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TOPIC OF INTEREST - "IAP - IJPP CME 2022"

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IAP - IJPP CME 2022

ABC OF CBC

***Remesh Kumar R**
****Sunitha GS**

Abstract: *Complete blood count is the most informative and useful single investigation which reflects the health status of a child. Automated analyzers are more accurate and the parameters provided are useful in the precise diagnosis and management. Automation complements manual microscopy and provide graphical representation of the results. A good history and clinical examination is essential for correct interpretation of the hemogram.*

Keywords: *Peripheral blood smear, Complete blood count, Hemogram, Red blood cell indices, White blood cell, Platelet count.*

The basic test performed on the peripheral blood, "complete blood count" (CBC) is the most informative single investigation, expressing the health and disease status of the body, in the whole menu of laboratory medicine. CBC is a window into the functional status of the bone marrow, the factory producing all blood elements.

With this single investigation, from the era of only hematocrit/hemoglobin as diagnostic tool to the most sophisticated present day multi-parameter automation, a lot has changed. Earlier days, reports were made manually using hematocytometers which were time consuming and difficult to perform. Automation, because of its accuracy, has changed principles and methodologies, approaches and conclusions of various disciplines of medicine. As the automated analyzers became more advanced, their precision has shown enormous improvement and manual blood smear review rates are on a steady decline. But, automation is no replacement for the study of peripheral smear rather, it just compliments manual microscopy. In automation generated CBC reports, graphical representation of results in the form of histograms or scatter plots, red cell distribution width (RDW), hemoglobin distribution width (HDW) and reticulocyte hemoglobin, etc. have largely been ignored in favor of traditional numerical parameters over the years. These CBC parameters are very important as they provide useful information for the precise diagnosis and management of the patient.

Hemogram and complete blood count

Hemogram or complete blood count (CBC) is a series of tests used to evaluate the composition and concentration of the various cellular components of blood (Fig.1). It consists of the tests like red blood cell (RBC) count,

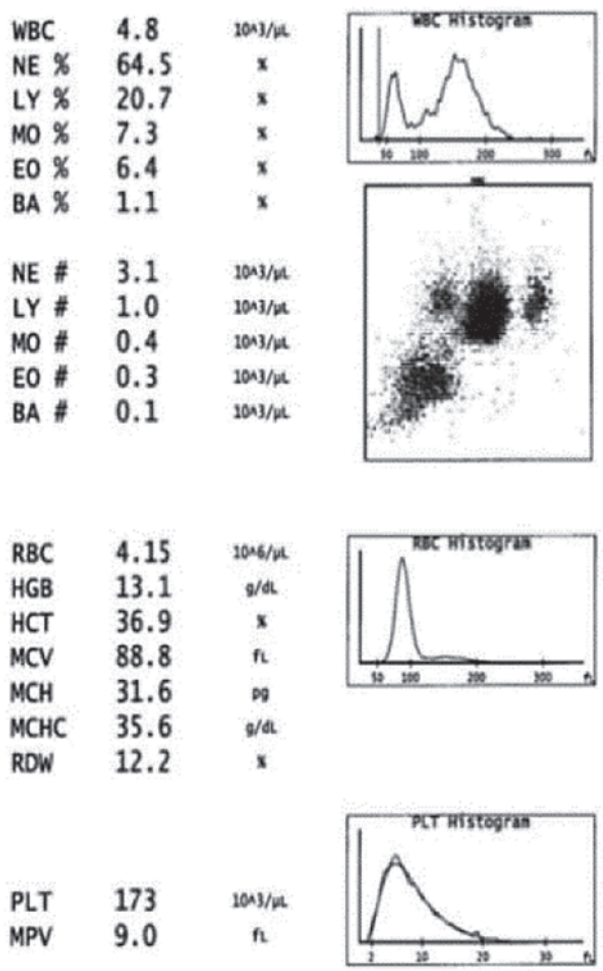

Fig.1. Hemogram

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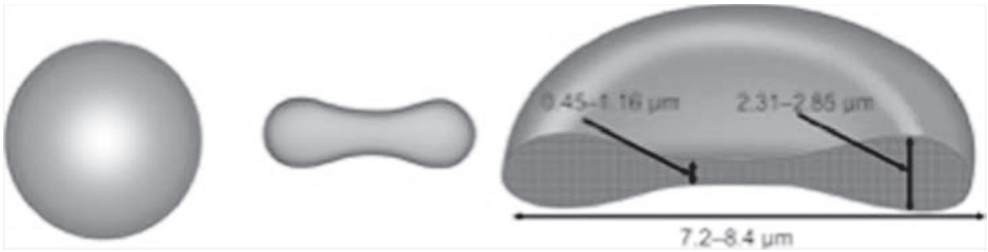

Fig.2. Red blood cells (RBC)

white blood cell (WBC) count and platelet count, estimation of hemoglobin, hematocrit and red blood cell indices, total white blood cells (WBC) and differential count, mean platelet volume, plateletcrit, platelet distribution width (PDW), etc. and histograms of RBC, WBC and platelets. The RBCs are shown in Fig.2. RBC indices include MCV, MCH, MCHC and RDW.

Assessment of the RBCs is to check for anemia and to evaluate normal erythropoiesis (the production of red blood cells). The number of red blood cells is determined by age, sex, altitude, exercise, diet, pollution, drug use, tobacco/ nicotine use, kidney function, health and disease status, etc. The clinical importance of the test is that it is a measure of the oxygen carrying capacity of the blood.

Broadly, the causes of decreased RBC count may be classified as: 1. Impaired red blood cell (RBC) production 2. Increased RBC destruction (hemolytic anemias) 3. Blood loss 4. Fluid overload (hemodilution).

Hemoglobin

Hemoglobin is the oxygen-carrying component of the red cell. By measuring the hemoglobin concentration of the blood, the oxygen-carrying capacity of the blood is evaluated. Both high and low hemoglobin counts indicate defects in the balance of red blood cells in the blood and may indicate disease.

Reticulocytes

In erythropoiesis, reticulocyte is a cell just one stage prior to the mature erythrocyte. Normal range of reticulocyte count is 0.5% to 1.5%. An increased number of reticulocytes is seen when the marrow RBCs are produced rapidly (presumably to make up for those lost to hemolysis or hemorrhage).[1] Reticulocyte count is usually performed when patients are evaluated for anemia and its response to treatment. The lifespan of erythrocytes is approximately 120 days, and about 0.8% of the red cells need to be replaced daily by young cells released from the bone marrow.[2] Various conditions leading to increased and decreased reticulocyte count are shown in Table I.

Mean corpuscular volume (MCV)

MCV is average volume of the red blood cell.

MCV = (hematocrit/red cell count in million) × 10.

Normal value is 80-90 FL.

Table I. Conditions presenting with increased and decreased reticulocyte count

Increased reticulocyte count	Decreased reticulocyte count
• Hemolytic anemias	• Decreased adrenocortical and anterior pituitary activity
• Response to treatment of iron and Vit B12 and folic acid in anemia	• Aplastic anemia
• Recent hemorrhage	• Cirrhosis
• Thalassemia	• Megaloblastic anemia
• Pregnancy	• Exposure to radiation
• Erythroblastosis fetalis	• Anemia of chronic diseases
• HbC disease	• Myelo-dysplastic syndrome
• Leukemias	
• Hypoxia	

Can be directly measured by automated cell counters. Cells are classified as microcytic if MCV < 79 fL and macrocytic when > 98 fL and normocytic when indices are within normal limits.[3]

MCV is higher at birth, decreases rapidly during first 6 months of life. Presence of microcytic and macrocytic cells in same sample may result in a normal MCV.

Mean corpuscular hemoglobin

Mean corpuscular hemoglobin is the amount of hemoglobin in a single red blood cell.

MCH is {Hb in (gm/L)/RBC in (million/microlitre)} x 10

MCH normal range 26.7–31.9 pg/cell.

The biconcave erythrocyte is thinner in the middle, creating a central pallor on blood smears that is ordinarily less than one third of the cell's diameter. Such a cell, possessing the normal amount of haemoglobin, is called normochromic.

Low MCH is considered as hypochromasia and if high it is known as hyperchromasia. MCH is decreased in microcytic and normocytic anemias. It is increased in macrocytic anemias and infants and newborns.

Mean corpuscular hemoglobin concentration (MCHC)

The average hemoglobin concentration per unit volume (100 mL) of packed red cells is indicated by MCHC. In contrast to MCH, MCHC correlates the hemoglobin content with the volume of the cell. It is expressed as g/dL of red blood cells.

MCHC is {Hb in (gm/dL)/hematocrit) x 100

Normal value 32-36 gm/dL

MCHC is decreased ($\leq$ 30.1 gm/dL) in hypochromic microcytic anemia. Normal value does not rule out any of these anemias. Low MCHC may not be found in iron deficiency anemia (IDA) when performed with automated instruments.

MCHC is increased in hereditary spherocytosis, the MCHC is increased due to loss of membrane and the consequent spherical shape assumed by the cell.[4] Other reasons include infancy and newborn period, auto agglutination and artefacts (abnormal MCHC may be most valuable clue to artifact).[5]

In IDA, MCHC is not proportionately reduced as MCH, as the size of the cell (MCV) is also reduced along with the hemoglobin content of the cell.[6] Hence, the concentration (MCHC) may drop only to a minimal extent.

Spurious elevation of MCHC: In cold agglutinin disease, when incubated at 37^0C, autoagglutinins get shed off and MCHC normalizes.[7] When MCHC is high, one must also be aware of spherocytes or sickle cells on smear.

Red cell distribution width (RDW)

Anisocytosis of RBCs is a variation of cell size in a given population of cells or excessive heterogeneity on smear or visual equivalent of increased CV (coefficient of variation). Normal range is 11.5 -13.5fL.

Mentzer Index

MCV in fL / Red cell count in millions.

Ratio of less than 13 is seen in thalassemia while ratio is more than 13 in iron deficiency anemia.[8] Comparison of other indices is helpful in differentiating microcytic hypochromic anemia of iron deficiency and thalassemia minor in Table II.

White Blood Cells (WBC) Count

White blood cells or leukocytes are cells of the immune system involved in defending the body against both infectious diseases and foreign materials. Blood plasma may sometimes have greenish tinge if there are large amounts of neutrophils in the sample, due to the heme-containing enzyme myeloperoxidase that they produce. Significant numerical threshold of leukocytosis is relative to baseline leukocyte counts of an individual in healthy status.

Neutrophilia

- Physiological - stress, exercise induced
- Acute bacterial infections

Table II. Indices in iron deficiency and thalassemia minor

Parameters	Iron deficiency	Thalassemia minor
RBC count	Low	High
Mentzer index (MCV/RBC)	High++	Low+
RDW	High	Normal
Ferritin	Low	Normal
Hb A2	Normal	High
Response to iron	Good	Poor

- Tissue injury- burns, collagen vascular diseases
- Myeloproliferative- leukemias
- Miscellaneous-hemolytic anemias, hemorrhage

Day 1 of viral infections - neutrophilic leucocytosis may be seen

Neutropenia

- Decreased or ineffective production-aplastic anemia, drugs, vit B12 deficiency, myelodysplastic syndromes.
- Increased circulatory removal - immunological (SLE etc.), hypersplenism
- Increased utilization - bacterial infections

Lymphocytosis

- Lymphoblastic leukemia
- Lymphoma
- Bacterial infections- pertussis
- Viral infections - EBV, CMV, hep A and B
- Parasitic infections like toxoplasmosis
- Drugs - phenytoin
- Serum sickness

Lymphopenia

- Viral infections- HIV, COVID
- Anticancer drugs like vinblastine, doxorubicin
- Marrow suppression/pancytopenia syndromes
- Primary immunodeficiency- SCID

Monocytosis (>1000/cu.mm.)

1. Infections including but not limited to tuberculosis, SABE, malaria, kala azar
2. Autoimmune disorders
3. Hematologic diseases: myeloproliferative disorders, monocytic leukemia, Hodgkin's disease
4. Others: chronic ulcerative colitis, Crohn's disease, sarcoidosis.

Eosnophilia

Normal range: 1 - 4% of total white blood cells; absolute count of 12-500 cells per microliter. Eosinophils demonstrate diurnal variation (related to cortisol levels), they are the lowest in the morning and highest in the evening.[9]

1. Mild (700-1500 cells/microlitre)
   - Allergic rhinitis
   - Extrinsic asthma
2. Moderate (1500-5000 cells/microlitre)
   - Intrinsic asthma
   - Pulmonary eosinophilia syndromes
3. Severe (>5000 cells/microlitre)
   - Parasites - trichinella, toxocara, hookworms, etc.
   - Eosinophilic leukemia
   - Severe drug reactions
   - Other causes - psoriasis, ulcerative colitis, hypereosinophilic syndromes, SLE

Eosinopenia (< 1 %)

- Cushing syndrome
- Enteric fever (leucopenia)
- Drugs - steroids, ACTH

Platelets

Platelet count

- Normal platelet count is 1.5 - 4.5 lakhs at any age including infants. Platelets are produced in bone marrow by megakaryocytes. Platelets are fragments of cytoplasm of megakaryocytes. One megakaryocyte produces about 4000 platelets.[10]

Thrombocytosis: defined as platelet count more than 4.5 lakhs/cubic mm. It is seen in

- Myeloproliferative disorders
- Primary thrombocythemia
- Polycythemia vera
- Chronic granulocytic leukemia
- Transfer from extravascular pool - splenectomy, exercise
- Secondary causes: malignancy, infections, IDA, kidney diseases, acute blood loss, hemolysis

Thrombocytopenia: decreased platelet count.

Grading of thrombocytopenia is as follows[11]

- Grade I 75,000 to 1.5 lakhs
- Grade II 50,000 to 75,000
- Grade III 25,000 to 50,000
- Grade IV<25,000

Causes of thrombocytopenia

- Decreased platelet production- aplastic anemia, B12 deficiency, Wiscott-Aldrich syndrome, infections
- Increased destruction
  - Immune mediated: SLE, ITP
  - Non immune mediated - DIC, vWD
- Abnormal distribution - massive transfusion, hypersplenism
- Pseudo thrombocytopenia - EDTA induced

Mean platelet volume (MPV)

- Normal value is 7.4-10.4 fL. Usually there is an inverse relationship with platelet numbers. In ITP, the MPV is increased. Changes in MPV occur even before a recordable thrombocytopenia sets in.[12]

Conclusion

A good history and clinical examination is a must before interpreting a CBC. CBC done on an automated cell counter provides valuable information for diagnosis and classification of anemia. It is imperative to pay attention to all the parameters and all the cell lines. Complete understanding and deciphering of the blood picture will help clinch the diagnosis in most cases and thus prevent unnecessary investigations.

Points to Remember

- ***A good history and clinical examination is a must before interpreting hemogram or complete blood count***
- ***RBCs are assessed for anemia and nature of erythropoiesis by hemoglobin estimation, reticulocyte count, MCV, MCH and MCHC and red cell distribution width.***
- ***Mentzer index and other indices are useful in differentiating microcytic hypochromic anemia due to iron deficiency and thalassemia.***
- ***Increase or decrease in WBCs and its components, neutrophils, lymphocytes, eosinophils and monocytes helps in the diagnosis of various diseases.***
- ***Platelet count and mean platelet volume are very useful not only for hematological conditions but also in various infections.***

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ACUTE DISSEMINATED ENCEPHALOMYELITIS

Shivan Kesavan

Abstract: *Acute disseminated encephalomyelitis is a clinico-radiological syndrome prevalent in children characterized by acute encephalopathy with multifocal neurological deficits. Magnetic Resonance Imaging shows diffuse white matter predominant demyelinating lesions. This disorder is considered to be antibody mediated and anti-myelin oligodendrocyte glycoprotein antibody is detected in up to 50% of the cases. Treatment with high-dose intravenous steroids results in complete resolution of the signs and symptoms in most patients, while some require further immunotherapy with intravenous immunoglobulins. It is a monophasic illness in the majority, while a small minority develop relapses, requiring long-term immunosuppression.*

Keywords: *Demyelination, Encephalopathy, Autoimmune, Reversible.*

Acute disseminated encephalomyelitis (ADEM) is clinically characterized by an acute encephalopathy with polyfocal neurological deficits, which are usually preceded by an infection.

Etiopathogenesis

Many patients with ADEM have preceding history of infection by measles, EBV, CMV, influenza, mumps, rubella and *Mycoplasma pneumoniae* or immunization with MMR (mumps, measles, rubella), rabies vaccine, DPT (diphtheria, polio, tetanus), influenza and Japanese encephalitis (JE) vaccine.[1] Considering the frequency of vaccinations and infections in young children, (up to 8 episodes of upper respiratory tract infections per year which are considered to be normal), a temporal association between ADEM and vaccination / infection is always not easy to establish.

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Pathology

Antibodies against myelin oligodendrocyte glycoprotein (anti-MOG) in the serum have been identified in several demyelinating diseases in children including less than 50% of children with ADEM. This is the most common antibody associated demyelinating disorder in children. High levels of antibodies have been detected during the acute disease and have been shown to diminish with recovery. The clinical relevance of these and other antibodies, however, is unclear. Interestingly, patients with anti-MOG antibodies and those without the antibodies have similar clinical courses, suggesting that there are multiple disease mechanisms at play. However, testing for these antibodies is useful, since, in a small proportion of patients, ADEM can be recurrent and may require prolonged therapy.

The hallmark of pathology in ADEM consists of perivenular sleeves of demyelination associated with inflammatory infiltrates of myelin-laden macrophages, T and B lymphocytes, occasional plasma cells, and granulocytes. Acute hemorrhagic leukoencephalitis (AHL) lesions are characterized by the presence of hemorrhages, vessel fibrinoid necrosis, perivascular exudation, edema, and granulocyte infiltration, with perivascular demyelination and reactive astrocytosis typically seen in disease evolution later.

Clinical features

ADEM predominantly affects children and the usual age of presentation is from 5 to 8 years with a slight male predominance. It is a heterogeneous clinical entity that is best viewed as a clinico-radiological syndrome, which means that the diagnosis is suspected clinically and confirmed radiologically. The characteristic feature of ADEM is encephalopathy with associated additional neurological symptoms and signs. ADEM typically follows a rapidly progressive monophasic course, followed by favourable long-term outcomes. Prodromal symptoms can include fever, malaise, headache, nausea, and vomiting progressing to encephalopathy and coma. The mean time for occurrence of symptoms and signs has been estimated to be 4.5 days. Fever, headache and seizures are more common in children. Multifocal neurologic abnormalities

at presentation are common and are dependent on the location of the CNS lesions. These neurologic findings are not limited to encephalopathy alone, but also include ataxia, hemiplegia, hemiparasthesias, paraplegia, cranial nerve palsies, visual changes, seizures, speech impairment and bowel-bladder dysfunction.[1] Though fever is absent or decrease by the time patients present with encephalopathy, it is not unusual for patients to continue to have high fever during the initial few days of presentation. Acute hemorrhagic leuko encephalopathy (AHL) is a hyper acute severe variant of this syndrome. It is characterized by a fulminant onset of symptoms with severe neurological deficits and slower, incomplete recovery. Whether it is truly a variant of ADEM or whether it represents a unique entity is controversial, but it is treated with aggressive immunotherapy on the lines on severe ADEM.

Diagnosis

CT head may be normal or may show bilateral hypodense lesions. MRI brain with contrast is the imaging modality of choice for making the diagnosis. MRI typically exhibits diffuse, poorly demarcated lesions involving the subcortical and periventricular white matter with variable diffusion restriction and contrast enhancement. The deep grey matter and often the grey matter of cerebrum (cortex), cerebellar and brain stem may also be involved. Spinal cord involvement may also be seen with or without clinical evidence of myelitis. Serial images after 3 months show improvement and often complete resolution within 12 months, but not necessarily in most children (Fig.1).[2]

CSF studies in ADEM are notable for their lack of confirmatory features. CSF leukocyte count has been described to be normal in 42%-72% of children with ADEM. Pleocytosis is typically mild, with a high percentage of lymphocytes and monocytes. CSF protein is increased (up to 1.1 g/L) in 23%-62% of pediatric patients with ADEM.[3]

Acute CNS demyelination can present without encephalopathy and classic white matter changes on the MRI. MOG-associated demyelination (MOGAD) can present as cortical encephalitis (without white matter lesions), aseptic meningitis (even with a normal MRI and only CSF pleocytosis) and transverse myelitis with asymptomatic brain lesions. The spectrum of this group of disorders seems to be expanding, calling for early recognition and treatment since these disorders have excellent outcomes with early immunotherapy.[4,5]

Red flags and differential diagnoses are shown in Table 1.

Table I. Red flags and differential diagnoses

Atypical Clinical features	Differential Diagnosis
Persistent meningeal signs and headache	Infectious encephalitis, SLE, CNS vasculitis
Stroke like events	CNS vasculitis, APLA, Mitochondrial disorders (MELAS)
Recurrent/refractory seizures	Infectious or autoimmune encephalitis
Neuropsychiatric symptoms	SLE, autoimmune encephalitis
Pre existent developmental delay, recurrent encephalopathic events	Genetic/metabolic disorders
Dystonia or Parkinsonian features	Infectious encephalitis, autoimmune encephalitis
Progressive course	Genetic/ metabolic disorders, malignancy
Atypical investigation findings	
Cell count > 50/mm^3, Neutrophilic predominance, high protein levels (>100 mg/dL)	CNS infections, SLE
Diffuse symmetrical brain lesions	Genetic/metabolic disorders
Ischemic lesions	Mitochondrial disorders, CNS vasculitis, CNS infections

SLE-systemic lupus erythematosis, APLA-antiphospholipid antibody, CNS- central nervous system, MELAS-metabolic encephalopathy lactic acidosis and stroke like episodes

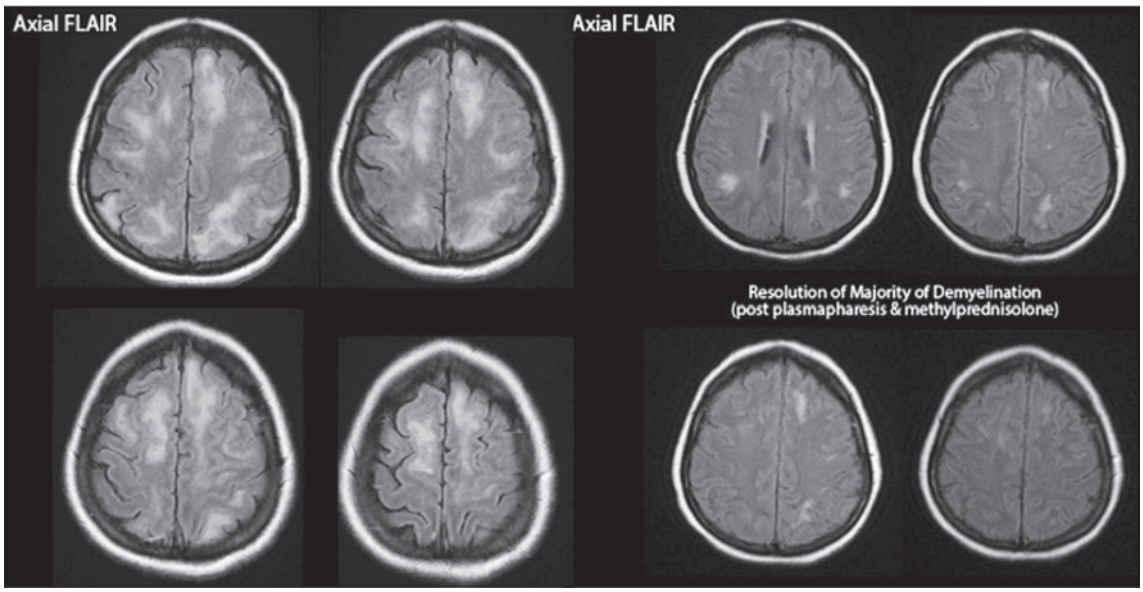

Fig.1. Axial FLAIR images in a child with ADEM before (Left) and after (Right) treatment with an interval of 4 weeks. The while matter lesions are diffuse and poorly demarcated and showed near-complete resolution with therapy.

Treatment

Systemic corticosteroids, are largely considered by consensus as first-line therapy for ADEM. Typical dosing regimens include methylprednisolone 20-30 mg/kg per day (max, 1 g) intravenously for 3 to 5 days, followed by oral prednisone at a dose of 1 to 2 mg/kg per day for 1 to 2 weeks and subsequently taper over 2 to 6 weeks. Therapies used in steroid-refractory cases typically consist of intravenous immunoglobulin (IVIG) and plasmapheresis. Plasma exchange may be considered in cases of ADEM refractory to high-dose steroid therapy. Currently, no evidence exists supporting the use of other immunomodulatory therapies in children with ADEM; however, rituximab and cyclophosphamide have been used in refractory cases.[3] However, the efficacy of these agents have been well-established as chronic immunosuppressive medications for those children who have a relapsing course. Supportive care is the cornerstone of achieving optimal outcomes for these patients, particularly for those in the ICU. This includes nutritional management, glycemic control, prevention of hospital-acquired infection and bowel-bladder management. Others include chest physiotherapy, deep vein thrombosis prophylaxis, contracture and bed sore prevention. Oral hygiene and eye care are also very important adjuncts in the management. Anticipating and managing dysautonomia, optimization of anti-epileptic drugs, antacids laxatives form an important part of treatment. Psychological support and cognitive rehabilitation should also be a part of management protocol.

Outcomes

The majority of children with ADEM are reported to have full recovery. Typically, neurologic improvement is seen within days following initiation of treatment and recovery to baseline will occur within weeks rather than months. Long- term cognitive deficits have been observed, affecting attention, executive function, verbal processing, and behaviour, as well as IQ scores, specifically in children with ADEM occurring before the age of 5 years.

Relapsing ADEM-multiphasic disseminated encephalomyelitis (MDEM) - has been reported, at a frequency of 10-20%. It is currently under debate whether patients with relapsing ADEM represent a distinct group of children with other neuro immunologic diseases like neuromyelitis optica spectrum disorder (NMOSD) or MOG-antibodies-associated disorders. Increasingly, it is being recognized that many cases of multiphasic/relapsing ADEM have persistent anti-MOG antibodies and will require chronic immunosuppression.

Children with anti-MOG antibodies can have a relapsing course without classic ADEM during relapses. They can present with isolated focal deficit including optic neuritis and transverse myelitis.[5] These patients will also require prolonged immuno suppression.

ADEM as a first manifestation of multiple sclerosis (MS) appears to be uncommon, occurring in 10% of patients with ADEM. Unlike ADEM, patients with a first

episode of demyelination who will progress to develop MS do not present with a history of a recent infection, nor do they have systemic symptoms (fever, headache, vomiting) or seizures or signs of meningeal irritation. Main differentiating features of ADEM compared to MS on MRI are periventricular sparing and absence of periventricular ovoid lesions perpendicular to the ventricular edge (Dawson fingers). CSF shows presence of oligoclonal bands which further helps in making a diagnosis of MS.

Points to Remember

- ***ADEM should be considered in every child with acute febrile/afebrile encephalopathy, especially with multifocal neurological deficits including seizures.***
- ***MRI is essential for the diagnosis. It shows diffuse poorly demarcated white matter predominant lesions, frequently involving the thalamus, basal ganglia, cerebellum, brainstem and spinal cord.***
- ***Anti-MOG antibody titres are frequently (upto 50%) raised. The detection of this antibody helps to confirm the diagnosis.***
- ***Early immunosuppression leads to prompt and complete recovery in most patients. IV methylprednisolone is the treatment of choice, followed by a slow steroid taper. IVIg/Plasmapheresis is used in refractory/severe cases.***
- ***Though ADEM is typically a monophasic disease, in a small minority (up to 20%) it may recur.***

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CLIPPINGS

Safety and adherence of pressure garment therapy in children with upper limb unilateral cerebral palsy. Results from a randomized clinical trial ancillary analysis.

This study was conducted to assess the safety and adherence of the use of a PGT (Pressure Garment Therapy) Lycra® sleeve to treat upper limb unilateral cerebral palsy (UCP) in children.This study was conducted as a prospective, placebo-controlled, double-blinded, randomized monocenter study. Included in the study were 58 UCP children, 49 of whom were analyzed. 25 children (mean age 6.6±1.6 years; 12 girls) were allocated to the active group vs. 24 (mean age 6.7±1.6 years; 10 girls) in the placebo group. The intervention consisted of an active PGT Lycra® arm sleeve manufactured to generate a homogeneous pressure ranging from 15 to 25mmHg. The placebo PGT Lycra® sleeve was manufactured to generate a homogeneous pressure under 7mmHg. The time of wearing period was set at 3h/day at minimum and 6h/day at maximum, over the course of 6 months.Conclusion: The use of PGT Lycra® arm sleeve in children with UCP is safe and well-tolerated with a very good adherence. The low rate of Adverse Events of Special Interests is promising for further randomized clinical trials on efficacy.

Béghin L, Mohammad Y, Fritot S, Letellier G, Masson S, Zagamé Y, et al. Safety and adherence of pressure garment therapy in children with upper limb unilateral cerebral palsy. Results from a randomized clinical trial ancillary analysis.Front. Pediatr., 11: 2023; DOI https://doi.org/10.3389/fped.2023.1043350.

IAP - IJPP CME 2022

ANAPHYLAXIS

Annamalai Vijayaraghavan

Abstract: *Anaphylaxis is derived from the Greek word 'ana' meaning again and 'phulaxis' meaning guarding which also means 'over protection' in Latin. Anaphylaxis is a severe life threatening systemic allergic reaction that is rapid in onset, associated with breathing, circulatory problems usually but not always with skin and mucosal changes. This can cause high mortality if not treated promptly and appropriately with epinephrine. Delayed epinephrine administration increases the mortality.*

Keywords: *Anaphylaxis, Epinephrine, Refractory, Biphasic reaction, Persistent hypotension.*

The term anaphylaxis generally refers to IgE-mediated reactions, whereas the term anaphylactoid refers to non-IgE-mediated reactions and anaphylaxis syndrome is used to describe clinical symptoms and signs. The variable and atypical presentations have to be recognized to commence management immediately because delayed epinephrine administration increases the mortality.[1]

The global incidence of anaphylaxis is between 50 and 112 episodes per 100 000 person-years while the estimated prevalence ranges from 0.3 -5.1%, variations depending on the definitions used, study methodology and geographical areas.[2,3] In children, the incidence of anaphylaxis varies from 1 to 761 per 100 000 person-years.[4] The recurrence of reactions occurs in 26.5-54.0% of anaphylaxis patients during a follow-up time of 1.5-25 years.[5] Despite an increasing trend over time for hospitalizations due to anaphylaxis, mortality remains low which is estimated at 0.05-0.51 per million persons/year for drugs, at 0.03-0.32 per million persons/year for food and at 0.09-0.13 per million persons/year for venom induced anaphylaxis, with no evidence in most regions of a change in incidence of fatal anaphylaxis.[6,7]

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Definitions

Various definitions were used by a number of societies since 2006, National Institute of Allergy and Infectious Diseases (NIAID) 2006, American Academy of Allergy Asthma and Immunology / American College of Allergy, Asthma, and Immunology (AAAAI/ACAAI) in 2010, World Allergy Organization (WAO) in 2011, European Academy of Allergy Asthma and Clinical Immunology (EAACI) in 2013, Australian Society of Clinical Immunology and Allergy (ASCIA) in 2016 and World Health Organization International Classification of Diseases (WHO ICD) 11th Edition in 2019.[8-14]

The revised definition of anaphylaxis mentioned in the position paper by the World allergy organization anapylaxis (WAOA) in 2020 states that "Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is a compromise in breathing and/or the circulation and may occur without typical skin features or circulatory shock being present." The amended criteria for the diagnosis of anaphylaxis, proposed by the WAO Anaphylaxis Committee, 2019 (Box 1).[15]

Etiology

The common causative agents are food items which can be a trigger for IgE mediated anaphylaxis like nuts, shellfish, finned fish , cow's milk, egg, wheat, soy, sesame, meat and certain food additives, drugs (pencillin, beta lactams, NSAIDS, aspirin), blood products, fluids, antivenins, vaccines, many biologicals, inhalants (grass pollens, dander) especially insects (bees,wasps, ants). Non IgE triggers include infections, opiates, radiocontrast dyes and exercise. Drugs and latex are common causative agents in hospital and food induced anaphylaxis is common in community settings, rarely there can be no cause when it is idiopathic. Exacerbating factors that decreases the threshold for anaphylaxis summarized in Box 2.

Severe/fatal anaphylaxis is associated with the conditions shown in Box 3.

Pathophysiology

IgE- and non–IgE-mediated reactions

Both IgE and non-IgE activation of mast cells and

Box 1. Criteria for diagnosis of anaphylaxis[15]

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND

at least one of the following:

a. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b. Low BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)

c. Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens

2. Acute onset of hypotension* or bronchospasm or laryngeal involvement[a] after exposure to a known or highly probable allergen[b] for that patient (within minutes to several hours[c]), even in the absence of typical skin involvement.

PEF- Peak expiratory flow; BP - blood pressure

**Hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, OR*

i. Infants and children under 10 years: systolic BP less than (70 mm Hg + [2 x age in years])

ii. Older children and adults: systolic BP less than <90 mm Hg.

a. Laryngeal symptoms include: stridor, vocal changes, odynophagia.

b. An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an IgE-mediated pathway, but some non-allergen triggers can act independent of IgE (for example, via direct activation of mast cells).

c. The majority of allergic reactions occur within 1-2 hours of exposure, and are usually much quicker however reactions may be delayed for some food allergens (e.g. alpha-gal) or in the context of immunotherapy, occurring up to 10 hours after ingestion.

Box 2. Exacerbating factors

- Fever
- Ingestion of nonsteroid anti-inflammatory drugs (NSAIDS)
- Emotional stress
- Exercise
- Upper respiratory tract infection

Box 3. Severe fatal anaphylaxis

- Mast cell disorders
- Failure to inject epinephrine promptly
- Concomitant asthma
- Use of beta-blockers or angiotensin-converting enzyme inhibitors

basophils ignites a cascade that results in the release and production of several inflammatory and vasoactive substances. These bioactive materials include histamine, tryptase, heparin, prostaglandins (PGD2, PGF2), leukotrienes (LTC4, LTD4, and LTE4), cytokines - tumor necrosis factor alpha (TNF α) and platelet- activating factor (PAF). In anaphylaxis, these substances most commonly involve the skin, respiratory, cardiovascular and gastrointestinal systems. As a result, urticaria, angioedema, bronchospasm, bronchorrhea, laryngospasm, increased vascular permeability, decreased vascular tone and bloody diarrhea can develop.

The most common cause of mediator release is due to an IgE-mediated reaction when a previously sensitized B lymphocyte produces IgE against a specific antigen which leads to release of several inflammatory and vasoactive substances. Non-IgE mediator release can be triggered by several different mechanisms including stimulation of the complement cascade to produce C3a, C4a and C5a anaphylatoxin, neuropeptide and cytokine activity and direct stimulation of the kallikrein-kinin system by certain agents (eg, opiates, radiocontrast media).

Activation of histamine receptors: Many of the clinical presentations seen in anaphylaxis are due to activation of multiple histamine receptors.[16] For example, acute bronchospasm (wheezing, dyspnea) is a result of the interaction between H1 and H2 receptor activity; bronchial smooth muscle constriction and increased mucus viscosity results from H1 receptor activity and increased mucus

Box 4. IgE independent mechanisms for anaphylaxis

- Direct degranulation of mast cells by drugs and physical factors - Morphine, cold, exercise
- COX 1 inhibition and synthesis of leukotrienes - aspirin & NSAIDs
- Immune aggregates and complement activation - blood products
- IgG mediated reaction - High molecular weight dextran, monoclonal antibodies.
- Probable complement activation - Radio contrast dyes, dialysis membranes
- Idiopathic

production from H2 receptor activity. The combination of H1 and H2 receptor stimulation results in increased vascular permeability, flushing, hypotension, tachycardia, and headache. H1 and H3 activity results in cutaneous itch and nasal congestion.

Other precipitating agents in anaphylaxis: Histamine is not the only agent to cause symptoms in anaphylaxis.[17] Prostaglandins, leukotrienes and PAF all contribute to the bronchoconstriction, vascular changes and changes in vascular capacitance (increased vascular permeability and vasodilatation). There is an inverse correlation between PAF acetyl hydrolase activity and the severity of anaphylaxis.[18]

Various IgE independent mechanisms are also involved in anaphylaxis (Box 4).

The symptoms, systems involved and their features seen in anaphylaxis are summarized in Table 1.

Median time to respiratory or cardiac arrest in fatal anaphylaxis varies with the etiology, it can happen in

Box 5. Atypical presentation of anaphylaxis in infants

- Nonspecific behavior changes include, sudden quietness or irritability or fussiness
- Excessive drooling, spitting or regurgitation
- Dysphonia
- Colicky abdominal pain
- Flushing
- Drowsiness

Table I. The features in anaphylaxis

Organs	Features
Cutaneous	Pruritus around mouth, face, flushing urticarial /hives, angioedema. Cutaneous symptoms may be absent in nearly10% of the cases
Respiratory	Tightness in the throat, dry staccato cough, edema of tongue, uvula and larynx, hoarseness, stridor, nasal congestion, sneezing, acute onset of bronchospasm; cough, wheeze, tachypnea, dyspnea, respiratory arrest.
Cardiovascular	Dizziness, tachycardia, pallor, cyanosis, hypotension, dysrhythmia, myocardial ischemia, cardiac arrest.
Gastrointestinal	Nausea, vomiting colicky abdominal pain and diarrhea.
Central nervous system	Irritability, headache, lethargy, drowsiness, fainting, loss of consciousness.

5 minutes after intravenous (IV) drugs, 15 mins after insect stings and 30 minutes in food induced anaphylaxis. However, regardless of the trigger, respiratory or cardiac arrest can occur within one minute in anaphylaxis.[19] Presentation in infants may be atypical (Box 5).

Signs of anaphylaxis in infants include the following (Box 6).

Investigations

Laboratory tests generally are not useful for the acute diagnosis of this condition, although serum histamine and tryptase may be of limited help in confirming the diagnosis retrospectively; other tests (e.g. specific antigen testing following recovery) may provide some clues to triggering agents.

Box 6. Anaphylaxis - Signs in infants

- Rapid onset of urticaria, angioedema (face, tongue, oropharynx)
- Rapid onset of coughing, dysphonia, choking, stridor, wheezing, dyspnea, apnea, cyanosis
- Sudden, profuse vomiting, spitting, regurgitation, drooling
- Weak pulse, arrhythmia, diaphoresis / sweating, pallor, collapse / unconsciousness
- Rapid onset of unresponsiveness, lethargy or hypotonia; seizures

Serum tryptase levels: The diagnosis of anaphylaxis is principally a clinical one. However, measurements of serum tryptase (upper normal -11.4 ng/mL)[20] may be helpful in confirming the diagnosis. Serial measurements are more helpful.[21] Levels may increase as soon as 15 minutes after onset of symptoms and can peak in 3 hours. Levels return to baseline in about 6-8 hours after onset of symptoms. A normal value does not rule out anaphylaxis, as tryptase levels does not increase in children with food-induced anaphylaxis.[22,23]

Other tests: Tests that may be useful in distinguishing anaphylaxis from other similar conditions include C1 inhibitor functional assay (C1INH) for hereditary angioedema and urine vanillyl mandelic acid (VMA) and serum serotonin levels for carcinoid syndrome.

Radioallergosorbent test (RAST) or cutaneous antigen testing can be used after recovery to try to identify the inciting antigen.

Box 7. Primary assessment

- Airway - Swelling of lips, tongue, uvula; stridor
- Breathing - Tachypnea, cough, dyspnea, wheeze, decreased oxygen saturation, hypoxemia
- Circulation - Tachycardia, prolonged capillary refill time, hypotension, shock
- Disability - Altered sensorium/ irritability
- Exposure - Hives, erythema, flushing, angioedema

Management

Assess ABCDE and care should be directed at stabilization of the airway, breathing and circulation (the "ABCs") and administration of intramuscular (IM) epinephrine simultaneously (Box 7) . The management of anaphylaxis is given in Fig.1.

a) First-line treatment: It is stressed that intramuscular (IM) administration of epinephrine in a dose of 0.01 mg/kg (1:1000 strength = 1 mg/mL) should be administered into the anterolateral portion of the thigh as the only first-line treatment for anaphylaxis.[22-24]

Its use should not be delayed by giving other medications such as antihistamines. Administration in the anterolateral thigh provides superior absorption compared with deltoid and subcutaneous injections. Because of the risk of potentially fatal dysrhythmias, intravenous (IV) and intraosseous (IO) administration should be limited to low dose infusions under closely monitored conditions for patients with refractory reactions.

Since delay in administration may lead to more prolonged symptoms, epinephrine should be administered when patients present with potential anaphylactic symptoms, whether mild or moderate in severity. There are no absolute contraindications to epinephrine use in the treatment of anaphylaxis.

b) Care of airway, breathing, circulation (ABC): If child develops rapid deterioration and cardiac arrest CPR should be started along with intramuscular epinephrine. First and foremost attention is directed at the stabilization of the patient's airway, breathing and circulation. Nebulized salbutamol (2.5-5 mg/dose) may be used for bronchospasm not responding to epinephrine. Nebulized epinephrine may be used for stridor secondary to laryngeal edema.

If the patient is hypoxic or has respiratory complaints, high-flow oxygen by non-rebreathing mask (NRM) should be given. In the awake child who is having some difficulty maintaining his or her airway, positioning and a nasopharyngeal (NP) airway may be helpful.

If the child is unable to maintain the airway, has decreased oxygen saturation and/or has a decreasing level of consciousness the use of noninvasive positive pressure ventilation (e.g., CPAP) may help to avoid the need for an advanced airway. In patients with signs of significant hypoxia, an advanced airway (e.g., supraglottic airway device, endotracheal intubation) should be considered. The airway should be secured with an endotracheal tube early in cases of upper airway obstruction.

c) Positioning: It is important to position the patient by lying flat or holding the young child flat not upright and is not to allowed to stand or walk. If the child has breathing difficulty, the child is allowed to sit with legs outstretched and if unconscious placed in recovery position.

d) Shock : Patients with signs of poor perfusion should be placed in a modified Trendelenburg position with the legs elevated. Crystalloids should be given rapidly if the patient is hypotensive or has other signs of shock.[25]

Few patients will present with shock, most will present with skin complaints (e.g, urticaria, angioedema), along with respiratory, gastrointestinal, or cardiovascular symptoms.

Primary attention is directed at the stabilization of the patient's airway, breathing and circulation. If not already given, epinephrine (which acts as a physiologic antagonist) should be administered as soon as the diagnosis is suspected. The role of antihistamines (H1 and H2 blockers) and corticosteroids are questionable.

