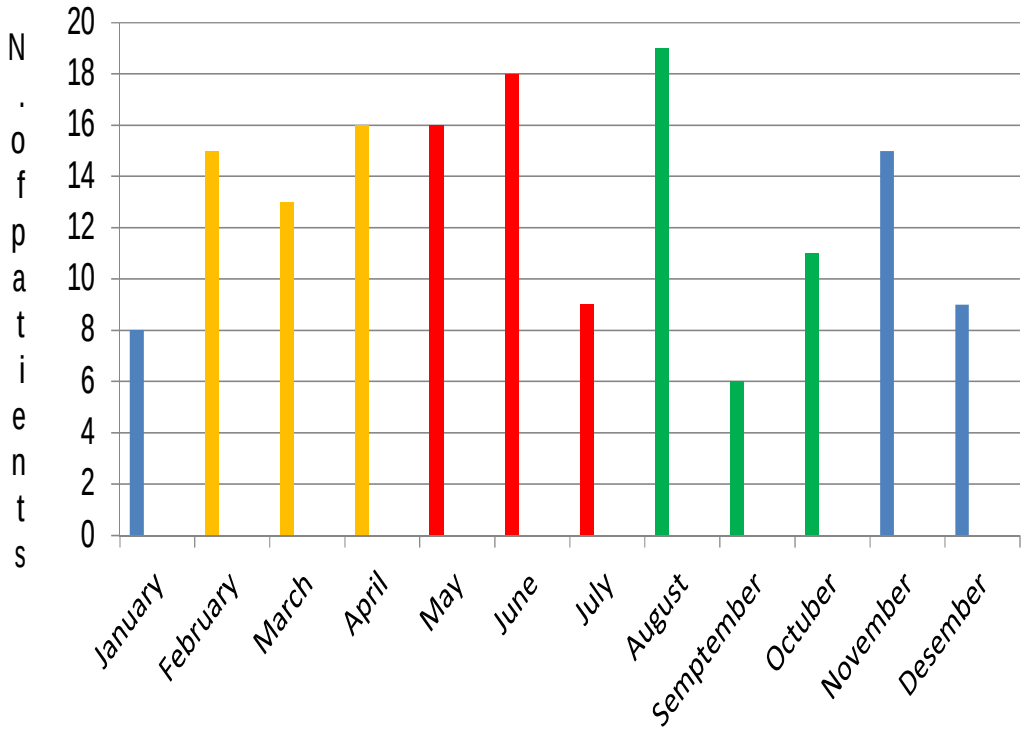

Fig. 10 Seasonal variation in 155 children of ITP

Table 4 Distribution according to Clinical features in 155 of ITP at Benghazi Children Hospital

Character	Number of children	
Cutaneous bleeding	**152**	**98%**
History of URTI	**61**	**39.4%**
Epistaxis	**26**	**16.4%**
Gum bleeding	**14**	**9%**
Haematuria	**7**	**4.5%**
Melena	**3**	**1.9%**
Rectal bleeding	**1**	**0.65%**
Fever	**1**	**0.65%**
Accidental	**1**	**0.65%**

Table 5:Bleeding symptoms and sign in155 patients of ITP

At Benghazi children Hospital

Character	Number o f cases	%
Ecchymosis and petechia	116	74.8
Ecchymosis Epistaxis	24	15.5
Ecchymosis Gum bleeding	14	9
Ecchymosis Haematuria	7	4.5
Epistaxis	2	1.3
Ecchymosis Rectal bleeding	1	0.6
Ecchymosis, Melena	3	1.9

N.B some patients have more than one character at the same time

Table : 6 Laboratory finding in 155 children with ITP at Benghazi children hospital

Character	Number of patients	%
WBC ×103/µL		
<4	2	1.29
4-11	116	74.8
>11	37	23.8
Hemoglobin g/dl		
7-8	2	1.29
8-10	37	23.87
>10-12>12	95	61.29
	21	13.54
Platelet× 103/µL		
<5	18	11.6
>5-10	27	17.4
>10-20	46	29.6
>20-50	40	25.8
>50	24	15
MPV/Fl		
≤8	28	34.5
>8-10	23	28.3
>10-12	17	20.9
>12	13	19
ESR mm/hr		
<20	46	82.1
>20	10	17.8

