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Theme : Algorithms in Pediatric Intensive Care (AI)

# Infanrix hexa

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<sup>1</sup> GlaxoSmithKline Biologicals, Infanrix hexa Summary of Product Characteristics, 2017. <sup>2</sup> Sakash, Peimar, SA. Review Summary of Product Characteristics, 2018. <sup>3</sup> Infanrix hexa prescribing information 2017. <sup>4</sup> Onofrei, P. et al. Pediatrics 2006;118(6):1292–1296. <sup>5</sup> Wang, J. et al. Acta Paediatr 2008;97(12):1248–1250. <sup>6</sup> Osterhoff, F. et al. Immunization of preterm infants with GSK's hexavalent combined diphtheria tetanus acellular pertussis hepatitis B inactivated poliovirus haemophilus influenzae type b conjugate vaccine: A review of safety and immunogenicity. Vaccine 2018; http://dx.doi.org/10.1016/j.vaccine.2018.01.055. <sup>7</sup> GlaxoSmithKline Data File: DNG 2017/03/25/04\_00 Number of GSK sponsored studies in which Infanrix hexa has been administered.

**Infanrix hexa**  
For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory  
Administrative/Prescribing Information of INHAXIBI 01204 Diphtheria, tetanus, pertussis (acellular component), hepatitis B (DNA), poliovirus (inactivated) and haemophilus type b conjugate vaccine (adsorbed) Ph. Eur.  
ACTIVE INGREDIENTS: Each 0.5 ml dose of opoalised vaccine contains: (i) Diphtheria toxin 2, 40 IU (80 IU diphtheria pertussis antigens (Pertussis toxin) 25 mcg, Pertactin 8 mcg), (ii) Hepatitis B surface antigen 10 mcg, (iii) Inactivated Poliovirus (Type 1, Mahoney strain) 40 D antigen unit, Type 2 (DF-1) strain 1 D antigen unit, Type 3 (Davis strain) 32 D antigen unit, (iv) Haemophilus influenzae type b polysaccharide (polyribosylphosphate) phosphate (PRP) 30 mcg conjugated to tetanus toxoid as carrier protein (approximately 25 mcg). INDICATIONS: Primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliovirus and diseases caused by Haemophilus influenzae type b. DOSE AND ADMINISTRATION: Preterm infants: 3-dose primary vaccination interval of 1 month between primary doses. Booster dose 2–6 months after last primary dose, preferably < 18 months of age. 2-dose primary vaccination interval of 2 months between primary doses. Booster dose 2–6 months after last primary dose, preferably between 11–13 months of age. Preterm infants < 24 weeks gestational age: 3-dose primary vaccination interval of 1 month between primary doses. Booster dose 2–6 months after last primary dose, preferably < 18 months of age. Administered according to official recommendations. Can be used in expanded program on immunisation (school) for infants aged 10–14 weeks of age if hepatitis B vaccine given at birth. <sup>†</sup> Hepatitis B vaccine given at birth, can also be replaced for supplementary dose of hepatitis B vaccine from age of 16 weeks. Safety and efficacy not been established in children > 36 months of age. Method of Administration: Deep intramuscular injection, preferably at alternating sites for subsequent injections. CONTRA-INDICATIONS: Hypersensitivity to any active substance or excipient or formaldehyde, mercury and polyvinylpyrrolidone. Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines. Encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis-containing vaccine. Preterm administration of acute severe febrile illness. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS: Precede vaccination by review of medical history and clinical examination. Protective immune response may not be elicited in all vaccinees. Will not prevent disease caused by pathogens other than Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis, hepatitis B virus, poliovirus or Haemophilus influenzae type b. Can be expected to prevent hepatitis B. Centrally combined diphtheria to give further doses of pertussis-containing vaccine if any following events have occurred on receipt of pertussis-containing vaccine: temperature of  $\geq 40.0^{\circ}\text{C}$  (or 48 hours of vaccination), not due to another identifiable cause (collapse or shock like state) 48 hours of vaccination, convulsions, convulsions lasting  $\geq 3$  hours or 48 hours of vaccination, convulsions with or without fever,  $\leq 3$  days of vaccination. Any repetitive medical treatment and supervision be available in case of any unexpected event. Carefully weigh risk/benefit of immunising or delaying vaccination in infant or child suffering from new onset or progression of severe neurological disorder. Administered with caution in thrombocytopenia or a bleeding disorder. Do not administer intramuscular or intradermal. History of febrile convulsions, family history of convulsions or Sudden Infant Death Syndrome (SIDS) not a contraindication for use. Follow up closely vaccinees with history of febrile convulsions. Note of febrile reactions higher when co-administered with pneumococcal conjugate vaccine, or with measles mumps rubella varicella vaccine; reactions mostly moderate less than or equal to  $38.5^{\circ}\text{C}$  and transient; initiate appropriate treatment according to local treatment guidelines. Special populations: HIV infection not a contraindication. Expected immunological response may not be obtained in immunosuppressed patients. Can be given to preterm infants, however lower immune response may be observed for some antigens. Consider potential risk of apnoea and need for respiratory monitoring for 48–72h when administering primary immunisation series to very preterm infants (born < 28 weeks of gestation) and particularly if history of respiratory instability. Benefit of vaccination is high. Vaccination should not be withheld or delayed. Interference with laboratory findings: Hib capsular polysaccharide antigen expected to be positive within last observed within 12 weeks. ADVERSE EFFECTS: Reactions in local reactivity and fever after booster vaccination with respect to the primary series. Very common ( $\geq 1/100$ ): Appetite loss, crying, diarrhoea, irritability, malaise, fever  $< 38.5^{\circ}\text{C}$ , local swelling at the injection site ( $\leq 50$  mm), fatigue, pain, redness. Common ( $\geq 1/100$  to  $< 1/100$ ): Nausea, vomiting, diarrhoea, vomiting, fever  $> 38.5^{\circ}\text{C}$ , injection site reactions, including induration, local swelling at the injection site ( $> 50$  mm). Uncommon ( $1/1,000$  to  $< 1/100$ ): Upper respiratory tract infection, otitis media, cough, diffuse swelling of the injected limb, sometimes involving the adjacent part. Rare ( $< 1/10,000$  to  $< 1/1,000$ ): Syncope, drowsiness, thrombocytopenia, anaphylactic reactions, anaphylactoid reactions (including convulsions), allergic reactions (including pruritus), collapse or shock like state (hypotension, hypoxaemia, apnoea), bronchitis, apnoea, rash, anaphylaxis, swelling of the urine injected limb, extensive swelling reactions, injection site rashes, injection site vesicles. Very rare ( $< 1/10,000$ ): Convulsions (with or without fever), drowsiness.

<sup>†</sup> Preterm: 10–14 weeks (0.5 ml) and aged 11–16 weeks (0.5 ml).

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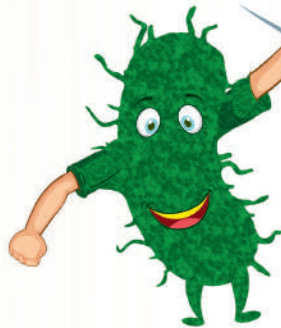
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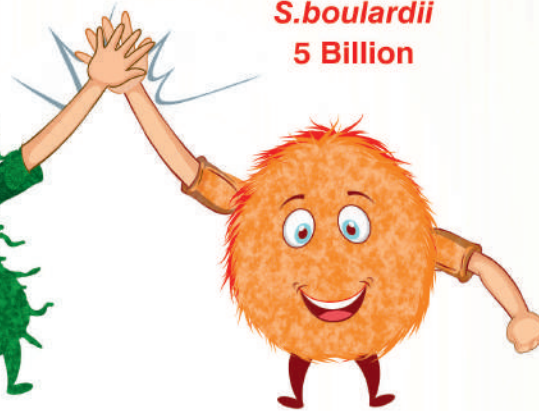
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<sup>^</sup> GALT - Gut Associated Lymphoid Tissue

<sup>†</sup> USFDA - United States Food & Drugs Association    <sup>‡</sup> EFSA - European Food Safety Authority

<sup>\*</sup> Adapted from : Suva MA, Sureja VP, Khenni DB. Curr Res Sci Med 2016;2:65-72.

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## **COVID-19 and *Indian Pediatrics***

All of us are experiencing the effects of the Coronavirus (COVID-19) pandemic – the proactive response of the Indian government has been widely appreciated. The associated lockdown; although essential, has led to difficult times for the journal, as it was not possible for the journal staff to visit the office, and consequently the editing of accepted manuscripts and other associated work of the editorial office had to be put on hold. Thankfully, the April issue was already near completion and the required editorial work could be done on soft copies. Similarly, the Editorial Manager website continued functioning uninterrupted and we could continue handling new and revised submissions. Our editors and reviewers, all busy clinicians and at the forefront of the COVID-19 response, kept on contributing to the journal work, so that manuscript handling continued without a hitch. However, due to the lockdown, the printing press could not continue operations, and the print issue would be delayed. But, we would be sending the electronic issue to all subscribers of the e-copy, and also uploading the full April issue at our website timely. It is likely that this issue may have more than its share of printing errors, as proof-reading could not go ahead as per schedule. However, bringing out the April

issue in time was our primary objective in these times of hardship, which we could achieve with the combined efforts of the journal team and our printers, Cambridge press.

On the brighter side, after an expedited review process, we are publishing two special articles on intensive care unit (ICU) management of children with COVID 19 infection in this issue. The pre-prints were uploaded at the journal website on 29 March, 2020 ([www.indianpediatrics.net/covidpapers](http://www.indianpediatrics.net/covidpapers)). We hope that these will be helpful to the pediatricians in handling affected children, as and when they present. In the Correspondence section, a reader has raised an interesting issue *vis-a-vis* measles vaccination and protection from COVID-19.

We aim to continue our practice of last more than fifty years of regular publication of journal issues, and look forward to your continuing support for all journal activities!

**DEVENDRA MISHRA**  
*Editor-in-Chief*  
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## Bioethics – The Secret Ingredient for a Successful Clinical Practice

BAKUL JAYANT PAREKH

President, Indian Academy of Pediatrics, 2020  
bakulparekh55@gamil.com

If scientific knowledge is the basis, ethics is the essence of the practice of medicine. In effect, when ethics are added to medical practice, it becomes the proverbial icing on the cake. You can achieve much more value by incorporating ethics into your daily clinical practice. To succeed, medical science needs an ethical framework, which respects the values and attitudes of patients, to make it humane.

Medical ethics are moral guidelines and values that guide practitioners of clinical medicine and scientific research. Medical ethics are values that doctors can refer to when confused or conflicted. In today's era, when the medical fraternity is losing the trust of the patients, the application of medical ethics is the need of the hour.

The term 'ethics' is derived from *ethikos*, which means 'moral character' in Greek. Ethics studies rational processes that determine the best actions when faced with conflicting choices. They are the moral principles based on the value system of what is good and bad, and what is right and wrong. Laws, religion, scientific studies, philosophies, and morals influence ethics. Some ethical issues are simple, such as differentiating between right and wrong. However, others can be complex, such as a decision between two 'rights' or two 'wrongs'; a pair of values that conflict with each other; or deciding between the interests and choices offered by two different value perspectives, such as those of the patient *versus* those of the doctor.

Thus, medical ethics is a system to judge which moral principles and values are applied to the practice of medicine, helping the doctor to decide what is morally right. In simpler words, we must always put ourselves in place of the patient and then think about what is expected from the doctor. This strategy will most of the time, help us in making the proper and ethical choice. A new concept is bioethics, which deals with typically controversial ethical issues emerging from new situations arising due to advances in medicine.

There are a lot of ethical challenges in medical practice and healthcare. Medical technologies dominate

present-day clinical practice and have not moved hand-in-hand with the changes needed in public policy to make the benefits accessible and affordable. About bioethics, the most critical part of the Hippocratic Oath is 'do no harm.' When we are almost certain that the patient is not likely to survive, and in case of survival, the patient begets a morbid/vegetative life, should we continue the use of life support? What about advising patients for proceeding with stem cell infusion without relevant, authentic data supporting this modality of management? Another very simple to understand example is whether we are morally/ethically right in using antibiotics for watery diarrhea, runny nose, and/or certain viral infections, which is leading to antimicrobial resistance globally?

As this field develops and changes, we must focus on fairness, balance, and moral thinking across various cultures and religious backgrounds. Medical ethics in clinical practice is practical and not theoretical. In short, it is the wisdom behind a successful practice. Medical ethics is a vast field, and it is not feasible to cover all of it here. I will elucidate some of the aspects that are more relevant to general practice.

Some doctors think that medical ethics is not essential and a very esoteric concept, far removed from the practical considerations of day-to-day clinical practice, and are more suited to the legal field. Laws have set rules which are followed by the Government, whereas ethics do not necessarily have a legal basis. They are based on human principles of right and wrong. We can indeed say that medical ethics is, first and foremost, a matter of conscience, but it also has some practical implications and applications.

Listening skills are essential to medical ethics. Ethical disputes are often due to not knowing all the facts, or not providing all the facts to patients. So you should be a good listener to get the best diagnosis from the history. Studies have shown that as soon as the patient starts to complain, we tend to interrupt them within a few seconds, thereby losing vital clues from history. Hence we should learn to be good listeners. A

### Box I Suggested Behaviors to Avoid Ethical Pitfalls in Clinical Practice

- Ethics requires thought. Think without inhibition.
- There is usually no single correct answer. Discuss these issues and seek advice freely.
- Ethical considerations must be recorded in the same way as clinical matters.
- Welfare of the patient takes precedence over everything else.
- Speak and communicate.
- Be conscious of the patient's right to make informed decisions, both good and bad.
- Patients may follow bad lifestyles, and a person may even life-saving treatment.
- Respect the Mental Health Act.
- Be accommodative of the fact that people have a right to differ and not have the same values as us.
- Not having the right to prevent a patient from inappropriate behavior is not the same as condoning it.
- We must exercise our right to express our views, though we may not have the right to enforce them.
- Always attempt to justify your position with reason.

well-constructed ethical decision may not work if we have not won the patient's confidence. Some suggested behaviors assisting ethical practice are listed in **Box I**.

Ethics is often seen as an activity that is telling us what we cannot do. However, unlike laws that bind us, ethics gives us the freedom to make the right choice. Relieved of nagging doubts, we can proceed more directly and more vigorously with our care plan. There are many reasons to take medical ethics seriously, and here are some:

- To solve disputes between family, patients, physicians, or others.
- In today's world of consumerism, being ethical is more important than making money or seeing as many patients as possible, which indirectly helps you in gaining the confidence of your patients and ultimately leading to a successful practice. This will also ensure a clear conscience.
- To maintain the respect and trust of patients. Ethical mistakes can destroy the bond between doctor and patient. Patients often implicitly trust their doctors,

but that trust is difficult to repair once it is breached.

- To maintain respectful relationships with other clinicians.
- To maintain efficiency. Although ethical decision-making often requires extra time, it also can save time by anticipating disagreements that can slow down the care process. If we are not ethical, patients or other caregivers who are upset with our decisions can seriously impede our work.
- To reduce burnout. One cause of burnout is incongruence between physicians' values and those of their organization. Physicians who can describe their ethical concerns and use negotiating skills may be able to change the organizational policies that produce burnout.

Let us put the effort of upholding ethics in the practice of medicine, which will help in our uniformity and unity. And always remember to put the beneficence of your patient first by doing no harm at all times.

*Jai Hind!  
Jai IAP!*

## Growth and Development of Preterm/Very Low Birthweight Infants at 12 to 24 Months of Corrected Age: A Marker of Quality Survival

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**G**rowth and development are the characteristics of infancy and childhood. Growth occurs by both hyperplasia and hypertrophy and can be measured in units that determine size. It can be assessed by age-dependent and age-independent parameters. Common age-dependent markers of growth are body weight, length/height, head circumference and body mass index. Growth monitoring is an invaluable, inexpensive, simple and acceptable tool for assessing health status of a child.

Development, on the other hand, denotes capacity and ability of an individual to integrate task performance, coordination, language, and social and behavioral adjustment. In general, growth and development go hand in hand in an orderly, organized, sequential and predictable manner [1]. Neurodevelopmental delay is a state of severe, lifelong impairment in areas of development that affects motor functions, socio-emotional behavior, sensory function, language, attention, memory and adaptive skills during the early period of a child's growth and development [2-4]. Neuro-development of a child is a result of complex interplays between genetic, environmental and nutritional factors profoundly affected by the intrauterine milieu and quality of transition at birth from the intra uterine sojourn to extra uterine existence. Intrauterine environment provides proper physical moorings for growth and development of the fetus like adequate temperature, moisture, and humidity; sufficient space for movement and sensory stimuli from the maternal heart beats, respiratory excursions, bowel sounds and locomotion; effective barrier to trauma, noise, light, external thermal changes and infection; constant supply of macro and micro nutrients for daily requirement and body stores; development of circadian rhythm for sleep and secretion of placental neuro-steroid hormones for GABA neurotransmitter regulation and neuroprotection; appreciation of smell from maternal pheromones, which drives the infant towards breasts, and immediate skin-to-skin touch at birth helps stabilizing the infant; acquiring

skills of sucking and swallowing of the amniotic fluid; conferment of passive humoral immunity and yet complete freedom to develop his/her own destiny. A shortened intra uterine period will adversely affect the fetus in all aspects described above. Preterm infant born too soon will be at a disadvantage compared to his peers born at term because adequate artificial 'intrauterine care' is a far cry today and whether that will ever be available in future is a million dollar question. Similarly a preterm infant subjected to intrauterine growth restriction will be doubly disadvantageous and will have greater risk of neurodevelopmental delay and poor physical growth.

In this issue of the journal, Mukhopadhyay, *et al.* [5] and Murki, *et al.* [6], from two different regions in India, reiterate that a significant number of preterm or very low birth weight infants suffer from growth failure and delays in cognitive, language and neurodevelopment at corrected age of 12 months to two years. Infants with intrauterine growth restriction, as expected, fared worse than appropriate for gestation age peers. In another study from one of these centers, Debata, *et al.* [7] had previously reported very high prevalence of language delay in very low birth babies at 6-36 months of corrected age. Similar observations have made by many authors from around the world.

A multifactorial etiology contributes to growth and developmental delay. These can be broadly divided into five categories: prenatal; perinatal; neonatal; post neonatal; and miscellaneous causes. Structural malformations and metabolic injury of the brain, genetic disorders, inborn errors of metabolism, early maternal infections and maternal substance abuse during pregnancy, preterm birth, intrauterine growth restriction, perinatal asphyxia and hypoxic ischemic encephalopathy, neonatal sepsis, hypoglycemia, micronutrient deficiency particularly iron and folic acid deficiency and inadequate infant feeding practices, especially deprivation of breastfeeding/breast milk feeding and, poor social interaction and separation from the mother are some of the important causes of neurodevelopmental delay.

Very preterm infants frequently require resuscitation in the labor room, NICU care, ventilatory support, surfactant and oxygen administration, body temperature management, intravenous fluids, vasopressive agents, antibiotics, and other medications like caffeine and PDA closing drugs. They suffer from many metabolic derangements like hypoglycemia, hypocalcemia and hypothermia; intraventricular hemorrhage and acidosis with resultant neuronal insult and injury. Achieving adequate enteral feeding of very preterm infants is a bigger challenge. Bronchopulmonary dysplasia and permanent brain damage are long term serious complications. Many of these complications were present in the subjects of the two studies [5,6].

In recent years, perinatologists have started looking at the fetal physiology beyond intrauterine weight gain and structural integrity. Sleep develops during fetal life with a recognizable pattern of sleep states in the preterm fetus associated with the development, maturation and neural connectivity within the brain. Impaired sleep development in the preterm infant may lead to altered neurocognitive, behavioral and motor capabilities in infancy and childhood and later on as adult [8]. Sleep is greatly disturbed in a preterm infant due to NICU protocols, noise, and intense light that may affect neurodevelopment.

It is, therefore, essential that assessment and monitoring of growth and development of all infants and children, especially high risk infants, should be carried out from early life. There is convincing scientific evidence that early identification of developmental delays and appropriate early intervention improve a child's long-term outcome and prognosis [10].

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## **BEMPU Bracelet: Potentially Useful But Still Requires Robust Validation**

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**T**hermal protection in neonates is one of the four basic elements of essential newborn care and is critical for newborn survival [1]. Hypothermia directly or indirectly has been implicated in the causation of deaths of neonates, thereby prompting the development of a variety of devices and tools for its early detection and timely management. These tools range from the simple ‘human touch’ to the automated hypothermia detection devices (AHDD). In the heterogeneous social and health systems in India, a simple, affordable and locally acceptable tool is needed to detect hypothermia and alert care providers.

Sharma, *et al.* [2] in this issue of *Indian Pediatrics*, present the findings of a clinical study about the effectiveness of one such device, the BEMPU bracelet. A previously published study on the same device was conducted in a tertiary-care hospital, which had round the clock nursing backup [3]. Promising results were reported with the reported sensitivity and specificity of over 95% to detect hypothermia; although, the diagnostic accuracy for different severity of hypothermia was not reported. The present study [2] is another step in evaluating the role of AHDD in community settings, and reports significant reduction in neonatal mortality in the intervention group. However, the results need to be interpreted carefully in the context of the caveats discussed below.

The direct attribution of hypothermia as a cause of neonatal mortality may not be true. Hypothermia and death in neonates indeed have a strong association but causality can not be established in majority of the cases. Hypothermia may be a consequence rather than cause of neonatal illnesses (*e.g.* sepsis) in many cases. This relative lack of clarity is further compounded by the existence of weak vital statistics in developing countries because of which outcome of a large number of enrolled neonates is not known. Undoubtedly, early detection of hypothermia plays an important role in limiting morbidity, but relating all instances of hypothermia to deaths that can be prevented by the device may overrate the effectiveness of the device.

This pilot trial conducted in Rajasthan [2] does illustrate the feasibility and acceptability of using the device at the community level; however, the families included in the trial were also provided regular weekly follow-up visits and reminder phone calls, which are potent co-interventions influencing mortality. While the device is designed in attractive colors, resembles a mini version of a modern smartwatch and emits multicolored lights signifying normo- and hypo-thermia, it is uncertain whether the illiterate tribal population can interpret these cues. The single-use device is priced at INR 2499 and once activated has a shelf life of 4 weeks. Affordable cost is the key to accessibility in developing countries [4], and the ‘prohibitive’ cost of the device may be a major barrier for its widespread use in the public sector. The authors themselves opine that in the context of India’s limited resources and to limit wasteful health expenditure, it is important to establish the cost-effectiveness of this device before its scaling up. The innovators should work to make this device as multi-use, which can not only make it affordable but also reduce its environmental footprint.

The authors [2] claim a positive behavior change in the parents of enrolled neonates as evident by higher follow-up rates at four weeks (59%) in the study group; however, the observed effect could be a consequence of performance bias wherein the study group has been given more attention. Performance bias is an inherent drawback of unblinded trials, and a well-conducted study with robust design and blinding (of the person making phone calls/home visits) could address this issue in future. The study also included neonates with malformations; it is also unclear as to how the causes of death were assigned to neonates.

A simple yet cost-effective method to detect hypothermia is by using the hand-touch method. Palpation of the forehead, abdomen and foot [5] has shown a reasonable sensitivity in the detection of hypothermia. Training mothers and healthcare workers in this skill is an effective method in a resource-limited setting. Any future study should include the ‘touch

method' of detecting hypothermia in the comparison arm thus evaluating the incremental benefit of the device.

Lastly, it is important to realize that an AHDD may be used as a tool to detect hypothermia that triggers corrective and preventive action like kangaroo mother care (KMC) and a hospital visit. It is just one component of care – we should not lose sight of the fact that only holistic care including optimum feeding practices, promoting KMC, hygiene, ensuring follow up care, and empowering health workers and mothers in detecting signs of severe illness for early care-seeking is going to save neonatal lives [6].

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## NOTES AND NEWS



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## **Cerebral Edema in Diabetic Ketoacidosis - Fluid Shifts and Shifting Paradigms**

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**D**iabetic ketoacidosis (DKA) is the most significant acute complication of type 1 diabetes mellitus (T1DM). DKA is a common presentation for new onset T1DM, occurring in up to 25%-40% of newly diagnosed children [1-3]. The essential components of the treatment regimen for DKA are fluid and electrolyte resuscitation and insulin therapy. Cerebral edema manifests clinically in approximately 1% of DKA patients with progression to brain herniation, representing the major cause of mortality and morbidity in DKA [4]. However, asymptomatic or subclinical cerebral edema, as detected by subtle brain computed tomography (CT) or magnetic resonance imaging (MRI) changes, can occur in as much of 50% of DKA patients. Hence, early identification of clinically relevant cerebral edema in DKA relies on clinical criteria rather than solely on radiological tests [5]. Clinical identification of cerebral edema is further confounded by alterations in mental status that are part of the clinical picture of DKA [4,5]. In DKA, cerebral edema usually occurs early (occurring within the first 7-8 hours in approximately 2/3rd) in the treatment of DKA with the remaining cases occurring up to 28-30 hours after fluid resuscitation and initiation of insulin treatment [3,6]. Notably, cerebral edema has also been reported, albeit rarely, prior to initiation of fluid resuscitation and treatment.

The mechanism(s) of cerebral edema in DKA continue to be debated and explored. The traditional model ascribes cerebral edema to retention of cerebral intracellular osmolytes causing fluid shifts into the intracellular space. Acceptance of this model resulted in an emphasis on rate and composition of intravenous fluid administration as significant parameters to mitigate the risks of cerebral edema. This dogma is being challenged by newer studies indicating role for vasogenic edema from blood-barrier destruction, and cytotoxic edema from ischemia in the development of cerebral edema in DKA. Furthermore, a recent landmark randomized control study [6] revealed no differences between intravenous administration of 0.45% vs 0.9%

normal saline at either rapid or slow infusion rates in children with DKA with Glasgow coma scale (GCS) >11. One caveat of this study is the exclusion of sicker children with GCS <11, due to obvious ethical concerns [6]. Risk factors predisposing to cerebral edema include new onset T1DM, younger age (<5 years) and markers of severe DKA such as higher serum urea nitrogen concentrations, severe acidemia (pH <7.1), lower initial bicarbonate and lower partial pressures of arterial CO<sub>2</sub> (< 20 mm Hg) [2,4].