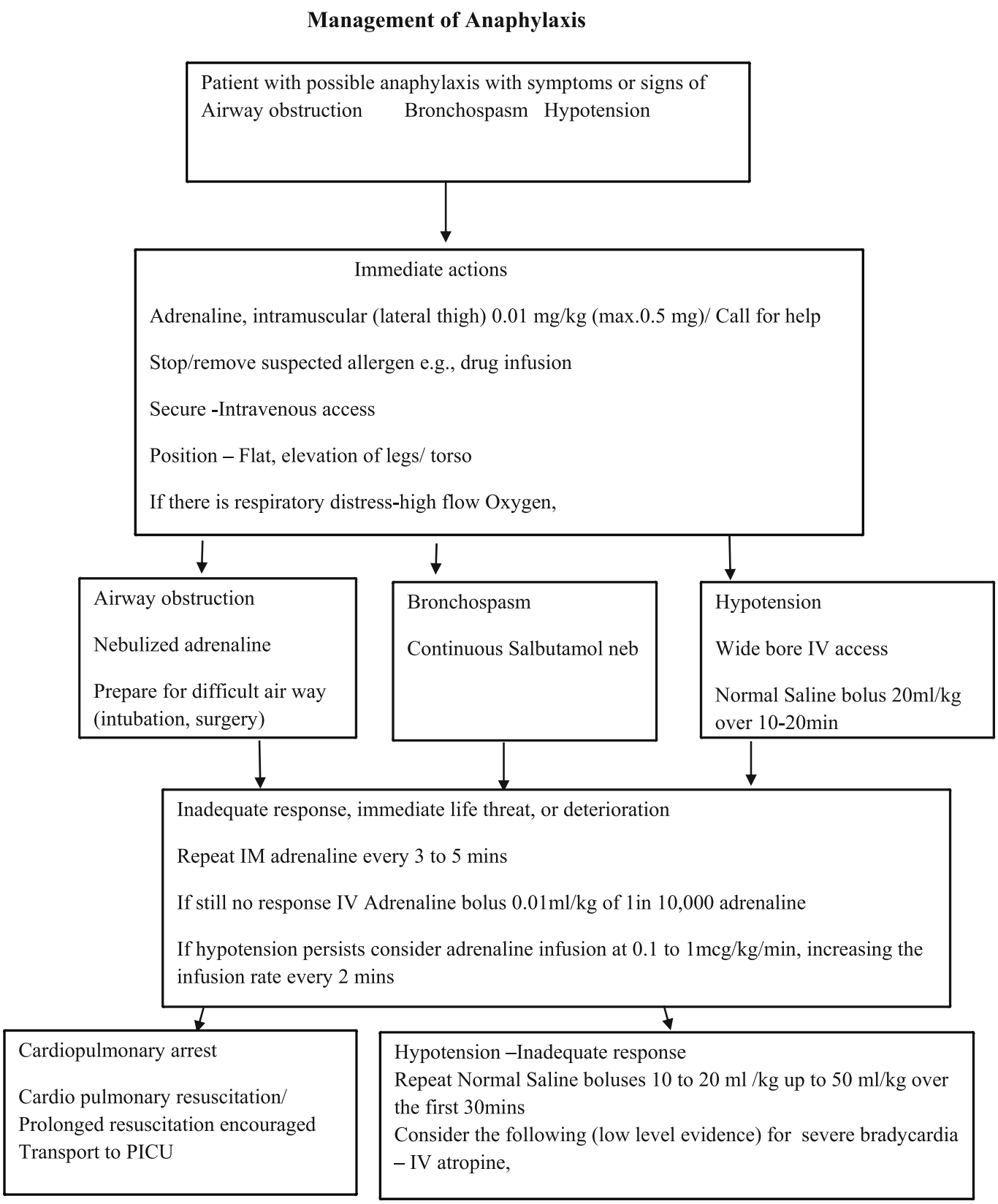

Fig.1. Management of anaphylaxis

Source: Modified from Anaphylaxis management flow chart. Blanca Sanchez. Scghed.com accessed on 19.1.2023

e) Monitoring : Even patients with mild symptoms should be observed for a minimum period of 12 to 24 hours. Duration of observational time should be based on factors including the severity of presentation, time to first dose of epinephrine, need for more than one dose and the inciting trigger. A period of 2-6 hours is appropriate in most circumstances.

Some children, nonetheless, may require up to 24 hours with certain triggers, e.g., bee stings or treatment with multiple doses of intramuscular (IM) epinephrine. In any case, the patient must be observed until all symptoms have cleared. Children who require fluid resuscitation, continuous epinephrine infusion, or repeated doses of a bronchodilator should be hospitalized. Children who require vasopressors or glucagon should be admitted to a tertiary pediatric intensive care center.

Epinephrine administration: Epinephrine is the first and definitive treatment of anaphylaxis and the details are discussed here. If administered early it will prevent the progression of symptoms. It is a non-selective adrenergic agonist that acts rapidly to increase peripheral vascular resistance, increases cardiac output, reverses bronchoconstriction and mucosal edema, also stabilizes mast cell and basophils. It is available as 1mg/mL ampoule of 1:1000 concentration. A dose of 0.01mg/kg (1:1000 strength = 1 mg/mL) should be administered into the anterolateral portion of the thigh. The intramuscular (IM) epinephrine may be repeated at 5 to 15 minutes interval for unresponsive symptoms.

Injectable prefilled syringes with epinephrine (Epipen®) if available can be used, a simplified IM dosing regimen can be used based on the child's weight (Box 8).

Intravenous (IV) bolus administration of epinephrine is to be avoided since it can result in dosing errors and cardiovascular complications. Patients with previous history of anaphylaxis and those with flushing, diaphoresis or dyspnea may need additional doses.

Epinephrine intravenous (IV) infusion: Patients not responding to multiple injections of IM epinephrine and IV fluid boluses may be given epinephrine as IV infusion. Muscle perfusion may be poor in them because of profound hypotension. It is preferably given in ICU setting under continuous cardiac and hemodynamic monitoring. The dose for IV infusion of epinephrine is 0.1 to 1μg/kg/minute titrated according to response.

Box 8. Pediatric weight based dose of prefilled epinephrine syringes

- 7.5-15 kg: 0.1 mg (0.1 mg/0.1 mL)
- 15-30 kg: 0.15 mg (0.15 mg/0.15 mL)
- >30 kg: 0.3 mg (0.3 mg/0.5 mL)

Adverse effects: Tremor, palpitation, restlessness, headache are transient and minimal.

Lack of response to epinephrine can occur in following situations.

i) Delayed identification of symptoms, delayed or wrong diagnosis (e.g. foreign body aspiration) lesser dose, degraded drug (stored in hot place/expired drug), wrong route or site of administration. Epinephrine continues to be under utilized in anaphylaxis.

ii) Those who are on betablocker therapy is another situation where it is less effective. Glucagon may help in the patient taking a beta-blocker with refractory symptoms. In children, 20-30 mcg/kg (not to exceed a cumulative dose of 1 mg) is given intravenously (IV) over 5 minutes followed by an IV maintenance infusion and titrated to clinical effect at 5-15 mcg/min.

Norepinephrine (0.1-2 mcg/kg/min IV) is a potent vasopressor. It is usually considered in children unresponsive to epinephrine.

Treatment of cutaneous symptoms: Anti histamines are useful only for this purpose either oral or IM injections can be used. Cetirizine is currently the only second generation IV H1 antihistamine approved for use. Studies have shown its efficacy in acute urticaria[26] and its potential usefulness in anaphylaxis.[27] It is recommended for use in Covid vaccine-related anaphylaxis.[28]

When cetirizine is not available, diphenhydramine 1 mg/kg (not to exceed 50 mg/dose) may be given IM/ per oral (PO). H2 antihistamine use has fallen out of favor for the most part, because these receptors have limited vascular smooth muscle distribution and have a minor place in anaphylaxis.[23,29] The pharmacological management is given in Table II.

Inhaled bronchodilators: IM epinephrine remains the first-line treatment for symptoms of upper or lower airway obstruction due to anaphylaxis with inhaled salbutamol and inhaled epinephrine useful for supportive management. Inhaled salbutamol can be used to relieve bronchospasm especially in children with history of asthma using metered dose inhaler (MDI) with spacer, or administered through nebulizer with oxygen. This doesn't relieve mucosal edema of airway. Children with stridor may find some relief with

Table II. Pharmacological management in anaphylaxis[30]

Drug	Dose (maximum dose)	Remarks
Adrenaline 1 in 1000	0.01mg/kg IM (0.5mg)	Repeat every 5-15 min
Antihistamine Cetirizine Diphenhydramine Pheniramine maleate	Cetirizine (0.25mg/kg) 6mo-5yrs:2.5mg Beyond 5yrs to 12yrs:5-10 mg Diphenhydramine:1.25mg/kg/dose(max.50mg) Pheniramine maleate IV: Can be repeated after 6 hrs. 1-6yrs:2.5-5mg Beyond 6 yrs to 12 yrs :5-10mg	Never given as first line drug. Always give after adrenaline
Salbutamol	5-10 puffs by MDI 2.5 to 5mg by nebulization	For bronchospasm
Epinephrine infusion IV	0.1 -1mcg/kg/min	For hypotension
Glucagon IV	20-30mcg/kg bolus (1mg) followed by infusion 5-15mcg/kg/min	For those on Beta blockers with refractory symptoms

inhaled epinephrine, the role of inhaled epinephrine to treat airway edema or stridor in anaphylaxis has not been proved.[30]

Corticosteroids: The onset of action is slow and they are not of much benefit in acute anaphylaxis. Oral prednisolone or IV methyl prednisolone were used to prevent biphasic or protracted reactions. But recent evidence doesn't recommend its use for such indications.

Care after resuscitation : The prognosis is good, especially if anaphylaxis is treated early with epinephrine. The overall fatality rate in children is very low (1 per 100,000 per population).[31] Prolonged observation is needed in the following situations;

i) Refractory anaphylaxis

ii) Biphasic reaction

iii) Persistent hypotension

In addition to above conditions, patients needing multiple doses of epinephrine, those with severe symptoms (e.g. hypotension, severe respiratory distress) on presentation, asthmatics and those on beta blockers need prolonged observation.

i) Refractory anaphylaxis: It is defined as no response to two or more doses of epinephrine.[32] It occurs mostly due to allergy to intravenously administered drugs in perioperative setting. Drugs like atracurium and rocuronium might trigger anaphylaxis by direct mast cell activation an IgE independent mechanism. Another common agent is radiocontrast medium (RCM) which also elicits IgE independent anaphylaxis refractory to adrenaline. Mortality is higher when compared to severe treatment responsive anaphylaxis which is less than 1%.

ii) Biphasic reaction anaphylaxis[23]

It is defined as reappearance of anaphylaxis symptoms after initial resolution. The overall risk of biphasic reactions appears to be < 1% to 20%. The secondary response may be milder, the same, or more severe than the initial presentation. Those at greatest risk, with certain triggers (e.g., bee stings) or treatment (e.g., multiple doses of IM epinephrine), may require up to 24 hours of observation. Severe initial presentation and need for multiple doses of epinephrine are suggested as risk factors for biphasic reactions. Even though most biphasic reactions occur 4 to 6 hrs after initial symptoms, it has to be anticipated from 1 to 72 hrs after the initial presentation. It is managed with repeat epinephrine administration along with oxygen, intubation, bronchodilators, fluids and vasopressors as needed.

iii)Persistent hypotension: This is managed with epinephrine infusion along with titrated fluid boluses. Repeated administration of IM epinephrine has no benefit in improving prolonged hypotension in anaphylactic setting.[33]

If cardiopulmonary arrest occurs during anaphylaxis: CPR (cardiopulmonary resuscitation) and ACLS (acute cardiac life measures) measures should be initiated. Prolonged resuscitation efforts are encouraged. Consider repeat doses of epinephrine, rapid volume expansion, atropine for asystole or pulseless electric activity, transport to emergency department or ICU.[34,35]

Box 9. Measures to prevent further attacks

Educate about early recognition of symptoms and prompt administration of epinephrine

Food induced anaphylaxis:

Avoid triggering agents

Make reading food labels a practice

Food -associated exercise induced anaphylaxis:

Avoid exercise within 2-3 hrs of food intake

Insects induced anaphylaxis:

Avoid potential insect nesting sites like trees/hollows (hornets, bees), under barns (wasps), grounds (ants, yellow jackets)

Immunotherapy may be useful for stinging insect anaphylaxis.

Drug induced anaphylaxis:

Oral less risk than IV

Avoid cross reacting drugs

If alternative drugs unavailable consider desensitization,

Low osmolar radiocontrast agents

Non latex gloves

Discharge plan

Patients should be given a prescription for self-injectable form of epinephrine.[36] Risk factors that need prescription for self- injectable epinephrine are:

- Concomitant asthma, patient on beta blockers,
- First episode required epinephrine,
- Patient living in remote area with poor access to medical care,
- Patient with allergy to common foods (nuts, seafood, milk) and have experienced severe/fatal reactions.

Anaphylaxis emergency action plan-which lists the symptoms and signs of anaphylaxis and instructions about how and when to use epinephrine auto injector. The measures to prevent further episodes of anaphylaxis is given in (Box 9).[36]

Differentials for anaphylaxis

Fainting (vasovagal attacks) and breath holding spells are some of the benign adverse events usually following immunization that should be differentiated from anaphylaxis. These do not require any aggressive management except observation in supine position.

Fainting: This is one of the common AEFI (adverse event following immunization), which is managed by simply placing the patient in recumbent position. One should be able to differentiate this from serious adverse events like anaphylaxis (Table III).

Breath holding spells: Common in children between 6 months to 6 years with history of previous breath holding spells. Following a provoking factor like pain during

Table III. Difference between fainting and anaphylaxis[36]

	Fainting	Anaphylaxis
Onset	Usually immediately after the injection	Usually some delay, 5-30 min after injection
Age group	Relatively common in older children, very rare in young pre-schoolers	Younger children with loss of consciousness (LOC) more likely to be anaphylaxis
Skin	Pale, sweaty, cold, clammy	Erythema, urticaria, swollen face, eyes
Respiratory	Normal to deep breaths	Noisy breathing. stridor, wheeze
Cardiovascular	Strong central pulse, bradycardia, transient hypotension	Weak central pulse tachycardia, hypotension
Neurological	Transient loss of consciousness (LOC), good response to keeping in recumbent position in a minute or two	LOC is not a sole manifestation. If LOC it takes longer time to recover

injection, child cries and holds breath in expiration, develops pallor or cyanosis with bradycardia and sometimes with transient loss of consciousness.

Red man syndrome during vancomycin infusion can mimic anaphylaxis, but it lacks other features except flushing. Anaphylaxis is to be differentiated from other causes of shock like cardiogenic or septic shock. Flushing syndromes like carcinoid, hereditary angioedema may also present with anaphylaxis like symptoms.

Points to Remember

- ***Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset potentially life-threatening and may cause death if not treated promptly with intramuscular epinephrine.***
- ***Severe anaphylaxis is compromise in breathing and/or the circulation and may occur without typical skin features or circulatory shock being present.***
- ***Epinephrine is the first and definitive treatment of anaphylaxis and if administered early will prevent the progression of symptoms and must be given in a dose of 0.01mg/kg (1:1000 strength = 1 mg/mL) intramuscularly into the anterolateral portion of the thigh.***
- ***Over reliance on second line agents like anti histamines and glucocorticoids are to be avoided as they are not life-saving in anaphylaxis.***
- ***Observation for long hours and management in the intensive care is needed for patients who develop refractory anaphylaxis, persistent hypotension, biphasic reaction, needing multiple doses of epinephrine, those with severe symptoms (eg, hypotension, severe respiratory distress) on presentation, asthmatics and those on beta blockers.***
- ***At the time of discharge the patients and caregivers must be provided with education about the exposure risk, early management access to medical care and if available taught to use epinephrine autoinjector.***

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CLIPPINGS

Long term kidney outcomes in non dialyzed children E.Coli associated HUS

A total of 122 children with median age of 1.62 years with Shiga toxin-producing Escherichia coli hemolytic uremic syndrome (STEC-HUS) who did not require dialysis during the acute phase of the disease were followed up for 11.3 years for their outcomes. Overall, 67.2% had complete recovery and 32.8% developed CKD - median time to CKD 5 years. 18% of patients developed CKD within 5 years, 28% at 10 years, 32% at 15 and 33% after 20 years.

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ANTIBIOTIC RESISTANCE TO COMMUNITY ACQUIRED INFECTIONS

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Abstract: *Antibiotic resistance is one of the biggest threats to human lives. It was once considered a major problem only in hospital acquired infections, but at present it is encountered even among the community acquired infections. New mechanisms are emerging and spreading rapidly across the globe leading to more resistant organisms. This has made infections like urinary tract infections, pneumonia, tuberculosis and salmonellosis difficult to treat and sometimes impossible.*

Keywords: *Antibiotics, Resistance, Tuberculosis, Salmonellosis, Community acquired pneumonia.*

On one hand we have drug resistant tuberculosis, urinary tract infection, community acquired pneumonia and salmonella infections, while on the other hand, some infections like acute pharyngotonsillitis due to group A beta hemolytic streptococcus have never developed resistance to penicillin. Similarly among non-meningeal isolates of pneumococcus, penicillin resistance is very less.

The problem of antibiotic resistance is accelerated by the misuse of antibiotics and lack of proper infection control measures. The direct consequences of antibiotic resistance are the need for hospitalisation, parenteral antibiotics usage, increased length of hospital stay and mortality, causing economic impact and a need to develop newer antibiotics. Hence, steps should be taken at all levels in the community to prevent spread of resistance. To tackle this problem, WHO has initiated the "Global action plan on antimicrobial resistance"[1] in 2015, the main objectives of which are:

- To improve awareness and understanding of antimicrobial resistance.
- To strengthen surveillance and research.
- To reduce the incidence of infection.
- To optimise the use of antimicrobials.
- To ensure sustainable investment in countering antimicrobial resistance

In this review, the changing antimicrobial susceptibility pattern in common community acquired infections will be discussed.

Resistance among common uropathogens

E.coli is the most common cause of UTI (nearly 85-90%) followed by *Klebsiella pneumoniae* and very rarely by *Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter spp, Citrobacter, Serratia, Enterococcus and Staphylococcus aureus*. Beta lactam antibiotics are the commonly used agents in the management of these infections, but β-lactamase production by these bacteria pose a great therapeutic challenge. Among the β-lactamases, original spectrum β-lactamase, extended spectrum β-lactamases (ESBL), Amp Cs and carbapenamases exist. Routine EBSL testing is not performed by most clinical microbiology laboratories. Rather, non-susceptibility to ceftriaxone (i.e., ceftriaxone minimum inhibitory concentrations [MICs] ≥2 mcg/mL), is often used as a surrogate marker for ESBL production. However this threshold has limitations, as organisms not susceptible to ceftriaxone for reasons other than ESBL production may be falsely presumed to be ESBL-producers. To overcome these resistance mechanisms, newer β-lactamase inhibitors are developed in combination with β-lactams to restore their activity. Therefore, understanding the local antibiogram will help to choose the appropriate empiric therapy. If local antibiogram is not available, national treatment guidelines can be followed.[2]

On analysing the current antimicrobial susceptibility patterns among *E.coli* and Klebsiella in India, ESBL rates are as high as 70%.[3] Therefore the empiric choice in the management of these infections may be piperacillin-tazobactam/cefoperazone-sulbactam or carbapenem based on the severity of infection. Once the susceptibility pattern is known, then a switch can be made to oral antibiotics like cefixime, amoxycillin-clavulanic acid or trimethoprim-

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sulfamethoxazole. Quinolones like ciprofloxacin can also be used if they are the only oral drug found to be susceptible. If oral antibiotics are not susceptible, switching to amikacin may be considered, if susceptible. Limiting the use of carbapenems will preserve their activity for more serious and resistant infections.

Carbapenem resistance rates are also increasing and in India, it was found to be 10% and 40% for *E.coli* and *K.pneumoniae* respectivel.[3] In case of carbapenem resistance, ciprofloxacin, levofloxacin and trimethoprim-sulfamethoxazole are preferred treatment options if their susceptibility is demonstrated. If carbapenamase production is identified, then depending on the molecular mechanism of resistance, newer β-lactam-β-lactamase inhibitors like ceftazidime avibactam with or without aztreonam can be tried. Other options includes cefiderocol and aminoglycoside. Nitrofurantoin and oral fosfomycin do not attain sufficient concentrations in renal parenchyma and hence they should be avoided for treating pyelonephritis.[4]

In older children with uncomplicated cystitis, nitrofurantoin and oral fosfomycin can be used if deemed susceptible, but fosfomycin use should be restricted to *E.coli* because fos A genes in other Gram negative organisms will hydrolyze the drug and may lead to clinical failure.

2. Resistance among salmonella species

Enteric fever caused by *Salmonella typhi* and *Salmonella paratyp*hi is one of the most common causes of blood stream infections among children. Initially ampicillin, chloramphenicol and co-trimoxazole were the drugs used in the management of enteric fever. Later in the 1970s resistance developed against these agents leading to the emergence of MDR Salmonella, which was defined as the isolate being resistant to ampicillin, chloramphenicol and co-trimoxazole. Then MDR isolates were increasingly reported and later fluoroquinolone became the drug of choice. Since 2000, resistance to fluoroquinolone is increasingly reported probably due to extensive use of the drug leading to the emergence of non susceptible clones and mutation in gyrase A gene.[5] Currently, MDR Salmonella is low and the reason could be limited use of these antibiotics.

Thus third generation cephalosporins to which *S. typhi* and *S.paratyphi* are uniformly susceptible have emerged as an empiric drug of choice in treating complicated enteric fevers. Azithromycin can be used in the management of uncomplicated enteric fever. Resistance to third generation cephalosporins are emerging and reported from neighbouring countries like Bangladesh and Nepal, and very rarely reported from India.[6-8]

Recently, a retrospective study of salmonella isolates in a pediatric tertiary care hospital over a period of 10 years revealed that MDR isolates among cases of *S. typhi* was only 2.12 %, whereas it was completely absent among cases of *S. paratyphi A.* Fluoroquinolone resistance was high (>95%) throughout the study period[9] and there were no cases of ceftriaxone and azithromycin resistance reported. Similar observations were noted in a multicentric study the Surveillance of Enteric Fever in India (SEFI).[10]

3. Resistance among non-meningeal isolates of *Streptococcus pneumoniae*

Streptococcus pneumoniae is the most common cause of bacterial pneumonia in children. A review by O'Brien, et al. suggests that 66% of the pneumococcal cases worldwide are from Asia and Africa, with the highest proportion (27%) being reported in India.[11] Worldwide, reports of antimicrobial resistance in *S. pneumoniae* have been increasing during the past decades. The revised CLSI susceptibility breakpoints for penicillin in 2008 resulted in decreased penicillin non-susceptibility amongst non-meningeal pneumococcal isolates due to the increase in non-susceptibility cut-offs to 4ìg/mL.[12] A laboratory based study conducted in Christian Medical college, Vellore done over a period of 8 years (2008-2016) showed that among the non-meningeal isolates, non-susceptibility to penicillin was seen in only in 0.60%. [13] The overall prevalence of non-susceptibility to penicillin in invasive pneumococcal disease during the study period remains low at 9.3%. But, when non-meningeal isolates were analysed, the non-susceptibility to penicillin was <1%. Hence, penicillin would continue to be appropriate therapy for such infections.

A recent systematic review of hospital based observational studies from India from January 1990 to December 2016 on the prevalence of serotype distribution and the antimicrobial resistance pattern of *S. pneumoniae* in children 5 years of age have shown a 10% resistance rate to penicillin among the invasive pneumococcal isolates (including both meningeal and non-meningeal).[14] Pneumococcal resistance to trimethoprim/ sulfamethoxazole, erythromycin, penicillin, chloramphenicol, levofloxacin and cefotaxime was seen in 81%, 37%, 10%, 8%, 6% and 4% respectively, while vancomycin resistance was not reported. They also reported 39% resistance to macrolides. Thus with increasing resistance of pneumococcus to macrolides, empiric use of

macrolide should be discouraged in the management of respiratory tract infections. Considering the low-level of penicillin resistance among the non-meningeal isolates, penicillin (or amoxicillin) should be the drug of choice in community acquired respiratory tract infections.

4. Resistance among meningeal isolates of *Streptococcus pneumoniae*

The most common cause of bacterial meningitis is *Streptococcus pneumoniae*. It causes significant neurological sequelae and the mortality can be up to 30% even if properly treated. Penicillin was the standard drug of choice for many years before the increasing incidence of resistance. Non-susceptibility to penicillin and cefotaxime is gradually increasing over time. Cefotaxime resistance parallels penicillin resistance with most studies documenting that cefotaxime non-susceptibility is predominantly seen amongst penicillin non-susceptible isolates.[12,15]

A recent study from Christian Medical College, Vellore from 2008 to 2016 among the invasive pneumococcal isolates, showed 43.7% and 14.9% of the meningeal isolates were non-susceptible to penicillin and cefotaxime respectively.[13] Even though many factors like misuse and overuse of antibiotics could account for these increasing resistance, other factors like dissemination of penicillin-resistant clones such as ST 63, could also contribute to rising penicillin resistance in our country.[16]

In the treatment of bacterial meningitis, the mortality will be higher if the child was not given an appropriate antibiotic to which the isolate was susceptible during the first 24 hours of treatment. Considering such increasing resistance of meningeal isolates of pneumococcus, the empiric antibiotic of choice should be cefotaxime or ceftriaxone along with vancomycin. Once the organism is identified, antibiotics can be de-escalated based on the susceptibility pattern.

5. Resistance among *Staphylococcus aureus*

Staphylococcus aureus is implicated as an important pathogen both in community acquired infections and hospital acquired infections. It is responsible for relatively mild localised skin and skin-structure infections to life-threatening systemic infections such as sepsis, necrotizing pneumonia, septic arthritis, endocarditis and osteomyelitis. Methicillin resistant *staphylococcus aureus* is increasingly reported not only from hospitals but also from the community. The incidence of MRSA varies from 25 per cent in western part of India[17] to 50 per cent in South India.[18] Community acquired MRSA (CA-MRSA) has been increasingly reported from India.[19] Similarly another study on staphylococcal isolates collected from children showed 80% of MRSA infections to be community acquired.[20]

A multicentric study on *staphylococcus aureus* isolates from 2008 to 2009 showed the rates of MRSA from outpatients, ward inpatients and ICU were 28, 42 and 43%, respectively in 2008 and 27, 49 and 47%, respectively in 2009.[21] A recent study from clinical isolates collected from children in a tertiary care hospital in Southern India showed 53% of the *Staph. aureus* to be Methicillin-resistant.[22] Therefore for the management of severe skin and soft tissue infections like necrotising fasciitis, toxic shock syndrome and osteomyelitis where staphylococcus is considered the common etiological agent, empiric choice should include coverage for MRSA also, even in community acquired infections. Vancomycin is bactericidal for MRSA and now there are emerging reports of increased vancomycin resistance from different geographical regions. A recent study from Eastern India showed 11.6% resistance to vancomycin among the staphylococcal isolates, which is worrisome.[23]

6. Resistance among *Mycobacterium tuberculosis*

Tuberculosis causes significant mortality and morbidity and it affects nearly 1 million children annually.[24] In 2019, there were an estimated 208,000 child deaths due to TB globally and more than 80% of TB deaths occurred in children <5 years of age.[25] Most of the deaths occurred in southeast Asian and African regions.[26] Drug-resistant TB (DR-TB, referring to any resistance to TB drugs), especially multidrug-resistant TB (MDR-TB, defined as resistance to rifampicin or to isoniazid and rifampicin), is a continuing threat in both children and adults, and more than 30,000 children had MDR-TB.[27] According to the WHO Global TB Report of 2020, an estimated 3.4% of new cases and 18% of previously treated cases had MDR/RR-TB among overall TB cases from all age groups.[25] Thus, even though the burden of MDR-TB is high, there is a paucity of data on the epidemiology and drug susceptibility pattern in paediatric TB. Every attempt should be made to prove tuberculosis microbiologically to get the sensitivity pattern and for the initiation of appropriate antimicrobials.

Points to Remember

- ***Antimicrobial resistance is on the rise, even for community acquired infections.***
- ***Extended spectrum beta lactamase production is seen in around 70% of E.coli and Klebsiella pneumoniae.***

- ***Isolates of Salmonella typhi and paratyphi are increasingly resistant to fluoroquinolones (nearly 95%), hence it should be avoided in the management of enteric fever.***
- ***Ceftriaxone is the drug of choice for complicated enteric fever.***
- ***Among the non-meningeal pneumococcal isolates, the resistance to penicillin is low and hence penicillin (or amoxicillin) is the drug of choice.***
- ***Among meningeal pneumococcal isolates, resistance to penicillin and third generation cephalosporins is very high.***
- ***Incidence of MRSA is on the rise even among community acquired staphylococcal infections.***

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CLIPPINGS

Association Between Antimicrobial Stewardship Programs and Antibiotic Use Globally - A Systematic Review and Meta-Analysis

Antimicrobial resistance continues to spread rapidly at a global scale. Little evidence exists on the association of antimicrobial stewardship programs (ASPs) with the consumption of antibiotics across health care and income settings. A systematic review and meta-analysis of 52 studies with more than 1.7 million patients was conducted in different health care and income settings. Studies were chosen after searching PubMed, Web of Science, and Scopus databases from August 1, 2010, to Aug 1, 2020. Additional studies from the bibliography sections of previous systematic reviews were included. The main outcome measures were proportion of patients receiving an antibiotic prescription and defined daily doses per 100 patient-days.

Overall, 52 studies (with 1,794,889 participants) measured the association between ASPs and antimicrobial consumption were included, with 40 studies conducted in high-income countries and 12 in low and middle-income countries (LMICs). ASPs were associated with a 10% reduction in antibiotic prescriptions and a 28% reduction in antibiotic consumption. ASPs were also associated with a 21% reduction in antibiotic consumption in pediatric hospitals and a 28% reduction in World Health Organization watch groups antibiotics.

In this systematic review and meta-analysis, ASPs appeared to be effective in reducing antibiotic consumption in both hospital and nonhospital settings. Impact assessment of ASPs in resource-limited settings remains scarce; further research is needed on how to best achieve reductions in antibiotic use in LMICs.

Ya KZ, Win PTN, Bielicki J, Lambiris M, Fink G. JAMA Network Open. 2023;6(2):e2253806. doi:10.1001/jamanetworkopen.2022.53806.

IAP - IJPP CME 2022

DEVELOPMENTAL SCREENING IN OFFICE PRACTICE

***Rema Chandramohan**

Abstract: *Developmental screening is an important part of the high-risk newborn follow up program / well baby visits wherein the babies are primarily brought for immunization, general check-up and for growth monitoring. These follow up visits continue for 24 months and this golden period can be utilized by the primary physician for recognizing developmental delay if any. With the increase in the recognition of developmental disabilities among children due to various factors in the recent past, it is prudent to identify developmental delays early, by using appropriate screening tools so that these children with delay can realise their optimum developmental potential through the early intervention services.*

Keywords: *Brain development, Development screening tools, Directly administered tools, Parent administered tools.*

Need for early screening

The brain architecture is constructed through an on going process that begins before birth and continues into adulthood. Early experiences affect the quality of this architecture by establishing either a sturdy or a fragile foundation for all the learning, health and behaviour that follow (Fig.1a). In the first few years of life, more than 1 million new neural connections are formed every second. After this period of rapid proliferation, connections are pruned to make the brain circuits more efficient. Sensory pathways for vision and hearing are the first to develop, followed by early language skills and higher cognitive functions (Fig.1b). Connections proliferate and get pruned in a prescribed order, with more complex brain circuits being formed over simpler circuits.[1]

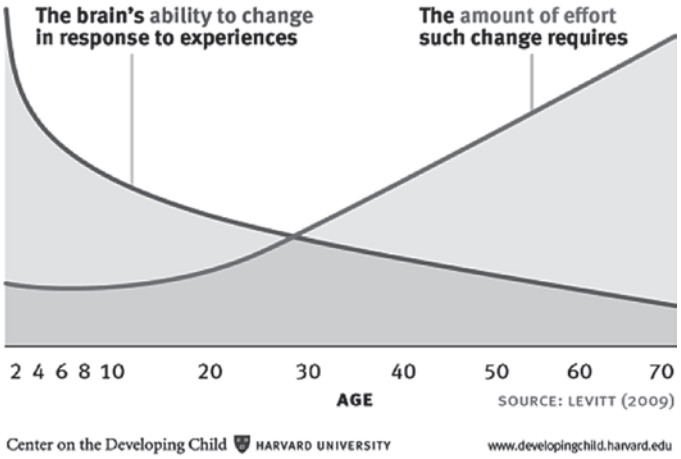

Fig.1a. Brain's response to experience

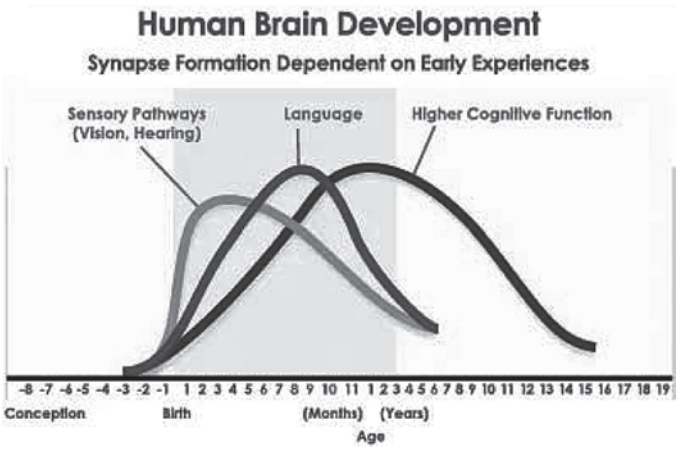

Fig.1b. Sequential development of human brain

Source: Center on a developing child. In brief : The Science of Early Childhood Development. Available at : https:// development child.harvard.edu / resources / in brief-science-of-ecd/ Accessed on March 2023.

With this background, the massive potential of the brain can be understood and the fact that, when it is put into optimum use at the right time maximum benefit accrues, and hence there is a need for early screening of every newborn / young infant.

Identification of developmental delays follows a 3 tier system.

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a) Developmental monitoring or surveillance

b) Developmental screening

c) Developmental assessment

a) Developmental monitoring or surveillance

This can be done by the primary physician, parents, grandparents or other caregivers using freely available checklists for children aged between 0-60 months or by comparing the child's development with that of his/her peers.

b) Developmental screening

Developmental screening is a brief testing procedure using a standardised tool designed to identify children with developmental delay who should receive a more detailed assessment subsequently. Screening can be done by the primary physician, early childhood teacher, or other trained provider using standardised tools. It should ideally be performed at 9,18 and 30 months of age of the child[2] and autism screening should be done at 18 and 24 months.

Need for developmental screening

As per the data published in 2018, based on a study by N K Arora, et al., 475 out of 3,964 children (between the ages of 2 and 9 years) had at least one neurodevelopmental disorder (NDD) [12.0% (95% CI - 11.0%-13.0%)].[3] Among these children, 21.7% (95% CI 18.1%-25.7%) had two or more NDDs. Children with autistic spectrum disorders (79.6%), neuromotor impairments - cerebral palsy (74.2%), intellectual disability (56.9%), and epilepsy (55.1%) had coexisting NDD.

Developmental delay affects 10-15% of the childhood population necessitating early identification by screening. However, in 2011, it was reported that only 48% of paediatricians were using a standardized developmental screening tool in practice.[4]

Box 1. Common barriers to developmental screening

- Time constraints-competing clinical demands
- Lack of adequate subspecialists for referral
- Lack of consensus on the best screening tools
- Lack of physician confidence in their ability to successfully manage behavioural and emotional issues of children.
- High staff turnover and difficulties in training.

According to to a study published by Vitrikas K, et al in 2017[5], only 52% of parents said they were informally asked about the development of their children, and only 21% reported filling out a questionnaire. Common barriers to developmental screening are given in Box 1.[5]

Screening can be done as a routine part of well-baby visits or as a focussed screening involving select groups of children.

Routine formal screening[6]

This entails systematic developmental screening of all children with the help of standardized screening instruments. However, such an approach is highly time consuming as it requires large number of trained manpower and it may not be feasible or cost effective.

Focussed screening

With time being the major constraint in developmental screening, it can be performed at least on a select group of infants.

The following children need focussed screening

(a) Children whose parents express developmental concerns or in whom teachers and physicians suspect problems.

(b) All newborns who are at high risk for developmental delay.

Choice of an ideal screening tool for practitioners

The screening tool chosen should be based on the factors as shown in Box 2.

Screening tools may be directly administered or completed by parents and reviewed by the doctor. Some of the commonly used directly administered tools are given in Box 3.

Box 2. Factors for choosing an ideal screening tool

- Sensitivity/specificity of at least 70-80%
- Adequate staffing
- Cost effectiveness
- Familiarity and time availability for parent-completed or directly administered tools
- Cultural and linguistic sensitivity

Box 3. Development screening tools

a) Development observation card (DOC)
b) Child development center - Grading of milestones card
c) Trivandrum Development Screening Chart (TDSC)
d) Language Evaluation Screening Trivandrum (LEST)
e) Ten questions screen tool
f) Denver Developmental Screening Test II (DDST-II)
g) Bayley Infant Neuro Developmental Screener (BINS)

Key milestones as per DOC	
Milestone	**Age**
Social smile	2 months
Head control	4 months
Sitting	8 months.
Standing	12months
Also make sure that the child can see, hear and listen	

Fig.2. Development observation card

a) Development observation card

This is a simple screening tool developed by Child Development Centre (CDC), Trivandrum, giving emphasis to the major milestones and their time of complete development, in addition to vision, hearing and cognition (Fig.2).

This card can be conveniently used even by the Anganwadi workers or affixed as a seal in the follow up record of the child for the parent to make a note of and seek early help and guidance.

b) CDC grading for motor milestones

All motor milestones go through several stages before they reach complete achievement (Fig.3). They are graded from 0-5. Grade 0 indicates that the milestone has not started establishing itself and grade 5 means complete achievement of milestone.

Grades 0, 1 and 2 mean abnormal development and 3, 4 and 5 are normal for that age.

CDC grading therefore helps to form an opinion about the developmental status of the child, to assess the improvement after therapy and to convince the mother about the improvements in the development.

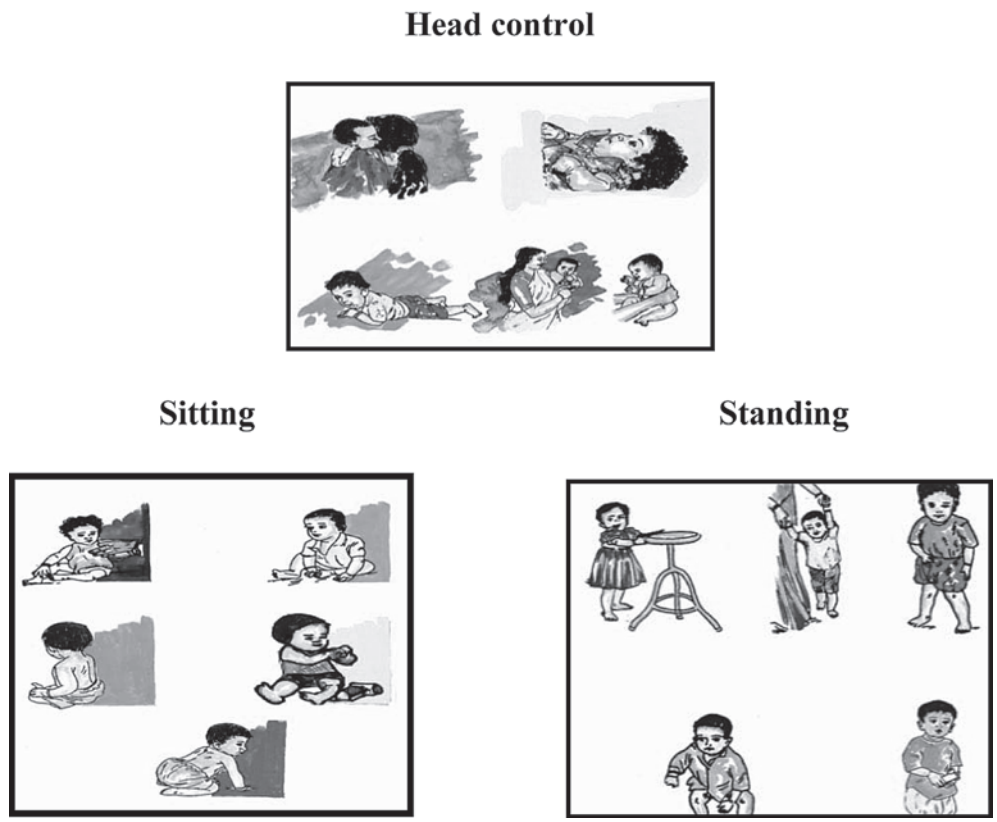

Fig.3. CDC Grading for motor milestones

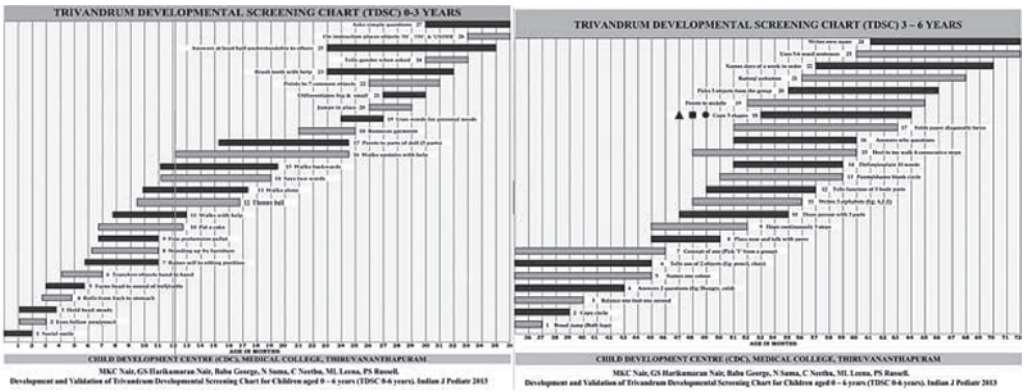

Fig.4a. Trivandrum Development Screening Chart - Fig.4a. 0 - 3 years Fig.4b. 3 - 6 years

c) Trivandrum Development Screening Chart (TDSC) 2013

A simple tool which can be used to pick up developmental delay even at the field level. A vertical line is drawn at the age of the child (e.g., 12 months as shown in the Fig.4a) and 3 items immediately to the left of the line is administered. If the child passes all the three items, the child is considered developmentally normal; if the child fails even one item, the child should be referred for further evaluation.

Two charts are available 1) between 0-3 years (Fig.4a) and 2) between 3-6 years (Fig.4b).

d) Language Evaluation Scale Trivandrum (LEST)

Since language delays are on the increase due to several factors, it is prudent to administer a separate screening tool to assess speech and language. LEST is available for screening for language delay and the same process as in TDSC may be followed.

Fig.6. Goodenough draw a man test. Using a blank piece of paper and a pencil, the seated patient must draw an entire man. The picture is scored by giving one point for the presence of each of the following body parts: head, trunk, right arm, left arm, right hand, left hand, right leg, left leg, right foot and left foot. The total score of this version of the test is 10.