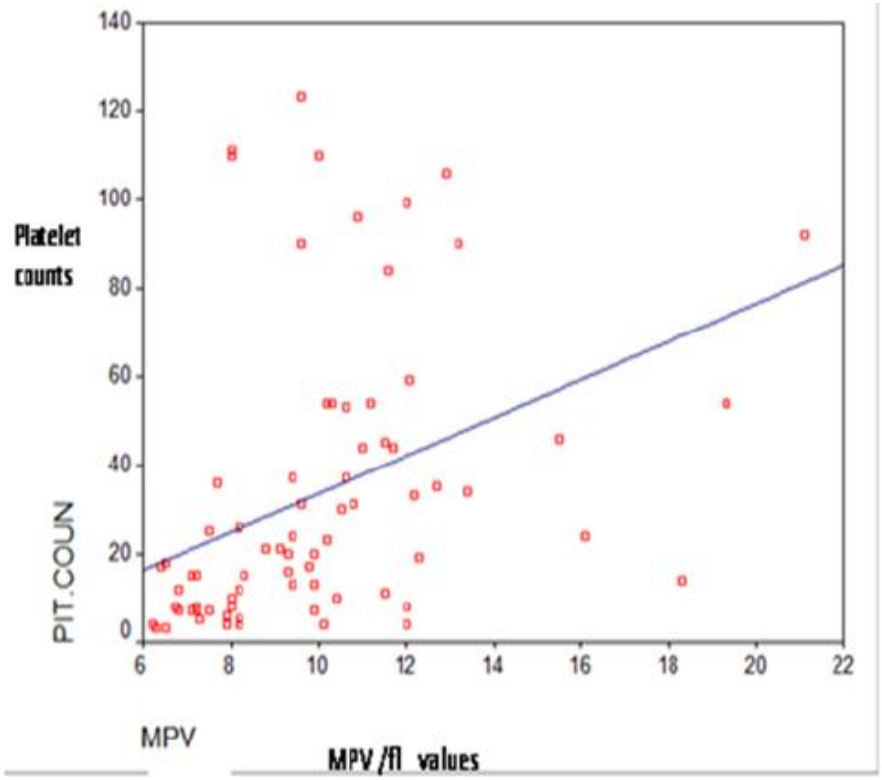

Fig.11 Correlation between MPV values and platelet counts

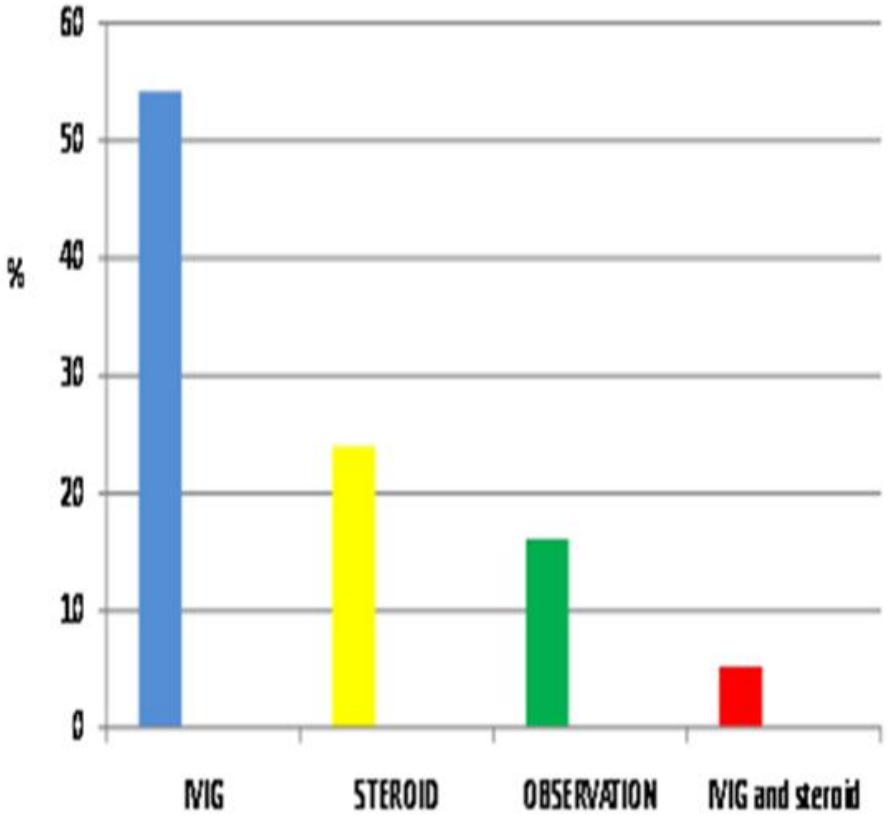

Fig .12 Types of treatment in 155 patients at Benghazi Children Hospital

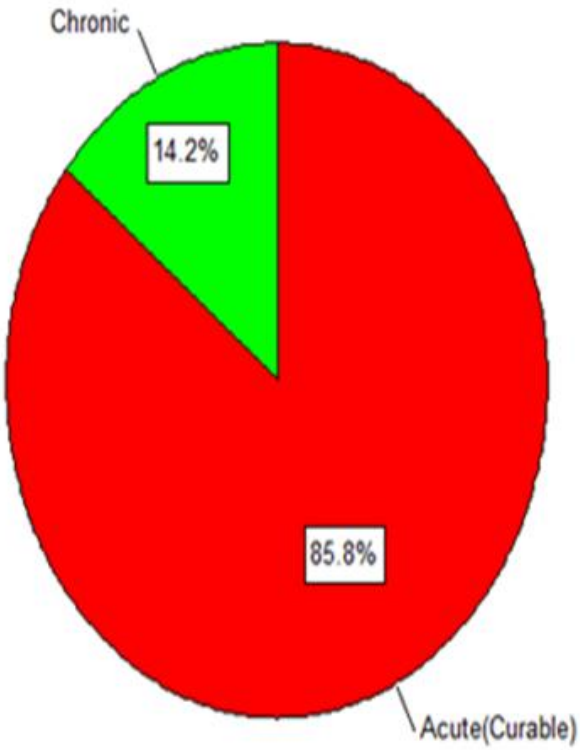