The study by Agarwal, *et al.* [7] in this issue of *Indian Pediatrics* highlights many of the factors that are known to be associated with increased risk for cerebral edema, such as lower partial pressures of arterial CO<sub>2</sub> and new onset diabetes. However, an unusual finding in this study [7] is the extraordinarily high rate (24.3%) of clinically diagnosed cerebral edema. Contemporary literature describes clinically apparent cerebral edema in ~1% of episodes of DKA [1,5]. In the current study, the diagnostic criterion used in 15 (68%) patients for diagnosing cerebral edema was abnormal central breathing pattern. It is not clear whether this criterion was applied at the time of diagnosis of DKA or after initiation of treatment. In the absence of the other diagnostic criteria (abnormal motor or verbal response to pain, decorticate or decerebrate posture, or cranial nerve palsy, especially involving III, IV, and VI cranial nerves) [5], Kussmaul breathing, a classic sign of DKA at presentation, would be difficult to differentiate from the cerebral edema criterion of abnormal central breathing. It is noteworthy that the rate of cerebral edema development during treatment was much lower at 4.7%. This study also highlights the importance of having complete information about fluid resuscitation in the transfer of care documents, since history of prior fluid treatment was a predictive factor for cerebral edema, especially in the cases where it developed after initiation of treatment post-admission. The development of cerebral edema in one of their patients 60 hours after initiation of treatment is unusual and exemplifies the need for continuous assessment by trained practitioners in



identifying changes in neurological status in these patients.



The only way to completely prevent cerebral edema in DKA is to avoid DKA. The study by Agarwal, *et al.* [7] highlights the critical importance of early diagnosis of new onset T1DM before the patient has progressed to DKA. In countries such as India, with a diverse healthcare delivery system, primary healthcare providers including community health care workers should be constantly vigilant to the possibility of the diagnosis of new-onset T1DM in a child presenting with suggestive symptoms such as polyuria (especially new onset nocturia or bed wetting), polydipsia, and weight loss.

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## Cognitive, Language, and Visuomotor Abilities of Very Low Birthweight Infants at Corrected Age of Two Years

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**Objective:** To assess the prevalence and predictors of language and visuomotor delay in very low birthweight ( $\leq 1250$  g) children at corrected age (CA) of 2 years.

**Design:** Prospective observational.

**Setting:** Neonatal follow-up clinic of a level III center.

**Participants:** Children with birthweight  $\leq 1250$  g and discharged alive ( $n=164$ ) from April 2012 to April 2013 were followed up till 2 years CA ( $n=126$ ).

**Methods:** Development, neurological status, and language/visuomotor cognitive skills were assessed by Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS). Development Quotient (DQ) was calculated.

**Main Outcome:** Prevalence and predictors for the language and visuomotor delay.

**Results:** At 2 years ( $n=123$  CAT, 126 CLAMS), 30 (24%) children had below average DQ ( $<90$ ) and 93 (74%) average and above average DQ ( $\geq 90$ ) in full scale CAT/CLAMS test. Small for gestation infants ( $n=86$ ) have higher risk of below average DQ ( $P=0.036$ ). Gestational age and socioeconomic status have a positive correlation with language development at 9 months and 2 years, respectively.

**Conclusions:** In VLBW (birth weight  $\leq 1250$  g) infants, the prevalence of language/visuomotor delay is high. Small for gestational age infants are at higher risk for language and visuomotor development delay at 2 years corrected age.

**Keywords:** Clinical Linguistic and Auditory Milestone Scale, Cognitive Adaptive Test, Language delay, Outcome, Visuomotor delay.

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Development is a complex, multidimensional, structured process, and aberration in it is associated with a delay and disability in later life. It is important to perform the developmental assessment of all children for early identification of the delays and timely institution of interventions to prevent adverse consequences [1]. Very low birth weight (VLBW) infants and neonatal intensive care unit (NICU) graduates have significant morbidities in neonatal period, which increase their risk of developmental delays in childhood [2,3]. The developmental delay may involve either all the five domains of development (language, gross motor, visuomotor, adaptive and social) or a particular domain. Multiple screening as well as diagnostic tools exist to identify the delay/dissociation in the development process [4,5].

The Bayley Scales of Infant Development (BSID) is a frequently used scale to evaluate the neurodevelopment in children; however, it requires expertise, training and is time-consuming which makes it difficult to use in general practice [4,6]. The Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS) was designed for cognitive, language and visuomotor

development assessment by pediatricians in general practice. It takes 10-20 minutes and has good correlation with BSID in normal as well as high-risk children [7,8].

*Accompanying Editorial : Pages 290-91.*

We aimed to evaluate the prevalence and predictors for delayed language and visuomotor development in babies with birthweight  $\leq 1250$  g at a corrected age of two years using CAT/CLAMS tool.

### METHODS

This prospective cohort study was conducted in the neonatal follow-up clinic of a tertiary center from April 2012 to April 2015. All babies born from April 16, 2012 to April 15, 2013, with a birthweight of  $\leq 1250$  grams were enrolled after taking written informed consent from the parents and followed up till 2 years corrected age (CA) for language and visuomotor assessment. The study was approved by the institute research ethics committee.

All cases were followed at neonatal follow-up clinic at CA of 40 weeks, 3 months, 6 months, 9 months, 12 months, 18 months, and 2 years. During these visits, anthropometry,

neurological examination [9] and development assessment [6] were done by a neonatologist. Brainstem evoked response audiometry (BERA) was performed in all children at CA of 3 months. At 9 months and 2 years CA, their language and visuomotor development skills were assessed by the Capute scale - Cognitive Adaptive Test/ Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS) by a trained clinical psychologist. The developmental quotient (DQ) scores were calculated in each domain by dividing the age equivalent score for the given scale by the chronological age and multiplying by 100 to express as a percentage. Full-scale CAT/CLAMS DQ (FS DQ) was calculated by averaging the CAT and CLAMS development quotients. The CAT/CLAMS/FS DQ was further categorized as follows: <70, delayed; 70-79, borderline; 80-89, below average; 90-109, average and  $\geq 110$ , above average. To simplify the analysis, these categories were further divided into below average if  $DQ < 90$ , and average and above if  $DQ \geq 90$ .

The Capute Scale (CAT /CLAMS) is a development assessment tool to quantitatively measure receptive and expressive language skills along with nonverbal problem-solving skills in infants from 0 to 36 months of age [8,10]. CLAMS is for language assessment and it relies mostly on parental history in the first 18 months of life and thereafter on a combination of parental history and observation skills of the examiner, whereas CAT deals with visuomotor problem-solving skills and requires direct observation of a child performing a specific task during the assessment. In contrast to other commonly used screening tools which give pass/fail results, this is a quantitative assessment tool that determines the degree as well as the type of the developmental delay. This tool has got importance due to its objective nature and quick administration even by trainee residents/fellows.

The primary outcome measure was to estimate the prevalence of cognitive and language delay and secondary outcome measure was to identify the risk factors for the delay in VLBW (birthweight  $\leq 1250$  g) children at 2 years corrected age.

**Statistical analyses:** The basic demographics were expressed as percentages for categorical variables, mean (SD) for normally distributed continuous variables on the Shapiro-Wilk test and as median (1st, 3rd quartile) for skewed distributed continuous variables. Categorical variables were compared between groups by chi-square test or Fisher exact test as applicable. The Pearson correlation coefficient (including Biserial correlation, if applicable) was used to assess correlation among groups with normally distributed continuous variables. SPSS version 20 software was used for analysis.

## RESULTS

A total of 341 babies with birth weight  $\leq 1250$  g were enrolled of whom 202 were admitted in NICU – 164 (48%) were discharged alive, 11 (3.2%) died in NICU and 27 (8%) left against medical advice. The remaining 139 (41%) had died in delivery room either due to resuscitation failure at birth, non-receipt of optimal care due to inadequate infrastructure, extreme prematurity or other reasons. Of the 164 discharged infants, 126 (85%) were assessed at 2 years, 16 infants had died (10%) and 22 were lost to follow up (13%). The demographic details and baseline characteristics of the discharged infants are shown in **Table I**. The outcome at 9 months and 2 years corrected age respectively, are shown in **Table II**. **Table III** presents the predictors for abnormal language development at 2 years. Small for gestational age status is associated with below average ( $DQ < 90$ ) language and visuomotor development [OR

**Table I Baseline Demographic Characteristics of the Very Low Birthweight Infants (N=164)**

| Characteristics                               | Value      |
|---|------------|
| *Gestation (wk)                               | 30.7 (2.8) |
| *Birthweight (g)                              | 1051 (147) |
| #Male   | 74 (39.8)  |
| #Appropriate for gestational age              | 78 (47.6)  |
| #Small for gestational age                    | 86 (52.4)  |
| #Rural residence                              | 74 (45.1)  |
| #Maternal education (n=120)                   |            |
| Illiterate                                    | 4 (3.3)    |
| Primary school certificate                    | 7 (5.8)    |
| Middle school certificate                     | 19 (15.8)  |
| High school certificate                       | 33 (27.5)  |
| Intermediate                                  | 14 (11.7)  |
| Graduate/Postgraduate                         | 39 (32.5)  |
| Professional/Honors                           | 4 (3.3)    |
| ##Socioeconomic status (Kuppuswamy scale)     |            |
| Upper   | 30 (18.3)  |
| Upper middle                                  | 42 (25.6)  |
| Lower middle                                  | 54 (32.9)  |
| Upper lower                                   | 30 (18.3)  |
| Lower   | 8 (4.9)    |
| #Absent/Reduced end diastolic flow on doppler | 37 (22.6)  |
| #Intraventricular hemorrhage                  | 49 (29.9)  |
| Grade I/II                                    | 43 (26.2)  |
| Grade III/IV                                  | 6 (3.7)    |

Values are expressed as \*Mean (SD) or #n (%), PCA: Post conceptional age; †antenatal doppler.

**Table II Language and Visuomotor Development at 9 Month and 2 Years Corrected Age**

| <i>Outcome parameter</i>                                | <i>9 mo (n=83)</i> | <i>2 years</i> |
|---|--------------------|----------------|
| <i>Cognitive adaptive test*</i>                         |                    | <i>(n=123)</i> |
| #Composite Score  | 101 (9)            | 95.3 (10.7)    |
| Delay (<70)   | 1 (1.2)            | 5 (4.1)        |
| Borderline (70-79)                                      | 2 (2.4)            | 3 (2.4)        |
| Low average (80-89)                                     | 3 (3.6)            | 21 (17.1)      |
| Average (90-109)  | 59 (71.1)          | 84 (68.3)      |
| Above average (110 or more)                             | 18 (21.7)          | 10 (8.1)       |
| <i>Clinical linguistic and auditory milestone scale</i> |                    | <i>(n=126)</i> |
| #Composite score  | 98.5(11.1)         | 94.9 (15.7)    |
| Delay (<70)   | 2 (2.4)            | 9 (7.1)        |
| Borderline (70-79)                                      | 3 (3.6)            | 9 (7.1)        |
| Low average (80-89)                                     | 9 (10.8)           | 21 (16.7)      |
| Average (90-109)  | 50 (60.2)          | 68 (54.0)      |
| Above average (110 or more)                             | 19 (22.9)          | 19 (15.1)      |
| <i>Full scale developmental quotient</i>                |                    | <i>(n=123)</i> |
| #Composite score  | 99.7(9)            | 95.0 (11.6)    |
| Delay (<70)   | 1 (1.2)            | 5 (4.1)        |
| Borderline (70-79)                                      | 2 (2.4)            | 6 (4.9)        |
| Low average (80-89)                                     | 7 (8.4)            | 19 (15.4)      |
| Average (90-109)  | 62 (74.7)          | 85 (69.1)      |
| Above average (110 or more)                             | 11 (13.3)          | 8 (6.5)        |

\*3 children were not cooperative for cognitive adaptive test; Figures expressed as n (%); #expressed as Mean (SD).

(95% CI) , 2.5 (1.1-5.8);  $P=0.036$ ]. DQ's correlation with other variables was also performed. Gestational age had a weak but significant ( $P=0.01$ ) positive correlation with CLAMS ( $r=0.38$ ) and full-scale DQ ( $r=0.33$ ) at 9 months; however, it was not significant at 2 years. A weak, but a significant positive correlation (using Biserial correlation) was also observed between higher socioeconomic status (score > 15 on Kuppuswamy scale) and CLAMS and full scale DQ score at 2 years ( $r=0.21$  and  $0.21$ , respectively,  $P<0.01$ ). Importantly, CAT score and CLAMS score at 2 years have moderate but significant positive correlation ( $r=0.53$ ,  $P<0.01$ ) with each other suggesting the development of one domain is closely related to another. CAT score at 9 months had weak, but the significant ( $P<0.01$ ) positive correlation with CAT DQ ( $r=0.28$ ) and full-scale CAT/CLAMS DQ ( $r=0.28$ ) score at 2 years. Language and visuomotor skill development (full scale DQ) at 9 months had a strong positive correlation with full scale CAT/CLAMS DQ at 2 years ( $P<0.01$ ). Overall, 9 months assessment correlates well with language/visuomotor development at 2 years.

## DISCUSSION

In the present study about one-fourth of the children had below average language and visuomotor development skills (composite DQ <90). SGA status was strongly associated with below average visuomotor and language development at 2 years. Higher gestational age and higher socioeconomic status positively correlate with better language development. Similarly, language and/or visuomotor development at 9 months had a significant positive correlation with the language and visuomotor skills at 2 years corrected age.

The observations on Language delay are in concordance with the previous studies [11-13]. A recent cross-sectional study from Indonesia among toddlers in community settings using CAT/CLAMS full-scale DQ scores found that 16 % babies had suspect/delay in cognitive development [14]. The higher prevalence noted in the present study is likely due to differences in the study population. Previous studies have shown conflicting results on association of language development and gender [11, 15,16]. However, no gender difference in language development was noted in the present study.

We found a significant correlation between socioeconomic status and language development, consistent with previous studies [17-19]. Just as in previous studies, the present study also noted that SGA babies had poor composite language and visuomotor outcome as compared to the appropriate for gestational age (AGA) babies [20,21]. This may be related to an insult to the neural architecture in the frontal lobe leading to the volume reduction of the frontal lobe.

The limitations of our study are that we had a low follow up rate at 9 months, hence, could not compare the outcomes between 9 and 24 months. Also, we assessed by using only one measure of language development and not by formal speech assessment scale. Multiple measures may have provided more accurate results. The strength of our study is its prospective nature, large sample size, detailed structured assessment with a validated tool, hearing assessment (BERA) for all subjects and good follow up (85%) till 2 years.

In conclusion, a quarter of VLBW (birth weight  $\leq 1250$  grams) children had below average DQ for language and visuomotor development. Higher gestation and socioeconomic status have a positive correlation with language development. We recommend that the structured language assessment, as well as speech stimulation, should be a part of the routine follow up in high-risk clinics.

**WHAT IS ALREADY KNOWN?**

- Language and visuomotor delay is a common problem in very low birth weight infants.
- There are several social, environmental, and biological risk factors for language and visuomotor delay.

**WHAT THIS STUDY ADDS?**

- One-fourth of VLBW (birthweight  $\leq 1250$  g) infants have composite language and visuomotor delay.
- Small for gestational age infants are at higher risk of language and visuomotor delay.

**Table III Predictors of Language and Visuomotor Development at the Corrected Age of Two Year**

| Parameter          | Category           | #CAT DQ              |                          | P    | CLAMS DQ             |                          | P     | FSDQ                 |                          | P    |
|--------------------|--------------------|----------------------|--------------------------|------|----------------------|--------------------------|-------|----------------------|--------------------------|------|
|                    |                    | Below Average (n=29) | Average and above (n=94) |      | Below Average (n=39) | Average and above (n=84) |       | Below Average (n=30) | Average and above (n=93) |      |
| Gestation (wk)     | <28                | 8 (24.2)             | 25 (75.8)                | 0.9  | 12 (27.3)            | 22 (72.7)                | 0.5   | 11 (33.3)            | 22 (66.7)                | 0.1  |
| Birthweight (g)    | < 1000             | 9 (21.4)             | 33 (78.6)                | 0.8  | 10 (23.2)            | 33 (66.8)                | 0.2   | 9 (21.4)             | 33 (78.6)                | 0.6  |
| Sex                | Female             | 15 (24.2)            | 47 (75.8)                | 1.0  | 23 (35.4)            | 42 (64.6)                | 0.3   | 16 (25.8)            | 46 (74.2)                | 0.8  |
| Maternal education | Less than graduate | 19 (27.1)            | 51 (72.9)                | 0.2  | 27 (28.1)            | 44 (71.9)                | 0.055 | 20 (28.6)            | 50 (71.4)                | 0.2  |
| Father's education | Less than graduate | 20 (26.0)            | 57 (74.0)                | 0.5  | 28 (35.4)            | 51 (64.6)                | 0.1   | 20 (26.0)            | 57 (74.0)                | 0.6  |
| Residence          | Rural              | 13 (25.5)            | 38 (74.5)                | 0.8  | 19 (35.9)            | 34 (64.1)                | 0.3   | 12 (23.5)            | 39 (76.5)                | 1.0  |
| *SES               | Lower              | 22 (23.2)            | 73 (76.8)                | 0.8  | 29 (29.6)            | 69 (70.4)                | 0.5   | 23 (24.2)            | 72 (75.8)                | 1.01 |
| SGA                | Yes                | 13 (24.5)            | 40 (75.5)                | 0.8  | 19 (35.2)            | 35 (64.5)                | 0.3   | 18 (34.0)            | 35 (66.0)                | 0.04 |
| IVH                | Yes                | 11 (30.6)            | 25 (69.4)                | 0.2  | 12 (32.4)            | 25 (67.6)                | 0.8   | 12 (33.3)            | 24 (66.7)                | 0.1  |
| BERA               | Abnormal           | 4 (50.0)             | 4 (50.0)                 | 0.08 | 4 (50.0)             | 4 (50.0)                 | 0.2   | 2 (25.0)             | 6 (75.0)                 | 1.0  |

CAT: Cognitive Adaptive Test; CLAMS: Clinical Linguistic and Auditory Milestone Scale; FS: Full scale CAT/CLAMS; DQ: Development quotient; IVH: Intraventricular hemorrhage; SGA: Small for gestational age; BERA: Brainstem evoked response audiometry; SES: Socioeconomic status; #CAT could not be performed in 3 cases;  $P < 0.05$  considered significant; \*Modified Kuppaswamy's socioeconomic status scale; lower (score  $< 15$ ); Below average ( $DQ < 90$ ) and average and above ( $DQ \geq 90$ ) for all scales.

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## Growth and Neurodevelopmental Outcomes at 12 to 18 Months of Corrected Age in Preterm Infants Born Small for Gestational Age

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**Objective:** To compare the growth and neurodevelopmental outcomes at 12 to 18 months of corrected age in preterm infants (gestation < 35 wks) born appropriate for gestation (AGA) with those born small for gestation (SGA). **Methodology:** This cross sectional, study assessed the growth outcomes in terms of underweight, stunting, microcephaly, overweight and obesity. Development delay was defined as developmental quotient < 70 on DASII. **Results:** Out of 178 infants enrolled in the study 119 were AGA and 59 were SGA. The mean gestational age of the study cohort was 30.45 (2.08) weeks. More infants in the SGA group were underweight (59.3% vs. 37.8%, RR: 1.79, 95% CI: 1.16-2.74), stunted (62.7% vs. 30.25%, RR: 2.19, 95% CI: 1.42-3.36) and had higher incidence of motor (6.7% vs. 0.8%, RR: 2.5, 95% CI: 1.5-4.1) and mental development (3% vs. 0, RR: 3.1, 95% CI: 2.5-3.8) delay. **Conclusion:** Preterm SGA infants are at an increased risk of underweight, stunting, motor and mental development delay when compared with preterm AGA infants in early childhood.

**Keywords:** Obesity, Development quotient, Stunting, Underweight.

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The rate of preterm birth ranges from 5% to 18% and India is the biggest contributor to the world's prematurity burden [1]. Neonates born preterm are more susceptible to growth and neurodevelopmental abnormalities when compared with neonates born at term gestation [2,3]. Preterm neonates who are SGA at birth are at double jeopardy because of their shortened gestation period and growth restriction [4]. A higher incidence of prenatal and perinatal complications, as well as lower cognitive scores and poorer growth during first years of life, has been reported in preterm small for gestational age (SGA) infants compared with those born appropriate for gestational age (AGA) at birth. This study was designed to assess the growth and neurodevelopment outcomes in preterm SGA infants (gestation <35 week) in comparison to their AGA counterparts when assessed at 12 to 18 months of corrected age.

### METHODS

This was a cross-sectional study conducted in the outpatient follow-up clinic of Fernandez hospital, Hyderabad after obtaining clearance from ethical committee and informed written consent from one of the parents. The study was conducted over a period of 2 years

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from May, 2016 to May, 2018. All preterm infants (till 34 6/7 days of gestation) born after May, 2015 with a corrected age of 12-18 months were eligible for enrollment. AGA and SGA were categorized based on infant's birthweight falling between 10<sup>th</sup> and 90<sup>th</sup> percentile and less than 10<sup>th</sup> percentile for gestational age on Fernandez growth charts [5], respectively. Infants with major congenital malformations were excluded from the study. The antenatal, perinatal and neonatal details of enrolled infants were collected in a predesigned proforma from the discharge summary, computerized database and case files. Feeding details during the first 6 months and that of complementary feeding were collected from the parents by asking direct or leading questions. A list of eligible infants was prepared from the existing computer database and parents of these infants were contacted on phone (maximum of 3 reminders) for a scheduled visit when they attained a corrected age of 12 months. During the visit growth was assessed by measuring weight, length, head circumference and mid upper arm circumference. These measurements were analyzed using WHO AnthroPlus software [6]. Developmental

assessment was by Developmental Assessment Scale for Indian Infants (DASII) by a certified pediatrician blinded to the baseline neonatal variables. Tone abnormalities were identified by detailed neurological examination of the child and neurosensory evaluation by a need for hearing aids and need for visual aids or blindness in one or both eyes.

Assuming the incidence of malnutrition to be (weight deviation for age > 2 z score from the reference mean for age) 40% in preterm SGA group and 20% in preterm AGA group [7], with an alpha error at 5% and a desired power set at 80%, with 2:1 ratio of AGA to SGA infants, the required sample size was 116 infants in the AGA group and 58 infants in the SGA group.

*Statistical analyses:* All the data was analyzed using software SPSS ver.20. Data was expressed as mean (with standard deviation) and proportions as appropriate. Chi square test and student *t* test were applied for qualitative and quantitative data respectively. A *P*-value of <0.05 was considered significant.

Incidence of undernutrition (underweight) defined as weight/age Z score >2 standard deviations below the reference mean (WHO Growth charts) [8] for that age

and sex was the primary study outcome. Incidence of stunting (length/age Z-score  $\leq$ -2.00), wasting (weight/length Z-score  $\leq$ -2.00), microcephaly (head circumference/age Z-score  $\leq$ -3.00), overweight (Body mass index (BMI)/age between 85-95 percentile) and obesity (Body mass index (BMI)/age  $\geq$ 95 percentile) and incidence of developmental delay defined as Motor Developmental quotient and mental developmental quotient <70 were the secondary study outcomes.

## RESULTS

During the study period, 610 infants were eligible for enrollment in the study but only 178 infants could be enrolled in the study. Of the 178 infants enrolled in the study, 119 infants were AGA and 59 infants were SGA at birth. **Table I** provides the baseline characteristics for the study population. Most neonatal morbidities were similar in infants of both the groups. The duration of exclusive breast feeding was similar between both groups, but complementary feeding was initiated one month earlier in SGA infants.

The mean corrected age at follow up in the study population was 14.4 months. **Table II** provides the outcomes for the study population. More infants in the

**Table I Baseline Variables In Preterm Small for Gestational Age Babies (N=178)**

| Variable   | Overall (n=178) | AGA group (n=119) | SGA group (n=59) | P-Value |
|--|-----------------|-------------------|------------------|---------|
| Gestation (wk) <sup>#</sup>                            | 30.4 (2.08)     | 30.1 (2.15)       | 31.0 (1.80)      | 0.006   |
| Birth weight (g) <sup>#</sup>                          | 1242.1 (354.4)  | 1349.7 (355.1)    | 1025.0 (234.6)   | <0.001  |
| Birth length (cm) <sup>#</sup>                         | 38.2 (3.2)      | 39.0 (3.0)        | 36.5 (3.0)       | <0.001  |
| Head circumference (cm) <sup>#</sup>                   | 27.4 (2.1)      | 27.7 (2.2)        | 26.6 (1.7)       | <0.001  |
| Male sex (%)   | 95 (53.4)       | 65 (54.6)         | 30 (54.2)        | 0.63    |
| Multiple pregnancy (%)                                 | 50 (28)         | 42 (35.3)         | 8 (13.5)         | 0.002   |
| Neonatal seizures (%)                                  | 5 (2.8)         | 2 (1.6)           | 3 (5)            | 0.19    |
| Culture positive sepsis (%)                            | 44 (24.7)       | 26 (21.8)         | 18 (30.5)        | 0.20    |
| hsPDA (%)  | 35 (19.6)       | 25 (21)           | 10 (16.9)        | 0.52    |
| NEC IIA or more (%)                                    | 9 (5)           | 2 (1.6)           | 7 (11.8)         | 0.004   |
| ROP requiring treatment (%)                            | 4 (2.2)         | 4 (3.3)           | 0 (0)            | –       |
| BPD (%)  | 17 (9.5)        | 11 (9.2)          | 6 (10.1)         | 0.84    |
| Cystic PVL (%)   | 3 (1.6)         | 3 (2.5)           | 0                | 0.21    |
| IVH grade 3 or more (%)                                | 2 (1.1)         | 2 (1.7)           | 0                | –       |
| Time to reach full feeds (d) <sup>#</sup>              | 7.8 (5.4)       | 6.6 (4.8)         | 10.3 (5.8)       | <0.001  |
| Time to regain birth weight (d) <sup>#</sup>           | 13.0 (4.79)     | 14.0 (4.55)       | 10.9 (4.6)       | <0.001  |
| Duration of hospitalization (d) <sup>#</sup>           | 26.6 (21.3)     | 27.1 (22.1)       | 34.6 (18.9)      | 0.02    |
| Duration of exclusive breast feeding (mo) <sup>#</sup> | 3.6 (2.2)       | 3.5 (2.3)         | 3.8 (2.0)        | 0.37    |
| Initiation of complementary feeding (mo) <sup>#</sup>  | 6.96 (0.95)     | 7.12 (0.92)       | 6.64 (0.96)      | 0.002   |

hsPDA: Hemodynamically significant patent ductus arteriosus; NEC: Necrotizing enterocolitis; ROP: Retinopathy of prematurity; BPD: Bronchopulmonary dysplasia; IVH: Intraventricular hemorrhage; PVL: Periventricular leukomalacia; <sup>#</sup>Mean (SD).