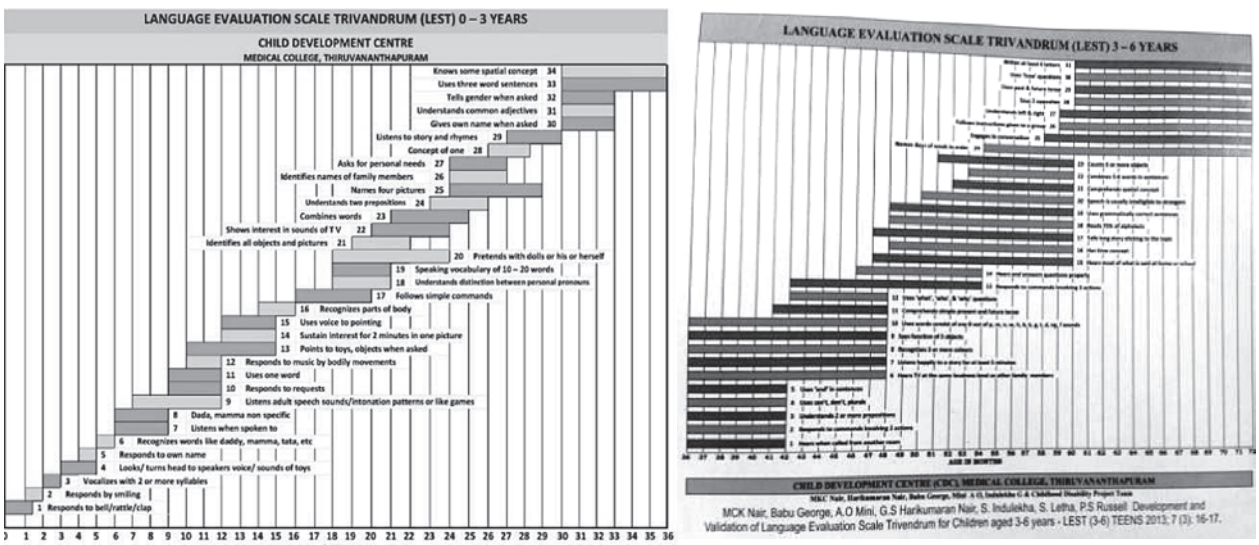

Fig.5. Language Evaluation Scale Trivandrum

e) Goodenough draw a man test (Fig.6)

This is a child friendly developmental tool which can be used for children above the chronological age of 3 years. With the available IQ tests at present, this tool is not very much used nowadays but the reader may benefit from knowing how this tool is administered and scored.

- The child is asked to draw the best person they can draw
- The starting point is a circle for the face at 3 years of age
- An additional point is then given for each item drawn, with each point being worth an extra 3 months

For e.g., if a child has drawn 6 parts of the body, then his score is -

3 years (starting point for circle) + (6x3 = 18 months) where 6 are the parts drawn and 3 is the number of months credited for each item)

Score = 6 = 4 ½ years mental age (MA) or it can be directly read from a table, where for the score of 6, the MA (mental age) is 4-6 years (Table I).

The above tests can be done in a clinic when an individual child is attended to, but when it is proposed to do a study in a large population, then the 10-question screen for childhood disability comes in handy which can be used in the age groups between 2-9 years.

Ten question screen (TQS) for childhood disability

Ten questions are addressed to the parent or caregiver in an yes/no format. It focusses on universal abilities and is cross-culturally comparable. Reliance however is on the caregiver's assessment of child's development and behavior. This is applicable in the 2-9 years age group.

Does the child:

(1) Have delay in sitting, standing or walking

(2) Have difficulty seeing, either in the daytime or at night

(3) Have difficulty hearing

(4) Have difficulty in understanding instructions

(5)Have difficulty walking or moving arms or has weakness or stiffness of limbs

(6) Have fits, becomes rigid, loses consciousness

(7) Not learn to do things like other children his/her age

(8) Not speak at all

(9) Speak differently from normal or cannot name at least one object

(10) Appear mentally backward, dull or slow

The sensitivity of the screen for serious cognitive, motor, and seizure disabilities is 80-100%, whereas the positive predictive values range from 3 to 15%. These results confirm the usefulness of the ten questions

Table I. Mental age for scores of Goodenough draw a man test

SCORE	MA	SCORE	MA	SCORE	MA	SCORE	MA
1	3-3	14	6-6	27	9-9	40	13-0
2	3-6	15	6-9	28	10-0	41	13-3
3	3-9	16	7-0	29	10-3	42	13-6
4	4-0	17	7-3	30	10-6	43	13-9
5	4-3	18	7-6	31	10-9	44	14-0
6	4-6	19	7-9	32	11-0	45	14-3
7	4-9	20	8-0	33	11-3	46	14-6
8	5-	21	8-3	34	11-6	47	14-9
9	5-3	22	8-6	35	11-9	48	15-0
10	5-6	23	8-9	36	12-0	49	15-3
11	5-9	24	9-0	37	12-3	50	15-6
12	6-0	25	9-3	38	12-6	51	15-9
13	6-3	26	9-6	39	12-9		

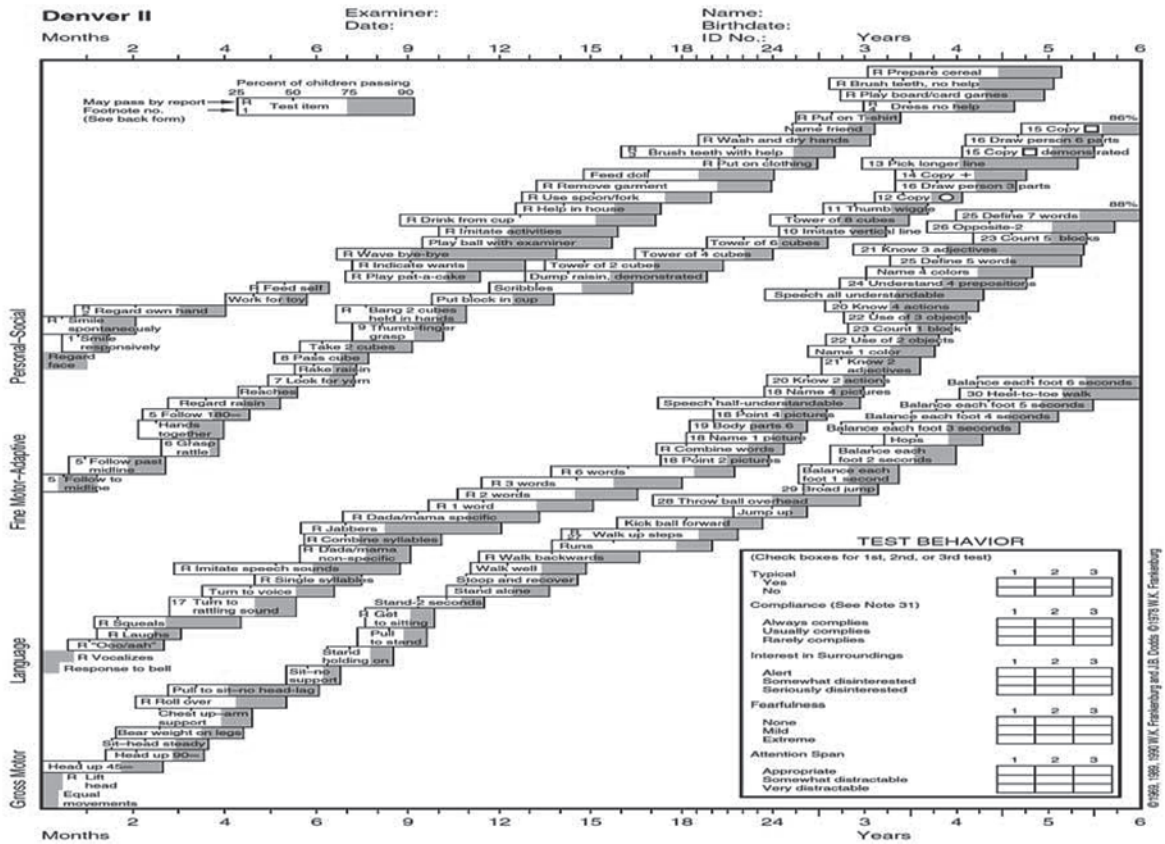

Fig.7. Denver Development Screening Tool II

as a low-cost and rapid screen for these disabilities, although not for vision and hearing disabilities.[7]

f) Denver Developmental Screening Test

Denver Developmental Screening Test (DDST) is a formal developmental screening tool that assesses children from birth to 6 years of age (Fig.7).This tool assesses child's development in 4 general areas: 1) personal-social (25 items), 2) fine motor- adaptive (29 items), 3) language (39 items), and 4) gross motor (32 items).

Screening with this tool generates 3 scores: normal, (when the child passes all administered items or if there is one caution), suspect (when the child has more than 2 cautions or 1 delay) and untestable (when the child refuses to cooperate or has no opportunity to have acquired that particular skill)

g) Bayley scales of infant and toddler development screening test

Bayley-4 Screening Test

Can be used for screening children from 16 days to 42 months for cognitive, language and motor skills. Requires a kit (Fig.8) and training.

Fig.8. Bayley kit

Parent completed screens

When the primary physician is unable to devote exclusive time for development screening, parents can be empowered to complete the screening tools and the advantage of these tools are accuracy, less physician time and cost effectiveness. Cooperation of the child is not an issue and more importantly parents are involved in the screening process.

Although many parent based tools are available, only three will be discussed in this article.

M CHAT **www.m-chat.org**

Child's name ..... Date .....

Age ..... Relationship to child .....

M-CHAT-RTM (Modified Checklist for Autism in Toddlers Revised)

Please answer these questions about your child. Keep in mind how your child usually behaves. If you have seen your child do the behavior a few times, but he or she does not usually do it, then please answer no. Please circle yes or no for every question. Thank you very much.

1. If you point at something across the room, does your child look at it? (FOR EXAMPLE, if you point at a toy or an animal, does your child look at the toy or animal?)	Yes	No
2. Have you ever wondered if your child might be deaf ?	Yes	No
3. Does your child play pretend or make-believe? (FOR EXAMPLE, pretend to drink from an empty cup, pretend to talk on a phone, or pretend to feed a doll or stuffed animal?)	Yes	No
4. Does your child like climbing on things? (FOR EXAMPLE, furniture, playground equipment, or stairs)	Yes	No
5. Does your child make unusual finger movements near his or her eyes? (FOR EXAMPLE, does your child wiggle his or her fingers close to his or her eyes?)	Yes	No
6. Does your child point with one finger to ask for something or to get help? (FOR EXAMPLE, pointing to a snack or toy that is out of reach)	Yes	No
7. Does your child point with one finger to show you something interesting? (FOR EXAMPLE, pointing to an airplane in the sky or a big truck in the road)	Yes	No
8. Is your child interested in other children? (FOR EXAMPLE, does your child watch other children, smile at them, or go to them?)	Yes	No
9. Does your child show you things by bringing them to you or holding them up for you to see not to get help, but just to share? (FOR EXAMPLE, showing you a flower, a stuffed animal, or a toy truck)	Yes	No
10. Does your child respond when you call his or her name? (FOR EXAMPLE, does he or she look up, talk or babble, or stop what he or she is doing when you call his or her name?)	Yes	No
11. When you smile at your child, does he or she smile back at you?	Yes	No
12. Does your child get upset by everyday noises? (FOR EXAMPLE, does your child scream or cry to noise such as a vacuum cleaner or loud music?)	Yes	No
13. Does your child walk?	Yes	No
14. Does your child look you in the eye when you are talking to him or her, playing with him or her, or dressing him or her?	Yes	No
15. Does your child try to copy what you do? (FOR EXAMPLE, wave bye-bye, clap, or make a funny noise when you do)	Yes	No
16. If you turn your head to look at something, does your child look around to see what you are looking at?	Yes	No
17. Does your child try to get you to watch him or her? (FOR EXAMPLE, does your child look at you for praise, or say "look" or "watch me"?)	Yes	No
18. Does your child understand when you tell him or her to do something? (FOR EXAMPLE, if you don't point, can your child understand "put the book on the chair" or "bring me the blanket"?)	Yes	No
19. If something new happens, does your child look at your face to see how you feel about it? (FOR EXAMPLE, if he or she hears a strange or funny noise, or sees a new toy, will he or she look at your face?)	Yes	No
20. Does your child like movement activities? (FOR EXAMPLE, being swung or bounced on your knee)	Yes	No

Fig.9. Modified checklist for autism in toddlers revised

a) Ages and stages questionnaire (ASQ)[8]

This is useful to screen infants and young children for developmental delays during the first 5 years of life. The assessment covers five key developmental areas: communication, gross motor, fine motor, problem solving, and personal-social skills.

1. Select the questionnaire: Select the questionnaire that matches the child's age.

2. Ask the parent to complete the questionnaire: Questionnaires may be distributed online through mail, on a home visit, or in-person.

3. The parent answers the questions: ASQ's items are easy for parents to try with their child and respond to questions such as "Does your baby pick up a raisin with the tips of his thumb and a finger?" The parent answers *yes*, *sometimes*, or *not yet*, then moves on to the next item. This process takes about 10-15 minutes.

4. Score the questionnaire: With ASQ online, the results are automatically scored quickly and accurately. The paper format can be easily scored by hand in just 2- 3 minutes. Then, compare the child's scores to the cut-off points listed on the scoring sheet.

5. Discuss results with parents and determine next steps: Communicate the screening results to the child's parents, and suggest resources for follow-up, monitoring, or further assessment if needed

6. Share activities with parents: Help parents encourage the child's development by sharing fun, fast learning activities.

b) Parents' Evaluation of Developmental Status: Developmental Milestones (PEDS:DM)[9]

The *PEDS:DM* is for children from birth to 8 years of age and consists of 6-8 items per visit, one per developmental domain: fine motor, gross motor, social, emotional, self-help, expressive language, receptive language and for older children, reading and math. Each item serves as a screen for the domain from which it is derived and problematic performance is tied to a cut-off at the 16th percentile or below (the point below which children have great difficulty with regular curricula). The *PEDS:DM* has sensitivity and specificity across domains as well as age ranges of 70% to 93%, well within standards for screening tools.

c) Screening for Autism by using M - CHAT R/F Tool

Modified checklist for autism in toddlers revised with follow up (M- CHAT R/F) done at 18-24 months. This is the most commonly used screen in primary care (Fig.9).

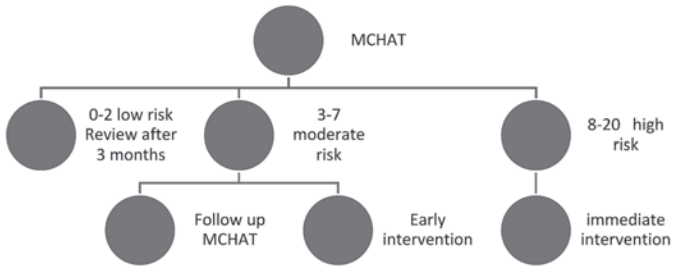

Fig.10. Screening with M-CHAT for autism - Algorithmic approach

- For most items, YES is a typical response and NO is an at-risk response.
- However, items 2, 5 and 12 are reverse scored, meaning that NO is a typical response and YES is an at-risk response.
- To score the M-CHAT-R, add up the number of at-risk responses, and follow the algorithm (Fig.10).

Criteria of a good screening tool

With many development screening tools in the market, which tool to use will be the concern for the primary physician. [10]

In this regard, all the commonly used screening tools can be reliable and used once the same has been incorporated into practice.

Depending on the personnel, the time and resources available, different screening tools will serve the purpose in different settings (Table II).

Table II. Developmental screening tools in various settings

Setting	Tool to be used
Community	Ten question screen, DOC, TDSC
Primary physician	CDC Grading of motor milestones, TDSC, ASQ
Developmental clinic	Denver, Bayley Screener

For the successful implementation of the development screening program at all levels, the choice and practice of using a screening tool should be continuous with increasing accuracy on repetitive efforts.

Screening tool should ideally be

SCREEN is a simple mnemonic **(S**imple, **C**ulturally, **R**apid, **E**ffective, **E**asy on the purse, **N**il or minimal training).

Dealing with results of the screening tests[11]

If the results are normal and had been administered in a well-baby clinic setting, parents may be informed about the results and asked to continue with other aspects of the preventive visit.

If the results are normal and was administered due to parental concerns, an early return visit for additional surveillance should be scheduled

If the results show "borderline" screen, clinical judgment should be made, based on the child, family, risk factors to decide on referral.

An early follow up visit should be scheduled for additional surveillance/screening.

When results are concerning, child should be referred for developmental evaluation and medical evaluation and should be enrolled in early developmental intervention/ early childhood services.

Points to Remember

- ***It is imperative to screen early to detect the developmental delays in the first few years of life.***
- ***The identification of developmental delay follows a 3-tier system of developmental monitoring or surveillance, screening and assessment.***
- ***Developmental monitoring can be done by the primary physician, parents, grandparents or other caregivers using freely available checklists.***
- ***Developmental screening is done by the primary physician, early childhood teacher, or other trained provider, using standardised tools and should ideally be performed at all well baby visits or at least at 9, 18 and 30 months of age of the child.***
- ***There are many tools available for developmental screening and the choice of the ideal tool depends on various factors.***
- ***Screening for autism spectrum disorders is to be done at 18 and 24 months using Modified checklist for autism in toddlers revised with follow up (M- CHAT R/F).***

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IAP - IJPP CME 2022

FEVER WITH THROMBOCYTOPENIA

***Sridevi A Naaraayan**

Abstract: *Thrombocytopenia refers to decrease in the number of platelets in the peripheral blood below 1.5 lakh cells/cu.mm. Fever with thrombocytopenia is commonly encountered in children, causes ranging from a simple viral fever to life threatening conditions like acute leukemia. This article covers common clinical conditions presenting as fever with thrombocytopenia in children beyond neonatal period.*

Keywords: *Fever, Thrombocytopenia, Dengue.*

Decrease in number of platelets in peripheral blood below normal values is termed as thrombocytopenia.[1] Thrombocytopenia is clinically suspected when there is a history of easy bruising or bleeding or as an incidental finding. Platelets are small blood cells devoid of nucleus, which measure around 2 to 3 microns in diameter. They have irregular shape with cytoplasmic processes.[2] (Fig.1). They remain viable in circulation for 10 days. About one-third of platelets are in spleen and the remaining in peripheral blood. Normal platelet count ranges from 1.5 to 4 lakhs/cu.mm.[3]

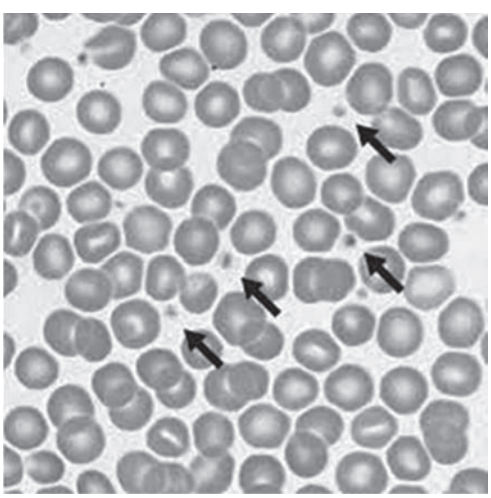

Fig.1. Normal platelets

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Thrombocytopenia has to be differentiated from pseudo thrombocytopenia which is in-vitro clump formation in blood sample collected in tubes with ethylene diamine tetraacetic acid (EDTA) resulting in falsely low platelet count. This occurs due to the presence of EDTA dependent anti-platelet antibody in some patients. EDTA induces changes in conformation of GpIIb / IIIa and hence neoantigen is exposed. This antigen-antibody reaction results in platelet clumping in-vitro. Peripheral smear shows large platelet clumps and platelets resetting around neutrophils (Fig.2).

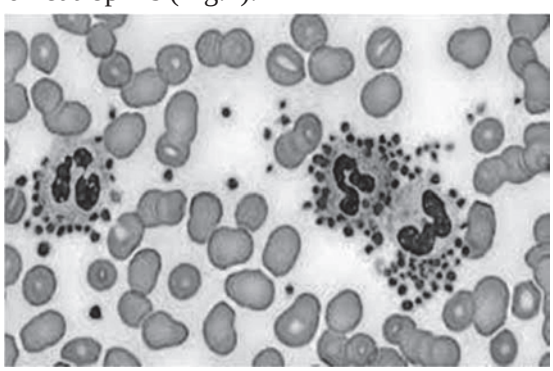


Fig.2. Smear showing pseudo thrombocytopenia

Platelet count in the peripheral blood below 1.5 lakhs/cu.mm is thrombocytopenia.[4] It can be classified as mild (platelet count 1-1.5 lakhs), moderate (platelet count - 50,000 to 1 lakh) and severe (<50,000). Mild and moderate thrombocytopenias are generally not associated with clinically significant bleeding. Platelet counts between 10,000 - 50,000cells/cu.mm usually cause bleeding with trauma or surgery or mild spontaneous bleeding. Platelet count below 10,000 cells/cu.mm is associated with risk of spontaneous severe hemorrhage.[5]

Thrombocytopenia results from 4 main mechanisms which are listed in Box 1.[6]

Box 1. Mechanisms of thrombocytopenia

1. Decreased production of platelets in bone marrow.
2. Increased peripheral destruction of platelets by immune and non-immune mechanisms.
3. Dilutional thrombocytopenia.
4. Sequestration in enlarged spleen.

Box 2. Causes of thrombocytopenia in children[7]

1. Decreased production -

a. Infections - virus - Parvo, dengue, mumps, rubella, varicella

b. Aplastic anemias

c. Bone marrow infiltration - storage disease, malignancies, osteopetrosis

d. Drugs - cytotoxic drugs

e. Deficiency - Vitamin B12 and folate

2. Increased destruction -

a. Immune mediated

- Immune thrombocytopenic purpura
- Infections - HIV, hepatitis C, malaria, Enteric fever
- Drugs - Antiepileptic drugs, digoxin, quinine
- Systemic lupus erythematosus
- Post transfusion

b. Non immune

- Infections - Dengue, scrub typhus, leptospirosis and sepsis
- Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura
- Disseminated intravascular coagulation
- Giant hemangioma

Few common causes of thrombocytopenia are listed in Box 2.

Fever with thrombocytopenia is a common clinical case scenario encountered in pediatric population. Few causes of the condition are categorized according to the frequency of occurrence and listed in Table 1.

Selected causes of fever with thrombocytopenia, particularly common tropical infections are explained herewith in detail.

Dengue

Dengue is a common disease encountered in tropical region. Dengue virus belongs to Flaviviridae family and is transmitted by *Aedes aegypti* mosquito. There are four sub types of the virus namely DENV-1, DENV-2, DENV-3 and DENV-4. All the 4 types can cause disease in humans.

Table 1. Causes of fever with thrombocytopenia in children

Common	Not uncommon	Rare
Dengue	Enteric fever	HCV infection
Scrub typhus	Measles	Parvovirus
Leptospirosis	Mumps	Zika
Malaria	Rubella	SLE
Viral fever	Varicella	Osteoporosis
Sepsis	HIV	Strongyloides

Primary infection often results in mild self-limiting illness of undifferentiated fever. Secondary infection with second serotype causes antibody dependent enhancement resulting in serious disease with worse prognosis.

There are three clinical phases of this infection namely: febrile phase, critical phase and recovery phase.[8] The febrile phase begins after incubation period of 3-14 days and lasts for 3 to 7 days. Fever is high grade, associated with headache, retro orbital pain, myalgia, nausea and vomiting. Dehydration may complicate this phase of illness. Leucopenia may occur during febrile phase and is the earliest laboratory parameter to get deranged during the illness. Following defervescence of fever the child passes on to critical phase which lasts for next 48-72 hrs. This phase may be characterized by warning signs namely abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation presenting as facial puffiness or pedal edema, mucosal bleed, lethargy, breathlessness and tender hepatomegaly.[9] Increase in hematocrit with rapid decrease in platelet count is

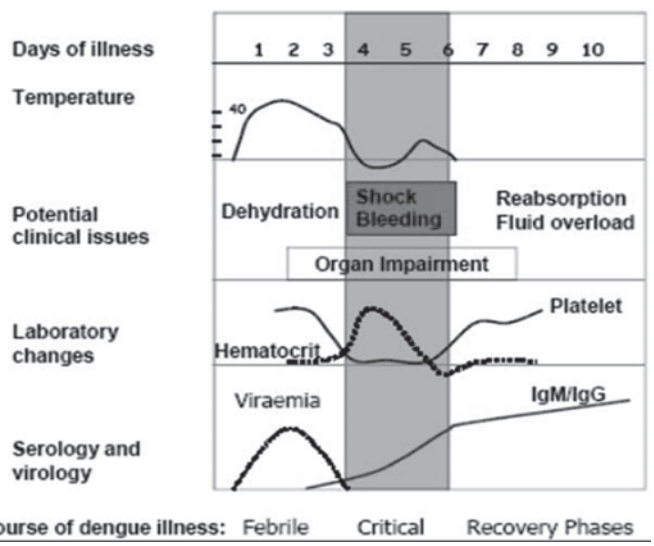
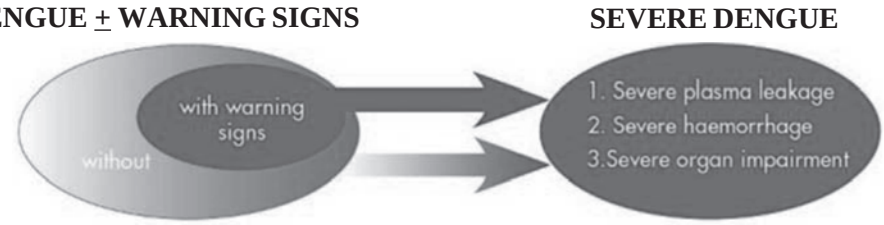


Fig.3. Course of dengue illness[8]



CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue

live in /travel to dengue endemic area.
Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue (important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage
leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding
as evaluated by clinician

Severe organ involvement

- Liver: AST or ALT >= 1000
- CNS: Impaired consciousness
- Heart and other organs

Fig.4. Severity of dengue[8]

commonly encountered in this phase.[10] Critical phase is followed by recovery phase in many patients, where as some cases may progress to severe dengue characterized by plasma leakage resulting in shock, fluid accumulation with respiratory distress, severe bleeding or severe organ impairment. Course of dengue illness and severity classification are shown in Fig.3 and Fig.4 respectively.

Thrombocytopenia occurs in upto 50% of cases. In addition, qualitative defects in platelets can occur. Proposed mechanisms of thrombocytopenia in dengue include megakaryocyte arrest due to direct dengue viral infection and non-immune mediated destruction of platelets.[11-14] Usually platelet count less than 1 lakh/cu mm indicates onset of critical phase and has to be monitored at least every 12 hours along with hematocrit during critical phase. Previous studies have shown that platelet count in dengue starts to decrease on day 4 of illness and continues to decrease till day 7. In patients who recover from the illness, it reaches normal level by eighth or ninth day.[15-17] Though there are clinical guidelines recommending platelet transfusion when platelet count falls below 20,000/cu mm in many conditions other than dengue, there is evidence that dengue patients who received transfusion had a higher frequency of pulmonary edema and increased length of hospitalization.[18] Hence, the available evidence clearly states that platelet transfusion should not be routinely performed in management of dengue.[19,20] It is indicated in conditions with severe thrombocytopenia (less than 10,000) with active bleeding.

Major bleeding may occur in dengue, the causes of which are multiple including severe prolonged shock with consequent combinations of hypoxia, metabolic acidosis, multi organ failure and consumption coagulopathy is the commonest cause for major bleeding.[21] Some patients present with severe bleeding without vascular leak. In such patients an ill understood vague vasculopathy is believed to be the underlying cause and is recognized as one of the forms of severe dengue in revised WHO classification. Severe dengue has lots of hemostatic changes including elevated prothrombin time, activated partial thromboplastin time, increased fibrinolysis and thrombocytopenia.

Viral hemorrhagic fever

Other viruses which cause dengue like illness associated with thrombocytopenia and viral hemorrhage fever include viruses belonging to flavivirus, bunya virus, arena virus and filovirus family.[22] The distribution of these viruses is restricted to limited geographical areas, humans do not act as natural reservoir and outbreak of hemorrhagic fevers occur irregularly and sporadically. Due to the increase in number of international travelers in the current era, outbreak of these diseases could occur anywhere. Apart from dengue, the viruses causing hemorrhagic fever include Ebola hemorrhagic fever, Marburg hemorrhagic fever, Yellow fever, Lassa fever, Crimean-Congo hemorrhagic fever, Rift valley fever. There is no specific treatment for these infections and management is largely supportive.

Scrub typhus

Scrub typhus is a rickettsial zoonotic disease transmitted by mites and caused by *Orientia tsutsugamushi*.[23] Scrub typhus is a severe public health problem that affects mainly Asia - Pacific areas.[24] The disease often presents as undifferentiated fever associated with severe headache, regional or generalized lymphadenopathy, generalized myalgia, eschar (seen in 60%), hepatosplenomegaly and clinical evidence of fluid accumulation as facial puffiness.[25] Blood counts show lymphopenia in early phase and lymphocytosis in late phase.[26] Thrombocytopenia is seen in 75-90% of cases and is mostly due to non-immunological destruction of platelets.[27] Though indirect immune-fluorescence assay (IFA) is gold standard, serology performed by ELISA is commonly used.

Leptospirosis

Leptospirosis is an endemic zoonotic disease of public health importance prevalent in tropical region especially during monsoon. Leptospirosis spreads through contact of humans with urine or tissues of infected animal.[28] The disease is caused by diverse serovars of pathogenic leptospira species.[29] Clinical presentation may vary from mild forms like simple febrile illness to severe disease such as multiple organ failure.[30] Modified Faine's criteria is used to diagnose leptospirosis.

Thrombocytopenia is commonly encountered in the disease and is postulated to be due to multiple mechanisms including non immune destruction of platelet by cytotoxin, DIVC and vasculitis.[31,32] Platelet count returns to normal on day 8 of illness in those with uncomplicated disease. Disease is diagnosed by direct fluorescent microscopy, microscopic agglutination test, though ELISA may be done if both are unavailable.

Malaria

Though malaria, a tropical disease is becoming less frequent in many parts of the world it is still seen in north eastern part of India and is one of the tropical infections with thrombocytopenia in children. Thrombocytopenia is seen in 24 to 94 % of malaria cases.[33] It is more commonly seen in falciparum rather than vivax malaria. Though thrombocytopenia is commonly seen, it is transient and overt clinical bleeding is however rare. Proposed mechanism include antiplatelet antibody causing immunological destruction, besides bone marrow suppression, splenomegaly and coagulation disturbances.[34, 35]

Fever with thrombocytopenia are also encountered in conditions like hematological malignancies, collagen vascular disorders and infiltrative disorders. The clinical presentation in these conditions is not limited to fever with thrombocytopenia and includes a wide range of symptoms and signs. Hence, these conditions are not included in this article.

Points to Remember

- ***Fever with thrombocytopenia is an important clinical condition in children, commonly caused by tropical infections like dengue, scrub typhus, leptospirosis and malaria.***
- ***In majority of patients, thrombocytopenia is transient and asymptomatic though bleeding manifestations are encountered in few cases.***
- ***Clinical outcome in patients having fever with thrombocytopenia is not directly associated with degree of thrombocytopenia but with concomitant involvement of other organs leading to multi-organ dysfunction.***
- ***There is no definite cut off value for platelet count below which platelet transfusion is routinely indicated in a patient having fever with thrombocytopenia.***

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IAP - IJPP CME 2022

INFANT AND YOUNG CHILD FEEDING - A PANACEA FOR CURRENT, FUTURE, HEALTH WITH MACRO AND MICRONUTRIENT SUFFICIENCY

***Elizabeth KE**

Abstract: *Revised guidelines and indicators of Infant and Young Child Feeding have set a new bench mark in infant feeding for current and future health, macro and micronutrient sufficiency. This review focuses on what is new and suggests some practical interventions like adding mother friendly components - Mother Infant Young Child, Mother Baby Friendly Hospital Initiative, Mother Newborn Care Units, Comprehensive Lactation Management centers, Maternal, Infant, Young Child Feeding, Millon Behavioral Health Inventory, Maternal baby friendly hospital initiative, Mother-Newborn Care Units and Comprehensive Lactation Management Centres. The importance of Zero-separation and Zero-alternate feeding, observing breastfeeding week, complementary feeding day, promoting 'Annaprasan ceremony', ensuring macro and micronutrient sufficiency, feeding 'the sick and the small' and those in difficult circumstances are highlighted. The role of pediatricians in achieving an integrated approach combining home Based New Born Care and Home-Based Care for Young Child Programme with the 11 well baby visits as per the Nurturing care (NC) early child development (ECD) programme is recommended.*

Keywords: *Infant and young child feeding, Mother friendly components, Integrated approach, Indicators.*

The first 1000 golden days including 9 months of intrauterine life to second birthday is considered as the 'Window of Opportunity'. The first 2 years of life are important, as optimal nutrition during this period lowers morbidity and mortality, reduces the risk of chronic non-communicable diseases (NCDs), and better overall development and immunity. Infant and young child feeding (IYCF) practices and indicators have been redefined in 2021.[1]

Comparison of National family health survey NFHS 4 and 5 data[2] and the comprehensive national nutrition survey (CNNS) data[3] reveal the alarmingly increasing trends of underweight, stunting, wasting and the creeping up of overweight/obesity across all age groups and the magnitude of micronutrient malnutrition-iron, folate, vitamins B12, A, D and zinc. The CNNS data clearly states that iodine sufficiency has been achieved across the various age groups.

In IYCF, breastfeeding is the single most important life saviour of young children, that also has positive impact throughout life with respect to intelligence, emotional wellbeing, immunity and prevention of non communicable diseases (NCDs).[4]

Currently, an 'extended window of opportunity' has been recognized from pre-conception to third birthday. Maternal, Infant, Young Child Feeding practices (MIYCF), incorporating maternal factors is another welcome addition in this regard. Mother-Baby Friendly Hospital Initiative (MBFHI) National health mission programme by adding the 11th mother friendly step to the existing Baby Friendly Hospital Initiative (BFHI) programme can go a long way in improving IYCF practices. Establishing Mother new born care Units (MNCUs) for continued care of the sick and the small babies will be another boon to improve IYCF practices. The establishment of Comprehensive Lactation Management Centres (CLMCs) is yet another intervention to ensure breastmilk to the needy ones.

Key facts on IYCF

- Every infant and child has the right to good nutrition according to the "Convention on the Rights of the Child".
- Under nutrition is associated with 45% of child deaths.
- Globally in 2020, 149 million children under 5 were estimated to be stunted, 45 million were estimated to be wasted and 38.9 million were overweight or obese.
- Only about 44% of infants 0-6 months old are exclusively breastfed.

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- Few children receive nutritionally adequate and safe complementary foods; in many countries less than a fourth of infants 6-23 months of age meet the criteria of dietary diversity and feeding frequency that are appropriate for their age.
- Over 820 000 children's lives could be saved every year among children under 5 years, if all children 0-23 months were optimally breastfed. Breastfeeding improves IQ, school attendance and is associated with higher income in adult life.
- Improving child development and reducing health costs through breastfeeding results in economic gains for individual families as well as at the national level.

WHO and UNICEF recommendation

- Early initiation of breastfeeding within 1 hour of birth;
- Exclusive breastfeeding for the first 6 months of life; and
- Introduction of nutritionally-adequate and safe complementary (solid) foods at 6 months together with continued breastfeeding up to 2 years of age or beyond.

Breastfeeding

Exclusive breastfeeding for 6 months has many benefits for the infant and mother.[4] Chief among these is protection against gastrointestinal (GI) infections which is observed not only in developing but also industrialized countries. Early initiation of breastfeeding, within 1 hour of birth, protects the newborn from acquiring infections and reduces neonatal mortality. The risk of mortality due to diarrhea and other infections like pneumonia can increase in infants who are either partially breastfed or not breastfed at all. The immunological benefits are numerous including secretory IgA that offers local protection to the gastrointestinal (GI) and respiratory tracts.

Breastmilk is also an important source of energy and nutrients in children aged 6-23 months. It can provide half or more of a child's energy needs between the ages of 6 and 12 months and one third of energy needs between 12 and 24 months. Breast milk is also a critical source of energy and nutrients during illness and reduces mortality among malnourished children.

Children and adolescents who were breastfed as babies are less likely to be overweight or obese. Additionally, they perform better on intelligence tests and have higher school attendance. Breastfeeding is associated with higher income in adult life. Improving child development and reducing health costs results in economic gains for individual families as well as at the national level.

Longer durations of breastfeeding also contribute to the health and well-being of mothers-it reduces the risk of ovarian and breast cancer and helps space pregnancies. Exclusive breastfeeding of babies under 6 months has a hormonal effect which often induces lactation amenorrhea, a natural (though not fail-safe) method of birth control. It has protective effect against maternal cancers as well.

The role of observing 'Breastfeeding week' every year, August 1st-7th is crucial in education of professionals and community regarding the importance of breastfeeding.

Complementary feeding

Around the age of 6 months, the infant's need for energy and nutrients starts to exceed than what is provided by breast milk and complementary foods are necessary to meet those needs. An infant of this age is also developmentally ready for other foods. If complementary foods are not introduced around the age of 6 months, or if they are given inappropriately, an infant's growth shall falter resulting in stunting and wasting.[5]

Ensuring minimum dietary diversity (MDD), minimum meal frequency (MMF) and minimum acceptable diet (MAD) during complementary and toddler feeding should become the new priority.[1] These are key indicators to ensure macro and micronutrient sufficiency. The percentage of 6-23 months-old-children receiving minimum acceptable diet was only 9.6% as per NFHS 4 and 11.3% as per NFHS 5.

WHO guiding principles for complementary feeding of 6-24 months-old breastfed children[6], along with those for non-breastfed children[7], provide global standards on optimal feeding practices for supporting growth and development.

Observing complementary feeding day on 6th day of 6th month i.e. June 6th is recommended to create awareness. Moreover, the rice-giving/ Annaprasan ceremony, which is deep routed in our culture should be revived and promoted to ensure optimum complementary feeding at the right age.

Feeding the sick and the small

Families and children in difficult circumstances require special attention and practical support. Wherever possible, practice 'zero separation and zero alternate feeding unless there is a medical indication'. Delaying breastfeeding is a risk factor for mortality.[8]

Breastfeeding remains the preferred mode of infant feeding including difficult situations.[9]

- Low-birth-weight or premature infants,
- Mothers living with HIV,
- Adolescent mothers,
- Infants and young children who are malnourished and
- Families suffering the consequences of complex emergencies.

Role of Comprehensive Lactation Management Centres

Practising 'Zero separation and zero alternate feeding' and ensuring 'Mother's own milk (MOM) and Pasteurised donor human milk (PDHM)' can go a long way in survival and quality of survival. This warrants the establishment of Comprehensive Lactation Management Centres (CLMCs) in medical colleges and referral centres, lactation management centres (LMCs) in district hospitals and maternity centres and lactation support units (LSUs) at all delivery points. These can be under public-private partnership and supported by National Health Mission (NHM).

HIV and infant feeding

Breastfeeding and especially early and exclusive breastfeeding, is one of the most significant ways to improve infant survival rates. While HIV can pass from a mother to her child during pregnancy, labour or delivery, and also through breast-milk, the evidence on HIV and infant feeding shows that giving antiretroviral treatment (ART) to mothers living with HIV significantly reduces the risk of transmission through breastfeeding and also improves her health. WHO now recommends that all people living with HIV, including pregnant women and lactating mothers living with HIV, take ART for life from the time when they first learn their infection status.

Recommendations have been refined to address the needs for infants born to HIV-infected mothers. Antiretroviral drugs now allow these children to exclusively breastfeed until they are 6 months old and continue breastfeeding until at least 12 months of age with a significantly reduced risk of HIV transmission.

Mothers living in settings where morbidity and mortality due to diarrhoea, pneumonia and malnutrition are prevalent and national health authorities endorse breastfeeding and mothers should exclusively breastfeed their babies for 6 months, then introduce appropriate complementary foods and continue breastfeeding up to at least the child's first birthday.

What is new in IYCF?

In 2021 edition, there are 17 recommended IYCF indicators.[1] Seven are new and four of the 2008 indicators have been excluded.

2021 IVCF indicators.

1. Breastfeeding indicators

1.1. Ever breastfed (EvBF) [9]

Percentage of children born in the last 24 months who were ever breastfed

1.2. Early initiation of breastfeeding (EIBF)

Percentage of children born in the last 24 months who were put to the breast within one hour of birth.[10]

1.3. Exclusively breastfed for the first two days after birth (EBF2D)

Percentage of children born in the last 24 months who were fed exclusively with breast milk for the first two days after birth

1.4. Exclusive breastfeeding under six months (EBF)

Percentage of infants 0-5 months of age who were fed exclusively with breast milk during the previous day

1.5. Mixed milk feeding under six months (MixMF)

Percentage of infants 0-5 months of age who were fed formula and/or animal milk in addition to breast milk during the previous day

1.6. Continued breastfeeding 12–23 months (CBF)

Percentage of children 12-23 months of age who were fed breast milk during the previous day

Complementary feeding indicators

1.7. Introduction of solid, semisolid or soft foods 6-8 months (ISSSF)

Percentage of infants 6-8 months of age who consumed solid, semi-solid or soft foods during the previous day.

1.8. Minimum dietary diversity 6-23 months (MDD)

Percentage of children 6-23 months of age who consumed foods and beverages from at least five out of eight defined food groups during the previous day.

1.9. Minimum meal frequency 6-23 months (MMF)

Percentage of children 6-23 months of age who consumed solid, semi-solid or soft foods (but also including milk feeds for non-breastfed children) the minimum number of times or more during the previous day

1.10. Minimum milk feeding frequency for non-breastfed children 6-23 months (MMFF)

Percentage of non-breastfed children 6-23 months of age who consumed at least two milk feeds during the previous day.[11]

1.11 Minimum acceptable diet 6-23 months (MAD)

Percentage of children 6-23 months of age who consumed a minimum acceptable diet during the previous day

1.12. Egg and/or flesh food consumption 6-23 months (EFF)[12, 13]

Percentage of children 6-23 months of age who consumed egg and/or flesh food during the previous day

1.13. Sweet beverage consumption 6-23 months (SwB)[14]

Percentage of children 6-23 months of age who consumed a sweet beverage during the previous day

1.14. Unhealthy food consumption 6-23 months (UFC)[15]

Percentage of children 6-23 months of age who consumed selected sentinel unhealthy foods during the previous day

1.15. Zero vegetable or fruit consumption 6-23 months (ZVF)[16]

Percentage of children 6-23 months of age who did not consume any vegetables or fruits during the previous day

Other indicators

1.16. Bottle feeding 0-23 months (BoF)

Percentage of children 0-23 months of age who were fed from a bottle with a nipple during the previous day

1.17. Infant feeding area graphs (AG)

Percentage of infants 0-5 months of age who were fed exclusively with breast milk, breast milk and water only, breast milk and non-milk liquids, breast milk and animal milk/formula, breast milk and complementary foods and not breastfed during the previous day.

The eight food groups for 6-23 months old (WHO)

1. Breast milk
2. Grains, roots, tubers and plantains
3. Pulses (beans, peas, lentils), nuts and seeds
4. Dairy products (milk, infant formula, yogurt, cheese)
5. Flesh foods (meat, fish, poultry and organ meats)
6. Eggs
7. Vitamin-A rich fruits and vegetables and other fruits and vegetables including iron rich foods

These seven food groups, in addition to breastfeeding can be added after 6 months of age, as per developmental readiness of the baby and locally prevailing cultural practices.

Added salt and sugar are not recommended in the initial phase of complementary feeding, when specially prepared semisolids are prepared for the baby. Sodium is present in most food items and kidneys are immature. Added sugar can lead to sugar craving and obesity. Infants are supertasters and have a greater number of taste buds/sq. cm. During transition to family pot feeding, salt and sugar can be added in moderation.

National Guidelines on Infant and Young Child Feeding (IYCF)

As per the National guidelines on Infant and Young Child Feeding (IYCF), infants should be exclusively breastfed for the first six months of life to achieve optimal growth, development and health and thereafter, to meet their evolving nutritional requirements, infants should receive nutritionally adequate and safe complementary foods while breastfeeding continues for up to two years of age or beyond. Infant milk substitute or infant food should only be used, if recommended on health grounds.

The following steps have been taken by Government to ensure optimum practices:

- Infant milk substitutes, feeding bottles and infant foods (Regulation of production, supply and distribution) Act 1993, as amended 2003, has been enacted in the country to protect, promote and support breastfeeding and ensure proper use of infant foods.
- Under the Anganwadi services scheme, counselling is provided to pregnant women and lactating mothers on infant and young child feeding practices.