Fig. 13 Distribution of 155 patients of ITP according to prognosis after 6 months of diagnosis

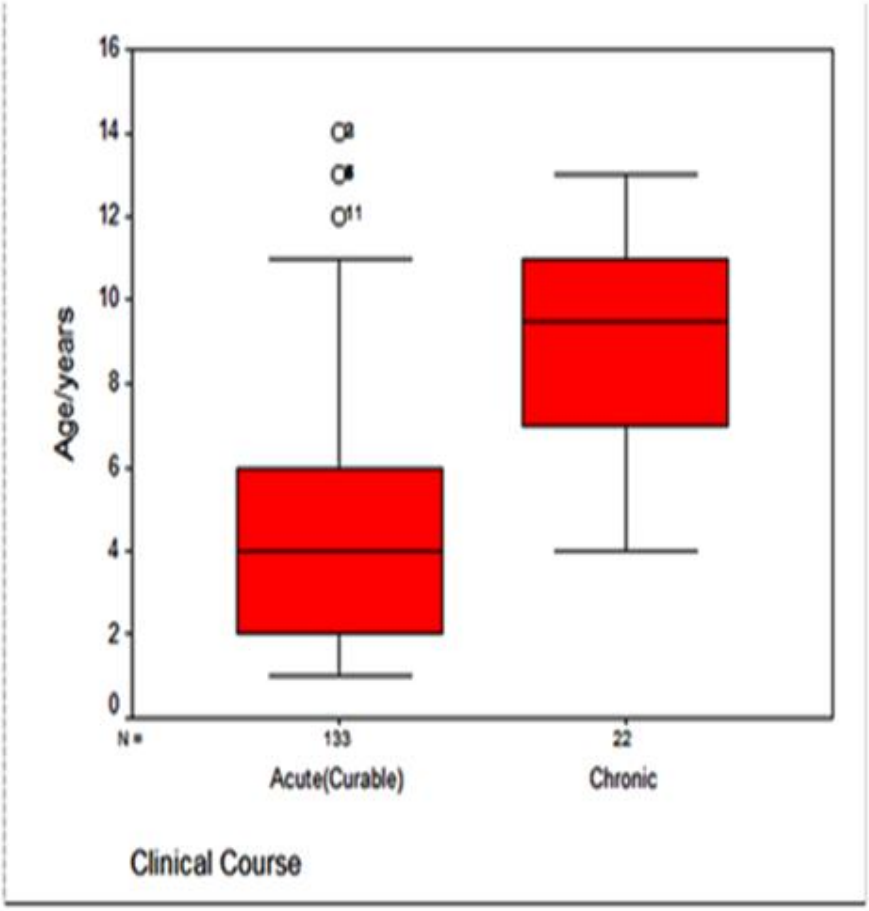

Fig.14 Significant differance in age between acute and chronic cases in 155 patients of ITP

