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From the Desk of Editor-In-Chief

Dear friends,

Thanks a lot for your encouraging feedback for inaugural issue of "CHILD INDIA". We are herewith bringing next volume for you. As promised, we have again planned contents to suit both practitioners and our postgraduate students. Idiopathic thrombocytopenic purpura is not uncommon in clinical practice, which has seen major change right from nomenclature to management. We hope review article on ITP will help you in updating yourself on management of ITP. We also have two interesting case reports, research methodology series and a PG case discussion in this volume. We have received answers of photo quiz from all corners and hope this trend will continue for this volume also.

Praveen Kumar

Golden Jubilee Pedicon 2013, Kolkata

A Brief report

Indian Academy of Pediatrics is celebrating Golden Jubilee this year. The Golden Jubilee celebration started with the Pedicon in Kolkata from 17 to 20 January 2013 at Science City Convention Centre. The comfortable weather in January coupled with the sprawling locale of Science City made the perfect ambience for this mega event. It was organised by West Bengal Academy of Pediatrics. Quite aptly the theme of the conference was "50 years of Child Care: Mission Achieved and Vision Ahead". Pedicon 2013 was attended by about 7000 delegates from all over India. It was also attended by delegates from Bangladesh, Nepal, UK, USA, New Zealand, Middle Eastern countries and Ukraine.

The Presidential Dinner was hosted on 16 January 2013 at the Serene Gold Acre of P C Chandra Greens. Dr N R Bahndari was the Chief Guest and he released the Golden Jubilee Logo of IAP. The memorable occasion was graced by many past Presidents of IAP. They were duly felicitated. Pandit Tanmoy Bose entertained the audience with his classical percussion ensemble Taaltantra.

On 15 and 16 January 2013 twelve Pre-conference workshops were arranged in various hospitals in Kolkata. All the workshops were very well attended. Five

training of trainers on NRP, BLS, Mission Uday, Mission Kishore Uday and Acute Care were also arranged as part of IAP President's Action Plan 2013.

The scientific extravaganza was set rolling with CME on 17 January 2013. Four concurrent CMEs were organized on CME for Post Graduate Students, Basic Pediatric CME, Advanced Pediatric CME and CME on Allied topics like Orthopedics, Ophthalmology, Otolaryngology, Gynecology and Dermatology.

The six scientific halls in Science City were named remembering the five stalwarts from five zones – Dr LSN Prasad, Dr PM Udani, Dr PN Taneja, Dr JN Pohowalla, Dr ST Achar and the main auditorium was named after Dr Tapan Kumar Ghosh.

Chief Guest Hon'ble Dr A P J Abdul Kalam, past President of India inaugurated the Golden Jubilee Pedicon on 17 January 2013 evening by floating 50 ceremonial lamps. He enthralled the huge audience with his inspiring speech. Dr Dilip Mahalanabis, the man who pioneered ORS graced as Guest of Honour and released the souvenir. To mark the occasion a book on 50 years of Pedicon was also released. Dr Shanti Ghosh, past President of IAP was decorated with lifetime achievement award. It was followed by FIAP and other awards and book releases. The evening ended with classical dance recital by Dona Ganguly and her troupe.

This year 700 faculty members participated in the scientific deliberations which covered every aspects of pediatrics. Many new speakers could be inducted this year as the policy of one session for each faculty member was followed. The packed halls during the scientific sessions were very encouraging. Dr Shantilal Seth oration was delivered by Dr M K Bhan. The Pedicon Swarna Jayanti oration was delivered by Dr Montek Singh Ahluwalia. Though he could not come in person, but he delivered the oration live from his office in Delhi by teleconferencing. The lively interaction with him was memorable. The two plenary sessions were on MDG 4 and on the theme 50 years of Child Care: Mission Achieved and Vision Ahead. The deliberation of the stalwart from Pakistan, Dr Zulfikar Bhutta will be remembered for a long time. Pediatric association of SAARC countries met for a symposium on typhoid on 18 January 2013 where members from various SAARC countries participated.

The morning of 18 January 2013 started with the "Dream Run". Members ran for the cause of "Prevent Teen Suicide, Prevent Thalassemia". About 300 enthusiastic members participated in the run in the early winter morning. The atmosphere took a festive look with banners, festoons, the horse carriage and a band in the forefront.

The Golden Jubilee Pedicon was a welcome change in many respects. Besides the one speaker one session norm, the speakers in the CMEs and conference were offered complimentary registration. None of the scientific sessions in the main scientific hours were sponsored by any pharmaceutical company. Neither the scientific halls were named after any pharmaceutical company. The conference also touched modern day innovations. It was the first medical conference in India which had its own downloadable app. The whole conference zone was also covered by wifi network.

I on behalf of the organizing committee express heartfelt thanks to all the members and partners for making this Golden Jubilee Pedicon a memorable event and a memory to cherish.

- Dr Jaydeep Choudhury

Organizing Secretary, Pedicon 2103

REVIEW ARTICLE

Recent advances in Immune Thrombocytopenic Purpura in Children

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Abstract:

Immune thrombocytopenic purpura (ITP), earlier known as idiopathic thrombocytopenic purpura, is one of the commonest acquired hemorrhagic disorders encountered in pediatric population. From idiopathic to immune, the changed nomenclature itself shows the growing awareness and improvement in the pathophysiology and management of the disease.

Earlier, due to lack of standardised definitions and international consensus on management guidelines, there used to be wide variation in the management of ITP. With better understanding of the disease, and many newer therapies available, there is need for update for diagnosis and management of ITP. There are now standard definitions not only to identify a case of ITP, but also to define response to treatment in a particular case.

Through this review article, we have tried to bring out the recent changes in terminologies related to ITP, advances in pathophysiology of disease, and latest guidelines for managing cases of both acute and chronic ITP.

Key Words: *immune thrombocytopenia, purpura, platelet*

Introduction:

Immune thrombocytopenic purpura (ITP) is not an uncommon problem encountered in childhood population. The disease usually follows a benign course in most children but can be life threatening in some. In children, acute ITP is often associated with a viral or bacterial infection and generally resolves spontaneously within 6 weeks. Approximately 20% of children with acute ITP progress to chronic form. This review focuses on advances in the pathophysiology and management of ITP in children.

New Definitions :

Until recently, the abbreviation ITP stood for idiopathic thrombocytopenic purpura, but awareness relating to the immune-mediated nature of the disease, and the absence or minimal signs of bleeding in a large proportion of cases have led to a revision of the terminology and renamed as Immune Thrombocytopenia [1]. ITP may occur in isolation (primary) or in association with other disorders (secondary). Various causes of secondary ITP are shown in following Box-1:

Box-1: Causes of secondary ITP :
Infection with CMV, H. pylori, Hepatitis C, HIV, Varicella
Vaccination side effect
Systemic lupus erythematosus
Antiphospholipid syndrome
Drugs like quinidine, sulphonamides, heparin etc
Common variable immune deficiency
Lymphoproliferative disorder
Post bone marrow transplantation

An International Working Group (IWG) consensus panel consisting of both adult and pediatric experts in ITP recently provided guidance on terminology, definitions, and outcome criteria for this disorder [1]. Primary ITP was defined by the IWG as a platelet count less than 100×109/L in the absence of other causes or disorders that may be associated with thrombocytopenia.

The IWG classified ITP as newly diagnosed (diagnosis to 3 months), persistent (3 to 12 months from diagnosis), and chronic (lasting for more than 12 months)[1].This classification appears to be more logical, considering the fact that most patients of ITP achieve spontaneous remission within few months of onset of disease.

The recommendations of IWG for assessment of response to ITP treatment is given in Table 1.

Corticosteroid dependence is defined as the need for ongoing or repeated administration of corticosteroids to maintain a platelet count in excess of 30×109/L and/or to avoid bleeding.

Severe ITP is the term reserved for patients who have clinically relevant bleeding, defined as bleeding at presentation of sufficient magnitude requiring treatment or by the occurrence of new bleeding symptoms requiring additional interventions or increase in drug dose.

Refractory ITP is defined as the presence of severe ITP occurring after splenectomy. Non splenectomized patients are classified as responders and non-responders to various drug therapies, but should not be labelled refractory.

Pathogenesis of IAP :

Earlier increased platelet destruction was thought to be the

Table 1: Classification of response to ITP treatment

Response	Criteria
Complete response (CR)	A platelet count ≥ 100 × 109/L measured on 2 occasions > 7 days apart and the absence of bleeding
Response (R)	A platelet count ≥ 30 ×109/L and a greater than 2-fold increase in platelet count from baseline measured on 2 occasions > 7 days apart and the absence of bleeding.
No response (NR)	A platelet count < 30 ×109/L or a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart
Loss of complete response	A platelet count < 100 × 109/L measured on 2 occasions more than a day apart and/or the presence of bleeding.
Loss of response	A platelet count < 30 × 109/L or a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart.