**Table II Growth and Neurodevelopmental Outcomes of Preterm Small for Gestational Age Infants at the Corrected Age of 12-18 Month**

| Variable  | Overall (n=178) | AGA group (n=119) | SGA group (n=59) | P value |
|---|-----------------|-------------------|------------------|---------|
| Age at follow up (mo) <sup>#</sup>              | 14.4 (2.2)      | 14.4 (2.3)        | 14.4 (2.1)       | 0.99    |
| Weight (kg) <sup>#</sup>                        | 8.5 (1.4)       | 8.8 (1.5)         | 7.8 (1.0)        | <0.001  |
| Length (cm) <sup>#</sup>                        | 74.2 (4.8)      | 75.1 (4.9)        | 72.4 (4.0)       | <0.001  |
| Head circumference (cm) <sup>#</sup>            | 44.0 (1.7)      | 44.4 (1.7)        | 43.3 (1.5)       | <0.001  |
| Underweight (%)                                 | 80 (45)         | 45 (37.8)         | 35 (59.3)        | 0.007   |
| Wasting (%)                                     | 34 (19.1)       | 21 (17.6)         | 13 (22.03)       | 0.48    |
| Stunting (%)                                    | 73 (41.01)      | 36 (30.25)        | 37 (62.7)        | <0.001  |
| Microcephaly (%)                                | 15 (8.4)        | 10 (8.4)          | 5 (8.4)          | 0.98    |
| Mean BMI (kg/m <sup>2</sup> ) <sup>#</sup>      | 15.3 (1.3)      | 15.5 (1.4)        | 14.9 (1.1)       | 0.004   |
| Overweight (%)                                  | 9 (5.0)         | 7 (5.8)           | 2 (3.3)          | 0.47    |
| Obesity (%)                                     | 2 (1.1)         | 2 (1.6)           | 0 (0)            | 0.31    |
| Mean MUAC (cm) <sup>#</sup>                     | 12.5 (1.1)      | 12.7 (1.1)        | 12.2 (0.9)       | 0.002   |
| Mean motor age (mo) <sup>#</sup>                | 13.5 (2.6)      | 13.7 (2.6)        | 13.0 (2.5)       | 0.1     |
| Mean motor developmental quotient <sup>#</sup>  | 93.1 (9.5)      | 94.5 (8.3)        | 90.2 (11.2)      | 0.005   |
| MoDQ <70 (%)                                    | 5 (2.8)         | 1 (0.8)           | 4 (6.7)          | 0.02    |
| MoDQ 71-85 (%)                                  | 20 (11.2)       | 12 (10)           | 8 (13.5)         | 0.48    |
| MoDQ >85 (%)                                    | 153 (85.9)      | 106 (89)          | 47 (79.6)        | 0.09    |
| Mean mental age (mo) <sup>#</sup>               | 13.7 (2.6)      | 13.9 (2.6)        | 13.1 (2.4)       | 0.048   |
| Mean mental developmental quotient <sup>#</sup> | 94.7 (8.6)      | 96.6 (7.9)        | 90.8 (8.8)       | <0.001  |
| MeDQ <70 (%)                                    | 3 (1.6)         | 0 (0)             | 3 (5.0)          | 0.03    |
| MeDQ 71- 85 (%)                                 | 19 (10.6)       | 10 (8.4)          | 9 (15.2)         | 0.16    |
| MeDQ >85 (%)                                    | 156 (87.6)      | 109 (91.5)        | 47 (76.2)        | 0.005   |
| Tone abnormalities (hyper/hypotonia) (%)        | 39 (22)         | 27 (22.6)         | 12 (20.3)        | 0.72    |

W/A: weight for age; L/A: length for age; HC/A: head circumference of age; W/L: weight for length; BMI: Body mass index; MUAC: Mid upper arm circumference; MUAC/A: Mid upper arm circumference for age; MoDQ: Motor developmental quotient; MeDQ: Mental developmental quotient; <sup>#</sup>Mean (SD).

SGA group were underweight (59.3% and 37.8%, RR: 1.57 and CI 1.15 - 2.14) and stunted (62.7% and 30.25%, RR: 2.07 and CI 1.48-2.90) when compared to AGA infants. Frequency of wasting (17.6% and 22.03% RR: 1.25 and CI 0.67-2.3), microcephaly (8.4% and 8.4%, RR: 1.0 and CI 0.36-2.81) and overweight (5.8% and 3.3% RR: 0.57 and CI 0.12-2.68) were similar in both AGA and SGA groups. Adjusting for birth gestation, gender, multiple pregnancy, mode of delivery and resuscitation at birth SGA independently predicted long term undernutrition (odds ratio: 2.5, 95%CI: 1.25-5). Infants in the SGA group had significantly lower motor and mental developmental quotients when compared to infants of AGA group.

## DISCUSSION

The present study observed that preterm SGA infants were at higher risk for underweight, stunting, motor and mental developmental delay when compared with preterm AGA infants at corrected age of 12 to 18 months.

The observations on the nutritional status reported in the present study are similar to that reported by Sharma, *et al.* [9] but different from that reported by Mukhopadhyay, *et al.* [10]. The differences in the incidence of long term growth outcomes between the studies is mainly due to the differences in study population, age at assessment and reference standards [11]. In a meta- analysis [12] of 19 birth cohorts from low and middle income countries it was noted that 12-60 months age, preterm SGA infants had the highest odds of stunting (4.51; 3.42, 5.93), wasting (4.19; 2.90-6.05) and underweight (5.35; 4.39-6.53).

In a prospective cohort study from northern India [12] that reported neurodevelopmental outcome at 1 year of corrected age, in preterm ( $\leq 34$  wk/infants <1500 g), it was noted that average motor and mental scores were similar between preterm AGA and SGA infants. In a study [14] that compared the neurodevelopmental outcomes of 45

### WHAT THIS STUDY ADDS?

- This study highlights the vulnerability of preterm SGA infants for poor growth and neurodevelopmental outcomes compared to preterm AGA infants.

preterm (<34 weeks) SGA infants with 46 preterm AGA infants matched for gender and gestation ( $\pm 2$  weeks) at 1 year of corrected age, the incidence of motor (2.7% vs. 8.3%) and mental developmental delay (18.9% vs. 16.7%) was similar between the SGA and AGA preterm infants, respectively. In a review [15] that reports the effect of gestation on long term neurodevelopmental outcomes of SGA/IUGR infants, preterm SGA infants were at higher risk of adverse neuromotor, cognitive, behavioral and scholastic achievement compared with preterm non-SGA infants. Studies of preterm infants revealed that IQ scores were on average approximately 5 to 7 points (0.5 SD) lower for preterm SGA infants compared with preterm AGA infants [19]. The observations of the latter studies are similar to the observations in the present study.

The main limitation of the present study is its cross-sectional design. However, the strength lies in the standardized protocol used to evaluate growth and neurodevelopment outcomes.

Preterm SGA infants are at an increased risk of underweight, stunting and lower motor and mental development scores when compared to AGA infants at a corrected age of 12 to 18 months. This suggests that preterm SGA infants probably need more intense follow-up and early and appropriate interventions to improve their outcomes.

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## Impact of a Novel Hypothermia Alert Device on Death of Low Birthweight Babies at Four Weeks: A Non-randomized Controlled Community-based Trial

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**Objective:** To study the effectiveness of a hypothermia monitoring device in reducing neonatal mortality and increasing Kangaroo Mother Care compliance.

**Design:** Non-randomized controlled trial.

**Setting:** 3 government Sick Newborn Care Units and 7 Primary Health Centers in Udaipur and Dungarpur districts of Rajasthan for 4 months. The follow-up period was 4 weeks for each baby.

**Participants:** Total 386 neonates were included in the study. 250 (64.76%) new-borns in the study group (BEMPU bracelet) and 136 (35.23%) enrolled in the control group. Clinically stable babies discharged below 2500 grams, whose parents could be reached by phone, and who could visit the facility for 4 weekly follow-ups were eligible for participation. Infants with complications or those leaving against medical advice were not eligible.

**Intervention:** The BEMPU Bracelet is a medical device that provides 4 weeks of continuous hypothermia monitoring for new-

borns, and emits an audio-visual alarm when the temperature of the newborn is below 36.5°C.

**Outcome:** Neonatal mortality over the 4-week period.

**Results:** Mortality data was obtained for 92% (229 babies) of the study group and 91% of the control group (124 babies) at the end of the 4-week period. The intervention group had a significantly lower mortality rate as compared to the control group (6% vs. 14%,  $P=0.013$ ). Weight data from 51% of the study group (128 babies) and 32% of the control group (44 babies) did not show a significant difference in weight gain between the groups.

**Conclusion:** The observed effect on mortality and qualitative feedback on KMC compliance suggest the utility of the device in the community settings.

**Keywords:** Body temperature, Kangaroo Mother Care, Neonatal mortality, Community health.

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Approximately 27 million babies are born in India every year and out of those 8 million are LBW [1], these include over 3.3 million preterm births per year [2]. Such babies are at a high risk of experiencing life-threatening illnesses. Neonatal hypothermia and infection, are among the leading causes of newborn deaths and illness in low-resource settings [3,4]. Infants who are premature and/or low birthweight struggle to regulate their own temperature, which may lead to hypothermia. If untreated, hypothermia may lead to reduced weight gain, which predisposes newborns to sepsis, pneumonia, and even death.

By providing skin-to-skin care, or Kangaroo Mother Care (KMC), caregivers can prevent or correct hypothermia in neonates without the assistance of

radiant warmers or incubators [4]. The World Health Organization recommends KMC for all low weight babies. However, despite national KMC policies, uptake of the practice has been low due to social and logistic barrier [5].

*Accompanying Editorial: Pages 292-93.*

The Indian state of Rajasthan has an infant mortality rate of 41 infant deaths per 1000 live births [6], which is comparable to the national average [7]. The National Health Mission (NHM) Rajasthan identified BEMPU bracelet, a hypothermia monitoring device, as an intervention with the potential to address neonatal mortality through hypothermia prevention. This pilot study was done to assess the effectiveness of this device on mortality amongst low birthweight neonates.

## METHODS

This non-randomized study was conducted in three government Sick Newborn Care Units (SNCUs) and seven Primary Health Centers (PHCs) in the Udaipur and Dungarpur districts of Rajasthan, India. The approval to conduct the study was sanctioned by the Mission Director of National Health Mission Rajasthan and the Chief Medical and Health Officer, Udaipur, Rajasthan. A team from the product developers trained the site doctors, nurses, data entry operators, and Auxiliary Nurse Midwives (ANMs) on the use of the bracelet, KMC, and data collection procedures. LEHS|WISH (Lord Education and Health Society|Wadhvani Initiative for Sustainable Healthcare) assisted with pilot initiation and oversight of data collection and analysis.

Staff of the facilities enrolled babies from 29 September, 2016 to 10 January, 2017. Clinically stable babies discharged weighing below 2500 grams, whose parents could be reached by phone, and who could come to the facility for 4-weekly follow-ups were eligible for participation. Infants with complications or those leaving against medical advice were not eligible for this study. After obtaining informed consent from parents, SNCU or PHC nurses enrolled the babies. Total 386 babies were enrolled, of which 250 (64.76%) were in the study (BEMPU bracelet) group, and 136 (35.23%) in the control group (routine care).

Families of babies in both the study and control groups received discharge instructions on hypothermia awareness and prevention, KMC, and swaddling techniques. Parents with babies in the study group also received instructions on how to use the device.

All participants were followed up for 4 weeks. Parents were also given a patient-diary to record hours of KMC. Families were asked to come back for weekly follow-ups for 4 weeks, so staff could collect anthropometric measurements on the newborns. Transportation charges for the follow-up visits were reimbursed to ensure regular follow-up.

Parents of newborns enrolled in the study also received three follow-up phone calls to collect information on the health status of their newborn, KMC compliance, and the device usage, if applicable. During this call, they were also reminded weekly about their follow-up appointment. If parents did not answer phone calls, the local ANM was called to gather follow-up data on mortality and encourage parents to attend their weekly follow-up. At the fourth follow-up appointment, parents submitted their patient diary and final anthropometric measurements were taken. Interviews with parents were

conducted to gather qualitative evidence on KMC compliance and attitudes towards the device.

Quantitative data on mortality and weight gain from patient diaries were entered by data entry operators. All quantitative data was analyzed using the program tool.

The BEMPU bracelet is a device that provides 4 weeks of continuous temperature monitoring to a preterm or LBW newborn. It emits an audio-visual alarm when a baby's temperature drops below 36.5 degrees, indicating that the infant is hypothermic and prompting caregivers to provide thermal care in the form of KMC (**Web Fig. 1**). The BEMPU bracelet indicators are explained in **Web Table I**. It has a sensitivity of 98.6% and specificity of 95% for detecting neonatal hypothermia [8].

The NHM/WISH pilot was completed in two southern districts of Rajasthan state, Udaipur and Dungarpur. The districts have predominately tribal populations, which represent 47.9% of the population in Udaipur and 70.8% in Dungarpur [9]. These are high-priority districts, having a heavy burden of LBW and neonatal mortality; 49.5% of babies born in Udaipur are LBW and the neonatal mortality rate in the district is 40 per 1,000 live births. In Dungarpur, the rate of LBW is 46.9%, with a neonatal mortality rate of 41 [10].

This pilot study was commissioned by the National Health Mission (NHM) of Rajasthan to assess the feasibility of the innovation, to inform potential adoption through state budgets. While this study was not approved by an Institutional Review Board, the research questions and methods were reviewed and approved by a panel of experts including senior NHM officials and Chief Medical Officers in Rajasthan. The study was conducted as per ethical approval carried out following Helsinki declaration.

## RESULTS

Total of 386 newborns were screened for eligibility, enrolled, and assigned to one of the two study groups; 35 of these were lost to follow up after discharge, and 31 died during the 4 weeks of study period (**Fig.1**). The

**Table I Baseline Characteristics of Newborns Discharged From Special Care Neonatal Units in Rajasthan**

|                       | Control group<br>(n=136) |             | Study group<br>(n=250) |             |
|-----------------------|--------------------------|-------------|------------------------|-------------|
|                       | No.                      | Mean (SD)   | No.                    | Mean (SD)   |
| Birthweight (kg)      | 132                      | 1.94 (0.43) | 243                    | 1.87 (0.38) |
| Discharge weight (kg) | 132                      | 1.88 (0.41) | 243                    | 1.89 (0.37) |
| Gestational age (wk)  | 94                       | 35.2 (3.1)  | 74                     | 35 (2.8)    |

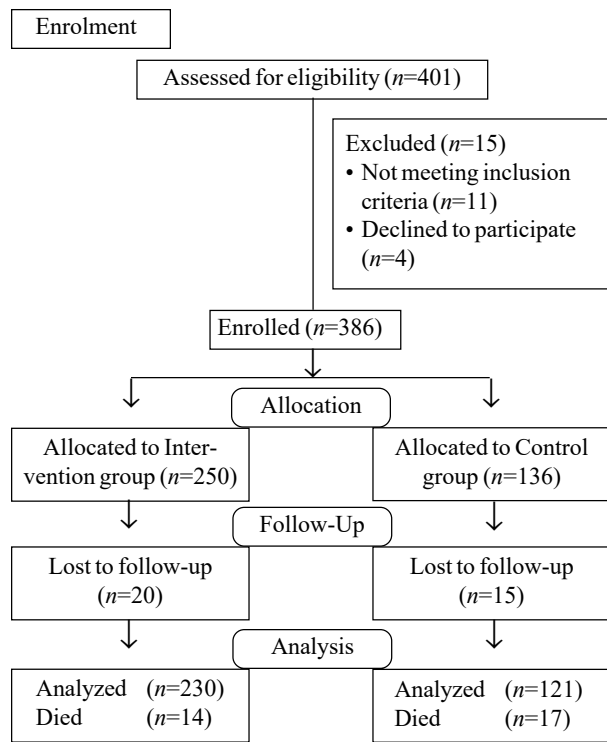


Fig. 1 Study flow chart.

baseline characteristics are shown in **Table I**. The primary conditions of SNCUs newborns enrolled in the studies are represented in **Fig. 1**.

Mortality data was obtained for 92% of the study group (229 babies) and 91% of the control group (124 babies) at the end of the 4-week period. Mortality differences between the groups were statistically significant. The study group had lower mortality rate

(6%) than control group (14%) [OR (95%CI) = 2.43, (1.59, 5.13);  $P=0.09$ ]. The characteristics of the newborns that died are shown in **Fig. 2**.

Due to the low rate of facility-based follow-up, weight data from only 51% of the study group (128 babies) and 32% of the control group (44 babies) was available for analysis. The weight gain in the two groups was similar [2.79 g, 95% CI (2.64, 2.94) vs 2.58 g, 95% CI (2.43, 2.73);  $P= 0.1019$ ].

The KMC tracking charts in patient diaries were inconsistently filled out making them impossible to be reliably analyzed; hence, researchers could not perform further quantitative analysis of this aspect. **Web box I** shows the findings of qualitative feedback through semi-structured interview with 11 parents.

The follow-up rate in BEMPU group (59.58 %) was higher than the control group (31.34 %), which indicates that the device promoted a positive behavior change in the parents on newborn care.

**DISCUSSION**

Providing appropriate thermal care can reduce a newborn’s risk of hypothermia-related morbidity and mortality [11]. In this pilot, the study group experienced a statistically significant lower rate of mortality than did the control group. Qualitative data collected from interviews with parents also suggested positive experiences. The follow-up rate of the study group was almost twice as that of the control group, suggesting a favorable behavioral change.

The anthropometric data could not be completely recorded due to various reasons such as high burden on healthcare staff and many families living far from the

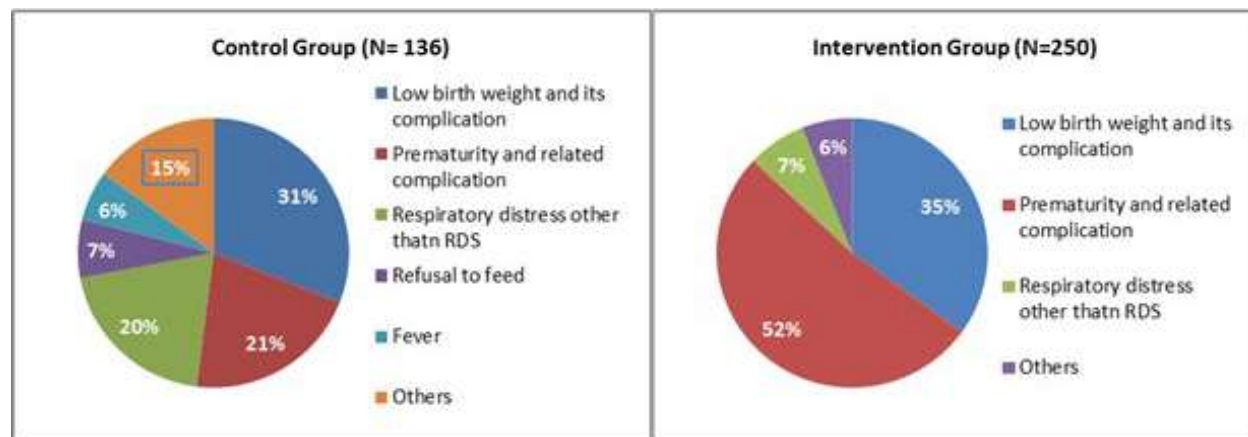


Fig. 1 Primary conditions of newborns enrolled in the study.

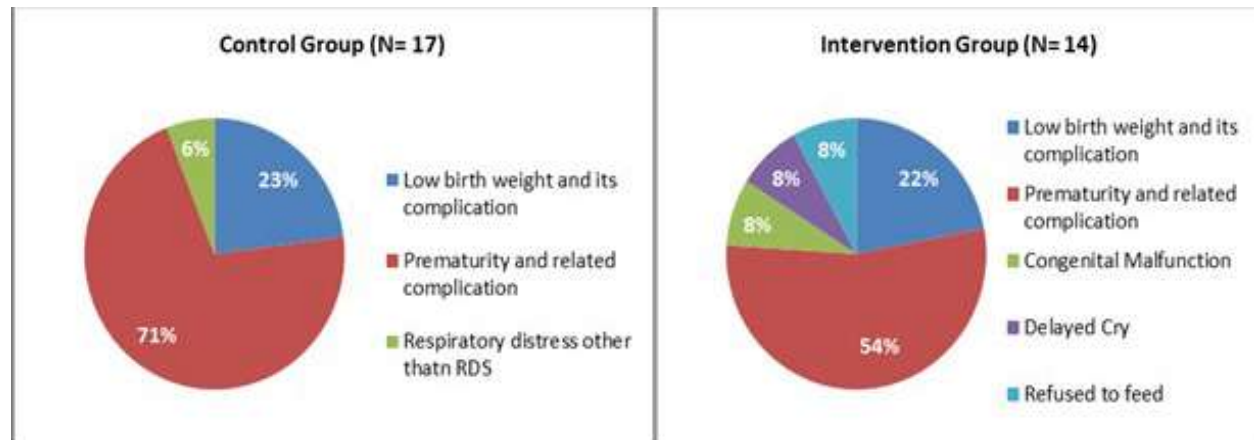


Fig. 2 Characteristics of the low birthweight newborns who died during the study.

health facilities; and it was a contributing factor to the loss to follow-up. A larger study is planned to address these limitations. Probably, due to low literacy levels, mothers/family members filled out the KMC tracking chart unsatisfactorily. Other methodologies should be employed in the future to quantitatively evaluate hours of KMC performed with and without the BEMPU Bracelet.

The data for weight gain was difficult to gather and not standardized between centers and nurses. Some newborns were weighed with their clothes on, some nurses rounded information to the nearest half kg, and some centers did not have proper scales.

A device called ThermoSpot, a non-invasive infant hypothermia indicator, that adheres to the skin of and indicates infant hypothermia or a fever by a change of color was studied in the community to understand the impact of behavior change on newborn care [12]. The results of the study revealed that there was an improvement in birth preparedness, hygienic delivery, thermal care (including skin-to-skin care), umbilical cord care, skin care, and breastfeeding [12]. There was little change in care-seeking. Many of the other hypothermia detection devices have not been studied in the community. BEMPU bracelet's simple, easy to understand audio-visual alarm feature distinguish it from other similar interventions. The audio-visual indications can be understood by any mother and family members across all socio-economic groups.

In areas where the risk of neonatal hypothermia is high due to the prevalence of preterm birth and low birth weight, use of the BEMPU Bracelet among these vulnerable babies could result in reduced mortality through provision of thermal care. The observed reduction in mortality and positive parental feedback on

KMC promotion in this study supports the BEMPU bracelet's potential to impact neonatal health outcomes. This warrants further research to assess the bracelet's impact on newborn care practices.

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*Contributors:* MS: conception and design of the study, VM: data analysis, drafting manuscript, MS: conception and design of study; DS: acquisition of data; RDB: implementation of the study, AS: data analysis. All authors approved the final version of manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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*Competing interests:* All data collection was overseen by the National Health Mission Rajasthan and the WISH Foundation. Data analysis and the authorship of this publication were shared between BEMPU Health and the WISH Foundation. BEMPU Health team conducted the training required for the bracelet use. Staff of the NICUs of the hospitals in the studies carried out the study.

