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**Towards Better Health
Of All Children**

Editor
Dr. Palash Ranjan Gogoi

LETTER FROM THE EDITOR:

It is my pleasure and honor to present the volume 9 and number 1 of The Journal of Indian Academy of Pediatrics Meghalaya State Branch. This is the first time we are bringing out the issue in the period of the year which coincides with the celebration of ORS week and World breastfeeding week.

This issue contains one very nice article on oral rehydration solution. In the second article the common breast feeding problems and their simple solutions are explained by the author. Another article on diagnosis of pediatric tuberculosis definitely carries a lot of practical tips to the readers. The article on use of surfactant in NICU is also an important topic for our young pediatricians who are closely associated with the newborn care in this region. I am sure the article on aerosol therapy also will not disappoint our readers. I believe that the article on diagnosing kidney diseases - is another important topic that will have a lot of practical issues for all of us.

I hope this issue of the journal will be informative to you all. I also sincerely request you to contribute scientific articles for the next issue.

With regards

Dr Palash Ranjan Gogoi

1-7-2016

SECRETARY'S REPORT

Dear members of IAP Meghalaya State branch

It gives me immense pleasure to address you all today. Through the efforts of our editor the Journal of our branch has become biennial. It is a great achievement for any state branch and specially for a small branch as ours. This effort will no doubt contribute a lot in improving the academic environment in our state.

This year has also been noteworthy in that we have been able to adapt the state logo. I would like to thank Dr.Sabrina Yesmin for her contribution in designing the state logo. Another very important achievement this year has been inauguration of our state branch website. This has been possible due to the efforts of our erstwhile member Dr. Richard M. Lurshay and the other members of Nazareth hospital Shillong. I would like to thank them for this.

A host of academic events are planned for this year. We have already held the New Pediatric TB module on 27th February 2016. There are several programmes that are slated for the rest of the year starting with the SOS Hope workshop in July. This has been enumerated in the academic calendar. I invite all members to participate in the events and make them successful.

Wishing you a very fruitful year ahead
Long live IAP

Dr.Saurabh G. Duwarah

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Oral Rehydration Salts (ORS): Saving Lives for Nearly 50 Years

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Introduction:

Globally, diarrheal disease remains one of the leading causes of childhood mortality and morbidity. Although the total number of deaths globally from diarrheal diseases remains high, the overall mortality rate has steadily declined over the last few decades. This decline, especially in developing countries, is largely due to the use of early and appropriate oral rehydration therapy (ORT).

Oral Rehydration Salts (ORS) is the non-proprietary name for a balanced glucose-electrolyte mixture, first used in 1969 and approved, recommended, and distributed by UNICEF and WHO as a drug for the treatment of clinical dehydration throughout the world.[1]

Background:

In the late 1970s, acute diarrhoea was killing around 5 million children each year. In 1968, researchers in Bangladesh and India discovered that adding glucose to water and salt in the right proportions enabled the liquid to be absorbed through the intestinal wall. So anyone suffering from diarrhoea could replace the lost fluids and salts simply by drinking this solution. One of the first large-scale field applications of oral rehydration salts took place in 1971 during the Bangladesh war of independence when outbreaks of cholera swept through refugee camps. Of the 3,700 victims treated with ORS, over 96 per cent survived.[2]

Composition of oral rehydration salts:

The initial ORS formulation contained 90 mEq/l of sodium with a total osmolarity of 311 mOsm/l. Subsequent studies showed that the efficacy of ORS solution for treatment of children with acute non-cholera diarrhoea is improved by reducing its sodium concentration to 75 mEq/l, its glucose concentration to 75 mmol/l, and its total osmolarity to 245 mOsm/l.[1] Studies have shown that with reduced osmolarity ORS solutions, **stool output was reduced by about 20% and the incidence of vomiting by about 30%.[1] In fact, ORS may prevent 93% of diarrhoea deaths.**[7]

TABLE 1. Composition of the new ORS formulation

New ORS	grams/litre	%	New ORS	mmol/litre
Sodium chloride	2.6	12.683	Sodium	75
Glucose, anhydrous	13.5	65.854	Chloride	65
Potassium chloride	1.5	7.317	Glucose, anhydrous	75
Trisodium citrate, dihydrate	2.9	14.146	Potassium	20
			Citrate	10
Total	**20.5**	**100.00**	**Total Osmolarity**	**245**

This ORS composition has passed extensive clinical evaluations and stability tests. The pharmacokinetics and therapeutic values of the substances are as follows[1]:

■ glucose facilitates the absorption of sodium (and hence water) on a 1:1 molar basis in the small intestine;

■ sodium and potassium are needed to replace the body losses of these essential ions during diarrhoea (and vomiting);

■ citrate corrects the acidosis that occurs as a result of diarrhoea and dehydration.

ORT based on Degree of Dehydration :

WHO/UNICEF guidelines suggest ORT should begin at the first sign of diarrhea in order to prevent dehydration.[1,3] ORS may be given by aid workers or health care workers in refugee camps, health clinics and hospital settings.[5] Mothers should remain with their children and be taught how to give ORS. This will help to prepare them to give ORT at home in the future. Breastfeeding should be continued throughout ORT.[4]

Assessment of Dehydration :

The degree of dehydration should be assessed before initiating ORT. ORT is suitable for people who are not dehydrated and those who show signs and symptoms of mild to moderate dehydration. People who have severe dehydration should seek professional medical help immediately and receive intravenous rehydration as soon as possible to rapidly replenish fluid volume in the body.[6]

Table II: Assessment of diarrhoea patients for dehydration

	A	B	C
LOOK AT: CONDITION[a]	Well, alert	Restless, irritable	Lethargic or unconscious
EYES[b]	Normal	Sunken	Sunken
THIRST	Drinks normally, not thirsty	Thirsty, drinks eagerly	Drinks poorly, or not able to drink
FEEL: SKIN PINCH[c]	Goes back quickly	Goes back slowly	Goes back very slowly
DECIDE	The patient has **NO SIGNS OF DEHYDRATION**	If the patient has two or more signs in B, there is **SOME DEHYDRATION**	If the patients has two or more signs in C, there is **SEVERE DEHYDRATION**
TREAT	Use Treatment Pan A	Weigh the patient, if possible, and use Treatment Plan B	Weigh the patient and use Treatment Plan C URGENTLY

[a] Being lethargic and sleepy are *not* the same. A lethargic child is not simply asleep: the child's mental state is dull and the child cannot be fully awakened; the child may appear to be drifting into unconsciousness.
[b] In some infants and children the eyes normally appear somewhat sunken. It is helpful to ask the mother if the child's eyes are normal or more sunken than usual.
[c] The skin pinch is less useful in infants or children with marasmus or kwashiorkor, or obese children.

Treatment Plan A: Home therapy to prevent dehydration and malnutrition[4]

There are ***four rules*** of Treatment Plan A:

Rule 1: Give the child more fluids than usual, to prevent dehydration

Home fluids wherever possible and these should include ***at least one fluid that normally contains salt***

- ORS solution
- salted drinks (e.g. salted rice water or a salted yoghurt drink)
- vegetable or chicken soup with salt.

Unsuitable Fluids:

Especially important are drinks sweetened with sugar, which can cause osmotic diarrhoea and hypernatraemia. Some examples are:

- commercial carbonated beverages
- commercial fruit juices
- sweetened tea.

Other fluids to avoid are those with stimulant, diuretic or purgative effects, for example:

- coffee
- some medicinal teas or infusions.

How much fluid to give

The general rule is: give as much fluid as the child or adult wants until diarrhoea stops. As a guide, after each loose stool, give:

- children under 2 years of age: 50-100 ml (a quarter to half a large cup) of fluid;
- children aged 2 up to 10 years: 100-200 ml (a half to one large cup);
- older children and adults: as much fluid as they want.

Rule 2: Give supplemental zinc (10 - 20 mg) to the child, every day for 10 to 14 days

Zinc reduces the duration and severity of the episode as well as the risk of dehydration and the risk of the child having new episodes of diarrhoea in the following 2 to 3 months

Rule 3: Continue to feed the child, to prevent malnutrition

What foods to give

This depends on the child's age, food preferences and pre-illness feeding pattern; cultural practices are also important. *In general, foods suitable for a child with diarrhoea are the same as those required by healthy children*.

How much food and how often

Offer the child food every three or four hours (six times a day). Frequent, small feedings are tolerated better After the diarrhoea stops, continue giving the same energy-rich foods and **provide one more meal than usual each day for at least two weeks**.

Rule 4: Take the child to a health worker if there are signs of dehydration or other problems

The mother should take her child to a health worker if the child:

- starts to pass many watery stools;
- has repeated vomiting;
- becomes very thirsty;
- is eating or drinking poorly;
- develops a fever;
- has blood in the stool; or
- the child does not get better in three days.

Treatment Plan B: Oral rehydration therapy for children with Some dehydration[4]

Children with some dehydration should receive oral rehydration therapy (ORT) with ORS solution in a health facility following Treatment Plan B.

How much ORS solution is needed?

If the child's weight is known, this should be used to determine the *approximate* amount of solution needed. The amount may also be estimated by multiplying the child's weight in kg times 75 ml. If the child's weight is not known, select the approximate amount according to the child's age.

How to give ORS solution

A family member should be taught to prepare and give ORS solution. The solution should be given to infants and young children **using a clean spoon or cup**. Feeding bottles should *not* be used. For babies, a dropper or syringe (without the needle) can be used to put small amounts of solution into the mouth. Children under 2 years of age should be offered a teaspoonful every 1-2 minutes; older children (and adults) may take frequent sips directly from the cup.

Vomiting often occurs during the first hour or two of treatment, especially when children drink the solution too quickly, but this rarely prevents successful oral rehydration since most of the fluid is absorbed. After this time vomiting usually stops. If the child vomits, wait 5-10 minutes and then start giving ORS solution again, but more slowly (e.g. a spoonful every 2-3 minutes).

Monitoring the progress of oral rehydration therapy

After four hours, reassess the child fully, following the guidelines in Table II.

- If signs of *severe dehydration* have appeared,

intravenous (IV) therapy should be started following Treatment Plan C.

■ If the child still has signs indicating *some dehydration*, continue oral rehydration therapy by repeating Treatment Plan B.