The duration of response is measured from the achievement of a first measured CR or R to the loss of CR or R.

only mechanism responsible for low platelet counts, but now there is evidence, to suggest that reduced platelet production plays an important role at least in some patients [2-5].

Two main mechanisms responsible for accelerated platelet destruction are:

1. Antibody mediated platelet destruction
2. Platelet lysis due to cytotoxic T lymphocytes

The initial stimulation for the production of platelet autoantibodies is unknown but undoubtedly is regulated by complex cellular and soluble mechanisms, primarily involving T helper (Th) lymphocytes and antigen presenting cells (APCs).

Platelets are the primary source of autoantigens which stimulate Th cells. Dendritic cells (DCs) or macrophages, which are responsible for the normal destruction of senescent platelets in vivo, are the initial APCs which stimulate platelet-reactive Th cells [2].Thus; the platelet first interacts with a major histocompatibility complex (MHC) class II-positive APCs, which subsequently processes platelet glycoprotein antigens into smaller antigenic peptides. These peptides are translocated to endosomal compartments and ultimately re-expressed on the APC surface in association with MHC class II molecules. If the Th cell receptor has a sufficient affinity for the antigen-MHC complex and appropriate co-stimulatory events are met (CD40 (APCs)/CD154 (Tcell) or B7 (APC)/CD28 (T cell)), the Th cell would be activated and would subsequently drive antigen-primed B lymphocytes to produce autoantibodies. After antibody binding, platelets can be removed from the circulation by either phagocytosis or complement-mediated platelet lysis. Engagement of the Fcγ receptor on the surface of human macrophages by anti-GPIIb-IIIa-coated platelets leads to engulfment of the opsonised platelets [2-5].

One of the suggested mechanisms in self-antigens recognition is molecular mimicry and cross-reaction due to viral/bacterial infection [4]. Another mechanism involves the generation of "cryptic" epitopes [6]. Semple et al. found that the production of platelet-specific auto reactive T helper cells was fundamental to induce auto-reactive anti platelet antibodies[7]. However, T cells were shown to be responsive only to platelet "cryptic" self-determinants, but not to the native molecule.

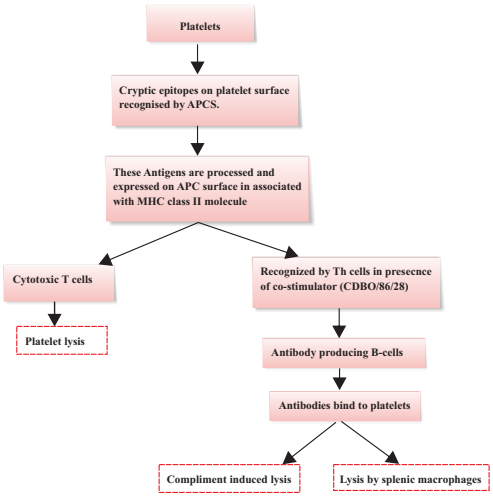
The finding that auto-reactive T cells found in patients with ITP are more easily activated than those from normal subjects, leads to the hypothesis that regulatory T cells (Tregs) may normally suppress the activation of self-reactive T cells and either deficient generation or reduced effector function of these cells plays a role in the development of autoimmunity. Tregs are CD4 positive cells, with high levels of cell surface expression of CD25. They can also be identified by their expression of the fork head family transcription factor p3 (Foxp3) and the expression of Foxp3 has been proposed to be the crucial switch factor in the induction of Tregs[8].A significantly high level of oligoclonal expansion of T cells in peripheral blood from ITP patients has been recently reported[5,9]. Olsson et al. analyzed genes and proteins involved in T-cell trafficking [10]. They found that ITP is associated with accumulation and activation of T cells in the bone marrow.

Patients of ITP often have elevated titers of anti platelet antibodies[11].Most commonly occurring autoantibodies are directed against the platelet surface glycoprotein complexes GPIIb-IIIa and GPIb-IX.Platelets coated with IgG autoantibodies undergo accelerated clearance through Fcγ receptors that are expressed by phagocytic cells, predominantly in the spleen, liver and bone marrow[4,6].

Anti platelet auto antibodies are generated by B cells under the control of Th cells and the cytokine they produce [12]. Two major helper T-cell cytokine profiles have been described: Th1 and Th2. Th1 cells produce interleukin-2 (IL-2), interferon (IFN)-γ, granulocyte macrophage-colony stimulating factor and tumor necrosis factor-α. Th2 cells produce IL-4,IL-5,IL-10. In general, Th1 cells promote organ-specific autoimmune disorders while Th2 cells tend to protect against them [13].

Several observations indicate that antibody-independent mechanisms of thrombocytopenia in ITP also exists, as anti-platelet antibodies are detected only in 50-70% of ITP patients, There is also evidence that suggests a direct cytotoxic effects of T cells on platelets[4,6,15,16].

Fig 1: Proposed mechanisms involved in destruction of platelets in ITP

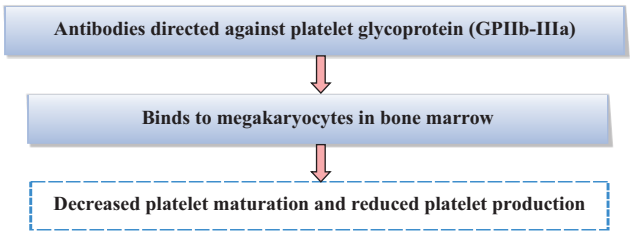


REDUCED PLATELET TURNOVER :

About one third patients of ITP fail to respond to aggressive immunosuppressive therapy or splenectomy has raised the suspicion that some other mechanisms may be involved in the development of the disease. Ineffective platelet production has been recently suggested in the pathogenesis of ITP.A shorter platelet life span is consistently seen in ITP patients compared with the 8- to 10-days platelet survival duration in healthy controls. The bone marrow contains normal or increased numbers of megakaryocytes. It has been suggested that some surface antigens (GP IIb-IIIa and GPIb-IX), which are co-expressed on platelets, megakaryocytes, and megakaryocyte precursors, are recognized by auto antibodies. Therefore the reduced platelet production is presumed to be due to a direct effect of antibodies on megakaryocyte maturation or platelet release [16] (Figure-2).

An ultrastructural analysis of megakaryocytes of patients with ITP showed that 80% of mature megakaryocytes had features of apoptosis and para-apoptosis, suggesting that the low platelet production rate or ineffective thrombopoiesis in ITP may be a result of greater apoptosis of platelet-producing megakaryocytes[17].

Fig 2: Proposed Mechanism of platelet production in ITP



DIAGNOSTIC CONSIDERATIONS:

A presumptive diagnosis of ITP is made when the history, physical examination, complete blood count, and examination of the peripheral blood smear do not suggest other etiologies for the thrombocytopenia. There is no "gold standard" test that can reliably establish the diagnosis of ITP.

Following diagnostic tools have been recommended by IWG for children and adults with suspected ITP:

PERIPHERAL BLOOD COUNT :

ITP is characterized by isolated thrombocytopenia with an otherwise normal complete blood count. Anemia from blood loss may be present, but it should be proportional to the amount, and the duration, of bleeding. If bleeding is prolonged and recurrent it may result in iron deficiency.

Peripheral smear may reveal abnormalities that are not consistent with ITP, such as schistocytes in patients with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome etc. Excessive numbers of giant or small platelets may indicate an inherited thrombocytopenia. Pseudo-thrombocytopenia due to EDTA–dependent platelet agglutination should also be excluded [18].

BONE MARROW EXAMINATIONS :

Bone marrow evaluation in children with newly diagnosed ITP is recommended only when abnormalities are present other than isolated thrombocytopenia in the blood count/smear, or if systemic features (eg, bone pain) are apparent, or if the patient has an otherwise unexplained enlarged spleen [19]. Bone marrow evaluation should be considered in cases who respond minimally or not at all to first-line therapies [20].

TESTS FOR HELICOBACTER PYLORI INFECTION-

Studies have shown association of H pylori infection with ITP in adults and its recommended to look for H. pylori with investigations like the urea breath test or the stool antigen test [21].However the evidence is not strong for this association in children .available literature does not support routine testing for H. pylori in children with ITP.

TESTS FOR HIV AND HCV INFECTION-

The thrombocytopenia associated with HIV and hepatitis C virus (HCV) infections may be clinically indistinguishable from primary ITP and can occur several years before patients develop other symptoms. Routine serologic evaluation for HIV and/or HCV infection in patients with suspected ITP, regardless of prevalence and personal risk factors is recommended. Control of these infections may result in complete hematologic remission [22].

