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# The Child and newborn

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# In Memoriam

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# *The Child and Newborn*

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## Editorial

According to international law, a 'child' means every human being below the age of 18 years. This is a universally accepted definition of a child and comes from the United Nations Convention on the Rights of the Child (UNCRC), an international legal instrument accepted and ratified by most countries.

India has always recognized the category of persons below the age of 18 years as distinct legal entity. That is precisely why people can vote or get a driving license or enter into legal contracts only when they attain the age of 18 years.

Indian constitution accords rights to children as citizens of the country. Constitutional Guarantees meant specifically for children in India are:

(a) Right to early childhood care and education to all children until they complete the age of six years

(b) Right to free and compulsory elementary education for all children in the 6-14 year age group

(c) Right to be protected from any hazardous employment till the age of 14 years

(d) Right to be protected from being abused and forced by economic necessity to enter occupations unsuited to their age or strength

(e) Right to equal opportunities and facilities to develop in a healthy manner and in conditions of freedom and dignity and guaranteed protection of childhood and youth against exploitation and against moral and material abandonment

Besides, Children also have rights as equal citizens of India, just as any other adult male or female:

(a) Right to equality

(b) Right against discrimination

(c) Right to personal liberty and due process of law

(d) Right to being protected from being trafficked and forced into bonded labor

(e) Right of minorities for protection of their interests

(f) Right of weaker sections of the people to be protected from social injustice and all forms of exploitation

(g) Right to nutrition and standard of living and improved public health

Protection of Children from Sexual Offences Act or POCSO Act, 2012 is a comprehensive law to provide for the protection of children from the offences of sexual assault, sexual harassment and pornography, while safeguarding the interests of the child at every stage of the judicial process by incorporating child-friendly mechanisms for reporting, recording of evidence, investigation and speedy trial of offences through designated Special Courts. The said Act defines a child as any person below 18 years of age.

In keeping with the best international child protection standards, POCSO Act also provides for mandatory reporting of sexual offences. This casts a legal duty upon a person who has knowledge that a child has been sexually abused to report the offence; if he fails to do so, he may be punished.

**Dr Jaydeep Choudhury**
*Editor-in-Chief*

# Clinical Pediatrics and Child Growth and Development

**Arun Phatak**

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## Basic Considerations

The study of growth and development (GD) is the foundation of pediatrics – it separates 'pediatrics' from 'adult' medicine. The neonate who is totally dependent on others, grows, develops and matures over two decades into a self reliant adult capable of managing self and even of guiding (at least partially) the future. Every aspect of clinical pediatrics is influenced by the level of maturity of the child. The symptoms, signs and short and long term complications of diseases are different at different maturity levels of the child and so are the details about their management. It is important that as the child grows, he/she learns to take 'no' without any violent reaction.

Four changes occur during growth and development. They are observable and many of them form a part of GD assessment. I consider that suppression or inhibition of certain 'old' features is a change that needs attention during child rearing. As the infant grows, the extensor plantar turns flexor as cortico-spinal tracts develop and suppress the reaction and similarly the childish reaction of crying, tantrums and at times aggressive behavior on frustration changes to mature, controlled response. In an event of brain injury, a reversion of the plantar reflex and at times of the behavior occurs when the cortical inhibition is lost.

GD is not a haphazard process. It has a schedule and follows certain principles.

(i) The GD is sequential – Cephalo-caudal, proximo-peripheral and from general or gross to specific or fine. This has important application in designing the development support program.

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(ii) Different organs and systems develop at different rates at different times. Four types of growth curves are known (Fig.1). The somatic curve decorates as the child approaches the first birthday and the deceleration that follows is at times worrisome to the parents. The neural growth rapidly rises during the first 2-3 years nearing the adult level. Insult to the brain during the first 2 years of life may have devastating, at times life long effects. It is important that any developmental delays or risks are identified early in infancy and the development support program initiated as early as possible. The genital growth is reverse of the neurologic growth – hardly any development till adolescence. A 9 year old girl with pain in chest may be in Tanner I or II stage and parents need to be told about menarche expected in 2-3 years and need for appropriate information to the girl. The lymphoid tissue reaches twice the adult size around 9-10 years and then decreases to the adult size. In the past, many a tonsils were removed at this age (and the adolescent growth spurt attributed to tonsillectomy. At times, a child during this period is misdiagnosed to have generalized lymhadenopathy.

(iii) There is a period (sensitive period) during which a given skill is learnt easily followed by a period (critical period) during which it is difficult (though not impossible to learn the given skill. This principle again has important bearing in development support programs.

(iv) Individual's rate of growth is maintained. A child when plotted on growth charts is expected to keep to the tract. A slow grower continues to grow slow and a fast grower continues to grow fast. The principle has a prognostic as well as

diagnostic value. Sudden change in the speed is a cause for worry. This principle makes the use of developmental follow up and of growth charts important tools for early detection of aberration.

Because the process of GD is orderly with time schedule, routine assessment of GD during infancy is important for diagnosis and prognosis of developmental delays, for designing and following the impact of the support programs.

**Norms**

Use of GD studies in clinical practice needs development of norms. Norms tell us what happens commonly in the given community at that time and not how all children should grow at all places. They are not benchmarks.

Statistically, when the sample is large, representative of the community and normally distributed the observations lying in the range of mean ± 2 standard deviations (a total of 95.44% - 47.72% on either side of the mean) are considered normal. Normal is a range and not a point.

Random mutations and specific selection is the underlying principle of evolution. Of the many variations in the phenotype, those suitable to the environment (in the case of humans the social environment as well) flourish. The genetic endowment will vary with race and closed communities because of inbreeding) and the physico-social environment changes from place to place and from time to time, it is understandable that norms would vary from place to place and from time to time. Local norms are therefore preferable to those established elsewhere. Thus many nations had their own norms and for specific groups of children (e.g. children with cerebral palsy or Down syndrome) separate anthropometric norms are available. Since the physical and social environments change rapidly it is desirable that the norms are revised every 15-20 years.

Sometimes I wonder if we tend to prefer foreign norms to local norms. Even when the norms for Bayley Scales were established in Gujarat, a number of centers were still using the Denver Development Screening Test. In 1972, ICMR had published anthropometric norms based on 125,000 children from 11 states of India. But we preferred the Harvard standard and then the NCHS and then CDC norms. Every time the norms were revised to a higher level and our nutritionists concluded that 'we were under-detecting malnutrition'.

Now, the WHO Multicenter Growth Reference Study (MGRS) have been adopted by more than 100 countries. Basically, the WHO growth charts are for reference i.e. for comparison of our observations with the children from the six cities that formed the sample of MGRS. Yet in 2006 WHO introduced it as "designed to show how children should grow". The MGRS charts have been adopted by more than 100 countries. A large systematic review[1] involving papers from 55 countries and a total sample of 11 million children reported that the weight and length/height norms are not optimal fits while there is a risk of over-diagnosis of microcephaly or macrocephaly.

I now wish express my personal opinions about the use for anthropometry in the diagnosis and management of conditions.

**Malnutrition**

In 2009, the WHO recommended that the MGRS charts be used to diagnose severe acute malnutrition (SAM) – weight for length/height = -3SD. Malnutrition is a deficiency disorder and weight is one of its manifestation. The length/height is mostly (90%) genetically guided. So anthropometry alone should not be the basis of diagnosis of malnutrition. It should be considered as a screening test and the final diagnosis with details of various deficiencies made after clinical and if necessary laboratory examination.

**Intrauterine Growth Retardation**

Epigenetic changes occur in a mother who has experienced restrictive environment during her childhood or fetal stage. This is often referred to as 'thrifty' gene, 'thrifty' phenotype or even 'thrifty' mother. These changes program the fetus to grow small and the influence continues after birth. If a child who is programmed to grow small is overfed to push him/her into the 'normal' weight tract, he/she will be at a risk of getting obesity and adult disease of fetal origin. This is what Barker observed in the Asian migrants in the UK.

**Clinical Assessment of 'Development'**

Three types of tests are available – the milestones, the full scales and the screening tests.

The milestones are really for common people. They are too few and identification of delay is very late. On the other hand, they are usually placed at average performance.

The full scales (often called laboratory tests) have large number of items (Developmental Assessment of Indian Infants has 230 items) which need standardized material to be administered in a standardized way by a trained tester. Testing, interpreting the observations and writing the report takes almost an hour. Full scales are out of bounds for the practicing pediatrician.

The screening tests have fewer items than the full scales but enough to make a reasonably correct opinion. They are quick, easy and cheap enough to screen a large number of children.

The objective of screening test is to pick up small number of 'suspects' (those with developmental delay and those at borderline) for detailed test for diagnosis. The cut off for screening is usually at the age placement of 97% pass level.

**Development Screening Tests**

Two tests for screening development of children in India were published in 1991 – Baroda Development Test (BDST)2 and Trivandrum Development Screening Chart (TDSC)3. Both the tests used the age placements of items selected from BSID (Baroda Norms) - 17 in TDSC for 0-24 months and 54 in BDST for 0-30 months. Both the tests assess unified motor and mental development.

TDSC was initially developed by selecting 17 items from BSID (Baroda norms). The chart was built up in the style of Denver Development Screening – Horizontal bars representing the age placement of the selected items (Y-axis). A vertical line from the chronologic age (X-axis) showing the performance expected by the child indicates whether or not the child is likely to be delayed. TDSC was validated against Denver norms. Recently, in 2013 it has been expanded and extended 4– 27 items for 0-36 months, 24 items for 37-60 months and a separate chart of 33 items for language development 0-36 months).

BDST was developed for the age group of 0-30 months by selecting 54 items from BSID (Baroda norms) and was validated against the full scales. It provides a check list and curves for 50% and 97% pass level age placement of the items. Like the original full scales, it is a point scale (one point for every item passed) and hence gives total score, and the developmental ages and quotients for 50% and 97% pass age levels. The child's progress can be easily followed on the charts.

**What are we doing?**

Study of GD is the foundation of pediatric practice, yet in my opinion, it is one of the most neglected fields in pediatric education, clinical practice and research. Every consultant and every hospital gives to the parents a file with growth charts printed on the 3rd cover page but sadly most of the charts usually remain blank. Every child is weighed but it is rarely charted to see where the child fits and even less often re-charted at a later visit to see how the child has grown. Other anthropometric and developmental assessment is done only occasionally. It seems that there is time constraint – there is time to attend to only immediate needs!

**What can we do?**

Tanner opined that the health of a population is accurately reflected in the rate of growth of its children and that a pediatrician should ascertain that the child is normal for age sex and race. I would put emphasis on 'rate' so that it is important to follow how the child is developing

(following the tract). If there is time constraint, priority should be given to infants (under the age of 2 years or at least under 1 year) and the weight, length, weight for length, head circumference and developmental screen followed on parent carried growth charts (Fig.1). This can be done by a trained assistant when the parents are waiting to see the doctor. The doctor needs to plot the chart and counsel the parents which would take a few extra minutes. If local growth charts are not available whatever available may be used with due consideration for the possible socio-cultural differences – it is not the exact position but the pattern of growth (faltering) that really matters.

Mo : Hypertensive
PT (30-32wks) 1·2Kg
Hypoglycemia, Hyperbiliaubinemia

Fig.2: Follow-up of DAM, a NICU graduate.