■ If there are *no signs of dehydration*, the child should be considered fully rehydrated.

■ Teach the mother how to treat her child at home with ORS solution and food following Treatment Plan A. Give her enough ORS packets for two days. Also teach her the signs that mean she should bring her child back

When ORT should not be given

In children with:

■ abdominal distension with paralytic ileus, which may be caused by opiate drugs (e.g. codeine, loperamide) and hypokalaemia;

■ glucose malabsorption, indicated by a marked increase in stool output when ORS solution is given, failure of the signs of dehydration to improve and a large amount of glucose in the stool when ORS solution is given.

In these situations, rehydration should be given IV until diarrhoea subsides; NG therapy should *not* be used.

Treatment Plan C: for patients with severe dehydration[4]

Guidelines for intravenous rehydration

The child should be admitted to hospital for intravenous rehydration. In addition, *all* children should start to receive some ORS solution (about 5 ml/kg/h) when they can drink without difficulty, which is usually within 3-4 hours (for infants) or 1-2 hours (for older patients).

Monitoring the progress of intravenous rehydration

Patients should be reassessed every 15-30 minutes until a strong radial pulse is present. Thereafter, they should be reassessed at least every hour to confirm that hydration is improving. If it is not, the IV drip should be given more rapidly.

When the planned amount of IV fluid has been given (after three hours for older patients, or six hours for infants), the child's hydration status should be reassessed fully.

What to do if intravenous therapy is not available

If IV therapy is not available nearby, health workers who have been trained can give ORS solution by NG tube, at a rate of 20 ml/kg body weight per hour for six hours (total of 120 ml/kg body weight). If the abdomen becomes swollen, ORS solution should be given more slowly until it becomes less distended.

Children receiving NG or oral therapy should be reassessed at least every hour. If the signs of dehydration do not improve after three hours, the child must be taken immediately to the nearest facility where IV therapy is available.

ReSoMal (**Re**hydration **So**lution for **Mal**nutrition)

ReSoMal is a powder for the preparation of an oral rehydration solution exclusively for oral or nasogastric rehydration of people suffering from severe acute malnutrition. It is used exclusively under medical supervision in inpatient care, and must not be given for free use to the mother or caregiver.

The original ORS (90 mmol sodium/L) and the current standard reduced-osmolarity ORS (75 mmol

Table III: Guidelines for intravenous treatment of children and adults with severe dehydration

Start IV fluids immediately. If the patient can drink, give ORS by mouth until the drip is set up. Give 100 ml/kg
Ringer's Lactate Solution[a] divided as follows:

Age	First give 30 ml/kg in:	Then give 70 ml/kg in:
Infants (under 12 months)	1 hour[b]	5 hours
Older	30 minutes[b]	2½ hours

- Reassess the patient every 1-2 hours. If hydration is not improving, give the IV drip more rapidly.
- After six hours (infants) or three hours (older patients), evaluate the patient using the assessment chart. Then choose the appropriate Treatment Plan (A, B or C) to continue treatment.

[a] If Ringer's Lactate Solution is not available, normal saline may be used.
[b] Repeat once if radial pulse is still very weak or not detectable.

sodium/L) both contain too much sodium and too little potassium for severely malnourished children with dehydration due to diarrhea. On the other hand, ReSoMal contains less sodium (45 mmol/l) and more potassium (40 mmol/l) as compared to reduced osmolarity ORS.

WHO recommends that children with severe acute malnutrition and who have some or severe dehydration but no shock should receive 5 mL/kg ReSoMal every 30 min for the first 2 h. Then, if the child is still dehydrated, 5–10 mL/kg/h ReSoMal should be given in alternate hours with F-75, up to a maximum of 10 h. ReSoMal can either be prepared from a ready-to-dilute sachet (as per supplier's instructions) or prepared with one sachet of WHO low-osmolarity oral rehydration solution plus 2 L of water with an added 50 g sugar and 40 mL mineral mix or one level scoop of combined minerals and vitamins.[8]

Barriers to Utilization of ORS in the Management of Diarrheoa in Children

Studies have shown that lack of ORS awareness, lack of knowledge on ORS composition and preparation methods and lack of direct medication dispensing in the private sector might be key barriers to ORS use[9]. One of the problems is that the medical establishment is still reluctant to accept ORS. In the United States, for example, it costs almost 10 times as much to treat dehydration with an intravenous drip in a hospital as it does to administer ORS, yet the intravenous method prevails. Drug companies, too, stand to gain more by selling antidiarrhoeal drugs, most of which are useless and some of which are dangerous.[2]

It is our duty as pediatricians to ensure that children with diarrhea have unrestricted access to ORS and its importance in reducing mortality and morbidity be made known to parents and health care professionals everywhere.

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Upcoming academic events:

1. SOS Hope workshop on 27th July, 2016
2. Asthma Training Module (ATM) on 27th August, 2016
3. Cradle to Crayon workshop on 22nd October, 2016
4. TOUCH workshop for Nurses along with Meghpedicon

Common problems of breastfeeding

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It so happens that just when you let out a long sigh of relief thanking the heavens that the birthing process was uneventful, you are bombarded with a zillion queries and problems regarding breast feeding. And we so often don't seem to have enough time to sort out those problems so we mumble and fumble and ultimately resort to bottle feeding to "Tide over" these issues. But a few moments of our time, a ton of patience and sound basics about the physiology of lactation and the knowledge of good attachment will go a very long way in helping the mother and baby take that one important step.

Here's a quick revision of the signs of good attachment of the baby at the breast–

a. The baby's chin is touching the breast–

b. Mouth is wide open–

c. Lower lip is turned outwards–

d. More areola is visible above the baby's mouth than below it–

On careful observation, it will be seen that the baby is taking slow deep sucks, pausing and then swallowing the milk.

A few common hurdles that we face during our post natal rounds and some simple solutions to address them.

Early breastfeeding problems

Baby is not taking feeds. He refuses to feed–

Mother will require practical help to assist her in breastfeeding during the first few days. Encourage the mother to relax, ally her anxieties by responding patiently to her queries, observe how she feeds her baby and teach her the steps of good attachment under supervision.

My milk has not started coming–

This is one of the most common complaints during post natal rounds and it's true that when you try expressing the breast milk manually, milk does not appear. We know that baby's tongue does most of the work in effective lactation process by a peristaltic wave like movement of the tongue which gently 'milks' the lacteal sinuses. Explain to the mother that the baby can get milk out of the breast because of its feeding action, which cannot be done adequately by manual expression and that though the quantity of milk maybe less during the first few days, the thick yellow milk known as the colostrum – it is adequate for the baby.

Breast Refusal and Late Starters

Some babies may have difficulty in attaching at the breast of the mother in spite of the mother being motivated and frequently attempting to breast feed the baby. This may occur without any apparent problem in the baby or the mother. In such infants the drop and drip method to assist the infants can be useful. Mother's milk is expressed into a container and dropped slowly on her breast when baby is assisted at her breast.

Breast conditions

Breast size and Breastfeeding

The breast milk production is dependent on the number of breast milk secreting acinar cells and not on the size of the breast.

Type of Nipple

Some types of nipple like the inverted nipple may pose some problem in breast feeding. Ideally the mother should be primed for breast feeding during her regular antenatal check up. Examination of the breast and a simple nipple protractility test can be done to help in identifying problems that will hamper breast feeding.

Nipple protractility Test: Using the thumb and index fingers the nipple is gently pulled out. A truly inverted nipples 'go in 'on performing this test, whereas average and flat nipples are easily pulled out.

Different types of nipple are the Normal/Ordinary nipples, Flat nipples, Inverted nipples and Long nipples.

Flat Nipples

Such mothers may need some help at the first feed with positioning. Ask the mother to support her breast using four fingers and lift her breast. Mother is then asked to touch the baby's mouth with the nipple, which should be hardened by gentle stimulation. When the baby searches and roots with its mouth wide open, the mother is helped to get a large amount of her areola into the baby's mouth above his tongue. With some help and support most mothers are able to do well. The nipple shape improves further by the baby's suck-

ing action at the breast.

Retracted or Truly Inverted Nipples

It is ideal for mothers with inverted nipples to be in the hospital or to have them come in more often till the baby settles down well at the breast. A simple technique using a disposable syringe can be done to correct inverted nipples. This has to be used several times a day and should also be used just before feeding.

Long nipples

Mothers with long nipples as such may not have feeding problems but sometimes the baby may such only on the nipple. Supervised breast feeding and teaching the mother about good attachment is enough.

Full breast

Few days after delivery, the breast may appear swollen, heavy and hot to touch which on examination feels lumpy. This is normal fullness, signaling the onset of copious milk production. Frequent breast feeding resolves the situation.

Breast Engorgement

A painful condition which usually occurs due to delayed initiation, poor attachment at the breast leading to ineffective removal of the milk or due to copious milk production.

The breasts are swollen and edematous with stretched shiny skin.

Management includes application of warm, moist heat to the breast alternating with cold compresses to relieve edema of the breast tissue; gentle hand expression of milk or by disposable syringe to soften areola to facilitate infant attachment at the breast, gentle massage of the breast and mild analgesic or anti-inflammatory may also be required. It is important to frequently remove the breast milk at least once in 2 hours for the next 3-5 days.

Plugged Ducts

A duct can get blocked by poor drainage of breast of that segment due to ill-fitting bra, tight, constricting clothing or a delayed initiation of feeding, resulting in retention of milk which presents as a palpable lump.

Improving and changing the position of the baby to drain the affected segment, increasing the length and frequency of feeding, gentle massage before and during feeding and warm compresses help to drain the breasts.

Mastitis and Breast Abscess

Mastitis is an inflammatory and/or infectious breast condition - usually affecting only one breast. Signs and symptoms include rapid onset of fatigue, body aches, headache, fever and tender, reddened breast area.

Treatment includes: Immediate bed rest concurrent with continued breast feeding, Frequent and effective milk removal, appropriate antibiotic for a sufficient period of about 10-14 days and comfort measures to relieve breast discomfort and general malaise like analgesics, moist heat or massage to breast.

Mastitis if not treated early, may lead to breast abscess. Breast abscess needs to be drained either by ultrasound guided wide bore needle or by surgical incision and drainage followed by antibiotics for 10 - 14 days and analgesics.