- The Pradhan Mantri Matru Vandana Yojana (PMMVY), which is a centrally sponsored conditional maternity benefit scheme of the Government for pregnant and lactating women, under which cash incentives are provided partly compensating for their wage loss to improve health seeking behaviour amongst the pregnant women and lactating mothers.
- Recent amendment in Maternity Benefit Act is another important step in strengthening the IYCF practices.
- The POSHAN Abhiyaan, currently named POSHAN 2.0, focuses on social and behavioural change communication and thus explicitly paving the way for a mass movement to promote a transformative change, to address the malnutrition related challenges and create awareness on holistic nutrition including promotion of optimal infant and young child feeding practices.
- Early initiation and exclusive breastfeeding for first six months and appropriate Infant and Young Child Feeding (IYCF) practices are promoted under Mothers' absolute affection (MAA) programme, in convergence with Ministry of women and child development.
- Home-based care for young children (HBYC) has been initiated as an extension of Home-Based New-born Care (HBNC) to provide community-based care by Accredited social health activist ASHA workers with focus on improvement in child rearing practices, nutrition counselling and breastfeeding promotion till 15th month of life.
- Village health sanitation and nutrition days (VHSNDs) are observed for provision of maternal and child health services and creating awareness on maternal and child care in convergence with Ministry of women and child development. Health and nutrition education through mass and social media is also promoted to improve healthy practices and to generate demand for service uptake.
- Revised mother and child protection card (MCPC) is the joint initiative of the Ministry of health and family welfare and the Ministry of women and child development. It is an effective counselling tool for use of front-line workers to address the nutrition concerns and improving IYCF practices in children.

These programmes should have a handholding by the pediatricians in the form of 11 well baby visits as per the NC-ECD programme.

Summary

Revised Guidelines and the revised 17 indicators of IYCF have set a new bench mark in infant feeding. Innovations and practical interventions such as adding mother friendly components like MIYCF, MBHI, MNCUs and CLMCs can go a long way in tackling macro and micronutrient malnutrition and ensuring current and future health. A will to observe Zero-separation and Zero-alternate feeding, Breastfeeding week, Complementary feeding Day, 'Annaprasan ceremony', minimum dietary diversity, frequency and acceptable diet to ensure macro and micronutrient sufficiency, can go a long way to success. An integrated approach combining HBNC and HBYC with the 11 Well Baby Visits as envisaged in NC-ECD to focus on basic needs, nutrition, growth monitoring, developmental surveillance, immunization and so on, is recommended.

Points to Remember

- ***Optimum IYCF practices with a thrust on maternal nutrition is the need of the hour for current and future health of children and the future generation.***
- ***Revised 17 IYCF indicators are comprehensive and have set a new bench mark in infant nutrition.***
- ***Zero-separation and Zero-alternate feeding, observing breastfeeding week, Complementary feeding Day, promoting 'Annaprasan ceremony', ensuring macro and micronutrient sufficiency, feeding 'the sick and the small' and those in difficult circumstances are new dimensions in IYCF.***
- ***Addition of mother friendly components-MIYCF, MBHI, MNCUs and CLMCs are value additions in IYCF.***
- ***The Pediatricians have a key role in achieving an integrated approach combining HBNC and HBYC with the 11 well baby visits as per the NC-ECD programme.***

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CLIPPINGS

Feasibility and Diagnostic Value of Recording Smartwatch Electrocardiograms in Neonates and Children

The objective of this study was to evaluate the agreement of smartwatch-derived single-lead electrocardiogram (ECG) recordings with 12-lead ECGs for diagnosing electrocardiographic abnormalities.

A 12-lead ECG and an ECG using Apple Watch were obtained in 110 children (aged 1 week to 16 years) with normal (n = 75) or abnormal (n = 35) 12-lead ECGs). All 12-lead ECGs were independently evaluated by 2 blinded cardiologists. Apple Watch ECGs were independently evaluated by another blinded cardiologist.

Results

In 109 children (99.1%), the smartwatch tracing was of sufficient quality for evaluation. Smartwatch tracings were 84% sensitive and 100% specific for the detection of an abnormal ECG. All 75 normal tracings were correctly identified. Of the 35 children with abnormalities on 12-lead ECGs, 5 (14%) were missed, most often because of baseline wander and artifacts. Rhythm disorders (atrioventricular block or SVT) and bundle branch blocks were correctly detected in most cases (11 of 12 and 11 of 12, respectively); preexcitation and long QT was detected in 4 of 6 and 4 of 5, respectively.

Conclusion

Smartwatch ECGs recorded with parental assistance in children aged up to 6 years and independently in older children have the potential to detect clinically relevant conditions.

Leroux J, Strik, M, Ramirez FD, Jalal Z Thambo JB, Bordachar P, et al. Feasibility and Diagnostic Value of Recording Smartwatch Electrocardiograms in Neonates and Children. The Journal of Pediatrics, 253 (E1): 2023; 40 - 45.

IAP - IJPP CME 2022

NONINVASIVE VENTILATION - BIPAP IN CHILDREN

Poovazhagi V

Abstract: *Noninvasive ventilation is the use of breathing support through an interface like nasal prongs, nasal mask, oronasal mask, full face mask and helmet which are carefully chosen to suit the needs of the child. BiPAP provides both inspiratory pressure and expiratory pressure. Sick children with respiratory failure can be given a trial of BiPAP. It can be be used in both acute conditions like asthma, bronchiolitis and chronic conditions such as cystic fibrosis, Duchenne muscular atrophy, spinal muscular atrophy and congenital muscular dystrophy.*

Keywords: *Noninvasive ventilation, Bilevel positive airway pressure, Children, Continuous positive airway pressure.*

Noninvasive ventilation (NIV) is a mode of respiratory support that is delivered to airway without entering the trachea. As the name indicates BiPAP is Bilevel positive airway pressure delivered during inspiration and expiration in a non invasive method and is used in the treatment of acute and chronic respiratory disorders in children. This review attempts to discuss the indications, contraindications, management strategies and benefits associated with the application of BiPAP in children during NIV. Respiratory failure is a major contributory factor for pediatric intensive care admission.

Indications for BiPAP: NIV can be used in both acute and chronic care settings. Common indications in pediatric intensive care for non invasive ventilation in acute care setting include bronchiolitis, post extubation respiratory failure, acute severe asthma, bronchopneumonia and acute chest syndrome. Long term NIV is indicated in children with respiratory disorders due to alveolar hypoventilation such as neuromuscular disease and obstructive sleep apnea.

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NIV is a potential therapy to avoid endotracheal intubation in children with respiratory distress. Continuous positive airway pressure (CPAP) is delivery of continuous positive pressure during the entire cycle of respiration while NIV-BIPAP is application of two different pressure levels during both inspiration and expiration so that a pressure gradient is created facilitating the flow of air through the airways. While CPAP improves oxygenation by increasing the functional residual capacity and lung inflation, BiPAP enhances both CO_2 elimination by increasing the minute ventilation and also oxygenation by increasing functional residual capacity (FRC) by recruiting more alveoli (Fig.1). Hence, NIV-BIPAP is indicated in disorders related to hypercarbia and/or hypoxemia. When BIPAP is delivered, one must take note of the mode to be used. In spontaneous mode it is the patient triggered mode and there is no back up respiratory rate while in timed mode set pressure is delivered in a set frequency (respiratory rate) and this may lead to asynchrony with patient breaths. Spontaneous timed mode is patient triggered mode with back up set respiratory rate which gives better patient safety and comfort.

When using BIPAP for children in NIV, expiratory positive airway pressure (EPAP) and inspiratory positive airway pressure (IPAP) need to be set. EPAP is the pressure that minimises alveolar collapse and increases oxygenation. IPAP is the pressure that should achieve adequate lung expansion and CO_2 removal. The pressure difference between the IPAP and EPAP is the pressure support. Inspiratory time is the time allotted for inspiration. Other settings depend on the device trigger sensitivity, rise time, ramp time, etc.

When the child is having hypoxemia, there is a need to increase oxygenation which is done by recruiting more alveoli and this is done by increasing functional residual capacity (FRC) using the EPAP. In children with hypercarbia, there is a need to increase the pressure support by increasing the difference between the EPAP and IPAP. This will lead to increase in tidal volume and enhanced CO2 elimination. For titration of settings in NIV the PCO_2 and PO_2 values will be useful. If the child is hypoxemic without hypercarbia, there is a need to increase oxygenation by increasing the EPAP alone. If the child has both hypercarbia and hypoxemia, there is a need to increase the

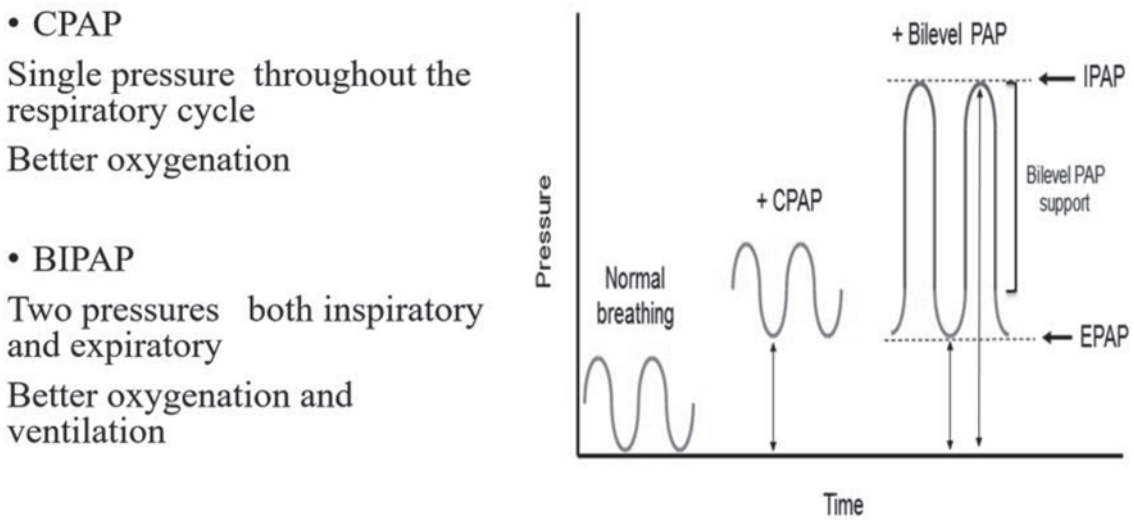

Fig.1. Comparison of CPAP and BIPAP

pressure support and EPAP respectively. Only increasing the EPAP and IPAP without increasing the pressure support ("Δp between EPAP and IPAP) will not be useful in hypercarbia. If the child has only hypercarbia, increasing the pressure support by increasing the IPAP will suffice.

Interfaces for NIV delivery: Commonly used interfaces for providing BiPAP include nasal prongs, nasal mask, oronasal mask, full face mask and helmet. The interfaces are carefully chosen to suit the child as this is an important factor for the success of NIV therapy. An ideal interface should be small, with minimal leaks, should be easy to apply and remove, non-traumatising, cost effective and should have a well-fitting head gear. Studies have shown that children on NIV have good tolerance level and comfort level with a good interface. Nasal masks are easy and better tolerated than oronasal or full-face mask in infants and small children. Children showing agitation can be sedated with dexmedetomidine infusion and is well tolerated.

All children on NIV need close monitoring to recognize NIV failure. Selection of children should be meticulous as NIV failure rates are very high in conditions like pediatric ARDS. Infants aged less than 6 months, higher IPAP, high heart rates and SpO2/FiO2 (S/F) ratio have been identified as risk factors for failure of NIV. Trial of NIV is given usually for 3-4 hours to decide the need to continue NIV or escalate to other modes of ventilation. Decision to escalate to intubation and ventilation should be done if hypoxemia and hypercarbia are not improving, there is increased nausea and vomiting, increased secretions with risk of aspiration, increasing work of breathing (WOB), exertion and worsening sensorium.

NIV is contraindicated in facial burns, facial infections, GCS less than 8, moderate to severe acute respiratory distress syndrome (ARDS) with respiratory failure, PaCO2 more than 65mmHg, pH less than 7.25, untreated pneumothorax, risk of aspiration, severe hemodynamic compromise, upper gastrointestinal tract surgeries, hematemesis and children with raised intra cranial pressure.

The advantages of NIV include the following :

- Less invasive
- Better patient tolerance
- Freedom to talk, eat or drink and more autonomy
- Less need for sedation
- Minimises ventilator associated infections
- Decreased length of hospital stay
- Decreased mortality

Disadvantages of NIV include mouth dryness, nasal dryness, bloating, runny nose, sinus pressure, skin irritation from the mask, discomfort with some types of mask, eye irritation and leaks through interface leading on to ineffective ventilation.

Complications of NIV include gastric distension, pneumothorax, pressure ulcers and aspiration. Majority of these complications are preventable with adequate monitoring.

If NIV is used in select situations with proper interface and adequate pressure settings, undercoupled with proper monitoring it can help avoid the need for invasive ventilation. If there are signs of failure of NIV, one should escalate to invasive ventilation early.

Points to Remember

- ***Non-invasive ventilation(NIV) in children is a respiratory support without intubation.***
- ***NIV is useful in children needing respiratory support for both hypoxemia and/or hypercarbia.***
- ***EPAP is useful to improve oxygenation and the pressure difference between EPAP and IPAP is useful for the management of hypercarbia.***
- ***Monitoring for improvement in the respiratory status during the first few hours of NIV helps in timely escalation to intubation, if NIV fails.***

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CLIPPINGS

Twenty-four-hour movement guidelines during adolescence and its association with obesity at adulthood: results from a nationally representative study.

To determine the association between adherence to the 24-h movement guidelines during adolescence with obesity at adulthood 14 years later in a nationally representative cohort. We analyzed data from 6984 individuals who participated in Waves I (1994–1995) and IV (2008–2009) of the National Longitudinal Study of Adolescent Health (Add Health) in the USA. Obesity was defined by the International Obesity Task Force cut-off points at Wave I and adult cut-points at Wave IV (body mass index [BMI]=30 kg/m2 and waist circumference [WC]=102 cm in male and 88 cm in female). Physical activity, screen time and sleep duration were self-reported. Adolescents who met screen time recommendation alone (β = -1.62 cm, 95%CI -2.68 cm to -0.56), jointly with physical activity (β = -2.25 cm, 95%CI -3.75 cm to -0.75 cm), and those who met all three recommendations (β = -1.92 cm, 95%CI -3.81 cm to -0.02 cm) obtained lower WC at Wave IV than those who did not meet any of these recommendations. Our results also show that meeting with screen time recommendations (IRR [incidence rate ratio] = 0.84, 95%CI 0.76 to 0.92) separately and jointly with physical activity recommendations (IRR = 0.86, 95%CI 0.67 to 0.97) during adolescence is associated with lower risk of abdominal obesity at adulthood. In addition, adolescents who met all 24-h movement recommendations had lower risk of abdominal obesity later in life (IRR = 0.76, 95%CI 0.60 to 0.97).

Conclusion: Promoting the adherence to the 24-h movement guidelines from adolescence, especially physical activity and screen time, seems to be related with lower risk of abdominal obesity later in life, but not for BMI.

García-Hermoso A, Ezzatvar Y, Alonso-Martinez AM et al. Twenty-four-hour movement guidelines during adolescence and its association with obesity at adulthood: results from a nationally representative study. Eur J Pediatr 182:2023; 1009-1017.

IAP - IJPP CME 2022

PRIMORDIAL PREVENTION OF ADULT CHRONIC DISEASE IN THE "FIRST 1000 DAYS"- AN INDIAN PERSPECTIVE

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****Sachdev HPS**

Abstract : *Epidemiological studies indicate that various insults during the intrauterine period are associated with adult chronic diseases. The "First 1000 days" is a vulnerable period influenced by several maternal and infant factors, which can affect the growth and development of the child leading to adverse outcomes into adulthood. Optimal child-bearing age (25-30 years), vaginal birth, no maternal smoking and breast-feeding are important factors for prevention. Individual, family-centered and community intervention, if begun early and continued later focusing on optimal diet and physical activity, are likely to be successful.*

Keywords: *Adult, Chronic disease, Infant, Growth and development.*

Epidemiological studies indicate that various insults during the intrauterine period are associated with adult onset chronic diseases. The term "First 1000 Days", first articulated by Hillary Clinton, includes the period from conception till the child is two years of age and is considered to be crucial in this context. This vulnerable period in humans can be influenced by several adverse maternal-infant factors including maternal health, psychological stress, nutrition, breast feeding, complementary feeding and socio-economic factors, all of which can affect the growth and development of the child, and lead to long-term outcomes extending into adult and geriatric life.

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Fetal programming

In the 1980s, David Barker hypothesized that the combined effect of environmental factors and inherited genes during this critical period of the first 1000 days could lead to the origin of adult disease.[1] This theory was later termed as the Developmental Origin of Health and Disease (DOHaD).[2] Barker proposed that a stimulus or insult during this sensitive or critical period of development could have a lasting or lifelong significance through alterations of structure, physiology and metabolism. Fetal programming is one of the adaptive mechanisms to maintain homeostasis when the fetus is exposed to a hostile environment during critical periods of development of essential organs. Evidence indicates an association between intra-uterine stress and permanent phenotypic changes secondary to fetal programming, leading to the development of future health problems. Placental function plays an important role in maintaining normal gestational environment. Any condition such as maternal psychological stress, psychosis, depression, anxiety or fetal hypoxia and oxidative stress to the fetus disrupts placental function, thereby triggering fetal programming and initiation of epigenetic alterations.[3] The mechanism of fetal programming and epigenetic memory is graphically summarized in Fig.1. Epigenetic memory is defined as a heritable change in the DNA and histones without an alteration in the DNA sequence, having the effect of modifying the genetic expression in response to environmental stimuli. Epigenetic mechanisms like DNA methylation and histone modification are known to be associated with an increase in the occurrence of chronic conditions such as obesity, insulin resistance, type 2 diabetes mellitus and cardiovascular diseases.[3]

First 1000 days: Supportive human evidence

There is substantial observational evidence in support of the DOHaD hypothesis, especially from long-standing birth cohorts from Low-and-Middle-Income-Countries (LMICs). In this context, the New Delhi Birth Cohort (NDBC) from India is one of the longest standing birth cohorts. It was initiated in 1969, has had follow- ups for five decades by now, and includes four generations. Data from this birth cohort have been pooled with data from four other similar cohorts from other LMICs, namely,

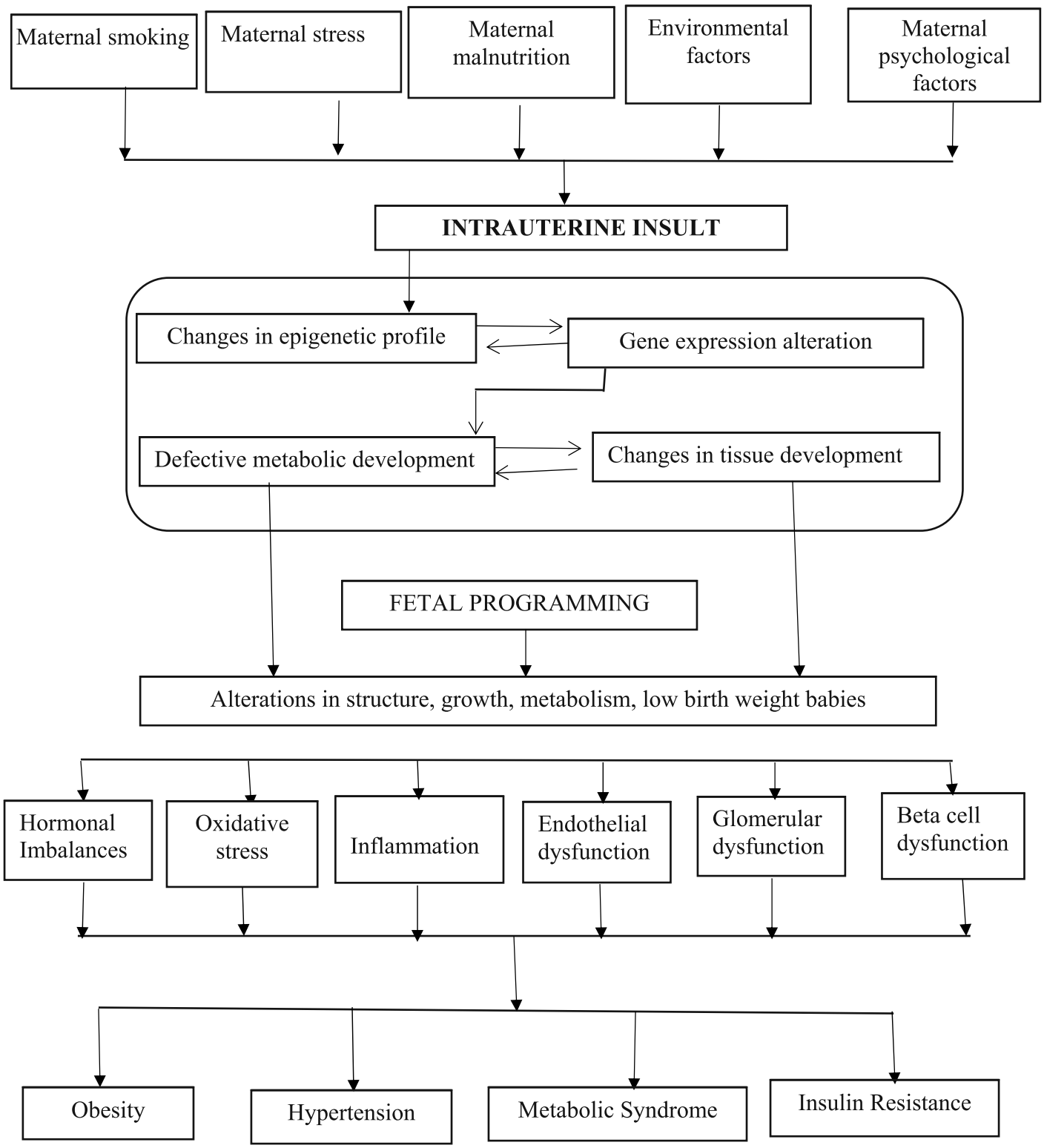

Fig.1. Mechanism of fetal programming and epigenetic factors

Guatemala, South Africa, Philippines and Brazil, to form the COHORTS collaboration.[4] In 2008, data from these five cohorts were reviewed to look for association between maternal and child under-nutrition on the one hand and the risk of developing adult-onset diseases on the other. Maternal and child under-nutrition markers, including maternal height, birth weight, intra-uterine growth restriction and weight, height and body mass index (BMI) at 2 years of age were related to adult outcomes such as height, schooling, birth weight of the off-spring, BMI, blood pressure and glucose concentration. It was concluded that larger size of the child at birth and in childhood was positively associated with higher BMI in adulthood and to a lesser extent with higher blood pressure, but no association was seen with higher blood glucose concentration. Lower birth weight and under-nutrition in childhood were positively associated with later onset of high blood pressure and high glucose concentrations, leading to increased risk of developing adult chronic diseases.[5] In the NDBC, the association between growth in early life and the incidence of glucose intolerance was evaluated in 1492 men and women between 26-32 years of age; these participants had been measured at birth and followed up every 3-6 months throughout infancy, childhood and adolescence.[6] Participants who developed impaired glucose tolerance or diabetes at 32 years of age had been thin at birth, became slightly thinner till 2 years of age and then showed a gradual and sustained increase in BMI; the change in BMI from the nadir to the peak was ~0.5 SD. Another important observation was that among those who had developed diabetes or impaired glucose tolerance in adult life, <1% had been obese in infancy and childhood, while one third or half (30-50%) of them had been underweight till 12 years of age. Similar findings have now been reported from other global datasets. Recently, NDBC data have been used for evaluating the association between human capital and physical growth from birth to adulthood. Higher linear growth in the first 2 years was associated with better school education and with a better occupation and financial status in adulthood. The small effect persisted even after adjusting for several confounders, although, from 2-5 years this effect was lower and inconsistent.[7] The above evidence reinforces the crucial importance of the first 1000 days and the need to explore relevant interventions during this period for improving human capital and preventing development of adult chronic diseases.

Limitations in translating evidence into interventions

There are some inherent limitations in translating the relevant human evidence into potential interventions, particularly in the Indian context. First, the exposure time required for primordial prevention spans at least one generation and long-term evidence of this nature may not be available. Thus, intermediary outcomes have to be used as surrogates (for example, hyperlipidemia instead of coronary artery disease). Second, several studies focus only on the anthropometric parameters, with limited information on relevant metabolic phenotyping of over-nutrition. Third, sometimes observational evidence has to be utilized, as randomized controlled trials would be unethical (for example, risk of developing coronary artery disease or diabetes mellitus with infant milk substitutes). Fourth, indirectness of the evidence, resulting from extrapolation from high income countries (HIC) settings to LMICs. Fifth, there has been intermingling of faith and evidence in some proposed interventions. Within this backdrop, the ensuing section summarizes the pertinent global evidence for potential preventive interventions in the mother and baby, with a primary focus on studies from India, where available.

Observational evidence

In 2015, the COHORTS collaboration reported a significant U-shaped relationship between the maternal age at childbirth and plasma glucose level and systolic blood pressure of offspring when they reach adulthood. The confounder-adjusted U-shaped quadratic trend was statistically significant (P0.005) for offspring of both young (<19 years) and old (>35 years) mothers to have a tendency for high plasma glucose as compared to 25-34 year age group which, in some datasets, translated into impaired glucose tolerance tests or diabetes; however, this trend was not statistically significant for systolic blood pressure.[8] There is thus, a case for propagating an optimal age of child bearing (25-34 years) for lowering the incidence of adult Non-Communicable Diseases (NCDs).

In the Parthenon study conducted at Mysore, maternal Gestational Diabetes Mellitus (GDM) was found to be associated with adiposity and higher glucose and insulin concentrations in female offspring at 5 years age. The absence of similar associations in offspring of diabetic fathers suggested a programming effect in the diabetic intra-uterine environment.[9] In a subsequent follow-up (9.5 years), the offspring of diabetic mothers had higher risk factors for diabetes and cardiovascular diseases and the effects strengthened with increasing age during childhood.[10] Similarly, observational evidence from several global studies indicates that maternal obesity, gestational diabetes, overt diabetes and pregnancy-induced hypertension predispose both the mothers and the offspring to develop

hypertension, diabetes and metabolic syndrome in later life, with biomarkers often being discernible in early childhood for the children.[11-13] However, there is limited evidence evaluating the effect of optimal treatment of these maternal conditions on subsequent reduction of risk of adult-onset disease in offspring. A pragmatic approach would, therefore, combine optimal maternal management with inculcating healthy life style habits in the offspring, along with their frequent screening for early indicators of developing a tendency for adult-onset chronic disease.

Systematic reviews indicate that prenatal maternal smoking is associated with an increased risk of overweight and obesity (ORs: 1.37-1.55) in the offspring till 18 years of age, which can track into adulthood.[14,15] However, the role of tobacco chewing, a practice prevalent in rural India, has not been systematically evaluated in this context. Maternal caffeine consumption at 50mg/day during pregnancy was found to be associated with a higher risk of childhood overweight or obesity, the association becoming even stronger when the coffee intake was ≥300 mg/day. The current recommendation of <200 mg/day of caffeine during pregnancy is likely to be associated with a lower risk of overweight or obesity in offspring, but avoidance of the substance has been recommended.[16] In comparison to vaginal delivery, Caesarean section has been associated with an increased risk of overweight and obesity in the offspring (ORs: 1.15- 1.33) at ages ranging from childhood to early adulthood.[17-19] In a large study evaluating 22068 children born to 15271 mothers aged 20-28 years, a vaginal delivery following a first Caesarean section resulted in a 31% (17-47%) lower risk of an obese offspring.[19] The biological postulates for this include changes in the microbiome and a greater propensity towards breastfeeding, or Caesarean delivery could be a proxy for underlying conditions such as vascular disease or pregnancy-induced hypertension. Exclusive breast feeding for the first 6 months of life is the global recommendation, based on the findings of systematic review by the WHO in 2013. Children who were exclusively breastfed were more likely to have lower levels of total blood cholesterol, less likely to have elevated blood pressure, had a lower risk of developing overweight, obesity and diabetes mellitus and performed better on intelligence quotient tests.[20] A systematic review of 282 studies documented some additional potential risk factors for developing childhood obesity. These include (i) excess gestational weight gain, (ii) high birth weight, (iii) accelerated infant weight gain, (iv) insufficient level of maternal - infant relationship and (v) antibiotic exposure of the infant.[21] However, no definitive priority interventions are agreed upon for the first three of the above, while the jury is still out for the other two. Recent evidence suggests that childhood exposure to particulate and nitrogen dioxide air pollution inside the home and urine nicotine levels indicative of second-hand smoke exposure, are associated with overweight and obesity.[22] Second-hand smoke exposure means exposure to exhaled smoke and other substances emanating from the burning tobacco products, that can get inhaled by others, who are not smoking.

Interventional evidence

Project Sarasin Mumbai conducted a randomized controlled trial of a micronutrient-rich food supplementation given to over 6000 women prior to their conceiving a child and during their pregnancy.[23] Of the 6513 randomized women, 1826 received the food supplements for more than 3 months before they became pregnant. The intervention effect on birth size was 50 grams overall but, paradoxically, the effect was greater in obese mothers than in normal or thin ones. Using the WHO-1999 criterion, gestational diabetes mellitus was halved (7.1% vs 13%) but not reduced significantly as per the WHO-2013 criterion. It is, therefore uncertain whether multi-micronutrient food supplementation prevents gestational diabetes in the Indian context. A systematic review evaluated the benefits of antenatal multiple micronutrient supplements on offspring, 2.5-8.5 years after birth. The review included studies (1-4 for various outcomes) conducted in South East Asia. There was no evidence of any beneficial effect on the evaluated outcomes including surrogates of adult- onset cardio-metabolic diseases. The various outcomes included childhood survival, growth, body composition, blood glucose, glycosylated hemoglobin, blood pressure, serum cholesterol, micro-albuminuria, renal volume and respiratory and cognitive measures.[24] In 29 randomized controlled trials involving 11,487 pregnant women, the effect of lifestyle intervention on the risk of GDM was evaluated.[25] In the pooled analysis, either diet or physical activity or their combination resulted in an 18% (95%CI 5-30%) reduction in the risk of GDM (P0.009). Subgroup analysis showed that such intervention was effective among women who received the intervention before the 15th gestational week (relative risk: 0.80, 95%CI 0.66-0.97), but not among women who received it beyond this window. The effect was similar across the BMI spectrum of the mothers (thin to obese). Two of the trials showed evidence of a lower maternal weight gain and a potential for reduction in the risk of pregnancy-induced hypertension. It was concluded that lifestyle modification during pregnancy, especially before the 15th gestational week, can reduce the risk of GDM. The concern about potential

adverse effects of maternal exercise on the offspring has been addressed in systematic reviews.[26,27] There was no evidence of higher incidence of fetal loss, prematurity or small-for-gestational-age babies, but there was a 31% reduction in large-for-gestational-age newborn babies, 20% fewer Caesarean section deliveries and a 5-year insulin resistance (one trial). The mean birth weight of the new born babies was 30 grams lower (95% CI 4, 57 grams). In another review of 20 trials comprising 11,385 women, lifestyle interventions during pregnancy were not associated with differences in weight, length, BMI, or corresponding z-scores, in children aged 1 month to 7 years.[27] The findings remained consistent when the studies were stratified by maternal baseline BMI or other risk factors, intervention content and duration. It was concluded that prenatal lifestyle interventions do not influence childhood weight or growth; nevertheless, women should be encouraged to pursue a healthy lifestyle during pregnancy.[27] In the Indian context, pregnant women who are thin or those from lower socio-economic strata are generally advised rest rather than lifestyle modification and physical activity during pregnancy.

In a Vitamin D supplementation trial conducted in New Delhi, 1400 IU per week was given to term newborns of low birth weight till 6 months of age.[28] The effects of the intervention on blood pressure and body composition were evaluated between 3 and 6 years of age. There was no evidence of any effect of Vitamin D supplementation on fat free mass, fat percentage, fat mass, or systolic and diastolic blood pressure. Emerging evidence indicates that early taste preferences track well into later life. All infants display an innate preference for sugar, salt and high energy foods with a dislike or lower preference for sour or bitter foods, as in some vegetables. The period of complementary feeding, therefore, presents a golden opportunity for modulating these innate tastes by limiting the child's exposure to sugar, salt and high energy foods, while simultaneously offering bitter and sour foods repeatedly to develop these tastes. The former tastes form an integral part of the ultra-processed foods, which are known to increase the risk of NCDs, whereas the latter tastes form a component of fruits and vegetables, which protect against NCDs. It is difficult to initiate these taste preferences in pre-school children, as they have 'neophobia', a tendency to reject unfamiliar tasting foods.[29] In this context, two[30,31] of the three randomized controlled trials from HMICs[30-32] indicate that sodium intake in infancy is positively associated with elevated blood pressure in the short term (6 months to 15 years) with average elevations of systolic blood pressure ranging from 2-5 mmHg. Results from two more trials that studied the effects of primordial prevention efforts on adolescent blood pressure outcomes have been summarized.[33] These two trials were: (i) STRIP (Special Turku Coronary Risk factor Intervention Project) trial from Finland and (ii) PROBIT (Promotion of Breastfeeding Intervention) trial in Belarus. In the individually randomized STRIP trial, mothers/children were counseled from infancy right through to 15 years of age to consume healthy fats and more fruits, vegetables and whole grains while reducing their intake of salt and sodium-rich foods. A decrease in systolic blood pressure of 1mmHg (-1.7,-0.2mmHg) was observed at 15 years of age. Also, at 15-20 years of age, metabolic syndrome halved in the intervention group as compared to the controls (6-7% vs 10-13%).[34] The STRIP trial concluded that ongoing and personalized dietary counseling lowered glucose and cholesterol levels, mitigated endothelial dysfunction and reduced the risk of metabolic syndrome. The PROBIT trial was a cluster randomized trial in which breast-feeding promotion was done in infancy and children were followed up till 11.5 years of age. There was no evidence of a beneficial effect on blood pressure in this trial. A systematic review of interventions for childhood obesity in the first 1,000 days identified 26 completed and 47 ongoing trials, mostly from high- and middle- income countries, primarily focusing on anthropometric criteria, especially Body Mass Index.[35] Of the 26 unique identified interventions, nine were effective, but the effect sizes were small. A high-protein and nutrient-rich formulated to greater risks of obesity and fat mass at 5-8 years of age. A combination of diet, physical activity and sleep counseling in five trials showed a positive effect. Effective interventions were focused on individual or family-level behavioral changes through home visits, individual counseling or group sessions in clinical settings, and a combination of home and group visits in a community setting. It may be concluded that, even though the effect size between 1 and 10 years of age was small, obesity prevention interventions may have the greatest effect if begun early in life. A combination of individual, family-centered and community interventions focusing on several components including diet and physical activity are more likely to be successful.

A recent systematic review evaluated the effect of early-life randomized controlled nutrition interventions on long-term cardio-metabolic outcomes.[36] It included 33551 participants from 21 countries. Interventions were initiated as early as conception and the longest went on until 7 years of age (except one study that ran from infancy to 20 years of age). The cohorts were followed up for between 3 and 73 years. The authors identified seven types of interventions (protein-energy supplements, long-chain PUFAs, single micronutrient, multiple micronutrients,

infant and young child feeding, dietary counselling and other) and four types of cardio-metabolic outcomes (biomarkers, cardiovascular, body size and composition, and subclinical/clinical outcomes). Most findings were null. In the intervention groups, fasting glucose was lower (0.04 mmol/L; 95% CI: "0.05, "0.02) in 15 studies, but BMI was higher (0.20 kg/m^2; 95% CI: 0.12, 0.28) in 14 studies. There was no evidence of effect for total cholesterol (12 studies) or blood pressure (17 studies). Ongoing and personalized dietary counselling was associated with lower glucose and cholesterol, better endothelial function, and reduced risk of metabolic syndrome. The timing of intervention mattered, with earlier initiation conferring greater benefit (improved lipid profile and marginally lower glucose concentration) as per the findings of two studies. The review concluded that maternal and child nutrition interventions should be evidence-based and tailored to specific populations to promote long-term cardio-metabolic health. Some futuristic interventions are under evaluation. These include designer diets depending on the child's genotype, new born and infants' gyms to build up muscle and improve the uptake of insulin, sleep kits and "poop" pills to transplant microbiome from NCD-free individuals.

Reorienting the ongoing programs

India is currently witnessing a rapid escalation in over-nutrition-associated NCDs. Importantly, the phenomenon has its origins in infancy and childhood and the related signals are seen in an alarmingly high proportion of children and adolescents at the national level, even among rural settings and socio- economically deprived segments. In the recently concluded Comprehensive National Nutrition Survey (2016-18), in 19143 participants of 5-19 years age, "metabolic obesity", characterized by the presence of at least one abnormal cardio-metabolic risk factor, was investigated.[37] Proportions with one or more abnormal "metabolic obesity" biomarker(s) (dysglycemia, dyslipidemia) were 56.2% in the entire dataset, 54.2% in thin (BMI-for-age <-2SD) and 59.3% in stunted (height-for-age <-2SD) participants. Among economically disadvantaged participants, triglyceride, glucose and high-density lipoprotein abnormalities were higher. It is, therefore crucial to prevent potential worsening of this situation through unintended consequences of some ongoing public health programmes, introduced at a time when under- nutrition and hunger were rife. The following three notable examples illustrate the urgent need for re- examining the prescribed food and energy-dense product supplementation in the first 1000days. The Integrated Child Development Services program provides for Take Home Ration (THR) of 500 Calories per day for children from 6 month to 2 years of age. This quantum was based on the energy gap calculated from the Recommended Dietary allowance (RDA), which is intended to cover the needs of 97.5% of the population. However, the energy gap at the population level in the latest National Nutrition Monitoring Bureau survey, using the appropriate Estimated Average Requirement (EAR), is 250 Calories per day (Kurpad A, personal communication).

Providing for supplementation upto double this energy requirement gap has potentially adverse implications, particularly in initiating or fuelling over-nutrition. The expense saved can be utilized for improving the quality(proteins, fruits and vegetables) of THR provided, which may be beneficial. For severe acute malnutrition (weight-for-height<-3SD of WHO reference), supplementation with therapeutic foods or ultra-processed energy-dense product (Ready to Use Therapeutic Food) supplementation has been evaluated,[38] and advocated to provide for supplementation of 175-200 Cal/Kg/day. However, considering the total energy requirement for a weight gain of 5-10 g/kg/day, in accordance with the WHO recommendations,[39] supplementation with 100-130 Cal/Kg/day is sufficient. It would be pragmatic, therefore, to reduce the calorie supplementation and provide these calories through food instead of energy-dense products. Further, the need for providing supplements to those with moderate acute malnutrition (weight-for-height <-2SD of WHO reference) must be carefully re-examined against the finding that, in apparently healthy children in India, the BMI is shifted to the left by ~1SD in comparison to the WHO reference,[40] and thin children who become obese relative to themselves by ~0.5 SD, tend to develop impaired glucose tolerance or diabetes as adults.[6]

The WHO recommendations on antenatal care for a positive pregnancy experience state that "in under-nourished populations, balanced energy and protein dietary supplementation is recommended for pregnant women to reduce the risk of stillbirths and small-for- gestational-age neonates".[41] This recommendation is being misused for commercial promotion of energy dense products. Recent evidence from pregnancy cohorts[23] personal communication indicate that the incidence of gestational diabetes is alarmingly high, ranging from 10-20% overall and 8-14% in undernourished women (BMI<18.5 kg/m^2). There is thus an urgent need for refining guidelines to accurately identify undersized pregnant women who will benefit from energy-dense or other nutrient supplements without escalating the risk of metabolic obesity and related diseases.

Conclusion

In conclusion, there is limited evidence to dogmatically recommend effective interventions in the first 1000 days for prevention of adult-onset diseases; "one size does not fit all" and the interventions need specific tailoring for individuals. The effect size is quite modest with no "magical bullets" on the horizon. A combination of individual, family-centered and community interventions, focusing on several components including diet and physical activity, are more likely to be successful, especially if these begin early and continue over several years. Fortunately, most of the promising interventions are in concurrence with the clinical guidelines and public health programmes. However, moral and ethical considerations obligate evidence-based reorientation of a few programs to prevent escalation of metabolic obesity and related diseases.

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Points to Remember

- ***The first 1000 days after birth are crucial and there is need to explore relevant interventions during this period for improving human capital growth and preventing development of adult chronic diseases. Fetal programming is one of the adaptive mechanisms to maintain homeostasis***
- ***Prenatal maternal smoking is associated with an increased risk of overweight and obesity in the offspring till 18 years of age, which can extend to adulthood. Maternal and child nutrition interventions should be evidence-based and tailored to specific populations to promote long-term cardio-metabolic health.***
- ***The period of complementary feeding, is a golden opportunity for modulating the innate tastes by limiting the child's exposure to sugar, salt and high energy foods which form the integral part of the ultra- processed foods, while simultaneously offering bitter and sour foods repeatedly to develop these tastes.***
- ***There is limited evidence to dogmatically recommend effective interventions in the first 1000 days for prevention of adult-onset diseases.***

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CLIPPINGS

Patterns in the Prevalence of Unvaccinated Children Across 36 States and Union Territories in India, 1993-2021

Children who do not receive any routine vaccinations (ie, who have 0-dose status) are at elevated risk of death, morbidity, and socioeconomic vulnerabilities that limit their development over the life course. India has the world's highest number of children with 0-dose status; analysis of national and subnational patterns is the first important step to addressing this problem.

This cross-sectional study aimed to examine the patterns among children with 0-dose immunization status across all 36 states and union territories (UTs) in India over 29 years, from 1993 to 2021 and to elucidate the relative share of multiple geographic regions in the total geographic variation in 0-dose immunization. All 5 rounds of India's National Family Health Survey (1992-1993, 1998-1999, 2005-2006, 2015-2016 and 2019-2021) were analysed to compare the prevalence of children with 0-dose status.

The study included a total of 125 619 live children aged 12 to 23 months who were born to participating women. Among this population, the national prevalence of those with 0-dose status in India decreased from 33.4% in 1993 to 6.6% in 2021. The prevalence in the northeastern states of Meghalaya (17.0%), Nagaland (16.1%), Mizoram (14.3%), and Arunachal Pradesh (12.6%) remained relatively high in 2021. Prevalence increased between 2016 and 2021 in 10 states, including several traditionally high-performing states and UTs, such as Telangana (1.16 percentage points) and Sikkim (0.92 percentage points). In 2021, 53.0% of children with 0-dose status resided in the populous states of Uttar Pradesh, Bihar and Maharashtra.

In this cross-sectional study, findings from approximately 3 decades of analysis suggest the need for sustained efforts to target populous states like Uttar Pradesh and Bihar and northeastern parts of India. The resurgence of 0-dose prevalence in 10 states highlights the importance of programs like Intensified Mission Indradhanush 4.0, a major national initiative to improve immunization coverage. Prioritizing small administrative units will be important to strengthening India's efforts to bring every child into the immunization regime.