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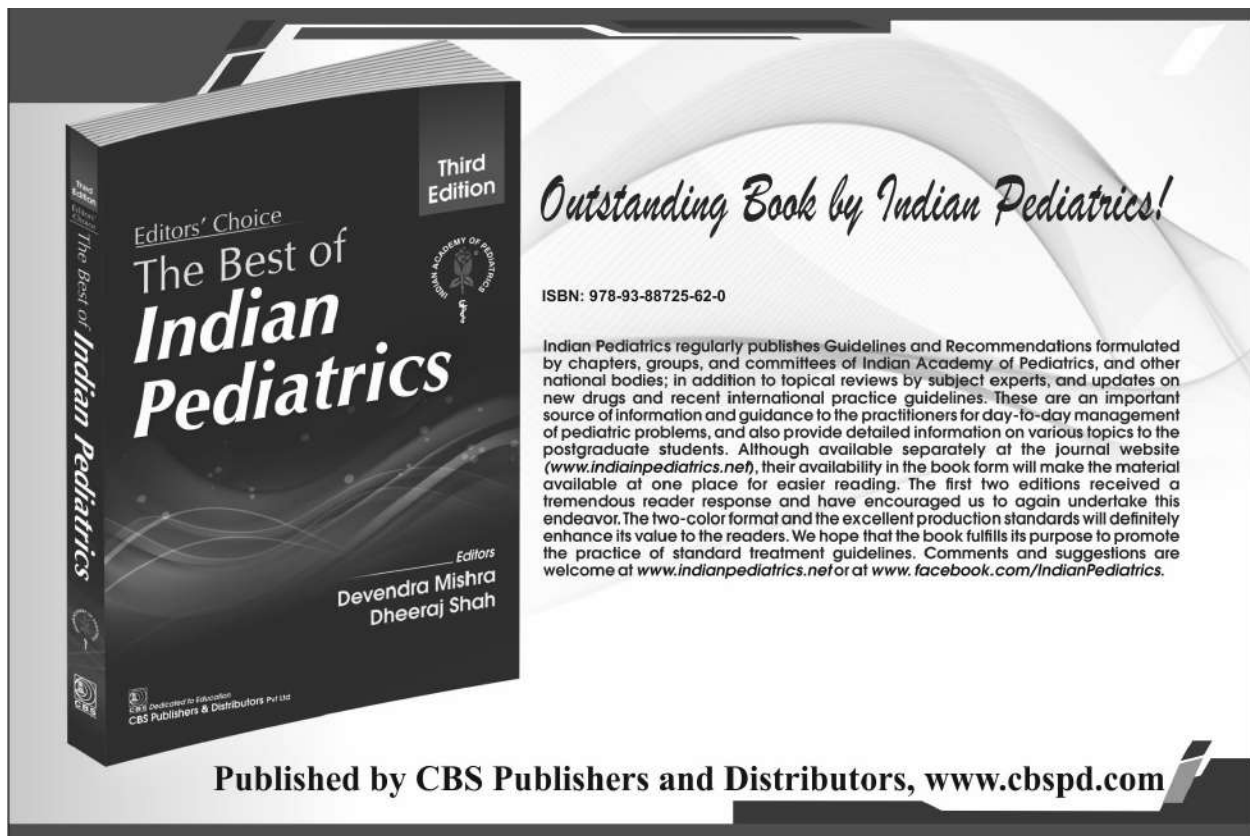
### WHAT THIS STUDY ADDS?

- Using a home-based hypothermia monitoring device among low birthweight neonates positively affects mortality by age of four weeks.

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### Web Box I Qualitative Feedback Through Semi-structured Interviews

- One mother with a low birth weight baby mentioned that “BEMPU showed a red light many times a day, especially in the early morning hours. I used to provide KMC so that BEMPU will not show a red light.” Another mother with a low birth weight baby said, “BEMPU beeped in the night and early morning hours. Whenever it beeped I provided KMC.” The BEMPU Bracelet’s beeping concerned one mother, who told the research team that “[BEMPU’s] beeping alerted me to the baby’s temperature and enabled me to perform KMC for my child. The alarm worried me and I would give KMC to stop the beeping.”
- Qualitative responses also revealed that the bracelet encouraged other family members to provide KMC. In one family, the mother, father, and grandmother reported that they performed KMC for an hour each time the bracelet beeped.



Web Fig. 1 BEMPU bracelet; a hypothermia monitoring device.

Web Table I BEMPU Bracelet Indicators

| State        | Alert   |
|--------------|---|
| Normothermia | <ul style="list-style-type: none"> <li>• Blue light blinks once every 30 seconds</li> <li>• No sound alarm</li> </ul>   |
| Hypothermia  | <p>Red light blinks once every 5-6 seconds</p> <p>Alarm sounds for 1 minute and repeats every 5-15 minutes</p> <ul style="list-style-type: none"> <li>• If temperature of the body drops below 0.5 degree with in duration of 5 minutes, then alarm repeats within 5 minutes.</li> <li>• If temperature is not dropping at faster rate, then the alarm repeats after 15 minutes.</li> </ul> |



## Factors Associated With Cerebral Edema at Admission in Indian Children with Diabetic Ketoacidosis

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**Objective:** To evaluate the time course and predictors of cerebral edema in diabetic ketoacidosis (DKA). **Methods:** Review of hospital records of 107 episodes of DKA between January 2013 to March 2019. **Results:** Cerebral edema was identified in 26 (24.3%; 22 at presentation and 4 during treatment). Cerebral edema at presentation was associated with lower (<10 mmHg) arterial carbon dioxide (OR 3.6, 95% CI 1.0,12.7;  $P=0.04$ ), prior fluid treatment (OR 4.7, 95% CI 1.8,12.7;  $P=0.001$ ) and new onset diabetes (OR 3.5, 95% CI 1.1,11.1;  $P=0.03$ ). Prior fluid was the only significant predictor on multivariate analysis ( $P=0.013$ ). Cerebral edema resulted in a longer ICU stay [4.1 (2.3) vs 1.8 (0.9) d;  $P<0.001$ ]. **Conclusion:** Cerebral edema at admission is common in Indian children with DKA and should be suspected with severe metabolic acidosis and inappropriate prior fluid treatment.

**Keywords:** Acidosis, Fluid therapy, Management, Outcome.

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Diabetic ketoacidosis (DKA) is the leading cause of mortality and morbidity in type 1 diabetes with cerebral edema being the major contributor [1,2]. Clinically significant cerebral edema is observed in around 2% children with DKA in Western settings with a higher prevalence in developing countries [3-6]. Timely identification and management of cerebral edema is mandatory for improving outcome of DKA. There is a paucity of Indian data regarding the same; therefore, we conducted this study to identify time course and predictors of cerebral edema in Indian children and adolescents with DKA.

### METHODS

Case records of children and adolescents with DKA admitted to pediatric intensive care from January 2013 to March 2019 were reviewed after approval by the Institutional ethics committee. Information regarding clinical profile (age at admission, gender, weight and pattern of type 1 diabetes, new onset or known diabetes), precipitating factors (infection, missed insulin dose or undiagnosed type 1 diabetes), course (duration of hospital stay and insulin infusion) and time of onset of cerebral edema was collected on a predesigned proforma. Records with incomplete details were excluded.

DKA was diagnosed, classified and managed as per

International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria [7] in accordance with the hospital policy. Prior fluid volume infused was deducted from fluid calculation if precise information was available. In the absence of written documentation of fluid therapy received elsewhere, the case was managed as a new case with fluid calculation based on the present clinical condition. Monitoring of vital parameters, hourly blood glucose, 4-hourly blood ketones, blood gas and electrolyte assessment were done. Cerebral edema was diagnosed in the presence of one diagnostic, two major or one major and two minor criterion [8]. Management of cerebral edema included mannitol (20% 5 mL/kg single intravenous dose followed by 2.5 mL/kg six hourly), head-end elevation, and fluid restriction. Intubation was done only if deemed necessary by both pediatric endocrinologist and pediatric intensivist.

*Accompanying Editorial : Pages 294-95.*

**Statistical analyses:** Data were entered and analyzed using IBM statistical package for social sciences (SPSS version 25.0, SPSS, Inc., Chicago, IL, USA) for Macintosh. Independent sample t-test and Chi-square test were used to compare continuous and categorical variables. Parameters significant on univariate analysis were included in multivariate analysis. Logistic

regression was performed to identify factors predicting cerebral edema at admission. *P* value less than 0.05 was considered significant.

**RESULTS**

Out of 126 episodes of DKA admitted during the study period complete details were available for 107 [mean (SD) age, 9.0 (4.3) y; 61 boys; 66 new onset type 1 diabetes]. Fifty seven (53.3%) had severe and 22 (20.5%) moderate DKA. Cerebral edema was observed in 26 subjects (24.3%, 22 at admission and 4 during treatment). Cerebral edema at admission was diagnosed based on one diagnostic criteria (abnormal central breathing pattern) in 15 (68%), 2 major criteria in 3 (13.6%) and 1 major and 2 minor criteria in 4 (18%). Four children who developed cerebral edema during follow-up had one diagnostic criterion. Cerebral edema developed at 60 hours in a patient with refractory metabolic acidosis requiring hemodialysis and between 16-48 hours of treatment in other three patients. Cerebral edema at admission was noted in those with severe DKA than mild or moderate DKA and was associated with lower pH [6.95 (0.10) vs 7.10 (0.18); *P*<0.001], lower bicarbonate levels [5.2 (2.2) vs 8.3 (4.4) mmol/L; *P*=0.003] and higher base deficit [-25.2 (3.2) and -20.5 (6.0) mmol/L; *P*=0.001], respectively (**Table I**). There was no difference in levels of blood sugar, ketone or partial pressure of carbon dioxide in arterial blood (PaCO<sub>2</sub>). Greater proportion of subjects with cerebral edema at admission had PaCO<sub>2</sub> levels below 10 mm Hg than those without it [OR (95% CI),

3.6 (1.0,12.7), *P*=0.04]. Prior fluid treatment [OR (95% CI), 4.7 (1.8,12.7) *P*=0.001] and new onset type 1 diabetes [OR (95% CI), 3.5 (1.1,11.1), *P*=0.03] increased the likelihood of cerebral edema at admission. Prior fluid treatment was the only predictor that remained significant on multivariate regression analysis [OR (95% CI), 4.5 (0.07, 0.73); *P*=0.013].

Four (4.7%) subjects developed cerebral edema after admission (median (range) 36 (17-60) h). Two of these developed cerebral edema at 48 and 60 hours after admission and were excluded from further analyses. The other two subjects had lower mean (SD) pH (6.9 (0.2) and 7.1 (0.2); *P*= 0.07) and PaCO<sub>2</sub> (17.3 (9.5) and 21.2 (8.1) mm Hg; *P*=0.5) than those who did not develop cerebral edema; though statistically not significant. Seventy five percent of those with incident cerebral edema (3 out of 4) received prior fluid treatment as against 24.7% (20 out of 81) of those without cerebral edema (OR (95% CI), 9.15 (0.9, 92.9) *P*= 0.027).

Treatment was associated with gradual resolution of hyperglycemia, ketosis, and acidosis after mean (SD) 7.0 (7.0), 13.5 (7.6) and 19.2 (9.4) hours, respectively. Favorable outcome was observed in 24 subjects with cerebral edema (92.3%) with mortality in two. A 14 year old girl with severe metabolic acidosis presented 2 days after receiving fluid and sodium bicarbonate at a different hospital and developed cerebral edema 16 hours after admission. During hospital stay, she developed acute kidney injury, acute respiratory distress syndrome, needed ventilation and died 5 days after admission. Second child was of a 5-year-old boy admitted with severe DKA who received prior fluid treatment and had cerebral edema at admission.

Additional interventions included ventilation in 14 and hemodialysis in two with cerebral edema. Ventilation and hemodialysis was not required in those without cerebral edema. Cerebral edema prolonged the duration of insulin infusion (35.8 (29.0) vs 16.1 (9.3) h; *P*<0.001) and ICU stay (4.1 (2.3) vs 1.8 (0.9) d; *P*<0.001).

**DISCUSSION**

Findings of the present study suggest high rate of cerebral edema at admission in Indian children and adolescents with severe DKA (38.6%). Importantly 86.4% of cerebral edema was noted at admission in contradiction to the previous reports of 22.2% [9]. This may be related to greater severity of DKA, delayed diagnosis and inappropriate fluid treatment before transfer. Prior fluid treatment was the only factor predicting cerebral edema at

**Table I Comparison of Children With and Without Cerebral Edema at Admission (N=107)**

| Parameters                 | Cerebral edema at admission |             | P-value |
|----------------------------|-----------------------------|-------------|---------|
|                            | Yes (n=22)                  | No (n=85)   |         |
| Age (y)                    | 8.2 (4.4)                   | 9.2 (4.3)   | 0.31    |
| Blood sugar (mmol/L)       | 29.9 (6.3)                  | 26.3 (6.5)  | 0.08    |
| pH                         | 6.95 (0.10)                 | 7.10 (0.18) | <0.001  |
| Serum bicarbonate (mmol/L) | 5.2 (2.2)                   | 8.3 (4.4)   | 0.003   |
| Base deficit (mmol/L)      | -25.2 (3.2)                 | -20.5 (6.0) | 0.001   |
| Ketone (mmol/L)            | 5.4(0.8)                    | 5.7 (1.0)   | 0.245   |
| PaCO <sub>2</sub> (mm Hg)  | 18.7 (7.9)                  | 20.9 (8.1)  | 0.287   |
| Sodium (mmol/L)            | 135.9 (6.1)                 | 133.4 (5.9) | 0.181   |
| Potassium (mmol/L)         | 4.8 (0.7)                   | 4.2 (0.9)   | 0.07    |
| #New onset Type 1 diabetes | 18 (81.8)                   | 48 (56.5)   | 0.03    |
| #Prior fluid treatment     | 14 (63.6)                   | 23 (27)     | 0.001   |

Data represented as mean (SD) or #no. (%).

### WHAT THIS STUDY ADDS?

- Cerebral edema is common at admission in Indian children and is frequently associated with inappropriate prior fluid treatment.

admission in accordance with previous studies [10]. High index of suspicion for cerebral edema in those with severe DKA and prior fluid treatment is therefore essential. Lower PaCO<sub>2</sub> levels predicted cerebral edema at admission, as seen in previous studies [11,12].

The rate of incident cerebral edema (4.7%) in our study is similar to Western reports in subjects with DKA of similar severity, suggesting similar risk profile. Recent studies have indicated a baseline rate of cerebral edema irrespective of rate of fluid administration or solute concentration [13,14]. Inclusion of greater proportion of subjects with milder DKA may limit their generalizability in Indian setting [14]. This has been attributed to intrinsic characteristic of DKA and not the effect of treatment [15]. All subjects with incident cerebral edema in our study had severe DKA (undetectable serum bicarbonate and pH below 7.0) highlighting the need for high index of suspicion in this setting. The present study suggests favorable outcome of DKA related cerebral edema with uneventful recovery in over 90% despite the need for ventilation in half. Moreover, the mortality in this study was unrelated to cerebral edema (renal failure in one and ARDS in other). This reflects the effects of close clinical observation, timely identification and treatment.

Cerebral edema imposes significant morbidity and mortality in DKA as reflected by doubling in duration of insulin infusion and intensive care stay. This is similar to previous observation of cerebral edema associated increased hospital stay and highlights the need for prevention of cerebral edema by early diagnosis and timely referral of DKA [16].

Retrospective design is a limitation of our study; however, protocolized management by the same clinical leads over the study period and close documentation ensured uniformity of treatment and availability of data. Lack of precise information regarding the amount and type of fluid administered before admission is a limitation but reflects real life circumstances where these details are usually not available. The diagnosis of cerebral edema was established on clinical grounds and not confirmed radiologically. However, this represents the standard of clinical care as diagnosis of cerebral edema is largely clinical and delay in treatment for radiological confirmation can be lethal. Robust clinical criteria

assessed by two pediatricians and response to mannitol substantiate our diagnosis.

This study has significant implications for DKA management in resource-poor settings receiving sick patients with unclear prior treatment. It emphasizes the need of specifying the amount and type of fluid therapy by referring physicians and suggests the key role of primary (prevention of DKA by early diagnosis), secondary (timely detection and treatment of DKA) and tertiary prevention (high index of suspicion for cerebral edema and urgent management) in limiting DKA related morbidity and mortality.

*Contribution:* NA,CD,RP: involved in patient management and data collection; NA: literature review, statistical analysis and drafted the initial manuscript; RK,RS,AB: involved in patient care; AB: conceptualized and planned the study, conducted statistical analysis, critically reviewed the manuscript and would act as guarantor of the paper.


*Funding:* GROW Society; *Competing interest:* None stated.

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## Clinicoepidemiological and Genotyping Correlation of Pediatric Scrub Typhus from Chandigarh, India

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**Objectives:** We studied the clinical phenotypes and prevalent genotypes of *Orientia tsutsugamushi* in our area using indirect immunofluorescence assay (IFA). **Methods:** We prospectively screened all febrile children presenting to our hospital over three years. From among children who were scrub typhus positive by ELISA we selected a sample of convenience for IFA testing to determine the genotypes of *O. tsutsugamushi* using four strains namely Boryong, Gilliam, Karp and Kato. **Results:** Of all scrub positive patients ( $n=77$ ), we tested 14 samples using IFA and all 14 samples were IFA positive. Karp genotype ( $n=7$ ) was most prevalent followed by Kato (3), Boryong (1) and Gilliam (1) genotypes; 2 patients were positive for mixed genotype. There was high prevalence of organ dysfunction among IFA positive children. Three most common organ dysfunctions included hematological derangement in all, liver involvement in 10 (71%), and encephalopathy and shock in 4 each. **Conclusions:** Karp was the most prevalent genotype of *O. tsutsugamushi* in our area.

**Keywords:** Antigenic variation, *O. tsutsugamushi*, Rickettsial infection, Outcome.

Scrub typhus is an endemic infection in Tsutsugamushi triangle, putting one billion people at risk annually [1]. The clinical presentation in scrub typhus is variable ranging from acute undifferentiated febrile illness to shock and multiorgan dysfunction [2]. Scrub typhus caused by *Orientia tsutsugamushi* has more than 20 antigenic strains, classified into high virulence group (Karp, Kato and KN-3 genotypes), an intermediate virulence group (Gilliam genotype) and a low virulence group (Kuroki, Kawasaki and KN-2) [3-5]. The severity of infection and nature of complications in scrub typhus vary with the genotype [6,7]. It has been reported that strains closely aligned with Karp prototype are associated with manifestations like hepatitis, meningitis and multiorgan dysfunction in adults [5,8]. There is paucity of data in children, hence we studied the prevalent genotype of *O. tsutsugamushi* in our geographical area using an indirect immunofluorescence assay (IFA).

### METHODS

This cross-sectional study was carried out in the Pediatric emergency of a tertiary-care referral teaching hospital in Chandigarh, India from June, 2013 to December, 2017. Ethical approval was obtained from the Institute Ethics Committee. We screened all children aged 2 months to 14 years, who got admitted to our emergency with the diagnosis of scrub typhus (positive IgM ELISA cut-off

optical density value  $\geq 0.5$ ) (InBios International Inc., USA) [9]. We excluded children with lethal malformations or known immunodeficiency. Out of the scrub positive cases, a convenient sample of children was tested for IFA. We obtained informed consent from one of the parents before enrolment in the study. The demographic profile, clinical presentation, laboratory manifestations and treatment history of all study children were noted.

IFA test for *O. tsutsugamushi* was performed to determine the prevalent genotypes in our area. IFA test kit (Fuller Laboratories, California, USA) semi-quantitatively determined IgM antibodies against four strains of *O. tsutsugamushi* namely, Boryong, Gilliam, Karp and Kato. The test samples were standardized for various dilutions ranging from 1:32 to 1:256. An IFA result in the acute phase was considered positive, if IgM antibody titres were  $\geq 1:64$  [10]. Additionally, all children were screened for malaria, typhoid, dengue, leptospira, and underwent other relevant tests, wherever indicated.

As we performed IFA on a convenient sample, we compared salient demographic and clinical characteristics of IFA-positive children with rest of scrub typhus positive children who were not sampled for IFA. Continuous variables were compared using independent *t* test or Mann-Whitney U tests as applicable. Proportions were compared using chi-square test. The analysis was performed using SPSS 20.0 (IBM, New York).

## RESULTS

Out of 77 scrub typhus ELISA positive children during the study period, we performed IFA test in 14 children. All samples were IFA positive. The salient demographic and clinical characteristics of the IFA positive children were comparable to remaining Scrub typhus children who were not sampled for IFA (**Table I**).

Salient demographic and clinical characteristics of the 14 IFA positive children is presented in **Web Table I**. We observed high incidence of organ dysfunction in the study children. Hematological derangements were universal [thrombocytopenia ( $n=11$ , 79%); anemia ( $n=10$ , 71%); and altered leucocyte count ( $n=5$ , 36%)]. Other common organ dysfunctions in our cohort include elevated serum transaminases ( $n=10$ , 71%), encephalopathy or seizures ( $n=4$ , 29%), shock ( $n=4$ , 29%), serositis ( $n=3$ , 21%), and pulmonary dysfunction ( $n=2$ , 14%). Physical examination did not reveal eschar in any child. Salient laboratory findings of the cohort included mean (SD) haemoglobin of 9.9 (1.7) g/dL, total leucocyte count of  $10.3 (5.9) \times 10^3$  cells/mm<sup>3</sup> and INR- 1.1 (0.1), the median (IQR) platelet count was  $78.5 \times 10^3$  /mm<sup>3</sup> (45.0, 142.5); Aspartate aminotransferase - 174 IU/dL (116, 236), Alanine aminotransferase - 86 IU/dL (44,151), and total serum bilirubin of 1.0 mg/dL (0.2, 2.8).

We observed maximum prevalence of Karp genotype (7) (**Web Fig. 1**), followed by Kato (3), Boryong (1) and Gilliam (1). Two patients were positive for mixed genotype *i.e.* one had both Karp and Kato and another was positive for Karp and Boryong. IgM IFA titres in most of the cases were 1:128 or more (**Web Table I**). Five of the 7 children (71%) with Karp genotype had multisystem involvement. All 14 children received doxycycline in recommended doses for 7 days [9,11]

and showed defervescence within 3 days of doxycycline. All patients survived, and no adverse reaction was noted following doxycycline.

## DISCUSSION

In our study group of 14 cases, Karp was the commonest genotype with a high prevalence of multiorgan dysfunction. Eschar was notably absent in all children.

Previous studies published from India and Himalayan regions of India reported Karp as the most prevalent genotype [1,8,12]. Findings of other endemic regions of tsutsugamushi triangle *i.e.* Thailand and Vietnam were similar [6,7]. In contrast, Kato strains are more frequently reported from Southern India [8]. This antigenic diversity is due to varied intragenomic rearrangements and recombinations, exact process of which is not clear. The virulence of Karp, Kato and Gilliam genotypes have been reported previously in mice and adults [4-6]. Acute encephalitis syndrome (AES) presentation was seen in 4 children, which has also been reported in young children with scrub typhus from Gorakhpur and north-eastern India [1,13]. An absence of eschar in predominantly Karp prototype has also been corroborated in other adult studies, especially from the Himalayan region [1,7,12,13]. Hematological and liver dysfunction was also conspicuous in children with scrub typhus from North-eastern and Southern India [13,14]. In the absence of eschar, diagnostics like serology attain importance for therapeutic and epidemiological purposes [9,12]. The sensitivity of scrub typhus IgM ELISA is 99.9% and specificity 99.1%, respectively and IgM IFA sensitivity 96.8% and specificity 99.7%, respectively across different regions in India [9,10]. Response to therapy occurred within 72 hours in all children following doxycycline, thereby reaffirming efficacy [9].

The study has few limitations. It is a single centre study with limited samples of scrub typhus children being tested by IFA. Two children in our cohort had mixed infections with dengue virus, which possibly suggests co-infection. The diagnosis of scrub typhus was supported by both IgM ELISA and IFA positivity. In endemic areas, co-infections are not uncommon [13]. However, a possibility of false-positive results of serologic tests cannot be completely ruled out. We did not perform molecular diagnosis by PCR. PCR has added advantage of phylogenetic tracing; however, results are best within the first week for blood samples because of presence of rickettsemia [1,8,9,11]. However, in the absence of availability of PCR and after the first week of illness, IFA remains an attractive option. Also PCR yield is higher on eschar samples [15]. As not all strains are likely to produce eschar, this could skew results [1,8].

**Table I Characteristics of Children with Scrub Typhus (N=77)**

| Characteristics                 | Sampled for IFA<br>(n=14) | Not-sampled<br>(n=63) |
|---------------------------------|---------------------------|-----------------------|
| Age, mo*                        | 92.7 (39.9)               | 85.8 (42.2)           |
| Weight, kg*                     | 23.3 (10.3)               | 21.0 (8.9)            |
| Male                            | 8 (57)                    | 35 (57)               |
| Fever duration (d) <sup>#</sup> | 7 (7, 10)                 | 6 (5, 8)              |
| Encephalopathy                  | 5 (36)                    | 13 (21)               |
| Hepatosplenomegaly              | 8 (57)                    | 26 (77)               |
| Shock                           | 4 (10)                    | 12 (19)               |
| Death/LAMA                      | 1 (13)                    | 4 (6.3)               |

Values in no.(%) except, \*Mean (SD), <sup>#</sup>Median (IQR); All  $P > 0.05$ , LAMA: Left against medical advice, IFA: Immunofluorescence assay.

### WHAT THIS STUDY ADDS?

- Karp was the most prevalent genotype isolated by Immunofluorescence assay among scrub typhus cases, which correlated with severe systemic manifestations in children.

IFA is the reference serological gold standard for diagnosis but cost and expertise limit its use. In clinical care, ELISA usually suffices [9,11].

Out data; although from a small number of children, provides important information for diagnostic and epidemiological purposes.

*Contributors:* NS: performed the serological tests, edited the manuscript and approved the final manuscript; VM: conceived the idea, enrolled the patients, managed the cases, analysed the data, wrote the 1st draft; JC: supervised laboratory analysis, critically evaluated the manuscript; VG: supervised the clinical management of the children, critically evaluated the manuscript. All authors approved the final manuscript.