TESTS FOR QUANTITATIVE IMMUNOGLOBULIN LEVEL -

Baseline immunoglobulin (Ig) levels (IgG, IgA, and IgM) should be measured in children with persistent or chronic ITP. Low levels may reveal conditions such as common variable immunodeficiency (CVID) or selective IgA deficiency.

Direct antiglobulin test& blood group Rh(D) typing

These investigations should be considered when anemia associated with reticulocytosis is found and if treatment with anti-D immunoglobulin is being planned [23].

Investigations with potential utility

Many other tests are available which may be useful in certain conditions. Assays for antibodies to specific platelet glycoproteins are not routinely recommended because platelet-associated IgG (PaIgG) is elevated in both immune and non-immune thrombocytopenia [24].Antiphospholipid antibodies (APLA), including anticardiolipin antibodies and lupus anticoagulant, can be found in approximately 40% of otherwise typical adult patients with ITP [25].Apositive antinuclear antibody (ANA) test may be a predictor of chronicity in childhood ITP [26]. Anti-thyroid antibodies may be present in around 8-14% of ITP patients [27].

Management of ITP:

General measures:

Most of the patients have mild symptoms. Only 3% of children with ITP have clinically significant symptoms such as severe epistaxis or GI bleeding. Severe bleeding is more likely in children with platelet counts less than 10 ×109/L [28]. The incidence of intra-cranial haemorrhage (ICH) in children with ITP is approximately 0.1% to 0.5%, and predicting with confidence which child will develop an ICH is not possible [29]. Risk factors for ICH in children with severe thrombocytopenia include head trauma and concomitant use of medications that adversely affect platelet function. Precaution should be taken in the management of children with ITP and coexisting vasculitis or coagulopathies, as may be seen in cases with varicella-associated ITP. Management guideline is summarized in Table 2.

Table 2: Clinical grading and management approach in ITP

Bleeding/quality of life	Management approach
Grade 1. Minor bleeding, few petechiae (≤ 100 total) and/or ≤ 5 small bruises (≤ 3 cm diameter); no mucosal bleeding	Consent for observation
Grade 2. Mild bleeding, many petechiae (> 100 total) and/or > 5 large bruises (> 3 cm diameter); no mucosal bleeding	Consent for observation or treatment in selected children
Grade 3. Moderate bleeding, overt mucosal bleeding, troublesome lifestyle	Intervention to reach grade ½ in selected children
Grade 4. Mucosal bleeding or suspected internal haemorrhage	Intervention

Health-related quality of life in children

Patient-reported outcomes, including health-related quality of life (HRQoL) measures, are useful components for evaluating and understanding the effects of symptoms and treatments from the patient's perspective. A disease-specific tool has now been developed— the Kid's ITP Tools (KIT)—that has reliable management properties [30].

Expectant "watch and wait" policy

The majority of children with newly diagnosed ITP lack significant bleeding symptoms and may be managed without therapy directed at raising the platelet count. Therefore, it is essential that parents and children with ITP understand the risks of serious or life-threatening hemorrhage, and are also aware that children for whom drug therapy is prescribed are at substantial risk of serious hemorrhage.

Hospitalization

For children with an established diagnosis of ITP, hospital admission should be reserved for those who have clinically significant bleeding. Problematic psychosocial circumstances of child and family (e.g., behavioural issues, remote residence from a health care facility) should also be considered.

First line therapy for acute ITP in children:

While most patients of acute ITP can be managed by observation alone, certain drugs are available which increases the platelet count more rapidly than if no treatment is given. All of these drugs have certain side effects (Table 3), and the decision to treat should be individualized.

Emergency treatment in children

In emergency situation or life-threatening situations, a larger-than-usual dose (2- to 3-fold) of platelets should be infused together with IV high-dose corticosteroids and IVIg or IV anti-D. The goal of treatment is to elevate the platelet count to a level where the risk of severe bleeding is minimized as soon as possible. In special circumstances, emergency splenectomy may also to be considered.

Table-3: Drugs for treatment of ITP [31-34]

Drugs	Approximate response rate	Approximate response time	Toxicities
IV anti-D 50-75µg/kg	50-77% achieve a platelet response depending on dose	≥ 50% respond within 24 hours	Headache, fever, chills, hemolysis, renal failure
IVIg single dose of 0.8-1 g/kg on day1	Effective in more than 80% of patients	1-2 days	Headache (can be severe), fever
Prednisone 1-2 mg/kg for 14 days, or 4 mg/kg for 4 days.	Upto 3/4th patient respond depending on dose	2-7 days	Transient mood changes, gastritis, weight gain.
Wait and watch	Approximately 2/3rd patients improved spontaneously within 6 months	Days to months	Preventable hemorrhage occurs, activity restriction, anxiety.

TREATMENT OPTIONS FOR CHILDREN WITH PERSISTENT OR CHRONIC ITP

The goal of treatment for children with persistent or chronic ITP is to maintain a hemostatic platelet count with first-line therapies and to minimize the use of prolonged corticosteroid therapy. Cytotoxic drugs should be used with extreme caution in children. All children with persistent or chronic ITP should have their case reviewed and managed by a hematologist experienced in the diagnosis and management of children with ITP.

Dexamethasone.

High dose Dexamethasone (0.6mg/kg/day for 4 days, every 4 weeks, for 6 cycles) has shown to achieve a complete or partial remission in 25% of children and adolescents with persistent or chronic ITP[35].

High-dose methylprednisolone (HDMP):

HDMP, 30 mg/kg/d for 3 days followed by 20 mg/kg/d for 4 days has been used as an alternative to IVIg[36].

Rituximab

Rituximab(375 mg/m2/week for 4 weeks) has been used with success in children with chronic ITP refractory to other treatments[37,38]. Overall, the response rate (≥ 50 ×109/L Platelet count) is between 31% and 68%. In all case series, rituximab was well tolerated with the exception of serum sickness.

TPO-RECEPTOR AGONISTS:

Two new thrombopoietin receptor agonists that stimulate platelet production, romiplostim and eltrombopag, are now approved for the treatment of adults with chronic ITP. The safety and efficacy of TPO-R agonists in pediatric patients are currently being investigated. A recently reported placebo-controlled trial indicates good response rates and good safety profile of romiplostim in children with chronic ITP [39]. The use of eltrombopag in children has not yet been reported, though adult data are promising [40].

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Clippings from
"GUIDELINES FOR ENHANCING OPTIMAL INFANT AND YOUNG CHILD FEEDING PRACTICES"
MINISTRY OF HEALTH AND FAMILY WELFARE 2013

a. Early initiation of breastfeeding; immediately after birth, preferably within one hour.

b. Exclusive breastfeeding for the first six months of life i. e 180 days (no other foods or fluids, not even water; but allows infant to receive ORS, drops, syrups of vitamins, minerals and medicines when required)

c. Timely introduction of complementary foods (solid, semisolid or soft foods) after the age of six months i. e 180 days.

d. Continued breastfeeding for 2 years or beyond

e. Age appropriate complementary feeding for children 6-23 months, while continuing breast feeding. Children should receive food from 4 or more food groups [(1) Grains, roots and tubers, legumes and nuts; (2) dairy products ; (3) flesh foods (meat fish, poultry);(4) eggs, (5) vitamin A rich fruits and vegetables; (6) other fruits and vegetables] and fed for a minimum number of times (2 times for breasted infants 6-8 months; 3 times for breastfed children 9-23 months; 4 times for non-breastfed children 6-23 months)

f. Active feeding for Children during and after illness.

International Guidelines Series

Antenatal Corticosteroids to Reduce Neonatal Morbidity andMortality

Royal College of Obstetrics & Gynaecology Guideline

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The aim of this guideline is to provide up-to-date information in form of frequently asked questions regarding use of antenatal corticosteroid therapy in women whose babies are at risk of complications owing to either preterm birth or elective caesarean section at term.

What are the benefits of antenatal corticosteroids?

Antenatal steroids are associated with a significant reduction in rates of neonatal death, RDS and intraventricular haemorrhage and are safe for the mother.Antenatal corticosteroids have no known benefits for the mother.

At what gestation should antenatal steroids be used?

Clinicians should offer a single course of antenatal corticosteroids to women between 24+0 and 34+6 weeks of gestation who are at risk of preterm birth.

How long after administration is a course of antenatal corticosteroids most effective?

Antenatal corticosteroids are most effective in reducing RDS in pregnancies that deliver 24 hours after and up to 7 days after administration of the second dose of antenatal corticosteroids.

Antenatal corticosteroid use reduces neonatal death within the first 24 hours and therefore should still be given even if delivery is expected within this time.

How safe is the use of antenatal corticosteroids?

Women may be advised that the use of a single course of antenatal corticosteroids does not appear to be associated with any significant maternal or fetal adverse effects.

Are there any contraindications to the use of antenatal corticosteroids?

Caution should be exercised when giving corticosteroid therapy to women with systemic infection including tuberculosis or overt chorioamnionitis.