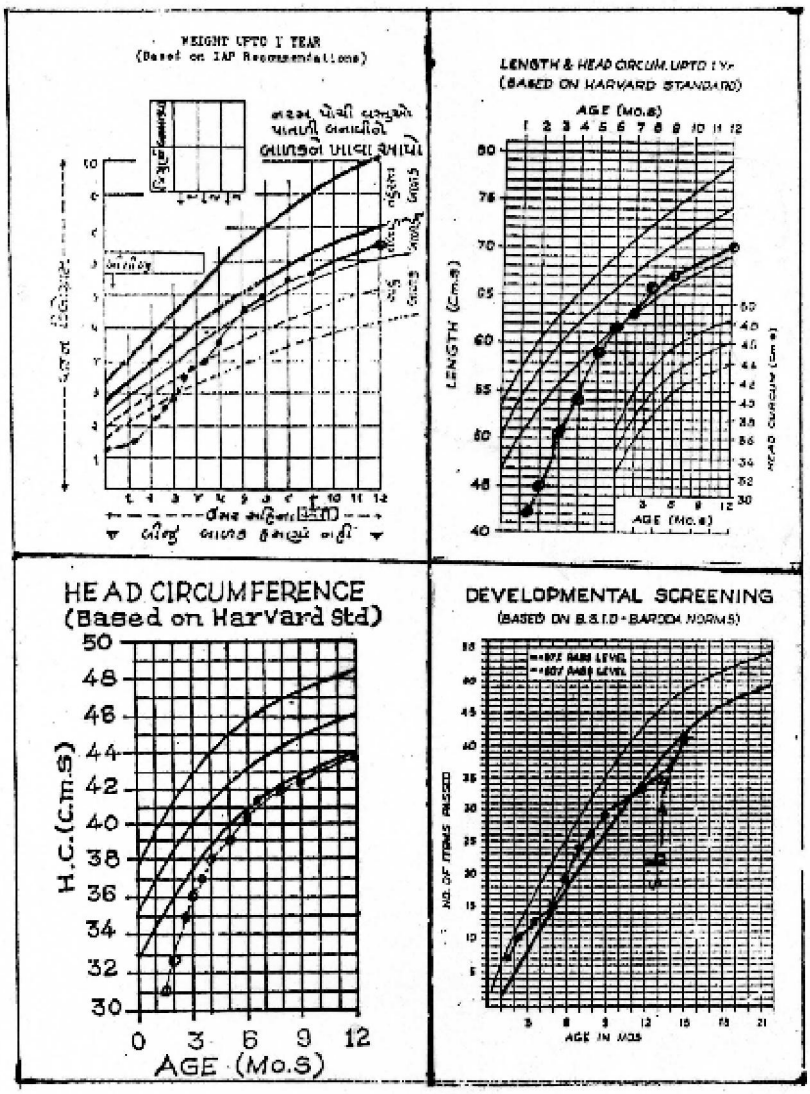


Fig 1: Monitoring Growth and Development of a baby at development risk in office practice

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*Transcript of Dr MKC Nair – Dr Dilip Mukherjee GDBP Chapter Oration at the 17th Annual Conference of GDBP Chapter of IAP, Ahmedabad 2018.*

# COVID 19 : Materno-fetal Transmission, Care of The Newborn of Covid Positive Mother, Breastfeeding by Covid Positive Mother and Testing of The Newborn of Covid Positive Mother

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## Materno-fetal transmission

No indication of this mode of transmission has been reported in multiple small studies. A study 38 pregnant women with COVID-19 and their newborns in China found no maternal deaths and no confirmed cases of intrauterine transmission of SARS-CoV-2 from mothers with COVID-19 to their fetuses[1]. All neonatal specimens tested, including in some cases placentas, were negative by rt-PCR for SARS-CoV-2. At this point, therefore, it needs to be emphasized that there is no evidence that SARS-CoV-2 undergoes intrauterine or transplacental transmission from infected pregnant women to their fetuses. To date, the virus has not been found in samples of amniotic fluid. However, another study of neonates with COVID 19 infection – all were mild disease except 1 baby who had other co-morbid conditions accounting for NICU care – a vertical transmission could not be ruled out[2]. Proper PPE may therefore be used. Neonatologists and pediatricians need to form local /hospital guidelines on attending low-risk deliveries of COVID positive mothers. This is important for conservation of PPEs. It is important to use airborne, droplet, and contact precautions-level PPE when attending high risk deliveries where neonatal emergencies are anticipated. This is to avoid maternal virus aerosols and protection when performing aerosol generating procedures like nasopharygeal suctioning, intubation and initiation of PPV.

## Care of the newborn of COVID positive mother

### *Studies have so far shown that*

Newborns should be bathed, wearing appropriate PPE as soon as reasonably possible after birth to remove virus potentially present on skin surfaces.

Most guidelines suggest separation of baby and mother after delivery [this needs to be included in the pre-delivery counseling], in many cases for prolonged periods of time; making study of postnatal mother to child transmission difficult. The benefits of separation may be greater in mothers with more serious illness. However, we need to consider, as of now, that neonates can acquire SARS-CoV-2 after birth; which could result in serious disease due to their immature immune system.

Hospitals must earmark in advance (like for COVID suspect and COVID positive isolation areas ad PICU beds for older children) single room with the potential for negative room pressure (or other air filtration systems) for these babies who might require NICU care. Preparedness for making PPEs available for a long haul is mandatory. Intubate earlier than usual to avoid CPAP and HFNC (and nebulization in older children).

## Breastfeeding by COVID positive mother

No study to date has demonstrated the presence of SARS-CoV-2 in breast milk. Mothers may express breast milk (after appropriate breast and hand hygiene) and this milk may be fed to the infant by designated caregivers to help establishment of breast milk secretion and provide baby with antibodies. Breast pumps and components should be thoroughly cleaned in between pumping sessions using standard hospital infection control practices.

If the mother chooses to room-in with her infant; or if the hospital cannot provide a designated area, the infant could remain at least 6 feet from mother at all times, with breast milk feeding per the above

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recommendations. Using a physical barrier such as a curtain between the mother and infant, may afford greater infant protection. If the mother also requests skin-to-skin contact with her infant, including direct breastfeeding, she should comply with strict preventive precautions, including the use of mask and meticulous breast and hand hygiene. Hospitals must have consent forms signed by the mother and caregiver regarding her choice in this regard after explaining hospital policy.

Ensure that only one bystander is allowed throughout the hospital stay. The bystander should not change, should not be allowed to roam around the hospital, should be healthy and less than 60 yrs of age, and must use PPEs as and when required.

**Testing of the newborn**

The optimal timing and extent of testing is currently unknown. It is recommended that, to distinguishing transient viral colonization from established infection: Molecular assay testing should be done first at around 24 hours of age; repeat testing should be done at around 48 hours of age. For well newborns who will be discharged prior to 48 hours of age, clinicians may consider not obtaining this 2nd test but need to ensure frequent follow-up via telephone, telemedicine, or in-person for 14 days after discharge.

Note that there have been reports of neonates who test negative at 24 hours but positive at 48-72 hours[3].

One swab that samples first the throat and then the nasopharynx may be used to conserve swabs and PCR testing reagents.

After hospital discharge, a mother with COVID-19 is advised to maintain a distance of at least 6 feet from the newborn, and when in closer proximity use a mask and hand-hygiene for newborn care until (a) she is afebrile for 72 hours without use of antipyretics, and (b) at least 7 days have passed since symptoms first appeared.

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# Difficult Asthma

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## Introduction

The exact prevalence of difficult severe asthma remains unknown but estimates from Scandinavian birth cohorts indicate 2%–5% of asthmatic children may have severe disease[1,2,3]. The ERS / ATS guidelines in identifying, evaluating and managing severe difficult asthma were published in 2014[5] and were modeled on earlier practice guidelines[4,6,7].

## Definition of "Difficult Asthma"

ERS / ATS definition of severe difficult asthma for patients aged > 6years.

A) Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier) or Systemic corticosteroids for ”50% of the previous year to prevent it from becoming "uncontrolled" or Asthma that remains uncontrolled despite this level of treatment.

B) Uncontrolled asthma defined as at least one of the following:

(i) Poor symptom control: ACQ consistently >1.5, ACT <20 (or not well controlled by NAEPP/GINA guidelines)

(ii) Frequent severe exacerbations: two or more bursts of systemic CS (>3 day each) in the previous year

(iii) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year

(iv) Airflow limitation: after appropriate bronchodilator withhold FEV1 < 80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

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(v) Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics).

*GINA Global Initiative for Asthma; LABA Long-acting $\alpha$2-agonists; CS Corticosteroids; ACQ Asthma Control Questionnaire; ACT Asthma Control Test; NAEPP National Asthma Education and Prevention Program; ICU Intensive care unit; FEV1 Forced expiratory volume in 1 s; FVC Forced vital capacity*

## Phenotypes :

Phenotypes of asthma in children is shown in table 1.

**Table 1 :** Phenotypes of asthma in children[1]

| Based on | Phenotypes |
|---|---|
| Symptoms Trigger | Age at onset / natural history / Severity Allergic / Non-Allergic / Exercise induced / Viral or Multi-triggered |
| Response to treatment | Corticosteroids |
| Inflammatory features | Eosinophilic / Neutrophilic / mixed |
| Non-invasive markers | Exhaled NO / Exhaled Breath Condensate |
| Pulmonary Function test | Fixed vs reversibleBronchial responsiveness to exercise, cold, chemicals |

Difficult asthma represents an umbrella term and can be subdivided into two distinct entities[1].

1) **'Difficult to treat asthma'** : having poor control due to incorrect diagnosis, poor adherence, environmental modifiers and co-morbidities.

2) **'Severe therapy resistant asthma' (STRA)** : where despite adequate control of modifiable factors and high medication use, asthma symptoms remain genuinely sub-optimally controlled.

3) '**asthma plus** : symptomatic asthmatic children with significant co-morbidities.

## Evaluation of a Child with Difficult Asthma

### *Confirming the diagnosis:*

As the first step, the clinical diagnosis of asthma should be first taken up, according to the GINA guidelines. Additionally, if asthma is suspected, this approach would allow identification of its components. A detailed 'asthma focused' history and a detailed physical examination, particularly exploring the symptoms of cough, shortness of breath, chest tightness and wheezing, it's onset, severity and triggers, previously offered treatment and response to treatment, and family history is often sufficient enough to point out mislabeling of asthma. There are various conditions which mimic asthma as shown in table 2.

**Table 2:** Asthma mimics

| Asthma mimics | Clinical clues | Confirmation |
|---|---|---|
| Dysfunctional breathing / vocal cord dysfunction | Inspiratory difficulty/ psychological stress | Flat Inspiratory loop in spirometry / laryngoscopy |
| Tracheomalacia and / or bronchomalacia | Early infancy / Biphasic cough worsening with bronchodilators | Bronchoscopy |
| Recurrent viral infections | Muti-system symptoms / close contacts / fever induced wheeze | Slow response to treatment / naso pharyngeal swab PCR to exclude RSV/ Adeno virus etc. |
| Non cystic fibrosis bronchiectasis | Persistent wet cough and wheeze / progressive | HRCT chest / Negative sweat chloride |
| Bronchiolitis obliterans | Prematurity / early infancy poorly responsive severe bronchiolitis | HRCT chest |
| Recurrent (micro) aspiration, reflux and swallowing dysfunction | Facial dysmorphism (e.g.Down's/ micrognathia) / CNS poor regulation ( cerebral palsy)/ GI anomalies etc. | Upper GI motility studies/ Genetic studies |
| Prematurity and related lung disease | Prematurity / recurrent bronchiolitis in infancy | HRCT chest if needed |
| Cystic fibrosis | Meconium ileus / infantile rectal polyp / persistent or recurrent pneumonia in different lobes / Malabsorption / FTT | Sweat chloride / Genetic analysis / Stool fat / elastase |
| Congenital or acquired immune deficiency | Multi systemic infection / persistent lung symptoms / absent thymus / no BCG Scar | Cellular and humoral immunity studies |
| Primary ciliary dyskinesia | Persistent poorly responsive symptoms/ rhinitis / ottitis media/ dextrocardia (?) | Ciliary motility studies / Nasal i-NO |
| Central airways obstruction and compression | Monophonic fixed wheeze / feeding difficulty with solid foods/ poor response to therapy | CT chest / Oesophagoscopy / bronchoscopy |
| Foreign body aspiration | Acute onset ( may be missed in children!) / symptoms may remain silent!/ unilateral diminished breath sound | Bronchoscopy |

Table 2 Cont...