Sore, tender nipples

Nipple soreness may be due to increased surface tension caused by the infant's sucking action. The soreness includes an intense onset at the initial latch on with a rapid subsiding of discomfort as milk flow increases. Nipple tenderness diminishes during the first few weeks. Expressed breast milk applied sparingly to the nipples following feedings may hasten this process.

Traumatized, painful Nipple (Syn: Nipple Fissures, Cracked Nipples)

The possible causes include: ineffective, poor latch-on at the breast, improper infant sucking technique, removing infant from breast without first breaking suction, underlying nipple condition or infection. Initially there may be no fissure or only a linear abrasion may be found but if the cause for the trauma is not attended to, the wound will further widen and deepen which can result in ulceration also.

Treatment include: Assessment of infant positioning and latch-on with correction of improper technique, diagnose any underlying nipple condition and prescribe appropriate treatment. If the nipple is severely traumatized, temporary cessation of breast feeding may be indicated to allow for healing. Ointments are not useful. Manual expression of milk and preferably leaving the affected side exposed to air, application of a few drops of hind milk on the affected side also hastens recovery.

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Paediatric TB diagnosis – hurdles and solutions

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Introduction

Paediatric TB diagnostic strategies differ a great extent from strategies followed in adults. Paediatric tuberculosis diagnosis continues to pose challenges to clinicians. The gold standard of tuberculosis diagnosis, i.e demonstration of *Myco TB* performs poorly in children. The reasons for difficulty in diagnosis in children are several fold and include the following –

i. Paediatric TB is paucibacillary disease – the number of organisms in primary TB lesions are far less than in adult forms of disease (Primary pulmonary complex $10^4 – 10^5$ vs Cavity 10^9 organisms). Because of less concentration of organisms, isolation techniques are less likely to pick up or detect *Myco TB*.

ii. Children of most ages cannot provide a sample of self-expectorated sputum. One therefore needs to collect the sample by other means such as gastric lavage or induced sputum. Adolescents and some older children are able to provide self-expectorated sputum.

iii. Paediatric patients have a **greater proportion of extrapulmonary tuberculosis** compared to adult patients. Collecting a sample for isolating *Myco TB* in such patients have their own set of challenges and frequently need expertise which is not available to the patient at primary levels of care.

In view of the above challenges, isolating *Myco TB* and therefore establishing a gold standard diagnosis is possible in only around **40– 50 %** suspects. Smear positivity rates are to the tune of only **10-15%** in children compared to **80 - 85%** in adults.

Diagnosis of Paediatric TB therefore has to rely on various indirect clues which is followed by attempt at bacteriological diagnosis. The logical sequence that is followed is as follows –

1. Suggestive symptomatology
2. History of contact
3. Suggestive radiology
4. Tuberculin skin test
5. Bacteriological diagnosis

Suggestive symptomatology: The common symptoms of tuberculosis in children are the following–

■ **Fever for 2 weeks or more –** It is of value if the fever has been documented at least once. Fever should be persistent for two weeks or more and unexplained (no other cause can be attributed to the fever).

■ **Unremitting cough for 2 weeks or more.** Cough is one of the most common symptoms with which children present to doctors. To qualify as a significant TB symptom, cough should be unremitting and gradually increasing in severity over 2 weeks.

■ **Loss of weight –** defined as weight loss of more than 5% in the past 3 months with no other apparent cause. In an infant or child in contact with an infectious TB case, not gaining weight should also arouse suspicion

Symptoms of TB are common and nonspecific. Therefore accurate symptom definition is important

■ **Peripheral painless swelling –** suggesting lymphadenopathy. Lymph nodes should be significantly enlarged and are frequently matted. There may sometimes be discharging sinus if the lymphadenopathy has been neglected for a long period.

■ **Meningitis of insidious onset**

■ **Spine gibbus**

■ Any **nonspecific symptoms** in a contact of an infectious TB case – such as anorexia, not playful etc

History of contact: Defined as –

a) In a symptomatic child, contact with a person with any form of active tuberculosis within last two years (One needs to take history of ATT intake in the past 2 years. Need not necessarily be sputum positive if the child is symptomatic because the contact may have had unrecognized pulmonary involvement)

b) Exposure to an infectious TB patient (any case

with laryngeal, airway or lung involvement).

Suggestive radiology: Despite the drawbacks of radiology such as being observer dependant and its inability to give an etiological diagnosis still has to be relied upon in paediatric TB suspects.

Quality of skiagram: While interpreting an x ray film or image one needs to first see that the quality of the film is acceptable. One should first look at **penetration** in the film. In a well penetrated film, the spine should be visualised well through the heart shadow. There should be no **rotation** of the chest skiagram (the costochondral junctions and anterior ends of the ribs should be equidistant from the midline). The film should preferably be an **inspiratory** film (in a good inspiratory film, more than five anterior ends of ribs should be visible above the dome of the diaphragm). There should be no motion artefacts.

CXR is an important tool in children :

Highly suggestive TB patterns: There are **three** patterns on the chest X-ray which are described as highly suggestive of TB –

- Hilar lymphadenopathy
- Miliary shadows
- Chronic fibro cavitatory disease

Only 3 highly suggestive TB patterns on CXR

CXR is an important tool in children

When one gets any of the above shadows on chest x – ray, one gives more weightage to the diagnosis of TB but even these patterns are not diagnostic and one can proceed for bacteriological diagnosis. Specificity increases with suggestive symptomatology and positive TST.

Other patterns on chest x –ray such as consolidations, thin walled cavities, ground glassing, non-homogenous opacities are not sensitive for TB and one may consider a course of antibiotics for 10 days followed repeat chest x- ray after 14 days to look for clearing. (While prescribing the course of antibiotics, one must not use antibiotics such as **aminoglycosides**, **macrolides**, **linezolide** or **clavulanate** which also have anti tubercular activity. Therefore, **antibiotics** such as **amoxicillin** or **cephalosporins** may be used).

Lateral view: lateral view chest x- rays may help to pick up an additional 12-19% of cases mainly from retro cardiac and hilar areas. Lateral views are associated with 3 times more radiation than frontal views.

CECT Thorax – Not routinely recommended because of high radiation cost. It may be asked for rarely, for example when one strongly suspects TB in a case of PUO without any lesion on the chest x-ray or for workup of persistent pneumonia not fitting into any pattern.

CECT thorax can show greater anatomical details such as in mediastinal lymph node size and its character (necrotising or not) or hidden areas and has better delineation of the types of shadows such as consolidation vs atelecto - bronchiectesis. But CT may be too sensitive for our current thinking increasing the risk of over estimation as every lymph node picked up on CT may not be abnormal (without a predetermined size threshold for abnormality). CT has difficulty in distinguishing normal thymus from lymphadenopathy also.

The signs which are considered suggestive of TB on CT are – Cavity, tree in bud pattern and lymph adenopathy with rim enhancement.

USG – USG Chest is a useful tool for detecting pleural effusion and identifying the best place for aspiration, for FNAC or biopsy. USG is the modality of choice to distinguish thymus from anterior lymph adenopathy.

Tuberculin skin test (TST):

Mantoux test is the most widely available and accepted tubercular skin test done in India. The tubercular skin test is a test for delayed hypersensitivity. A positive skin test indicates present or past infection with *MYCO TB* and not necessarily disease. **It is an adjuvant to diagnosis and not a confirmatory test.** TST can be used to screen children exposed to TB or at increased risk of *MYCO TB* infection such as contact with people with contagious TB and HIV infected children.

Points to remember –

- A positive TST is defined as 10 mm or more induration after 48-72 hrs using no more than 2TU RT23 tuberculin
- In HIV co infected, 5 mm may be taken as cut off
- 2 TU dosage is considered most appropriate for routine diagnostic use
- If not available; no more than 5TU should be used
- TST results have to be interpreted with caution because there are several reasons for false positive TST such as use of higher strengths of PPD, BCG vaccination and infection with mycobacteria other than TB.

■ Causes of false negative TST are incorrect technique of administration or interpretation, improper storage of tuberculin, immunodeficiency – primary or acquired, viral infections such as measles or varicella, bacterial infections such as typhoid, leprosy, pertussis, vaccination with a live vaccine in the past 6 weeks, in severe forms of TB such as military or meningitis and in neonates

Bacteriological diagnosis :

Bacteriological diagnosis is the Gold standard and must be attempted in all children with suspected tuberculosis.

Hurdles to bacteriological diagnosis:

Hurdle 1: Access to specimen – most children do not expectorate. Even if they have sputum, they do not cough violently enough to bring it out. They tend to swallow sputum rather than spit it out. Hence sputum in children need to be retrieved.

Solution: In lieu of self-expectorated sputum (which may be available only in adolescents and older children), one may consider the following in children–

I. Gastric aspirate/ Gastric lavage – ideally needs overnight fasting and hospitalisation though one can go ahead with few hours of fasting and one may do the procedure on an ambulatory setting. The procedure is more invasive and needs better trained staff.

II. Induced sputum – fasting is not required (better keep NPO for 3 hours). Can be collected in an ambulatory setting. It is less invasive. Can be learnt easily by paramedics. But the risk of transmission to health care providers is higher with this method hence one should do the procedure taking all precautions to prevent droplet spread such as using a N95 mask or doing the procedure in a negative pressure room

III. Bronchoscopy & broncho alveolar lavage – There is definite utility as workup for persistent pneumonia – when routine investigations for TB are negative and to rule out alternative diagnosis. Bronchoscopic findings of mucosal involvement is more likely to yield AFB in BAL. Also compression of airways, caseation or bronchiectesis may be visualised directly. This is an add on test and stand alone does not give better yield than gastric aspirate. There are no clear recommendations on whether to use it in all patients who have sputum / GA negative with characteristic radiology or to use it selectively. It is therefore guided mainly by the facilities available and the need to arrive at a definite diagnosis.

IV. **For extrapulmonary TB** - One must attempt bacteriological diagnosis by all means – specimens could be pleural biopsy in pleural effusion, FNAC of lymph nodes, CSF in meningitis, intestinal biopsy in intestinal TB etc. But in all cases of extrapulmonary TB, one must try to collect respiratory specimen because, yield is higher in respiratory specimens, e.g: In children with pleural effusion, *Myco TB* culture is positive in 28-40% on GA/IS whereas culture yield from pleural fluid is only about 5%.