Who should receive antenatal corticosteroids?

Antenatal corticosteroids should be given to all women at risk of iatrogenic or spontaneous preterm birth up to 34+6 weeks of gestation.

Antenatal corticosteroids should be given to all women for whom an elective caesarean section isplanned prior to 38+6 weeks of gestation.

1. In multifetalpregnancy: Clinicians should continue to offer a single course of antenatal corticosteroid treatment to women with multiple pregnancy.
2. In women with diabetes mellitus: Diabetes mellitus is not a contraindication to antenatal corticosteroid treatment for fetal lung maturation.
3. In women undergoing elective caesarean section: Corticosteroids should be given to reduce the risk of respiratory morbidity in all babies delivered by elective caesarean section prior to 38+6 weeks of gestation.
4. In pregnancies with fetal growth restriction: Pregnancies affected by fetal growth restriction between 24+0 and 35+6 weeks of gestation at risk of delivery should receive a single course of antenatal corticosteroids.

What is the best dose and route of administration for a course of antenatal corticosteroids?

Betamethasones 12 mg given intramuscularly in two doses or dexamethasone 6 mg given intramuscularly in four doses are the steroids of choice to enhance lung maturation.

When should an antenatal course of corticosteroids be repeated?

Weekly repeat courses of antenatal corticosteroids reduce the occurrence and severity of neonatal respiratory disease, but the short-term benefits are associated with a reduction in weight and head circumference. Weekly repeat courses are not recommended.

A single rescue course of two doses of 12 mg betamethasone or four doses of 6 mg dexamethasone should only be considered with caution in those pregnancies where the first course was given at less than 26+0 weeks of gestation and another obstetric indication arises later in pregnancy.

REFERENCE:

Antenatal Corticosteroids to Reduce Neonatal Morbidity andMortality: RCOG Green-top Guideline No. 7: Oct 2010: Royal College of Obstetricians and Gynecologists.

LINK FOR FREE DOWNLOAD:

http://www.rcog.org.uk/womens-health/clinical-guidance/antenatal-corticosteroids-prevent-respiratory-distress-syndrome-gree

Immune Thrombocytopenic Purpura in association with Hepatitis A virus Infection

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Abstract

Hepatitis A virus infection is usually a benign self-limiting disease during childhood. Immune thrombocytopenia is a benign, self-limiting disease in children, generally associated with viral infections. Immune thrombocytopenic purpura is rarely reported as a complication of acute hepatitis A. We report a 4 year old male child with immune thrombocytopenic purpura complicating acute hepatitis A infection. The case highlights that Hepatitis A should be included in the etiological work up of immune thrombocytopenic purpura. A review of literature regarding this association is presented.

Keywords: *Hepatitis A, immune thrombocytopenic purpura, child*

Introduction

Hepatitis A virus, a RNA-containing picornavirus, is a very common cause of infectious hepatitis in children. Up to one-quarter of adults and over two-thirds of children with hepatitis A have no symptoms. A significant proportion of young children with HAV infection remain anicteric during the illness [1]. Extrahepatic autoimmune manifestations have been rarely reported in children. One such extra- hepatic complication is autoimmune thrombocytopenic purpura that has been reported to occur with hepatitis A, mostly in adults [2]. Here we report a 4 year old male child who had immune thrombocytopenic purpura associated with hepatitis A infection.

CASE REPORT

Case Report

A 4 year old male child was brought with complaints of epistaxis for 2 days, and one episode of altered blood in vomitus. There was no associated fever. There was no history of similar complaints or blood transfusions in the past. There was no history of easy bruisability or prolonged bleeding from injury sites. On examination, the child had associated icterus. The child had no pallor or lymphadenopathy. Multiple petechiae were seen. Abdominal examination revealed hepatomegaly with a liver span of 8 cm. There was no sternal tenderness.

Investigations revealed a hemoglobin of 9.7 g/dl, total leokocyte count of 8800 per cu.mm with normal distribution and no atypical cells. Platelet count was 12000 per cu.mm. Serum creatinine was 0.4 g/dL. Liver function tests showed total serum bilirubin 2.2 mg/dl (direct bilirubin 1.2 mg/dL), Aspartate aminotransferase of 800 IU/L and Alanine transaminase of 1085 IU/L and mildly raised alkaline phosphatase (152 IU/L). Ultrasound abdomen revealed enlarged liver. Prothrombin time and activated partial thromboplastin time was normal. Fibrin degradation product (FDP) was negative. Direct Coomb's test was negative. Bone marrow examination showed megakaryocytic thrombocytopenia with no abnormal cells. A diagnosis of immune thrombocytopenic purpura was considered. HIV ELISA was negative. IgM anti hepatitis A virus antibody was positive. Anti-HAV IgG, HBsAg and HCV serology were negative. His tests for infectious mononucleosis, Dengue hemorrhagic fever, and leptospirosis were negative. He was diagnosed as Hepatitis A associated immune thrombocytopenic purpura.

The child needed platelet transfusions twice. He was Rh positive and was given anti D immunoglobulin. As there was persisting gum bleed and epistaxis despite anti D treatment, IVIg 1 g/kg was given. Platelet count improved to 32000 per cu.mm and bleeding ceased. At discharge, the platelet count was 42000 per cu.mm. On follow up after one month, his icterus had subsided. His bilirubin was 0.6 mg/dl and ALT was 60 IU/L. Repeat platelet count was 1.6 lac per cu.mm.

Discussion

Immune thrombocytopenia is a benign, self-limiting disease in children, generally associated with viral infections like hepatitis B and hepatitis C[3]. Immune thrombocytopenic purpura is rarely reported as a complication of acute hepatitis A especially in children[2,4-6]. Among the reported cases, in a few patients who were anicteric with no other associated symptoms, autoimmune thrombocytopenic purpura was the sole manifestation of hepatitis A (which was found only on serological examination). In others, thrombocytopenia was noted after the onset of jaundice [7]. There were no cases with simultaneous onset of thrombocytopenia with jaundice [7]. Our case had a simultaneous onset of thrombocytopenia and jaundice.

The proposed theories to explain thrombocytopenia in hepatitis A patients are direct marrow suppression, viral-associated hemophagocytosis syndrome, immune-mediated peripheral destruction of platelets or increased platelet consumption associated with disseminated intravascular coagulopathy[8]. In our case, bone marrow showed features of megakaryocytic proliferation. This observation is suggestive

Contd ... 11

ISOLATED SPLENIC TUBERCULOSIS IN A CHILD

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Abstract

We are reporting a 10 years old child who presented to us with acute pain abdomen. A diagnosis of isolated splenic tuberculosis was established and child showed significant improvement after receiving antitubercular therapy . Splenic tuberculosis should be considered as one of the differential diagnosis in patients presenting fever and splenomegaly in endemic counties.

Key Words- *Splenic Tuberculosis,child*

INTRODUCTION:

Despite of the latest advances in knowledge and technology tuberculosis still remains a major health problem in developing countries. Diagnosis of abdominal tuberculosis in spite of advancement in radiologic technologies still remains a challenge today [1]. In a suspected case of abdominal tuberculosis radiological findings may vary from bowel thickening, lymphadenopathy, ascites, free gas suggestive of perforation to abscesses [2]. Tuberculosis (TB) of the spleen may manifest as an extra pulmonary manifestation of disseminated miliary TB or as an isolated entity without any evidence of the presence of a tubercular lesion elsewhere in the body. The latter is an extremely rare clinical entity particularly among immunocompetent persons. Various cases of isolated splenic tuberculosis have been reported in adult age group [3-5]. We are herewith reporting one such rare case in pediatric age group.