Rajpal S, Kumar A, Johri M, Kim R, Subramanian SV. Patterns in the Prevalence of Unvaccinated Children Across 36 States and Union Territories in India, 1993-2021. JAMA Network Open. 2023; 6(2):e2254919. doi:10.1001/jamanetworkopen.2022.54919

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RATIONAL ANTIBIOTICS IN GASTROINTESTINAL INFECTIONS

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Abstract: *Acute gastroenteritis, dysentery, cholera, enteric fever and appendicitis are among the common gastrointestinal infections encountered in clinical practice. Acute gastroenteritis caused by viruses, bacteria and protozoa can be conservatively managed without the need for antimicrobial agents in most cases. Dysentery which is commonly caused by Shigella, needs antibiotic therapy- Azithromycin is preferred in western nations and cefixime in India. Cholera canbe treated with single dose azithromycin or doxycycline. Enteric fever is most commonly caused by MDR strains of Salmonella typhi/ paratyphi. Hence ceftriaxone is the parenteral drug of choice and cefixime is the oral drug of choice in our country. Drugs used to treat Helicobacter pylori are Amoxicillin and clarithromycin along with metronidazole. Appendicitis is managed with appendectomy and antibiotics. Ceftriaxone along with metronidazole is preferred to cover Gram-negative and anerobic organisms. In all these infections, appropriate antimicrobial therapy in appropriate dosages targeting the causative agent is recommended. Rising antimicrobial resistance is a concern that has to be addressed by regular microbe isolation and susceptibility testing.*

Keywords: *Gastroenteritis, Antibiotics, Resistance, Azithromycin, Ceftriaxone*

Infections affecting the gastrointestinal tract can be grouped broadly as non-surgical and surgical infections. The non-surgical infections include the common acute watery diarrhea, dysentery, cholera and the systemic infection enteric fever. Apart from these, *Mycobacterium tuberculosis and Helicobacter pylori* are the organisms which can cause chronic infections of the gastrointestinal tract. The common surgical infections of the pediatric age group include appendicitis, peritonitis and intra-abdominal abscess. Though being treated widely by physicians, there is a lack of consensus in the antibiotic therapy of these infections. This article discusses the management of commonly encountered gastrointestinal infections.

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Acute gastroenteritis

Acute gastroenteritis (AGE) is the presence of diarrhea defined as either a decrease in stool consistency and/or an increase in stool frequency to ≥3 episodes in 24 hours, with or without fever or vomiting. Broadly, the differential diagnosis for a child presenting with loose stools include acute watery diarrhea, dysentery and cholera apart from intussusception and diarrhea associated with recent broad-spectrum antibiotic use.[1] Infectious diarrhea in children can be due to a variety of organisms (Table I).[2]

Knowledge about the possible etiology of diarrhea is vital before initiating therapy in order to treat effectively and judiciously. While gastroenteritis caused by different organisms have overlapping clinical features, there are some unique distinguishing features:

- Viral gastroenteritis: Vomiting precedes the loose stools which usually settles within 7 days
- Bacterial gastroenteritis: Presence of high fever, blood in stools, abdominal pain and a high stool frequency of >10/day.

Table I. Etiological agents of infectious diarrhea in children

Viruses	Bacteria	Parasites
Rotavirus	*Bacillus cereus*	*Entamoeba histolytica*
Enteric adenovirus	*Escherichia coli*	Giardia
Astrovirus	*Salmonella*	Cryptosporidium
Norovirus	*Shigella*	Cyclospora
	Staphylococcus	
	Campylobacter jejuni	
	Vibrio cholerae	
	Yersinia enterocolitica	

- Cholera: A child >2 years presenting with profuse watery stools leading to severe dehydration or shock during an outbreak and those with positive stool culture for *Vibrio cholerae* O1 or O139 (WHO definition).
- Protozoal gastroenteritis: Usually self-limited in healthy children, but also has the tendency to cause prolonged symptoms >2 weeks. Entamoeba commonly causes dysentery while Giardia is capable of causing varying degrees of malabsorption of sugars and fats leading to abnormal stool patterns and ultimately weight loss.

According to the universal recommendations from the Federation of International Societies of Pediatric Gastroenterology, Hepatology and Nutrition (FISPGHAN) for management of acute diarrhea in infants and children in 2018, acute diarrhea does not usually warrant microbiological investigations except in the situations listed in Box 1.[3]

The main line of management is the administration of reduced osmolality ORS according to the degree of dehydration and adjunctive zinc therapy. Regardless of the etiology, acute gastroenteritis in otherwise healthy children is usually self-limited with microbiological clearance of the organism and clinical recovery occurring in few days. This is the reason why there is no routine indication for empiric anti-infectious treatment in children with AGE. However, the few situations where empiric antibiotics maybe started immediately are shown in Box 2.[3]

Box.1 Indications for microbiological investigations

- Children with prior underlying chronic conditions
- Prolonged symptoms >7 days
- Children with high fever and severe bloody diarrhea
- In severe clinical sepsis
- During outbreaks
- History of travel to at-risk areas

Box.2 Indications for empiric antibiotic therapy in AGE

1. Infants younger than 3 months
2. Children with underlying chronic conditions such as malnutrition, immunodeficiency and sickle cell anemia who are at risk of severe and disseminated disease
3. Dysentery (mostly due to Shigella) and travelers' diarrhea
4. Pseudomembranous enterocolitis
5. Cholera

Empiric therapy should be pathogen-based and taking into consideration of the local epidemiological pattern of antibiotic resistance. Some of the specific pathogens targeted in the empiric therapy are *Shigella*, enterotoxigenic *E. coli, Vibrio cholerae*, *Yersinia enterocolitica* and *Entamoeba histolytica.*

Neonates and young children: In this age group, dysentery is unusual and life-threatening bacterial sepsis has to be suspected always for which antibiotics are started after obtaining blood cultures. Ampicillin along with an aminoglycoside or ampicillin with an expanded-spectrum cephalosporin are acceptable empiric regimens which are modified according to the clinical response and sensitivity reports. Additional anaerobic cover in the form of metronidazole or clindamycin or single agent piperacillin-tazobactum is needed when necrotising enterocolitis is suspected.[4] When omphalitis or pustules are present, anti-staphylococcal coverage has to be given with cloxacillin, clindamycin or vancomycin based on hemodynamic stability. Immunocompromised children may have febrile neutropenia in addition to diarrhea and they require antipseudomonal coverage with Piperacillin-Tazobactum, Ceftazidime or Cefaperazone.

Dysentery: Most of the episodes of dysentery are caused by *Shigella* which has the potential to cause complications like hemolytic uremic syndrome, toxic megacolon and intestinal perforation. WHO recommends empiric treatment targeting *Shigella* for all cases of dysentery in developing countries. At present, there is widespread resistance of *Shigella* to chloramphenicol, cotrimoxazole, tetracycline, gentamicin, ampicillin and first and second generation cephalosporins with increasing resistance to ciprofloxacin as well. In cases of campylobacter colitis, antibiotics have to be started within first 2 days and at present, many strains are resistant to cephalosporins and has to be treated with azithromycin or doxycycline.

Azithromycin is effective against majority of agents such as *E. coli, shigella, salmonella*, non-typhoidal salmonella, *aeromonas* and *campylobacter*. Hence, it is preferred as first line in western nations. But in India, where epidemiologically the burden of enteric fever is large, it is wise to reserve azithromycin for resistant typhoid infections and hence, oral cefiximeis the preferred first line treatment. However, the WHO guidelines are outdated which state

ciprofloxacin as the antibiotic of choice for childhood diarrhea which is no longer sensitive in many regions.[1,4,5] Dysentery can be either bacillary or amoebic but cannot be both. Hence, there is no rationale in combining ofloxacin with ornidazole which is a commonly committed prescription error. When two antibiotics against *Shigella* fail to show response, considering amoebiasis, metronidazole can be given.[1] In cases of travelers' diarrhea, CDC prefers early treatment over prophylaxis. Azithromycin is the agent of choice and rifaximin is the alternate.[6] Table II shows the drugs which are useful in the management of dysentery.

Persistent diarrhea: Cases of persistent diarrhea need evaluation and management taking care of nutrition as well. In high prevalence areas, HIV infection has to be suspected in the presence of other suggestive clinical features and stool microscopy for parasites such as *Isospora* and *Cryptosporidium* is needed. Cases of persistent diarrhea may also have non-intestinal infections such as sepsis, pneumonia, urinary tract infection or otitis media which might need appropriate antibiotics without which diarrhea might not improve. There is no routine indication for antibiotics in cases of persistent diarrhea.[1] When such children have bloody stools, an antibiotic effective against *Shigella* can be used. In cases where microscopic examination of fresh feces shows RBCs with ingested trophozoites of *Entamoeba histolytica* or cysts of *Giardia lamblia*, oral metronidazole can be given. In cases of cyclospora and isospora, cotrimoxazole at a dose of 10 mg/kg/day is given.

Cholera

Cholera is a diarrheal disease with high potential to cause mortality in endemic regions. Young children are particularly affected due to lack of protective immunity and prevention of infection through sanitation and hygiene is most important. Usually, treatment of cholera is initiated based on the clinical features while confirmation of infection requires isolation of the organism from stool. Adequate fluid resuscitation is the cornerstone in the management to reduce mortality. Since the toxin binds to the intestinal cells, antimicrobial therapy does not have immediate effect. Antibiotics inhibit the toxin production or promote bacterial death thereby limiting pathogen excretion. Various randomized trials have shown that antibiotics decrease stool output and duration of diarrhea, thereby hastening clinical recovery. However, antibiotics work in conjunction with hydration to decrease mortality and are ineffective when used alone.[7]

Hence, WHO recommends starting antibiotics in patients aged >2 years having cholera with severe dehydration[8] and CDC extends antibiotic therapy to patients with moderate dehydration and continuing fluid loss despite rehydration.[7] Since, antibiotics are beneficial in patients with moderate dehydration without added adverse effects, various international guidelines extend antibiotic treatment to patients with milder degrees of dehydration also.[8] However, none of the guidelines support prophylactic antibiotics for cholera prevention.[7]

Tetracyclines and macrolides such as azithromycin, erythromycin and clarithromycin are the broad-spectrum antibiotics effective in cholera. Fluoroquinolones which were widely used in yester years are no longer recommended due to increasing minimum inhibitory concentration (MIC) and inferior activity. Among these, tetracycline used to be the first drug of choice in cholera but at present there is increasing resistance and risk of adverse effects like photosensitivity and enamel dysplasia. Hence, recent systematic reviews and guidelines establish single-dose azithromycin to be a safe and effective empirical therapy for pediatric cholera.[8] Availability of syrup formulation and ease of single dosing are factors which make it a feasible option in the pediatric age group. It attains high concentrations in the stool owing to its biliary and trans-intestinal excretion and has been shown in trials to be superior to tetracyclines and ciprofloxacin. Erythromycin has similar bacteriological effects but erratic

Table II. Antibiotic schedules in the management of dysentery

Scenario	Antibiotic	Dosage per day	Duration
Western nations- first line therapy	Azithromycin	12 mg/kg6 mg/kg	1st day Next 4 days
India- first line therapy	Cefixime	8 mg/kg	5 days
Sick children	Ceftriaxone	50-80 mg/kg	3 days
WHO recommendation	Ciprofloxacin	30 mg/kg	3 days
Suspected amoebiasis	Metronidazole	10 mg/kg	5 days

Table III. Drug schedules in cholera

Drug	Dosage	Duration	Notes
Azithromycin	20 mg/kg/d OD	Single dose	Recommended first-line therapy[8]
Erythromycin	12.5 mg/kg Q6H	3 days	Recommended second-line[8]
Doxycycline	2-4 mg/kg OD	Single dose	Recommended first-line by CDC[7]
Tetracycline	12.5 mg/kg Q6H	3 days	In children >12 years[8]
Ciprofloxacin	15 mg/kg BD	3 days	Increasing MIC, reserved for susceptible strains[8]

in absorption, poor oral tolerance, longer treatment duration and comparatively inferior activity which make it a second-line drug.

Many international guidelines prefer doxycycline as the first-line treatment for cholera in adults excluding pregnant women and children <12 years. However, CDC prefers single dose doxycycline as the first choice in children <12 years also.[7] Both doxycycline and azithromycin are effective as single dose therapy which makes treatment more affordable and compliant, thereby decreasing the chances for resistance.[8]

While parenteral azithromycin use is associated with documented risk of cardiac death in adult patients, reports are inconclusive in pediatric population. However, hypokalemia occuring in severe cholera which by itself is a risk factor for arrhythmia. This emphasizes the need for adequate fluid replacement which takes precedence over other management. Various schedules of drugs for cholera are summarized in Table III.

Enteric fever

Enteric fever is an infection of the reticuloendothelial system with predilection for intestinal lymphoid tissue and gallbladder. It is common in resource limited settings with poor sanitation like our country and commonly presents with step ladder pattern of fever, anorexia, vomiting, loose stools and abdomen pain. Culture in automated systems such as BACTEC is the gold standard investigation for diagnosing enteric fever and only those cases with a positive blood, bone marrow or bowel fluid culture of *Salmonella typhi* or *Salmonella paratyphi A* are confirmed cases of enteric fever. The yield of blood culture drops from 90% in the first week to about 40% in the fourth week while bone marrow culture remains positive even after antibiotic therapy.[9] A clinically suspected patient with positive serodiagnosis alone without a positive culture is a probable case of typhoid.[10] Based on the antimicrobial sensitivities of the infecting strains, the cases of enteric fever can be categorized as follows:

- Susceptible typhoid fever: Caused by strains that are sensitive to ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol and/or fluoroquinolones.
- MDR typhoid: Caused by strains that are resistant to the above first line drugs and sensitive to third-generation cephalosporins.
- XDR typhoid: Caused by strains which are resistant to all the above antibiotics and sensitive to azithromycin and carbapenems.

Recently, ESBL producing strains of *Salmonella* are also being reported.

In the past, the fluoroquinolones ciprofloxacin and ofloxacin were considered to be the most effective drugs for enteric fever. However, their increasing resistance and risk of adverse effects like bone or joint toxicity and growth impairment has led to the use of third generation cephalosporins as the initial therapy at present.[10]

Ceftriaxone, cefotaxim and cefoperazone are the commonly used injectable cephalosporins and cefixime is the widely used oral form. Cefixime is the first line drug for those who are treated as outpatients. Patients who require admission due to persistent vomiting, severe abdominal pain, inability to take feeds or complications are treated with ceftriaxone till they become afebrile or clinically stable followed by a switch to oral cefixime to complete the course of 14 days. Patients have to be treated for at least 7 days after defervescence or a total of 14 days whichever is later.[9] When there is no clinical improvement at the end of 5 days, a second line drug such as azithromycin or any other drug as suggested in the sensitivity pattern is added. Dosage schedule of the commonly used anti typhoid drugs are discussed in Table IV.

Alternatively, the chances of using combination therapy in enteric fever has recently sparked interest. Since cephalosporins eliminate bacteria in the extracellular compartment and azithromycin eradicates the intracellular

Table IV. Anti-typhoid-drugs

Drug	Dose (mg/kg/d)	Maximum dose (per day)	Duration
Ceftriaxone	100	4g	10-14 days
Cefotaxim	150-200	8g	10-14 days
Cefixime	20	1200mg	10-14 days
Azithromycin	20	1g	7-10 days
Aztreonam	50-100	8g	10-14 days

bacteria in the reticuloendothelial niche, co-administration of the drugs is expected to have pharmacokinetic benefits. Adult trials have also shown earlier defervescence in typhoid patients treated with combination of third generation cephalosporins and azithromycin and such a combination therapy is an option in cases with fever lasting for more than 7 days.[11] However, further data is required in pediatric population before recommendations can be made.

The current challenge in managing enteric fever is the increasing resistance to the first-line antibiotics and hence, ciprofloxacin is no longer the empirical drug of choice in India. Multidrug resistant strains are being isolated globally and are causing outbreaks in India also. MIC ≤1 for ceftriaxone in susceptibility testing is associated with favorable clinical results. The MIC breakpoints to define ceftriaxone resistance in enteric fever is ≥4 as per CLSI and >2 as per EUCAST standards.[9] Rising MICs for ceftriaxone are being reported in India causing suboptimal response. These warrant treatment with azithromycin or meropenem (if hemodynamically unstable).

Typhoid carrier is an asymptomatic person who continues to shed *Salmonella* in stool or urine for more than 3 months after the episode of enteric fever. Since children become carriers rarely, routine screening after the illness is not done. However, if detected they are managed with trimethoprim-sulfamethoxazole (10 mg/kg/day) for 6-12 weeks or high dose amoxicillin (75-100 mg/kg/day) for 4-6 weeks.[9]

Helicobacter pylori

H. pylori infection is one of the many causes of gastric and duodenal ulcers in children, a treatable condition and its successful eradication leads to peptic ulcer disease (PUD) cure. Majority of children infected with *H. pylori* are asymptomatic and when compared to adults, are at low risk of developing complications. At present, there is increasing antibiotic resistance and the treatment recommendations in children differ from that of adults due to different risk-benefit ratio and available antibiotics. Hence, the decision to investigate and treat a child for *H. pylori* should be clinically indicated and backed by a clear benefit for the child. Taking all this into account and based on a systematic review of literature on *H. pylori* infection in children and adolescents from 2009 to 2014, ESPGHAN and NASPGHAN released a joint statement in 2017 providing recommendations for testing and treating the infection in children.[12] When ulcers are found during endoscopy, biopsies may be taken to look for *H. pylori* infection. *H. pylori* associated gastritis without mucosal lesions is rarely progressive and does not warrant invasive tests. *H. pylori* infection is diagnosed based on a positive culture or suggestive *H. pylori* histopathology along with another positive biopsy-based test (such as rapid urease test or molecular assay such as PCR or FISH). Antibody-based tests and noninvasive tests such as urea breath test or stool antigen test should not be used for initial diagnosis.

Present eradication protocols of *H. pylori* are triple therapies consisting of at least 3 drugs given for 10 to 14 days. Amoxicillin (AMO), clarithromycin (CLA) and metronidazole (MET) are the antibiotics along with proton pump inhibitors (PPI). Higher degree of acid suppression improves the success of the therapy. Clarithromycin resistance is increasing beyond acceptable threshold (15%) in many regions of the world and hence it is recommended to obtain the antimicrobial susceptibility of the infecting strains by molecular methods like PCR before starting therapy and to restrict clarithromycin containing regimes to patients infected with susceptible strains only.[12] Evaluation of regional resistance pattern and effectiveness of the first-line therapy at national/ regional centers is recommended. The various regimes to treat *H. pylori* infection in children are shown in Table V.

Table V. Treatment regimes for *H.pylori* infection

Scenario	Recommended regime
Preferred first line	AMO + CLA + PPI
Failure of first line	AMO + MET + PPI
Susceptible to CLA but resistant to MET	AMO + CLA + PPI
Resistant to both CLA and MET or Primary sensitivity unknown or Rescue therapy	High-dose AMO + MET + PPI

Alternatively, based on literature and adult studies, bismuth quadruple therapy (bismuth+ PPI+ MET+ AMO/ tetracycline) can be used where available. While adult guidelines support the use of concomitant quadruple therapy (PPI+ AMO+ MET+ CLA) for 10-14 days as a first-line option, there are no pediatric studies available to support this use. This can however be a better option in children with dual resistance to clarithromycin and metronidazole. Previously, sequential therapy of 5 days of PPI+AMO followed by 5 days of PPI+CLA+MET was practiced which is no longer recommended due to exposure to 3 different antibiotics.

Regimes with 14-day duration have shown better eradication rates compared to shorter duration regimes in studies and continuing PPI for additional 2 to 4 weeks post eradication therapy is recommended. Treatment failure occurs not only because of the antimicrobial resistance, but also due to poor adherence. Studies have shown that eradication is successful in children who take at least 90% of the medication and that an eradication rate of at least 90% is needed to prevent the induction of secondary resistance. Hence it is imperative to explain the importance of adherence to parents prior to therapy.[12]

Four weeks after the completion of anti- *H. pylori* treatment, outcome of therapy is assessed in all patients by the non-invasive tests like the 13C-urea breath test or the 2-step monoclonal stool H. pylori antigen test. In cases of treatment failure, rescue therapy is given according to the age of the child, antibiotic susceptibility profile and the employed initial regimen. High dose amoxicillin regime and bismuth-based regimes are available the rescue options. However, there are limited options available for second-line therapies in children when compared to adults which further emphasizes the need to prescribe appropriate first-line regimens.

Appendicitis

Acute appendicitis is the most common pediatric surgical emergency globally and occurs as a result of luminal obstruction by varied causes along with superimposed infection. Tissue ischemia and eventual perforation are the feared complication which usually occurs within 48 hours of initial presentation. Younger children with less developed omentum are at a greater risk of developing generalized peritonitis while other children may develop walled-off abscess. The microbiota of the appendix differs from the rest of the gastrointestinal tract. Specimens of pediatric appendicitis have shown excess of Fusobacteria and reduced amount of Bacteroides although its role in the pathogenesis of appendicitis is unclear. Diagnosis of appendicitis is based on a combination of clinical findings, imaging and laboratory parameters. After diagnosis, management of appendicitis depends on whether it is simple or complicated and timely management is vital to prevent complications like rupture. Suspected appendicitis cases with equivocal findings are usually observed without antibiotic treatment and among them, approximately half can be discharged without any additional intervention.[13]

The standard treatment for simple appendicitis is single-dose preoperative prophylactic antibiotic along with timely surgical removal of the inflamed appendix. In such cases with a normal appendix, studies have shown minimal beneficial effect of antimicrobial prophylaxis over placebo.[14] However, considering the morbidity associated with its various complications, many authors recommend antibiotic prophylaxis for appendicitis. Additional antibiotics administered postoperatively usually do not decrease the rate of surgical site infections. The rate of SSI however seems to increase when surgery is delayed for more than 48 hours from admission.[13] Recent adult studies have shown the feasibility of non-surgical management of early appendicitis with a success rate of 60% and there are also pediatric trials showing feasibility of managing acute non-perforated cases of appendicitis non-operatively.[15] However, data is insufficient to recommend this as a safe option.

In cases of complicated appendicitis, immediate appendectomy is performed when there is no appendiceal mass or abscess. Laparoscopic appendectomy in particular is associated with lower risk of wound infection when compared with open appendectomy. Studies have shown higher morbidity in patients with abscess who undergo immediate appendectomy when compared with patients who are managed conservatively. Antimicrobial treatment and interval appendectomy is usually favored in non-toxic patients while appendectomy is performed in patients with appendiceal mass or abscess who are ill-appearing. For children with perforated appendicitis, duration of administration of broad-spectrum IV antibiotics postoperatively depends on clinical criteria such as fever, pain, WBC count and return of bowel function and is usually for 5 days. Following up this with a course of oral antibiotics has similar effects.[16] In patients who are critically ill, the total course of antibiotics has to be extended up to 10 days.[13]

The empiric antibiotic chosen should cover both Gram-negative organisms and anerobes. Recently the ESBL pattern of resistance among Gram negative organisms is on the rise to the level of even 60-93%. The antibiotic

choices include second-generation cephalosporin with anerobic activity or third-generation cephalosporin (ceftriaxone) along with metronidazole. Piperacillin-Tazobactum is a broad-spectrum antibiotic which has activity against both anerobes as well as ESBL producing Gram-negative organisms. A broad-spectrum single to double drug therapy is more effective than triple drug therapy.[16] In patients who are allergic to beta-lactam antibiotics, clindamycin along with amikacin can be given, however amikacin penetrates the intestinal mucosa poorly.

Points to Remember

- ***Routine microbiological investigations and anti-infective therapy are not recommended in all cases of pediatric acute gastroenteritis***
- ***Empiric antibiotics targeting shigella are to be started in cases of dysentery. Azithromycin is preferred in western nations and cefixime in India***
- ***Cholera is suspected when there is profuse loose stools leading to severe dehydration and treated with single dose azithromycin or doxycycline in addition to aggressive rehydration***
- ***The treatment of choice for the systemic infection enteric fever is parenteral ceftriaxone or oral cefixime and for resistant strains azithromycin and meropenem***
- ***Initially ciprofloxacin was used for enteric fever, dysentery and cholera, which is now ineffective.***
- ***In cases of simple appendicitis, appendectomy is performed under cover of single dose preoperative prophylactic antibiotic to cover Gram-negative and anerobic organisms, while in cases of perforated appendicitis, postoperative antibiotics are continued for a minimum of 5 days.***

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CLIPPINGS

Reclassification of the Etiology of Infant Mortality With Whole-Genome Sequencing

Congenital malformations/chromosomal abnormalities have been the leading cause of US infant death for more than 50 years. National vital statistics indicate that malformations account for more than one-fifth of infant deaths, followed by preterm birth/low birth weight (prematurity), pregnancy complications, and sudden infant death syndrome (SIDS).

Accurate etiologic classification of infant mortality is important for families and the public. Prior etiologic studies of infant mortality are generally retrospective and based on electronic health record (EHR) and death certificate review, potentially leading to underdiagnosis of genetic diseases. Furthermore, at least 30% of death certificates have inaccuracies. The effect of such imprecision could be large since many genetic diseases have treatments that can improve outcomes, and undiagnosed genetic diseases often recur within families, causing preventable deaths.

Early implementation of genomic sequencing could improve understanding about causes and suggest novel strategies to reduce infant mortality. Genomic sequencing has shown that single-locus genetic diseases are a leading cause of some categories of infant deaths, such as SIDS, but their association with overall infant mortality has not been well quantified.

This cohort study was conducted at a large pediatric hospital system in San Diego County (California) and included 546 infants (112 infant deaths [20.5%] and 434 infants [79.5%] with acute illness who survived; age, 0 to 1 year) who underwent diagnostic whole-genome sequencing (WGS) between January 2015 and December 2020. Data analysis was conducted between 2015 and 2022.

Infants underwent WGS either premortem or postmortem with semiautomated phenotyping and diagnostic interpretation. Among 112 infant deaths in San Diego County between 2015 and 2020, single locus genetic diseases were the most common identifiable cause of infant mortality, with 47 genetic diseases identified in 46 infants (41%). Thirty-nine (83%) of these diseases had been previously reported to be associated with childhood mortality. Twenty-eight death certificates (62%) for 45 of

the 46 infants did not mention a genetic etiology. Treatments that can improve outcomes were available for 14 (30%) of the genetic diseases. In 5 of 7 infants in whom genetic diseases were identified postmortem, death might have been avoided had rapid, diagnostic WGS been performed at time of symptom onset or regional intensive care unit admission.

In this cohort study of 112 infant deaths, the association of genetic diseases with infant mortality was higher than previously recognized. Strategies to increase neonatal diagnosis of genetic diseases and immediately implement treatment may decrease infant mortality. Additional study is required to explore the generalizability of these findings and measure reduction in infant mortality.

Owen MJ, Wright MS, Batalov S, Kwon Y, Ding Y, Chau KK et al. Reclassification of the Etiology of Infant Mortality With Whole-Genome Sequencing. JAMA Netw Open. 2023;6(2):e2254069. doi:10.1001/jamanetworkopen.2022.54069.

IAP - IJPP CME 2022

ROLE OF ULTRASONOGRAM AND ECHOCARDIOGRAPHY IN ER/PICU

Seenivasan Subramani

Abstract: *Ultrasonography and echocardiography have been widely used by physicians of varied specialties such as radiology, cardiology and obstetrics. Currently this imaging modality is used as a focused 'point of care' investigation to aid in immediate assessment and management of critically ill children most often in the intensive care setting by making use of the advancements in ultrasound related technology. Clinical studies have demonstrated its utility in practice.*

Keywords: *Ultrasonography, Echocardiography, Point of care, Emergency room, Pediatric intensive care.*

Ultrasonography /Echocardiography is an investigatory procedure used in the emergency rooms (ER) and pediatric intensive care units (PICU). This article, describes various situations wherein ultrasound/ echocardiography is found to be useful and the article is presented with relevant illustrations wherever needed with minimum theoretical description for easy understanding for practicing pediatricians and pediatric postgraduates.

Inferior vena caval dimensions

To assess inferior vena caval dimensions in volume sufficiency (adequacy): The probe used is a 6S or 3S square cardiac probe to assess inferior vena cava (IVC) in dynamic motion. The probe is kept in the lower chest to the right of the midline or in the epigastrium pointing superiorly, to visualize the IVC, 1 cm caudal to junction of hepatic vein joining the IVC to measure IVC diameter. The respiratory variations of IVC diameter are recorded and measured in M Mode (Motion mode). In spontaneously breathing children, IVC diameter decreases during inspiration and increases during expiration. However, in ventilated

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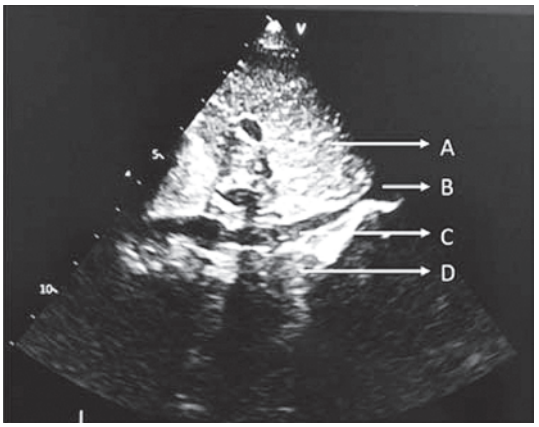


Fig.1. Inferior vena cava.

A. Liver, B. Right Atrium, C. Inferior Vena cava, D. Liver (Note liver is present on either side of IVC).

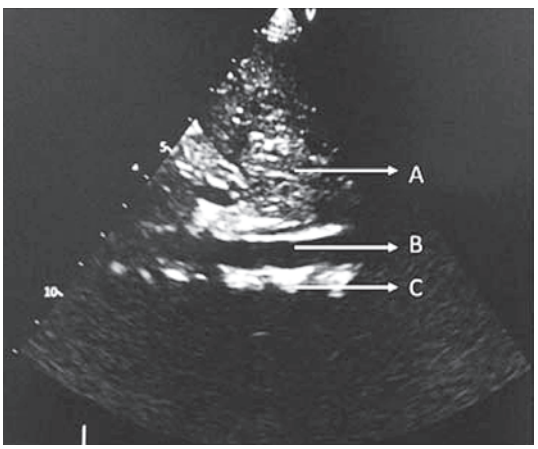


Fig. 2. Abdominal aorta.

A. Liver, B. Abdominal Aorta, C. Vertebral body

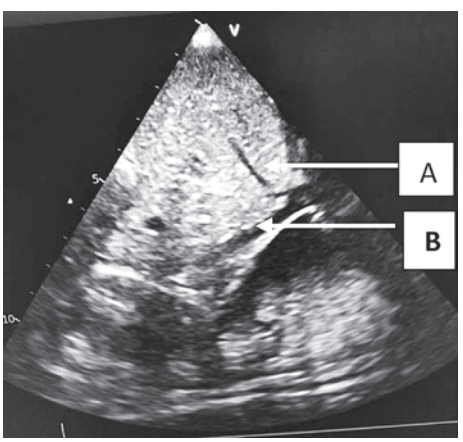


Fig. 3. Collapsed IVC (better seen dynamic)

A. Hepatic Vein, B. IVC

Table I. Comparison of echo findings of IVC and abdominal aorta

	IVC	Abdominal aorta
1.	Right of midline	Left of midline
2.	Can be traced into right atrium	Not traceable to heart
3.	Liver is seen both anteriorly and posteriorly and IVC is within liver shadow	Liver is seen anterior to aorta
4.	Vertebral bodies not seen	Vertebral bodies seen posterior to the aorta
5.	Hepatic vein joins proximally	Superior mesenteric artery branches distally
6.	Non pulsatile	Pulsatile
7.	Thin walled	Thick walled
8.	Compressible	Non compressible

children, IVC diameter increases during inspiration and decreases during expiration. The points one would see for IVC and abdominal aorta dynamics in echocardiogram are shown in Fig.1 and Fig.2 respectively. Table I explains how to differentiate IVC and abdominal aorta in echo.

The echo showing collapsed IVC with hepatic vein in Fig.3 and Fig.4 in M mode. Distended IVC is seen in Fig.5.

IVC Collapsibility vs distensibility in assessing fluid sufficiency: Collapsibility index helps in assessing fluid sufficiency.

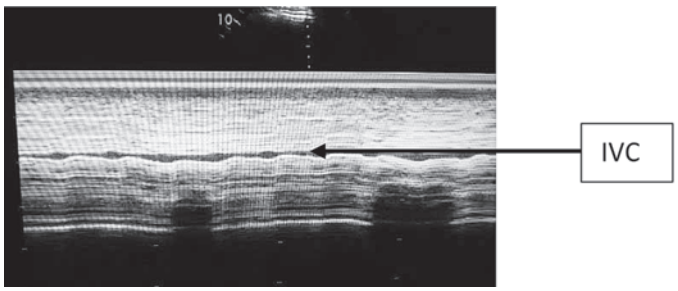


Fig.4. Collapsed IVC in M mode

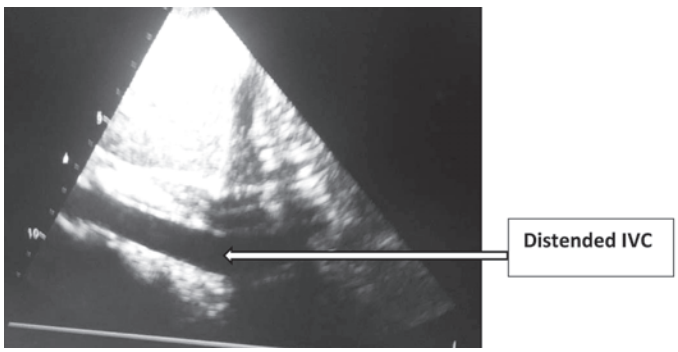
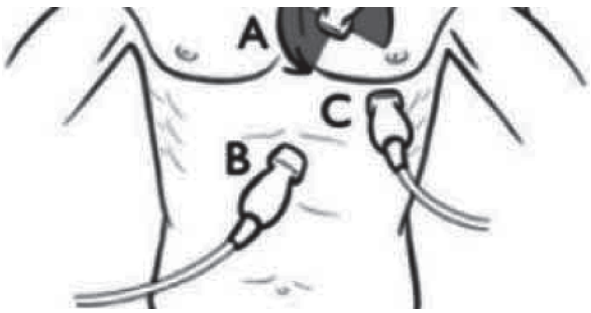


Fig.5. Distended IVC

Collapsibility Index = Maximum diameter – Minimum diameter / Maximum diameter (of IVC). In spontaneous breathing children when, collapsibility index is more than 50% it suggests volume depletion.



Cardiac views in echo cardiography

Fig.6. Markings - A, B, C

A. Parasternal short axis (PSAX) and long axis (PLAX)

B. Subcostal view

C. Apical long axis

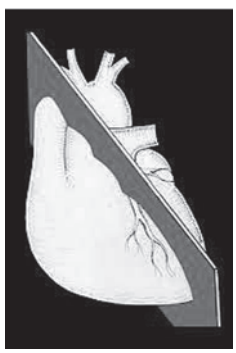


Fig.6i. PLAX - cut

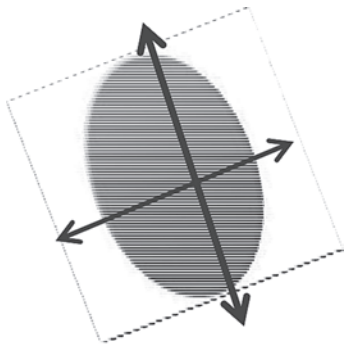


Fig.6i. Illustrative long and short axis cuts

Distensibility index = Maximum diameter- Minimum diameter / Minimum diameter

In mechanically ventilated children (mandatory breaths), distensibility >18% suggests that the child is likely to respond to vascular filling (there is a need for fluid bolus).

Cardiac views

The cardiac views in echocardiography are parasternal long axis view (PLAX - 6i, parasternal short axis view (PSAX - 6i, apical view (four chamber view and five chamber view), subxiphoid (subcostal) view and IVC view. Parasternal long axis view is the longitudinal cut section of heart (cutting through antero posterior), when probe is placed in left sternal border at 2nd to 4th intercostal spaces with marker dot pointing towards right shoulder. It shows left ventricle (LV), left atrium (LA), mitral valve apparatus and left ventricular outflow tract (LVOT), partially seen right ventricular outflow tract (RVOT) and interventricular septum (Fig.6, 6a, 6b - Guided by 6i).

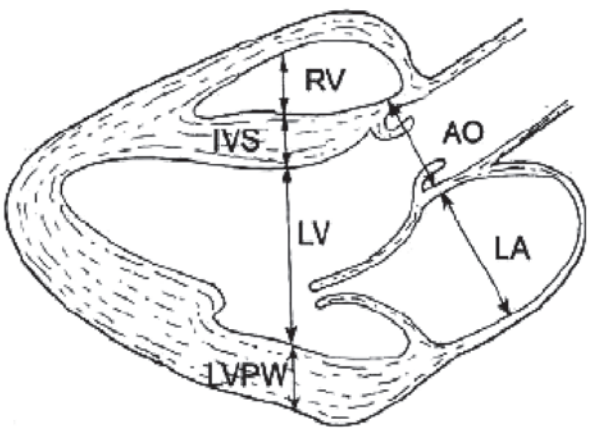


Fig.6a. Illustrative diagram - PLAX

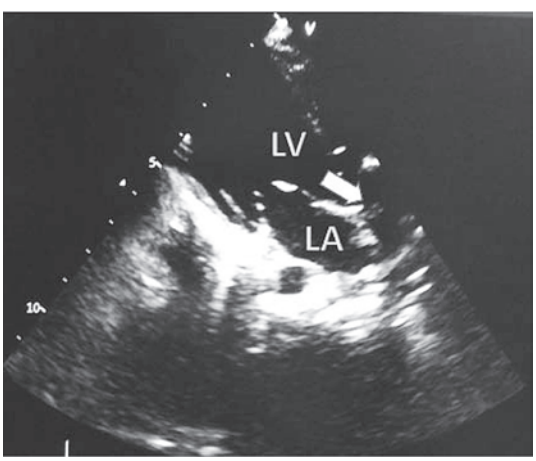


Fig.6b. Parasternal long axis view

Illutrative diagram - PSAX

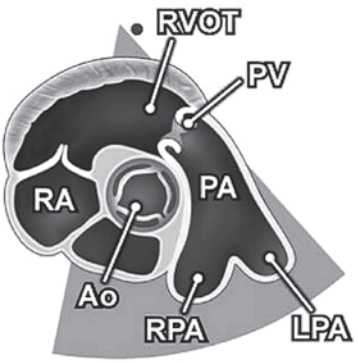


Fig.7. Parasternal short axis view - Cross section of aorta with pulmonary artery and pulmonary valves

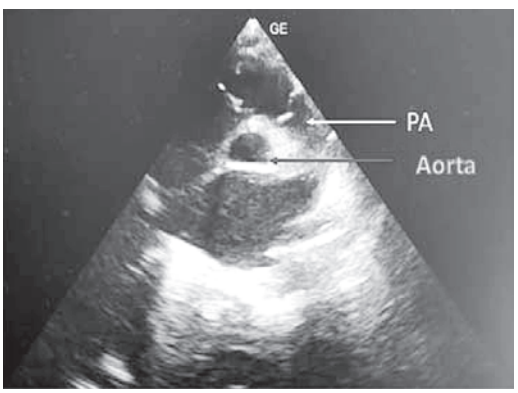


Fig.7a. Parasternal short axis view - Cross section of aorta with pulmonary artery and pulmonary valves

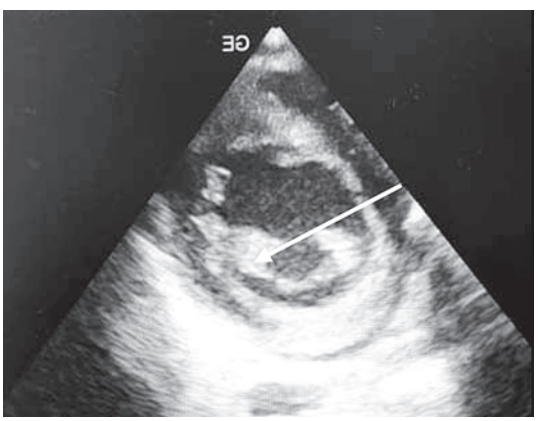


Fig.8. Parasternal short axis view showing mitral valve cross section

Parasternal short axis view is taken perpendicular to PLAX at the same points (left sternal border at 2nd to 4th intercostal space) with marker dot pointing towards left shoulder. From above downwards this view can show aortic valve and pulmonary artery (Fig.7,7a), mitral valve apparatus (Fig.6b) consisting of mitral valve ring, cauda

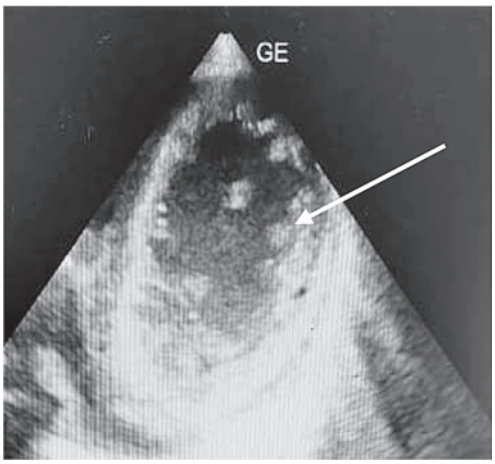


Fig.8a. Parasternal short axis view LV and papillary muscles

tendinae (Fig. 8, 8a) and papillary muscles (Fig.8a) in successive cuts towards the apex.

The apical four chamber (A4C) view is obtained by placing the probe in the apex of heart with marker dot pointing towards left shoulder. This view shows the four chambers, inter atrial septum (IAS) and inter ventricular septum (IVS) (Fig.9, 9a). The apical five chamber (A5C)

Apical 4 Chamber view

Illustrative diagram

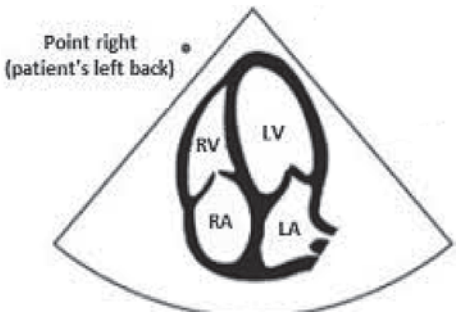


Fig.9. Apical 4 Chamber view

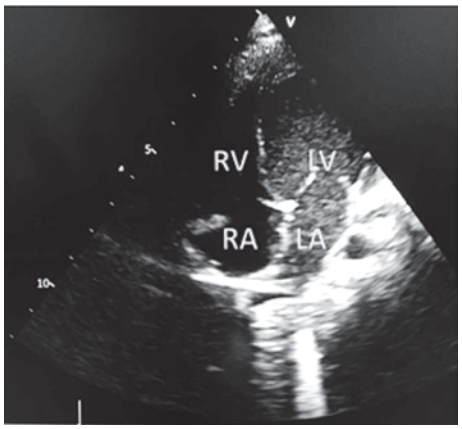


Fig.9a. Apical 4 Chamber view showing LA, LV, RA, RV, IAS and IVS

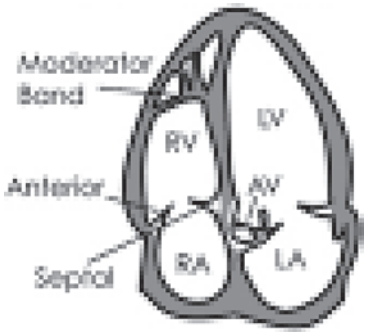


Fig.10. Five chamber view- Illustrative diagram

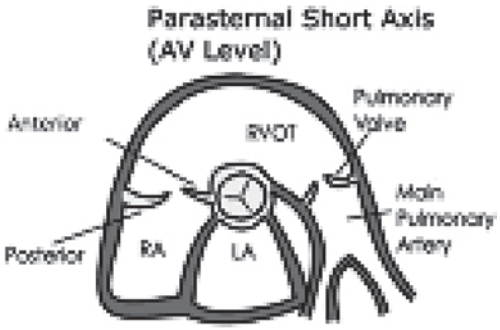


Fig.10a. Five chamber view with tilt with RVOT seen, LV not seen

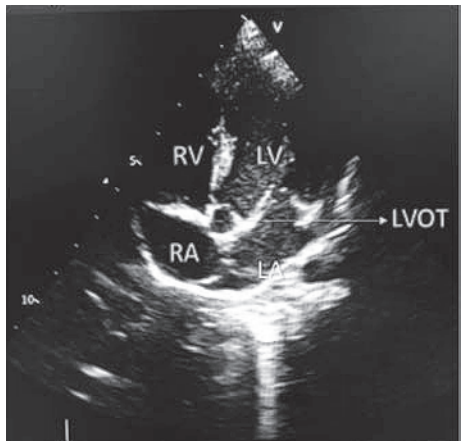


Fig 10b. Apical 5 chamber view showing four chambers and aortic opening in the center

view is obtained in the same point with slight anterior angulation, which shows LVOT in addition to the above structures seen in A4C (Fig.10, 10a, 10b).