Collection of respiratory specimen must be attempted in all cases

■ ***Recommended – Self expectorated sputum or Gastric aspirate on 2 consecutive days***

■ ***Other options could be – GL + IS on Day 1, Induced sputum on two days***

■ ***Repeat collections may be tried if suspicion remains strong***

■ ***BAL may tried in special situations***

Hurdle 2: Low sensitivity of smear and moderate sensitivity of culture examination in children: the following methods to test the respiratory specimens-

I. Smear for AFB: ZN staining is done on the smears. Cheapest, simple, point of care confirmatory test. There is high level of agreement between observers and sensitivity increases with increased number of bacilli on smears. But yield is low for children. Overall smear positivity is only 10-15% in children. Can be performed in sputum and gastric aspirates. LED microscopy may increase the yield marginally.

II. Cultures: Cultures may be done in both liquid and solid media. Almost all specimens may be subjected to culture. Culture greatly increases the yield of detection of *Myco TB*. *Myco TB* culture has a sensitivity of about 45 – 55%. But getting results of culture take time (about 6 wks on an average). One can at the same time get results for drug sensitivity of the specimen isolated. Testing for drug resistance by any method for all retreatment or treatment failure cases is the national strategy at present. This strategy will ultimately be adopted for all pediatric patients.

III. CBNAAT: Cartridge Based Nucleic Acid Amplification Test – In this test amplified DNA is detected in as rapidly as 2 hrs. This is a PCR based test which not only detects *Myco TB* but also provides information on Rifampicin resistance. The test is more

sensitive than smear microscopy for both sputum and gastric aspirate and overall yield in respiratory specimens is about as much or less than cultures. The test has good sensitivity for tissue biopsies, fine needle aspirates, gastric aspirates, sputum, pus samples, CSF and urine but low sensitivity for pleural fluid samples and other body fluids such as pericardial, peritoneal and synovial – therefore the test can be used to diagnose *Myco TB* in various extra pulmonary samples. Limitation of this test may be the cost and scare availability of this test. To circumvent this problem, RNTCP is tying up with a network of labs all over the country to provide this test at subsidised cost and plans are afoot to put at least one machine in each district of the country.

The availability of CBNAAT is expected to solve the problem of low sensitivity of smear examination in children. The test is currently available in the country as Xpert *MYCO TB*/ RIF™ (aka Gene Xpert). CBNAAT will provide results comparable to culture on the same day of collection of sample with additional information on Rifampicin resistance. The test is done in a closed system with automatic processing unlike earlier PCR based tests and is much less likely to be contaminated.

CBNAAT is a new, rapid and highly sensitive tool for TB diagnosis especially for children

The national strategy would be to subject all pediatric samples to CBNAAT upfront. With use of CBNAAT which is a molecular diagnostic technique, one should use the term **"Bacteriologically positive TB"** rather than smear positive TB.

Other tests which are of little utility –

1. IGRA – Interferon Gamma Release Assays – roughly these tests can be called *in vitro* TST using specific antigens that do not cross react with BCG. The information provided by a positive IGRA is that the patient is truly infected (no cross reaction with BCG). Like TST, it also does not make any distinction between infection and disease. Being expensive and more resource demanding, it has little added value in the diagnostic algorithm. Like TST, these also have potential for errors in conducting and interpreting the test. There is also limited data on usage of IGRA below 5 yrs of age. Consensus statement by WHO states that there is not enough data to replace TST by IGRAs in low and medium income countries, typically those with a high TB/ HIV burden.

2. TB serology by ELISA – These tests have poor specificity and sensitivity and are **banned** in India

3. Complete Blood Count & ESR – of no utility because of numerous pre-test variables

4. BCG test – No role

5. ADA in pleural fluid or any other fluid – ADA is a product of both neutrophils and lymphocytes and therefore does not help to distinguish tubercular infection from any other bacterial infection.

Key Messages :

- Diagnosis of pediatric TB is difficult because isolation of *Myco TB* which is the gold standard for diagnosis is difficult in children
- One has to rely on several indirect clues for diagnosis such as suggestive symptomatology, history of contact, suggestive radiology and TST in addition to attempt at bacteriological diagnosis
- Unremitting symptoms persisting for more than two weeks is significant rather than intermittent symptoms
- TB suggestive patterns on chest x- ray are hilar lymphadenopathy, military mottling and chronic fibro cavitatory disease
- While doing Mantoux test, one should use tuberculin of 2 TU strength. If 2 TU tuberculin is not available, no more than 5 TU may be used
- CBNAAT is a new diagnostic modality which is much more sensitive than smear examination, almost as sensitive as culture, is rapid and must be used extensively for bacteriological diagnosis in children
- There is no role of IGRA, TB Elisa, CBC, ESR, BCG test and ADA in any fluid for diagnosis of TB.

Procedure for collecting induced sputum

1. Take consent
2. Explain the procedure
3. Exhaust fan should be working and all personnel should be wearing facemask during procedure
4. Nebulise with Salbutamol (0.2mg/kg in 5 ml NS OR 200 micrograms by MDI with spacer)
5. Nebulise with 5 ml hypertonic sterile saline (3%) via nebuliser attached to oxygen at a flow rate of 7-10 L/min
6. Then do chest wall percussion after nebulisation with salbutamol and hypertonic saline
7. Collect sputum by expectoration if child can expectorate OR suction through naso/oro pharynx by sterile mucus extractor
8. Send the collected samples for smear examination/ CBNAAT/ Culture
9. Monitor patient for 30 mins after the procedure for any respiratory complications

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First

"IAP-Meghalaya State Branch" academic award winner

Henam Sonica Devi

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For securing the highest marks in the subject Pediatrics in the final MBBS examinations held in 2014 under North East Hill University from the state of Meghalaya

The award was presented during XII MEGHPEDICON in December 2015

Aerosol Therapy in Pediatrics : is it helpful?

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Introduction:

Aerosolized medications have been used for centuries to treat respiratory diseases, recently aerosol therapy was revolutionize in the 1950s with the development of efficient jet nebulizer devices and the pressurized meter dose inhaler (pMDI). Aerosol medications are common treatment of asthma and chronic obstructive pulmonary disease (COPD). Since then there was a growth in the industry and came up with another new delivery called dry powder inhaler (DPIs).

An aerosol is a suspension of solid or liquid particles in gas. Nature aerosols are pollen, spores, dust, smoke, fog and mist. Medically generated devices are atomizers, nebulizers or gas inhalers. Aim of medical aerosol therapy is to deliver a therapy dose of the selected agent to the desired site of action

Modern technology along with increasing understanding of human pulmonary physiology has aided the development of improved systems of aerosol delivery. This form of therapy has revolutionised the management of patients with various pulmonary diseases. Many of these devices can make the drug sizes more precise, less wasteful and potentially much easier for the youngest and most incapacitated of patients.

When inhaled drugs are delivered directly to the conducting airways, systemic absorption is limited and systemic side effects are minimized, providing high therapeutic index (*Jason C, 1991*).

An increase understanding of pharmocokinetics and effects of aerosol medications gives us the opportunity to deliver a variety of novel medication using the lung as a systemic portal.

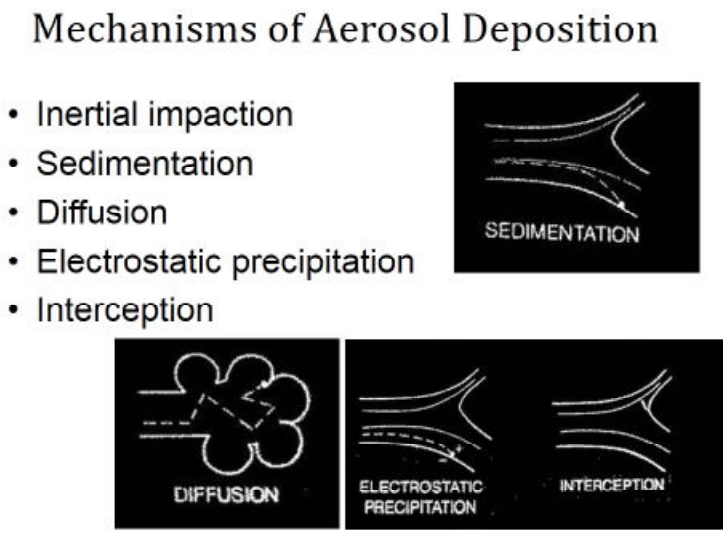
Physical mechanism of aerosol deposition

Inertial Imapction: Inertial impaction has a greater effect on larger particles (>3μm) in the oropharynx and upper airways where the velocity of the inhaled particles is highest. The aersosl particles possessed momentum which determined both the mass and velocity of the particles. When they approach a sufrace such as the back of a throat or bifurcation of airway the direction of airflow changes. If particle sizes are more than 15 μm they hardly reaches the trachea and if less than 15μm they further deposits at the bifucation of trachea. As the larger particles gets deposited or filtered out and as the velocity of particles decreases, impaction becomes less important as a mechanism of deposition in smaller airways.

Sedimentation: Particles less than 3μm will probably not deposit owing to inertial impaction. Sedimentation caused by gravity is the most important mechanism for deposition in the smaller airways. The effect of sedimentation is greatest on the larger particles (>0.5 μm) that have escaped deposition owing to inertial impaction. Breath holding after inhalation of the aerosolized particles helps deposition in the airways owing to sedimentation.

Diffusion: Particles <0.5 μm will move by diffusion (impaction with gas molecules) towards the surface of the respiratory tract. Movement of particles by diffusion decreases with increasing particle diameter, and hence has a greater effect on small particles (<0.1 μm). Deposition in the airways due to diffusion is helped by breath holding after inhalation. Without breath holding most small particles <0.1 μm are likely to be exhaled rather than depostion.

Electrostatic precipitation and interception: Depostion may occur because of attraction between charged particles in the inhaled aerosol and an induced charge on the mucosa of the respiratory tract. The importance of this factor of aerosol therapy has not been investigated in detail but will presumably vary greatly depending on drug formulation being administered. Irregularities in airway structure and inhalation flow pattern leads to non uniform deposition of aerolized drugs. The greater the degree of airway obstruction due to disease, the more central the depostion in the airway; thereby reducing therapeutic effeciency. Depth of penetration of aerolised particle in the airways also depends on physiologic factors such as tidal volume,



respiratory rate, and breath-hold capability.