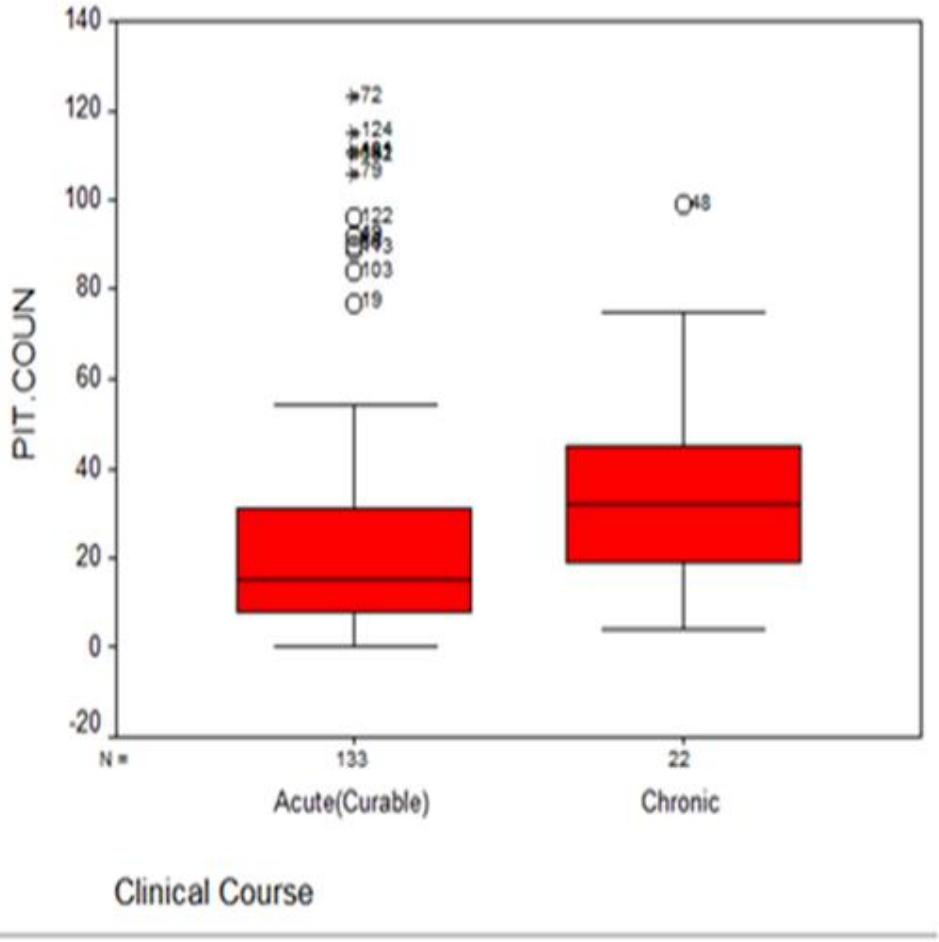

Fig .15 Difference in platelet count between acute and chronic in 155 cases of ITP

Table7: Risk factors for prognosis in 155 patients of ITP at Benghazi children hospital

Character	*Acute*	*Chronic*	*P-value*
Sex			
Male	*76*	*6*	
Female	*57*	*16*	*0.009*
Age /years			
N umber	*133*	*22*	
Mean	*4.7*	*9.2*	0.000
SD	*3.2*	*2.5*	
Platelet count/mm3			
Number	*133*	*22*	
Mean	*26.1*	*34.3*	*0.216*
SD	*2.4*	*23*	
MPV /fl			
number	*66*	*15*	
Mean	*9.1*	*12.7*	*0.000*
SD	*2.4*	*2.9*	
Clinical feature			
Dry hemorrhage	*100*	*14*	*0.503*
Wet hemorrhage	*2*	*0*	
Both	*31*	*8*	
H/O URTI	*55*	*6*	*0.210*

Chapter V

Discussion

Discussion

Immune thrombocytopenic purpura is a common benign bleeding disorder in childhood , occurring with annual incidence of 2-8 /100,000 children per year as reported by others **(Medeiros &Buchanan, 1996) (Blanchette&Carcao, 2000) (Sutor et al, 2001)**.

In this study,182 children with ITP were assessed in period of 9years,and a similar annular incidence was observed , in average 5.6 per100,000/year at Benghazi city, our results are higher than the ones observed in previous study done at Benghazi city which reported the incidence was 2.8 per100,000/year **(Amina Beayou &NureddinDaghman, 2004),** but still not as high as 12.5/100,000/year in children as at Kuwait **(Mohamed Zaki et al,1990)**.Among the children assessed(155), 133(85.8%) presented with acute ITP, and 22 went to chronic ITP(14.2%), the rate of chronic ITP(14.2%) in our study was in accordance with the reported for children below 15 years(15 to 20%)as reported by others **(Robb&Tiedeman,1990)(Shahid et al, 2004)**, on other hand our results were less than the rate in Qatar (38%)as reported by others**(Naima et al, 2009)**, and in Egypt (34.9%) as reported by others(**El Alfyet al, 2010**), and in one study in adults shows 9% of chronic cases was reported by others **(Portieljeet al, 2001)**.Most children with acute ITP were in 1 to 4 years age group (50%), this is comparable with results reported byothers**(Ahn&Horstman, 2002)(Imbach, 2006)**, on the other hand most children with chronic ITP presented at age more than 6 years, this is similar with the results reported by others**(Kuhne et al, 2003)(Watt, 2004)(Glanz et al, 2008)**.In this study, acute ITP was higher in males 82 (53%) when compared with girls, this is similar to previous studies **(Michael, 2009)(Naima et al, 2009),**whereas chronic ITP was predominant in females as age increases as reported by others**(Kuhne et al, 2001) (Naima et al, 2009)**.