Assessment of LV systolic function

Systolic function of heart is assessed by 1) fractional shortening (FS) and 2) ejection fraction (EF).

1. Fractional shortening (FS - normal is 28% to 45%)

LVEDD - Left ventricular end diastolic dimension

LVESD - Left ventricular end systolic dimension

FS = (LVEDD – LVESD) / LVEDD X 100

2. Ejection fraction (EF - Normal is - 55% to 75%)

There are three methods of calculating the above

1. Simpson's method
2. Teichholtz's method
3. Eye balling

Simpson's method : Is through apical 4 chamber view or apical 2 chamber view (Fig.11, 11a).

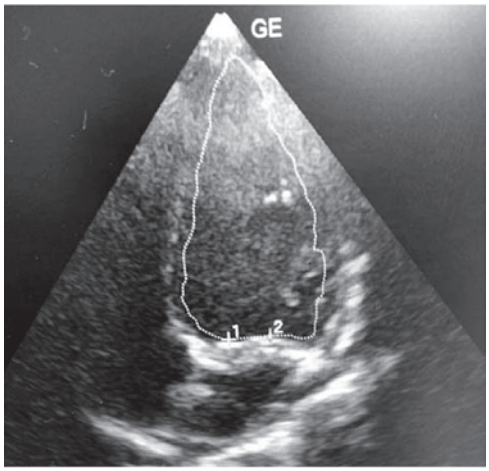


Fig.11. Simpson's method - Apical 2 chamber (A2C) view by drawing endocardial border

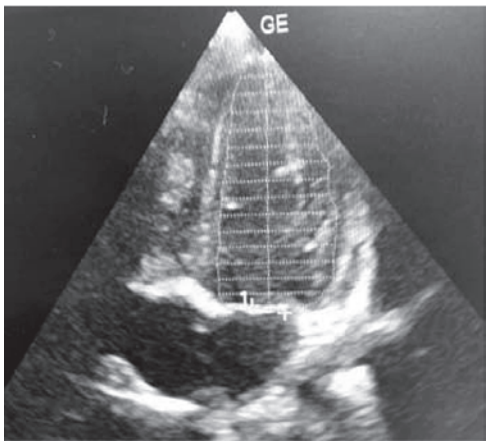


Fig.11a. Apical 4 Chamber (A4C) - calculating the area

Freeze the image at end diastole (beginning of QRS wave), then scroll around the endocardial borders (Fig.11). Calculate the area as in Fig.11a, by inbuilt software in ECHO machine. Similarly measure the area in end systole. With these two measurements, EF is calculated by the Software and displayed.

Teichholtz method

Measurement of EF by Teichholtz method uses Parasternal long axis (PLAX) or Parasternal short axis views (PSAX) as in Fig 12, 12a & 12b explained by the M-Mode.

M-mode cursor is placed across the ventricular septum and LV posterior wall just beyond the tip of the mitral leaflets when they are apart. Measure RV internal dimension, interventricular septum thickness, LV internal dimension and LV posterior wall thickness at end-diastole and end systole. Machine will automatically calculate FS and EF.

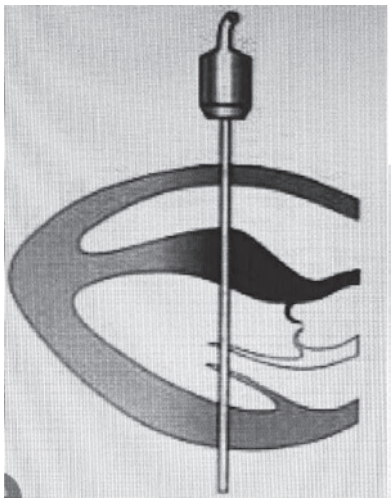


Fig.12

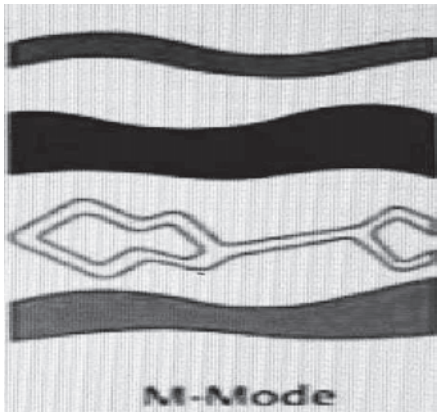


Fig.12a

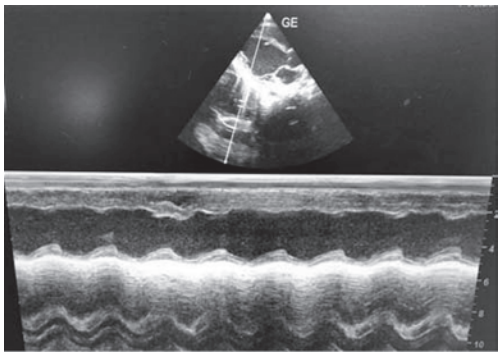


Fig.12b

Fig.12,12a and 12b for Teichholtz method

Pericardial effusion (Fig.13 and Fig.14)

Pericardial effusion can be quickly assessed by echocardiography and can be seen as non-echogenic clear fluid around the heart within the pericardium. If purulent can be seen as echogenic flakes.

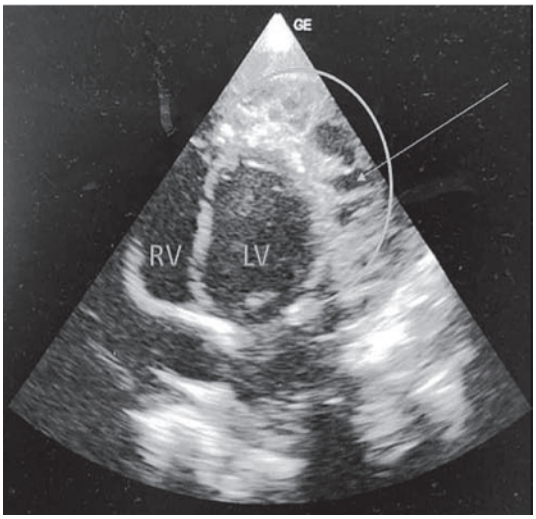


Fig.13. Loculated pericardial effusion

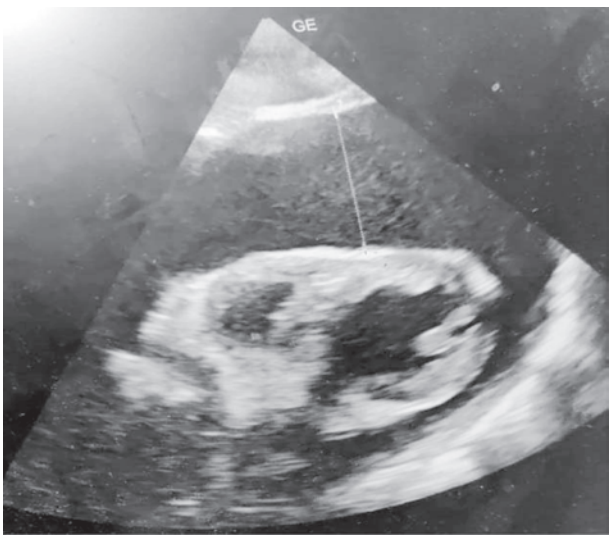


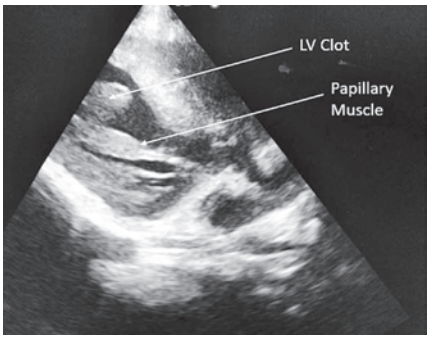
Fig.14. Pericardial effusion

Intra ventricular clots (Fig.15 and Fig.15a)

Can be seen as echogenic irregular shadows within the cavity or attached to the valve apparatus or to the valves. Have to be differentiated from vegetations clinically.

Assessment of coronary artery dimensions

Dilated coronaries are shown in Fig.16 and Fig.17. (as seen in PSAX)



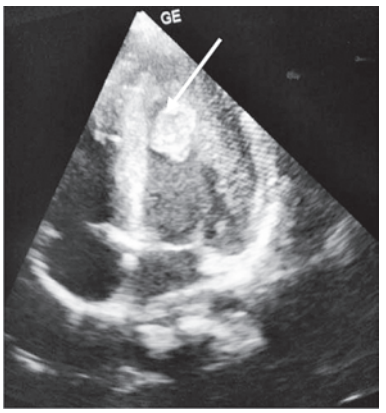


Fig.15. LV clot in PLAX view
Fig.15a. LV clot in A4C view

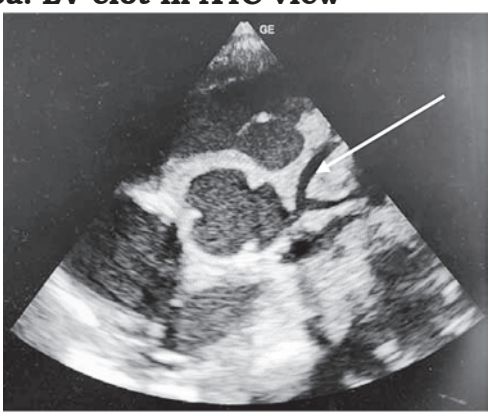


Fig.16. Dilated coronaries Arrow shows LAD (Left anterior descending artery)

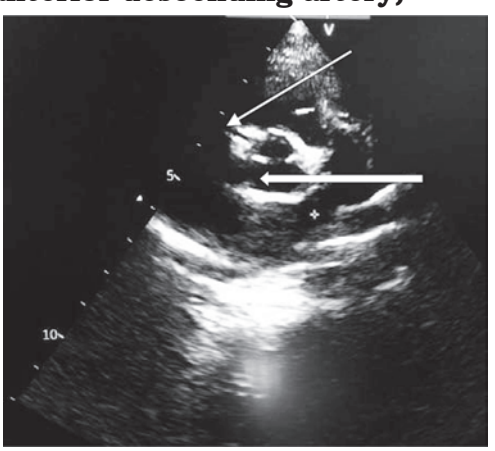


Fig.17. Right coronary artery (Thin arrow), aortic valve cross section (Thick arrow)

Pleural effusion

Normal lung is seen as sea shore sign (Fig.18) by lung USG.

Pleural effusion is shown in Fig.19 and Fig.20 pneumonia by shred sign in Fig.21.

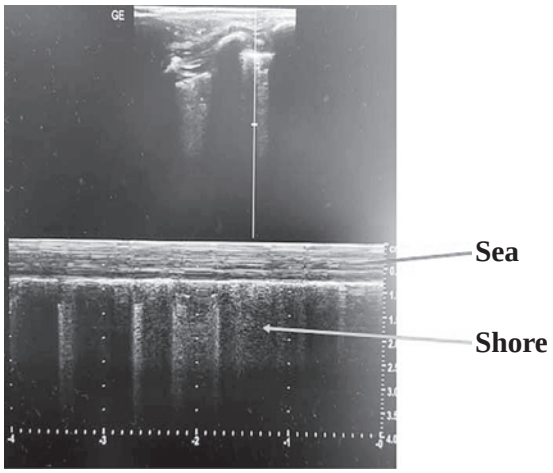


Fig.18. Sea shore sign (Normal lung)

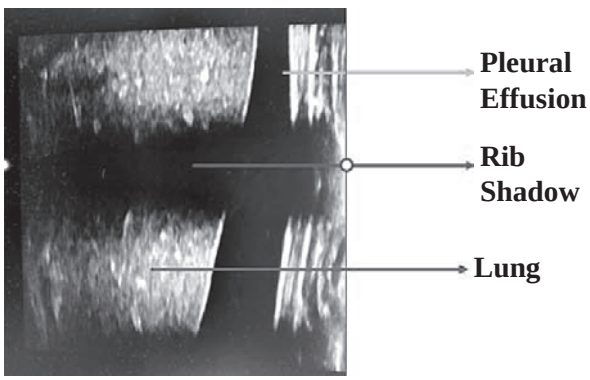


Fig.19. Pleural effusion

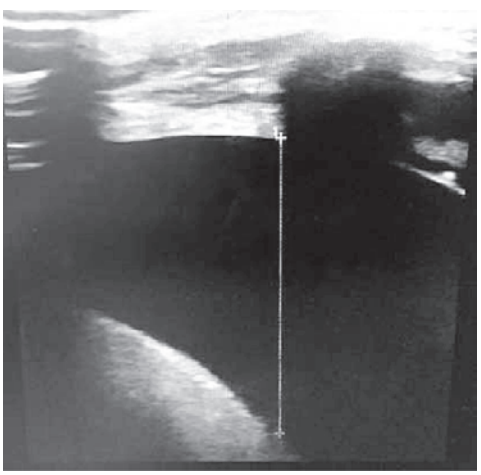


Fig.20. Pleural effusion

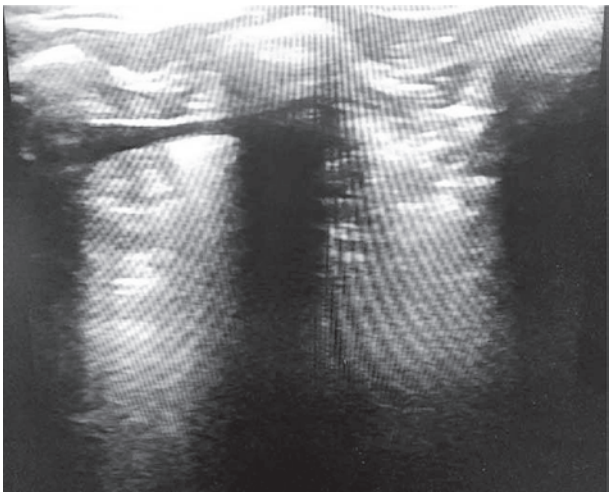


Fig.21. USG lung - Pneumonia (Shred sign)

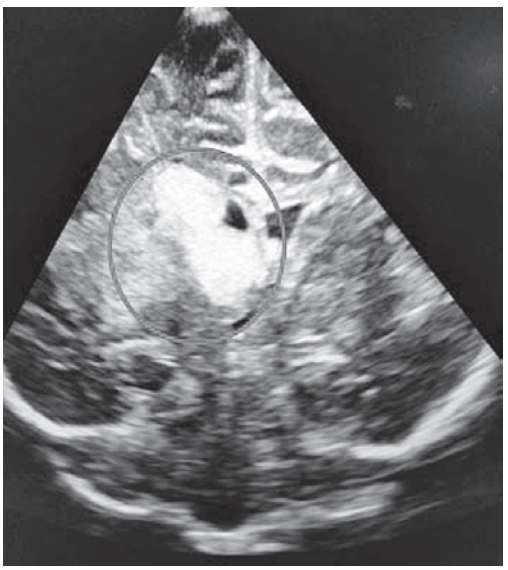


Fig.22. USG cranium - Intra cranial bleed

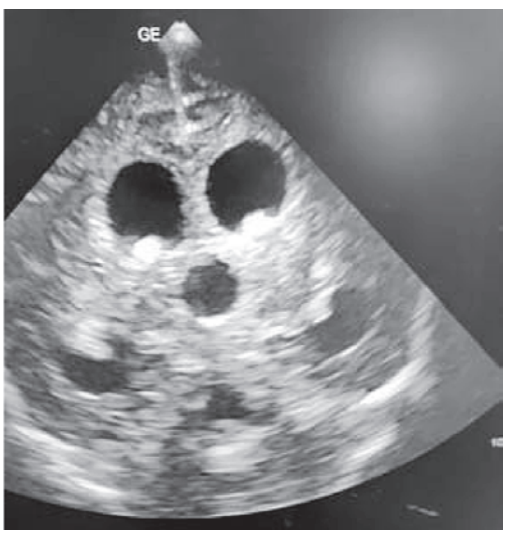


Fig.23. USG cranium - Tetra ventricular hydrocephalus

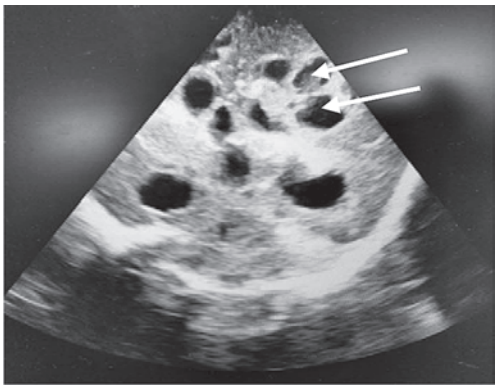


Fig.24. USG cranium-Multiple cerebral abscesses

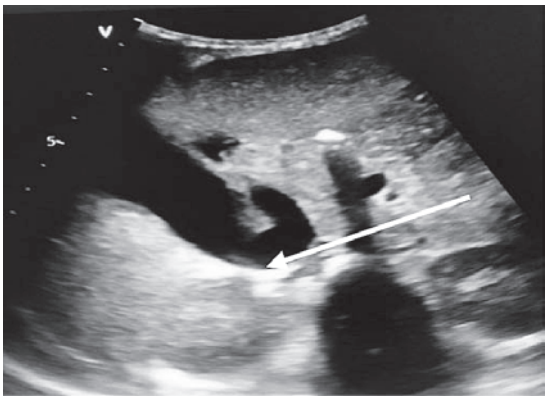


Fig.25. USG abdomen - Distended gall bladder with biliary sludge

USG cranium

USG cranium is useful for diagnosing intracranial bleed (Fig.22), hydrocephalus (Fig.23) and multiple cerebral abscesses (Fig.24).

Case scenario

A 4 year old girl presented with fever for 7 days. She had jaundice and hepatomegaly. Investigations showed TC 12,000, PCV 33, Platelet 92,000. Dengue NS 1 and IgM ELISA negative, typhidot, lepto and scrub negative HBsAg, IgM Anti HAV negative. USG showed distended gall bladder with sludge (Fig.25). Blood culture grew *Salmonella typhi*. Biliary sludge is seen in tropical fevers like typhoid, dengue, scrub typhus, leptospirosis and with ceftriaxone use.

Extended - Focused assessment with sonogram in trauma (E FAST)

Done in polytrauma at five sites to diagnose injury of organs at their respective sites:

1. Right upper quadrant (liver)
2. Left upper quadrant (spleen)
3. Epigastrium (heart)
4. Pelvis (pelvic bleed)
5. Pleural cavities (hemo / pneumothorax)

Other useful ultrasound findings in PICU

Meninges are extended over optic nerve. Any intra cranial pressure (ICP) may tend to distend the optic nerve sheath which is harnessed in ultrasound as an indirect evidence of ICP. Optic nerve sheath diameter (ONSD) (Fig. 26) is measured 3 mm distal to globe. The cut off for increased intra cranial pressure is 4 mm in infants and

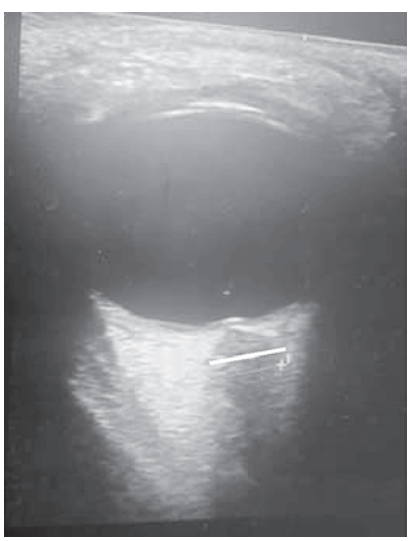


Fig.26. Optic nerve sheath diameter

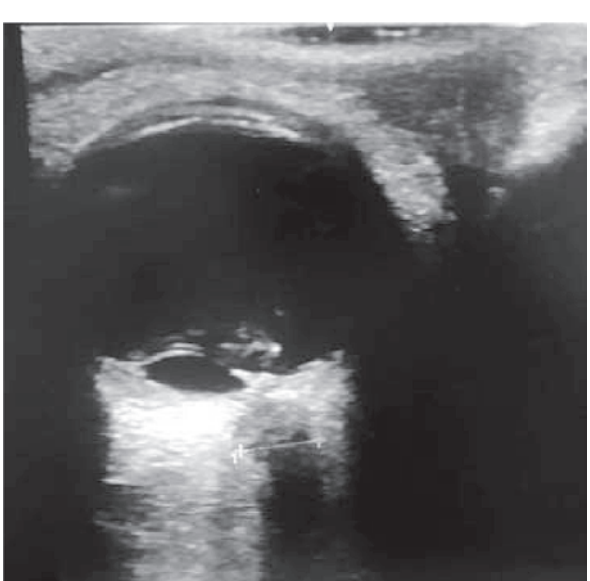


Fig.27. Retinal detachment

4.5 mm in children more than 1 year. Note that lens should not come in the cut section of globe while measuring OSND. Retinal detachment is also can be assessed by ultrasound (Fig.27).

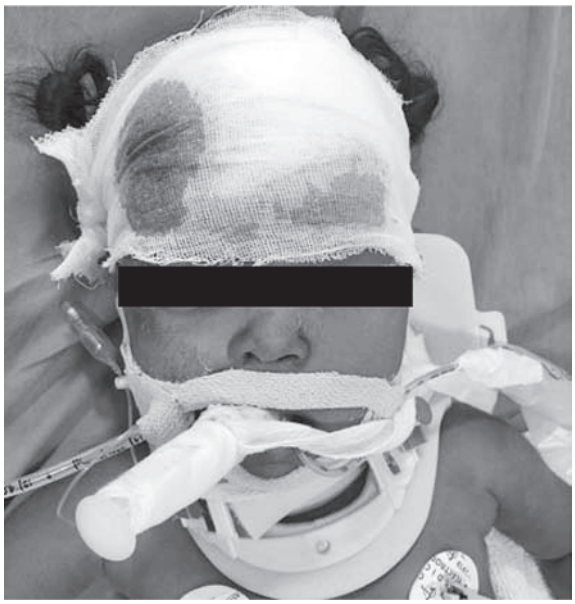


Fig.28. Head injury
(Picture with permission)

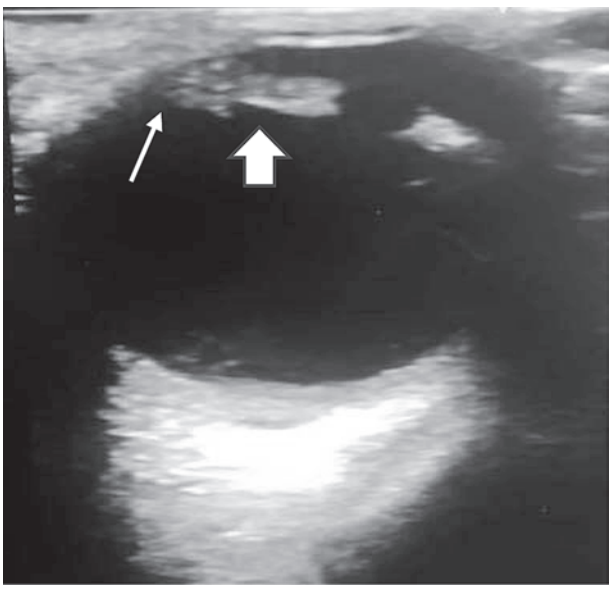


Fig.29. Iris and pupil

Sometimes in head injury, the eyelids are swollen so that pupils can not be seen by torch light (Fig.28). In those situations, ultrasound may be used to see pupillary reactions in critically ill children (Fig.29, Fig.30a and 30b).

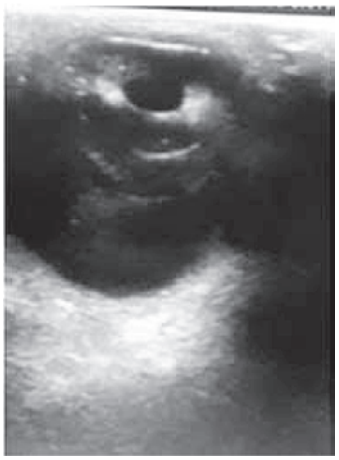


Fig.30a. Pupillary reaction before light

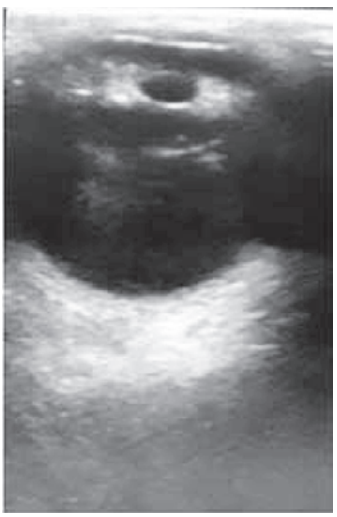


Fig.30b. Pupillary reaction after light

Points to Remember

- ***In the ER and PICU ultrasonogram and echo are used as low risk, non-invasive modality to diagnose and help in the management of critically ill children.***
- ***Volume status can be assessed using the collapsibility index and distensibility index using USG.***
- ***Left ventricular dysfunction can be diagnosed in pediatric patients at point of care based on fractional shortening and ejection fraction.***
- ***Pericardial effusion, dilated coronary artery, pleural effusion, pneumonia, biliary sludge and injuries to organs are diagnosed with USG.***
- ***Cranial USG is useful for the diagnosis of intracranial bleed, communicating hydrocephalus and cerebral abscesses.***

- ***When the eyelids are swollen pupillary reactions can be assessed by USG retinal detachment, raised intracranial pressure also can be assessed by USG using optic nerve sheath diameter***

Acknowledgement : All illustrative diagrams are from Science direct images

Bibliography

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CLIPPINGS

Ultrasound-guided reduction of intussusception in infants in a developing world: saline hydrostatic or pneumatic technique?

Non-operative reduction has emerged as first line in the management of uncomplicated intussusception. The aim of this study was to compare the outcome of ultrasound-guided saline hydrostatic reduction and ultrasound-guided pneumatic reduction of intussusception in infants. This is a prospective study of infants with uncomplicated intussusception confirmed by ultrasound over a period of 21 months from December 2018 to August 2020. Fifty-two (69.3%) out of seventy-five infants were eligible and randomized based on simple random sampling technique into two groups: Group A included patients who had ultrasound-guided hydrostatic (saline) reduction; Group B included patients who had ultrasound-guided pneumatic (air) reduction. The success rates, time to reduction and complication rates were assessed.

Conclusion: Saline hydrostatic reduction and pneumatic reduction of uncomplicated intussusception under ultrasound guidance in infants might have comparable outcomes. However, pneumatic reduction may be faster.

Chukwu IS, Ekenze SO, Ezomike UO, Chukwubuike KE & Samuel C. Ekpemo. Ultrasound-guided reduction of intussusception in infants in a developing world: saline hydrostatic or pneumatic technique?Eur J Pediatr 182, 1049-1056 (2023). https://doi.org/10.1007/s00431-022-04765-5.

Gadget addiction among school-going children and its association to cognitive function: a cross-sectional survey from Bangladesh

People are becoming more dependent on technology than ever before. Today's children and adults are heavily plugged into electronics, which raises concerns for their physical and cognitive development. This cross-sectional study was conducted to assess the relationship between media usage and cognitive function among school-going children.This cross-sectional study was conducted in 11 schools in 3 of Bangladesh's most populous metropolitan areas: Dhaka, Chattogram and Cumilla. A semistructured questionnaire with three sections was used to obtain data from the respondents: (1) background information, PedsQL Cognitive Functioning Scale and (3) Problematic Media Use Measure Short Form. Stata (V.16) was used for statistical analysis.Conclusion This study found digital media addiction as a predictor of decreased cognitive performance in children who use digital gadgets regularly. Although the cross-sectional design of the study precludes causal relationships from being determined, the study finding deserves further examination via longitudinal research.

Liza MM, Iktidar MA, Roy S, et alGadget addiction among school-going children and its association to cognitive function: a cross-sectional survey from BangladeshBMJ Paediatrics Open 2023;7:e001759. doi: 10.1136/bmjpo-2022-001759.

GENERAL ARTICLE

MEDICATION ERRORS IN PEDIATRIC INTENSIVE CARE UNIT

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****Kalaimaran S**

Abstract: *Medication errors are one of the commonly encountered problems in hospitalised patients especially seen more in the ICU setting. If not appropriately identified and addressed these may lead to dangerous complications and even fatality. Though adverse drug events seen with commonly prescribed medications are unavoidable, those that are due to medication errors can be prevented with appropriate check points and drug safety monitoring. This article highlights the types of medication errors, how to approach them and the steps needed to curb their occurrence for prevention of untoward effects.*

Keywords: *Medication errors, Adverse drug event, Prescription, Pediatrics, Drug safety.*

Incidence

Medication errors (ME) in hospitals are one of the leading causes of death worldwide.[1] A 2013 study by James et al found that between 200,000 and 400,000 Americans die each year in the U.S due to unsafe medical care.[2] Similarly, every year in low- and middle-income countries (LMICs), 134 million adverse events occur due to unsafe care, resulting in 2.6 million deaths.[3] ME are also commonly encountered in intensive care unit (ICU) settings. A systematic review analysing the ME in pediatric ICU, showed the median rate of medication errors was 14.6 per 100 medication orders (interquartile range 5.7- 48.8%) and between 6.4 and 9.1 per 1000 patient days.[4] Prescription errors and medication administration errors were found to be the most common errors, with dosing errors being the most frequently reported subtype.[5] Anti-infective agents were commonly involved with medication errors or preventable adverse drug events.[5] In India, few studies have documented ME rate to be as high as 36%, 25.7% and 15.34%, respectively, in hospitalized patients.[6-8] Total national costs in the US (lost income, lost household production, disability, health care costs) are estimated to be between $37.6 billion and $50 billion for adverse events and between $17 billion and $29 billion for preventable adverse events.[1]

The situations more common for me are shown in (Fig.1).[9]

Definitions

As per the report by Institute of Medicine (IOM) 2000, To Err is Human: Building a Safer Health System[1], safety is defined as freedom from accidental injury and error as failure of a planned action to be completed as intended (i.e., error of execution) or use of a wrong plan to achieve a goal (i.e., error of planning). Two types of execution errors exist: errors of commission and errors of omission.

Adverse drug events (ADEs) are defined as any injury resulting from medication use, including physical harm, mental harm, or loss of function.[10] Adverse drug reactions (ADRs), or non-preventable ADEs, are ADEs that occur due to pharmacologic properties of the drug. Preventable ADEs are ADEs resulting from a medication error that can be avoided. At least a quarter of all medication-related injuries are preventable.[11] Potential ADEs are events in which an error occurred but did not cause injury for whatever reason (e.g. error was intercepted before the affected patient received a wrong dose hence no harm occurred).[12]

Medication Errors (ME) are defined by the National Coordination Council for Medication Error Reporting and Prevention (NCC MERP) as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. Such events may be related to professional practice, health care products, procedures and systems, including prescribing, order communication, product labelling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use."[13]

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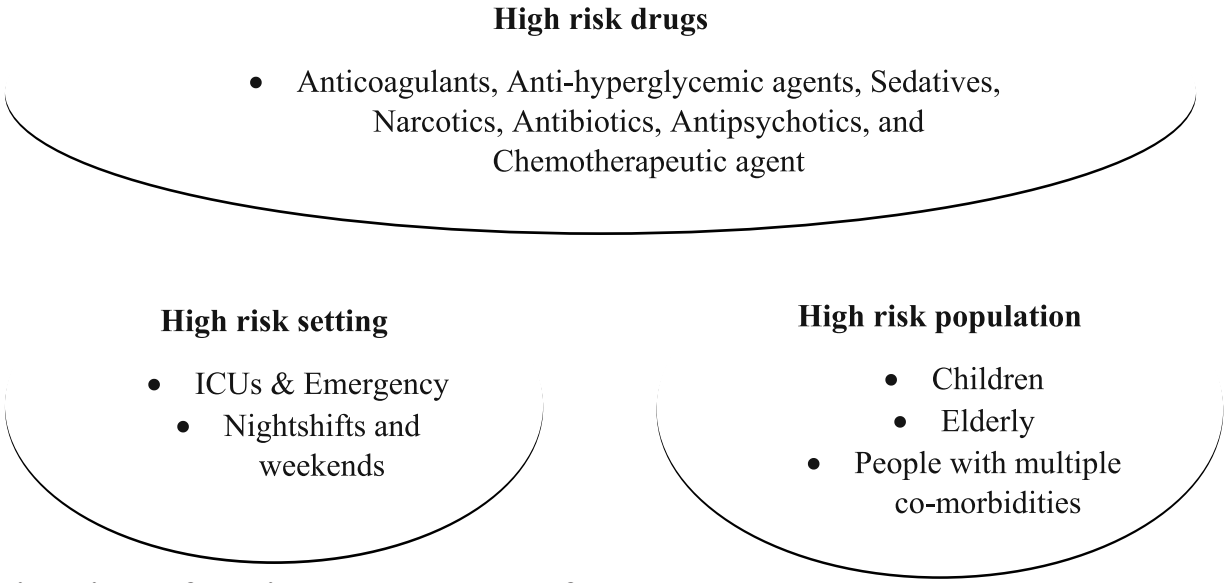

Fig.1. Situations of maximum occurrence of ME

Unsafe medication practices and medication errors are a leading cause of injury and preventable harm in health care systems across the world.

The relationship between medication errors and adverse drug events are shown in Fig.2. This shows that while medication error is a broad terminology for mistakes occuring in the process of drug ordering to patient receiving the drug, potential ADEs or "near misses" are medication errors that have a significant chance of causing harm to a patient. Intercepted potential ADEs are those that are caught by a system before an untoward event occured and non intercepted potential ADEs are those that unfortunately reached the patient but did not cause any significant harm. In addition ADEs are further classified into preventable ADEs if associated with a medication error and non preventable ADEs if due to other causes.

Types of medication errors

According to the American Society of Health System Pharmacists (ASHP)[14], MEs can occur at any of the following stages as depicted in Table I.

Severity of harm due to ME

The severity of adverse effects can be categorized according to WHO classification as follows[15]

Category A: Circumstances or events that have the capacity to cause error.

Category B: An error occurred but the error did not reach the patient.

Category C: An error occurred that reached the patient but did not cause patient harm.

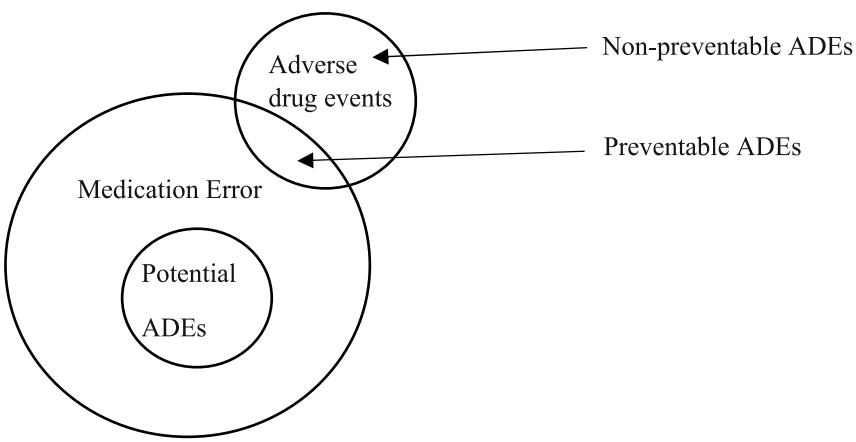

Fig.2. Relationship between ME and ADE

Table I. Types of Medication error

Prescription	Omission, incomplete and unclear orders, wrong drug, wrong time, wrong dose, wrong dosage form, patient allergy and wrong patient.
Transcription	Wrong drug name, dose, route, frequency, or patient.
Preparation	Wrong concentration, wrong drug, wrong dose, wrong base solution/ diluent, wrong volume, preparations made for the wrong patient, and preparations prepared for administration by the wrong route.
Dispensing	Suspension instead of syrup, wrong drug, wrong strength, wrong combination.
Administration	Wrong patient, wrong route, wrong dosage form, wrong time, wrong dose or rate and wrong drug may include errors of omission or missed doses, wrong rate or incompatibility at the site of the infusion, Accidental connections between enteral feeding tubing and epidural and/or IV tubing connections can have catastrophic patient effects.
Monitoring	Failure to monitor medication effects, incorrect interpretation of laboratory data used to monitor medication effects, incorrect transcription of laboratory test values, incorrect timing of monitoring, incorrect timing of serum concentration monitoring.

Category D: An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

Category E: An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.

Category F: An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G: An error occurred that may have contributed to or resulted in permanent patient harm.

Category H: An error occurred that required intervention necessary to sustain life.

Category I: An error occurred that may have contributed to or resulted in the patient's death.

Risk factors for the occurrence of medication errors[16]

Various risk factors have been identified for the occurrence of ME. Of these, increased workload in terms of hours of work, days of work, number of patients cared for and complexity of work plays a major role. More number of shifts, inadequate briefing during handover, unclear hand-over notes and handover gaps are other factors. ME incidence increases when there is lack of expertise, qualification and experience amongst the health care workers along with insufficient training, upgrading of knowledge and opportunities for their further training. If there is inadequate communication among health professionals, unhealthy working relationship, varied emotional condition of colleagues, poor conflict resolution and staff/patient relation there are more chances of an error occurring.

Lack of appropriate technologies such as computer aided diagnosis, digital prescription and ordering can result in occurrence of more manual errors. Inaccurate prescription can result from poor legibility of handwriting, typographical error, or improper labelling of the medications. Others include lack of patient/relative participation in reporting as they may be unaware about the diagnosis, dosage and dosage regimen of drugs.

Causes for more incidences in PICU

The ME rate in paediatric patients is almost three times higher than the rate for adults.[17] This could be attributed to the fact that the ICU is comprised of complex and highly intense settings with varied number of medications administered for each patient and requiring more of injectable drugs. The pediatric population are more vulnerable because they are smaller in size, fragile with immature organ systems and they lack the ability to verbally express pain or physical discomfort, which could imply an overmedication when treating these symptoms. In addition, for each child, weight based calculation of drugs are done which increases the chance of error occurrence.

How to approach an error?

Swiss cheese pattern of medication errors James Reason explains the ME using Swiss cheese as a model (Fig.3).

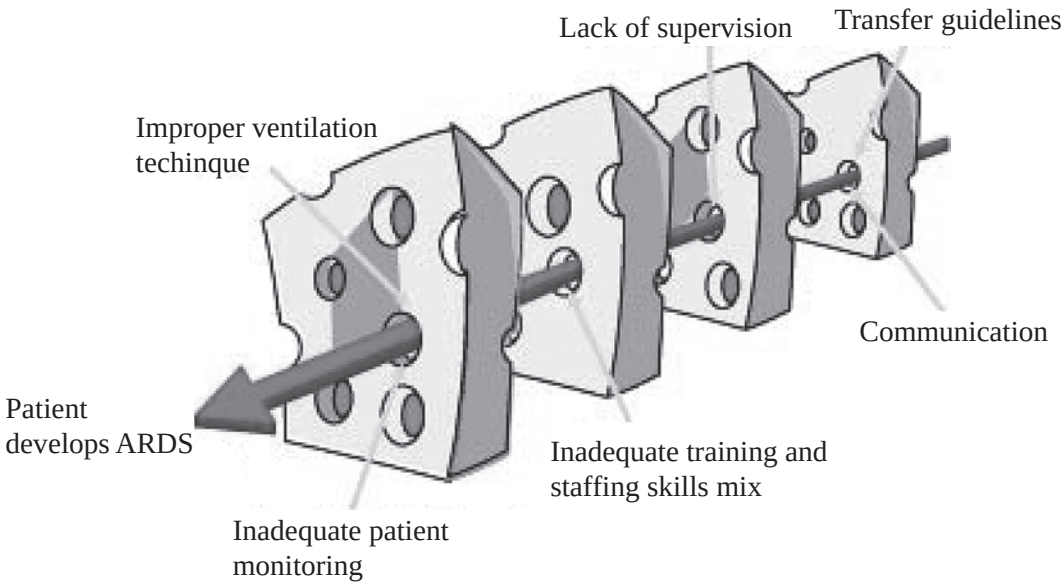

Fig.3. Swiss cheese pattern of medication error

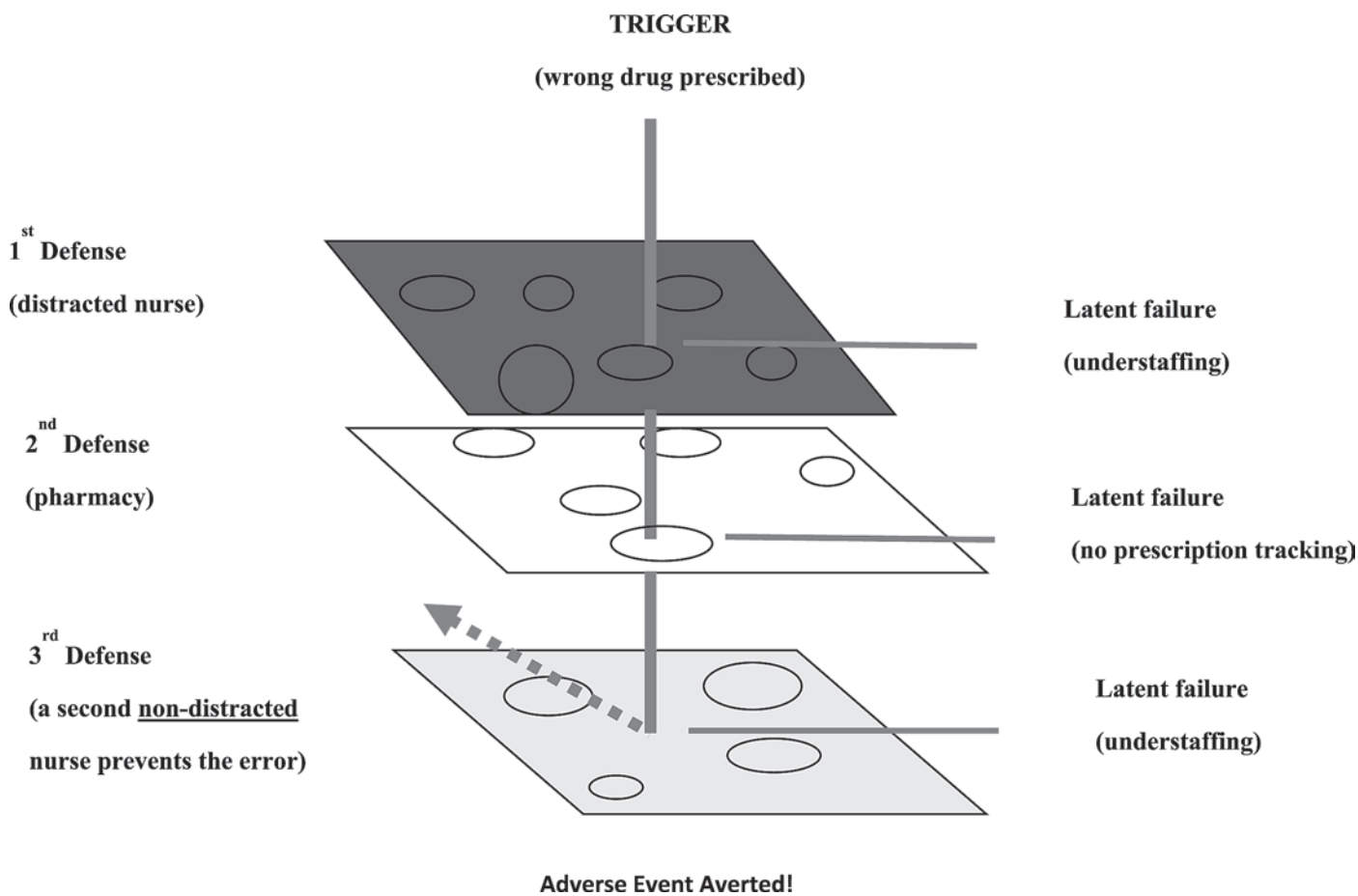

Fig.4. Swiss cheese model of how ME can be avoided

Quality indicators of ME (Table II)[19]

Table II. Quality indicators for ME

Indicator	Criterion	Measure: Rate	Target
Patients with MEs	Patients in whom an error was detected at any stage of the pharmacotherapeutic process.	(No. of patients with ME / Total number of patients) x 100	40%
MEs per patient	Errors detected by patient.	(Total number of MEs detected / Total number of patients) x 100	1

According to him, our defences against adverse events are imperfect like slices of Swiss cheese. These holes continually open, close, and shift their locations. An adverse event occurs when the holes in many layers of defence momentarily line up (Fig.4).