**Table 2:** Asthma mimics **(Cont..)**

| Asthma mimics | Clinical clues | Confirmation |
|---|---|---|
| Carcinoid or other tumor | Depends on area of compression | CT chest / Biopsy |
| Congenital malformations including vascular ring | Monophonic fixed wheeze / feeding difficulty with solid foods/ poor response to therapy / but starts in early infancy | CT chest / bronchoscopy |
| Mediastinal mass / enlarged lymph node (e.g., Tuberculosis, sarcoidosis, lymphoma, etc) | Monophonic fixed wheeze / feeding difficulty with solid foods/ poor response to therapy/ may be asymptomatic / accidental diagnosis | CT chest / bronchoscopy RNTCP guidelines Serum ACE / Urinary calcium 24 hrs etc |
| Congenital heart disease with / without heart failure | Silent tachypnea / exercise induced distress / progressive with other features of CCF | Echo- cardiography |
| Interstitial lung disease | Silent tachypnea / exercise induced distress / progressive | HRCT / Lung biopsy |
| Connective tissue disorders | Multisystem / skin, kidney/ present like ILD | Collagen disease investigations |
| Hypereosinophilic syndromes (Churg – Struss Syndrome) | Persistent or recurrent wheeze / progressive/ eosinophilic / multisystem involved | HRCT / blood and sputum eosionphil / allergy test |
| Hypersensitivity pneumonitis | Persistent or recurrent wheeze / progressive/ eosinophilic / multisystem involved | HRCT / blood and sputum eosinophil/ allergy test |

**Identification of comorbidities and contributing factors :**

Co-morbidities can contribute significantly in rendering asthma control difficult. A thorough search for these conditions is mandatory and appropriate therapy directed as shown in table 3 and contributing factors in table 4.

**Algorithm : Managing Difficult Asthma:**

- ***Step I:*** Evaluate diagnosis : Not asthma ?? ——————Treat accordingly

**Asthma Confirmed**

- ***Step II:*** exclude co-morbid condition; (Allergic rhinitis/sinusitis/GORD/VCD / **ASPERGILLUS** etc.)
  - Yes ——Treat
  - No
- ***Step III:*** Check:
  - **Trigger avoidance, Skin Prick Test** (HDM/ Cockroaches/pets/moneyplant/smokes/ pollens/danders/pollutants/AC filters)
  - ***Treatment adherence:*** Compliance/regular visit with inhalers / daily observed therapy/ App or smart phone controlled monitoring (8)
  - ***Drug/Device/Delivery:*** demonstrations by doctor / nurse
  - ***Malingering:*** adolescence/family disharmony etc. (counseling)
- Manage by increasing ICS/LABA/dose as advised in GINA guidelines:
- Add Oral Steroids For 2 Weeks
- ***Step IV:*** No response after addressing above points:

**Frequent Hospitalization/labile Asthma**

**a) Brittle asthma**

- ***Type I:*** Female/atopic/pefr Variation > 40% in half of last 150 days
- ***Type II:*** Neurogenic/sudden exacerbration < 3hrs without trigger
- ***Mangement:*** Hospitalize/trigger avoidance in Type I/ Subcut. Terbutaline in refractory asthma/

**Table 3 :** Comorbidities

| Co-morbidity | Diagnosis |
|---|---|
| Exercise Induced Laryngeal Obstruction (EILO) | 1) functional (without any structural abnormality with preponderant //psychological issues)<br>2) background of structural laryngeal disorder (previous laryngomalacia or recurrent laryngeal nerve palsy)<br>3) indeterminate etiology<br>4) Confirm : Video / Direct laryngoscopy. |
| Obesity and asthma | Postulated hypotheses include mechanistic, inflammatory, shared genetics pathways and shared co-morbidities[9]. Obesity may also increase bronchial hyper-responsiveness and lung atelectasis and OSAS. Weight loss is associated with an improvement in asthma control |
| Atopy, Aeroallergen Sensitisation and Food Allergy | Atopy – asthma relationship is stronger in children/Strong predictors of asthma attack needing hospitalization include allergen sensitization and allergen exposure (and viral infection)[10]. |
| Rhinosinusitis | Rhino-sinusitis can mimic asthma and potentially worsen vocal cord dysfunction. Symptoms of rhino-sinusitis can be quite disturbing and merit treatment, but they may also benefit asthma control[10]. |
| Gastro-oesophageal Reflux Disease (GERD) | GORD can worsen vocal cord dysfunction and mimic asthma symptomatology. Despite this, treatment with anti – reflux therapy has not been met with improved asthma control in randomized controlled studies[11] |
| Obstructive sleep apnea | Obesity, adeno-tonsillar hypertrophy , allergic rhinitis to be looked into. OSAS is pro-inflammatory. |
| Hormonal influences: | Premenstrual, menarche, menopause, thyroid disorders |
| Drugs: | Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs),â-adrenergic blockers, angiotensin-converting enzyme inhibitors |

**Table 4 :** Contributing Factors

| | |
|---|---|
| Aspergillus co infection | Construction site / IgE > 1000 IU/ml / specific to aspergillus IgE high / HRCT chest / suspect / good response to itraconazole and OCS |
| Addressing Adherence to Prescribed Regime | Poor adherence is common (30% to 70% non-adherence rates)[12]./ Adolescents are particularly vulnerable/ Other factors include complicated treatment plans, poor child supervision, unstable family dynamics Administration at school under direct supervision, motivational interviews and behavioral interventions improving self - management skills with demonstrated improved outcomes may be helpful[8]. |
| Environmental Issues | Home assessments by a trained nurse and school visit to assess school environment may provide valuable insight to plan further strategy. |
| Exposure to Nicotine | Nicotine exposure accelerates airway inflammation and renders steroid resistance and is associated with poor outcomes[13]. |
| Outdoor Air Pollution | Nevertheless, this issue is far more deep-rooted . |
| Psychosocial Aspects | Adolescent asthmatics in particular often have anxiety and depression[14]./ Stressful situations aggravate airway inflammation and conversely, airway inflammation may affect central nervous system, presumably through vagal and nor-adrenergic pathways . |

or Subcut. adrenaline in anaphylactoid reaction / Novel therapies.

**b) Relatively stable patients**

Test for

- ***Bronchial responsiveness:*** Positive methacholine/Exercise test: Steroid sensitive asthma: eosinophilic in sputum/TM: high dose Triamcinolone.
- ***Inflammation:*** BAL/Sputum/Induced sputum/ Nasal scrapings/Exhaled breath Condensates etc:
  - ***Eosinophils:*** Steroid resistant eosinophilic asthma: Cyclosporin ?? / novel therapies
  - ***Neutrophils:*** Steroid resistant neutrophilic asthma: Macrolides/theophylline ??

– ***No specific inflammations:***
  - BHR +++: Persistent BHR: High dose ICS+ LABA/Subcut Terb.
  - No BHR: PAL: No specific treatment

Multidisciplinary team (MDT) for difficult asthma and pediatric domains of steroid responsiveness are shown in table 5 and 6.

**Managing severe therapy resistant asthma**

***Trial of triamcinolone and assessment of steroid responsiveness:***

Objective confirmation of fixed airflow obstruction (making further escalation therapy pointless), tweaking out dissociation between inflammation and symptoms, confirmation of airway inflammation (endobronchial biopsy and BAL cytology) and establishing steroid responsiveness.

The protocol involves a single intramuscular injection of triamcinolone followed by 1 mg of salbutamol given 4 wk later. A majority (approximately 70%) of children undergoing steroid trial respond in some but not all domains; complete responsiveness is seen in 15% whereas total unresponsiveness is seen in the rest 15%[8]. The questions remains as to the practicability of using such 'mega' doses in clinical practice.

**Specific therapies**

***Allergen immunotherapy*** *:*

If specific allergen sensitization is confirmed, a trial of allergen immunotherapy may be justified in stable asthmatics. Allergen immunotherapy may benefit the control of asthma symptoms, medication use and bronchial hyper-responsiveness[10].

***Omalizumab :***

Omalizumab is a subcutaneous injectable recombinant humanized IgG1 monoclonal anti-IgE antibody and is approved in children 6 y or older. Administered every 2–4 wk, it is indicated in children with allergic severe asthma who are sensitised to at least one perennial allergen along with elevated serum IgE. Omalizumab reduces inhaled corticosteroid usage and rates of exacerbations[15].

**Mepolizumab and other Anti-Interleukin (IL) 5 Agents (> 12yrs)**

IL-5 is a pro-eosinophilic cytokine and a potent mediator of eosinophil hematopoiesis and

*ACT Asthma control test; FeNO Fractional exhaled nitric oxide; FEV1 Forced expiratory volume in 1 s*

**Table 5:** Multidisciplinary team (MDT) for Difficult Asthma[1]

| Team member | Summary of role |
|---|---|
| Pediatrician | Diagnostic evaluation / Therapeutic decisions / Monitoring progress |
| Specialist nurse | Initial detailed evaluation / Home and school visits / Monitoring progress |
| Clinical psychologist | Initial evaluation of psychosocial factors in child and family / Follow-up depending on initial findings |
| Physiotherapist | Evaluation of breathing patterns / Evaluation of physical fitness and rehabilitation programmes as appropriate |
| Social worker/ safeguarding team/ Pharmacist | Evaluation of child protection issues / Pharmacist Evaluation of therapeutic regimes / Regular follow-up as appropriate |
| Respiratory technician physiologist | Lung function, FeNO and induced sputum measurements |

**Table 6.** Pediatric domains of steroid responsiveness[8]

| Domain | Definition of response post triamcinolone |
|---|---|
| Symptom response | ACT score > 19/25 or an increase of e"50% |
| FEV1 response | Pre-bronchodilator FEV1 of 80% of predicted value or greater or an increase of 15% or greater |
| FeNO response | Normal FeNO (<24 ppb) |
| Sputum response | Normal sputum eosinophil count (<2.5%) |

eosinophilic airway inflammation. Mepolizumab is administered every 4 wk and is shown to be effective in steroid reduction along with reduced exacerbations and improved symptom control[15].

**Long-acting anticholinergic bronchodilator (Tiotropium) (> 6yrs)**

Tiotropium is an inhaled long-acting anticholinergic agent and is administered once daily through a specialist inhaler device. Recent pediatric experience suggests Tiotropium to be safe and effective in children with significant improvement in lung function but no improvement in asthma control[16].

**Other agents and therapies**

Dupilumab (monoclonal antibody to IL 4 receptor) / Thymic stromal lymphopoietin (TSLP; an epithelial cell derived cytokine that may initiate allergic inflammation early in the allergy – inflammation cascade)./ Tezepelumab is human monoclonal immunoglobulin G2 lambda antibody that binds TSLP and prevents its interaction with the TSLP receptor complex.