CASE REPORT

CASE REPORT

A 10 year old male child was admitted with complaints of acute pain abdomen. Pain abdomen was vague, diffuse but more marked in the left upper abdomen. There was a history of low grade fever, decreased appetite and undocumented weight loss for last 5 months. Before admission, he had been treated at different setups without having any definite diagnosis. There was no other significant past illness. No contact with a patient of tuberculosis was reported. There was no history of recurrent illnesses or any previous blood transfusion. At admission the patient was anxious with a toxic look and stable vitals. Physical examination revealed high temperature (up to 39.5 °C), some pallor, icterus and a palpable tender spleen 4cms below the left costal margin. Laboratory investigations revealed microcytic hpochromic anemia, total leucocytes count: 7,500 (N-44,L-52,E-3,M-1), ESR: 84mm/h, Serum ADA: 84 U/L (normal: up to 45 U/L), LDH 535 U/L (normal 110-295 U/L at 37C). IGM

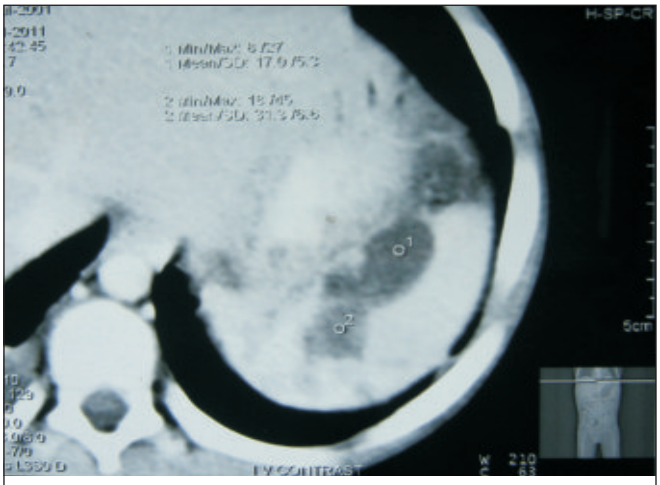

Fig I :CT Scan Abdomen showing multiple splenic abcess

for TB was positive. PPD was negative and there was no lab finding suggesting immunodeficiency or HIV. Abdominal sonography showed splenomegaly with multiple hypoechoic and hypodense areas, suggestive of splenic abscess. Patient was started on broad spectrum antibiotics with anti Staphylococcus aureus coverage. Fever persisted in spite of 14 days of antibiotic therapy. Gastric aspirate for AFB and culture were inconclusive. CT scan was done to review the spleen and re examination of the patient was performed with a thorough contact survey. CT scan showed a multiple large irregular hypodense lesions in the spleen suggestive of a tubercular splenic abscess (Fig 1).

An ultrasound guided fine needle aspiration cytology (FNAC) was performed which revealed chronic granulomatous

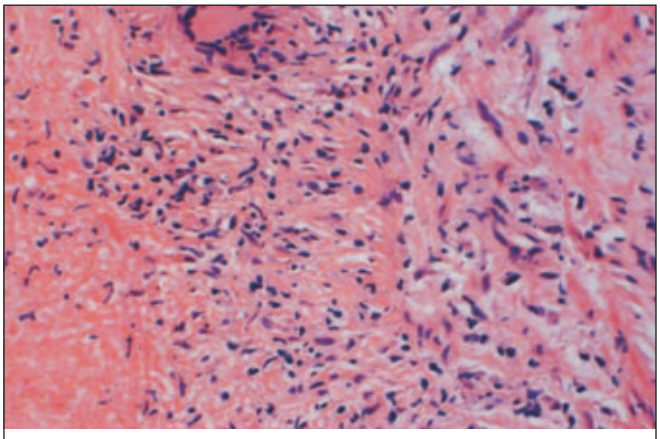

Fig II : Microphotograph of FNAC of splenic lesion showing chronic granulomatous inflammation with multinucleated giant cells and focal necrosis again suggestive of tuberculosis (100X)

inflammation with multinucleated giant cells and focal necrosis again suggestive of tuberculosis (Fig II).

Thus, a final diagnosis of isolated splenic tuberculosis was made. On contact survey patient's paternal uncle was found to be a diagnosed case with progressive pulmonary tuberculosis.

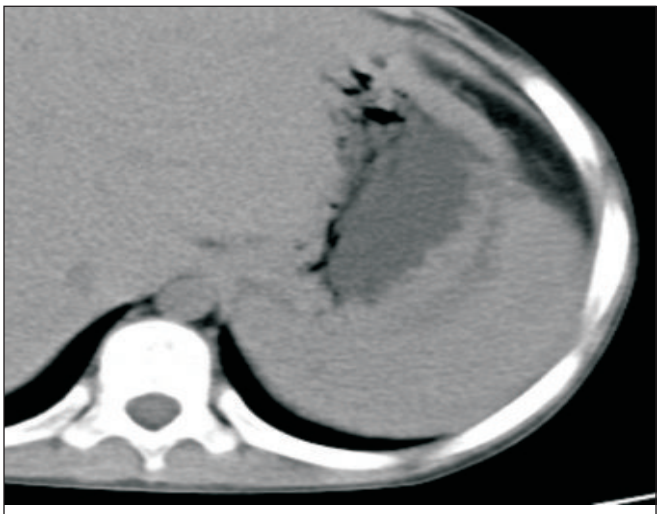

Fig-3 : Follow Up CT Scan showing significant improvement(resolution of splenic abscess)

Patients was put on anti tuberculous therapy (ATT) . Patient responded well with a review CT scan done after 4months of treatment showed significant resolution (Fig-III).

Discussion

Diagnosis of a case of splenic tuberculosis involves a wide range of modalities ranging from non invasive ultrasonography to invasive procedures like splenectomy and biopsy. However, recently non invasive and minimally invasive procedures are being preferred to diagnose these cases [4]. The yield of various modalities is variable in making a diagnosis of splenic tuberculosis. Suri et al have reported up to 88% sensitivity of FNAC for diagnosing a tuberculous pathology in the spleen [6].

Splenic abscess in pediatric age group is uncommon and are associated with previous trauma, metastatic hematogenous infection (e.g. bacterial endocarditis), immunosupression or hemoglobinopathies. The most common pathogens isolated from splenic abscess are staphylococcus and streptococcus [7].Conservative management of patients with splenic abscess is recently being advocated [8]. Our patient, who was admitted with acute pain abdomen, was diagnosed as a case of isolated splenic tuberculosis and showed significant improvement after receiving antitubercular therapy. Our case suggests that splenic tuberculosis should be considered as one of the differential diagnosis in patients presenting with FUO and splenomegaly especially in areas where the disease is prevalent. Rare cases of isolated splenic tuberculosis have been recently reported. Splenic tuberculosis can even affect immunocompetent individuals. To the best of our knowledge no case has been reported in an immunocompetent pediatric patient. Since it is difficult to establish diagnosis of tuberculosis especially in pediatric patients' use of non invasive modalities like ultrsonography and CT scan can be helpful in making the diagnosis.

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Immune Thrombocytopenic Purpura ...

of immune-mediated platelet destruction rather than marrow suppression. The dramatic response observed with use of IVIg and anti D is noteworthy as it favours an auto-immune mechanism as the underlying cause. We ruled out the other causes of thrombocytopenia in Hepatitis A infection by appropriate investigations.

Considering the fact that Hepatitis A infection is a very common infection among children in endemic countries like India, with a significant proportion of the young children remaining anicteric during the illness, the possibility of HAV infection should be considered in the etiologic work up of children with thrombocytopenia in these endemic countries. The exact burden of this rare complication of HAV can be ascertained only if routine testing is carried out in all children with ITP. Such a study may be worthwhile considering the fact that an effective vaccine is available for HAV which can potentially prevent the occurrence of this serious condition in children.

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PG Case Discussion

Dr Deepak Bansal, Additional Professor | **Dr Annapoorani**, Senior Resident
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Post Graduate Institute of Medical Education & Research, Chandigarh

4-years-old female, resident of Chandigarh presented with:

- Fever - 8 months. Low grade, off and on
- Progressive abdominal distension - 6 months

There was history of lethargy, intermittent skin bruises and epistaxis and received two blood transfusions in previous 3 months. Child had loss of appetite with undocumented weight loss. There was no history of bone pains or jaundice.

Summary of Examination Findings

- Severely wasted with pallor and petechiae
- Lymphadenopathy in cervical, axillary and inguinal region: maximum 2 x 2 cms
- Mild bilateral pedal edema
- No bone tenderness or hemolytic facies
- Splenomegaly - 8 cm below the costal margin. No free fluid
- Other systemic examination - unremarkable

Clinical Differential Diagnosis

Infections

- Visceral leishmaniasis (though not from endemic region)
- Tuberculosis (large spleen size would be odd)
- HIV
- Chronic active Ebstein Barr virus infection
- Hematological malignancy – Acute leukemia, though duration of 8 months would be very odd.

First Line Investigations Findings

Hemogram	
Hemoglobin	6.5 gm/dL
Reticulocyte count	6%
TLC	26,000 cells/mm3
Differential	Polymorphs 13%; Lymphocytes 85%; Monocytes 2%
Platelets	25,000 cells/mm3
Peripheral smear	Spherocytes and target cells with macrocytic anemia

Thus the first line investigations indicated anemia, thrombocytopenia with lymphocytosis. The peripheral smear had some evidence of hemolysis. So the child was further investigated.