Familial predisposition has been reported for cases of ITPsuggesting a genetic susceptibility**(Rischewski *et al*, 2006),** this aspect was not observed in the clinical experience of Qatar and Kuwait, as in this study no familial ITP was recorded.

Other recent studies noted that AfricanAmericans seem to be under represented among patients diagnosed with ITP**,** this observation may suggest unknown genetic factors that are protective against platelet autoimmunity **(Terrell et al, 2005)**.A seasonal fluctuation for a diagnosis of ITP was noted, with a peak in spring and early summer and a nadir in winter **(Diana, 2006)**, in our study 91 children (59%) with ITP presented in summer and spring, in contrast with these reports, ITP was found mainly in winter and spring at Egypt **(Khalifa *et al*, 1993)**, in Qatar, no significant seasonal variation was observed **(Naima *et al*, 2009),** even in Kuwait, no association was observed between incidence and the season**(Mohamed Zaki et al ,1990)** another observational study reported the peak occurrence of childhood ITP during Spring and a nadir in autumn**(Kuhne et al, 2001)**.

History of viral upper respiratory tract infection or immunization in weeks preceding the onset of purpura was reported by many studies **(Sutor et al, 2001)(Imbach, 2006**),in this studypreceding history of URTI within 1-2 weeks before diagnosis was more common in acute ITP than chronic ITP (41% , 27%), our results were in accordance with the one observed in Egypt (50%,10%) **(Khalifa et al, 1993)**, in contrast with these reports, another study documented that preceding viral infection was common in both acute and chronic ITP cases (71%,63.2%)**(Naima et al, 2009)**.

No detailed history of vaccine in relation to ITP was reported in our cases,MMR vaccine that is given in the second year of life is associated with an increased risk of ITP, since its introduction in the 1960s, the MMR vaccine has reduced the incidence of wild type measles by nearly 100% in the United States, although this vaccine is associated with an increased incidence of ITP, the attributable risk is low (~1 case/40000 doses of MMR) and disease associate with MMR vaccination is mild and resolves, on an average, within seven days, therefore does not suggest a need to alter current immunization policies **(Eric et al, 2008)**. One Turkishstudy of 93 children with ITP, reported seven infants had a probable relationship with vaccination, none of these infants progressed into chronic ITP**(Faith Demirciogiuet al, 2009)**. The diagnosis of ITP in our hospital is based principally on the history, physical examination, complete blood count and examination of the peripheral blood smear as reported by others**(George et al, 1996)(Cines &Blanchette, 2002) (Blanchette&Carcao, 2003)(Provan et al, 2003)**.

Although bone marrow aspiration (BMA) is not mandatory in children with typical features of acute ITP as reported by many researchers**(Eden&Lilleyman, 1992)** we found high frequency of BMA (69%)was performed and was normal but less than reported by previous study at Benghazi Children Hospital **(Amina Beayou &Nureddin Daghman, 2004)**, also American Society of Hematology group2011, suggested that BMA is not necessary in typical features of acute ITP patients before initiation of steroid treatment **(Cindy et al**, **2011**).

In our study, most of patients presented with ecchymosis and petechiae (98%), some of them have mucosal bleeding epistaxis, gastrointestinal bleeding and hematuria, the same presentationswere reported by others (**Sutor et al, 2001)(Imbach 2006)**.

None of our patients reported to have ICH, some recent studies have set the risk of ICH around (0.1-1%)**(Fogarty et al, 2007)**(**Philip,2011)**.

In this study most of the patients have normal WBC count,1.3% of children presented with low WBC as reported by others**(Catherine &Manno, 2005)**.

An observation that 25% of children with hemoglobin below 10g/dl may be explained by presence of sever hemorrhage, iron deficiency anemia or due to hemoglobinpathywhich need further prospective study to compare the severity of the bleeding with hemoglobin level and looking for other causes of anaemia. Eighty five percent of children presented with platelet count under 50×10^9 /L , 58% of them presented with platelet count under 20×10^9 /L , 29% with platelet count $<10\times10^9$ /L, no one had ICH, while some recent studies have shown that most of patients who developed ICH had platelet count $<10\times10^9$/L**(Butros et al, 2003).**

In some cases precipitating causes like arteriovenous malformation, head injury or aspirin use were identified**(Lilleyman, 1994)**.