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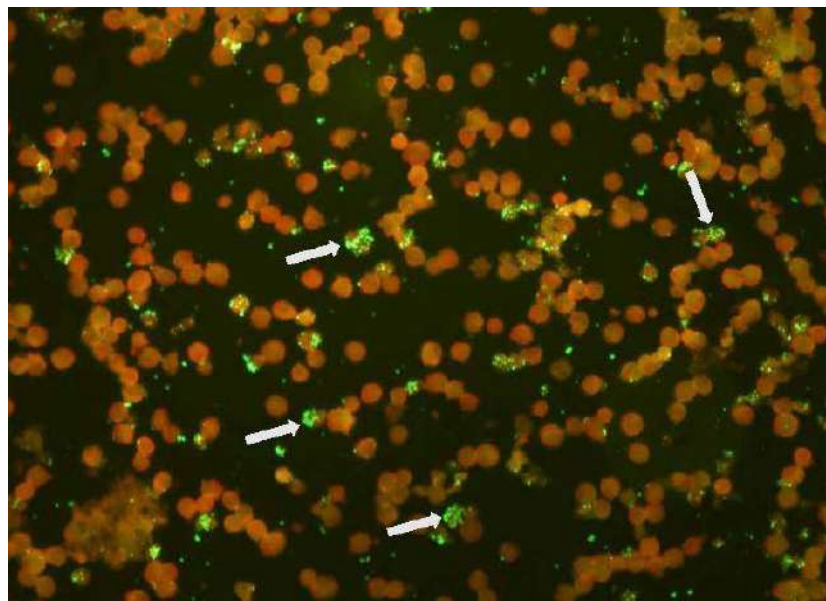
*Competing interest:* None stated.

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**Web Table I** PHENOTYPE-GENOTYPE CORRELATION IN CHILDREN POSITIVE FOR IMMUNOFLUORESCENCE ASSAY FOR SCRUB TYPHUS IN CHANDIGARH, INDIA

| SNo | Genotype       | IFA titre | Phenotype | Clinical presentation   | Lab investigations                     |
|-----|----------------|-----------|-----------|---|--|
| 1   | Karp           | 1:256     | F/10 y    | Acute undifferentiated febrile illness; hepatitis; Fever × 15 d; abdominal pain & vomiting; serositis, hepatomegaly           | Leucocytosis                           |
| 2   | Karp           | 1:256     | F/10 y    | Acute undifferentiated febrile illness; Fever × 6 d   | Thrombocytopenia; leucopenia           |
| 3   | Karp           | 1:256     | M/8 y     | Acute encephalitis; shock; hepatitis; Fever × 7 d; seizures, altered sensorium; hepatomegaly                                  | Anemia, thrombocytopenia               |
| 4   | Karp           | 1:256     | M/6 y     | Acute encephalitis; shock; hepatitis; pneumonia; Fever × 9 d; seizures, altered sensorium, respiratory distress, crepitations | Anemia, thrombocytopenia, leucocytosis |
| 5   | Karp           | 1:128     | M/2 y     | Acute undifferentiated febrile illness; Fever × 5d  | Anemia, thrombocytopenia               |
| 6   | Karp           | 1:128     | M/4 y     | Acute encephalitis; hepatitis; Fever x 4 d; seizures, altered sensorium, hepatosplenomegaly                                   | Anemia, thrombocytopenia               |
| 7   | Karp           | 1:256     | M/6 y     | Acute undifferentiated febrile illness; hepatitis; shock; Fever × 5d  | Anemia, thrombocytopenia               |
| 8   | Kato           | 1:256     | F/11 y    | Acute undifferentiated febrile illness; shock; hepatitis; Fever × 7d  | Anemia, thrombocytopenia; leucocytosis |
| 9   | Kato           | 1:256     | F/11 y    | Acute undifferentiated febrile illness; Fever x 14d   | Anemia                                 |
| 10  | Kato           | 1:128     | F/7 y     | Acute undifferentiated febrile illness; hepatitis; Fever × 10d; ascites, serositis  | Anemia                                 |
| 11  | Gilliam        | 1:128     | M/7 y     | Acute undifferentiated febrile illness; hepatitis; Fever × 10 d; hepatomegaly   | Thrombocytopenia                       |
| 12  | Boryong        | 1:256     | M/12 y    | Acute encephalitis; shock; hepatitis; Fever x 4 d; seizures, altered sensorium, hepatosplenomegaly                            | Anemia, thrombocytopenia               |
| 13  | Karp + Kato    | 1:128     | M/3 y     | Acute undifferentiated febrile illness; hepatitis; Fever × 10 d; hepatosplenomegaly; ascites, serositis                       | Anemia, thrombocytopenia               |
| 14  | Karp + Boryong | 1:128     | F/13 y    | Acute undifferentiated febrile illness; Fever × 7d  | Thrombocytopenia, leucopenia           |

**Web Fig. 1** Immunofluorescence assay of scrub typhus IgM ELISA positive child showing Karp genotype seen as immunofluorescent bodies (white arrows); orange rods are the controls.



## Status of Oxygen Monitoring in Four Selected Special Care Newborn Units in India

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**Objective:** To investigate the status of oxygen monitoring in Special Newborn Care Units. **Methods:** Observations were made and records reviewed of infants on oxygen in all four Special Newborn Care Units of a state delivering a model program for retinopathy of prematurity. Multiple choice questions were administered to nurses, semi-structured interviews conducted with pediatricians, ophthalmologists and senior nurses. **Results:** All units had more than 100% occupancy. The number of functioning pulse oximeters was 73% of that recommended. None of the units had air-oxygen blenders. The upper oxygen saturation alarm was set accurately only for 1 out of 18 babies receiving oxygen and none of the infants had continuous saturation monitoring. 84% of nurses did not know optimal oxygen saturation targets. Most interviewees attributed suboptimal care to overcrowding. **Conclusion:** Compressed air, air-oxygen blenders, sufficient functioning pulse oximeters, rational admission policies and training of nurses are needed to improve oxygen related practices.

**Key words:** Public health system, Knowledge, Retinopathy of prematurity.

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Many middle-income countries are facing an epidemic of blindness due to retinopathy of prematurity (ROP) as a result of a combination of uncontrolled oxygen delivery and greater survival of preterm babies [1]. In India, even though neonatal mortality rates have declined [2], awareness and interventions for preventing vision impairment from ROP have not increased proportionately [3]. Poorly regulated supplemental oxygen is an important risk factor for ROP [4]. Estimates suggest that 32,300 infants, approximately 10% of whom are in India, become blind or visually impaired from ROP every year [5]. A program to reduce blindness from ROP was launched by the Ministry of Health in 2013, supported by the Queen Elizabeth Diamond Jubilee Trust, and managed by the Indian Institute of Public Health (IIPH), Hyderabad [6]. Conducted in one of the four states delivering the program, which includes nurse training, this study investigated whether oxygen was being monitored satisfactorily in four district level Special Newborn Care Units (SNCU).

### METHODS

A state reflecting the demographic profile of India, with an infant mortality rate within the range likely to make the state at risk of ROP blindness [7] was selected. In

this state, the program was implemented in four SNCUs – one in a medical college and three in district-level hospitals. During eight weeks in mid-2017, each SNCU was visited once for three days. Each SNCU was allocated a code (A-D) to maintain anonymity. In units A and B, only the nurses in-charge and ROP nurses (not directly involved in patient care) had been included in the training; whereas in units C and D, all nurses were included.

To assess nurses' understanding of ROP, multiple-choice questions (MCQs) were administered to nurses on duty (excluding nurses in-charge) on the first day of the visit. Questions included risk factors for ROP, saturation limits for alarm settings on monitors, criteria and timing of ROP screening according to RBSK guidelines [8] and drops used to dilate pupils before screening (MCQs available at [https://figshare.com/articles/ROP\\_annexure/9757223/1](https://figshare.com/articles/ROP_annexure/9757223/1)). Most questions had been used by the National ROP Task Force in an earlier gap analysis [6]; new questions were validated by a neonatologist involved in ROP care.

On the second and third days, semi-structured interviews to assess ROP – related attitudes and practices were conducted with the ophthalmologist involved in ROP screening, pediatrician in-charge, nurse in-charge and ROP nurse. Questions covered their induction into

and perceptions of the program, challenges in the management of ROP and suggestions for improvement. Topic guides for interviews were developed (available at [https://figshare.com/articles/ROP\\_annexure/9757223/1](https://figshare.com/articles/ROP_annexure/9757223/1)), and piloted before administration. Each participant provided informed consent, and was assigned a unique code to maintain confidentiality. On day three, equipment to deliver and monitor oxygen were assessed and compared with national guidelines [9]. Finally, medical records of infants receiving oxygen at the time of the visit were reviewed for documentation of oxygen saturation and frequency of monitoring.

Ethical approval for the study was obtained from the London School of Hygiene and Tropical Medicine and Indian Institute of Public Health; permission was obtained from the State National Health Mission. The study adhered to the recommendations of Declaration of Helsinki.

*Statistical analyses:* Qualitative data were manually coded and analyzed thematically. Similarities and differences in responses from different cadres and centers were analyzed. Triangulation was provided by observation of practices. Quantitative data were analyzed for proportions, confidence intervals and Z test for differences in proportions using STATA 2014. A *P*-value less than 0.05 was considered statistically significant.

## RESULTS

All Newborn care corners located in labor rooms or

operating theatres had provision to start oxygen but none had air-oxygen blenders and none used pulse oximeters to monitor oxygen. Only SNCU A was able to provide continuous positive airway pressure (CPAP).

All SNCU nurses had a bachelor qualification but their number, according to SNCU guidelines [10], was adequate in only one SNCU (**Table I**). All SNCUs had more than 100% occupancy, which staff considered to be the main challenge in providing high-quality care (**Web Table I**). Only two SNCUs had enough pulse oximeters to comply with the national guidelines [9], and the number of functioning oximeters was 73% of that recommended. Of the 14 infants where pulse oximeters were being used, accurate alarms for lower limit of saturation were set in 13, and upper limit only in one. Among the four senior nurses interviewed, two stated that alarms were not routinely set; another said only lower limits were set, while the other said that alarms for both upper and lower limits were set. Ophthalmologists interviewed admitted that they did not focus on oxygen saturation while visiting SNCUs.

In all SNCUs, none of the neonates receiving oxygen had continuous saturation monitoring. Saturations had been recorded in medical records for all babies receiving oxygen. During interviews, three of the four neonatologists stated that oxygen saturations were monitored every 1-2 hours, whereas one acknowledged that continuous monitoring was only provided for critical neonates. Among senior nurses, two said that monitoring took place every two hours or according to doctors'

**Table I Equipment for Oxygen Delivery and Oxygen Monitoring Practices in Four Special Newborn Care Units (SNCU)**

| Characteristics   | Only ROP nurses sensitized |         | All staff sensitized |          | All SNCUs |
|---|----------------------------|---------|----------------------|----------|-----------|
|   | A                          | B       | C                    | D        |           |
| SNCU centre   |                            |         |                      |          |           |
| Occupancy (bed strength)  | 42 (30)                    | 27 (20) | 32 (27)              | 28 (20)  | 129 (97)  |
| Nurses, no. (recommended)*  | 18 (25)                    | 15 (17) | 17 (22)              | 20 (17)  | 70 (81)   |
| Babies receiving oxygen at the time of visit                            | 12                         | 2       | 3                    | 1        | 18        |
| Preterm infants receiving oxygen  | 7                          | 1       | 2                    | 1        | 11        |
| Blenders  | 0                          | 0       | 0                    | 0        | 0         |
| Equipment for CPAP  | Yes                        | Yes     | Yes                  | Yes      |           |
| No. of pulse oximeters that should have been there <sup>#</sup>         | 21                         | 14      | 21                   | 14       | 70        |
| Adequate functioning pulse oximeters <sup>#</sup> , Yes/No (actual no.) | No (8)                     | No (3)  | Yes (24)             | Yes (16) | 51        |
| <i>Oxygen monitoring of all babies receiving oxygen</i>                 |                            |         |                      |          |           |
| Pulse oximeters being used  | 8                          | 2       | 3                    | 1        | 14        |
| Upper alarms on   | 0                          | 0       | 1 (in CPAP)          | 0        | 1         |
| Upper limit set (target SpO <sub>2</sub> )                              | 0                          | 0       | 1 (100)              | 0        | 1         |
| Number of lower alarms on (%)   | 8 (67)                     | 1 (50)  | 3 (100)              | 1 (100)  | 13        |
| Correctly set lower limit alarms <sup>‡</sup> (%)                       | 8 (100)                    | 1 (50)  | 3 (100)              | 1 (100)  | 13        |

\*As per ref. 10; <sup>#</sup>At least 14 per 20 beds recommended as per ref. 9; <sup>‡</sup>88-89% SpO<sub>2</sub>; CPAP: Continuous positive airway pressure.

### WHAT THIS STUDY ADDS?

- This mixed-method study identified the limitations in the equipment and deficiencies in practices of delivering and monitoring oxygen in four Special newborn care units in one state in India.

instructions. One stated that all neonates receiving oxygen received continuous monitoring whereas another stated that this was only done for critically ill neonates. The frequency of documentation varied from two-hourly for critical to six-hourly for less critical babies. Most cadres identified shortage of equipment and poor maintenance as reasons for irregular monitoring (**Web Table I**).

MCQs were administered to 19 nurses (four each in SNCUs A and D, five in B and six in C). In units C and D, nurses' combined score was 80.0% (95% CI, 68.7-88.6), which was significantly higher than in units A and B (39.5%, 95% CI, 27.6-52.8%;  $P < 0.001$ ). Overall, only 16% of answers to questions on upper and lower oxygen saturation targets were correct; the three nurses with correct answers worked in unit C. All the pediatricians interviewed were aware of the appropriate settings. Regarding gestational age and birthweight criteria for ROP screening, none of the nurses in SNCUs A and B and 5 of 10 nurses in C and D answered correctly. All nurses knew that preterm babies should be screened for ROP by 30 days after birth.

### DISCUSSION

Our study found overcrowding, lack of adequate knowledge among nurses, inadequate equipment, and inefficient use of available equipment to be challenges in providing good oxygen practices. Overcrowding, which was the main challenge, leads to a relative shortage of nurses which can compromise the quality of care [11]. Although all the pediatricians knew the optimal target oxygen saturations, these were known by only a few (16%) nurses, which may explain why most alarms were not set or were incorrectly set. A shortage of functioning pulse oximeters was a reason given for lack of continuous oxygen saturation monitoring, but two SNCUs were not continuously monitoring despite having adequate oximeters. Despite existing International recommendations [12], air-oxygen blenders were not available in any newborn care corner or SNCU, making delivery of 100% oxygen the only alternative. The higher MCQ scores obtained by nurses in SNCUs C and D could be because unlike in centers A and B, all the nurses involved in patient-care had been included in ROP orientation sessions.

Since this study was planned as an early assessment

of the ROP program in India, many of the planned interventions had not been implemented before the visits. The findings are not, therefore, likely to reflect the full impact of the interventions planned. The small number of SNCUs covered by the program in the state, and low number of infants receiving supplemental oxygen at the time of observation may limit generalizability of findings. Further, since MCQs were administered only once in each unit to avoid contamination, the number of nurses assessed was limited.

In India, SNCU nurses undergo only short-term formal training in neonatology and most training is in-service. Previous studies have recommended training and sensitization of nurses to improve practices [13,14] as nurses play an important role in the prevention of ROP [4]. Similar findings on inadequate personnel, equipment and inconsistencies in knowledge of ROP have been observed in Peru [15].

A ROP program supported by the Trust is presently being implemented within the government health system as a pilot, with a potential for national scalability. Although the program has increased awareness about ROP among healthcare professionals and provided ROP services, our study highlights that better oxygen delivery and saturation monitoring are required. Based on our findings, we recommend making available positive pressure air supply, oxygen blenders and one pulse oximeter per infant [16] with spare probes in SNCUs. Repeated training and sensitization of SNCU nurses to improve their knowledge and use of equipment is also needed to reduce the incidence of ROP, as has been reported in Peru [15]. Rational admission policies to reduce overcrowding and an increase in beds and staff could also improve practices. An assessment of quality of care regarding oxygen administration is being planned after all the quality improvement interventions have been delivered, and data from this study will allow comparisons to be made.

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*Contributors:* SS: conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, drafted the initial manuscript and revised the

manuscript; CG: conceptualized and designed the study, supervised the designing of data collection instrument and critically reviewed the manuscript for important intellectual content; AF: supervised the designing of the study and critically reviewed the manuscript for important intellectual content; PK: provided the inputs of the ongoing program, provided intellectual content regarding neonatal care, supervised finalising the data collection instrument and reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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*Competing interests:* None stated.

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**Web Table I Quotes from the Interviews With Medical Personnel**

| <i>Theme</i>           | <i>Quotes</i>  |
|------------------------|--|
| Over-crowding          | <ul style="list-style-type: none"> <li>• “The most difficult to control is admission...” (ROP Nurse, SNCU B)</li> <li>• “Whom can we refuse? We cannot refuse” (Pediatrician, SNCU C)</li> <li>• “Because of overcrowding they do everything with a shortcut and that becomes a habit” (Pediatrician, SNCU D)</li> </ul> |
| Equipment availability | <ul style="list-style-type: none"> <li>• “Equipment is also a problem, like oximeters, [which] have to be removed from one baby and put on the other” (Nurse in-charge, SNCU B).</li> </ul>  |
| Equipment maintenance  | <ul style="list-style-type: none"> <li>• “Monitors are there but repairing [them] is a big problem.....process takes a long time” (Pediatrician, SNCU A)</li> </ul>  |

## Non-immune Hydrops in Neonates: A Tertiary Care Center Experience

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**Objective:** To evaluate the clinical profile and outcome of neonates with non-immune hydrops (NIH). **Methods:** Data of all the NIH cases admitted to neonatal intensive care unit at our center, New Delhi from January, 2010 to October, 2017 were extracted from hospital records, which included clinical profile and outcomes. **Results:** Of the 17,299 total births, 27 neonates were identified to have NIH. Antenatal interventions were undertaken in five (18.5%) cases. The most common etiology of NIH was cardiac ( $n=5$ ; 18.5%). Two babies with chylothorax were successfully managed with octreotide infusions. Overall survival rate of NIH was 70.3% ( $n=19$ ). All neonates with a suspected genetic syndrome died. **Conclusion:** Multidisciplinary team including obstetricians, pediatric surgeons, geneticists and neonatologists can improve outcome in neonates with NIH.

**Keywords:** Antenatal diagnosis, Chylothorax, Nonimmune hydrops fetalis.

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**H**ydrops fetalis (HF) is defined as the presence of extracellular fluid in at least two fetal body compartments or one body compartment with the presence of skin edema ( $>5$  mm thickness) [1]. The incidence of non-immune hydrops (NIH) varies between 1 in 1700 to 3000 live births [2]. Over the years, there has been a trend towards increased incidence of NIH with the advent of Rh-immune globulin for prevention of immune hydrops [3]. The reported global incidence of non-immune cases is nearly 90% of all cases of hydrops fetalis; however, this may not hold true for Indian subcontinent as the coverage of Rh-immune globulin is still not universal [4].

With recent advances in antenatal diagnosis and management, survival rate of NIH has improved significantly to the tune of 50%. Prognosis depends mainly on the underlying etiology. The present study aims to delineate the etiological profile and evaluate outcome of the neonates with NIH at a tertiary care center in India.

### METHODS

Data of all NIH cases delivered between January, 2010 and October, 2017 was analyzed retrospectively. Diagnosis of NIH was as per standard criteria [1].

Data on demographic variables, antenatal and postnatal course of the fetus and neonates was extracted from case records using standard predesigned proforma. The antenatal work up of NIH at our center includes hematological evaluation, serology for fetal infections,

ultrasound doppler to assess fetal anemia, fetal echocardiography and evaluation of ascites and pleural fluid wherever feasible. Delivery room management is carried out by a team, ventilation is supported by T-piece resuscitator for delivery of positive pressure ventilation with higher initial pressures of 20 cm H<sub>2</sub>O and intubation as per Neonatal resuscitation program (NRP) protocol.

Details of management in the NICU including ventilator support [conventional or high frequency ventilation (HFOV)], use of inotropes, inhaled nitric oxide (iNO), and evidence of persistent pulmonary hypertension of newborn (PPHN) and shock were extracted from the neonatal case records. Interventions such as use of anti-arrhythmics, octreotide infusion and surgery, where applicable were also noted.

**Statistical analyses:** All the data extracted were compared between babies who survived and expired in hospital. Chi-square test or Fisher exact test, was used for categorical variables and student t test for comparing continuous variables with normal distribution and Mann Whitney U test for skewed data. Univariate followed by multivariate analysis was done to assess the risk factors for mortality. Statistical analysis was done using Stata 13.0 (Stata Corp, College Station, TX).

### RESULTS

There were 27 cases of NIH diagnosed among the 17,299 births during the study period providing an incidence (95% CI) of 1.5 (1.0-2.2) per 1000 total births. There was a

slight female preponderance (55.5%). The mean (SD) birth weight and gestational age was 2315 (543) grams and 33.9 (3.1) weeks, respectively. Majority of them were diagnosed antenatally ( $n=26$ ). Major clinical features identified were ascites ( $n=20$ ), skin edema ( $n=16$ ), pleural effusion ( $n=14$ ) and pericardial effusion ( $n=12$ ), which were not mutually exclusive.

**Table I** provides the etiology of NIH in this study. Of these, etiology was identified antenatally in 12 cases and fetal treatment was undertaken in five of these cases which included pleuro-amniotic shunt ( $n=2$ ), peritoneo-amniotic shunt ( $n=1$ ) and maternal digitalization/antiarrhythmics ( $n=2$ ). Delivery room intubation was required in 13 cases, intravascular volume expanders in four and chest compressions with intravenous adrenaline in three cases. Emergency paracentesis and thoracocentesis were required in nine cases and 13 cases had severe birth asphyxia. There were 14 neonates who required mechanical ventilation and ten had shock requiring inotropic support. Three neonates had persistent pulmonary hypertension of newborn (PPHN) requiring inhaled nitric oxide (iNO) support. Other interventions included octreotide infusions ( $n=2$ ), and surgical exploration for meconium peritonitis ( $n=1$ ).

Overall survival rate of NIH cases was 70% ( $n=19$ ). All three neonates with suspected genetic syndrome died. On univariate analysis, only APGAR score at 1 and 5 minute were found to be statistically significant; median (range) APGAR score at 5 min in survivors being 8 (6-9) compared to 6 (2-6) in those who died.

**Table I Etiology of Non-immune Hydrops (N=27)**

| Diagnosis                                | No. (%)  |
|--|----------|
| Cardiovascular                           | 5 (18.5) |
| Arrhythmia (all)                         | 3 (11.1) |
| Others                                   | 2 (7.4)  |
| Chylothorax                              | 4 (14.8) |
| Suspected genetic syndrome               | 3 (11.1) |
| Down syndrome                            | 1 (3.7)  |
| Smith Lemli Opitz syndrome               | 1 (3.7)  |
| Pena Shokier syndrome                    | 1 (3.7)  |
| Chorioangioma placenta                   | 2 (7.4)  |
| Meconium peritonitis                     | 2 (7.4)  |
| Suspected glycogen storage disease (GSD) | 2 (7.4)  |
| Twin to twin transfusion syndrome (TTTS) | 1 (3.7)  |
| Anemia of unknown cause                  | 1 (3.7)  |
| Congenital lobar emphysema               | 1 (3.7)  |
| Idiopathic                               | 6 (21.4) |

## DISCUSSION

In the present study, an incidence of 1.5 per 1000 live births over an 8-year period was observed, with a median age at antenatal diagnosis being 26 weeks. In a cohort of 3137 stillbirths, NIH was diagnosed in 9% of the fetuses [5]. The difference from the present study could be due to the fact that only live born were included by us, whereas a large proportion of NIH probably die *in utero*.

Cardiovascular etiology ( $n=5$ ;18.5%) was the most common etiology of NIH in the present study, which is similar to that observed in other studies [3]. Other significant causes include infectious (parvovirus, fetal toxoplasmosis, CMV, syphilis), hematological (alpha thalassemia), genetic (chromosomal abnormalities, skeletal dysplasias, metabolic causes like Gaucher, GM1 gangliosidosis, autosomal diseases like Noonan syndrome and placental causes (Twin-twin transfusion syndrome) [6]. Etiology could not be elucidated in 22% of cases, which is similar to the range of 15-25% reported in literature. Metabolic causes like lysosomal storage disorders may account for 29.6% of idiopathic NIH cases, if appropriate workup is done [7-9].

In a study from India reporting a 10 year experience of 33 cases, LSDs were observed to make up 22% of the etiology [10]. With the advent of newer diagnostic tools like next generation sequencing (NGS), it is possible to diagnose metabolic disorders causing NIH, like inborn errors of metabolism (IEM), which previously remained underdiagnosed. Retrospective study of amniotic fluid samples using hydrops fetalis (HydFet) panel making use of NGS led to significant improvement in diagnosis of IEM as a cause for NIH in a recent study [11].

Clinical outcome and survival rates depend largely on the underlying etiology. All neonates with cardiac and chylothorax as etiology survived while those with a suspected genetic syndrome died. In a large national database study, mortality rates were highest among neonates with congenital anomalies and lowest with congenital chylothorax [12]. Reported survival rates (excluding congenital anomalies) in NIH varies up to 31%-48% [13]. Overall survival rate in our cohort was 70% which was significantly higher than published survival rates. The possible explanation for the higher survival rates in our study could be strict protocol-based management and our preparedness in management, as majority of our cases were antenatally diagnosed.

Exclusion of stillbirths and fetal deaths was a limitation of our study. We could not confirm genetic diagnosis of the suspected syndromic cases. Moreover, the data was incomplete with respect to antenatal genetic work up done.

### WHAT THIS STUDY ADDS?

- We report on etiology, fetal interventions, postnatal management and outcomes of non-immune hydrops in neonates from India.

Non-immune hydrops fetalis is a rare clinical entity with varied etiology. Prognosis depends on the underlying etiology and chromosomal abnormalities generally tend to have a poor outcome. Efforts from multidisciplinary team including obstetricians, geneticists and neonatologists are required to achieve a favorable outcome.

*Contributors:* SM: writing the protocol, collecting data and having written the first draft of the manuscript; PA: helped in writing initial protocol, collection of data and contributed to the final manuscript; MJS: helped in interpretation of outcome measurement and contributed to final manuscript; AT: conceptualized the protocol, helped in writing protocol, and critically reviewed the final manuscript; AV,RA: helped in writing initial protocol and contributed to the final manuscript; AKD: gave critical inputs in final protocol and critically reviewed the manuscript.