Liver function tests	
Total proteins	6.8 gm/dL
Albumin	2.0 gm/dL
Globulin	4.8 gm/dL
Total bilirubin	0.5 mg/dL
AST	42 U/L
ALT	38 U/L

HIV serology	Negative
RK39 antibody	Negative
Cxy	Normal
Mantoux	Negative
EBV antibody (VCA and EBNA)	Negative

Second Line Investigations

- Fine needle aspiration cytology of lymph node revealed nonspecific reactive follicular lymphoid hyperplasia.
- Bone marrow examination revealed cellular marrow with myeloid and erythroid hyperplasia, increased megakaryocytes with no excess of blast cells. No Lleishman-donovan bodies identified.
- Other Investigations are summarized below

Plasma Hb	250 gm/dL
Urine Hb	Raised
LDH	2000 U/L
Direct coombs test	Positive
Antinuclear antibody	Negative
HBsAg	Negative
Hepatitis C antibody	Negative
Rheumatoid factor	Negative
Ig G	1950 mg/dl (345-1236)
Ig M	350 mg/dl (43-207)
Ig A	390 mg/dl (14-160)

With features of chronic lymphoproliferation, autoimmune hemolytic anemia and hyper-gammaglobulinemia, a possibility of autoimmune lymphoproliferative disorder (ALPS) was considered. With this suspicion in mind, flow cytometry of blood was requested to look for evidence of raised double negative T cells.

- CD3+ CD4- CD8- (double negative T cells): 14% of total lymphocytes.
- Subsequent immunohistochemistry of lymph node revealed increased population of double negative cells as well.

DISCUSSION:

WHEN TO SUSPECT ALPS?

You should suspect ALPS if there is evidence of

- Non-malignant and non-infectious lymphoproliferation with lymphadenopathy and hepatosplenomegaly
- Autoimmunity with hyper-gammaglobulinemia.

Autoimmunity in ALPS can virtually affect any organ; most common identified is autoimmune cytopenia.

PREVALENCE:

Exact prevalence is unknown due to varied clinical presentation.

AGE OF PRESENTATION:

Majority are symptomatic by 5 years of age (range 6 months to 18 years)

PATHOGENESIS

Mutations in FAS gene leads to impaired apoptosis with proliferation of lymphocytes, manifesting as lymphadenopathy, autoimmune phenomena and high risk of developing malignant lymphomas.

Revised diagnostic criteria for ALPS

REQUIRED CRITERIA

1. Chronic (> 6 months), nonmalignant, noninfectious lymphadenopathy and/or splenomegaly
2. Elevated CD3+ CD4- CD- Double negative T cells (> 1.5% of total lymphocytes or >2.5% of CD3+ lymphocytes) with normal or elevated lymphocyte counts.

ADDITIONAL CRITERIA

PRIMARY

1. Defective lymphocyte apoptosis in 2 separate assays
2. Somatic or germ line pathogenic mutation in FAS, FASLG, or CASP10 genes

SECONDARY

1. Elevated plasma serum FAS ligand level (>200 pg/mL), IL-10 levels (>20 pg/mL), vitamin B-12 levels (>1500 ng/L) or IL-18 levels (>500 pg/mL)
2. Typical immunohistologic findings as reviewed by a hematopathologist
3. Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) with elevated IgG levels (polyclonal hypergammaglobulinemia)
4. Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity

DEFINITIVE DIAGNOSIS: Both required criteria + one primary accessory criterion.

PROBABLE DIAGNOSIS: Both required criteria + one secondary accessory criterion.

MANAGEMENT

Significant number of ALPS patients does not need any intervention for asymptomatic lymphadenopathy and splenomegaly that often regresses with age.

Management of cytopenia:

- **Steroids:** IV pulse methyl prednisolone (5-30 mg/kg) for 3 days followed by oral prednisolone (2 mg/kg). Taper over next 8-12 weeks.
- **IV immunoglobulin** (1-2 mg/kg) given concomitantly with IV steroids.
- **G-CSF:** In patients with isolated chronic neutropenia with infections.
- **Immunosuppresants:** Mycophenolate mofetil, sirolimus, hydroxychloroquine, methotrexate, mercaptopurine, vincristine, azathioprine and cyclosporine can also be considered as a steroid-sparing measure.
- **Rituximab:** for treatment of refractory, chronic cytopenias
- Splenectomy is avoided.
- **Hematopoietic stem cell transplantation:** In severe phenotype due to homozygous FAS mutation and refractory cytopenias.

Genetic counseling and screening all family members as autosomal recessive and dominant mutations are described. Follow up for evaluation of lymphoma.

PROGNOSIS

Morbidity and mortality in ALPS depends on the severity of the autoimmune disease, hypersplenism and asplenia-related sepsis and development of lymphoma. Good prognosis relies on early diagnosis, appropriate treatment regimen and avoiding splenectomy.

MANAGEMENT IN INDEX PATIENT

Pulse methylprednisolone was administered for three days. Child responded well. She became afebrile with improving blood counts. Oral prednisolone was started at 2 mg/kg, with a plan to taper in accordance with clinical/hematological response during follow-up in the Pediatric Hematology clinic.

SUGGESTED READING

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Q1. A 3 day old sick male neonate has presented with lethargy and multiple purplish macular and papular cutaneous lesions over the extremities. Fibrin degradation products are positive. What is the diagnosis??

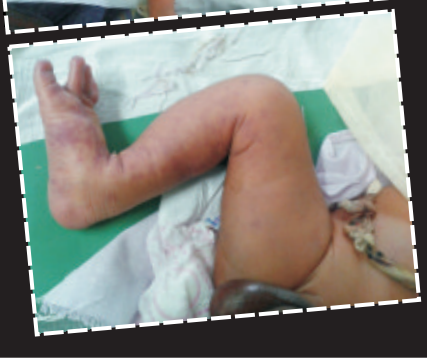
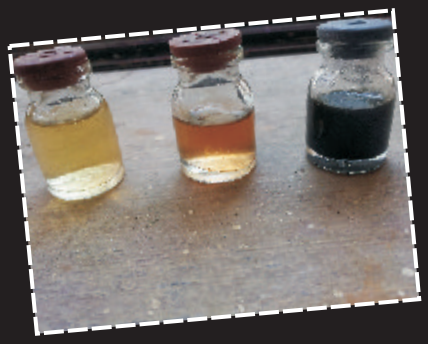


PHOTO QUIZ

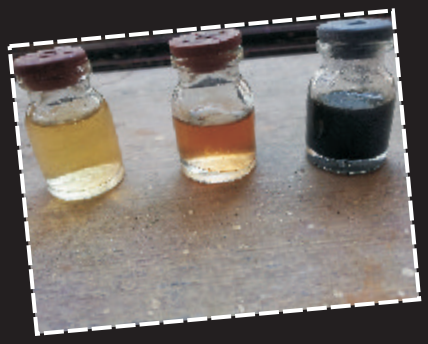
Readers are requested to mail their answer with name and place to

editoriapnewsletter@gmail.com

Names of first 10 people sending correct answer will be published in next issue (June 2013)



Q2. A 4 year old girl has been brought with complaints of the urine changing color on exposure to air. On performing Benedict's test, the urine shows a black color. What is the clinical diagnosis?



Answers of PHOTO-QUIZ of January Issue

KLIPPEL TRENAUNAY WEBER SYNDROME

Klippel Trenaunay Weber Syndrome (nevus vasculosus osteohypertrophicus) is a non-heritable disorder comprising of a macular vascular nevus (port-wine nevus, that is a nevus flammeus type of hemangioma) in combination with bony and soft tissue hypertrophy and venous varicosities.

Although usually unilateral, this anomaly may affect two or all four limbs including trunk and face. The affected part may be larger at birth or the rapid growth may only gradually become apparent. Legs are more often affected than arms. This syndrome appears to be commoner in boys. Thrombophlebitis, dislocation of joints, congestive cardiac failure, recurrent bouts of cellulitis, gangrene of the affected extremity, hematuria secondary to bladder hemangiomas, colonic and rectal hemangiomas, pulmonary lesions and malformations of the lymphatic vessels are rare complications.

Surgical correction or palliation is difficult. The swelling may be controlled with elastic garments or wearing of a fitted pneumatic graduated compression lymphatic pump at night.

LEUKEMIA CUTIS

Leukemia cutis is an infiltration of skin by neoplastic leukocytes (myeloid/lymphoid) resulting in clinically identifiable cutaneous lesions. It is most commonly seen in congenital leukemia and acute myeloid leukemia (AML).In the pediatric population, the frequency of leukaemia cutis is higher in pediatric AML (approximately 10%) than in pediatric acute lymphoblastic leukemia (ALL)(1%). It can occasionally precede the development of blast cells in marrow and blood. The condition is then known as aleukemic leukemia cutis.

The most common manifestation is described as erythematous or violaceous plaques, papules or nodules involving the face, trunk and extremities. Less common appearances include macules, maculopapules or plaques. Leukemia cutis has a poor prognosis.

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Research Methodology Series

Planning for Research – The Initial Steps

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Research is an important component of all scientific endeavors including clinical pediatrics whether one is learning it or practicing it. Not only doing the research but also understanding and using the research are vital in clinical practice. Appropriate understanding of research is critical to understand and to use appropriately the vast amount of research happening and presented to common pediatrician through journals, news papers, and pharmaceutical company representatives. These are the reasons research is integral part of post graduate medical courses.