In this study, no case with life threatening hemorrhage was found as reported by others (**Dickerhoff et al, 2000**).

The mean platelet volume (MPV) was elevated with MPV value>8fl in 68.2% of our children and MPV was more elevated in chronic ITP similar to many results of previous studies (**Isam Haddadin,2005)**.

. All our ITP patients were admitted to the hospital regardless of platelet count and clinical bleeding, many studies reported that hospitalization is inappropriate for children with platelet count of 20-30×10^9/L who are asymptomatic or with count more than 30×10^9/L whom is asymptomatic or has minor purpura **(George et al, 1996)**.

Guidelines from the American society of hematology 2011, recommended that observation and education are appropriate for the child with no clinical bleeding or mild bleeding regardless of platelet count **(Cindy et al, 2011).**

Eighty three percent of our children were treated with IVIG or steroids as reported by many centers in the world, although the high cost of IVIG treatment, it represented the first drug of choice for treatment of our patients as reported in many centers in USA **(George et al,1996) (Diana, 2006)**.Although the undesirable side effects of steroids, they are still the treatment of choice in many countries **(Ramyar&Kalantari, 2008)**.Most of cases with mucocutaneous bleeding received combination therapy of steroids and IVIG as reported by others**(George et al,1996)**, sixteen percent of our patients with platelet above 20×10^9/L and without mucosal bleeding were treated with observation as in many centers in the world **(Diana, 2006),** most hematologists in the United States choose to treat a child with a platelet count <10 ×10^9/L , or with mucous membrane bleeding**(Philip, 2011) (Diana, 2006)**.

American Society of Hematology, 2011 practice guideline, recommended that children with no bleeding or mild bleedingbe managed with observation alone regardless of platelet count **(Cindy et al**,2011),intermittent treatment with IVIG or anti D can be used to minimize the risk of bleeding due to severe thrombocytopenia while awaiting a spontaneous remission **(Diana, 2006**).

Splenectomy of chronic ITP children or ITP unresponsive to initial measures produces remissionin about 80% of patients**(Eden & Lilleyman, 1992**)(**Kojouri et al, 2004**).However, the relatively high rate of spontaneous remission supports delaying splenectomy for at least 12 months unless the child has sever disease and unresponsive disease as recommended by ASH,2011 and in this study splenectomy was carried out in two patients with chronic ITP, one was cured and one was not improved.No one of our patients received anti D therapy, although it is the first or second choice of therapy in many centers in Rh positive patients **(Cooper et al, 2002),** few studies showed one death because of severe hemolysis and renal failure**(Gaines 2000) (Kees et at,2002)**.We found less number of patients received blood transfusion as compared to previous study was done at Benghazi Children Hospital since 1995 to 1999**(Amina Beayou & Nureddin Daghman, 2004)**, some studies reported over use of platelet transfusion (**James & Corrigan , 1997**).Rituximab in children with chronic immunethrombocytopenic purpura showed a success of sustained platelet counts above 50 $x10^9$/L in 31% of 36 patients and the anti -CD20 therapy was well tolerated (**Bennett et al,2006)**and another study of rituximab therapy in children with severe chronic ITP showed stable platelet count (more than 150 x 10^9/L) in 63% of 24 patients**(Wang et al, 2005)**.In this study one patient of chronic ITP received 3 doses of anti-CD20 Rituximab, but no improvement in platelet count was reported.Other trials of treatment of chronic ITP like vincristine, Cyclophosphamide was not tried because of their side effects as reported by others **(Manoharan, 1986) (Srichaikul et al, 1980)**.

We do not have any experience with other recent therapies like oral Thrombopoietin receptors agonist or Romiplostim, which increase the platelet production in management of ITP **(Bussel et al, 2006) (Bussel et al, 2007)**.

Thrombopoietic agents and recombinant human megakaryocyte derived growth factor (MGDF) report promising responses in adults with chronic ITP refractory to other treatments**(Nomura et al, 2002) (Bussel et al, 2006)**.

We found older patients (more than 6 years) have statistically significant risk factor for developingchronic ITP(P= 0.000) as demonstrated significantly occurrence of chronic ITP in children over10 years of age by many researches**(Kuhne et al, 2003)(Glanz et al,2008**), however, other study consider age as an independent prognostic variable for chronic ITP**(Shahid et al, 2004)**.