Pediatric airway physiology and medication delivery :

The size of airway changes dramatically within first five years of life. Breathing patterns, flow rate and volumes all changes with growth and development. The resting respiratory rate decreases with age as tidal volume and minute ventilation increases. Tidal volume is approximately 5-7ml/kg in newborns, with a 300% increase in tidal volume in the first year. Inspiratory flow also increases with vital capacity. Low tidal volume, vital capacity, functional residual capacity, and respiratory cycles of infants results in low residence time for small particles, resulting in a further decrease in pulmonary deposition.

Optimal target of drug delivery into the lung was to reach systemic circulation through alveolar region. Alveolar region is composed of resorptive surface; mucocialiary clearance is minimal and cell barrier for absorption is extremely thin. These advantages led to increase residence time for the drug and a large absorptive surface.

Factors effecting Aerosol Deposition :

There are certain factors which reduces the rate and depth of aerosol particles deposition in the neonatal and pediatric patients *(Ruben BK et al, 2001)*:

- Large tongue in proportion to oral airway
- Nose breathing
- Narrow airway diameter
- Fewer and larger alveoli
- Fewer generation of airway
- More rapid respiratory rate
- Small tidal volumes
- Inability to hold breath and coordinate inspiration

High inspiratory flow rate during respiratory distress

There are limited research data regarding regional deposition of aerosols in neonates, infants and young children. Never the less a data by Ruben BK *(Ruben BK et al, 2001)* suggested that aerosol deposition is less than 1% of the nominal dose being nebulized in neonates compared to 8-22% in adults.

Looking into the data of *Wildhaber and Collegues* which demonstrated that deposition of aerosol from pMDI with nonelectro-static valved holding chambers varies with child age, the amount of drug per kilogram of body weight is consistent across age. The data does suggest that the same dosage that is effective for adult will be probably safe in infants.

Tidal volume, inspiratory to expiratory (I:E) ratio, and inspiratory flow rates are the key to efficiently inhale output from a nebulizer. In infants less than 6 months of age, reduced inspiratory flow rates and broad I:E ratio result in less aerosol inhaled than by a larger child or adult.

For correction of these factors, the innovation of pediatric face mask analysis was done to prevent leak and proper seal of the device during aerosol therapy *(Israel Amirav et al, 2013)*.

According to Sutton's law, the disease being treated is usually an airway disease, the medication can be aerosolized without degeneration, it is effective at the airway surface, and the medication usually have no adverse effect when administered effectively *(Bruce K Rubin, 2011)*.

- **Devices used for Pediatrics Age Group**

Pressured Metered dose inhalers (pMDI):

A pMDI is a pressurized canister containing a drug in the form of a micronized powdered solution that is suspended with a mixture of propellant along with a surfactant or a dispersal agent *(Rubin BK, 2000)*. These are the frequently prescribed device for aerosol delivery. Pressure metered dose inhaler are inexpensive, easy to use, and disposable. For pMDI inspiratory effort and coordination is required from the patient's part in order for the metered dose to be dispensed. When used without a spacer, pMDI actuation must be closely coordinated with the start of the patient inhalation; a difficult coordination for many older children, and impossible for young children to achieve.

Valved holding chambers or spacers eliminate the need of coordination, but are less convenient and portable. However, spacer must be used with pMDIs when treating children younger than 6 to 7 years of age, and are highly recommended for all patients when using corticosteroids. Face mask must be used for infants and toddlers (less than 3 years of age); however these encourage nasal inhalation which will filter out much of the aerosolized drug. Children more than 3 years of age can be taught to use mouthpiece; this greatly increase the amount of drug delivered to the lungs.

Comparison of bronchodilator delivery with pMDI spacer and nebulizer has shown increased efficiency of drug delivery via pMDI spacer and equivalent clinical outcomes in both adult and children.

Problem with home use pMDI devices includes not only poor technique but also poor storage. The pMDI should always be stored with cap on, both to prevent foreign objects from entering the boot and to reduce humidity and microbial contamination. Proper education and techniques should be taught to both patients and parents.

pMDI with Accessory devices :

In proper designs spacers and holding chambers can reduce oropharyngeal deposition, eliminate the cold feron effect, decrease aerosol MMAD and improves lower respiratory tract deposition.

■ Technique to use pMDI with holding chambers:

■ Warm the pMDI to hand or body temperature

■ Shake the canister vigorously, holding it vertically

■ Assemble the apparatus

■ Ensure that there are no loose objects in the device that could be aspirated or could obstruct outflow

■ Place holding chamber with mask to completely seal the mouth nose.

■ Have the patient breath normally, and actuate at the beginning of inspiration

■ For small children and infant have them continue to breath through the device for 10-15 times.

Dry Powder Inhaler (DPI):

A dry powder inhaler (DPI) is typically a breath-actuated dosing system. With a DPI a patient creates aerosol by drawing in air through a dose of finely milled drug powder in the air. DPIs is relatively inexpensive, do not require propellants, and do not require the hand-breath coordination needed for pMDI. However dispersed of the powder into respirable particles depends on the creation of turbulent flow in the inhaler.

The turbulent flow is a function of the ability of the patient to inhale the powder with a sufficiently high inspiratory flow rate. In terms of good lung deposition and drug response, DPI are as effective as pMDI. *(Jim Fink, Egans, 2009)*

The particle size of DPI ranges from 1 to 3μm, but the size of the lactose or glucose particles can range from approximately 20 to 65μm, so most of the carrier is deposited in the oropharynx. Performance of the DPIs can be effected by the materials used in the production and manufacturing.

Pneumatic nebulizers (Small volume Nebulizers)

Pneumatic nebulizers uses Bernoulli's principle to drive a high pressure gas through a restricted orifice and draw fluids into the gas stream through capillary tube immersed in the solution. Shearing of fluid stream in the jet, forms aerosol stream that impacts against a baffle removing larger particles that may return to the reservoir.

The effective pneumatic nebulizer should deliver more than 50% of its total dose as aerosol in the repairable range in 10 minutes or less of nebulization time. Performance varies with diluent volume, operating flow, pressure, gas density and manufacturer *(Hess et al, 1996)*.

Nebulizer selection effects aerosol delivery. Only nebulizers that have been shown to work reliably under specific conditions, with specific medications and with specific compressor should be used *(Thomas SH et al 1988)*.

When used for treating children and patients on ventilator nebulizers producing aerosol with MMaD of 0.5 to 3.0 micron are more likely to achieve greater deposition in the lower respiratory tract *(Rubin BK,*

Fink JB, 2001).

The viscosity and density of drug formulation affects both the output and particle size. Some of the drugs, such as antibiotics are so viscous they cannot be effectively nebulized in some standard SVNs. This is also an issue with suspensions in which some aerosolized particles contain no active drug, where as other particles, generally larger, carry the active medication.

Large Volume Nebulizers:

These are reservoir volumes greater than 100ml and can be used to administer an aerosol solution over a prolonged time. Indication for using this nebulizer is to administer bland solutions like sterile water or saline for the need of humidify medical gases when upper airway is bypassed, to control stridor and to induce sputum.

An alternative approach of large volume nebulizers with high output are High-output extended aerosol respiratory therapy nebulizer (HEART), Westmed and HOPE. These have greater than 200 ml reservoir that produces an aerosol with an MMAD between 2.2 and 3.5 μm. The potential problem with continuous bronchodilator therapy (CBT) is that drug concentration increases. Patient receiving CBT requires close monitoring for signs of drug toxicity such as tachycardia and tremor.

Another special purpose LVN is Small Particle Aerosol Generator (SPAG). This is a jet aerosol generator used to nebulize antiviral agent ribavirin. SPAG incorporates a secondary drying chamber that reduced the MMAD to 1.2 micron. SPAG reduces medical gas source from a normal 50 psig (pounds per square inch guage) line to as low as 26 psig with an adjustable regulator.

There are two specific problems associated with SPAG in delivery of ribavirin. Firstly, caregiver exposure to drug aerosol. Secondly to deliver ribavirin through a mechanical ventilation circuit cause heavy precipitation which can jam the breathing valves present in the expiratory limb causing occlusion. These problems can be overcome by placing a one way valve between the SPAG and the circuit and diltering out the excess aerosol particles before it reaches the exhalation valve *(Kacmarek RM, Kratohvil J, 1992.)*.

Ultrasonic Nebulizer (USN):

They uses a piezoelectric crystal vibrating at a high frequency (1.3 to 1.4 mHz) to create an aerosol. The crystal transducer converts electricity to sound waves in the liquid immediately above the transducer, forming a geyser of droplets. USNs are capable of a border range of aerosol output and higher aerosol densities that most conventional jet nebulizers. Output is determined by the amplitude setting; the greater the signal amplitude the greater the aerosol output. Particle size is inversely proportional to the frequency of vibration. Example DeVilbiss Portasonic nebulizer operating at a frequency of 2.25MHz producing particle sizes of 2.5 μm.

They are mainly of two types the Small volume USN and Large volume USN. Small volume USN have been promoted for administration of a wide variety of formulation, ranging from bronchodilators to anti-inflammatory agents and antibiotics *(Nakanishi AK et al,1997)*. Advantage of USN is they have less residual volume hence the treatment time is reduced with small volumes. Ventilators like Seimens, Nellcor Puritan Bennett have promoted the use of USNs for administration of aerosol during mechanical ventilation. Unlike SVNs, USNs do not add extra gas flow to the ventilator circuit during use. This features reduces the need to change and reset ventilator and alarms settings during aerosol administration *(Thomas SH, O'Doherty MJ, Page CJ, et al, 1993)*. Large volume USNs incoperates large blowers to carry the mist to patients. Low flow through USN is associated with smaller particles and higher mist density. High flow yields larger particles and less density. Unlike jet nebulizers, the temperature of the solution placed in the USN increases during use. As the temperature increases the drug solution increases, as does the likelihood of undesired side effects.