None is recommended in children till now. A novel non-steroidal glucocorticoid receptor agonist **AZD5423 / Fevipiprant is a PD2 receptor antagonist** and early studies indicate a beneficial effect on quality of life scores and reduced sputum eosinophilia[1]./

**Bronchial thermoplasty (BT)** is an emerging discipline in adult bronchology but no pediatric data is available. BT involves application of thermal energy (by locally controlled radiofrequency waves aiming for a target tissue temperature of 65°C) to all accessible airways distal to main stem bronchi (3–10 mm in diameter). The procedure is undertaken in 3 separate bronchoscopy sessions about 3 wk apart. However, a Cochrane review of only 3 trials (n = 429) observed that the improved quality of life was not significant at 12 mo and there was no difference in symptoms and lung function indices[1].

**Agents not found to be helpful**

Macrolide antibiotics, anti-TNF-alpha agents, methotrexate, gold, cyclosporine, colchicine, hydroxychloroquine, immunoglobulin therapy, dapsone, nebulised lidocaine and heparin and antifungal agents[1].

**Conclusions:**

Problematic severe asthma is often a misunderstood and poorly managed entity. A coordinated multidisciplinary team approach approach confirming the diagnosis and clarifying its co-morbidities and aggravating factors is associated with an improved outcome.

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# Biologics to Biosimilars:Bombshell to Boon!

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***Abstract:***

*In recent years, the introduction of the highly effective and innovative biologic drugs had changed the management of high burden chronic diseases like autoimmune diseases, cancers, and chronic renal failure radically. Biologics are one of the top selling drugs worldwide but its major drawback is its exorbitant pricing which makes it unaffordable and inaccessible to a wide section of patients[1,2]. This demand-supply gap has led to the emergence of a new class of drugs, the biosimilars whichpromises to be an equally efficient but more cost-effective alternative. In 2015, the first biosimilar, Filgrastim-sndz, a biosimilar of the granulocyte colony-stimulating factor Filgrastim, was approved by the United States Food and Drug Administration (FDA)[3,4]. In Europe and many other countries like India they have been in used for over a decade. Ever since, several other biosimilars have been approved worldwide and widely used while many others are waiting in the pipeline. Many key biologics are scheduled to lose their patent in the near future, thus opening avenues to the marketing of a growing number of biosimilars worldwide, which are products similar in terms of quality, safety, and efficacy to already licensed reference products, thus allowing for potential savings in pharmaceutical expenditure. However, their arrival also will introduce challenges, like pharmacy and supply chain management and the need for education and awareness of clinicians and patients about the efficacy and safety of these agents. Numerous debates about the interchangeability between biosimilars and reference products are still ongoing, owing to concerns about potential immunogenicity raised by switching, which may cause a lack of effect and toxicity. Although before approval, biosimilars must undergo a rigorous development process using state-of-the-art technologies to establish biosimilarity to the reference biological product, the benefit-risk profile of biosimilars has been often questioned by clinicians owing to the limited amount of pre-marketing information on clinical efficacy and safety.Postmarketing surveillance programs will be required to evolve and ensure optimal pharmacovigilance reporting, because the potential for unexpected adverse events with biosimilars is higher than with conventional generic agents as a result of different manufacturing processes and different clinical trial designs and durations. This article reviews the relevant considerations and for ensuring appropriate, rational integration of biosimilars into mainstream medicine practice and how to overcome the existing hurdles in doing so.*

## Introduction

The FDA has defined Biosimilars as a biologic product, highly similar to and having no clinically meaningful differences, notwithstanding minor differences in clinically inactive components, from an existing FDA approved reference product[5,6]. A biosimilar establishes high resemblance to the reference product in terms of quality characteristics, biological activity, safety, immunogenicity and efficacy based on comprehensive comparability studies. Regulatory agencies, such as the FDA, allow at least 1 of the approved indications for the reference biologic agent to be listed as an indication of the biosimilar, once similarity is established[7]. The availability of biosimilars has paved the chance to lower health care expenditures due to inherent price competition with their reference product[8]. Specifically, the approval of oncologic biosimilars

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arrives at a time when the cost of cancer drugs exceeds that of any other therapeutic category[7]. Despite expected cost advantages of the biosimilars, established safety and efficacy profiles, a long history of their use for non-oncology indications in Europe, and their successful application in non-malignant conditions, the uptake and manufacturing of oncology biosimilars in the US have been slow, partly due to existing patents for anticancer biologics[9].The patents for several mabs with widespread use in the treatment of cancers, such as trastuzumab, bevacizumab, rituximab and cetuximab, either have expired or will soon expire[10-13], and biosimilars for these biologics are in the late stages of clinical development. As part of this expansion of new agents, clinicians should be prepared to understand the chemical nature of biosimilars; similarities and differences between biosimilars and their reference products as well as generic drugs; clinical safety and efficacy profiles; and current oncology therapeutic areas currently under investigation.

**Difference between biosimilars and generic drugs**

Generic medicines are an exact copy of a brand-name medication. Manufacturers are able to make identical versions of a medication when the ingredients are simple chemicals. However, the ingredients in some medicines, such as vaccines, growth factors, or monoclonal antibodies used in cancer, are made from living cells and are too complicated to make into a generic version. These complex medications are referred to as biologics. Biosimilars are medicines that are very similar to these biologics but are not exact copies. The biologic medication that the biosimilar is based on is called the ReferenceProduct. In contrast to generics, biosimilars are allowed minor differences because they are created through processes found in living organisms that are less predictable and reproducible[14]. Comparison between Generics, Biologics and Biosimilars shyows in Table 1.

***Chemical composition and manufacturing of therapeutic proteins and biosimilars:***

Biologics are complex molecules synthesized in living organisms with inherent minor variations based

**Table 1[15].** Comparison between Generics, Biologics and Biosimilars

| Characteristic | Nonbiologic Generic | Biologic | Biosimilar |
|---|---|---|---|
| Size | Small | Large | |
| Molecular weight | <1000 Da | 200-1000 times the size of a small molecule | 4000 to>14000 Da |
| Structure | Simple to relatively simple | Complex | Designed to be highly similar to reference product but potentially have structural variations |
| Manufacturing | Predictable and bioequivalent to the brand name | Piece of DNA added to a cell; a protein is generated and becomes the biologic | Stepwise process to make a similar compound |
| Complexity | Easy to characterize | Difficult to characterize | Difficult to characterize |
| Stability | Stable | Sensitive to handling and storage | Sensitive to handling and storage |
| Immunogenicity | Low potential | High potential | Variable. Assessed by evaluating upper limit of immunogenicity incidence of the reference product |
| Approval requirements | Small clinical trials in healthy volunteers | Standard FDA guidelines | Large clinical trials; development of a biosimilar must include =1 clinical study, including assessment of immunogenicity and PK or PD; licensure pathway for a biosimilar is an abbreviated pathway |
| Class example | Loop diuretics, NSAIDs | | Therapeutic proteins and mAbs |

on process; the process and product for which are both regulated. These therapeutic proteins may be classified in groups that include cytokines and glycoproteins (eg, granulocyte and granulocyte macrophage colony stimulating factors, interferons, interleukins, erythropoietin/darbepoetin alfa), monoclonal antibodies (eg,rituximab, bevacizumab, trastuzumab,daratumumab), and enzymes (eg: asparaginase, glucarpidase). Through the manufacturing process and via protein chemistry manipulation, these agents often undergo various alterations, such as pegylation to increase circulating half-life or addition of other proteins, cytotoxic linkages, or radionuclides as therapeutic payloads which create new molecular entities with unique patent protections, and aid in clinical use. A number of posttranslational modifications (PTMs) may occur during the manufacturing of all proteins(reference/ originators as well as biosimilars),as natural consequences of the use of eukaryotic cellular systems in their production. One of these PTMs, glycosylation, is the addition of carbohydrates to specific amino acids and its degree is dependent upon the system and culture conditions, and the amount and type of glycosylation of proteins may have effects on receptor binding and structure of the crystallizable fragment(Fc) portion of monoclonal antibodies; for example, Darbepoetin is manufactured with intentional extensive N-linked glycosylation that leads to longer mean residence times after dosing[16]. Clinically, the challenge is to predict to what degree subtler glycosylation and other PTMs like deamidation or oxidation may affect elimination, distribution, or potential immunogenicity[17-20] of therapeutic proteins manufactured through different cellular systems.

Biosimilars are expected to have no clinically meaningful differences from the reference product in terms of the safety, purity, and potency of the product. The first step in the manufacture of a biosimilar is the transfection of a cell line, with the help of a DNA vector, typically one unique from the reference product line[21]. Different factors like source of the raw materials, order of protein structures, additives and stabilizers and degree of PTMs, all affect the heterogeneity of the final product and target should be to minimize eventual contrasts from the reference product. In 1998, a sharp increase in the incidence of pure red cell aplasia associated with anti-erythropoietin antibodies was seen in patients who received subcutaneous epoetin alfa for anaemia of chronic kidney disease[22] and on further investigation, it was discovered that a small formulation change that replaced human serum albumin with polysorbate 80 as a stabilizer increased the immunogenicity of the product. Hence it is of paramount importance to reduce differences from the reference product in all aspects of manufacturing and the existence of a rigorous approval system for a biosimilar is essential.

**How are biosimilars named?[14]**

Unlike generic medication, which can have the same chemical name as the brand name, biosimilars must include 4 lowercase letters after the name of the medication. For example, the biosimilar for the reference product Infliximab is called Infliximab-dyyb. The biosimilar and the reference medication always have the same active ingredient. The addition of the 4 lowercase letters lets us know that the medication is a biosimilar.

**Toxicity and pharmacovigilance**

By definition, the toxicity profile of a biosimilar cannot differ from the branded reference product in any clinically meaningful way, and this typically is confirmed through at least one comparative trial in the patient population and therapeutic indication for which it is most likely to detect a difference, if there is one. Because of the limited duration of confirmatorytrials, there is a formal possibility that a unique long-term toxicity could emerge, but postmarketing pharmacovigilance and registry studies would detect such an anomaly.Information about drug safety is generally collected in thepost-marketing period from spontaneous reporting systems,post-marketing observational studies, and pragmatic clinicaltrials. The spontaneous reporting system represents animportant tool for the detection of safety signals and consequencesof immunogenicity (especially if mild to moderate), though an improvement in specific tools andalgorithms to identify potential cases is still needed.Concerning biosimilars, their benefit-risk profile hasbeen often questioned by clinicians because of the limitedamount of pre-marketing information on clinical efficacyand safety, despite

biosimilarity approval being based onan extensive comparability exercise with the referenceproduct and no[23] proof of any difference in safety profile between biosimilars and its originators. However, monitoring the useof biologics, including biosimilars, is particularly needed inthe pediatric setting as risks and co-morbidity profiles inchildren may be different from adults[24,25].

**The indian perspective**

India approved its firstbiosimilar much before the United States and Europe and has a thriving ecosystem for biosimilars which is why Indianpharmaceutical companies have risen as the globalmarket leaders in biosimilars.The first biosimilar was approved and marketed in Indiain 2000 for hepatitis B[39], although no specific guidelinewas available at that time for the development andmarketing of biosimilar in India. Since then many other biosimilars have been approved and marketed by various pharmaceutical countries. Herceptin (Active drug Trastuzumab) was the first biologic manufactured by an Indian company to get approval from FDA and was marketed in the USA.No specific guideline was availablefor "similar biologics" (biosimilars are called Similar Biologics in India), despite the fact that Indiawas one of the first countries in the world to use it,and approval process of biosimilars is more cumbersome and complicated than other genericdrugs. To address the issues and challenges associated with the development of similar biologics, CentralDrugs Standard Control Organization (CDSCO) in collaboration with the Department of Biotechnology(DBT) has developed "Guidelines on Similar Biologics;Regulatory Requirements for Marketing Authorization in India in 2012 and revised it in 2016[40-42]. It addresses the regulation of manufacturingprocess as well as quality, safety, efficacy of similar biologics along with the pre and post marketing regulatory requirements for them.