Our multivariable analyses showed female patients more prone to develop chronic ITP (P= 0.009) as reportedby others **(Rosthojet al, 2003)(Imbach, 2006**)**(ElAlfy et al,2010**) In contrast to other studies in Vietnamese and German children patients were found that predominance of chronic ITP in males (**Kuhne *et al*, 2000**), although it has been suggested that sex is an independent risk of developing chronic ITP as documented by others **(Shahid et al, 2004)(Glanz et al, 2008)**.

History of upper respiratory tract infection 1-2 weeks before diagnosis was reported in 61 patients in our study and considered statistically insignificant risk factor of chronic ITP(P=0.10) as reported by others **(Shahid *et* al,2004)(Naima et al, 2009**)while other studies considered lack of previous acute illness as a significant predictor of chronic ITP **(ElAlfyet al, 2010)**.

Many studies focused on clinical manifestation that might help in assessment of risk variables in developing chronic ITP at time of diagnosis, in our study we found 98%of patients presented with skin manifestations (ecchymosis and petechiae) and some of them have mucosal bleeding, while the others have mucosal bleeding alone, there was no significant difference in prognosis between the presented type of skin lesion and mucosal bleeding(p-0.503) while other study considered lack of mucosal bleeding at time of presentation is significant prognostic variable of chronic ITP**(Glanze etal, 2008)**.

Although it has been suggested that platelet count >20x 10^9/L at diagnosis is high risk to progression to chronic illness (**Lusher *et al*,1966) (Glanz et al,2008)(ElAlfyet at,2010)** our multivariable analyses showed that statistically insignificant platelet count (P=0.216)as predictor factor of chronic ITP.

We found mean platelet volume is powerful indicator of the course of ITP(P=0.000), when it is below /above 8flpredicated of favorable outcomesimilar to many results of previous studies (**Isam Haddadin,2005)** while the other studies reported MPV is an independent predictor for chronic ITP as reported by others**(Shahid et al, 2004)**.

We found ESR is insignificant statistically as a prognostic factor of ITP(P=0.295)and no study before focused on it.

We found no effect of all trials of treatment on prognosis as reported by others where studies recognized that the initial drug treatment does not seem to alter the clinical course of the disease but it may shorten the period of profound thrombocytopenia as reported by others**(Gadner, 2001)**.

No available data of autoantibodies at time of diagnosis to be studied as significant prognostic factor of ITP, while as reported by others ,acute patients who have autoantibodies may be more likely to develop chronic ITP**(Tarantino etal,2005)**.

No facilities to study genetic aspect as potential factor for development of chronicity.

Eighty percent of children with persistent thrombocytopenia recovered from ITP between7-12 months after diagnosis as reported byIntercontinental Childhood ITP Study Group **(Imbach et al, 2006)**andcurrently chronic ITP defined as persistent thrombocytopenia more than12 months from the diagnosis**(Philip, 2011)**.

Conclusion

This study highlights the situation of ITP in Libya, the incidence of ITP in Benghazi city2-8 per100,000 of children, most of our ITP patients presented in Spring and Summer, the diagnosis and clinical finding are in line with other international reports, we observe hemoglobin between 7-10g/dl in25% of children.

All of our patients were admitted to the hospital regardless of platelet count and clinical bleeding.

Most of our patients subjected to the practical guidelines for the American Society of hematology for ITP in treating patients with platelets count $<30\times10^9$/L with IVIG and steroid, We found less number of patients received blood transfusion as compared by previous study, most acute cases can be managed by pediatrician in general ward without hematology referral.

The overall prognosis in childhood ITP is excellent. Approximately 85.8% of children had spontaneous remission, the risk for chronic ITP was predicted by older age 6years ; female gender; initial high MPV value >8fl, we found no effect of all trials of treatment on prognosis, no patient died and no patient had ICH, the previous predictors help the pediatrician when counsel the patients and families about the potential resolution of ITP.

Recommendations

- We need to follow a new international guideline to select the ITP children for admission and management according to the severity of bleeding and platelet count.
- Most cases of acute ITP can be managed by pediatrician in general ward without hematology referral.
- Bone marrow examination is mandatory in patients with atypical cases of ITP
- We need further prospective study to compare the severity of the bleeding with hemoglobin level and looking for other causes of anemia.
- Certain characteristic of ITP in this series such as viral infection; bacterial infections; seasonal variation and post vaccine ITP have to be further defined in large prospective studies.
- Weather ethnic or environmental factors play a role in the phenotype of ITP need epidemiological studies.
- Future studies to help to define a more precise timeline that differentiate chronic from acute course of ITP .
- Further studies are required for establishment the role of auto antibodies and H pylori associated antigen at time of diagnosis on the course of ITP.
- Future studies of genetic aspect as potential factor for development of chronic ITP.
- Optimal treatment will eventually be targeted toward a better delineation of the disease phenotype.