Vibrating Mesh Nebulizer (VMN)

This device uses electricity to stimulate piezo element to vibrate a ceramic or metal disk, which in turn presses or pumps medication through multiple orifices. This can be optimized for different drugs by adjusting the pore size of the mesh, the aerosol chamber size, the reservoir size, and the output rate. In general these devices have a low residual volume, silent operation, and rapid output. They are small and portable and can be powered either by battery or alternating current; they are faster than jet nebulizers, and higher doses are possible.

Two types of vibrating mesh nebulizers are present, the active and passive are currently available commercially. Active VMN utilizes a dome-shaped aperture plate, containing more than 1000 funnel shaped apertures. This dome shaped is attached to a

plate that is also attached to a piezo ceramic element. Electricity applied to the piezo element causes the aperture plate to vibrate at a frequency of 100 khz moving the aperture up and down by 1 to 2 μm. The particle sizes it generates is approximately 2 to 3 μm. An example of active VMN is Aeroneb professional Nebulizer (Aeroneb Pro; Aeroneb, Inc).

The passive VMN utilizes a mesh separated from an ultrasonic horn by the liquid to be nebulized. A piezo vibrates the ultrasonic horn, which then pushes fluids through the mesh. An example of passive VMN is NEU-22 (Omron).

Breath-Activated and Breath-Controlled Nebulizers :

Breath-activated nebulizers like the AeroEclipse (Trudell Medical International, London, Ontario, Canada) are a technology that senses the patient's inspiratory flow and delivers aerosol only when flow triggers the opening of a valve. These nebulizers decrease medication wastage but can increase delivery time. Breath-controlled nebulizers use computer technology to determine a patient's inspiratory flow and volume, and use those to deliver the medication at the beginning of inhalation, allowing the inspired air at the end of inhalation to drive the aerosol deep into the airway. This permits improved dose precision, particularly to the smaller airways, and decreases upper-airway deposition.

Nebulization on Ventilated patients:

Traditionally, jet nebulizers were used to deliver medication to patients through ventilator circuits, but there are many problems with his form of therapy, since only a small proportion of the nebulized drug is actually delivered to the patient. The use of pMDI with suitable adaptors allows more efficient delivery, particularly when used with small volume chambers, which appears to be more suitable for all patients from preterm to adults (Lynn M Taussing, Pediatric Respiratory Medicine). Medication delivery via endotracheal tubes is also possible using ultrasonic nebulizers. However not all drugs required for delivery to ventilator patients are available in pMDI formulations, requiring the continued use of nebulizers for this purpose. More recently, vibrating membrane nebulizers have been investigated for use in ventilator circuits and have been shown to markedly improve drug delivery.

The ventilator breathing pattern and waveform will direct the aerosol medication to be driven into the lungs with help of a flow rate. The airway with an endotracheal tube quite narrow may influence the delivery but due to the smooth structure of the inner surface of the ETT, it creates a laminar flow pathway with less barrier to aerosol delivery than the ventilator circuit.

Response of bronchodilator administration in ventilator patient is seen in the change of expiratory flow. It's also seen in decreased in peak pressure required for a set tidal volume, decreased in mean airway pressure and decrease requirement of oxygen supplement *(Brian Walsh et al, 2010).*

In conditions where the USN nebulization are being used; the patient inspiratory flow draws the aerosol from the nebulizer into the lungs. As the USN operates, the aerosol remains in the medication chamber until the flow of gas draws the aerosol from the nebulizer. Thus during exhalation, aerosol generated by the USN remains in the chamber awaiting the next breath.

Another advantage of USN during mechanical ventilation is that no driving force or gas flow is added to the circuit changing ventilator parameters and alarm setting.

Summary of Advantages and Disadvantages of Aerosol Drug Delivery Systems

Knowledge of advantages and disadvantages of various aerosol delivery system is critical for proper selection and application. The following table compares the pMDI, DPI, SVN and SVN delivery systems.

Advantages	Disadvantages
MDI	
Convenient Inexpensive Portable No drug preparation required Difficult to contaminate	Patient coordination required Patient activation required High percentage of pharyngeal deposition Risk of abuse Difficult to deliver high dose Not all medication are available Most units still use ozone-depleting CFCs
MDI with Accessory Devices	
Less patient coordination Less pharyngeal deposition No drug preparation required	More complex for some patients More expensive than an MDI alone Less portable than an MDI alone Not all medications available
DPI	
Less coordination required Breath activated Breath-hold not required Can provide accurate dose counts No CFCs	Requires high inspiratory flow Most units are single dose Risk of pharyngeal deposition Not all medications are available Difficult to adhere high doses
SVN	
Less patient coordination required High dose possible (even continuous) No CFC release	Expensive Wasteful Drug preparation required Contamination possible if device not cleaned carefully Not all medication available Pressurized gas source required Long treatment time
USN	
Small residual volume Quiet Aerosol accumulates during exhalation	Expensive Prone to electrical or mechanical breakdown Not all medication available Drug preparation required

Guidelines for the use of Aerosol Devices in the Care of infants and Children

According to Egan's Fundamental of Respiratory Care the rules of thumb so selection of devices is based on the following table.

Devices	Age Group
SVN	**Neonates**
pMDI	>5 years
pMDI with valved chamber with mouth piece	>4 years
pMDI with valved chamber with mask Endotracheal tube	Neonates/infants/toddler Neonates
Breath actuated	>5 years
DPI	>6 years

Recent Advances of Aerosol Therapy

In recent studies it has been found that medications for systemic administration can also be delivered by using an ultra-fine aerosol targeted to the alveolar surface, and thereby they can be rapidly absorbed. Some Recombinant proteins or complimentary DNA for gene therapy can also be delivered to the airway *(Bruce K Rubin, 2011)*

Aerolization can deliver a high concentration of antibiotics to the proximal airway, with minimal systemic absorption or toxicity. Some studies does mention that it may not penetrate deep in the lungs, especially when the alveoli are filled with puss as cystic fibrosis. The concentration decreases as the gradient gets deeper hence its not enough to kill the bacteria, but instead may induce resistance. The first officially available antibiotic for aerosol therapy was trobamycin solution for inhalation (TOBI).

Mucolytics are a type of mucoactive drug that breaks down polymere bond of mucins or the secondary polymers of DNA and filamentous actin. Mucolytics helps to decrease the mucus viscosity which will improve clearance. N-acetylcysteine reduces the disulfide bonds that linearly oligomerize gel forming mucin monomers. Studies did show that acetylcysteine has minimal effect and could also damage the airway surface; it cause irritation with ph of 2.2 and induces cough. Dornase Alfa is the only approved peptide mucolytic for the treatment of CF.

Aerosol surfactant mobilizes secretions as a mucokinetic or adhesive medication and not a mucolytic. There are few clinical data on the use of surfactant aerosol; due to its high viscosity. An invitro study suggest the surfactant and perfluorocarbons can be aerosolized using inhalation catheter.

Drugs given through Aerosol for Pediatrics

Some drugs given through nebulization are in the following table

Drug	Nebulization dose	pMDI dose
Salbutamol (Asthalin)	0.15-0.25 mg/kg/dose (max dose of 2.5mg)	100
Terbutaline	0.01-0.03 ml/kg mixed in 2-3 ml NS every 4-6 hrly	200mg/puff 1 puff 4-6 hrly
Ipratropium bromide	0.5-1mg/kg (max 15 mg) every 8 hrly	18 mcg/puff <12 yrs: 1-2 puff 8 hrly for 6days >12 yrs: 2-3 puffs 8hrly max 8 days
Racemic Epinephrine	22.5 mg/ml (2.25%) 0.25-0.5 ml(2.25%) in 2.5 diluent Croup <5kg:0.25ml/dose >5kg:0.5 ml/dose	
Acetylcystine	20%solution: (200 mg/ml) it is diluted 1:1 with NS Infants: 1-2 ml Child: 3-5ml >12 yrs: 5ml	

Conclusion :

In recent times, pMDI-spacers have become the most commonly used approach to aerosol therapy in children. They can be used for all ages and for both long-term, preventive therapy, and for short-term treatment for acute exacerbations. One of the main advantages of pMDI-spacer use is that normal tidal breathing can be used during aerosol administration, which makes them ideal for infants and younger children.

However the use of therapeutic aerosol medications is evolving from a basis of optimizing the delivery of asthma medication to the airway to understanding how the extensive pulmonary bed can be used for the systemic administration for the variety of macromolecules.

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Surfactant therapy:
what else if not prematurity and RDS?

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INTRODUCTION :

Clinical research in the field of surfactant therapy started in mid 1950s when Pattle and others described a thin layer of material lining the alveolar surface of the lungs, this material was capable of reducing surface tension to a lower level during the respiratory cycle [1]. In 1959, Avery and Mead published their milestone article demonstrating that hyaline membrane disease (HMD) was due to lack of surfactant [2].

SURFACTANT AND SURFACE TENSION :

Surfactants are agents that reduce surface tension between the gaseous and aqueous lining of the lung alveoli. Pulmonary surfactant is produced by the type II pneumocytes and is composed of lipids and proteins.

Phospholipids comprise approximately 90% of pulmonary surfactant, of which almost 80% is phosphatidylcholine, 10% is phosphatidylglycerol, and the remainder is made of small amounts of other phospholipids and neutral lipids including cholesterol. The principal surface-active material in surfactant is di-palmatoyl phosphatidylcholine (DPPC).

Protein constitutes about 8% -10% of its bulk. Four types of proteins are identified and designated as surfactant protein [SP], A through D. SP-A and SP-D are hydrophilic , SP-B and SP-C are hydrophobic .SP-B and SP-C are the main protein responsible for rapid absorption and spreading of phospholipids on the surface of alveoli and hence to facilitate the development of low surface tensions. Surfactants prepared by organic solvent extraction of natural surfactants or from lung tissue contain SP-B and SP-C, but l ack SP-A and SP-D.

EXOGENOUS SURFACTANTS :

Exogenous surfactants are classified into natural and synthetic surfactants. The natural ones are purified and extracted from either lung minces or lung lavages. Their phospholipid concentration is above 80% and all contain the proteins SP-B and SP-C, but not SP-A. Porcine-minced-lung extract surfactant undergoes an additional purification step that removes neutral lipid; whereas free fatty acids and DPPC are added to the bovine-minced-lung extract surfactant. SP-B concentration is lower in the lung minced preparation compared with lung lavage extracts. The entirely synthetic surfactant preparations are composed mainly of DPPC and are free of surfactant-associated proteins. Animal-derived surfactants contain foreign proteins that are potentially immunogenic [1].