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## Novel Coronavirus 2019 (2019-nCoV) Infection: Part I - Preparedness and Management in the Pediatric Intensive Care Unit in Resource-limited Settings

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First reported in China, the 2019 novel coronavirus has been spreading across the globe. Till 26 March, 2020, 416,686 cases have been diagnosed and 18,589 have died the world over. The coronavirus disease mainly starts with a respiratory illness and about 5-16% require intensive care management for acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. Children account for about 1-2% of the total cases, and 6% of these fall under severe or critical category requiring pediatric intensive care unit (PICU) care. Diagnosis involves a combination of clinical and epidemiological features with laboratory confirmation. Preparedness strategies for managing this pandemic are the need of the hour, and involve setting up cohort ICUs with isolation rooms. Re-allocation of resources in managing this crisis involves careful planning, halting elective surgeries and training of healthcare workers. Strict adherence to infection control like personal protective equipment and disinfection is the key to contain the disease transmission. Although many therapies have been tried in various regions, there is a lack of strong evidence to recommend anti-virals or immunomodulatory drugs.

**Keywords:** COVID-19, Guideline, Pandemic, SARI, Treatment.

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The year 2020 started with the emergence of the 2019 novel corona virus (2019-nCoV) as a threat to the world; shortly afterwards the World Health Organization (WHO) declared it a pandemic. Having begun in China, globalization and travel led its spread all over the globe, overwhelming the healthcare resources and resulting in high mortality and morbidity. About 5% of adults, especially those with comorbidities, were critically ill and required intensive care unit (ICU) care [1]. People of all ages were found to be susceptible but severe illness was rare in children [2]. Most of the experience of critical care management of pediatric patients with coronavirus disease 2019 (COVID-19) is derived from the affected children of present epidemic in China, as well as from the previous coronaviral outbreaks *viz.* Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). We write this review as a guidance statement for preparedness and managing children with suspected or confirmed COVID-19 requiring intensive care in a resource-limited setting like India.

### BURDEN

*Global:* Till March 26, 2020, a total of 416,686 confirmed cases from 197 countries with 18,589 deaths have been reported by WHO. China has reported the maximum cases with a total of 81,869, followed by Italy with 69,176 cases. However, mortality is more in Italy with 6,820 (9.9%) deaths followed by China having 3,287 (4%) deaths. The United States of America has surpassed Spain and Germany over the last few days with 51,914 cases and 673 deaths [3].

*Indian scenario:* A total of 606 cases with 10 deaths have been reported from India as on March 26, 2020 as reported by the WHO. Among these cases, only one child from Kerala has been tested positive.

### EPIDEMIOLOGY

The 2019-nCoV belongs to a group of enveloped positive-sense RNA viruses in the family, Coronaviridae with 4 genera *viz.*, alpha, beta, gamma and delta. Human coronaviruses (HCoV) belong to alpha and beta genus

and are mostly implicated in endemic respiratory infection with mild severity [4]. However, the novel coronaviruses infecting humans namely, SARS-CoV, MERS-CoV and SARS-CoV-2 are believed to have originated from bats with few intermediate hosts like civet cats, camels and pangolins [5]. RNA viruses mutate faster than DNA viruses, single-stranded viruses mutate faster than double-strand virus, and genome size appears to correlate negatively with mutation rate.

### Transmission Characteristics

It is speculated that it originated in bat (genetic character matches to bat corona virus) then it got transmitted to pangolins, or scaly anteaters. Humans seem to be accidental host who got this virus from pangolins in Wuhan seafood market. Human to human transmission of COVID-19 started in Wuhan city, Hubei Province of China where it was initially labelled as ‘Pneumonia of unknown etiology’. Epidemiological investigation of early transmission dynamics revealed that 55% of the cases of COVID-19 during December, 2019 were linked to the human seafood wholesale market. The mean incubation period has been reported to be 5.2 days with the 95<sup>th</sup> centile being 12.5 days. The main modes of transmission include droplet and fomites followed by airborne transmission. Reproduction number of nCoV-19 is between 2.2 to 3.6, which is comparable to SARS-CoV but higher than MERS-CoV[6].

*Less severe affection in children:* Children less than 10 years of age accounted for 1% of the total cases [1]. The median age among pediatric cases was 6.7 years [7]. The lesser proportion of severe cases among children has been attributed to lesser opportunities for exposure and immaturity of angiotensin converting enzyme 2 receptors, which are proposed to be the binding sites for coronaviruses [8,9].

### Case Fatality Rate

The overall case fatality rate as per China Centre for Disease Control and Prevention (CDC) is 2.3%, which is much lower compared to SARS (9.6%) and MERS (34%) but significantly higher compared to the latest H1N1 influenza pandemic (0.001 – 0.007%)[1]. However, as per WHO, the global case fatality rate is as high as 4.4% with absolute number of deaths already higher than the total fatality of SARS and MERS combined [10]. The case fatality reported from Italy is 7.2% which has gone up to 9.8% as per WHO (as on March 26, 2020) [11].

### CLINICAL MANIFESTATIONS

The common clinical features reported in the critically ill patients include fever (98%), cough (77%), dyspnea

(63%), malaise (35%), myalgia, headache, nausea, vomiting and diarrhea [12]. A prospective study from China involving 171 children with confirmed COVID-19 reported fever (41%) with a median duration of 3 days (1-16), cough (48%), pharyngeal erythema (46%) tachypnea (28%) and diarrhea (8.8%). The cohort had 15% asymptomatic, 19% upper respiratory infection, and 65% pneumonia. Only 3 children (1.7%) required care and mechanical ventilation. All three of them had comorbidities, and one died [7].

### ICU Requirements in COVID

The severe and critical categories require admission and management in ICU. Among adults, 7% of patients admitted with SARS-CoV-2 pneumonia required ICU care. The mean age of these ICU patients was 60 years with male: female ratio of 2:1 and 50% had chronic illness. Majority had Multi-organ dysfunction syndrome (MODS) with ARDS (67%), acute kidney injury (29%), liver dysfunction (29%) and cardiac injury (23%). Of the ICU admissions, 71% required mechanical ventilation, 35% vasoactive support, 17% renal replacement therapy and 11% ECMO. Mortality was as high as 61% among the critically ill [12]. As per unpublished data from Italy, 16% of admitted patients with COVID-19 needed ICU care [13]. In the Chinese pediatric cases, 5.9% of all pediatric cases belonged to the severe or critical categories. Based on the experience in managing community-acquired pneumonia, high-risk pediatric population includes children with underlying conditions such as congenital heart disease, broncho-pulmonary hypoplasia, airway/lung anomalies, severe malnutrition, and immunocompromised state; however, more information is needed in the setting of COVID-19 [2].

### DIAGNOSIS

Case definitions for suspected, probable and confirmed COVID-19 cases as given by WHO are in **Box I** [16]. The largest series on children analyzing suspected and confirmed COVID cases is from the electronic data base of Chinese CDC [17]. Cases were suspected based on the presence of clinical features and exposure history. They also identified high-risk cases and categorized into groups based on severity (**Box II**).

Laboratory testing of suspected cases is based on clinical and epidemiological factors. Screening protocol should be adapted to local situation and may change with the evolution of the outbreak scenario in the local population. Recent testing strategy in India (as on March 20, 2020) given by ICMR is as per algorithm in **Fig. 1**[18]. Specimen handling for molecular testing would require Biosafety 2 (BSL-2) or equivalent facilities.

**BOX I World Health Organization Case Definitions for Coronavirus Disease 19 (COVID-19)****Suspect case**

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness of breath), AND with no other etiology that fully explains the clinical presentation AND a history of travel to or residence in a country/area or territory reporting local transmission (See situation report) of COVID-19 disease during the 14 days prior to symptom onset.

OR

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to onset of symptoms

OR

C. A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness breath) AND requiring hospitalization AND with no other etiology that fully explains the clinical presentation.

**Probable case**

A suspect case for whom testing for COVID-19 is inconclusive. Inconclusive being the result of the test reported by the laboratory

**Confirmed case**

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms

Source: World Health Organization [16].

**BOX II Risk Stratification and Severity Categorization for Coronavirus Disease-19 (COVID-19)****High risk cases**

|                   |  |
|-------------------|--|
| Clinical features | Fever, respiratory/ digestive symptoms, fatigue  |
| Laboratory tests  | Leukopenia, lymphopenia, high C-reactive protein |
| Radiology         | Abnormal chest ray                               |

**Severity categorization**

|                        |  |
|------------------------|--|
| Asymptomatic infection | No clinical or radiological features but tested positive   |
| Mild                   | Upper respiratory or gastrointestinal symptoms and signs   |
| Moderate               | Clinical/radiological features of lower respiratory involvement  |
| Severe                 | Presence of dyspnea or hypoxemia requiring oxygen, refusal to feed, altered sensorium  |
| Critical               | Organ dysfunction including Acute respiratory distress syndrome (ARDS), shock, encephalopathy, myocardial dysfunction, coagulation dysfunction and acute kidney injury |

Modified From Dong, et al. [17].

Attempts to culture the virus require minimum of BSL-3 facilities [19].

**Type of Sample**

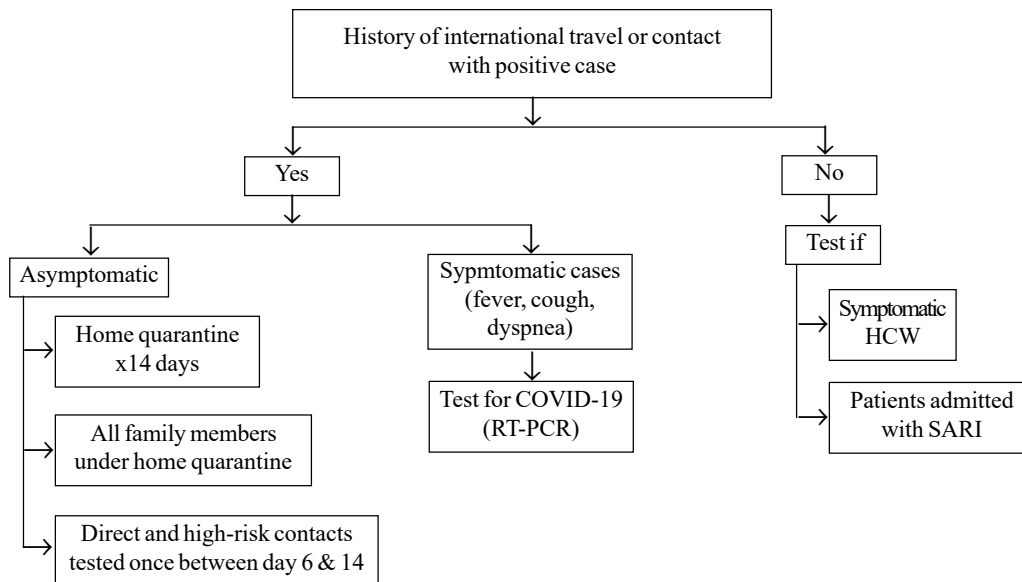
*Upper respiratory specimens:* nasopharyngeal and oropharyngeal swabs; both swabs are placed together in a viral transport medium and transported to the laboratory in ice.

*Lower respiratory specimens:* sputum and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease (obtained with aerosol precautions)

**Confirmatory Tests**

- Respiratory tract or blood samples tested positive for 2019-nCoV nucleic acid using Real-time Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR)
- Genetic sequencing of respiratory tract or blood samples is highly homologous with the known 2019-nCoV, but this is not done routinely.

Serological tests may help in epidemiological investigation but there could be cross reactivity with other coronaviruses. Viral isolation is not done routinely for diagnosis. Rapid diagnostic test kits like Xpert Xpress



**Fig. 1** Testing strategy for suspected cases as per Indian Council of Medical Research.

SARS-CoV-2 by Cepheid has been approved by the US-FDA (United States Food and Drug Administration) for Emergency Use Authorization (EUA) and RealStar SARS-CoV-2 RT-PCR kit 1.0 by Altona Diagnostics and Patho Detect by MY LAB have been approved by ICMR[20,21].

### Ancillary Investigations

**Complete blood count:** Lymphopenia was seen in 85% of critically ill adults, suggesting it a marker of severe disease while among the overall pediatric cases, it was seen in 3.5% [7,12].

**Infection markers:** Elevation of C-reactive protein (CRP) was reported in 20% and procalcitonin in 64% of cases [7].

**Radiological findings:** Chest radiography (CXR) or computed tomography (CT) are not recommended as a routine for children but only in specific cases presenting with pneumonia and/or acute respiratory distress syndrome (ARDS). Parenchymal abnormalities with peripheral consolidations on CXR have been reported in a small case series from Korea [14]. Ground glass opacities (32%), local patchy shadows (18%) and bilateral patchy shadows (12%) on CT chest were the common findings in children [7]. Bilateral pneumonia (75%), unilateral pneumonia (25%) and multiple mottling and ground-glass opacity (14%) were reported based on CXR and CT findings from adult patients in Wuhan, China [15].

**Laboratory markers of organ dysfunction:** Elevation of transaminases is seen in 12-14% and d-Dimer in 14% cases [7].

### PREPAREDNESS AND ADMINISTRATIVE CONCERNS FOR ICU

A phased and tiered plan for ICU during the pandemic needs to be made based on the assessment of healthcare burden and resource utilization [13,22,23].

**Intensive care units:** Create cohort intensive care units where critically ill confirmed COVID-19 patients will be managed. This would be a different area from where other PICU patients are being managed in order to reduce transmission within the hospital. In addition, a separate area should be developed where suspected COVID-19 patients will be managed. With increasing burden of patients, general beds may have to be converted to ICU beds and provided with suitable infrastructure. Predictive models based on local epidemic need to be developed for expected number of patients as well as need of equipment.

**Setting up of isolation rooms :** Negative pressure isolation is the standard recommendation for management of a suspected or proven COVID-19 patient. However, in case of non-availability of these rooms, use single rooms with separate air outlet/exhaust, preferably on the higher floor of the building. These rooms should be equipped with resuscitation trolley, essential drugs, multipara monitor and ventilator. Positive pressure rooms

like operation theatres are not suitable for airway management as aerosol generation is higher.

*Reducing the ICU burden:* All elective non-urgent admissions and surgeries need to be halted during the outbreak in order to rationalize resource-utilization, and ensure adequate back-up to handle the crisis.

*Re-allocation of staff:* During the crisis, there may be acute shortage of critical care specialists and nursing staff. It is essential to identify staff from respiratory medicine, infectious disease and other units who may be trained in infection control, personal protective equipment (PPE) use and management of critically ill patients.

*Rotation of staff and reserve for back-up:* Adequate reserve of healthcare providers needs to be ensured as a back-up in case of emergencies or healthcare professionals falling sick. The team members should be working on rotation (in a shift of 4-7 days) with adequate rest in between.

*Training of all staff:* All those who are likely to come in close contact with the patient or are handling equipment, surroundings, and waste management should receive training regarding infection control including correct technique of donning and doffing of PPE and disinfection of surfaces and equipments. Proper training and a written plan (Standard Operating Procedure) should be there for waste disposal.

*Rational use of PPE:* In view of current global shortage, WHO has formulated guidelines for the rational use of PPE. This includes co-ordination of PPE supply chain management mechanism, appropriate PPE use based on indication, minimizing the need of PPE by bundling activities, using physical barriers and telemedicine where appropriate, and restricting visitors [24].

## MANAGEMENT IN RESOURCE-LIMITED SETTINGS

### Triage and Transport

A dedicated area for screening and triaging of patients with suspected COVID-19 is essential. Once the patient fits to the case definition and requires admission, unnecessary movement must be avoided and minimum staff should accompany the patient. Ensure that the patient (if self-breathing) and the accompanying persons should be on a 3-ply surgical mask.

### ICU Management

Severe and critical cases need ICU care for monitoring, ventilation and organ support therapy.

*Severe acute respiratory illness (SARI):* SARI is defined by the presence of cough and fast breathing plus at least one of the following [25]: (i) Oxygen saturation ( $SpO_2$ ) <90%, (ii) severe chest indrawing and grunting, and (iii) altered mental status.

SARI is the most common indication for ICU transfer and most guidelines are similar to management of any viral pneumonia with ARDS with an emphasis on minimizing risk of transmission to others, especially healthcare workers [26,27]. The details on the management of SARI are given in Part II of this write-up and **Table I**.

*Septic shock:* Management of septic shock in COVID is not very different from the routine. However, the Surviving Sepsis Campaign (SSC) guidelines for COVID-19 recommend conservative fluid strategy, avoiding colloids as resuscitation fluid, and to use low dose steroids in catecholamine refractory shock [28]. In children, epinephrine is the first vasoactive of choice for septic shock.

*Co-infections:* Co-infections like secondary bacterial pneumonia are common, especially in children (50%) and addition of broad spectrum antibiotic to cover gram positive, gram negative, and staphylococcal infection is recommended [29].

*Myocarditis:* Cardiogenic shock with elevations in hypersensitive Troponin-I have been seen in 12% of patients. Management includes inodilators like milrinone, diuretics, immunomodulators (methylprednisolone and IVIG) and circulatory support with ECMO (extra-corporeal membrane oxygenation) have also been used in a few cases [30,31].

*Acute kidney injury :* This has been reported in 7% and renal replacement therapy may be necessary [32].

*Supportive care:* This includes conservative fluid management, nutrition, appropriate sedo-analgesia, and prevention and treatment of healthcare associated infections.

### Specific Therapy

Although no definitive therapy till date has proven benefit for SARS-CoV2, antiviral drugs like Remdesivir, Lopinavir/Ritonavir are being used in over 50% of the critically ill adults based on *in vitro* viral inhibition and recovery in SARS and MERS but there is no strong evidence [33–36]. Chloroquine has been found to increase endosomal pH and hinder virus cell fusion and also interfere with ACE2, a receptor for binding of SARS-CoV2 [37]. A combination of hydroxychloroquine and azithromycin showed reduction in viral load [38].

**Table I Treatment Based on Severity of Disease in Proven Coronavirus Disease-19 (COVID-19)**

| Symptomatic proven case | Admit in                        | Treatment  | Discharge   |
|-------------------------|---------------------------------|--|---|
| Mild                    | Designated COVID isolation room | Symptomatic treatment  | Discharge if 72 h afebrile or 7d after symptom onset and two samples negative 24 h apart followed by home quarantine for total 14 d |
| Moderate                | Designated COVID isolation room | Supportive care, oxygen<br>Oseltamivir   | Clinical improvement and two negative nCoV PCR tests 24 h apart   |
| Severe                  | COVID ICU                       | Provide nasal prong oxygen<br>Escalate to invasive ventilation if worsening<br>Avoid HFNC/NIV<br>Oseltamivir Ritonavir/Lopinavir<br>OR Hydroxychloroquine<br>Supportive care   | Clinical improvement and two negative nCoV PCR tests 24 h apart   |
| Critical                | COVID ICU                       | In addition to the above:<br>Intubate based on clinical/blood gas/radiological features<br>Use all airborne precautions<br>Ventilation ARDS protocol<br>Other organ support<br>Once improving, wean from ventilator and extubate as per protocol | Clinical improvement and two negative nCoV PCR tests 24 h apart   |

HFNC: High-flow nasal cannula, NIV: Non-invasive ventilation, ICU: intensive care unit, ARDS: Acute respiratory distress syndrome.

Interferons, IVIG, and convalescent plasma from recovered SARS patients are other tested treatment options [39]. Vaccination for RNA viruses (measles, influenza, polio) has shown higher titers of neutralizing antibodies against SARS-CoV [40] (**Table II**). Based on the current experience, we may use broad spectrum antibiotics, oseltamivir, protease inhibitors, hydroxychloroquine and azithromycin. Lopinavir/Ritonavir along with Chloroquine should be avoided in combination.

### Course and Recovery

In adult patients with COVID-19 pneumonia, onset of symptoms to respiratory failure takes an average of 7 days with peak severity at 10 days. Signs of improvement starts occurring by day 14. However, at the time of reporting of most studies, many patients were still admitted and their course needs to be followed to know the exact prognosis [40].

### INFECTION PREVENTION AND CONTROL

In the intensive care setting, disinfection of high-touch surfaces like monitors, ventilator screen, other equipment, resuscitation trolleys etc are essential and need to be carried out every 4 hours.

*Surface decontamination:* Alcohol (e.g. isopropyl 70%

or ethyl alcohol 70%) can be used to wipe down surfaces where the use of bleach is not suitable for e.g. Mobiles, laptops, keys, pens etc.

*Disinfection:* Freshly prepared 1% sodium hypochlorite should be used as a disinfectant for cleaning and disinfection with at least 10 minute contact period.

*Aerosol:* Ensure room disinfection within 20 minutes of any procedure generating aerosol.

*Social distancing:* Maintain at least 1 meter distance unless required for examination or procedure.

*Contact and droplet precautions:* minimize direct contact, ensure hand hygiene, and cough etiquette.

### Healthcare Worker (HCW) Risks

Apart from risks related to droplet spread and from contaminated surfaces, ICU professionals face the challenge of acquiring infection during aerosol generating procedures (*see table in Part II*). HCW should wear a medical mask and gown when entering a room where patients with suspected or confirmed COVID-19 are admitted and use full personal protective equipment (PPE), which includes N95 mask, goggles or face shield, cap, full sleeve gown and shoe cover, when performing aerosol-generating procedures [41]. The entire PPE is

TABLE II Pharmacotherapy in COVID-19

| Drug class              | Drug name; stage                           | Mechanism   | Dose   | Additional points  | Evidence  |
|-------------------------|--|---|--|--|---|
| <i>Antiviral drugs</i>  |  |   |  |  |   |
| Nucleoside analogue     | Ribavirin; Pneumonia                       | Inhibits RNA synthesis and viral replication  | IV 8 mg/kg 8 hourly × 14 d   | Side effects:<br>Hemolytic anemia,<br>Hypocalcemia,<br>Hypomagnesemia<br>May increase viral load in combination with steroid | In vitro studies<br>SARS data<br>Not recommended  |
| Neuraminidase inhibitor | Oseltamivir; Pneumonia                     | Reduces viral replication   | <12 mon: 6 mg/kg/dose BD<br>>12 mon:<br><15 kg: 60 mg/d<br>15-23 kg: 90 mg/d<br>23-40 Kg: 120 mg/d<br>>40 kg: 150 mg/d<br>Given PO /BD for 5 d<br>(max dose 150 mg)  | If co-infection with influenza suspected   | MERS-CoV data   |
| Protease inhibitor      | Lopinavir/<br>Ritonavir;<br>Early ARDS     | Inhibit CoV main protease required in replication   | Low dose: 200/100 mg BD<br>High dose: BD for 6-15 d<br>14 d-12 mon: 16 mg/kg/dose<br>< 15 kg: 12 mg/kg/dose<br>15-40 kg: 10 mg/kg/dose<br>(Based on Lopinavir)<br>>40 kg: 400/100 mg<br>Given PO/BD for 5-14 d<br>(Max dose Lopinavir 400 mg/<br>ritonavir 100 mg) |  | In-vitro studies<br>SARS data [33]<br>Weak recommendation [44]  |
| Adenosine analogue      | Remdesivir; Pneumonia                      | Incorporates into viral RNA and leads to premature chain  | Adult dose: 200 mg IV on d 1 followed by 100 mg daily ×5-10 d  | Avoid in children, pregnant, renal and hepatic impairment  | In vitro studies [35]<br>Case report in US [36]<br>On-going trials termination  |
| Aminoquinoline          | Chloroquine Hydroxy-chloroquine; Pneumonia | Increases endosomal pH and hinder virus cell fusion<br>Inhibits viral binding to ACE-2<br>Immunomodulatory effect | CQ: 10 mg/kg base stat followed by 5 mg/kg base BD<br>HCQ: 8 mg /kg/ loading dose, then 4 mg/kg /dose PO /BD/ 5 d<br>(max dose 400 mg)<br>Prophylaxis: 400 mg BD on d 1 then 400 mg weekly   | Inhibits pneumonia exacerbation<br>Negative conversion<br>Shortens disease   | Unpublished data [45]<br>Ongoing phase III trial for prophylaxis and reducing transmission<br>ICMR recommendation for prophylaxis |

Contd....

Table 1 Contd....

| Drug class                            | Drug name; stage                             | Mechanism                        | Dose   | Additional points             | Evidence  |
|---------------------------------------|--|----------------------------------|--|-------------------------------|---|
| <i>Immuno-modulators</i>              |  |                                  |  |                               |   |
| Corticosteroids                       | Methylprednisolone; Pneumonia ARDS           | To suppress cytokines storm, HLH | 1-2 mg/kg/day × 5-7 d  | Delays clearance of viral RNA | Reduced duration of supplemental oxygen and radiological improvement [46]<br>SSC guidelines recommend use in ARDS but meta-analysis in viral pneumonia- harm > benefit [28] |
| Immunoglobulin                        | IVIg/Convalescent plasma; Critical stage     | Immunomodulator                  | 1-2 g/kg over 2-5 d  | After all therapies failed    | Critically ill SARS [47]  |
| <i>Immuno-modulator and antiviral</i> |  |                                  |  |                               |   |
| Immunomodulator & antiviral           | Interferon-α; Early phase of URTI, Pneumonia | Reduces viral load               | Nebulization of 200,000 -400,000 IU/kg (2-4 µg/kg) in 2 mL sterile water BD for 5-7 d                                    |                               | Weak recommendation [48]  |
|                                       | Interferon-α2b spray; Close contacts URTI    | Reduces viral load               | 1-2 sprays (8000 IU/spray) on each side of the nasal cavity, 8-10 sprays on the oropharynx, once every 1-2 hrs for 5-7 d |                               |   |
| <i>Immunotherapy</i>                  |  |                                  |  |                               |   |
| Interleukin -6 inhibitor              | Tocilizumab; Cytokine release syndrome       | Immunosuppression                | <30 kg - 12 mg/kg/dose<br>>30 kg - 8 mg/kg/dose IV BD as infusion 1-2 d (max dose 800 mg)                                | For HLH and cytokine storm    | On-going clinical trials  |



recommended to be used for 4-6 hours and changed earlier if there is any soiling. Team should not include staff vulnerable to infection like immunocompromised person, pregnant ladies, age >60 years or those with comorbidities. In the event of exposure and manifestation of infection, management as per guidelines as well as psychosocial support needs to be ensured. Adequate communication, education and adherence to strict personal protection can minimize the risk of transmission to HCW [26]. ICMR recommends prophylactic use of hydroxychloroquine 400 mg twice a day on day 1, followed by 400 mg once weekly for next 7 weeks for HCW managing suspected or confirmed COVID-19 patients [42].