Chapter VI

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دراسة احصائية لمرض نقص الصفائح الدموية المناعي و خصائصه و العوامل التنبوئية لمساره في مستشفى الاطفال ببنغازي

2000-2008

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دراسة احصائية لمرض نقص الصفائح الدموية المناعي و خصائصه و العوامل التنبوئية لمساره في مستشفى الاطفال ببنغازي 2000-2008

ملخص الاطروحة

مرض نقص الصفائح الدموية من اكثر امراض نزف الدم شيوعا عند الاطفال والذى في الغالب تسبقه فترة اصابة بفيروسات او تطعيمات مما قد تؤدي لاضطرابات في جهاز المناعة و زيادة غير محدودة في الاجسام المناعية المضادة والتي تسبب تكسر في الصفائح الدموية ونقصها في الدم مما يؤدى الى نزف في الجلد و الأغشية المخاطية ولا يزال السبب غير معروف

- **الغرض من الدراسة :**
  - مراجعة التطبيقات العالمية للتشخيص و العلاج
  - العوامل التنبوئية لمسار المرض بمستشفى الاطفال بنغازي من شهر يناير 2000م الي شهرديسمبر2008م

- **الطريقة :**
  - تمت دراسة 155 ملف مريض من 182 مريض دخلوا لمستشفى الاطفال ببنغازي من يناير الي شهر ديسمبر2008م, بينما لم تتم دراسة 27 ملف مريض لعدم اكتمال المعلومات .
  - اعمار المرضى في الدراسة عند بداية المرض من 5 شهور الي 14 سنة المرضى
  - تمت دراسة المرضي من حيث مكان الاقامة, التهابات بالجهاز التنفسي العلوي بفترة اسبوع الي اسبوعين قبل المرض , الاعراض الابتدائية للمرض , عدد الصفائح الدموية و حجمها عند بداية المرض و نوع العلاج

- **النتائج :**
  - 123مريض من مدينة بنغازي ومعدل الحدوث السنوي للمرض بمدينة بنغازي 100,000/5.6في السنة ونسبة حدوث المرضفي الذكور للإناث 1.1:1 ونسبة حدوث المرض الحاد في الذكور للإناث 1.3:1, بينما نسبة حدوث المرض المزمن (اكثر من 6 اشهر) في الاناث اكثر من الذكور 1 : 2.6
  - اغلب الاصابة بالمرض الحاد (50%) في الاربع سنوات الاولى من العمر

- (39.4%)من المرضى كانوا مصابين بالتهابات في الجهاز العلوي التنفسي بفترة اسبوع الي أسبوعين قبل المرض,واكثر الاصابة بالمرض فى فصلي الصيف و الخريف واكثر الاعراض الابتدائيةنزف تحت الجلد(98%) واحيانا يكون النزف تحت الجلد مصاحبا بنزيف للأغشية المخاطية
- عدد الصفائح الدموية يتراوح من 0 الي123x10^9/ لتر وحجمها من 5.9 الي 21.2 فم عند بدء النزف , (69 %) منهم اجري لهم فحص نخاع العظم .
- (16%) عدد صفائحهم اكثر من 20x10^9 / لتر لديهم نزف تحت الجلد فقط لم يعط لهم العلاج في الوريد
- (54.2%) أعطيت لهم جزيئات مناعية في الوريد ، (24.5%) اعطي لهم الكورتيزون(4.5,%)اعطي لهم الاثنين معا وتم نقل الصفائح الدموية لاثنين من المرضى ونقل الدم لمريض واحد فقط و تم استئصال الطحال لمريضين.
- لا توجد حالات نزف بالدماغ ولاوفيات نتيجة للمرض
- (85.8%) من المرضي تم شفاؤهم في فترة 6 اشهر من المرض و بينما (14.2 %) استمر معهم المرض لمرحلة مزمنة (اكثر من 6 اشهر).

v الاستنتاج :

- معدل حدوث المرض سنويا عند الاطفال بمدينة بنغازي 5.6/ 100,000/ سنة ترسيخا لتقارير الدراسات العالمية .
- اغلب التطبيقات العلاجية مع التعليمات العالمية لكيفية العلاج .
- اغلب حالات المرض الحاد تعالج من طبيب الاطفال خارج قسم امراض الدم

v العوامل التنبوئية للمرحلة المزمنة للمرض كالاتي :

- بداية المرض بعد 6 سنوات من العمر .
- الاناث اكثر عرضة للمرض المزمن
- كبر حجم الصفائح الدموية اكثر من 8فم عند بداية المرض .