How to approach a medication error [18]

There are two types of approach to medication error. One is the "person approach" which is based on assigning blame, focuses on individuals and is punitive in nature. Another is the "systems approach" which is based on preventing recurrence of errors by focusing on system vulnerabilities that allow errors to occur and actions that can be taken to mitigate them.

Risk reduction / Prevention strategies[14]

1. Safe medication practices

- Supportive environment - key supporting elements include a culture of safety that is supported at all levels of the organization, an event-reporting system, an interdisciplinary medication safety team, a continuous improvement project regarding evaluation of errors and harm and strong designs that assess and reduce the risk of errors.
- Supporting the second victims, i.e., healthcare providers who are involved in an unanticipated adverse patient event, a medical error, or a patient-related injury
- Having a medication safety leader, who plays a crucial role. Use of proactive risk assessment tools for risk assessment which are available in Institute for safe medication practice (www.ismp.org/selfassessments/default.asp)
- Reducing the risk of errors- to make a specific list of high alert medication with the hospital's patterns of medication use and harmful events. Examples include:
  - Using oral syringes that cannot be connected to i.v. tubing ports along with education on the existence of oral syringes and its safe usage.
  - Using epidural tubing without ports.
  - Dispensing oral and parenteral medications in ready-to-administer formulation.
  - Independent double checks should be applied.

2. Selection and procurement

- Having a well-made formulary system will help clinicians to prescribe the safest and most cost-effective medicine for treating a particular condition.
- It also helps to standardize the content of pharmacy information system
- In addition, the pharmacist should review if the particular medication has any safety issues, especially dosing or duration limitations, admixture or administration handling precautions, specific requirements on storage or waste, management of extravasations and significant serious adverse effects.
- Use of standard checklist for medication safety review in formulary.
- Hospitals should standardize and limit the number of medication concentrations available.
- Safety alert monitoring: continuous monitoring of the literature for new medication safety warnings, review and analysis of the institution's medication error reporting data.
- Safe procurement - pharmacy department should take responsibility for all procurement of medications within the organization. Medication should not be brought in from outside sources without collaboration with the pharmacy department.
- They should have a process to communicate medication shortages, including alternatives and

substitution protocols to prescribers and other clinical staff; to address shortage and its correction, once shortage resolves.

3. Storage

- Steps to be taken to minimize selection of the wrong product or dosage form in the pharmacy. eg: separate frequently confused pairs, segregate high-alert medications and look alike sound alike (LASA) medications, use labelling and alerts when appropriate, etc.
- Same nomenclature should be used throughout entire medication use process (ER, ICU, pharmacy, smart pumps, etc)
- A system for rotating stock must be established, and all areas should be monitored for expired medications and storage at appropriate temperatures
- Specific medications that should not be stored outside of the pharmacy include
    - concentrated electrolytes (i.e., potassium chloride, 3%sodium chloride)
    - concentrated oral opioid solutions
    - concentrated insulin u-500
    - sterile water in bags
    - concentrated epinephrine multidose vials
    - neuromuscular blocking agents
- Use of automated dispensing cabinets with ready to use preparation

4. Patient admission

- Obtaining a medication history and performing medication reconciliation on admission are very important.

The process of medication reconciliation has three steps as follows[20]

- Verification - to review the patient's medication history and develop an accurate list of medications.
- Clarification - to ensure that the medications and doses are appropriate and use the current list when writing medication orders.
- Reconciliation - to identify any discrepancies between medication ordered for patients and those on the list, make appropriate changes to the orders, document any changes, and communicate the updated list to the next provider within or outside the hospital. Written information on the medications should be provided to patients when discharged from the hospital.

5. Prescription and transcription

- Prescribers should stay updated about the current state of pharmacotherapy practices and clinical practice guidelines
- Medication orders should be complete and in compliance with the hospital's medication order policy.
- The intent and indication of medication orders should be clear.
- Prescriber should follow certain guidelines such as:
    - type or write out instructions and avoid using abbreviations
    - Should not use vague or blanket instructions, such as "take as directed" or "resume pre op meds".
    - limit the number of as-needed orders
    - avoid range-of-frequency orders
    - specify exact dosage strengths (such as milligrams or milliliters) rather than dosage form units (such as 1 tablet or 1 vial).
    - prescribe by standard nomenclature, using the drug's generic name or trademarked name (if deemed medically necessary).
    - should be both in units/weight and total individual dose, if possible.
    - use a leading 0 before a decimal expression of <1 (e.g., 0.5 mL) always.
    - metric system to be used.
- Maximize the use of computerized prescriber order entry (CPOE).
- All unclear orders should be regarded as potential errors, as staff should not have to interpret what the physician is ordering
- Verbal or telephonic medication orders should be reserved only for emergency or compelling situations. The recipient must read back the order to the prescriber slowly. While reading back, the medication name should be spelled out and the drug dosage (e.g., 25 mg. should be repeated as "two-five") and directions must be confirmed.

- Use of hold orders should be avoided as much as possible.
- Automatic dosing protocols, such as therapeutic class substitutions/interchange, IV.-to-oral switch, renal dosing, dose rounding, and automatic stop orders, should be clearly written or placed into the patient chart.
- Pharmacists must prospectively review all medication orders before the preparation and dispensing of medications, with only a few exceptions in emergency.

6. Preparation

- Preparation of the medications should occur under appropriate conditions that is clean, ventilated and secure room with temperature, light and moisture control.
- An independent double check of the preparation should be done by a licensed pharmacist.
- Double check should include verification of the ingredients used, the quantities of the ingredients, and the expiry dates of all components.
- Medications should be available for In-patient use in unit-of-use and ready-to-administer form without further manipulation by the administering person.
- Personnel should have knowledge of storage requirements, expiry dates of products, and beyond use dates of preparations to ensure that a properly prepared compound maintains its integrity during the transport and storage phases.
- IV Workflow software and technology must be used for the preparation of sterile admixtures. eg: obtaining 12% Dextrose from 5% and 25% Dextrose, software will give how much ml. to be taken to get required conc.
- Products intended for other routes (e.g., potentially containing particulates or pyrogens or not sterile) should not be dispensed in an IV bag to avoid inadvertent administration by the parenteral route.

7. Dispensing medication

- Pharmacists should participate in a self-checking process in reading prescriptions, labelling (drug or ingredients and pharmacist-generated labelling), and dosage calculations.
- High-alert drug products should be independently double checked by a second individual before dispensing.

8. Administration

- The “5 rights of medication administration” are - the right patient, the right drug, the right dose, the right route and the right time should be checked before administration.
- Designing new devices that do not allow to connect unrelated delivery systems.
- Barcode-assisted medication administration (BCMA) can improve medication safety by verifying that the right drug is being administered to right patient.
- Administration of IV. medications via smart infusion pumps.
    - Pumps that include built-in medication libraries or guidelines that provide a range for safe administration doses, concentrations and rates of administration.
    - If excessive alerts are created, alert fatigue will occur and key safety information alerts will be bypassed.
    - Quality-improvement data programs to generate reports
- Education and training should be conducted periodically or as needed and documented in the staff competency files.
- Patients should also be educated about their drugs, so that they can act as a final check in preventing error.

9. Monitoring

- Guidelines for the correct time to obtain blood for serum concentrations and laboratory values should be created collaboratively by pharmacists, nurses, physicians and laboratory staff.
- Critical values should be determined with action alerts generated electronically for clinicians.
- Root causes like distractions, interruptions, workload, lack of training, confusing protocols and incorrect documentation should be addressed.
- Standardization of medication administration timings and pertinent monitoring timings should be built into the workflow as much as possible. e.g. Factor Xa level in relation to enoxaparin dose timing.
- All values should be documented with time and date so that the clinician reviewing the data has the proper frame of reference for the values.

10. Patient discharge

- Proper medication reconciliation process before discharge.
- Education and counselling are most effective when conducted in a room or space that ensures privacy and opportunity to engage in confidential communication of patient.
- The practice of carrying an updated list of medications that the patient is on should be encouraged.

11. Evaluation

- **Root cause analysis (RCA)** is done to identify system vulnerabilities after an event or close call and to develop an action plan that will prevent the same event from occurring again or at least minimize the possibility of reoccurrence. The RCA should be conducted and recommendations should be implemented within a timely manner.
- **Medication-use evaluation (MUE)** is a performance improvement tool that evaluates specific medication issues or audit a specific high-alert medication, a frequently occurring event, or any other high-alert or error-prone system or medication.
- **Quality improvement** is a systematic and continuous analysis of actions that lead to measurable improvement in healthcare services and the health status of targeted patient groups.
- **Event detection**[9] - This is done using the methods as follows:
    - Voluntary reporting by clinicians

      Limitations include underreporting due to time constraints, lack of adequate reporting systems, fear of litigation, a reluctance to report one's own errors, uncertainty of the clinical importance of the occurred events, and the lack of changes or response after reporting.
    - Medical record or chart review is a more systematic method

      Limitations are time-consuming, absence of electronic medical records, paucity of resources for performing the reviews, failure to standardize the terminology, variability in the terms used to label adverse events, and spelling mistakes.
    - Direct observation by trained staff is regarded as the most effective method

      Limitations are need of a trained clinical research assistant/ pharmacists and more time consuming
    - Automated computerized surveillance - to monitor a large patient population continuously, provide real-time surveillance information.

      Limitations include need of computer skilled personnel, chance of error in choosing drop down list
    - Reports by patients and family members

Limitation are patients may be critically ill to recognize error or afraid to ask questions.

Combination of these methods to get robust reporting of medical errors and adverse events is important to obtain a whole picture of care delivery in the ICU.

Pharmacovigilance centers

India has pharmacovigilance centres funded by the World Bank for reporting scanning instances of adverse drug reaction since January 2005. They form a network of regional and peripheral centres at medical colleges in several states and are responsible for collecting and interpreting the data, and for reporting their findings to the Drug Controller General of India.[21]

Challenges of typical pharmacovigilance centers[21]

1. Lack of spontaneous reporting due to lack of awareness.
2. Inconsistency in reporting (more reporting generally seen after a meeting or awareness program).
3. Difficulty in recruiting new reporters by the pharmacovigilance staff (new recruiters tend to join because of their peers and not the pharmacovigilance staff).
4. Lack of improved infrastructure in terms of scientific support, academic resources, staff training, dedicated telephone line and internet access.
5. Lack of comparison of the reports generated by a single center to the global database.
6. Lack of feedback about the activities of other centers.
7. Lack of indicators for assessment of quality of the reports generated at the center.
8. Lack of national internet assessable error reporting software like the ones prevalent in the western countries.

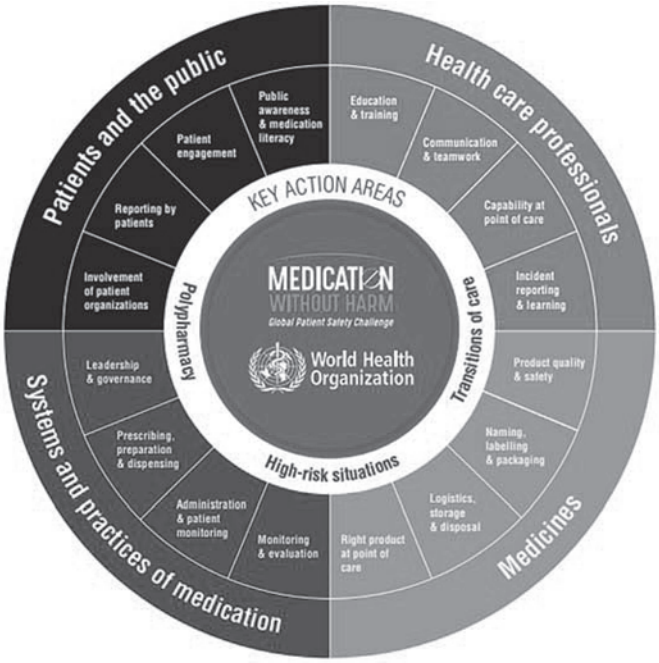

Fig.5. WHO strategies to prevent ME

Communication is an important tool to convey medication safety information. Any "message" must be received, understood and acted upon appropriately before any statements are made on the success of the communication.

WHO initiative on patient safety[22]

WHO Patient Safety Flagship (2020) has initiated a series of monthly webinars on the topic of "WHO Global Patient Safety Challenge: "*Medication Without Harm*". Contemplating the huge burden of medication-related harm, medication safety has been selected as the theme for World Patient Safety Day 2022. The World Health Organization has made reducing patient harm due to MEs as its current global patient safety challenge with the aim of reducing severe harm associated with MEs by 50% within 5 years. The strategies to prevent MEs by WHO are shown in Fig.5.

Conclusion

We should try and understand the causes of errors, to implement an informative reporting system of adverse events as an essential prerequisite, to measure them, and to choose the best approach for minimizing the harm to patients. A New Health System for the 21st Century" attributes medication errors to system failures or errors.[21] The work environment should be designed in a way that minimises errors: as stated by Reason, "We cannot change the human condition, but we can change conditions under which humans work."[18] Burn out syndrome can adversely affect healthcare worker performance, thereby contributing to medical errors and adverse events.[23] So it is time to change our system and not to blame to ensure our patient safety.

Points to Remember

- ***Prescription errors and medication administration errors are the most commonly encountered medication errors.***
- ***Preventable adverse drug events are those that occur due to medication errors that can be avoided.***
- ***Medication error rate is more in the pediatric patients especially those in ICU due to their vulnerability and high risk category.***
- ***Safe medication practices are imperative in the prevention of medication errors to avoid harm to the vulnerable patients.***
- ***Appropriate drug safety monitoring and pharmacovigilance are needed in every hospital to screen for these medication errors.***
- ***Once an error has occurred, the root of the problem should be identified and rectified immediately to avoid recurrence in the future.***

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CLIPPINGS

Burosumab in management of X-linked hypophosphataemia: a retrospective cohort study of growth and serum phosphate levels

This single-centre retrospective review compares clinical outcomes in children with X-linked hypophosphataemia (XLH) on long-term burosumab treatment who achieved normal phosphate versus those who did not. Growth and bone mineral profile biochemical markers of bone health in those who did compared with those who did not achieve normal plasma phosphate concentration. 55 children with XLH with median age of 11.7 years were included. 27 (49%) had low plasma phosphate concentration and 27 (49%) had normal phosphate after a median burosumab treatment duration of 3.3 years. 1 (2%) did not have a recent phosphate level recorded. No difference in growth was found between normal and abnormal phosphate groups (p=0.9). Authors concluded that young children with XLH had sustained growth on long-term burosumab treatment, although plasma phosphate had not normalised in many. Therefore change in burosumab dosing recommendations may be made to target normalisation of alkaline phosphatase, as against plasma phosphate concentration.

Walker EYX, Lindsay TAJ, Allgrove J, Marlais M, Bockenhauer D, Hayes W, et al. Burosumab in management of X-linked hypophosphataemia: a retrospective cohort study of growth and serum phosphate levels. Arch Dis Child 2023;108:379-384.

DRUG PROFILE

DOSAGE ADJUSTMENTS FOR ANTIFUNGAL DRUGS IN CHILDREN WITH RENAL IMPAIRMENT

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****Jeeson C Unni**

Abstract: *Immunosuppressed pediatric patients and newborns, particularly preterm babies are at high risk for fungal infections. Most of the times these children are critically ill and have coexisting renal and liver impairment. Appropriate dosing of these agents are extremely crucial for proper management of the infection and prevention of toxicity at the same time. It is important to know the drug dosages and pharmacokinetics of commonly used systemic antifungals.*

Keywords: *Antifungals, Renal impairment, Amphotericin B, Fluconazole, Itraconazole, Voriconazole, Caspofungin, Micafungin.*

This article is the second of the three articles planned as a series covering the dosage adjustment for antivirals, antifungals and antibiotics in renal impairment. The basic concepts of glomerular filtration rate (GFR) calculation and principles of dose adjustment have already been discussed.[1] Kindly refer to that for further information. This article focuses on the dose adjustment for anti fungals in the setting of renal impairment.[2]

The commonly used systemic antifungals can be divided into four groups namely a.Polyenes, b.Azoles, c.Echinocandins, d.Others.

a.Polyenes

Amphotericin B (D-AmB and L-AmB)

Conventional AmB is complexed with deoxycholate (D-AmB), a detergent, to make the drug soluble in water. It quickly disassociates from its carrier after infusion and becomes highly (>95%) protein bound. AmB is not metabolised and two-thirds of D-amB doses are excreted unchanged in the urine and feces. Standard dosing of D-AmB in neonates and children is 1mg/kg/dose, but dosages as high as 1.5mg/kg/day OD could be considered in serious or resistant infections.To reduce the likelihood of infusion reactions, D-AmB should always be administered as a slow infusion.

Lipid preparations of AmB were specifically designed to be renoprotective.[3] Approximately 2-5% of the dose is excreted unchanged in the urine. The excretion of liposomal amphotericin (L-AmB) has not been studied and the metabolic pathways are unknown, however due to the size of the liposomes the degree of glomerular filtration and renal elimination is very low and it is not removed by dialysis. Dose of L-AmB is 3-5mg/kg/day 24 hourly.[4]

Nephrotoxicity (reduction in GFR) and electrolyte lossess are the major adverse events associated with AmB. Nephrotoxicity occurs in 15% to >50% of children and hypokalemia requiring supplementation occurs in upto 40% of children so frequent monitoring is warranted.

No dose adjustment is needed in renal impairment, hemodialysis, peritoneal dialysis or continuous renal replacement therapy (CRRT).

b.Azoles

Triazole antifungals (the first triazole, fluconazole), newer triazoles such as itraconazole, posaconazole and voriconazole, have extended spectrum of activity against invasive filamentous fungi, such as Aspergillus species.

Fluconazole

Fluconazole is a hydrophilic molecule with low protein binding and is well absorbed. It is predominantly renally cleared, with approximately 80% of a dose excreted unchanged in the urine. Fluconazole is used both for prophylaxis and treatment. Dosages are given in Table I.[5]

In GFR>50 ml/min, no dose adjustment is needed. In GFR <50 ml/min, normal dose is given initially, followed by 50% of the dose. Fluconazole is dialyzable hence

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Table I. Fluconazole dosage for prophylaxis and treatment

Prophylaxis dose	Treatment dose
< 2weeks of life: 3mg/kg 72 hourly PO/IV	<2weeks of life: 6-12mg/kg 72 hourly IV/PO
2-4weeks of life: 3mg/kg every 48 hours PO/IV	2-4weeks of life: 6-12mg/kg (max 800mg) every 48hours PO/IV
>4weeks of life: 3mg/kg (max 400mg) every 24 hours PO/IV	>4weeks of life: 6-12mg/kg 24 hourly PO/IV

PO- per oral, IV- intravenous

Table II. Voriconazole dosage intravenous and oral route

Intravenous dose	Oral dose
<2 years of age –IV: Loading dose of 6mg/kg every 12 hours for two doses, followed by 4mg/kg every 12 hours	9mg/kg (max350mg) every 12hours. If response is inadequate, the enteral dose may be increased by 1mg/kg increments or by 50mg increments if the patient is on 350mg.
2-14 years-(<50 kg)- IV: Loading dose of 9mg/kg every 12 hours for two doses, followed by 8mg/kg every 12hours. If response is inadequate, the IV dose may be increased by 1mg/kg increments. If treatment is not tolerated, dose may be reduced by1mg/kg decrements.	If treatment is not tolerated, dose may be reduced by 1mg/kg decrement or by 50mg decrement if the patient is on 350mg.

50% of normal dose is given in hemodialysis (HD)/ peritoneal dialysis (PD) or 100% dose is given post hemodialysis session thrice weekly. In CRRT, upper range of normal dose is given.

Itraconazole

The dose of itraconazole recommended in children is 3-5mg per kg per day but higher doses up to 8 mg per kg per day can be used. It is extensively metabolised in liver by CYP 3A4 enzymes and are prone for multiple drug interactions. The IV formulation of the drug has a carrier-hydroxy propyl-beta-cyclodextrin which accumulates in renal failure and is best avoided in children with GFR<50 ml/min. Itraconazole needs caution when using in children with hepatic dysfunction.

Voriconazole

Voriconazole is a structural analogue of fluconazole but with wide spectrum of activity. It was the first triazole to demonstrate better efficacy in comparison to Amphotericin B in the treatment of invasive aspergillosis. It is extensively metabolised in the liver and almost all metabolites including the main circulating metabolite, Voriconazole N-oxide is renally eliminated. The pharmacokinetics of Voriconazole is non linear and significant inter individual variability. The dosages are given in Table II.[6]

In renal dysfunction oral preparation does not need dose modification. Regarding IV preparation, if GFR is less than 50ml/min it is better to avoid the drug due to chance of accumulation of the carrier molecule. Voriconazole is not removed by dialysis hence no dose adjustment is needed in HD, PD or CRRT, but should be used with caution, only if benefits outweigh risks.

c. Echinocandins

Echinocandins inhibit β (1-3)-glucan synthase and prevent fungal cell wall synthesis. They have potent fungicidal activity against yeasts, mostly Candida species and fungistatic activity against Aspergillus species. They have little or no activity against *Cryptococcus neoformans*, *Trichosporon species* and Mucorales.[7] Echinocandins are large molecules with poor bioavailability and are only available for parenteral administration. Caspofungin and Micafungin are the echinocandins available for pediatric use. They are highly protein bound (92-99%) and have long half-lives in plasma of upto 24 - 72hours.

Table III. Dosage of caspofungin in various age groups

Age groups	Dosage Schedule
Infants up to 3months	25mg/m^2 24 hourly
3 months to1year	50mg/m^2 24 hourly
Children 1-18 years	70 mg/m^2 as a loading dose followed by 50 mg/m^2 for maintenance 24 hourly

Caspofungin

Caspofungin undergoes spontaneous degradation and further metabolism involves peptide hydrolysis and N-acetylation in the liver. 35% of dose is excreted in feces and 41% in urine as metabolites. Clearance and volume of distribution of caspofungin are closely related to body surface area (BSA) than weight and dosing is based on BSA (Table.III).[8]

No dose adjustment is needed in renal failure. It is not dialyzable hence no adjustment is needed in patients on dialysis, but dose adjustments are recommended in patients with hepatic dysfunction. It is advisable to reduce dose by 30% in the presence of moderate hepatic dysfunction

Micafungin

Micafungin undergoes hepatic metabolism and excretion in the faeces. Less than 1% of the dose is removed through kidneys.[9]

The dosages of micafungin are as follows:

Age<4weeks: 2mg/kg IV once daily, increased upto 4mg/kg IV once daily (if inadequate response)

4weeks to <40 kg: 2mg/kg IV once daily, increased upto 4mg/kg IV once daily (max200mg)

Weight >40 kg: 100mg IV once daily (increased upto 200mg IV once daily if inadequate response)

Children show inverse relationship between weight and clearance of micafungin. As weight decreases, relatively larger dosages are needed to attain similar concentration. So European guidelines advocate higher doses upto 5-10mg/kg/day in neonates and infants, especially in those with disseminated candidiasis and CNS infections.

No dose adjustment is needed in renal failure or dialysis. Even though no dose adjustment is required in renal impairment, micafungin should be used with caution,as it may cause further deterioration in renal function. No adjustment is needed in mild-to-moderate hepatic impairment; the effect in severe hepatic impairment is not known.

D.Others

Flucytosine, terbinafine and griseofulvin are the other systemic agents which may be used in certain situations.

Flucytosine

Flucytosine is one of the oldest antifungal drugs and is active in vitro against many yeasts. Its clinical utility is limited to adjunctive therapy for cryptococcal meningitis. Because of the rapid emergence of resistance it is not used as monotherapy and is almost always administered in combination with an AmB product.[10] The standard dosage of Flucytosine is 100 mg/kg/day divided every 6 hours, which is recommended for both children and adults.

Dose adjustment is needed in GFR below 40ml/min (Table.IV).

Table IV. Dose adjustment of flucytosine with various levels of GFR

GFR	Dosage Schedule
GFR 20 to 40 ml/min	25mg/kg orally 12 hourly
GFR 10 to 20 ml/min	25 mg/kg orally 24 hourly
GFR<10 ml/min	25 mg/kg every 48 hourly

Terbinafine

Terbinafine is FDA-approved for children 4years and older and is exclusively used for treatment of tinea infections and onychomycosis. It is administered orally. The dosage advised is 125 mg(<25kg), 187.5 mg(25 to 35kg) and 250 mg(35kg) once daily.[11] The renal dose modification is unclear but is advisable to avoid use if GFR less than 50ml/min.

Griseofulvin

Griseofulvin is a fungistatic antifungal with good activity against organisms that cause dermatophyte infections. The drug is made soluble through its preparation as microsize and ultra microsize particles, which increases the surface area of the drug and enhances its absorption. The dosage and duration of treatment depends on the site affected, age of the patient and type of preparation.

The dose for ultra microsize ranges from 5-15mg/kg/day divided in 12 hourly doses, not to exceed 750mg per day.

No dose adjustment is needed in renal dysfunction.

Conclusion

Systemic antifungals are commonly used in sick children in pediatric and neonatal ICUs. But luckily, most of the antifungals are metabolised through liver and may not need a dose modification in renal impairment which is also quite common in intensive care units. But few of them utilise CYP 3A4 enzyme system for metabolism and are prone for drug interactions, which has to be kept in mind. Some of the drugs need caution while using in children with hepatic impairment.

Points to Remember

- ***Systemic antifungals are commonly used in sick and immuncompromised children.***
- ***Most of the drugs except amphotericin B are not having significant renal adverse effects.***
- ***Few drugs need dose modification and must be used with caution, but are generally safe from renal point of view.***
- ***Drug interactions with drugs utilising CYPA4 enzyme are common, use of these drugs in hepatic impairment need caution.***

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CLIPPINGS

Efficacy of Nebulised Salbutamol with Ipratropium Bromide in Magnesium Sulphate Base in Acute Flare-up of Wheeze among Children Aged 1-12 years

Children (1-12 years) with acute flare-up of wheeze were randomized to receive either nebulized salbutamol with ipratropium bromide either in isotonic magnesium sulphate base(n=52) or in normal saline (NS) base (n=48). In the magnesium sulphate group none had moderate severity vs 8% in NS group ($p < 0.05$). The authors concluded that salbutamol nebulization in isotonic magnesium sulphate base results in signifcantly higher improvement in asthma severity scoring.

Rajashekar C, Shankar NC, Sharada RC, Nedunchelian K. Efficacy of Nebulised Salbutamol with Ipratropium Bromide in Magnesium Sulphate Base in Acute Flare-up of Wheeze among Children Aged 1-12 y. Indian J Pediatr. 2023; 90(5):520.

RADIOLOGY

EVALUATION OF PULMONARY TUBERCULOSIS - II COMPUTERIZED TOMOGRAPHY OF CHEST

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In the previous issue tuberculous (TB) disease patterns in the chest X-ray were discussed. Chest X-ray is sufficient to screen children with presumptive pediatric tuberculosis or those with a history of exposure. The chest X-ray is very simple and informative that it has almost replaced the sputum test as the initial specific investigation in the evaluation of suspected cases of tuberculosis in children. In overt disease the chest X-ray shows the type and extent of involvement which can be followed to resolution. Imaging in general establishes the presence and extent of the disease but does not provide etiological diagnosis. While there is no doubt of the necessity of computerized tomogram (CT) in neurological tuberculosis, CT in pulmonary TB has a limited role. It is not mentioned in the guidelines or algorithm for evaluation of pulmonary tuberculosis. However, it cannot be denied that it has a place in certain clinical situations. It can be used in children with persistent pneumonia, persistent fever without focus, unchanging appearance in X-ray or any other lesion that needs further delineation. It can also be used as a tool for CT guided biopsy.

Some radiological manifestations of the disease in CT scans are discussed here.

Alveolar opacities: Just as in the X-ray, alveolar opacification in CT is seen as white shadows replacing black air filled lung. These appear as multiple, fluffy shadows with a peribronchial (Fig.1) or subpleural distribution usually in the lung apices or superior segments of the lower lobes. This is in accordance with the route of entry of infection and the sites of maximum ventilation. Only rarely is it lobar.

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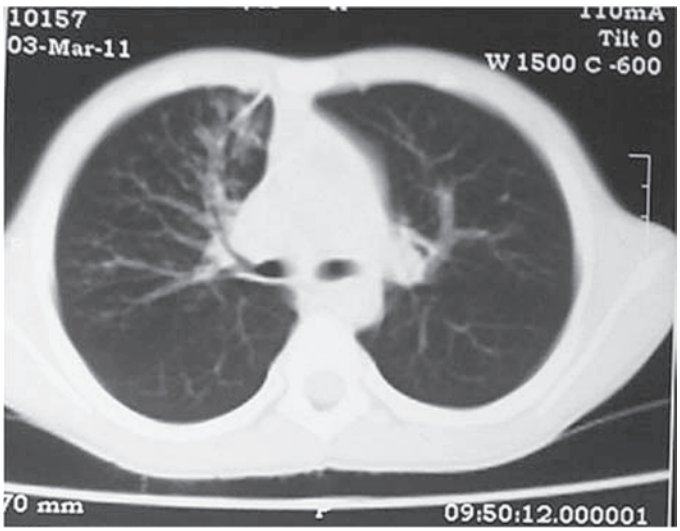

Fig.1. Peribronchial alveolar opacities

Bronchiolar opacities: Thin section high resolution computed tomogram (HRCT) can show inflammatory exudate in the pre-terminal bronchioles that supply the pulmonary lobule. The pulmonary lobule is the basic functional unit of the lung that is supplied by a pre-terminal bronchiole and a distal pulmonary arteriole and is bound by interstitial fibrous septa. The pre-terminal bronchiole is about 1mm in thickness and is normally not seen. But when they are distended by exudate and their walls are thickened by inflammation they become visible as small linear shadows with branching along with tiny nodular thickenings likened to a 'tree in bud' appearance. Fig.2 shows widespread tiny nodules, some of them

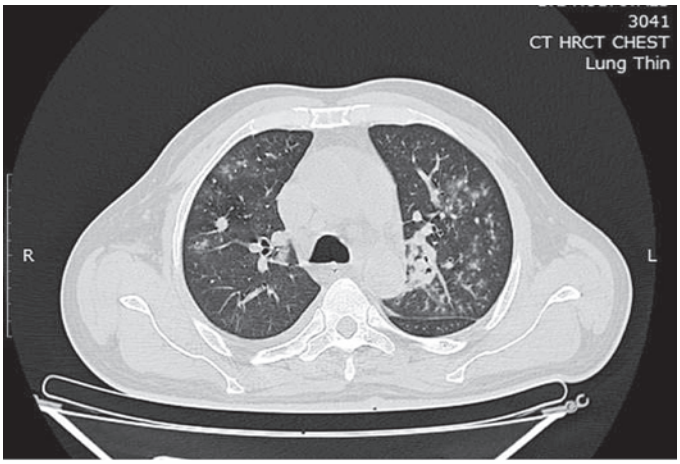

Fig.2. Tree in bud appearance

forming tiny branching linear shadows. The tree in bud appearance represents active inflammation and exudate in the tiny airways. When seen around a cavity or around consolidations they imply endobronchial spread of the infection. However, it should be remembered that the feature may be seen with all types of infection and inhaled irritants as also cystic fibrosis and connective tissue disorders. This detail is not seen in the plain X-ray.

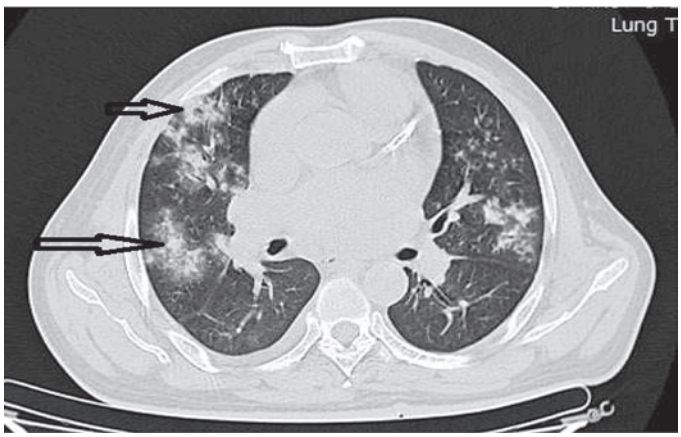

Fig.3. Granulomas and galaxy sign. There is cavitation in the anterior one (arrows)

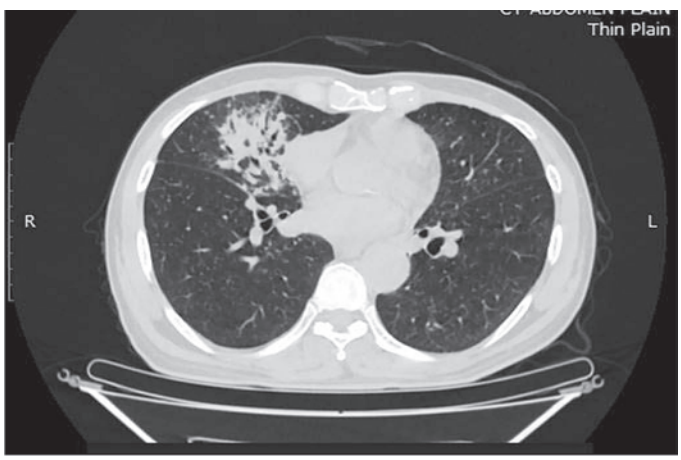

Fig.4. Consolidation with air bronchogram

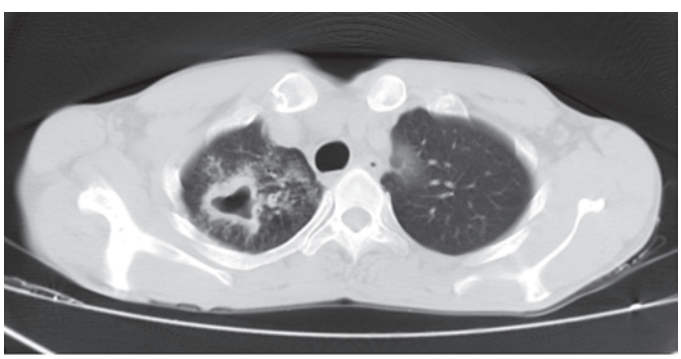

Fig.5. Cavity in right upper lobe

Consolidation and cavity formation: Coalescence of bronchiolar and alveolar opacities result in larger nodules as in Fig.3. A small round shadow in the centre, which is the granuloma, with clusters of tiny nodules around is called the galaxy sign (arrows). The one (short arrow) seen anteriorly also shows liquefaction or caseation within. Fig.4 shows an area of consolidation with characteristic air bronchogram. When the tissue in a larger area of consolidation breaks down, a cavity is formed. The cavity in Fig.5 shows a thick wall. There are surrounding opacities and tiny nodular shadows indicating active disease. Evolution to cavitary disease is rare in children unlike adults. Cavities can be secondarily infected. Cavities with air-fluid levels have been found to be due to secondary bacterial or fungal infection. They can also harbour fungal ball.

Lymphadenopathy: All the afore mentioned features do not compulsorily mean tuberculosis. The pathognomonic feature of the disease is the presence of hilar and mediastinal nodes. Parenchymal lesions along with enlarged regional nodes is strong evidence for tuberculosis. In Fig.6 there is an enlarged paratracheal node just behind the confluence of the left brachiocephalic vein with the right. Right paratracheal, hilar and subcarinal lymph nodes are the most common sites of nodal involvement. It may be seen with or without parenchymal infiltrates. In Fig.7, there are large mediastinal nodes with very distinctive, though not pathognomonic, rim sign consisting of a low density centre representing caseous necrosis and a peripheral enhancing rim due to granulomatous inflammation. Matting is reported to occur more often in children. Nodes can compress a bronchus or erode into a bronchus, usually the bronchus intermedius. CT is more sensitive than plain radiography in detecting tuberculous lymphadenopathy.

Miliary tuberculosis: Miliary TB is hematogenous spread of bacilli seen in primary and post primary TB and is commonly seen in chidren and immunocompromised

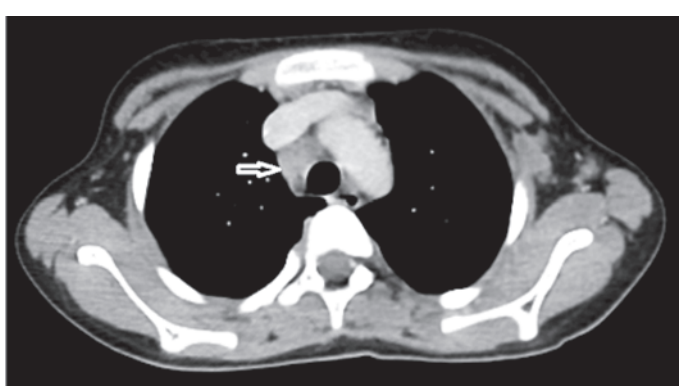

Fig.6. Paratracheal node

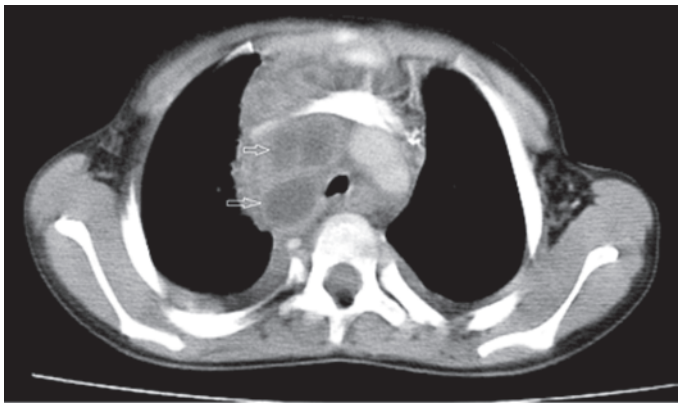

Fig.7. Multiple mediastinal nodes

adults. X-rays shows features about four weeks after the onset of symptoms. CT can demonstrate miliary TB much earlier. It consists of multiple 1 to 3 mm diameter nodules randomly distributed throughout both lungs. Other parenchymal lesions may coexist and thickening of interlobular septa may occur (Fig.8). In contrast to the nodules of tree in bud which are found a little away from the pleura and away from the fissures, the nodules of miliary TB have a random distribution.

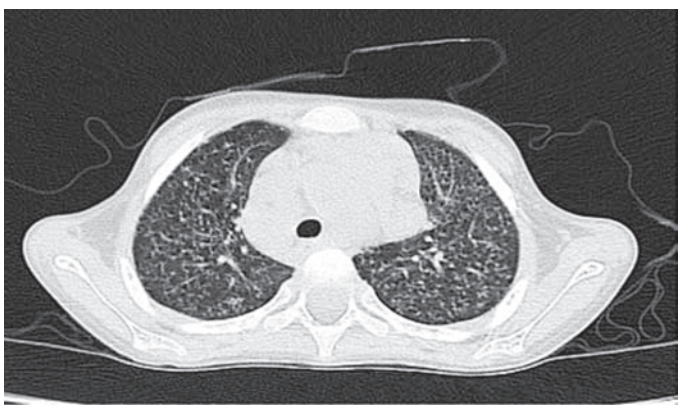

Fig.8. Miliary TB

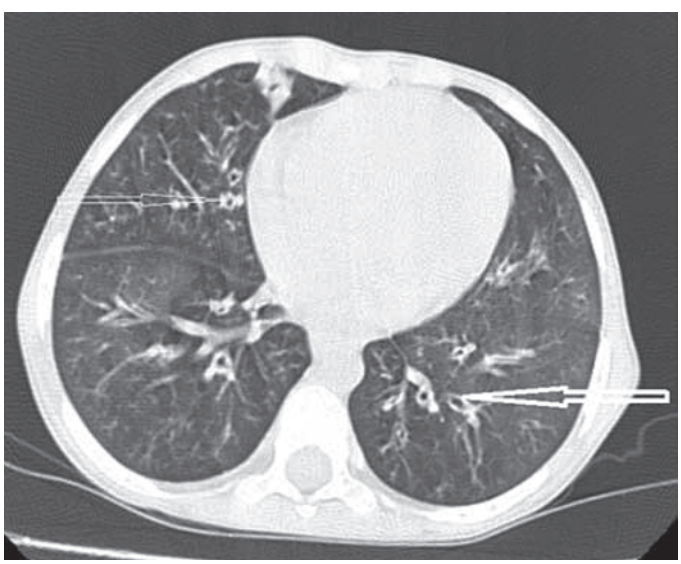

Fig.9.Bronchiectasis (Arrow points to bronchus)

Bronchiectasis: A common cause for bronchiectasis in children is cystic fibrosis especially if it is in the upper lobe and chronic, prolonged lower respiratory infection including tuberculosis, if it is in the lower lobe. Bronchial occlusion due to endobronchial tuberculosis leads to collapse of the distal lung, pent up secretions, destruction of the walls of the bronchi and irreversible dilatation. Bronchiectasis is diagnosed more often nowadays because of the widespread use of CT that clearly depicts the internal architecture of the lung. The normal bronchi are as wide as the accompanying branch of the pulmonary artery. In bronchiectasis the airway is wider (Fig.9). With progression of inflammation there is destruction of the intervening parenchyma and all that is left is a bunch of dilated bronchi as air filled cystic spaces (Fig.10) that get repeatedly infected.