OTHER USES OF SURFACTANT :

Although surfactant therapy have been traditionally used for hyaline membrane disease , there are few interesting studies and research work going on regarding few other indications of surfactant therapy , few of them are described below.

Meconium Aspiration Syndrome

The pathophysiology of meconium aspiration syndrome (MAS) is attributed to mechanical obstruction of the airways, chemical injury to the respiratory epithelium and surfactant inactivation by meconium. Meconium aspiration syndrome results from acute deposition of meconium in previously healthy and normally developed airways. Two approaches have been attempted: surfactant replacement and surfactant lavage.

In surfactant replacement therapy bolus doses or slow infusion of surfactant mixture with or without lavage therapy is used .Surfactant-saline dilute is the most commonly used mixture in several trials; combinations of polymers and synthetic surfactants are currently under trial.

Findlay, et al. in a trial of 40 term neonates, reported a statistically significant reduction in the length of hospital stay (mean difference - 8 days, 95% CI -14 to-3 days). There was no statistically significant reduction in mortality, duration of assisted ventilation, duration of supplemental oxygen, air leaks, chronic lung disease, need for oxygen at discharge or intraventricular hemorrhage [3].

Another meta-analysis incorporated eight RCTs of surfactant therapy for MAS with a total of 512 patients. It reported that surfactant therapy significantly reduced oxygenation index, increased arterial oxygen/ alveolar oxygen ratio, shortened hospitalization [4].

Lavage therapy is based on the principle that

detergent like property of the lung surfactant will cause the meconium to be solubilized and washed away from the lung hence removing particulate meconium and preventing some of the pathophysiology attributed to obstruction and toxicity.

The very well known RCT, "lessMAS" trial, reported reduced mortality and need for ECMO (10% vs. 31%) (OR 0.24; 95% CI: 0.06–0.97) and a trend to reduce mortality in centers where ECMO is not available (5.3% vs. 29%) (OR 0.14; 95% CI: 0.02–1.3) but no difference on duration of ventilation, oxygen therapy or hospital stay was noted [5].

Pneumonia

Several studies suggest that pnemonia may be assosiated with surfactant inactivation which is directly correlated with the degree of respiratory failure.

Herting et al, reported that using surfactant in an experimental neonatal GBS pneumonia as a vehicle for specific GBS immunoglobulin resulted in a greater reduction in GBS proliferation than with using either surfactant or antibody therapy alone [6].

In 2000, the Collaborative European Multicenter Study Group reported that the response to surfactant in neonatal pneumonia was slower than in infants with RDS and that repeated doses were needed more often [7].

Tan K et al, in a small randomized trial of surfactant rescue therapy reported that the subgroup of infants with sepsis showed better oxygenation and a reduced need for ECMO compared with a similar group of control infants . Newborn infants with pneumonia or sepsis receiving rescue surfactant also demonstrated improved gas exchange compared with infants without surfactant treatment [8]

Pulmonary Hemorrhage

In massive pulmonary hemorrhage the proteins in the blood components are known to inactivate the surfactant. Exogenous surfactant replacement may be capable of reversing this process even in the continued presence of inhibitor molecules [9].Clinical data related to the effect of surfactant therapy on pulmonary hemorrhage are very limited in the literature.

Bozdao, et al. In an RCT compared efficacy of two natural surfactants (poractant alfa and beractant) for pulmonary hemorrhage in 42 very low-birth-weight (VLBW) infants. They concluded that both natural surfactants improved oxygenation, and the type of surfactant did not seem to have any effect on BPD and mortality rates in this patient [10].

Congenital Diaphragmatic Hernia (CDH)

CDH is associated with lung hypoplasia and pulmonary hypertension along with immaturity of lung tissue leading to surfactant deficiency. Exogenous surfactant as adjuvant treatment for the severe respiratory distress associated with this disease is an attractive concept .The two pathophysiological alterations in babies with CDH were high turnover of phosphatidylcholine and either reduced or normal concentration of SP-A in the tracheal aspirate[1] .

Janssen, et al. found that patients with severe CDH who required ECMO have a decreased surfactant phosphatidylcholine synthesis that may be part of the pathogenesis of severe pulmonary insufficiency and has a negative impact on weaning from ECMO [11].

Cogo, *et al*. found that infants with CDH had a lower rate of synthesis of SP-B and less SP-B in tracheal aspirates. In these infants, partial SP-B deficiency could contribute to the severity of respiratory failure [12].

There have been reports of small series of human infants with CDH who have some improvement with surfactant treatment and prophylaxis. However, larger case series have not confirmed these results [13].

Bronchopulmonary Dysplasia (BPD)

In BPD there is chronic inflammation that develops in the immature lung when it is exposed to repetitive ventilator stretch with oxygen-enriched gas, often complicated by infection. Surfactant dysfunction occurs in a high proportion (43-76%) of preterm infants who remain intubated and ventilated at 1-2 weeks of age [1].

Bissinger, et al. demonstrated a transient improvement in oxygenation of premature infants >7 days after treatment with two doses of surfactant [14].

Katz and Klein in a retrospective cohort study of 25 premature infants, found that late surfactant treatment was well tolerated, and that 70% of those treated had a short-term improvement in respiratory status [15].

Keller et al. conducted a study to assess the safety and efficacy of late administration of SP-B containing surfactant (calfactant) in combination with prolonged inhaled nitric oxide (iNO) in infants d"1,000g birth weight with BPD .They concluded that late therapy with surfactant in combination with iNO is safe and transiently increases surfactant SP-B

content, possibly leading to improved short- and long-term respiratory outcomes [16].

Minimally invasive surfactant therapy

Surfactants traditionally have been administered via intratracheal instillation. Since intubation is difficult in premature babies and also associated with several side effects, many researchers started searching for lesser invasive methods of surfactant administration. These methods are collectively referred to as minimally invasive surfactant therapy (MIST).

Intra-amniotic instillation of surfactant near the fetus's mouth and nose via an ultrasound-guided needle has been described. Two non-randomized studies evaluating this method have been published; in the first study the investigators reported success in a series of six babies ,with no RDS in four and only mild RDS in the other two [17]. In the second study the treated women had proportionately more babies with biochemically defined lung maturity and milder RDS [18].

Nasopharyngeal administration of surfactant has also been described in a study of 23 infants. Surfactant was given after delivery of the head but before delivery of the body. 10 of the 23 infants treated this way (43%) required intubation before 72 hours of life [19]. In another study, *Trevisanuto et al* reported the successful instillation of surfactant via a laryngeal mask airway (LMA) without sedation in a group of 8 preterm infants. Improvement in oxygenation was noted in all of them. The applicability of this technique seems limited, however, due to the lack of familiarity and the difficulty with placement of the device in infants lesser than 28 weeks' gestation [20].

Tracheal catheterization followed by bolus surfactant therapy has been developed in German neonatal units. This technique involves placement of a fine intra-tracheal catheter while babies keep spontaneously breathing on nCPAP. Pilot studies reported that the procedure was tolerated well with good outcomes in comparison with historical controls [21].

CONCLUSION:

In cases of MAS pooled data from randomized controlled trials suggest a benefit in terms of reduction in the requirement for ECMO but no diminution of air leak or ventilator dependent days. Current evidence supports the use of bolus surfactant therapy on a case to case basis in nurseries with a relatively high mortality associated with MAS, or the lack of availability of other forms of respiratory support such as high-frequency ventilation or nitric oxide.

Further studies should focus on carefully designed RCTs of surfactant replacement therapy in term or late preterm infants with proven bacterial pneumonia, pulmonary hemorrhage, CDH and BPD.

Future studies on pharmacokinetics, optimal dose and dosing interval, concentration, method of delivery and duration of treatment regimen in each of these conditions are needed.

Although instilling surfactant through an endotracheal tube is currently the recommended mode of drug delivery, the noninvasive methods such as nebulized surfactant are being trialed with some success, nonetheless, further improvements in surfactant therapy are dearly needed.

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Diagnosing kidney diseases : How big is the challenge !

(The 10 red flags)

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Renal diseases -The problem:

Renal diseases are common in childhood. Many of these are treatable and progression can be prevented. Therefore early detection is the key. However renal disease can present with subtle and non-specific features making its diagnosis difficult. It may also remain hidden and have a silent presentation or sometime mimic other common childhood illnesses. These make it a challenge to diagnose kidney diseases in children.

Glomeruli and tubules: functional components of kidneys:

Edema, hematuria and oliguria are obvious signs of renal disease. The kidney has two different functional components - the glomerular and the tubular. Different signs of renal diseases can give us a clue as to which component is primarily affected in a child.

Box 1: Challenges in diagnosis of renal disease

Challenges	Example of diseases
Subtle features:	Tubular disorders
Non specific:	UTI in infancy
Silent:	Hypertension
Hidden:	Hereditary Nephritis
Mimics:	Chronic renal failure

The 10 red flag of renal disease :

It cannot be overemphasized that high index of suspicion is important to diagnose kidney diseases in children. They can present with host of clinical features over and above the obvious features of edema, hematuria and oliguria. The situations under which a diagnosis of underlying kidney disease needs to be considered are summarized below as "10 red flags".

Box 2: Presenting features of tubular and Glomerular diseases

Glomerular	Tubular
Edema	Short stature
Proteinuria	Failure to thrive
Oliguria	Polyuria
Hypertension	Bony deformities
Hematuria	

1. GROWTH RETARDATION

Growth retardation is hallmark of renal diseases. Bony deformity can be a part of presentation of chronic renal failure. However in certain conditions like tubular disorders, vesicoureteral reflux, renal rickets, renal dysplasia, and polycystic renal disease etc, bony deformity can be seen in spite of normal creatinine. Height weight and BMI should be routinely monitored in these children and treatment of polyuria/ polydipsia, metabolic acidosis, hypokalemia and nutrition in these children may result in improved growth.

2.ANEMIA

Anemia can be prominent sign in hemolytic uremic syndrome, lupus nephritis, acute renal failure with hemolysis. It is important to keep in mind that hematuria does not cause anemia. Also one should rule out chronic renal failure in children with chronic anemia refractory to hematenics.