Through this series of articles we shall present various aspects of research in general and specifically in children. The primary focus would be the post graduate students of Pediatrics but everyone would be benefitted by these articles as we shall be presenting basics of research with a brief view of advanced aspects of it. First of these articles is on conceptualizing research, research questions, hypothesis and outcome variables.

Conceptualizing Research

Post graduate medical students learn by doing and research is no exception. As part of postgraduate course you have to do an original research. Others do research as they find it interesting and useful in furthering their carriers. Some researchers carry out research to find answers to clinical or other questions. Thus depending on our aims we need to find the area of research or a broad research topic. The latter is the beginning point and sets the foundation stone for useful research.

Where do the research topics come from? How does one know that this is an important area of research? Which aspects of a particular topic should be worked upon? How would the research be conducted? What are the resources needed for research? What would be the use of this research? We need to answer these questions while searching for a good research topic.

It is worthwhile to see the national/local priorities in a particular subject. Some agencies like Indian Council of Medical Research or Indian Academy of Pediatrics or Ministry of Health and Family Welfare, etc. do identify research priorities for our country and it would be quite useful if one of these topics may be taken up. Sometimes, certain committees also identify the research areas. Often, some clinical question bothers you and you need to find answers scientifically. Seniors and teachers can guide you to find a suitable research area. You may work on some innovative ideas too.

Developing the Research Concept

When you identify a research area the next step is to foster it. Explore the subject from all aspects and read the old and new literature about the topic. Learn about the current understanding of the topic. Find if any less understood areas are there or if some controversial aspects have been raised. You may challenge the established facts too. You can investigate geographic or genetic variations of known facts. Use of modern technologies (like internet, cellular phones, smart phones, or other newer devices, etc.) could also be investigated to aid in traditional medicine. You should remember that topic should be such that it generates adequate enthusiasm and motivation in the researcher and is relevant for our community and country as we do not have unlimited resources.

Aims of Research

Aim of any research is a general statement where the proposed research topic is described in brief but broad terms. This should encompass the broad area of research topic. For example, if you want to study the use of needles used to administer the vaccines then the Aim of the study may be "To study the gauge of the needle for administration of vaccines" other example may be "To find appropriate fluid for intravenous maintenance fluid therapy". Aim(s) would indicate broad focus of the research and many questions can be framed to study this area. However, the appropriately framed research question will make it simple to understand the real issue of research.

Research Question

The research question (RQ) brings clarity in research as many a time, the researchers wish to study many aspects of an issue. Moreover, several questions can be found related to 'Aim' of the study. Zeroing on a single question is important as studying several questions together will complicate the research and may possibly lead to 'less than required' attention of the researchers and to the division of already limited resources (time, money and manpower).

Framing an appropriate Research Question (RQ) is vital to any research plan as it helps you to identify an appropriate method of research study, and the basis of sample size calculation in most of the cases. The method and the structure of RQ for a 'quantitative' study and for a 'qualitative' study are different. As most of the studies in Pediatrics are quantitative this article is about RQ of a quantitative study.

A good research question should be FINER and should preferably follow the PICOT approach.

Characteristics of Research Question - FINER

For drafting an appropriate research question, we must remember F.I.N.E.R. aspects of it.

Feasible. The proposed Research Question should be such that the needed study is feasible in terms of patients (clinical material), laboratory tests (if needed), and availability of expertise, time, and money. This may be a great limiting factor for determining the research area as for example, for MD thesis longitudinal studies lasting for 2 or more years cannot be done as it has to be completed within the duration of MD course (i.e. 2-3 years).

Interesting. The study subject should be of interest to the researchers and to others also as the inferences of the proposed study should be usable by others in different settings.

Novel. The proposed research should be able to provide either some new findings or to confirm previous findings or to refute the known facts. Novelty is an important condition in thesis for MD course. Universities' guidelines ask for novel idea in research. Novelty is pre-requisite of innovation and for new research the RQ should be novel.

Ethical. Ethical principles say that the patient should never be put to potential harm because of his/her participation in research. The harms include both physical and psychological harms, short term or long term. Ethical guidelines are available from ICMR and must be followed in all research whether as a part of MD course or otherwise.

Relevant. The research should be relevant to the local population, scientific knowledge, clinical practice, and health policy.

These FINER aspects should be taken care of while searching for a good research topic and RQ.

Structuring a Research Question – PICOT

Your research idea needs to be developed into RQ. Type of study or study design is an important determinant of RQ. It should have certain components as denoted by PICOT. This is a 5 step process. Considering the AIMS of study the RQ should specify Population, Intervention, Comparator, Outcome, and Time frame.

These 5 components of RQ apply fully to Randomized Controlled trials e.g. **Whether administering DPT vaccine intramuscularly in infants at 6 weeks of age (P) by 1" long needle of guage 22 (I) cause less pain and swelling (O) during first 7 days (T) after vaccination than that when narrower needle (gauge 24) (C) is used?**

For other types of studies too PICOT formula can be used, however all the components may not be there e.g. **Whether the Quality of Life score (O) of adolescents with transfusion dependent thalassemia (P) is comparable to their adolescent siblings or unrelated controls (C)?**

This RQ seems to be adequate but it does not include Intervention and Time frame. So, a better RQ may be **Whether the Quality of Life score (O) as assessed by WHO BREF (I) of adolescents with transfusion dependent thalassemia (P) is comparable to their adolescent siblings or unrelated controls (C) at least 5 years after the initiation of regular transfusion?**

Thus, PICOT may be included in nearly all types of research questions in Pediatrics. This make the thinking process much easy and streamlined for developing the complete research protocol.

Research Hypothesis

It states the explanation for an observable phenomenon. Generally, research hypothesis (RH) answers the question asked in RQ. The answer should come from previous studies, or extension of scientific theories and principles. When you are planning an innovative study then you may not have data from previous studies. Then you need to presume some values for the proposed observations whether it is incidence or prevalence or change in some parameters or proportions, etc. However, these presumptions should be biologically plausible and feasible in the given circumstances. The RQ and Hypothesis determine the selection of type of study and the sample size.

Few examples are given below-

RQ - Whether administering DPT vaccine intramuscularly in infants at 6 weeks of age (P) by 1" long needle of gauge 22 (I) cause less pain and swelling (O) during first 7 days (T) after vaccination than that when narrower needle (gauge 24) (C) is used?

Hypothesis -Administering DPT vaccine intramuscularly in infants at 6 weeks of age (P) by 1" long needle of gauge 22 (I) causes 30% less swelling and 30% reduction in pain score (O) during first 7 days (T) after vaccination than that when narrower needle (gauge 24) (C) is used.

RQ – Whether isotonic maintenance fluid (I) causes less hyponatremia (O) in first 48 hours (T) in children 2 months to 5 years with CNS infections (P) in comparison to hypotonic fluids?

Hypothesis - Isotonic maintenance fluid (I) causes hyponatremia (O) in first 48 hours (T) in children 2 months to 5 years with CNS infections (P) in 25% less patients in comparison to those who receive hypotonic maintenance fluids.

Thus, appropriately framed RQ and hypothesis not only provide a lot of information but also determine the direction of the study and the most important outcome measure which is vital to sample size determination.

Null / Alternative Hypothesis

These are statistical concepts where the null hypothesis is written in a manner to suggest reverse direction and alternate hypothesis is stated just opposite to null hypothesis. When the null hypothesis is rejected the alternate hypothesis is considered accepted. However, the latter is not documented and we state whether 'null' hypothesis has been "rejected" or "not rejected". So in case of rejection of null hypothesis, alternate hypothesis is presumed as accepted. These concepts are useful while analyzing the data.

Objectives of the Proposed Study

After finalizing the Research Question and Research Hypothesis, it is time to write Objectives of study. These are written in affirmative sentences generally beginning with 'To

do'. This 'do' may be 'find', 'explore', 'compare', 'assess', 'correlate', etc. The objectives must describe nearly everything you plan to do in the proposed study. However, you should avoid having too many objectives.

Every objective must specify a different aspect of the study. Out of all the objectives identified, you should put the most important one (the one which is included in the RQ and RH) as primary objective and others may be listed as secondary objectives. The primary objective is the main 'purpose' of doing a study and is used for calculating the sample size of study population. However, some experts opine to calculate sample size for 'all' objectives and to choose the largest sample size.

Outcome Variables

This is another vital and important part of study protocol. For every objective you need to identify one or more outcome variable. The latter is the measurement of the process or object defined in objective e.g. if objective is to find the prevalence of anemia in adolescents then the outcome variable will be percentage (or proportion) of adolescents with anemia. Another example, if the objective is to compare the pain relieving effect of drug A with that of drug B then outcome variable may be pain score of the identified pain scale.