### Special Considerations for Resuscitation

It is important to minimize the number of people inside the room during high aerosol generating events like cardiopulmonary resuscitation. One airway specialist, one nurse/doctor for chest compression and one nurse for medication are essential. Other assistants may remain outside the room and may enter only if necessary after donning full PPE. Hand bagging needs to be avoided. During any disconnection from ventilator, endotracheal (ET) tube needs to be clamped and/or viral filter attached to the ET tube. In case re-intubation is required, follow the standard procedure described (*see Part II in this issue*).

### CONCLUSION

The COVID-19 pandemic caused by 2019-nCoV has become a serious concern for mankind all over the world. It has challenged and overwhelmed the existing intensive care facilities globally. SARI is the most common indication for intensive care management and is associated with high mortality. The disease so far appears to be less common in children and seems to have a milder course. Preparation for handling crisis during this outbreak is essential for early identification, stratification and management of cases. Prevention by ensuring strict infection control practices minimizes transmission to other patients and healthcare workers, especially in intensive care units.

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## Novel Coronavirus 2019 (2019-nCoV) Infection: Part II - Respiratory Support in the Pediatric Intensive Care Unit in Resource-limited Settings

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The 2019-novel coronavirus predominantly affects the respiratory system with manifestations ranging from upper respiratory symptoms to full blown acute respiratory distress syndrome (ARDS). It is important to recognize the risk factors, categorize severity and provide early treatment. Use of high flow devices and non-invasive ventilation has been discouraged due to high chances of aerosol generation. Early intubation and mechanical ventilation are essential to prevent complications and worsening, especially in resource-limited settings with very few centers having expertise to manage critical cases. Hydrophobic viral filter in the ventilator circuit minimizes chances of transmission of virus. Strategies to manage ARDS in COVID-19 include low tidal volume ventilation with liberal sedation-analgesia. At the same time, prevention of transmission of the virus to healthcare workers is extremely important in the intensive care setting dealing with severe cases and requiring procedures generating aerosol. We, herein, provide guidance on non-invasive respiratory support, intubation and management of ARDS in a child with COVID-19.

**Keywords:** 2019-nCoV, Aerosol generation, ARDS, Management, Pandemic, SARI.

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**N**ovel coronavirus 2019 (2019-nCoV) infection has been declared a pandemic by the World Health Organization (WHO). We elaborated the epidemiology, preparedness of intensive care units, clinical course, intensive care needs and complication of patients with Coronavirus disease (COVID-19) in a previous article [1]. In this write-up, we will focus on the respiratory manifestations, progression and intensive care management of respiratory complications of COVID-19. As we learn more about the 2019-nCoV (novel coronavirus) and the impact this has had on the patients and health care workers (HCW) globally, the focus has shifted to safety of the HCW so that the patients can be treated appropriately and kept safe. This is based on the lessons learned from previous epidemics and mitigating steps to reduce risks to HCW. Most of the following suggestions are based on expert opinion on providing safe care in these challenging times.

### RESPIRATORY DISEASE DUE TO 2019 NCOV INFECTION

#### Clinical Course

The most common presentation is short history of

prodrome with myalgias, malaise, cough and low-grade fever. As per the case series from China, only 40-70% of the pediatric patients have fever as an initial presentation [2-4]. During the second week of illness, progression of the disease gradually leads to difficulty in breathing. Reports from China have suggested that it takes an average of 8 days for the development of dyspnea and 9 days for the onset of pneumonia/pneumonitis [5].

#### Investigations

CDC does not currently recommend chest radiography (CXR) or computed tomography (CT) to diagnose COVID-19 [6]. Viral testing remains the only specific method of diagnosis and has been discussed in detail in part-I [1]. Confirmation with the viral test is required, even if radiologic findings are suggestive of COVID-19 on CXR or CT scan [7].

#### Differential Diagnosis

The clinical presentation and findings on chest imaging in COVID-19 are not specific. The clinical presentation of COVID-19 overlaps with other infections like influenza, respiratory syncytial virus (RSV), adenovirus, human

meta-pneumovirus, non COVID-19 coronavirus, atypical organisms (mycoplasma, chlamydia) and bacterial infections. It is not possible to differentiate COVID-19 from these infections clinically or through routine laboratory tests. In the context of pandemic and local transmission setting in, the travel history will become irrelevant. There are some radiological and hematological findings that may help indicate COVID-19, even though they are not very specific [1].

### Classification of Severity

Severity of illness is based on the presenting symptoms and has been discussed previously [1]. Patients can shed RNA from 1-4 weeks after symptom resolution, but it is unknown if the presence of RNA equals presence of infectious virus. As per current guidelines, COVID-19 patients are “cleared” of isolation once they have 2 consecutive negative RNA tests collected >24 hours apart. This practice may not be clinically possible in our setting due to various constraints. Therefore, keeping them in isolation for longer duration is the key.

### MANAGEMENT OF HYPOXEMIC RESPIRATORY FAILURE

One of the key considerations during management is mitigating risk to health care workers. Hypoxemia can be present due to impaired respiratory functions in COVID-19. Oxygen supplementation treatment can correct hypoxemia and relieve secondary organ damage caused by hypoxemia[8]. The management of children with Severe acute respiratory illness (SARI) in COVID is similar to any other viral pneumonia with ARDS but with strict precautions to reduce risk of transmission[9].

### Protection From Aerosol

All aerosol generating procedures/events require donning of personal protective equipment which includes N95 mask, goggles or face shield, cap, full sleeve gown and shoe cover (**Table I**) [10]. Where possible, a nebulizer may be replaced with an MDI and spacer for administration of bronchodilators. NIV generates droplets >10 µm in size and most fall on local surfaces within 1-meter distance. Learning from droplet dispersion studies, HCWs who are providing NIV, chest physiotherapy or working within 1 meter of an infected patient should have a high level of respiratory protection [11-13].

### Oxygen Therapy

Oxygen therapy is necessary for patients with oxygen saturation (SpO<sub>2</sub>) less than 90% and/or with signs of respiratory distress. It has been noted that many elderly patients with severe hypoxemia may not have obvious

symptoms of respiratory distress [14]. It is pertinent that the evaluation of all children with respiratory symptoms should include pulse oximetry. Low flow oxygen devices are recommended as high flow devices have the potential for risk of spread through aerosol generation. Nasal cannula at flows of 2-4 L/min is a good choice for milder forms of SARI. A triple layer mask should be used to cover the mouth and nose of the patient over the nasal cannula, especially during transport, unless the child does not tolerate [15].

### Heated Humidified High Flow Nasal Cannula (HHFNC/HFNC)

HFNC therapy can be useful in special situations for hypoxia. A flow of 2-3 mL/kg with FiO<sub>2</sub> targeted to SpO<sub>2</sub> is used. However, it is necessary that when patient is on HFNC interface, HCW are wearing optimal airborne PPE and child is managed in negative pressure rooms, if available [16]. In infants, while HFNC is being given they can be placed in an oxygen hood to minimize dispersion. Surviving Sepsis Guidelines recommend HFNC in milder cases of adult SARI [17]. However, no such guidelines are there for children. HFNC should be tried for a maximum of 1-2 hours. Signs of improvement are decrease in heart rate and respiratory rate by 10-20%, decrease in FiO<sub>2</sub> requirement to less than 50% and improvement in oxygen saturations.

Patients with worsening hypercapnia, acidemia, respiratory fatigue, hemodynamic instability or those with altered mental status should be considered for early invasive mechanical ventilation.

### Non-invasive Ventilation

Over the last two decades, the use of non-invasive ventilation (NIV) is increasing in children with viral illness and the rates of intubation are reducing. At the same time there is paucity of literature regarding the use of NIV in respiratory pandemics.

**Table I Aerosol Generating Events and Procedures in the Intensive Care Unit**

| <i>Aerosol generating events</i> | <i>Procedures vulnerable to aerosol generation</i> |
|----------------------------------|--|
| Inadequate seal during           | Laryngoscopy                                       |
| NIV or HFNC                      | Intubation   |
| Nebulization                     | Front of neck access                               |
| Endotracheal suction             | Laryngoscopy                                       |
| CPR prior to intubation          | Bronchoscopy                                       |
| Extubation                       |  |
| Coughing/sneezing                |  |

*NIV-non-invasive ventilation; HFNC – High flow nasal cannula.*

In a Chinese observational study in adults of the SARS outbreak, it was shown that NIV was effective in preventing the use of endotracheal intubation in 70% of patients because of early initiation of NIV. In this study, none of the HCW acquired SARS from the patients. This was attributed to NIV being applied in a negative-pressure environment with strict PPE regime and close monitoring of the HCW involved [18]. In another study from Toronto during SARS, the use of NIV was discouraged after clinicians contracted the disease when a patient was intubated following NIV failure [19]. Therefore, some clinicians consider NIV is contra-indicated for acute respiratory failure due to airborne respiratory diseases unless it is used in a negative-pressure isolation room and strict precautions are taken [19].

After the two viral pandemics, most of the professional societies including the European Respiratory Society, European Society of Intensive Care Medicine, and American Association for Respiratory Care have recommended against NIV use to treat acute respiratory failure due to H1N1 influenza, particularly in severely ill patients. Thus, NIV is accepted as a high-risk procedure that should be used cautiously because of possible spread of infection [20-23].

Routine use of NIV is not recommended in COVID-19. It should be used only in selected patients with hypoxemic respiratory failure. Ideally, negative pressure single rooms are preferable for patients on NIV. However, in an outbreak of such a magnitude, some professional societies recommend keeping a distance of at least two meters between two beds. Due to the high percentage of failure with NIV and the rapid progression of the hypoxemic failure due to COVID-19, all patients receiving NIV need a clear plan for treatment failure.

Selection of interface is the key for success and protection of the HCWs. Preferred interfaces are helmet, total face mask and oro-nasal non-vented masks. Risks of NIV include delayed intubation, large tidal volumes and injurious trans-pulmonary pressures. Limited data suggest a high failure rate in patients with other similar viral infections such as MERS-CoV [24].

$\text{PaO}_2/\text{FiO}_2$  is a sensitive and accurate indicator of oxygenation function on NIV and can be used to define the severity of ARDS once the patient has been on a PEEP of 5 cm for a minimum of 30 minutes. Invasive ventilation must be considered if  $\text{PaO}_2/\text{FiO}_2$  ratio is below 300. In the absence of an ability to do an arterial blood gas, the  $\text{SpO}_2/\text{FiO}_2$  can also be used to identify oxygenation failure as long as the  $\text{FiO}_2$  has been titrated to get saturations between 92%-97%.

The most recent World Health Organization (WHO) interim guidance on management of the novel-CoV has also recommended the use of NIV for mild cases of ARDS without hemodynamic instability [8].

Conventional ventilators with NIV option having double lumen tubing is a safer option than NIV ventilator with single lumen tubing requiring exhalation port to washout the  $\text{CO}_2$ . Antiviral/Antibacterial filters should be attached to the exhalation limb of the circuit to reduce environmental contamination. Alternatively, when these options are not available, home ventilators with built-in oxygen blender or transport ventilators can provide adequate mechanical ventilation.

### **Bubble CPAP**

In situations where both non-invasive and invasive mechanical ventilation are not available, bubble nasal CPAP (commercial or indigenous) may be used for newborns and children with severe hypoxemia as these are readily available alternative in resource-limited settings. To minimize environmental contamination the infant could be placed in an oxygen hood to reduce droplets.

These patients should be on continuous monitoring and cared for by experienced personnel capable of performing endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 2 hours).

Patients with known contraindications for NIV like moderate/severe ARDS with  $\text{PaO}_2/\text{FiO}_2$  ratio below 200, hemodynamic instability, multi-organ failure, or abnormal mental status should receive invasive ventilation from the very beginning.

### **Intubation**

During the previous SARS epidemics in China and Singapore, infection rates were higher in doctors and nurses carrying out endotracheal intubation [relative risk (95% CI)-13.3 (2.99-54.04)] [20]. In an observational study of influenza-A and influenza-B in exhaled breath, viral RNA was seen in one-third of infected patients and 99% of particles had a diameter of  $<5 \mu\text{m}$  when sampled during tidal breathing [25]. Studies have demonstrated that particles  $<10 \mu\text{m}$  in diameter are more likely to cause infection in the lower respiratory tract [9,10]. Coronavirus virions (or 'particles') are spherical particles with diameters of approximately 125 nm (0.125  $\mu\text{m}$ ) [26].

Tracheal intubation should be performed as early as possible for patients with  $\text{aPaO}_2/\text{FiO}_2$  ratio  $<300$ , worsening trend of the  $\text{SpO}_2/\text{FiO}_2$  ratio  $<200$ , worsening respiratory distress, high concentration ( $>60\%$ ) of oxygen on HFNC or multiple organ dysfunction.

**Preparation** : Prepare the plan, ready the equipment and set-up the ventilator prior to intubation (**Table II**). At least three personnel are needed namely, airway operator, airway assist and a nurse for medication. The most experienced person should intubate to ensure minimum number of attempts to decrease aerosol generation. Wherever possible, use disposable equipment. Video laryngoscopy is ideal to protect the intubating HCW from operating too close to the airway (**Fig.2**). If equipment or expertise is not available, take measures to reduce droplets during the procedure using a plastic sheet (**Fig. 1**).

**Pre-medication**: Use benzodiazepine (midazolam 0.1-0.2 mg/kg) with opioid (fentanyl 2-3 µg/kg) combination for sedation and analgesia. Short acting neuromuscular blockers like rocuronium is preferred (if unavailable, use a higher dose of vecuronium or atracurium as per availability).

**Pre-oxygenation**: After a quick assessment for anatomically difficult airway, pre-oxygenation is carried out with non-rebreathing mask (NRM) or tight-fitting face mask attached to a self-inflating ambu-bag with 100% oxygen for 5 minutes. A hydrophobic viral filter between the mask and ambu-bag is recommended and some units cover the head, neck and chest with transparent plastic apron/sheet to prevent aerosol contamination (**Fig.1**). Avoid bag and mask ventilation (BMV) to limit aerosol and if needed, use low tidal volume with lesser breaths.

**Intubation**: Cuffed endotracheal tubes (ETT) must be used in all ages and cuff needs to be inflated immediately following intubation. Disposable ventilator circuit with a viral filter attached at the expiratory limb (between circuit and machine) is used. Heat moisture exchanger (HME) is preferred for humidification. Ventilator should be in 'stand-by' mode and only to be turned on after connected

to the patient. Prior to connecting to ventilator, the ETT can be clamped or attached to a viral filter. Closed suction (inline suction catheters) is preferred to prevent aerosol generation. If not available, open suction may be performed with aerosol precautions and after administering a dose of short acting neuromuscular blocking agent.

### Invasive Mechanical Ventilation

Lung protective mechanical ventilation (MV) is recommended strategy for management of acute hypoxemic respiratory failure. SSC guidelines in adults recommend low tidal volume strategy (4-8mL/kg), limiting plateau pressures to <30 cmH<sub>2</sub>O and using higher PEEP (>10 mm Hg) [17]. Permissive hypercapnia is well tolerated and may reduce volu-trauma. Viral filters should be utilized, and circuits should be maintained for as long as allowable (as opposed to routine changes) (**Table III**).

### Prone Ventilation

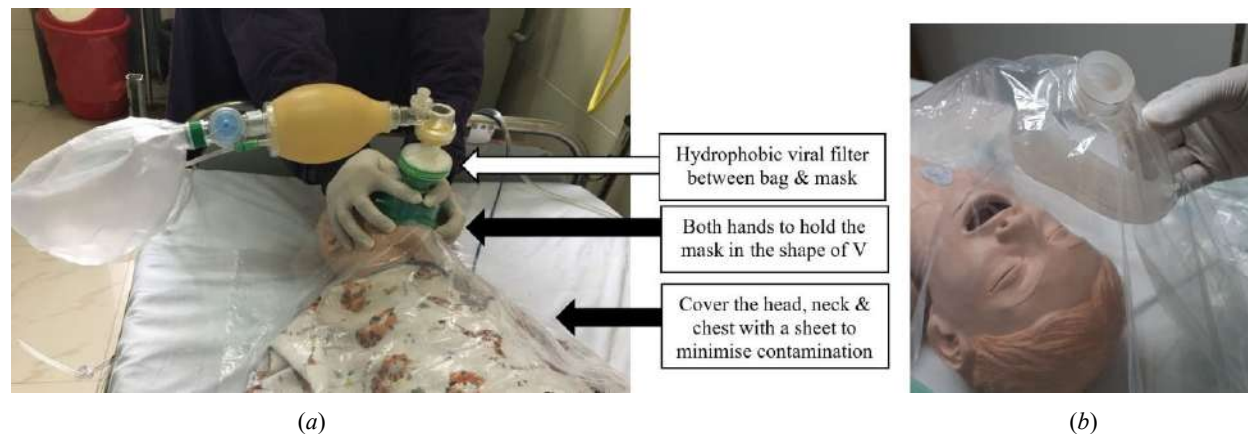
Prone ventilation is a recommended strategy in adults with PaO<sub>2</sub>/FiO<sub>2</sub> <150 to improve lung mechanics and oxygenation. Patient is usually kept prone for 12-16 hours. Prone ventilation can be ceased once PaO<sub>2</sub>/FiO<sub>2</sub> is > 150 for more than 4 hours in the supine position. However, in children and resource-limited setting, due to limited availability of HCWs and PPEs, it may not be possible to prone the child and may unnecessarily increase the risk of infection to the healthcare workers.

### Fluid Management

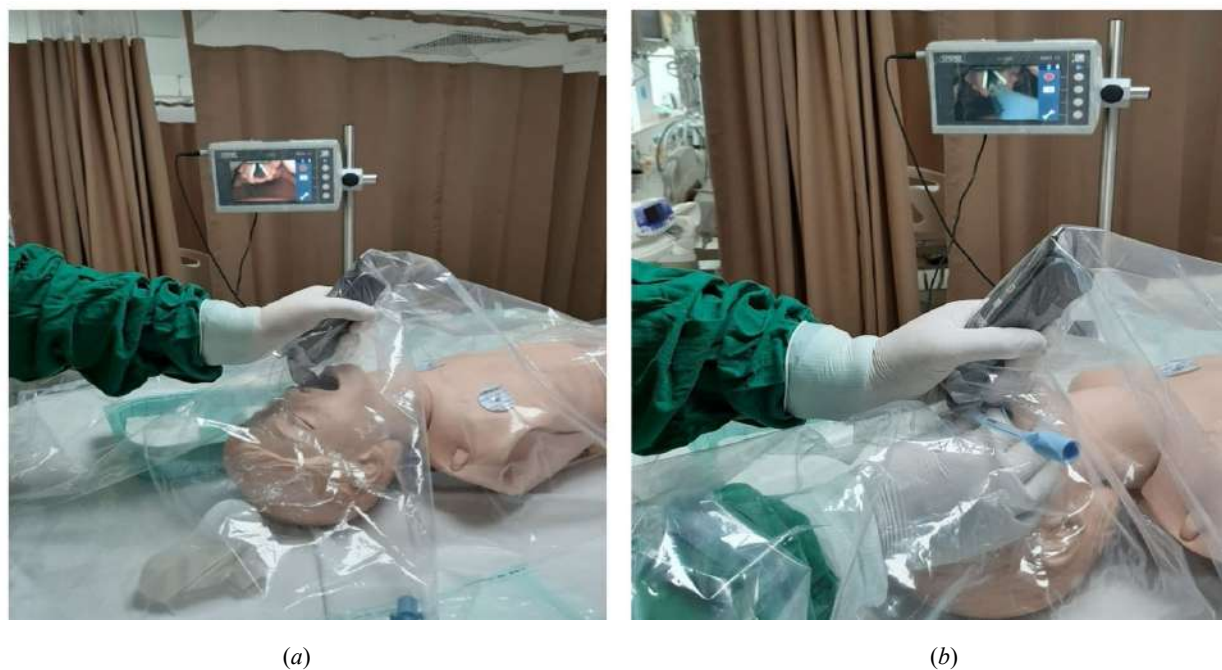
To reduce pulmonary exudation and improve oxygenation, the fluid balance should be strictly controlled while ensuring adequate end-organ perfusion. Fluid restriction to 70-80% maintenance is necessary to prevent fluid overload.

**Table II Intubation Trolley and Tray and Modifications for Use in COVID-19 Patients**

| <i>Equipment (size appropriate)</i>             | <i>Specific for COVID-19 patients</i>   |
|---|---|
| Laryngoscope with blade                         | Video laryngoscope is preferred to increase the distance between the health worker and patient  |
| Endotracheal tube                               | Micro-cuffed and cuffed tubes to minimize aerosol as well as leak in acute respiratory distress syndrome (ARDS)   |
| Suction catheter                                | Closed suction to minimize contact with secretion, aerosol release & de-recruitment   |
| Hydrophobic viral filter                        | Used between the ambu bag and mask as well as in the ventilator circuit at the expiratory end   |
| Oxygen & ventilation delivery devices           | For pre-oxygenation, use non-rebreathing mask or a flow inflating device (Jackson Rees) Ensure adequate mask seal Avoid bagging if using self-inflating bag |
| Drugs – Sedo-analgesia & neuromuscular blockade | Use liberal sedation & neuromuscular blockade to avoid coughing and ultra-rapid sequence intubation   |
| Adjuncts  | Stylet, Bougie and second-generation laryngeal mask airway (LMA) devices readily available if initial plan fails  |



**Fig. 1** (a) The assembly of bag, viral filter and mask along with plastic sheet to minimize aerosol; (b) Preparing the sheet with an opening for the mask.



**Fig. 2** (a) Video-laryngoscope assisted intubation; (b) shows a sheet covering the face and chest during intubation.

### Strategies to Prevent Ventilator-Associated Pneumonia (VAP)

VAP bundled strategies should be strictly implemented as per recommendations [27].

### Weaning and Extubation

Once the patient's  $\text{PaO}_2/\text{FiO}_2$  is more than 300 the neuromuscular blockade and sedatives must be weaned and discontinued. Extubation should be performed if the patient is considered ready for extubating to nasal  $\text{O}_2$  as post-extubation NIV is avoided where possible. Aerosol

precautions are essential during extubation. Few units practice extubating using a plastic bag over the face with a tight seal after inflating with oxygen (**Fig. 4**) or some units use a transparent large plastic sheet over the face and chest to capture droplets from coughing and suctioning. Post-extubation, the need for HFNC or NIV can be assessed while reducing monitoring.

Various professional bodies have given their recommendations for respiratory support in pediatrics and adult [8,15,17,28] and these are summarized in **Table IV**.



**Table III Strategies in the Management of Acute Respiratory Distress Syndrome in COVID-19**

| <i>Management similar to any ARDS</i>   | <i>Specific with respect to COVID</i>                     |
|---|---|
| <i>Lung protective ventilation</i>  | Early invasive ventilation – avoid HFNC and NIV           |
| Tidal volume 4-6 mL/kg  | Avoid steroids – may prolong viral shedding               |
| Limit Plateau pressure <28 cm H <sub>2</sub> O  | Use liberal neuromuscular blockade to prevent coughing    |
| PEEP start with 7-10 and titrate to 15 cm H <sub>2</sub> O                            | Proning involves risk of exposure to HCW and best avoided |
| Limit FiO <sub>2</sub> <60% with permissive hypoxemia                                 | Avoid nebulization  |
| Avoid fluid overload (FO) - target FO <5%   |   |
| Sedo-analgesia titrated to sedation scores  |   |
| Early enteral nutrition – initiate within 24 hours and achieve full feeds by 48 hours |   |
| Transfusion trigger hemoglobin <7 g/dL if stable hemodynamics and oxygenation         |   |
| Target hemoglobin 10g/dL in refractory hypoxemia or unstable shock                    |   |

*NIV – non-invasive ventilation; HFNC – high flow nasal cannula; HCW-healthcare worker; PEEP – peak end-expiratory pressure.*



**Fig. 3** Use of expiratory filter in single limb NIV tubing (use a non-vented mask).



**Fig. 4** Covering the face with a plastic bag or a sheet, to prevent aerosol spread during extubation.

**CONCLUSION**

SARI is the most common presentation of COVID-19 and requires intensive care support. Low flow oxygen devices are preferred to high flow devices to prevent aerosol generation. Early intubation and mechanical ventilation are recommended to delay progression and need for emergent intubation, which poses significantly higher risk of transmission of infection to HCW. Use of HFNC and NIV is to be avoided routinely and if necessary, a full PPE with aerosol precautions is a must. Management of ARDS includes lung protective ventilation with liberal sedation-analgesia and avoidance of steroids.