Pleural fluid: When the chest x-ray reveals pleural fluid in suspected tuberculosis, pleural fluid analysis is the next step. The effusions that occur in older children as an immunological response to the bacterial antigen are free and large and devoid of septations. When pleura is involved

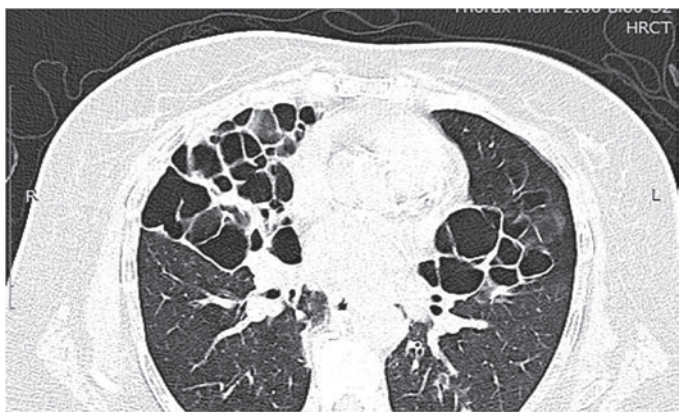

Fig.10. Advanced bronchiectasis

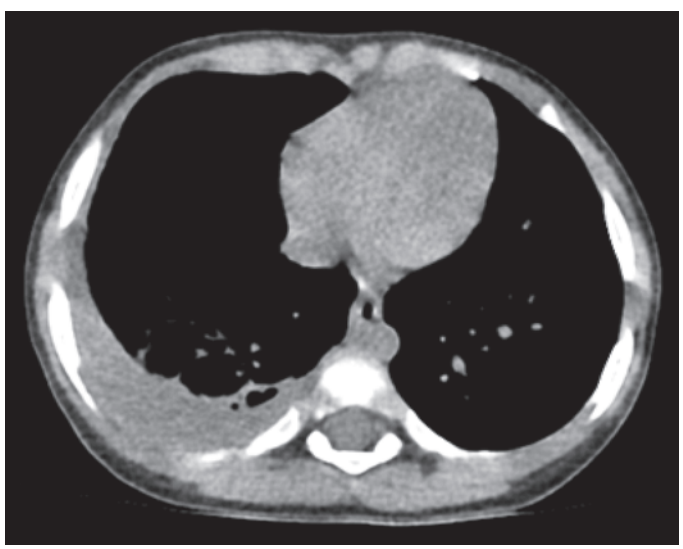

Fig.11. Pleural fluid-right

there is thickening, septations and turbidity. With contrast there is enhancement of pleura. Thin strands and turbidity of content is better appreciated only with ultrasound. CT can unveil lung that is masked by pleural fluid in the X-ray (Fig.11).

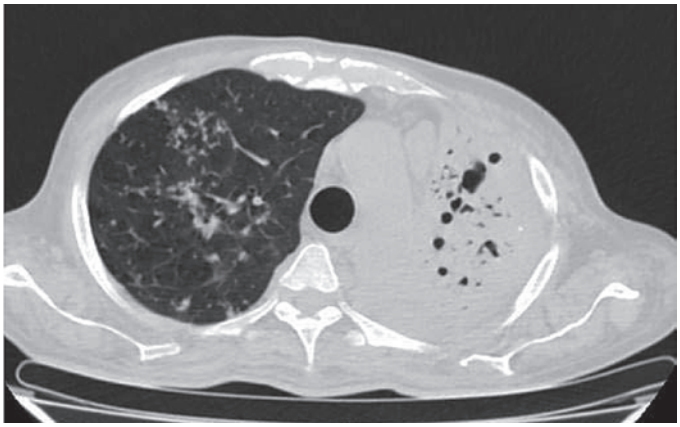

Fig.12. Destroyed left lung

Destruction of lung: Children with tuberculous infection are as prone to develop destruction of the lung as adults. The morbidity due to sequelae is a great burden due to their longer life. Fig.12 shows a collapsed left lung that shows only a number of cystic air spaces. The mediastinum is pulled to the same side. The right lung shows small nodular shadows of active inflammation.

Healed TB: Granulomas heal with calcification either within the lung parenchyma or in lymph nodes (Fig.13). Pleura heals with thickening and calcification. Cavity walls become thin, as inflammation in the wall and in the pericavitary area subsides. They may remain if communication with an airway persists or may contract and form a scar. Thin walled cavities look like pneumatoceles.

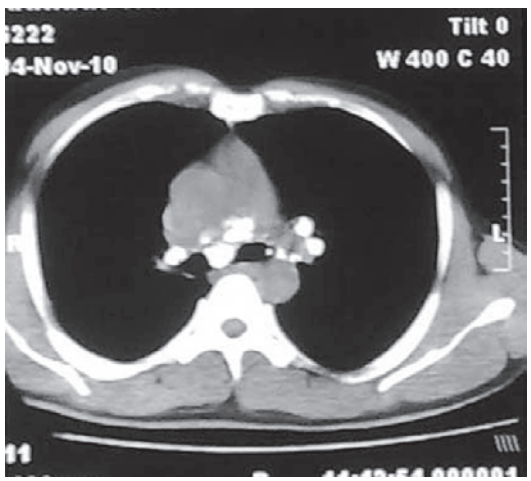

Fig. 13. Calcified nodes

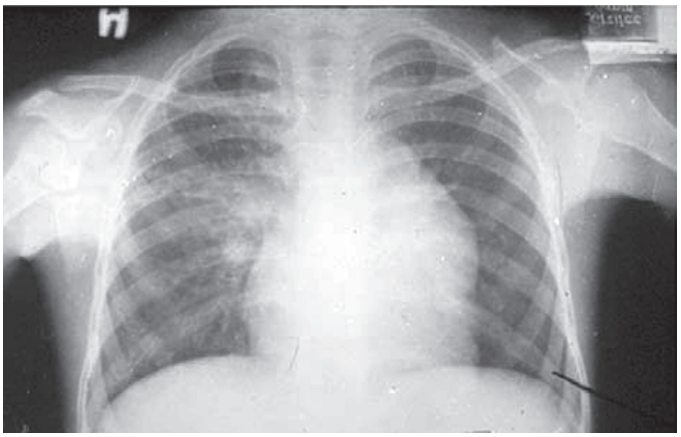

Fig.14. TB pneumonia with probable left hilar node (bulge)

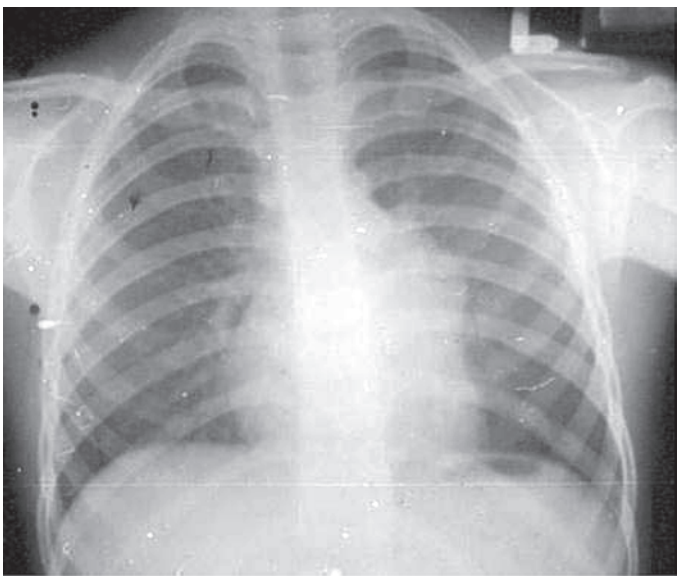

Fig.15. Resolved TB pneumonia. Persistent bulge

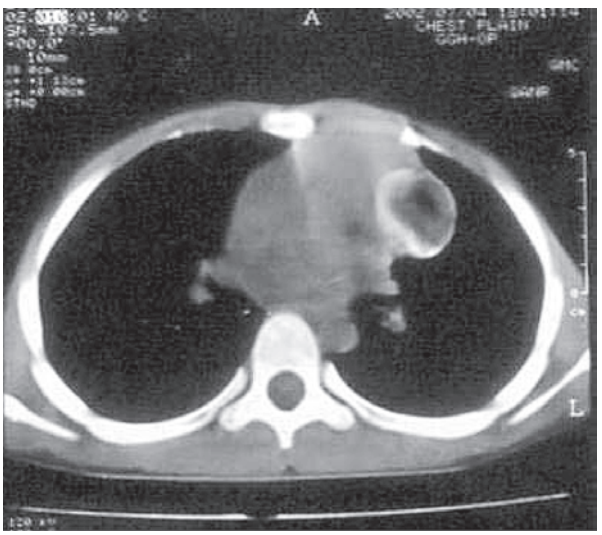

Fig. 16. CT showing mediastinal teratoma

TB with associated lesion: CT is useful for diagnosis of coexistent lesions. Fig.14, 15 and 16 are of a child who was diagnosed to have tuberculosis. There is a patch of pneumonia in the right parahilar region and a bulge in the left hilar region presumably due to nodes. Following ATT, the pulmonary lesion disappeared but the left hilar shadow remained. Subsequently CT revealed a mediastinal teratoma with calcification and fat containing foci the reason for the persistence of the left hilar shadow.

Conclusion: CT can resolve some diagnostic dilemmas due to its ability of cross-sectional imaging without superimposition as in the X-ray. Mediastinal involvement or lymphadenopathy is best seen in CT. Virtual CT bronchoscopy can reveal endobronchial tuberculosis and the airway beyond the stenosis can also be visualised. Information from CT, like small cavities, tree in bud changes and upper lobe involvement can point to probability of higher smear positivity and likely community spread. Persistent lesions, radiographic worsening or equivocal chest X-ray with absence of proportionate clinical or treatment response are also indications for CT.

CLIPPINGS

False-Positive Results in Rapid Antigen Tests for SARS-CoV-2

Concerns have been raised whether rapid antigen tests for SARS-CoV-2 can result in false-positive test results and undermine pandemic management for COVID-19. This study investigated the incidence of false-positive results in a large sample of rapid antigen tests used to serially screen asymptomatic workers throughout Canada.

Rapid antigen tests for SARS-CoV-2 were implemented as an extra layer of protection to control transmission in workplaces throughout Canada by the Creative Destruction Lab Rapid Screening Consortium (CDL RSC). Asymptomatic employees were screened twice weekly. Workplace participation was voluntary. From January 11 to October 13, 2021, tests were conducted by employees, with some workplaces providing at-home screening and others on-site screening programs. Over this period, Canada experienced 2 significant Delta variant–driven waves from March to June and August to October. Screening results were recorded, including a deidentified record identifier, the place of employment, the test, and (optionally) the lot number. If a test result was positive, the patient was immediately referred for a confirmatory polymerase chain reaction (PCR) test to be completed within 24 hours. Initial data validation was completed at the point of collection. False-positive results were matched to lot number and test manufacturer. A false-positive result was defined as a positive screen on a rapid antigen test and a subsequent negative confirmatory PCR.

The number of false-positive results was 462 (0.05% of screens and 42% of positive test results with PCR information). Of these, 278 false-positive results (60%) occurred in 2 workplaces 675 km apart run by different companies between September 25 and October 8, 2021. All of the false-positive test results from these 2 workplaces were drawn from a single batch of Abbott's Panbio COVID-19 Ag Rapid Test Device.

The overall rate of false-positive results among the total rapid antigen test screens for SARS-CoV-2 was very low, consistent with other, smaller studies. The cluster of false-positive results from 1 batch was likely the result of manufacturing issues rather than implementation. These results inform the discussion of whether rapid antigen tests will result in too many false-positives that could overwhelm PCR testing capacity in other settings. 1,2 3

Also, the results demonstrate the importance of having a comprehensive data system to quickly identify potential issues. With the ability to identify batch issues within 24 hours, workers could return to work, problematic test batches could be discarded, and the public health authorities and manufacturer could be informed. Aside from issues with the batch, falsepositives are possible due to the timing of the test (ie, too early or too late in the infectious stage) or quality issues in how the self-test was completed.

Limitations of the study include the convenience sample of workplaces and that reporting of PCR confirmatory results and identification of lot number was not compulsory. In addition, these results reflect the epidemiology experienced in Canada and may not generalize to other countries experiencing different COVID-19 incidence.

Gans JS, Goldfarb A, Agrawal AK, Sennik S, Stein J, Rosella L. JAMA. 2022;327(5):485-486. doi:10.1001/jama.2021.24355.

CASE REPORT

ADENOVIRUS PNEUMONIA WITH HEMORRHAGIC PLEURAL EFFUSION IN AN INFANT

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Abstract: *Adenovirus infections requiring hospitalization are on the rise in recent times.We report a 55 days old infant who presented with fever and breathlessness and chest x-ray revealed patchy infiltrates on the right side with bilateral pleural fluid. Pleural tapping revealed uniformly hemorrhagic effusion. Nasopharyngeal aspirate and pleural fluid were positive for adenovirus PCR. Child subsequently developed multiorgan dysfunction and died at 58hours of hospital stay with pulmonary hemorrhage despite intensive care. Adeno viral infections in infants can be severe with multiorgan involvement and can be fatal.*

Keywords: *Human adenovirus, Hemorrhagic pleural effusion, Multiorgan failure.*

A 55 days old male infant (one of twins) was referred with fever, breathlessness and poor feeding from a peripheral tertiary care center. Infant was on mechanical ventilation for bronchopneumonia of 8 days duration and was shifted to our institution for further management. Other twin sibling and his mother had respiratory illness in the previous week and had recovered. This baby was a product of twin pregnancy, first of twins with a birth weight of 1.9 kg SGA and had neonatal hospitalization of 14 days, the details of which could not be traced. Infant was received at our emergency department with intubated airway and had no shock and hemodynamically stable but with poor Glasgow Coma Scale (GCS). He was febrile and pale. Subsequently infant developed shock which was managed with normal saline bolus followed by adrenaline and noradrenaline infusions. Child received ventilatory support, antibiotics, PRBC transfusion and supportive care. Chest X ray showed infiltrations over the right side with bilateral pleural fluid (Fig.1 and Fig.2).

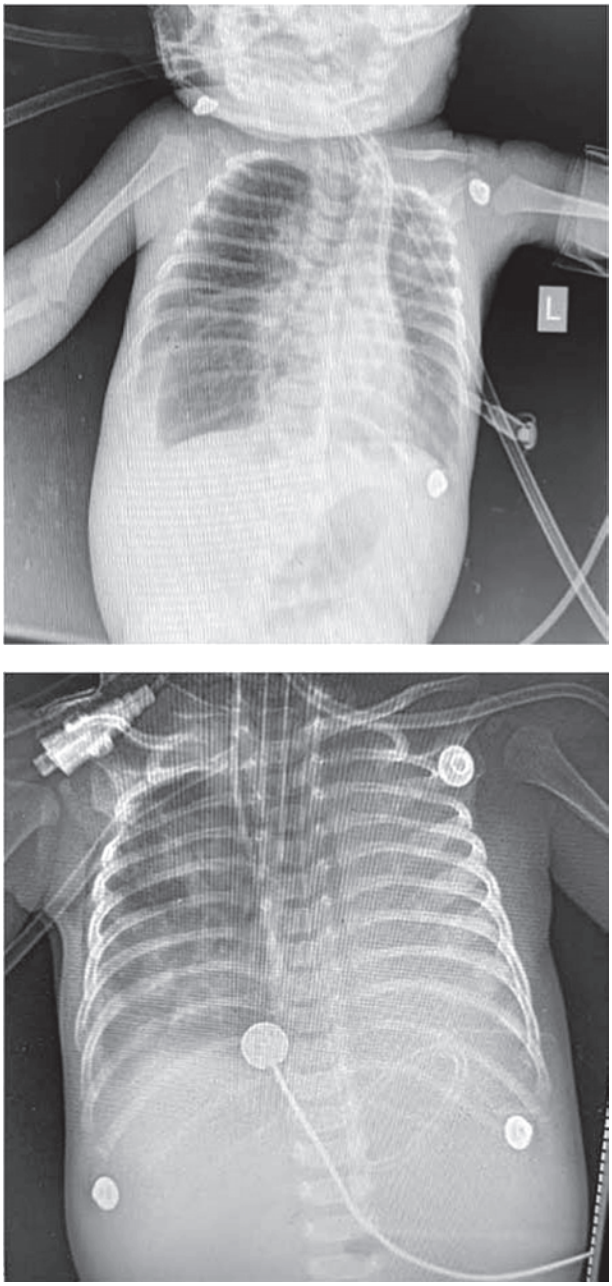

Fig.1 and Fig.2 showing the X-ray chest

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Total white cell count was 10.3 X10 ^{9}/L, hemoglobin was 5.6 g/dL, Hematocrit was 17%, platelet count was 69 x10^{9}/L which soon declined to 14 x10 ^{9}/L. Differential count showed 80% polymorphs and 18% lymphocytes. Peripheral blood smear showed neutrophilic predominance, normocytic normochromic anemia with thrombocytopenia and no blast cells. C reactive protein was 120mg/L, serum ferritin was 16214 pmol/L(N -218-1104), triglycerides was 113mg/dL (N-160-303), lactate dehydrogenase (LDH) was 2833U/L (N-170-450). Serum amylase and lipase were normal. SGOT was 138 U/L(N-28-75U/L) and SGPT was 20 U/L (N- 17-59U/L). Serum albumin was 2.1gm/dL (N-2.6-3.4gm/dL), Blood urea was 33mg/dL, creatinine was 0.8mg/dL. Blood gases revealed severe respiratory and metabolic acidosis with hypoxemia despite appropriate ventilatory strategies. Diagnostic pleural fluid aspirate revealed hemorrhagic fluid and pleural fluid protein was 1.9gm/dL, LDH was 47.5U/L and microscopy revealed sheets of red blood cells. Ultrasonogram abdomen revealed small hepatomegaly. Bedside echocardiogram was suggestive of left ventricular dysfunction with an ejection fraction of 40% with a structurally normal heart. Nasopharyngeal aspirate and pleural fluid were positive for adenovirus PCR. Infant received 1g/kg of intravenous immunoglobulin. Pleural fluid, blood, and urine cultures were sterile. Child was tested negative for tuberculosis using cartridge based nucleic acid amplification test (CBNAAT). Mothers' retroviral status was negative. Child progressed to refractive shock with multiorgan dysfunction and died at 58 hours of hospital stay with pulmonary hemorrhage.

Discussion

Adenovirus is known to cause upper respiratory infections and can present as bronchitis, bronchiolitis, pneumonia, gastroenteritis, cystitis, myocarditis, cardiomyopathy, hepatitis and meningoencephalitis.[1] It is increasingly being reported to have caused severe disseminated infections in children both immunocompetent and iummunodeficient. They can have persistent symptoms for 4 weeks and radiological features may take few weeks to resolve. Exacerbations occur following recovery.[2,3] Pleural effusion in adenovirus has been reported in children[4] and adenovirus infections in infancy can be fatal or can lead to residual lung damage and chronic lung disease.[2,3] Viral etiology in adenoviral infections is established by nasopharyngeal samples, endotracheal aspirates or bronchoalveolar lavage samples and body fluids like pleural fluid, peritoneal fluid or cerebrospinal fluid PCR. Lymphopenia, thrombocytopenia, elevated C reactive protein and lactate dehydrogenase are common findings, as seen in this infant. Disseminated and multiorgan involvement has been reported in 2.5% of adenovirus patients with 60% mortality even in immuno competent host.

Adenovirus pneumonia is known to mimic bacterial pneumonia and causes consolidation in lungs. Also higher CRPs[5] in adenovirus pneumonia makes it difficult to differentiate it from bacterial pneumonia. However, presence of diffuse wheeze beyond the zones of consolidation, multifocal and bilateral radiological findings in chest Xray helps. However in infants diffuse wheeze is the presentation most often. Normal or decreased total leucocyte counts, persistence of fever, progression of illness despite appropriate antibiotic therapy may be clinical clues to suspect adeno virus pneumonia. Studies have identified longer duration of fever, anemia, pleural effusion, higher LDH, higher procalcitonin to be associated with severe adenovirus pneumonia.[6] Literature shows that CD4+ CD8+ and CD 20 + levels to be significantly lower in those with pleural effusion and hence may be a marker of depressed host cell immunity.[7]

Management is supportive and if worsening despite adequate ventilatory support may need Extracorporeal membrane oxygenation (ECMO) to improve survival. Antiviral therapy in adenovirus infections is not well established in immuno competent hosts. Role of cidofovir in adenoviral pneumonia as a therapeutic option needs to be weighed against nephrotoxicity of the drug in the presence of shock. Virus specific lymphocyte infusion have been tried as therapeutic options in neonates.[8] The role of glucocorticoids and immunoglobulins need to be studied. The limitation of this case report is that serotyping of adenovirus or quantification of the viral copies were not done. Screening for viral organisms is not a part of initial routine evaluation in childhood pneumonia with existing guidelines. In non-responsive pneumonia screening for viral etiology may be required early, as positive results might help indiscontinuing or not escalating to higher antibiotics.

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CLIPPINGS

Cardiopulmonary fitness in children with asthma versus healthy children

The team of researchers comprising pediatric cardiologists and pulmonologists from Montpellier University Hospital, France aimed to evaluate the cardiopulmonary fitness of children with asthma in comparison with healthy controls, with a cardiopulmonary exercise test (CPET). Besides they also aimed to identify the clinical and CPET parameters associated with the maximum oxygen uptake (VO_{2max}) in childhood asthma. They carried out a cross-sectional controlled study in CPET laboratories from two tertiary care paediatric centres. The predictors of VO_{2max} were determined using a multivariable analysis.

A total of 446 children (144 in the asthma group and 302 healthy subjects) underwent a complete CPET. Mean VO_{2max} was significantly lower in children with asthma than in controls. The proportion of children with an impaired VO_{2max} was four times higher in the asthma group (24% vs 6%, $p<0.01$). Impaired ventilatory efficiency with increased VE/VCO_2 slope and low breathing reserve (BR) were more marked in the asthma group. The proportion of children with a decreased ventilatory anaerobic threshold (VAT), indicative of physical deconditioning, was three times higher in the asthma group (31% vs 11%, $p<0.01$). Impaired VO_{2max} was associated with female gender, high body mass index (BMI), FEV1, low VAT and high BR.

They concluded that **c**ardiopulmonary fitness in children with asthma was moderately but significantly altered compared with healthy children. A decreased VO_{2max} was associated with female gender, high BMI and the pulmonary function.

Moreau J, Socchi F, Renoux MC, Requirand A, Abassi H, Guillaumont S et al. Cardiopulmonary fitness in children with asthma versus healthy children. Archives of Disease in Childhood 2023;108:204-210.

Feasibility of and experience using a portable MRI scanner in the neonatal intensive care unit

This study was aimed to assess the feasibility of using a portable low-field MRI system at the bedside in a neonatal intensive care unit (NICU) that could be completed without artefacts that would hinder diagnosis. This prospective cohort study was conducted in neonates >2 kg. Findings were compared between portable MRI examinations and standard of care examinations. 18 portable, low-field MRI examinations were performed on 14 neonates with an average age of 29.7 days. 94% of portable MRI examinations were acquired without significant artefact. Significant intracranial pathology was visible on portable MRI, but subtle abnormalities were missed. The examination reads were concordant in 59% (10 of 17) of cases and significant pathology was missed in 12% (2 of 17) of cases. Authors concluded that portable MRI examinations can be performed safely with standard patient support equipment present in the NICU.

Sien ME, Robinson AL, Hu HH, Nitkin CR, Hall AS, Files MG et al. Feasibility of and experience using a portable MRI scanner in the neonatal intensive care unit. Arch Dis Child Fetal Neonatal Ed 2023; 108:45-50.

LEARNING TOGETHER

BLS, ALS

*Thangavelu S
**Annamalai Vijayaraghavan

Questions

1. A four year old girl is brought with complaints of fever of five days, increasing lethargy and skin lesions which have become red, tender and swollen since 12 hours.

Child lying supine, ill looking, respiratory rate (RR) 60/min with deep breaths, heart rate (HR) 175/min, proximal pulses felt and distal pulses are feeble cool below knees, elbows, mottled, capillary refill time (CRT) 6 seconds, blood pressure (BP) 70/ 30 mm Hg, pain responsive, temperature 103^0 F. Weight was 15Kg.

a) What is the initial assessment?

b) What is the initial treatment?

c)What is the probable cause and how will you manage?

d) What are the medications advised?

e) How to prevent progression to cardiac arrest?

2. A three year old boy with fever, difficulty in swallowing and swelling of the neck of three days, developed breathlessness in the morning which is present for the past five hours.

Initially child was anxious, with increased work of breathing, stridor and normal color. The child had a low pitched inspiratory stridor, respiratory rate 40 / min with suprasternal retractions, reduced breath sounds, SpO_2 90%.

Heart rate 130/min., sinus rhythm, central and peripheral pulses well felt, warm extremities, capillary refill time (CRT) less than 2 secs., BP 90/60 mm Hg, intermittent drowsiness, pupils reacting to light equally, blood sugar 92 mg/dL, temperature 37^0C.

White patch over tonsils, swelling over left lateral aspect of the neck with cervical lymphadenopathy.

a) What is the initial impression?

b) Inference after primary assessment?

c) What is the intervention after primary assessment?

d) Identify the problem after secondary assessment.

e) What specific investigation is advised and what is the preparation advised ?

3. A one year old infant is brought to the emergency room with history of loose stools and vomiting of one day duration, parents are not able to tell about the urination.

On examination infant has, respiratory rate 60/min, no retractions, bilateral air entry normal, with no adventitious sounds on auscultation of the chest , SpO_2 93%, heart rate 200/min., weakly palpable brachials and femorals, extremities cool and mottled below the elbows and knees, capillary refill time 6 secs, BP 60/36 mm Hg, lethargic, pain responsive, temperature 36.8^0C. weight 10 Kg.

a) What is the impression initially, after primary and secondary assessment?

b) What are the action to be taken?

c) What are the priorities for rapid assessment of circulation?

d) How will you identify hypotension in infants?

e) What actions are unacceptable?

4. Two year old boy brought with cough, cold and low grade fever of 3 days duration, not accepting feeds today with lethargy, tachypnea and increased respiratory efforts. On examination child has respiratory rate 58/min, intercostal retractions, good chest rise, bilateral equal air entry, with basal crepitations, SpO_2 98% in room air, heart rate 180/ min, sinus rhythm, good central pulses and poor

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peripheral pulses, cold and clammy skin and appears dusky, abdominal distension, soft hepatomegaly 4 cm below the right costal margin, CRT > 3 sec., BP 84/50 mm of Hg,drowsy, pupils equal and reacting to light equally, blood sugar 80 mg/dL. On auscultation gallop present, heart sounds muffled, no murmur.

a) What is the initial impression?

b) What is the evaluation after primary assessment?

c) Mention the intervention needed?

d) What is the secondary assessment and how is evaluation done?

e) What are the other interventions required?

5. A ten months old female child brought with history of cough and breathlessness of 1 day which has increased for the past two hours. On examination child is irritable, anxious, pink, tachypneic with increased respiratory efforts, audible wheeze, respiratory rate of 50/min, intercostal retractions, good chest rise, bilateral expiratory wheeze, SpO_2 93% in room air, heart rate 145/min, sinus rhythm, central and peripheral pulses well palpable, warm extremities, capillary refill time 2 sec., BP 80/50 mm Hg, pupils equal and reacting to light, blood sugar 80 mgm / dL, temperature 37^0C.

a) What is the initial impression and intervention?

b) What is the evaluation after primary assessment?

c) What is the intervention after primary assessment?

d) What is the evaluation after secondary assessment?

e) What is the intervention?

6. A seven months old infant admitted in the PICU with severe pneumonia on mechanical ventilator after failure of HFNC becomes agitated and cyanosed after a bout of coughing.

On further evaluation, it is seen that the ET tube size 4 mm is fixed at 12 cm and mist is present, there is asymmetric chest rise, decreased chest rise on the left side with decreased air entry on auscultation and normal breath sounds on auscultation of the right side without any added sounds, SpO_2 68% heart rate 170/min, sinus rhythm, central and peripheral pulses feeble, CRT 5 secs, BP 54/30 mm of mercury, Temp. 98.6^0F, skin normal.

a) What is the initial impression and steps in management?

b) After primary assessment what is your inference?

c) What is the intervention you do and why?

d) After the intervention what do you expect on reassessment?

e)What is the complete assessment and further plan of action?

7a.A two years old child is brought to ER. No pulse, unresponsive, no respiratory movements cardiopulmonary resuscitation (CPR) started after assessment.

What are the components of high quality CPR in adult, child and infants?

b.A three years old boy fell down from the balcony and brought to ER in an unconscious state.

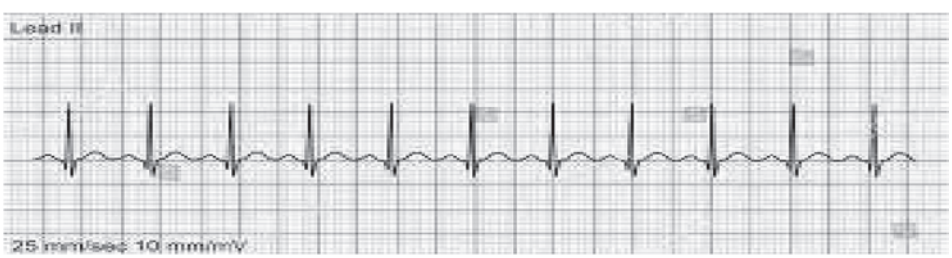

Fig.1

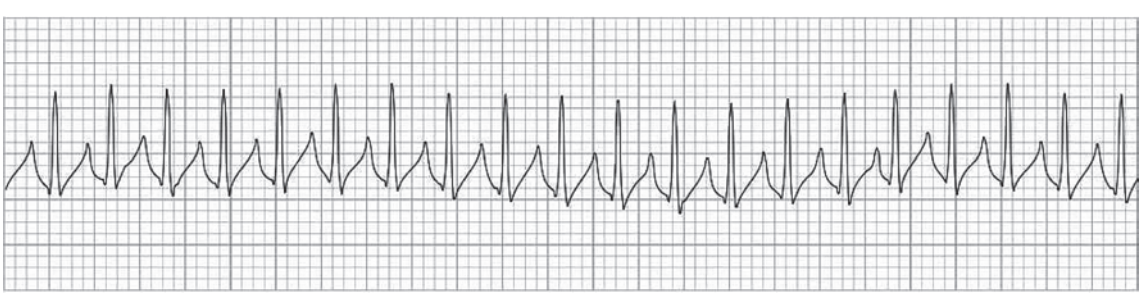

Fig.2

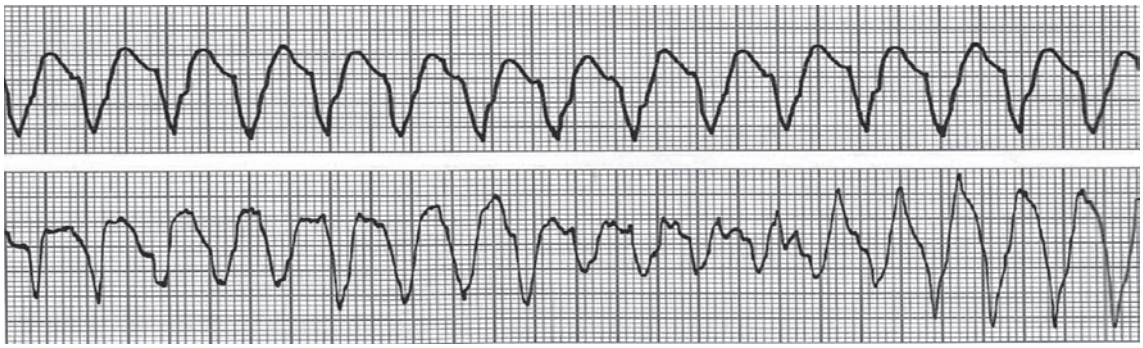

Fig.3 and Fig.4

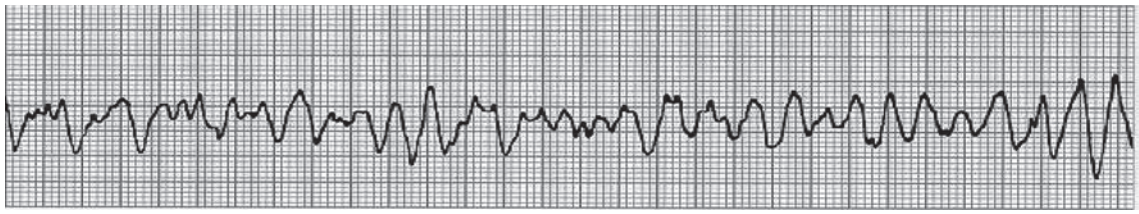

Fig.5

What are the five components of primary survey in trauma resuscitation?

8a). Identify the type of tachycardia from Fig.1 and Fig.2, describe the characters and at least five differences between the two.

b) Fig.3,4 and 5, show three different rhythms. Identify them and mention the supporting features for the diagnosis.

9. A five years old child is brought with hypotensive shock and IV access has become difficult even after 3 attempts. Hence decided to start intraosseous (IO) infusion

a) What are the indications for IO infusion?

b) What are the contraindications?

c) What are the ideal sites?

d) How do you confirm the correct position of the needle insertion?

e) What are all the complications expected?

10. A child brought in cardiac arrest, undergoing CPR and during resuscitation found to have pulseless ventricular fibrillation and defibrillation was done.

a) About the infant paddle, what is its size, below what age, infant paddle is used? If infant paddle is not available, how will you defibrillate with adult paddle?

b) What are the two types of defibrillators?

c) What are the contraindications for defibrillation?

d) What are the precautions to be taken?

e) How is an automated external defibrillator (AED) different from manual defibrillator?

Answers

1a) The child is in hypotensive shock as the child has altered sensorium, tachycardia, tachypnea, hypotensive as the BP is less than 78mm systolic, feeble peripheral pulses and cool extremities.

b) Position the airway and administer 100% O_2 through NRM, Monitor effectiveness of ventilation (chest expansion and breath sounds). Start continuous ECG monitoring and pulse oximetry for SpO_2 and secure intravenous access for giving fluid bolus.

c) With features of shock and history of infected skin lesions, probable septic shock. Start intravenous isotonic crystalloid (NS / RL) 20 ml / Kg. 150 ml rapidly by push pull technique, repeat two more boluses of 150 ml each after repeated reassessment to improve systemic perfusion and BP to achieve end points of treating shock. Watch for signs of increase in respiratory distress and palpate for hepatomegaly i.e, increase in liver span.

d) Medication to improve blood pressure by using inotropes like epinephrine if not improved with three boluses or if signs of congestive cardiac failure due to myocardial dysfunction develop. First dose of antibiotics given after taking blood for investigations.

e) Progression to cardiac arrest prevented by the use of inotropes, fluids, ventilatory support, treating the cause, and frequent reassessment.

2a) Potentially life threatening illness

b) The child has respiratory distress impending respiratory failure.

c) Start 100% O_2 after clearing the airways, attach monitor, pulse oximeter and call for help. Allow the child to maintain position of comfort, maintain a clear airway after suctioning and prepare for advanced airway to protect airway.

d) Respiratory distress, upper airway obstruction.

e) Order for investigations including throat swab for microbiological studies, arrange for anti-diphtheria serum, and prepare for advanced airway

3 a) The child has acute life threatening problem - Hypotensive shock with hypovolemia.

b) Universal precautions to be taken, rapid cardio pulmonary assessment to be performed, identify hypotensive shock, administer O_2 by non-rebreathing mask (NRM), cardiorespiratory monitoring, quickly establish vascular access through peripheral vein, if difficult, IO access to be started ,administer isotonic fluid NS in 20 ml/kg fluid boluses (200 ml) in 5 to 10 minutes, reassess after each bolus and give additional boluses, bedside glucose estimation initially and later serum electrolytes, urea, creatinine.

c) Mental status, appearance, response to stimulation, AVPU scale, heart rate, central peripheral pulses, skin temperature, capillary refill time, end organ perfusion, blood pressure, urine output.

d) Hypotension is systolic BP below 5th centile, BP < 1mon.- 60 mm, 1 month to 1 year- 70 mm Hg. > 1year - 70 + age in year x 2.

e) Failing to use universal precautions, failure to identify hypotensive shock, treating tachycardia with drugs or cardio version, failure to perform airway interventions before establishing vascular access, repeated peripheral line access instead of attempting IO access, administering hypotonic fluid or glucose containing fluids, inadequate volume of fluid and failing to reassess after each bolus.

4a) Probable life threatening illness as evidenced by lethargy, increased respiratory rate, effort dusky appearance.

b) Child has compensated shock with respiratory distress

c) Initially call for help, start 100% O_2 with the help of NRM, delegate responsibilities, attach cardiac monitor, pulse oximeter, arrange for vascular access and start IV crystalloid (NS) and proceed for secondary assessment

d) During secondary evaluation signs and symptoms, allergy, medication, past illness, last meal, events (SAMPLE) history and focused physical examination, head to foot and systemic examination, cardiovascular and abdominal examination to be done.

After secondary evaluation compensated cardiogenic shock identified based on the history, clinical findings auscultation findings of gallop, muffled heart sounds, no murmur, basal crepitations and abdominal examination showing soft hepatomegaly.

e) Restriction of fluids to 5ml/ Kg given slowly over one hour. To arrange and start early inotropes (dobutamine), and shift to pediatric intensive care unit (PICU) for further investigations and to correct the metabolic abnormalities .

5a) A life threatening illness because of the anxiety, tachypnea, audible wheeze and after activating the emergency response , 100 % O_2 started with NRM after clearing the airway. Cardiac monitor and pulse oximeter attached and child allowed assuming position of comfort.

b) After primary assessment respiratory distress probably due to lower airway obstruction.

c) After O_2 by non-rebreathing mask (NRM) and bronchodilation with salbutamol nebulization, reassess and repeat nebulization.

d) After secondary assessment respiratory distress, lower airway obstruction evaluated.

e) After nebulization with salbutamol every 20 minutes with oxygen for one hour one can consider heated high flow nasal cannula and further management in PICU.

6a) The child has a severe life threatening situation, call for help and ensure 100% oxygenation by bag and tube after detaching from the ventilator, confirm the attachment of monitors, pulse oximeter, ventilator connections and O_2 connection to rule out displacement, obstruction, pneumothorax, equipment failure (DOPE)

b) On primary assessment respiratory failure with hypotensive obstructive shock probably due to tension pneumothorax is made out due to cyanosis, decreased chest rise, hypotension and other evidence feeble central pulses, CRT of 5 sec.

c) Because of decreased air entry on left side needle decompression is to be done with butterfly needle on the left 2nd intercostal space with the other end kept underwater to see for the gush of air bubbles which confirms pneumothorax. This will relieve the obstruction and reverse the obstructive shock.

d) After the procedure look for equality of the chest movements on both sides and breath sounds assessed by five point auscultation which will be equal on both sides with no sounds over epigastrium, the shock will improve and BP will normalize, color, pulses, CRT will become normal, SpO2 will become normal >95%.

e) Reassess for equality of chest movements, breath sounds by auscultation, SpO2, blood pressure, plan for intercostal drainage tube and confirm with investigations, chest X ray (CXR)and arterial blood gas (ABG).

7 a) i. Compression rate: In all age groups 100-120/min

ii. Compression depth: In adults - 5 cms; In children 1/3 of AP diameter of chest or 5 cms; in infants In children 1/3 of AP diameter of chest or 4 cms;

iii. Hand placement: Adults: Two hands on the lower ½ of sternum; 1 or 2 hand over lower ½ of sternum; Infants single rescuer; 2 fingers in the chest below the nipple line; infants double rescuer 2 thumbs encircling hands in the centre of the chest, below nipple line.

iv. Chest recoil: Allow full chest recoil after each compression.

v. Minimizing interruptions: Limit interruption in chest compression to < 10 seconds (for delivering shock, rescue breaths, rhythm analysis, pulse-checks)

vi. Compression/ventilation ratio without advanced airway:

Adults - 30:2

Children & Infants: Two rescuers - 15:2

One rescuer - 30:2

vii. Compression/ventilation ratio with advanced airway:

Compression rate 100-120/min

Give one breath every 2 seconds (20-30 breaths/min)

b. i.Open airway using jaw thrust maneuver and simultaneous cervical spine stabilization.

ii.Look for life threatening chest injuries (hemothorax, pneumothorax, flail chest) to ensure effective ventilation and oxygenation.

iii. Control bleeds: ensure vascular access.

iv. Evaluate level of consciousness and prevent secondary brain injury.

v. Maintain normothermia and identify bleeding points, hematoma, fractures and deformities

8a). Fig.1 shows sinus tachycardia and Fig.2 shows supraventricular tachycardia.

b) Fig.3 shows rate 200, regular. broad QRS complex, p wave absent and T wave (upright) opposite to that of QRS (inverted and seen as s wave) suggestive of monomorphic ventricular tachycardia.

Fig. 4 shows rate 190,irregular, broad irregular QRS, varying voltage and varying polarity. P wave absent suggestive of polymorphic ventricular tachycardia.

Fig.5 shows chaotic, no identifiable QRS complexes, coarse to fine fibrillatory wavessuggestive of ventricular fibrillation.

9. Intra osseous needle (Fig.1)

Fig.1. Intraosseous needle

Characters	Sinus tachycardia	Supraventricular tachycardia
i. Onset	Gradual	Abrupt
ii. Clinical features	Predisposing causes such as fever, pain, hypovolemia	Absence of predisposing causes, features of heart failure
iii. Heart rate beats/min	Infant < 220, child < 180/ min	Infant > 220, child > 180/min
iv. ECG - P waves	Present, normal (upright in L2, aVF)	Absent, abnormal (inverted in L2, aVF)
v. Beat to beat variability	Present	Absent

a) Indications - i) In any child requiring IV access, but still IV access is not possible after 3 attempts or > 90 seconds ii) Cardiac arrest, hypotensive shock or recurrent seizures.

b) Contraindications: Fracture of the bone or when a previous attempt is made in that bone, osteoporosis, infection of the overlying skin.

c) Upper end of tibia - Anteromedial surface, 2-3 cm below the tibial tuberosity.

Distal end of tibia - Proximal to the medial malleolus.

Lower end of femur - In the midline, 2-3 cms above the lateral condyle.

d) When needle is inserted sudden give away feeling, needle stands firmly without any shaking, when able to aspirate blood (not always expected), when flushed with saline, fluid flows freely without any extravasation.

e) Extravasation around the prick, chip fracture, epiphyseal plate injury, penetration of bone through and through, local site infection, osteomyelitis, compartment syndrome, fat and bone micro emboli.

10a) Infant paddle size is 4 cms diameter and is indicated for a child less than one year or weighing less than 10 kg or length less than75 cm. If infant paddle is unavailable, child can be kept in right or left lateral position and keeping adult paddles in front of chest and just behind the heart in the back so that the shock is delivered through the heart.

b) Monophasic: Delivers current in one direction

Biphasic: Delivers current in the reverse in the last phase of shock. Requires less energy dose, greater first shock efficacy approaching 90% and decrease the risk of burns and myocardial damage. Biphasic defibrillators are more effective than monophasic defibrillator.

c) Cardiac rhythms like sinus rhythm, asystole, pulseless electrical activity and bradycardia.

d) Patient must be moved from wet ground or water. Sparks can cause fire so O2 delivery device removed about 1 meter away from the paddle. All rescuers should not be in contact with patient or bed during delivery of the shock.

e) Automated external defibrillator (Fig.2)

Both are available in the same instrument. But outside the hospital, stand-alone AEDs are available.

Fig.2. AED

AEDs are portable, battery operated with sticky pads meant for operated by lay persons outside the hospital (not by doctors in the hospitals) in the road side, malls, parks, railway stations and airports. It delivers a fixed dose between 150-360 joules. A patient with ventricular fibrillation can be defibrillated immediately even by lay persons, as they don't have time to reach. Because these patients are at risk of death if not intervened within few minutes. AED has 3 buttons. Instructions are given in brief written messages and interactive voice prompt by the machine.

Manual defibrillators are used by trained doctors in the hospitals. Here contact device is called paddle (instead of Pads in AED) dosage is selected by the doctor based on the weight and exact calculated dose is delivered. In addition to defibrillation, another electrical therapy termed as synchronized cardioversion is also delivered by manual defibrillator.

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