Although the biosimilar space is still growing and evolving in the United States, India is a significant player in the world in manufacturing and using of biosimilars[43] and has the potential to become a global leader in the future. The examples of some FDA approved biosimilars and their uses[10-13,26-38] are shown in Table 2.

**Conclusion:**

In conclusion, it is clear that the introduction of biosimilarsinto the conventional treatment landscape is imminent. These agents have the potential to increase competition and minimize rapidly increasing healthcare costs and at the same time enable greater patient access.However, in order for the full potential of biosimilars to manifest,several challenges such as distribution considerations, pricing and reimbursement,and formulary decisions, must be faced. Increased education and awareness of all involved parties, from treating physicians, pharmacists,and health care administrators to patient consumers,will be the cornerstone for building widespread acceptance.These educational efforts will need to emphasize an understanding of regulatory standards for biosimilar approval, preclinicaland clinical data requirements, and the meaning ofsimilarity with regard to efficacy and safety.

**Table 2.** Examples of some FDA approved biosimilars and their uses:[10-13,26-38]

| Reference product | Class/mechanism of action | Patent expiration | Biosimilars with phase III clinical trials/comments |
|---|---|---|---|
| Filgrastim | G-CSF | 2013 | Filgrastim-sdnz |
| Epoetin alfa | Erythropoeitin | 2013 | Epoetin zeta |
| Pegfilgrastim | Pegylated G-CSF | 2015 | MYL1401H(Mylan/Biocon) and CHS-1701 (Coherus)accepted for FDA review |
| Cetuximab | EGFR inhibitor | 2016 | ABP94 (Amgen) |
| Rituximab | CD 20 inhibitor | 2016 | BCD-020 equivalent PK/PD, efficacy, safety in indolent NHL;RTXM83 equivalent PK, safety in DLBCL |
| Bevacizumab | VEGF inhibitor | 2019 | BCD-021 showed equivalent efficacy, safety, immunogenicity in NSCLC; |
| Trastuzumab | HER2 inhibitor | 2019 | CT-P6 (Biocon) showed equivalent efficacy, safety; Myl1401O (Mylan/Biocon) accepted for FDA review |

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# Anxiety Disorders : A Brief Delineation

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Anxiety disorders are the most common psychiatric disorders of childhood. Symptoms of anxiety affect many children. Anxiety is a normal phenomenon and is not always considered pathologic. But when it is highly activated and becomes disabling and significantly interferes with social interaction, development or quality of life and produce low self-esteem, social withdrawal and academic underachievement, it can be termed a disorder.

**Normative fears**

Fears follow a predictable developmental pattern. Neonates are believed to have no fear, whereas young infants whose faces are covered with a sheet of cloth struggle to toss off the same.

**Stranger anxiety**

Most infants exhibit stranger wariness or anxiety in response to unfamiliar person, place and object, beginning at 7 to 9 months of age.

**Behavioral inhibition**

Behavioral inhibition in children include shyness, fearfulness and withdrawal about unfamiliar people and new places associated with physiological arousal. Most children with behavioral inhibition do not develop anxiety disorders in future. It is seen in about 10-15% of the children at 12 months of age. Behavioral inhibition is a stable trait in a subset of children. The children with stable and high level of inhibition are more likely to develop anxiety disorder in future than those whose behavioral inhibition fluctuates over time. A family history of anxiety disorders in behaviorally inhibited children predicts a significant anxiety level in later life. The infant who is excessively clingy and difficult to calm during pediatric visits should be followed for signs of anxiety disorders.

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**Age of anxiety (2 to 5 years)**

Preschoolers typically have specific fears related to the dark, animals, loud noise, monsters and normative separation anxiety. They are also particularly fearful of physicians, hospitals and getting hurt. “Just right” phenomenon often is a cause of anxiety for preschool children. “Just right” obsessions are thoughts and/or feelings that something is not quite right or that something is incomplete. “Just right” phenomenon is said to be present when children insist on certain routine or orderliness and have obsessiveness of how they want things to be. It peaks at 3 years old and starts decreasing with age.

**School-aged children**

between 6 years and adolescence tend to have more abstract thoughts. Most of them abandon the imaginary fears of early childhood. They develop other fears like getting ill, natural disasters, traumatic events, going into the next grade, being alone and being kidnapped. They are also afraid of death of their parents.

**Fears during adolescence**

These are related to social functioning such as public speaking or talking to members of opposite sex. They are concerned about their appearance and peer rejection. Often previously resolved anxiety issues occur again in adolescence. General worrying about school performance, fear of negative evaluation and anxiety about social competence are common and subsides as the teen matures.

The anxiety disorders can be broadly classified by the primary symptom they present with. According to the primary symptom, they may be categorized into the following conditions.

(a) Worry

(b) Fear

(c) Panic

**Worry**

Worries can be described as "internal rumination about the potential to experience negative outcome from typically benign, everyday events". It is focusing one's thoughts on all negative outcomes and spiraling into extremes. It is often accompanied by somatic symptoms such as stomach upset and headache. The typical feature of these disorders is the persistence of worry in one or more areas of child's life. These conditions can be classified into two categories by its association with unusual behavior or not.

**(A) Worry without unusual behavior**

***Generalized anxiety disorders*:**

It is characterized by excessive worry over many issues. Children tend to worry excessively about their competence or the quality of their performance at school or in sporting events. If chronic, it may lead to symptoms of depression or somatic complaint like abdominal pain, nausea, appetite loss and headache. Diagnostic criteria are as follows –

(i) Excessive worry about various issues for more than 6 months

(ii) Difficulty in controlling worry

(iii) Anxiety and worry are associated with 3 of the following -

  (a) Restlessness
  (b) Being early fatigue
  (c) Difficulty in concentration
  (d) Irritability
  (e) Muscle tension
  (f) Sleep disturbance

(iv) Anxiety, worry or physical symptoms cause significant distress or impairment.

***Adjustment disorder with anxiety :***

It is an excessive or maladaptive response to a stressor, which is out of proportion to that stressor. The maladaptive response is manifested as excessive worry. The stressors may be parental divorce, social separation, illness, injury, moving, academic failure or peer conflict. DSM-5 diagnostic criteria are as follows :

(a) Symptoms develop within 3 months of stressor

(b) Significant impairment results

(c) Symptoms do not meet the criteria for an alternative anxiety disorder

(d) The symptoms do not represent bereavement

(e) The symptoms subside 6 months after termination of stress.

**(B) Worry with unusual behavior**

***Obsessive compulsive disorder (OCD) :***

It is characterized by obsessive worries that are briefly relieved by compensatory compulsive behavior. ***Obsessions*** are recurrent and persistent thoughts, urges or images that the individual attempts to ignore or suppress. Common obsessions are fear of contamination or illness, thoughts of harming loved ones or oneself, guilt regarding sexual thoughts and images of violent or horrific scenes. ***Compulsions*** are repetitive and excessive acts that the patient performs to reduce the anxiety elicited by obsession. Compulsion may include actions such as repetitive hand washing, checking locks or mental acts such as repeating certain words or counting internally. Some patients need to perform a particular action a specific number of times in order to satisfy the compulsion. Children generally present with vague anxiety symptoms or poor concentration before clear obsession and compulsion are seen. In children, OCD is highly co-morbid with tic disorders and ADHD.

***Pediatric autoimmune neuropsychiatric disorder associated with streptococcus pyogenes ( PANDAS ) :***

This term has been proposed for a group of neuropsychiatric disorders (particularly OCD and tic disorder) for which a possible relationship with Group A Streptococcal (GAS) infection has been hypothesized. It has been suggested that this group of patients with OCD and tic disorders may produce autoimmune antibodies in response to a GAS infection and then that antibodies cross-react with brain tissue. Increased antibody titers of antistreptolysin O and antideoxyribonuclease B along with increased basal ganglia volume have been observed in this subtype of OCD patients.

**Fear**

Fear is traditionally defined as "an unpleasant emotion caused by the belief that someone or something is dangerous, likely to cause pain or a threat." Many times fear is based on projection of what could happen and not what actually is occurring in the moment.

All people experience fear as an emotion. It becomes a disorder when it causes significant functional impairment. Fear may be spontaneous or may arise from previous traumatic experience.

**(A) Fear arising spontaneously**

***Specific phobias :***

It is intense fear upon exposure to a particular stimulus or situation or sometimes thinking about the stimulus. Common specific phobias include animals, height, enclosed spaces, exposed blood, needle etc. The fear is out of proportion to the actual danger. The fear in children may be expressed by clinging, crying, having a tantrum or freezing. Specific phobias peak in childhood and early adulthood.

***Social anxiety disorder (social phobia) :***

It is a specific phobia where there is marked fear or anxiety about one or more social situation in which the individual is exposed to possible scrutiny by others. In children, the anxiety must occur in peer settings and not just interaction with adult. Children with social anxiety often refuse group play, stay close to familiar adults and appear excessively timid in unfamiliar situations. Children may have somatic complaints like headache or stomachaches which subside when the child is allowed to remain in home. In adolescence, social phobias are twice more common in boys than in girls.

***Separation anxiety disorder*** :

The fear in this disorder is separation from a specific attachment figure or figures. Fear of separation is normal in infants and children aged 6 to 30 months, but should be considered abnormal if increasing or not declining beyond this age. Diagnosis requires the presence of symptoms for more than 4 weeks. At least 3 of the following symptoms should be present.

(a) Distress with separation

(b) Worry about losing someone

(c) Worry about an event causing separation

(d) Refusal to go away from home

(e) Refusal to fall asleep

(f) Repeated nightmares of separation

(g) Somatic complaints when separation occurs or anticipated (stomach ache on school days)

***Selective mutism*** :

This is persistent failure to speak in specific, but not all, situation. Children with selective mutism talk almost exclusively at home but shy in public, school or daycare center. Diagnostic criteria include the following.

(a) Consistent failure to speak in specific social situation

(b) Failure to speak interferes with achievement or social communication

(c) Duration of at least 1 month

(d) Failure to speak is not due to lack of knowledge of the spoken language

(e) Disturbances is not better explained by a communication or other psychiatric disorders.

**(B) Fear arising from traumatic events**

***Post-traumatic stress disorder (PTSD) :***

It is the development of characteristic symptoms following exposure to a traumatic event. A traumatic event is defined as an exposure to actual or threatened death, serious injury, sexual violence or physical abuse. Exposure to a traumatic event may be directly experiencing the event, witnessing the event, learning the event occurred to a family member or close friend. Sometimes the parents may be unaware of exposure to trauma like bullying in school or in the community. Sometimes the trauma may be within the family like pending divorce or serious illness in parents. Three clusters of symptoms are essential for the diagnosis of PTSD.

***Re-experiencing :***

Persistent re-experiencing of the stressor through :

(1) Distressing memories of the event

(2) Dreams in which the content or effect of the dream is related to the event (in children does not need to be related to the event )

(3) Dissociative reaction in which the individuals feel the event is recurring (flashbacks)

(4) Psychological distress at exposure to reminders of the event

(5) Marked physiological reaction to the reminder of the event

***Avoidance :***

Avoidance of external reminders – Children may avoid people, conversation or they may avoid physical activities, places or physical reminders that arouse recollection of the traumatic event.