3. BONY DEFORMITIES

Pointers for underlying kidney diseases in a child with bony deformity include-

- Age > 2yrs
- Polyuria / Polydipsia
- Growth retardation
- Seizures / tetany
- Metabolic acidosis/alkalosis
- Poor response to vitamin D
- Positive family history

4. HYPERTENSION

Hypertension is most often asymptomatic. It is hallmark of glomerulonephritis and also can be manifestation of renal failure. Hypertensive crisis mimics encephalitis and may be missed if blood pressure is not measured.

Table 1: summarizing clinical clues for specific renal diagnosis in children with hypertension

Clinical clue	Possible renal disease
Asymmetry of kidney size	Reno vascular hypertension, reflux nephropathy
Abdominal bruit	Reno vascular hypertension
Abdominal mass	Wilm's tumour
Metabolic alkalosis, hypokalemia	Genetic causes

5.URINE

Urine Analysis: There can be transient findings or persistent findings. Persistent abnormal urine analysis should arouse suspicion of underlying kidney diseases.

Urine Stream: Abnormal urine stream is a marker for neurogenic bladder or posterior urethral valve. It is important to examine the urinary stream by the pediatrician, as history given by parents can be falsely reassuring. It is also important to remember that every enuresis is not bed wetting.

Urine Output: Though urine output is regarded an obvious marker of kidney health but it is not a reliable marker of renal function. Usually glomerular diseases present with oliguria. An increased volume of urine can be a useful clue to diagnose tubular diseases.

6. SYSTEMIC FEATURES

Certain systemic features also should raise suspicion of a kidney disease. Mentioned below is a brief list.

Table 2: Systemic features with kidney diseases:

Systemic feature	Kidney disease
Prolonged fever	UTI, Lupus nephritis
Joint and skin involvement	Lupus nephritis. HSP
Hemoptysis, sinusitis	Pulmonary renal syndrome
Seizures	Glomerulonephritis, lupus

7. RECURRENT PROBLEMS

Some kidney diseases can present with recurrent problems and it gives clue to the underlying kidney disorders.

Table 3: Recurrent problems and the kidney diseases:

Reccurent problem	Kidney disease
Edema	Nephrotic syndrome
Fever	UTI
Dehydration	Tubular diseases
Vomiting	Tubular disease, HTN, Uremia
Seizures	HTN, Vasculitis, Hypocalcemia
Hypotonia	Hypokalemia
Infections	Rickets, Immunosuppression

8. SYNDROMES

Various syndromes can present with renal involvement and sometimes it can be picked up at birth. Some markers of renal involvement identifiable at birth include oligohydramnios, polyhydramnios, hydronephrosis, single umbilical artery, ear lobe defects,spinal and genital deformities, a palpable bladder or renal mass, hypoplastic lungs and Potter's facies.

Box 3

Look for following as clue to syndromic renal disease:

1. Developmental delay
2. Dysmorphism
3. Neonatal events
4. Ophthalmological and auditory defects
5. Ambigous genitalia

Box 4

Syndromes with renal diseases:

Potter's syndrome
Nail Patella syndrome
Galloway Mowat syndrome
Bardet biedl syndrome
Denys Drash syndrome

9.FAMILY HISTORY

Family history is important in the following conditions:

Glomerular diseases:
Steroid resistant nephrotic syndrome
IgA nephropathy
Membrano proliferative GN
Hereditary nephritis

Tubular diseases
Barter's syndrome
Renal tubular acidosis
Hypophosphatemic rickets
Nephrogenic diabetes Insipidus
Polycystic kidneys
Stone disease
VUR

10. THERAPY

High index of suspicion for renal involvement is important in certain disease states. Possibility of renal involvement should be considered in situations like hypercatabolic states, sepsis, hematogenous malignancies, hemolysis, obstruction and nephrotoxic drugs therapy. Fluid - electrolyte imbalance like shock, hypokalemia, metabolic acidosis also should arouse suspicion of kidney diseases.

Conclusion:

Early diagnosis of renal diseases is very important for optimal outcome. However renal diseases may remain hidden or mimic common childhood diseases to evade diagnosis. High index of suspicions is required for early diagnosis. Keeping these "10 red flags" will help to suspect kidney diseases and aid in early diagnosis.

Clinical case diary from a NICU: A case of persistent hyperinsulinemic hypoglycaemia of infancy (PHHI)

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Characteristics: A Newborn with resistant and prolonged hypoglycaemia with repeated seizures, with increased fasting insulin level, managed on subcutaneous octreotide.

Case history: This is a term, female, large for gestational age neonate, born out of a non-consanguineous marriage on 06-05-2016, was assisted by forceps at a local hospital in Jowai with a birth weight of 4500 gm. As per the history the baby was vigorous at birth. There is no history of diabetes mellitus or gestational diabetes in mother. There is previous history of 1 still birth and 1 neonatal death at 2 weeks (cause not known).The neonate was admitted in our NICU on day 2 of life with complain of not sucking well and repeated jerky movements of all limbs. On examination the reflexes were poor with reduced overall tone. Blood sugar at admission was 32 mg % (by glucometer with reagent strips). She was managed with 10% dextrose bolus and started on intravenous fluid along with empirical antibiotics according to our NICU antibiotic protocol. Initial sepsis screen was found negative.

On day 3 of life, the newborn was on orogastric feeding but the blood sugars started falling again and glucose infusion was titrated gradually up to 12 mg/kg/min to maintain euglycaemia. On day 5, the newborn suddenly developed apnea and desaturated. The baby was intubated and put on mechanical ventilator and was extubated after 4 days. During those days on ventilator the newborn was having repeated subtle seizure daily and was found excessively jittery. Post-extubation, orogastric tube feeding with expressed breastmilk was re-started slowly and increased to full feeds by day 12 of life. In addition to feeds, she was in need of higher dose of intravenous glucose infusion. Inspite of the maximum dose of glucose infusion and full feeds, her hypoglycaemic episodes continued. Most of the hypoglycaemic episodes were symptomatic and were associated with subtle seizures, lethargy and feeding intolerance. A total of 4 doses of injection hydrocortisone were tried with no benefit. The baby was investigated in the line of resistant and prolonged hypoglycaemia. The urine ketone was found negative; thyroid function test was normal; urine culture was sterile, neurosonogram and ultrasound abdomen was normal, CSF cyto-chemical analysis was normal. The arterial gas didn't show acidosis. On day 12 of life, the blood sample for serum insulin, serum cortisol, galactosemia screeing was collected and sent to a laboratory outside the Northeast.

The serum insulin was high (3.5 μU/ml). Since glucagon and diazoxide was not available locally, injection octreotide (2-10 μg/kg/day) was started subcutaneously. As soon the baby was put on injection octreotide the blood sugar increased and it reached up to 200 to 250 mg %. Then glucose infusion was tapered to 6 mg/kg/min within next 48 hours. The tone and reflexes become almost normal and she started sucking at breast like a normal baby. The repeatedly occurring seizures disappeared completely and the anticonvulsant was stopped.

The newborn was discharged home with proper counseling of early stimulation along with injection octreotide twice daily. Neuro imaging (MRI brain) and genetic work up was planned for the next review. The growth, neurodevelopment, vision and hearing function will be assessed on follow up visits. *This is a rare case of resistant hypoglycaemia which causes a lot of practical hurdles in a resource poor setting where the physicians have to wait for the blood reports those are not routinely performed in the local laboratories and the family's financial constraints add to the problems many folds.*

Discussion: Persistent Hyperinsulinemic Hypoglycaemia of Infancy (PHHI):

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) represents the most common cause of hyperinsulinism in neonates; currently, many authors prefer the term congenital hyperinsulinism (CHI). It was first identified in 1938, when *Laidlaw* coined the term nesidioblastosis to describe the neodifferentiation

of islets of Langerhans from pancreatic ductal epithelium (a term since replaced by PHHI and CHI).

Reports of PHHI are rare in literature. An estimated incidence of 1 in 50,000 live births in a random-mating US population has been reported. Worldwide, the incidence may be as high as 1 in 2500 live births in populations with high rates of consanguineous unions. The proposed mode of inheritance is autosomal recessive. Genetic mutations are identified in 50% of these patients whereas in the remaining 50%, no known genetic mutation has been identified. Age of presentation is from birth to 18 months, but most patients present immediately after birth.

This condition is characterized by macrosomia and prolonged neonatal hypoglycemia due to hyperinsulinism. Several different accidents of development at the cell morphologic and molecular level cause persistent fetal and neonatal hyperinsulinism. Classically, in nesidioblastosis, pancreatic ductular cells are found in acinar tissue. In persistent hyperinsulinemic hypoglycemia, there can be focal hyperplasia of pancreatic islet cells or diffuse lesions of the entire pancreas. Focal lesions correspond to somatic defects and are, in some cases, related to mutations of sulfonylurea receptor 1. Other forms include mutations of the potassium linked ATP channel in beta cells.

Persistent hyperinsulinemic hypoglycaemia of infancy (PHHI) should be considered whenever macrosomic newborn has hypoglycaemia with elevated plasma insulin level. PGI (Chandigarh) NICU protocols consider hyperinsulinism if plasma insulin is more than 2 μU/ml in presence of documented laboratory hypoglycaemia and/or evidence of excessive insulin effects. Rebound hypoglycaemia in response to excessive glucose administration is another characteristic. Increased insulin/glucose ratio and glucose requirements exceeding 10 mg/kg/min support the possibility of PHHI.

Surgical excision of a portion of the pancreas can provide the definitive diagnosis and therapy. However, over the long term this may result in the development of diabetes mellitus in the patient. Both somatostatin and diazoxide have been used successfully to limit the insulin release for as long as several months and may produce remission.

Hypoglycaemia is a common metabolic problem in newborn babies. It is very important to recognize and treat any hypoglycaemia promptly to prevent neurological morbidity in the long term. This is because newborn brain is almost exclusively dependant on glucose for its energy metabolism. Rarely, hypoglycaemia is resistant and prolonged. This requires careful investigations and aggressive treatment to identify the cause and to prevent any neurological morbidity. The management of medically unresponsive hyperinsulinemic hypoglycemia remains a challenge.

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