Thus, an outcome variable should always a measurable entity and the unit of measurement should always be defined. Outcome variable of Primary Objective should be designated as ***Primary Outcome Variable*** and others should be called ***Secondary Outcome Variable.*** The Primary Outcome variable must be used to determine the sample size.

Key Points

For conceptualizing a research plan, you need to find a research area and aims of the research, then frame a good research question and answer it by a research hypothesis. Based on these parameters you must identify objectives and outcome variables. These "initial steps" will form the foundation on which you have to develop a scientific plan for your research in form of Research Protocol. It is always useful to make a research protocol whether you are planning a prospective or retrospective study or even planning a review or meta-analysis.

1 For the management of severe haemorrhage in dengue fever, there is no evidence to support the use of platelet concentrates, fresh frozen plasma or cryoprecipitate. Their use could contribute to fluid overload. Platelet transfusion is not recommended for thrombocytopenia (no prophylaxis platelet transfusion). It may be considered in adults with underlying hypertension and very severe thrombocytopenia (< 10,000 cell/mm^3).

(Ref: Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever, WHO 2011)

2 Growing pains, the benign nocturnal pains of childhood, occur in 10-20% of children, with a peak age incidence between 4-8 year, affects thigh and calf, but not the joints.

(Ref: Nelson textbook of Pediatrics 19th edition)

3 **Paradise criteria for tonsillectomy** (American Academy of Otolaryngology, Head & Neck Surgery)

Documented sore throat with *at least*

7 episodes in the previous year, or

5 episodes in each of the previous 2-years, or

3 episodes in each of the previous 3-years,

Sore throat plus *at least one* of the following features qualifies as a counting episode:

Temperature > 100.9°F (38.3°C)

Cervical adenopathy

Tonsillar exudate

Positive culture for group A β-hemolytic streptococcus

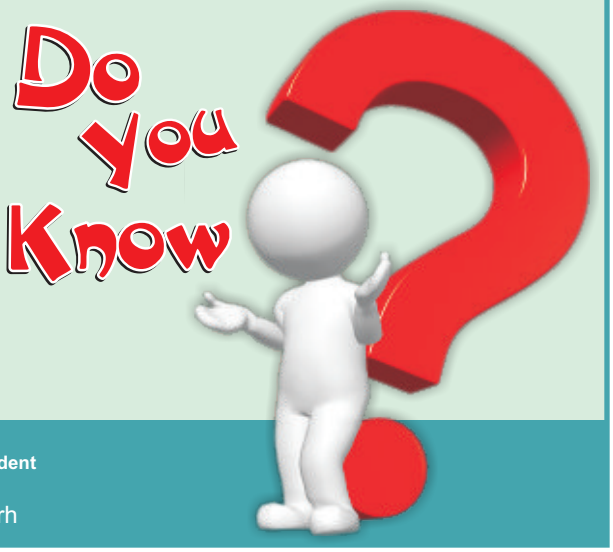
(Ref: Am Fam Physician 2011;84:566-573)

4 Intrapleural fibrinolytics shorten hospital stay and are recommended for any complicated parapneumonic effusion (thick fluid with loculations) or empyema (overt pus).

(Ref: BTS guidelines for the management of pleural infection in children. Thorax 2005;60 (Suppl I):i1 i21)

5 In iron deficiency anemia, oral administration of simple ferrous salts (most often ferrous sulphate) is inexpensive and effective. Intolerance to oral iron is uncommon in children.

(Ref: Nelson textbook of Pediatrics 19th edition)



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Journal Watch

Contributed by:
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1. Risk factors of HBV intrauterine transmission among HBsAg-positive pregnant women.

Guo Z, Shi XH, Feng YL, et al. J Viral Hepat. 2013 May; 20(5):317-21

Maternal HBeAg positive was a strong independent predictor for intrauterine transmission (OR = 2.56, 95% CI: 1.54, 4.27). Maternal HBIG administration during pregnancy, family history of HBV infection and premature rupture of membranes were not associated with the risk of intrauterine transmission. The study also found higher transmission in presence of menstrual irregularity and severe nausea during the first trimester.

2. Neurodevelopmental Outcome of Extremely Premature Infants Exposed to Incomplete, No or Complete Antenatal Steroids.

Chawla S, Bapat R, Pappas A et al. J Matern Fetal Neonatal Med. 2013 Apr 8. [Epub ahead of print]

The neurodevelopmental outcomes of extremely premature infants (< 28 weeks gestational age) exposed to a complete course, an incomplete course or no dose of antenatal steroids (ANS) at 18-22 months' corrected age were compared. Severe intraventricular hemorrhage (IVH) was significantly lower and intact survival higher in the complete ANS group ($p<0.01$). On logistic regression, with gestational age, gender, maternal insurance and ANS exposure as covariates, an incomplete (vs. complete) course of ANS ($p=0.006$) and gestational age were significantly associated with lower intact survival at 18-22 months.

3. Association of maternal vitamin D status during pregnancy with bone-mineral content in offspring: a prospective cohort study.

Lawlor DA, Wills AK, Fraser A et al. Lancet. 2013 Mar 18.pii: S0140-6736(12

Study found no relevant association between maternal vitamin D status in pregnancy and offspring BMC in late childhood.Associations between maternal serum 25(OH) D concentrations and offspring total body less head (TBLH) and spinal BMC were assessed. TBLH and spinal BMC did not differ between offspring of mothers in the sufficient versus deficient or insufficient groups.

4. Is the light-emitting diode a better light source than fluorescent tube for phototherapy of neonatal jaundice in preterm infants?

Mohammadizadeh M, Eliadarani FK, Badiei Z. Adv Biomed Res. 2012.

A total of 64 infants with gestational age of 33.5 ± 1.2 weeks received phototherapy through devices with LEDs or special blue fluorescent tubes. The rates of fall of TSB were 0.20 and 0.12 mg/dL/hour in the LED and fluorescent groups, respectively ($P = 0.472$). Treatment duration was 37.5 ± 26.8 and 45.3 ± 32.1 hours in the LED and fluorescent groups, respectively ($P = 0.292$). There was no treatment failure in the two groups. Mild hyperthermia was occurred in 3.1% and 28.1% of infants in the LED and fluorescent groups, respectively ($P = 0.006$). This study concluded that LED light source is as effective as fluorescent tubes for phototherapy.

5. Mortality after Fluid Bolus in Children with Shock Due to Sepsis or Severe Infection: A Systematic Review and Meta-Analysis

N, Hargreaves S, Shanks L.

This systemic review included 13 RCTs and found that no bolus has significantly better mortality outcomes at 48 hours for children with general septic shock (RR 0.69; 95%CI 0.54–0.89), and children with malaria (RR 0.64; 95%CI 0.45–0.91) when compared to giving any bolus. However authors reported that there is no evidence investigating bolus vs no bolus in children with Dengue fever or severe malnutrition. Colloid and crystalloid boluses were found to have similar effects on mortality across all sub-groups (general septic shock, malaria, Dengue fever, and severe malnutrition)

CALL FOR PAPERS

Editorial board invites papers for following categories :

1. Review Article: State-of-the-art review articles or systematic, critical assessments of literature are invited. The typical length for review articles should be ***2500 words*** (excluding tables, figures, and references). Authors submitting review manuscripts should include an unstructured abstract of up to 200 words describing the main findings. Up to 40 references can be included.
2. Case Reports: Clinical cases highlighting uncommon condition or presentation. The text ***should not exceed 1000 words*** and should be arranged as introduction, case report and discussion.
3. Reader Forum: Questions of common interest from members are invited. Editorial board will try to elicit answers from the experts; and publish them, if found suitable.
4. Images section: Only clinical photographs with/without accompanying skiagrams or pathological images should be submitted. Image should clearly identify the condition and have the classical characteristics of the clinical condition. Photographs should be high quality, high resolution (>300 dpi). The following file types are acceptable: TIFF, and JPEG. A short text of about 150 words depicting the condition is needed. No references are needed.
5. Short write up on recently published International / National guidelines related to diagnosis/management of common pediatric conditions in 250 words, with the link for free download, if any.

Preparation & Submission of the Manuscript

Manuscript should contain (i) the title of the article; (ii) initials and surname of each author with the highest academic degree(s) and designation at the time when the work was done; (iii) name of department(s) and institution(s) to which the work should be attributed; (iv) disclaimers, if any; (vii) name, address, telephone, fax, e-mail address of the corresponding author, (v) declaration on competing interests; and vi) Also, indicate on top the category (i.e. Review, Case Report, Images), for which the article is being submitted. Once a manuscript has been accepted for publication, it will undergo editing, typesetting, and reference validation by section editors

Manuscripts should be prepared in accordance with Indian Paediatrics authors guidelines and should be submitted by email to editoriapnewsletter@gmail.com with a copy to pkpaed@gmail.com.

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