***Hyper-arousal :***

(a) Irritable behavior and angry outburst with little provocation

(b) Reckless or self-destructive behavior

(c) Exaggerated startle response

(d) Problems with concentration

(e) Hypervigilance

(f) Sleep disturbance

***Acute stress disorder :***

It is another diagnostic category. It is the persistence of some symptoms for 3 days to 1 month. The difference between acute stress disorder and PTSD is that PTSD must include symptom from each of the three symptom clusters, which is not needed for the diagnosis of acute stress disorder.

**Panic**

***Panic disorder :***

Panic disorder is characterized by recurrent and unexpected panic attacks. Panic attack occurs suddenly, peaks within 10 minutes and often resolves without intervention. For the diagnosis of the panic attack at least 4 of the following symptoms should be present.

1. Palpitation
2. Diaphoresis
3. Trembling or shaking
4. Shortness of breath or sensation of smothering
5. Feeling of choking
6. Chest pain
7. Nausea or abdominal discomfort
8. Dizziness or feeling faint
9. Chills or heat sensation
10. Paresthesia
11. Derealization ( feeling of unreality )
12. Feeling of losing control or going crazy
13. Fear of dying

The hallmark of panic disorder is persistent concern about having future attacks and avoidance of situation where attacks have occurred. PD is uncommon before adolescence. Peak age of onset is 15 to 19 years and occurs more often in girls.

***Agora phobia :***

It is characterized by intense anxiety over developing a panic attack or other incapacitating or embarrassing symptoms in a place from which the person cannot escape or in which help may not be available. For the diagnosis of agoraphobia there should be anxiety manifestation in at least 2 of the 5 following situations.

1. Riding public transportation
2. Being in open spaces
3. Being in enclosed spaces
4. Standing in a line or in crowd
5. Being outside of home alone

The anxiety is present almost every time an individual is exposed to a particular situation. The agoraphobic situations are actively avoided. The situations are endured with intense anxiety and often require the presence of companion. Agoraphobia may be present in childhood but the peak age of onset is late adolescence.

**Further reading**


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# Cardiological Manifestations Evolving as Systemic Autoimmune Diseases with Myocarditis: Two Case Reports

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***Abstract:***

*Children sometimes present to the emergency with cardiac manifestations, some of which eventually are diagnosed as manifestations of rheumatological diseases like Systemic Lupus Erythematosus (SLE) or arthropathies. While cardiac involvement is known in these cases, but their presentation solely as a cardiologic event initially is not widely known. The following two case reports depict how cardiological emergencies ultimately evolves as systemic autoimmune diseases with atypical involvement like myocarditis with heart failure.*

***Key words:*** *Myocarditis, SLE, SJIA, Cardiac manifestations.*

## Introduction

Childhood rheumatic diseases comprise of a heterogeneous group of uncommon diseases which are categorized under autoimmune and auto-inflammatory conditions[1] collectively termed systemic auto immune diseases (SIDS). These diseases have multisystem involvement with a variety of clinical manifestations which represent diagnostic and therapeutic challenges. Systemic lupus erythematosus (SLE) is a common chronic autoimmune disorder causing injury to many organ systems. Cardiac complications of lupus affect most parts of the heart which has been described since the early 20th century and include pericarditis, myocarditis, endocarditis and coronary artery disease[2].The cardiac involvement in Systemic Juvenile Idiopathic Arthritis (sJIA) was first described by Still in 1897[3]. Symptomatic cardiac involvements in the form of pericarditis and peri-myocarditis and heart failure is known though uncommonly in children with sJIA[4]. Myocarditis as a cardiological manifestation is less known in these rheumatological disorders, further uncommon is their presentation as an emergency or at the onset, at the time of diagnosis.The cardiovascular system and in particular the myocardium are often critical targets in SIDs, even in asymptomatic patients, leading to a relevant negative burden on prognosis[5]. Hence following case reports focusses on atypical cardiological presentation and involvement of rheumatological disorders which has a significant role in morbidity and mortality if not detected early.

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## Case report 1

A young boy of 6 years was admitted with history of fever and respiratory distress of increasing severity for about a week referred as a case of pleural effusion with intercostal chest drain i*n situ*. The child also had antecedent history of cough for last three months with loss of weight, though no contact history of tuberculosis was reported. Examination revealed tachycardia, tachypnea and auscultatory findings of bilateral basal crepitations, decreased breath sounds and gallop rhythm without any murmur. There was tender hepatomegaly (5cm) without any ascites or splenomegaly. Initial investigations revealed anemia (Hb 5 gm/dl)with leucocytosis (22400/cu.mm.) and high ESR (65mm/1st hour), while other laboratory parameters were within normal limits. The pleural fluid when analysed, was reported to have high protein 5gm/dl, cell count 3500/cu.mm (predominantly lymphocytic and increased mesothelial cells). Electrocardiogram showed ST-

T changes and a bed side echocardiography suggested pericarditis with poor biventricular systolic function (EF 43%) with mild pericardial effusion. The child was managed in PICU conservatively and started on anti-tubercular drugs based on above reports alongside management of heartfailure.

Though there was initial response over next few days, subsequently there was again an effusion on the right side of chest requiring intercostal chest drain (Fig 1). A repeat echocardiography showed further accumulation of pericardial fluid requiring peri-cardiocentesis. Meanwhile CBNAAT report came to be negative and symptoms of persistent heart failure, recurrent pleural and pericardial effusion, recurrent pallor and chest infiltrates on HRCT prompted for immunological testing and the child was started with pulse methyl prednisolone therapy for five days. This time the child improved gradually by day 9 of admission and eventually ANA report came out to be positive in 1: 320 dilution with low C3 (59mg/dl), positive dsDNA, corroborating the diagnosis of SLE with suspected myo-pericarditis. Here CPK-MB was high though Troponin levels were normal. He was continued on oral corticosteroids and kidney biopsy later revealed class II B lupus nephritis. Child is now doing well on regular follow up.

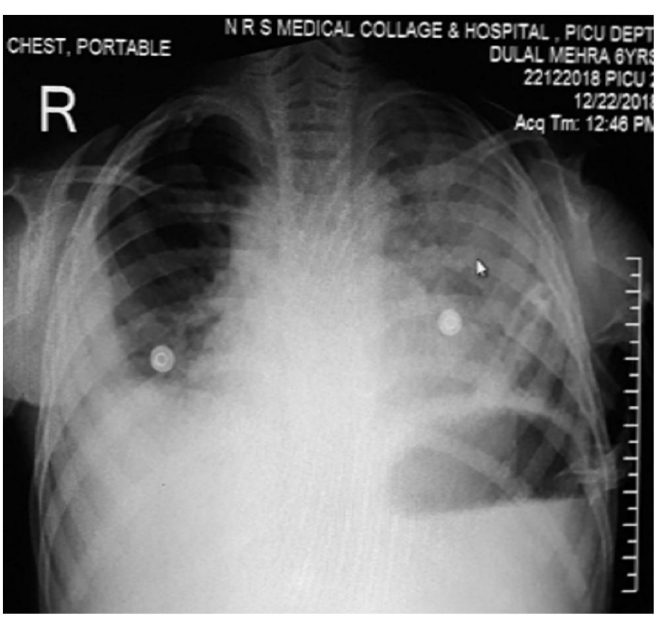


Fig 1: Chest X-ray of Case 1 showing bilateral pleural effusion and left sided ICD in situ

**Case report 2**

Eight year old girl child admitted with history of worsening respiratory distress with palpitations since last fifteen days worsening on supine position.She had a past history of painful restricted neck movements since 4 years of age with painful swelling of large and small joints of bilateral upper and lower extremities (Fig 2) along with fever requiring hospital admissions. Child was non-compliant and lost to follow up suffering from recurrent similar episodes. This time she had tachycardia, tachypnoea, and low volume irregular pulses with hypotension and pallor with axillary and cervical lymphadenopathy on admission. There was bilateral basal crepitations with hyperdynamic apex, hepatosplenomegaly, engorged jugular venous pressure and gross musculoskeletal abnormality with signs of inflammation in bilateral upper and lower limbs small

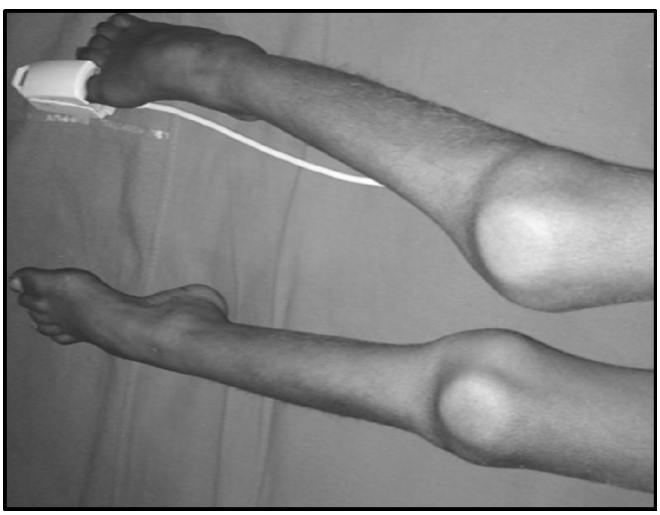

Fig 2: Joint changes in Case 2.

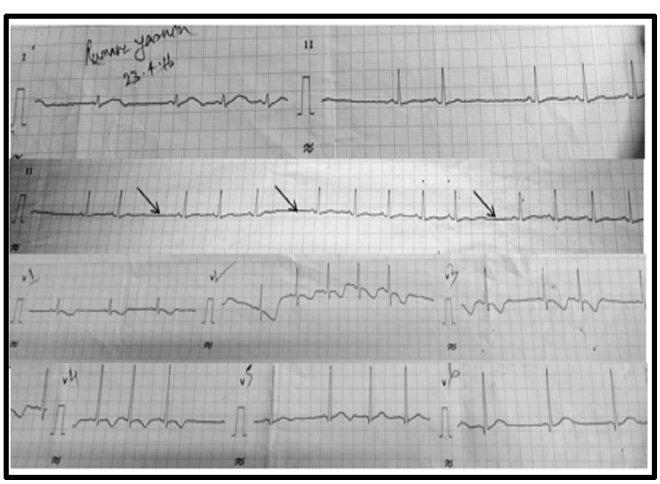

Fig 3: ECG Tracing of Case 2.

and large joints. Investigations revealed anemia (Hb 8.1gm/dl), high ESR (85mm in 1st hour) and average CRP (20mg/dl) with cardiomegaly in chest skiagram while others were within normal limits. CPK-MB levels reached 2500 IU/L. Electrocardiogram features were suggestive of type II heart block with ST-T changes in chest leads (V2-V7) with Qtc 480 ms (Fig 3). Echocardiography corroborated the features of heart failure showing left ventricular dysfunction with a LVEF of 35%. Child was managed in PICU with initial inotropic support and other supportive treatment. X-ray neck and hand revealed osteopenia around joints, bony fusions with reduction in joint spaces and hence this case was provisionally diagnosed to be SJIA with cardiac decompensation possibly due to myocarditis. Loading dose of methyl prednisolone initiated along with ibuprofen and methotrexate as anti-inflammatory therapy. Repeat echocardiography and electro-cardiogram showed reversal of abnormalities with LVEF 50% after 5 days of definitive management. Child is now on regular follow up and doing well.

**Discussion**

SLE is an immunological disorder involving multiple organ systems with varied manifestation. Cardiovascular (CVS) manifestations involving pericardium, myocardium and endocardium are known to occur in upto 30% of children with SLE[6,7]. Myocarditis and heart failure as initial manifestation or presenting symptom is rare[8]. The clinical diagnosis of myocarditis happens only in around 10 % cases, but it is more commonly found in autopsy studies, thereby stating sub-clinical nature of lupus-associated myocarditis[9].

SJIA is a chronic auto-inflammatory disease of childhood characterized by quotidian fever, evanescent rash, serositis, lymphadenopathy, splenomegaly, and synovial joint inflammation[10]. Myocarditis with or without pericarditisproduces more expressive clinical manifestations like congestive heart failure and arrhythmias, and even death, though its presentation as an isolated emergency is rare in this age group[3].

Endomyocardial biopsy though is a gold standard for the diagnosis of myocarditis[11], using current histological, immunological, histochemical, and molecular tools, it provides differentiation between infectious and non-infectious myocarditis but carries a high risk of mortality in sick children, hence not carried out both the cases. In such scenario, the presence of global hypokinesia with a low LVEF on echocardiography is a strongly points towards the diagnosis as suggested in previous these case reports and in present literature.

Recently cardiac involvement in SIDs can be assessed by CMR tissue characterisation with T1 and T2 weighted imaging and late gadolinium enhancement cardiac magnetic resonance imaging is being used for myocarditis which also helps in classification and prognostication with the help of Lake Louis classification[12], but was out of scope in our set up.

Myocarditis in the second case was presumed due to the disease activity of sJIA because of simultaneous clinical deterioration with serositis, acutely raised inflammatory parameters. It was further supported by marked improvement with aggressive immunosuppressive therapy. Treatment with NSAIDs, DMARDs like methotrexate and glucocorticoids have been recommended by American college of rheumatology guidelines following which our case was treated with beneficial result[13]. Anakinra a novel IL-1 receptor antagonist and tocilizumab IL-6 receptor antagonist are now being used as new modalities of treatment as depicted by some case reports[14].

There is lack of proper guidelines or evidence based on randomised controlled trials for treatment of lupus myocarditis. Immunosuppressive drugsand decongestants remain treatment of choice[15], as depicted in available literature. Intravenous pulse corticosteroid therapy is an effective option, as has been used in our case. Other options like cyclophosphamide, Intravenous Immunoglobulins and even rituximab have been used effectively in patients with lupus myocarditis[16].

**Conclusion**

These cases highlight systemic autoimmune diseases like SLE and SOJIA though rarely, may even present with features of myocarditis and heart failure and requires urgent diagnosis and treatment. We should always think out of the box while dealing cardiac emergencies and explore rheumatological possibilities. It is high time we start considering rheumatological causes among first line investigations for rapid diagnosis and early therapy.

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*Informed consent taken from both cases and photographs reproduced with permission.*

Source of support and conflict of interest nil.

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# Purpura Fulminans

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A late preterm (36 weeks) baby presented on day twelve with poor feeding, lethargy and bluish discolouration of right foot and leg (Fig 1) and (Fig 2). At the time of admission, vitals were stable, $SaO_2$ 95% in room air, femoral pulse was palpable, capillary blood glucose was normal. Complete blood count shows Hb 11.7 gm%, TLC 27,000 N60, L33, Platelet 76,000, CRP 70.7. Urea 117, creatinine 1.79, Sodium 159, potassium 3.6. PT, APTT was prolonged. FDP- 4960 ng/ml (N < 500ng/ml). Protein C and protein S activity value was in the lower range of normal limit.The baby was managed with IV antibiotic (Meropenem, teicoplanin), FFP transfusion,correction of dehydration, sodium-correction and regular dressing. Blood culture showed growth of MRSA. CSF study was normal. IV antibiotic was continued along with meticulous assessment of the damaged tissue. The baby improved and discharged without any need of amputation Fig 3. by supportive management and antimicrobial therapy.

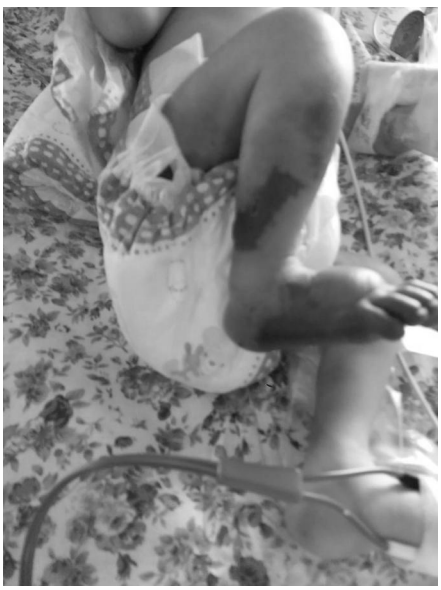

Fig 1: Bluish discoloration of the right foot and leg (Lateral view)

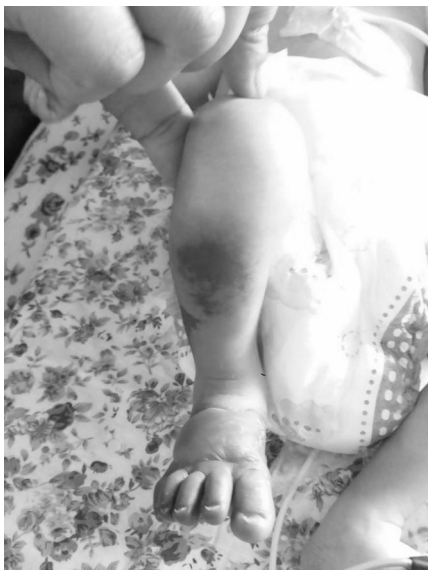

Fig 2: Bluish discoloration of the right foot and leg (Front view)

Fig 3: Restoration of colour with intact skin following supportive management and antimicrobial therapy

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Purpura fulminans is an emergency medical condition and requires prompt diagnosis and management.First described in 1884, purpura fulminans remains a relatively rare disease. It is an acute rapidly progressive purpuric rash characterized by coagulation of the microvasculature, which leads to purpuric lesions and skin necrosis.It is often accompanied by disseminated intravascular coagulation,circulatory collapse and multiorgan failure.Purpura fulminans is associated with a more than 50% mortality rate in children and is usually associated with major long-term morbidity in those who survive The mortality rate is now decreasing with supportive care, improved management of secondary complications, and in some cases specific treatments, but it remains a disabling condition often resulting in major amputations in those who survive.

Based on the triggering mechanism purpura fulminans may be classified into three forms.Hereditary deficiency of the anticoagulants protein C, protein S, and antithrombin III presents as neonatal Purpura fulminans. It manifests very early in life and treatment is aimed at these deficiencies[1]. The hereditary neonatal form with severe protein C deficiency occurs in about 1:1,000,000 live births[2]. Acute infectious purpura fulminans is the most common type. It manifests as a skin finding in the most severe septic patients as well as in necrotizing fasciitis with a predilection to certain infectious agents.Acute infectious purpura fulminans can be seen in up to 10% to 20% of patients who develop *meningococcal septicemia. Meningococcus* and *Streptococcus pneumoniae* were identified as the most common bacterial triggers. *H. influenzae,Staphylococcus aureus and* Plasmodium falciparummay also cause Purpura fulminans. Rarely it may occur following varicella infection. Acute infectious purpura fulminans has been found to be more common in patients who are physically or functionally asplenic. The organisms responsible for acute infectious Purpura fulminans in neonatal period are gram negative bacteria, staphylococcus and Gr B streptococcus.Idiopathic purpura fulminans, the third type and is thought to be a post-infectious autoimmune disorder often following an initiating febrile illness, which later leads to rapidly progressive purpura. In this form, a relative deficiency of protein S is believed to be cause of the disorder.The idiopathic post-infectious form is very rare with only a few hundred cases reported.

**Pathophysiology**

Neonatal purpura fulminans is associated with a hereditary deficiency of the anticoagulants protein C and S. These proteins are vitamin-K dependent cofactors which are pro-fibrinolytic. Protein C is one of the major inhibitors of the coagulation system which when activated inhibits factor Va and VIIIa which in turn down-regulate thrombin synthesis. Neonates typically present with massive venous and arterial thrombosis of the skin and other organs within 5 days of birth.

Acute infectious purpura fulminans is the most common type and is associated with an acquired deficiency of protein C. The mechanism involves a disruption of the coagulation balance. Bacterial endotoxin triggers consumption of proteins C and S and antithrombin III. This pro-coagulative state leads to thromboses of dermal vessels and is associated with disseminated intravascular coagulation. The skin lesions may present early as petechial rashes. These rapidly progress to larger ecchymotic areas. Later in the course, hemorrhagic bullae may form which contribute to the classic hard eschars characteristic of purpura fulminans.

Idiopathic purpura fulminans, the rarest form of the disease, has been associated with the development of anti-protein S antibodies. These antibodies bind to protein S and get excreted. This causes to a transient protein S deficiency which leads to hypo-activation of the protein C pathway and a hypercoagulable state similar to what was described above.

**Evaluation in a case of neonatal purpura fulminans**

Specific levels of antithrombin III, free protein C, and free and total protein S may help to establish the diagnosis of hereditary form of the disease.

Searching for inciting infection with labs (Sepsis screen), cultures, and imaging according to neonatal sepsis guidelines.

Because of the strong association with disseminated intravascular coagulation, one should also evaluate for thrombocytopenia, elevated coagulation factors

(PT, PTT), increased d-dimer assay (or serum fibrin degradation products), and a decreasing fibrinogen level.

**Management**

The treatment of all types of purpura fulminans starts with supportive care and adequate hydration. This is important because of the widespread thrombosis associated with this disease can lead to damage of multiple end organs. Simultaneously, finding and treating the underlying cause is essential. Antibiotic should be continued till acute infectious purpura fulminans is ruled out.Anticoagulation may be stared to prevent further necrosis. There may need for replacement of blood, factors, and platelets lost because of both the pro-coagulable state and DIC. Finally, early surgical debridement for areas which have become necrotic has been shown to decrease mortality.

In the neonatal form of the disease hydration, platelet transfusion, followed by an assessment of protein C and S levels followed closely with fresh frozen plasma transfusions are the mainstay of treatment. Heparin and warfarin have been used as anticoagulants, and later protein C concentrate can be added if this deficiency is found[3].

The treatment of idiopathic purpura fulminans is similar to what is described above. Additionally, there may be a role for immunomodulation with corticosteroids.

In the acute infectious form, broad-spectrum antibiotics should include coverage of *Neisseria meningitidis, Streptococcus, Staphylococcus*, and Clostridia species and additionally a gram negative coverage for neonatal Purpura fulminans. Often carbapenem and vancomycin or teicoplanin are used.Beta lactam-beta lactamase inhibitor combinations may be used in less severe cases and when CNS infection has been ruled out . Clindamycin is often included as it has specific properties which inhibit some of the toxins which allow this disease to progress. IVIg therapy is also used because of antibodies to these toxins. In acute infectious purpura fulminans, the decision to anticoagulated is based on the occurrence of concurrent DIC[4,5].

In all types of purpura fulminans, the role of repeated tissue assessments , regular dressing with debridement of affected areas if needed should get priority and then only we will be able to save many amputations.

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# Sinister Guests And A Single Host

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*Abstract*

*The association between Leptospirosis and hepatitis A has not been frequently referred to in medical literature, despite being one of the most prevalent diseases in the developing countries consequent to the region's poor health conditions[1,2]. We have reported 2 cases. There is co-infection of Hepatitis A, Leptospiroris and Influenza H1N1in case 1 and co-infection of Hepatitis A and Leptospirosis in case 2.*

## Introduction

Hepatitis A virus (HAV) infection occurs throughout the world but occur more frequently in developing countries like India. Classical presentation of Hepatitis A is that jaundice occurs after prodromal illness like fever and vomiting and by the time jaundice appears fever disappears.However spectrum of leptospirosis ranges from mild infection to severe form of multiorgan dysfunction. Icteric form of leptospirosis occurs in < 10% of cases, and is less common in children[3]. The majority of leptospira occurs from exposure to water contaminated with rat urine. Spread of Hepatitis A is predominantly by feco-oral route. The mean incubation period of HAV is about 3-4 weeks whereas it is 2-20days for leptospira[3,4]. Similar clinical presentation and simultaneous transmission of these diseases can cause substantial misdiagnosis.

Influenza A virus is a single-stranded ribonucleic acid (RNA) that belongs to the orthomyxoviridae family. The virus usually affects the respiratory tract endothelium, and its shedding lasts for 2–5 days after symptoms begin. The majority of health care providers focus on the respiratory complications attributed to H1N1 infection, and overlook possible multi-organ involvement.

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## Case 1

A 4 year male child admitted with history of fever for last 3 days, vomiting 2-3 episodes and cough for the last 2 days. On examination child was febrile and having tachycardia and tachypnea. He had soft, tender hepatomegaly 4cm below right costal margin and splenomegaly 2 cm below left costal margin. Subsequently,there was deterioration of respiratory symptoms and development of jaundice and yellow discoloration of urine. Baseline investigation were sent and injection ceftriaxone started. Investigation reveals Hb% 10.8 gm/dl, WBC 4000, platelet 1lakh, Ur 28mg/dl, Cr 0.5mg/dl, TB 4mg/dl, DB 2.6, IB 1.4, SGOT 744, SGPT 589. Typhoid, Malaria and Dengue tests were negative. He was positive for hepatitis A and we managed accordingly. Child was deteriorating clinically with high grade fever, worsening of respiratory symptoms and development of ascites. Child was diagnosed to have H1N1 infection and after starting Oseltamivir respiratory symptoms subsided, LFT parameters also started to normalize but the fever was still persisting. Suspecting clinically as scrub typhus, we started doxycycline 5mg/kg/day BD dose, after sending investigations for scrub typhus and leptospirosis. Child dramatically responded within 48 hours and became afebrile and ascites subsided. After that we had report in our hand and it was positive for leptospirosis not for scrub typhus.

**Case 2**

A 2 year female child admitted with history of fever for the last 15 days and jaundice for the last 5 days. On examination the child was irritable, had pallor, icterus and no rash or bleeding. She had hepatomegaly 5 cm below right costal margin, soft, tender, smooth surface and sharp margin, spleen 2 cm below left costal margin. During hospital stay, there was development of ascites, epistaxis, altered sensorium, child was intubated and was on ventilatory supports.

Investigation reveals Hb% 8gm/dl, WBC 18500, N 72%, L 20%, Platelet 1.5 lakh, CRP 10mg/dl, Ur 34 mg/dl, Cr 0.8mg/dl, Bilirubin 8.9gm/dl, SGOT 928, SGPT 526, Albumin 2.9, Globulin 3.4, PT 24.8 INR 2.1, APTT 70.9. Malaria, dengue, typhoid, Hep B, Hep C, and scrub typhus teata negative. Child was positive for hepatitis A and Leptospirosis. MRI report reveals abnormal signal intensities in bilateral periventricular region with small area of restricted diffusion, changes may be due to metabolic encephalopathy, HIE or encephalitis

Child was deteriorating with bleeding from multiple sites, ascites, worsening of jaundice and development of hepatic encephalopathy. Further, there was more derangement of PT, APTT, INR and LFT parameters.

Child was managed symptomatically as viral hepatitis. PRBC, platelet and FFP transfusion were done several times. Child was on injection ceftriaxone initially, after getting leptospirosis IgM report positive, we had started tab doxycycline but there was no sign of improvement. As Penicillin G is not available now a days so we had started Benzathine penicillin but child died on 25th day of admission due to development of DIC as a consequence of hepatic failure caused by co-infection Hepatitis A and Leptospirosis.

**Discussion**

Human infection with leptospira may range from asymptomatic infection to severe and often fatal multiorgan involvement. Symptomatic infection presents as a relatively mild anicteric febrile illness in over 70% of patient, aseptic meningitis in about 20%, severe leptospirosis with hepatorenal dysfunction (Weils disease) develops in 5-10 % individuals[5,6].

Acute fever with jaundice is diagnostic challenge to the clinicians because many infections caused by hepatotrophic viruses, malaria, enteric, leptospira, dengue can present in a similar way. Thrombocytopenia occurs in more than 50% of pediatric leptospirosis whereas in 4.1% of acute hepatitis A infection[4].Our first case also had thrombocytopenia and it may be because of concurrent involvement by two infections. In our first case, it may be anicteric mild form of leptospirosis and jaundice was due to hepatitis A infection and second case is severe form of leptospirosis, causing death of child due to DIC and hepatic failure.

Coinfection of leptospira and Hepatitis A could be due to exposure of our patient to water contaminated with both organisms. Rodents and domestic animals harbour leptospira and shed the bacteria in urine. They may disseminate the organism to drinking water source[3,4].Cases with mixed infection in clinical practice are diagnostic dilemma to medical fraternity. Various co-infections with Leptospira have been reported with malaria, dengue, and enteric fever[7,8]. Even Hepatitis E and Hepatitis B co infection with Leptospira reports are also available[9,10,11]. Because of epidemiological similarities it is not unusual to see leptospirosis with other infections in tropical countries.

Our cases are probably the first report of mixed infection of Hepatitis A and Leptospira and H1N1 infection in jaundiced children to the best our knowledge.We have not found any cross reactivity of antibody between leptospirosis and hepatitis A. It is imperative to look for leptospira in appropriate setting particularly if jaundice is associated with fever and conjunctival suffusion. It is important that high index of suspicion should be there in endemic areas. Appropriate use of antimicrobials may be lifesaving and decreases the mortality in leptospira. Awareness and optimal use of microbiology lab can overcome such diagnostic dilemma.

H1N1 mainly involve respiratory system[13]. Extra pulmonary problem are not common. Liver involvement is rare and need early identification and treatment. A lack of early intervention can lead to worse outcome. There are few case reports on Acute Hepatic Failure, Liver enzyme dysfunction due to H1N1. We would like to draw attention to the hepatic aspect of human H1N1infection in order to recognise it early and treat it in a timely manner.

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# Spot The Diagnosis : Pre Sternal Swelling in A 10 Year Old Boy

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A 10 year old boy presented with a, soft, diffuse, flat and painless swelling over the sternum. The size of the swelling was 10cm x 10cm and it obliterated the supra-sternal notch. The feel of the swelling was neither cystic nor solid and non- pitting. He had a history of painful enlargement of parotid and sub-mandibular salivary glands following a high grade fever four days before.

The case was diagnosed clinically as presternal lymphedema following mumps. This is also called Gellis sign as described by Sydney S Gellis in 1976[1,2].

Mumps, caused by paramyxovirus, may involve submandibular salivery glands in addition to parotids. Enlargement of submandibular glands might cause obstruction to the lymphatic channels from the anterior-superior chest wall[3] .As a result sternal lymphedema may develop. This is a self liming condition and our patient recovered completely in few days with symptomatic management only. Such a presentation in case of mumps is rare but the clinician should be familiar with this feature which might prevent unnecessary investigations.

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*Figure in the facing page*

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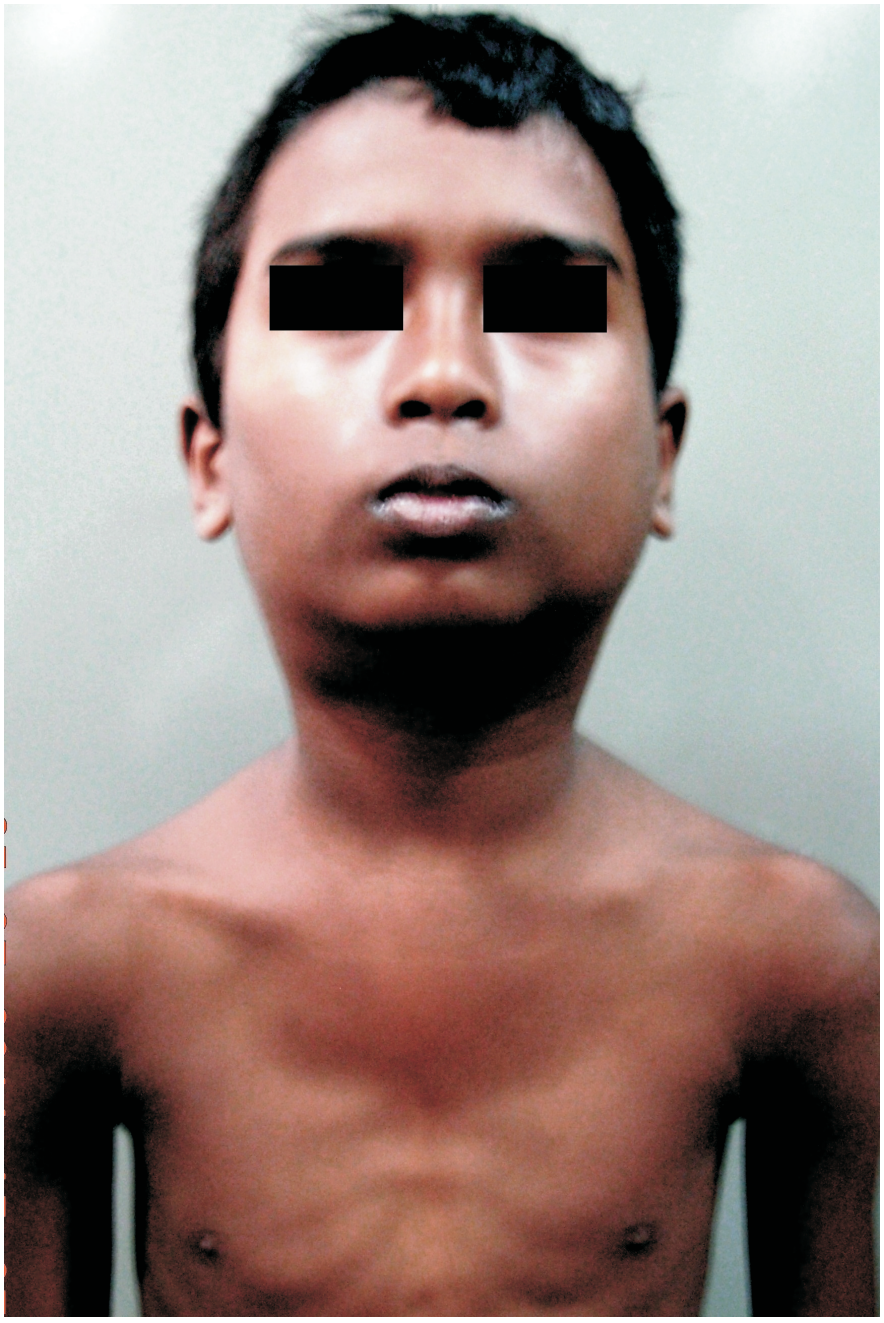

Fig 1: Sternal lymhedema in a patient of Mumps with bilateral parotid and submandibular sialo-adenitis