*Contributors:* MS, NR, AB, KN: substantial contribution to the conception and design of the work, and drafting the work; GVB, RL, DG, MPO, ARRN, MJ: substantial contributions to the acquisition and interpretation of data for the work, and revising it

critically for important intellectual content. All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Table IV Summary of Respiratory Support Guidelines for COVID-19 Patients**

|                       | <i>WHO [7]</i> | <i>SCCM [16]</i> | <i>PICS UK [27]</i> | <i>ANZICS [14]</i> |
|-----------------------|----------------|------------------|---------------------|--------------------|
| HFNO with precautions | +/-            | +                | +                   | +                  |
| NIV with precautions  | +/-            | +/-              | +                   | -                  |
| Invasive ventilation  | +              | +                | +                   | +                  |


*WHO – World health organization, SCCM – Surviving sepsis campaign, PICS UK – Pediatric intensive care society UK, ANZICS – Australian and New Zealand Intensive Care Society.*

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## Therapeutic Enteral Formulas in Children

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**Purpose:** A variety of enteral formulas for various diseases have become available in India in the last few years. Awareness among pediatricians about the availability and indications for these therapeutic formulas is low. **Methods:** A literature search was conducted in PUBMED and relevant data collected from all English language publications available. Data on the commercial preparations was sourced from the individual companies, the Diet 4 life initiative as well as FSSAI (Food safety and standards authority of India). **Conclusions:** Therapeutic enteral formulas, which are indicated in various disease states belong to four categories - lactose modified, hydrolyzed, MCT based and metabolic disease specific formulas. Lactose modified formulas which are used in temporary or permanent lactose intolerance and Galactosemia are either casein or soy protein based. Hydrolyzed formulas could be partially hydrolyzed, extensively hydrolyzed or amino acid based. Only extensively hydrolyzed formula should be recommended in milk protein allergy. Amino acid (elemental) formulas are mainly indicated in patients with diffuse intestinal mucosal disease. MCT formulas are used in chronic liver disease with cholestasis, and have 30 to 80% MCT. Formulas for inborn errors of metabolism are free of specific carbohydrate, amino acid or fatty acid. Proprietary formulas presently available in India with their specifications have been listed.

**Keywords:** Elemental formula, Hydrolyzed formula, Lactose intolerance, MCT based formula, Therapeutic enteral formula.

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**T**herapeutic enteral formulas are those that are indicated in specific situations of disease or need and are not substitutes for breast milk. They can be divided into the following broad categories - lactose modified formulas, hydrolyzed formulas, medium chain triglyceride (MCT) based formulas and disease-specific enteral formulas, which include those for various inborn errors of metabolism and specific clinical settings such as liver or renal disease. A thorough understanding of the underlying nutritional requirement in each disease state as well as the ingredients present in each formula is important to ensure their optimum use. Literature search was conducted in Medline through PUBMED, using MeSH terms. Data on the commercial preparations was sourced from the individual companies, the Diet 4 life initiative, as well as FSSAI (Food safety and standards authority of India). Copies of the FSSAI license for each product were also obtained from the companies. Authors have taken extreme care in reviewing the proprietary food products. This review article provides guidance regarding the various categories of enteral formulas and their indications, so that pediatricians can use them rationally in clinical practice.

### AVAILABLE FORMULAS

#### Lactose Modified Formulas

Lactose, the carbohydrate component of milk is not

only a source of energy, but also supports linear growth and neuro-development of the growing infant. Lactose is broken down into glucose and galactose in the small intestine by the action of the enzyme lactase, present at the tip of the microvilli of enterocytes. Mild lactose malabsorption is desirable in early infancy since lactose acts as a prebiotic in the colon facilitating growth of bifidobacterium rich fecal microbiota. When the lactase enzyme activity is critically reduced or absent, either temporarily (secondary lactase deficiency following small bowel disease like acute diarrhea, persistent diarrhea, giardiasis, celiac disease, crohn's disease etc) or permanently (primary lactase deficiency attributed to a relative absence of lactase in childhood, which is common in many racial groups including Indians), a reduced or lactose-free diet is necessary. Lactose-free diet is also indicated in galactosemia; an autosomal recessive disease, where patients cannot metabolize galactose due to a congenital enzyme defect.

Diarrhea as a manifestation of lactose intolerance occurs mainly in infants and young children, since they lack the ability to compensate by colonic reabsorption. In older children, colonic reabsorption of fermentation products (e.g. short chain fatty acids, lactate) results in less osmotic diarrhea, but more abdominal bloating from the hydrogen produced [1]. Most patients with acute

gastroenteritis do not have lactose intolerance and recover well with continued intake of breast or standard milk. Routine use of lactose-free formula is not recommended in acute diarrhea, since it neither results in faster recovery nor prevents complications [2]. However, in persistent diarrhea, a lactose modified diet is indicated [3]. Unlike cow milk protein allergy, lactose intolerance is quantity-related and most patients with secondary lactose intolerance require reduced amounts of lactose rather than a totally lactose-free diet. Low lactose formula may be used in young infants with temporary lactose intolerance that are not breast-fed. Studies do not support the use of lactose-free diet to improve crying or fussy infant behaviour [4]. Lactose-free formulas are either milk protein- or soy protein-based.

### Milk Protein-based Lactose-free Formulas

Milk protein based lactose free formula has malt dextrin as the carbohydrate. Even though the calorie content is the same, they have very little iron, and lower fat than standard formula. They should be used only when lactose intolerance is strongly suspected or proven. In temporary lactose intolerance, they should be used only for a few weeks, since recovery of the mucosa and lactase enzyme activity occurs by then.

### Soy-based Lactose-free Formulas

Soy-based lactose-free formulas are made of proteins extracted from soybean. The source of carbohydrate is corn malt dextrin, corn syrup solids and sucrose and it is completely lactose free. It contains essential fatty acids which can be easily absorbed, and is fortified with methionine, carnitine and taurine. Being a vegetable protein, the bioavailability is lower and so the overall protein content is higher than in milk-based formula [5]. Soy protein is heat stable and nutritionally optimum even after heating. There are concerns regarding use of soya protein below 6 months of age due to high concentration of aluminum (600-1,300 ng/mL vs. 4-65 ng/mL in human milk) and excess of phytoestrogens [6]. Since calcium absorption is sub-optimal in lactose free formula, all soy-based formulas contain 20% more calcium and phosphorus than standard cow's milk-based formulas. In addition, because soy phytates bind iron and zinc, they are fortified with these minerals. [7]. Soy formulas contain very small amounts of galactose, but they are considered safe for use in classic galactosemia [8].

Soy formula is used in clinically significant secondary lactose intolerance as well as primary lactose intolerance [9]. A soy formula may also be considered in infants with cow milk protein allergy (CMPA), if the extensively hydrolyzed formula is not available/

affordable/acceptable/ tolerable or if there is a strong parental preference for a vegan diet [10]. About 15-20 % of infants with CMPA also may have soy protein allergy.

The various lactose free formulas available in India are shown in **Table I**.

### Hydrolyzed Formulas

Hydrolyzed formulas were originally developed to enhance tolerability and reduce allergenicity, compared with intact cows' milk protein formula. It was therefore believed to have the potential to decrease the incidence of atopic diseases as well as management of cow milk protein allergy (CMPA). Milk proteins are hydrolyzed by enzymes, heat pressure and /or ultrafiltration. Currently they are classified based on the degree of hydrolysis and accordingly there are partially hydrolyzed formulas (pHF), extensively hydrolyzed formulas (eHF), and amino acid formulas. While amino acid formulas are referred to as elemental formulas, eHF and pHF are called semi-elemental formulas. The lesser the degree of intact protein, enhanced is the immunologic tolerability; however, more the degree of protein hydrolysis, worse is the taste of the formula. In general, pHFs have peptides which are 5-10 kDa, whereas in eHFs they are <3 kDa [11] while amino acid-based formulas contain only free amino acids and are devoid of any peptides (**Table II**). Both casein and whey hydrolyzed formula products exist worldwide. **Table I** shows the hydrolyzed formulas available in India.

In the past, the term 'hypoallergenic' has been used to refer to any formula that is used in cow milk protein allergy. Therefore, both pHF and eHF were referred to as hypoallergenic. However, recent literature prefer to avoid this terminology as it is potentially misleading. Presently its use is restricted to individual eHF that have clinical studies documenting therapeutic hypoallergenic effect in cow milk protein allergy.

### Partially Hydrolyzed Formulas

They are made by hydrolyzing the intact milk protein. The average peptide size in pHF varies from 3-10 kDa (mean 5) and they retain some antigenicity of the milk protein. These are therefore beneficial as an alternative to intact cow milk protein formula for tolerance induction in infants [12,13]. Tolerance induction is; however, not an accepted practice in international management protocols on CMPA. pHF should not be used for patients with documented CMPA. While pHF are safe and are allowed by the USFDA (United States Foods and Drugs Authority) and EFSA (European Food Safety Agency) as an alternate protein source for all babies, there are limited studies evaluating the allergy-prevention role in the

**Table I Lactose Modified, Hydrolyzed and MCT-based Formulas Currently Available in India**

| Category  | Brand                 | Manufacturer       | Remarks   |
|---|-----------------------|--------------------|---|
| <i>Lactose modified formulas</i>                |                       |                    |   |
| Low lactose                                     | NAN lo Lac            | Nestle             | 5 g lactose /100g   |
| Milk protein-based                              | Nusobee Casein        | Nutricia           | Lactose and sucrose free.   |
|   | Zerolac Casein        | Raptakos Brett     | Lactose and sucrose free.   |
|   | Simyl MCT             | FDC Ltd.           | Lactose <i>and</i> sucrose free. MCT only 7.4%.   |
| Soy protein-based                               | Isomil                | Abbott             | Lactose free. Has sucrose (10g/100g powder)   |
|   | Nusobee Soy           | Nutricia by Danone | Lactose, sucrose free   |
|   | Zerolac               | Raptakos Brett     | Lactose, sucrose free.  |
| <i>Hydrolyzed formulas</i>                      |                       |                    |   |
| Partially hydrolyzed                            | Peptamen Jr           | Nestle             | Lactose free, Age 2-10 yrs  |
|   | Similac total comfort | Abbott             | Has lactose, 100% Whey, Age <2 y  |
| Extensively hydrolysed                          | Alimentum             | Abbott             | Lactose free Casein based, Age <2 y   |
|   | Nutramigen LGG        | Mead Johnson       | Lactose free, Has Lactobacillus GG  |
|   | Althera               | Nestle             | Has lactose, 100% whey  |
|   | Alfare                | Nestle             | Lactose free, 100% whey   |
|   | Amino acid-based      | Neocate LCP        | Nutricia  |
|   | Alfamino              | Nestle             | Age <1 y  |
|   | EleCare Infant        | Abbott             | Age <1 y  |
|   | EleCare Jr            | Abbott             | Age 1-2y  |
| <i>Medium chain triglyceride based formulas</i> |                       |                    |   |
| For infants/children                            | Monogen               | Nutricia           | 420 kcal, Protein: 12.5g, Fat: 11g, MCT 84%   |
| For infants                                     | Pregestimil           | Mead Johnson       | 500 kcal, Protein: 14g, Fat: 28g, MCT 55%, Lactose free, Extensively hydrolyzed.              |
| For infants/children                            | Metanutrition LD      | Pristine Organics  | 462 kcal, Protein: 12.5g, Fat: 20g, MCT 80%.  |
| > 2 years of age                                | PediaGold plus        | Hexagon Nutrition  | 475 kcal, Protein: 14.25g (whey peptide) Fat: 18.5g, MCT 70%, Gluten <i>and</i> lactose free. |

**Table II Comparison of Extensively Hydrolyzed and Partially Hydrolyzed Formula**

| Contents*        | Extensively hydrolyzed           | Partially hydrolyzed      |
|------------------|----------------------------------|---------------------------|
| Energy (kcal)    | 70                               | 70                        |
| Protein (g)      | 1.8                              | 1.3                       |
| Maximum MW       | <1.2 kDa peptide                 | <10 kDa peptide           |
| Carbohydrate (g) | #7.8 (as Dextrin, starch, sugar) | 8.7 (as Dextrin, Lactose) |
| Fat (g)          | 3.5                              | 3.3                       |
| LCT (%)          | 75                               | 83.0                      |
| MCT (%)          | 25.0                             | 17.0                      |

\*Per 100 g; Protein source for both formulas is casein hydrolysate; LCT: Long chain triglycerides; MCT: Medium chain triglycerides; MW: Molecular weight; #some are lactose free.

healthy population. While some studies in high-risk infants with an individual formula have shown benefit, these benefits have not been universally reproduced with other pHFs [14,15]. It is therefore important to evaluate the clinical evidence of each pHF from an allergy prevention perspective. pHF contain lactose and so cannot be used in galactosemia or lactose intolerance. Their taste is not comparable to standard infant formula, but is not as unpleasant as the extensively hydrolyzed formula.

#### Extensively Hydrolyzed Formulas (eHF)

eHF is made by hydrolyzing milk protein to a peptide size that does not usually elicit an immune response [16]. Most eHF are lactose-free and the main source of carbohydrate is malt dextrin, with the remainder being, sugar, starch and corn syrup. Vegetable oil or MCT oil is the source of fat, which is easily absorbed, and also

contains essential fatty acids. The formula has a relatively high osmolality, and can sometimes cause osmotic diarrhea. They are recommended in the treatment of cow's milk and soy protein allergy. However, since antigenicity has not been totally eliminated, a few children with severe disease may not respond [17]. eHF can also be used in those with serious malabsorption due to intestine failure, short bowel syndrome, as well as, Crohn disease and pancreatic disease. Those eHF that do not contain lactose can be used for galactosemia or lactose intolerance. The role of these formulas in prevention of allergies and autoimmune diseases is controversial [17]. Few studies are available which report some benefit in adding the probiotic lactobacillus GG in eHF to enhance the immune regulatory mechanism and lead to earlier immune tolerance [18,19]. However, evidence is insufficient to recommend addition of probiotics in eHF. Palatability is an issue, but eHF taste better than amino acid-based formula.

### Amino Acid-based Formulas

Amino acid-based formula has no peptide at all and the protein is in the form of free amino acids. It is lactose free and the source of fat is MCT oil. In children with milk or soy protein allergy, this formula can be used in the small minority of patients who do not respond to eHF [20,21]. It can also be used as an enteral nutrition therapy for individuals with Crohn disease (polymeric formulas are equally good) as well as in children with severe malabsorption from diffuse intestinal mucosal disease; who do not respond to eHF.

### MEDIUM-CHAIN TRIGLYCERIDES-BASED FORMULAS

MCTs are triglycerides whose fatty acids have an aliphatic chain of 6–12 carbon atoms. They passively diffuse from the GI tract to the portal system without emulsification, unlike long-chain fatty acids (LCTs) or very-long-chain fatty acids. Thus they are not dependent on bile salts or lipase for absorption. The energy-enhancing properties of MCTs are attributed to the fact that they cross the double mitochondrial membrane rapidly, and do not require the presence of carnitine, unlike LCTs [22].

There is no clear guideline regarding the percentage of MCT that needs to be in a formula for it to be classified as MCT formula. Most commercially available preparations have between 30% and 80% MCT. **Table I** gives the various MCT formulas presently available in India. MCTs provide about 10% fewer calories than LCTs (8.3 calories/g for MCTs vs 9 calories/g for LCTs);

thus, it should be supplemented. All MCT formulas have relatively higher osmolality, and hence should be introduced at lower concentrations [22]. Their use should be strictly limited to specified medical indications, and these are not recommended to complement standard formulas for healthy children.

The common indications of MCT-based formulas are given in **Box I** [23].

*Liver disease:* Growth failure and malnutrition are important components that need to be addressed in patients with liver disease. Nutritional need depends on the type of liver disease (cholestatic or hepatocellular, acute or chronic), severity of the disease as well as age of the patient. In patients with chronic liver disease (CLD) malnutrition and negative nitrogen balance are negative prognostic indicators for overall survival [24].

Estimated energy requirement (EER) in children with CLD can be up to 140% nutrient reference value for age or 120–150 kcal/kg/day initially [25]. MCT-based diets are the standard in CLD, particularly when there is significant cholestasis. It is recommended that between 30% and 50% of the fat requirement should be provided as MCT. In children with cholestatic CLD, long chain polyunsaturated fatty acid (LCPUFA) metabolism is disturbed and therefore more than 10% of total energy should be provided as PUFA [26]. In older children, LCPUFA containing foods like Canola, sunflower, soybean oils, walnut oil, fish oil and egg yolk can be added to the diet. Children with CLD have deranged amino acid metabolism, with lower levels of branched-chain amino acids (BCAA) and elevated aromatic amino acids. Some studies have shown that adding BCAA to feeds can improve nitrogen retention, reduce protein catabolism

#### Box I Indications for Medium-chain Triglyceride Formulas

- Liver disease, particularly cholestatic liver disease
- Malabsorption with steatorrhea
- Malnutrition (Preoperative and postoperative)
- Primary intestinal lymphangiectasia
- Chylolthorax
- Long chain acyl-CoA dehydrogenase (LCHAD) deficiency
- Carnitine palmitoyl transferase deficiency (CPTD)
- Primary and secondary lipoprotein lipase deficiency
- Short bowel syndrome
- Inflammatory bowel disease
- Cystic fibrosis

and increase protein synthesis [27]. CLD patients have deranged gluco-neogenesis as well as delayed insulin catabolism and so are at increased risk for hypoglycemia in fasting state. Hence, adequate amount of simple carbohydrate need to be provided in the formula or diet.

### **Specific formulas for Inborn Errors of Metabolism**

Inborn errors of metabolism (IEM) are a group of genetic disorders where a specific enzyme deficiency causes block in a metabolic pathway leading to clinically significant consequences [28]. The disease state is a consequence of any of the following:

- The block can lead on to non-availability of essential substrates that are required for normal metabolism *e.g.* glucose production from glycogen is affected in GSD leading to non-availability of glucose
- The intermediary product that builds up due to the block can be toxic *e.g.* build up of leucine in maple syrup urine disease.
- The intermediary product is converted to a toxic by product causing clinical manifestation *e.g.* succinylacetone in tyrosinemia
- The intermediary product that builds up in sub-cellular level impacts the cellular physiology (lysosomal/peroxisomal storage disorders *e.g.* lysosomal acid lipase deficiency)

Management of these patients aims to remove the offending substance from diet and/or to supplement the end product that is essential for metabolism. Disease-specific proprietary foods are now available with absent specific carbohydrate, amino acids or fatty acids [29]. However, it needs to be stressed that diet plan has to be individualized even when patients have the same disease. Essential amino acids as the name suggests are required for anabolism. Therefore children with metabolic defects involving essential amino acids require their supplementation at minimum daily requirements. Their total avoidance could result not only in relevant symptoms but also in poor growth, while any excess would lead to metabolic decompensation. This is the concept of 'metabolic paradox'.

Details of individual IEMs are beyond the purview of this paper and readers are advised to refer to standard textbooks. **Web Tables I, II and III** give the various formulas currently available for disorders of carbohydrate, protein and lipid metabolism, respectively.

### **CONCLUSIONS**

The four basic categories of formulas available in India are the lactose modified, hydrolyzed, MCT-based and

metabolic-disease specific formulas. Lactose modified formulas are either casein- or soy protein-based. Most children with acute diarrhea do not need a lactose free diet, though some may need a low lactose diet. Soy protein formulas, are best avoided below 6 months of age. Hydrolyzed formulas are either partially or extensively hydrolyzed or amino acid-based. Extensively hydrolyzed formula should be the first choice in milk protein allergy. Amino acid formula, also called elemental formula, are needed only in a minority of children with cow's milk protein allergy or diffuse intestinal disease, who do not respond to eHF. MCT formulas are used in chronic liver disease particularly with cholestasis. Formulas for inborn errors of metabolism are free of the specific carbohydrate, amino acid or fatty acid. Choice of such formula and diet for metabolic diseases should be individualized and made in consultation with a specialist.

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*Disclaimer:* This paper does not claim to enumerate all the products available in market, and the purpose is to give only an overview. Although authors have taken extreme care in reviewing the proprietary food products, we strongly recommend checking product information resources. The FSSAI licenses are for a limited period and companies are expected to renew it at the appropriate time. It is also advisable to consult the appropriate specialists, if necessary, before disease-specific formulas are used.

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**Web Table I Formulas for Carbohydrate Metabolism Disorders**

| <i>Metabolic disease and dietary intervention</i>                    | <i>Products and age recommended</i>                            | <i>Company</i>    | <i>Remarks (Nutrients/100 g)</i>   |
|--|--|-------------------|--|
| Galactosemia diet - Galactose free                                   | Galactomin 17  | Nutricia          | 514 kcal, Protein Eq: 10.3g, Fat: 27.3g, CHO: 57.1g.   |
|  | Milupa basic; Infants/toddlers                                 | Nutricia          | 645 kcal, Protein: 28.3g, Fat: 58g, CHO: <0.1g   |
|  | Metanutrition GLC Infants/Children                             | Pristine Organics | 528 kcal, Protein Eq: 14.4g, Fat: 30g, CHO: 50g  |
|  | Pregestimil; Infants   | Mead Johnson      | 500 kcal, Protein: 14g, Fat: 28g, CHO: 51g. MCT 55%, Lactose free Extensively hydrolysed casein. |
| Other carbohydrate metabolism disorders diet - Free/Low carbohydrate | Nutramigen LGG; Infants  | Mead Johnson      | Same as pregestimil, but fat: 26g, CHO: 55 g.  |
|  | Milupa basic-ch; Infants/toddlers                              | Nutricia          | Details under galactosemia. Also suitable for Ketogenic diet                                     |
|  | RCF (Ross Carbohydrate free); Infants                          | Abbott Healthcare | Per100mL. 81 kcal, Protein: 4g, Fat:7.2g,CHO:0.07g, Soy base, Gluten free. Ketogenic diet.       |
|  | Metanutrition CMD; Infants/Children                            | Pristine Organics | 538 kcal, Protein Eq: 22g, Fat: 50g, No CHO  |
|  | Metanutrition GTD (Glucose transport defect); Infants/Children | Pristine Organics | 720 kcal, Protein Eq: 14.4g, Fat: 70g, CHO: 8g. Ideal for Glucose transport defect (Glut 1 def)  |

*\*\* All lactose free soy formulas can be used in galactosemia; \*\*Other CMD disorders include Sucrase/ Isomaltase deficiency, Fructosemia, Glucose transport defect (Glut 1 def), Glucose-Galactose malabsorption etc. Formula for these should be individualized and chosen in consultation with a specialist; \*\*All the above free/low carbohydrate diet contains essential/non-essential amino acids, fats, vitamins and minerals.*

Web Table II FORMULAS FOR PROTEIN/AMINO ACID METABOLISM DISORDERS

| Metabolic disease/<br>Dietary intervention  | Products/ Age recommended  | Company           | Remarks (Nutrients/100 g)  |
|---|--|-------------------|--|
| Urea cycle disorders (UCD)/<br>Diet: Low in Non-essential amino acids. High in essential AA | Milupa UCD- 1 (Mixt)<br>Anamix; Infant UCD (Form); below 1       | Nutricia          | Milupa UCD 1: 280 kcal, Protein Eq: 50 g, Fat: 0 g, CHO: 19.9 g (After 1 y: Milupa UCD 2 - Prima Mixt)   |
|   | Cyclinex-1; Infants/toddlers                                     | Abbott            | Cyclinex 1 (Per 100 ml): 77 kcal Protein : 1 g, Fat: 4 g, CHO: 9 g (Children/adults: Cyclinex -2)  |
|   | Metanutrition UCD-1; below 3 y                                   | Pristine Organics | 483 kcal, Protein Eq: 12.5 g, Fat: 25 g, CHO: 52 g (>3 y: Metanutrition UCD-2)   |
|   | UCD Trio; above 1 y  | Nestle (Vitafo)   | 393 kcal, Protein Eq: 15 g, Fat: 14.3 g, CHO: 51 g.  |
| Phenylketonuria (PKU)/<br>Diet – Phenylalanine free   | Milupa PKU-1 (Mixture)<br>Anamix Infant PKU (Form)<br>Below 1 y  | Nutricia Intl     | Milupa PKU-1: 302 kcal, Protein: 50 g, Fat: 0 g, CHO: 25.6 g (After 1 y: Milupa PKU 2 - Prima Mixt)  |
|   | Phenex 1; Infants/toddlers                                       | Abbott Healthcare | Phenex 1 (Per 100 mL): 72 kcal, Protein Eq: 2 g, Fat: 3 g, CHO: 8 g. (After 3 y: Phenex 2)   |
|   | Phenyl-Free-1; For infants                                       | Mead Johnson      | 500 kcal, Protein: 16.2 g, Fat: 26 g, CHO: 51 g. Iron fortified.   |
|   | Metanutrition PKU-1; below 3 y                                   | Pristine Organics | 483 kcal, Protein: 12.5 g, Fat: 25 g, CHO: 52 g (Above 3 y: Metanutrition PKU-2/3)   |
|   | PKU Gel; 6 mo to 10 y  | Nestle (Vitafo)   | 339 kcal, Protein Eq: 41.7 g, Fat: 0.05 g, CHO: 42.9 g 405 kcal, Protein: 30 g, Fat: 14.3 g, CHO: 38.9 g. Contains milk and soya. 297 kcal, Protein: 60 g, Fat: 0.2 g, CHO: 13.7 g. Contains soya. |
| Tyrosinemia (TYR)<br>Diet – Phenylalanine and Tyrosine free                                 | Milupa TYR-1 (Mixture)<br>Anamix Infant TYR (Form);<br>Below 1 y | Nutricia          | Milupa TYR -1: 302 kcal, Protein: 50 g, Fat: 0 g, CHO: 25.6 g (Above 1 y: Milupa TYR 2 - Prima Mixt)   |
|   | Tyrex- 1; Infants/toddlers                                       | Abbott            | Tyrex 1 (Per 100 mL): 72 kcal, Protein: 2.25g, Fat: 3.25g, CHO: 7.95g, has L-carnitine and taurine (Children/adults: Tyrex-2)  |
|   | Tyros 1; for infants<br>Mead Johnson                             | Mead Johnson      | 500 kcal, Protein: 16.7g, Fat: 26g, CHO: 51g; Iron fortified   |
|   | Metanutrition Tyros-1; below 3 y                                 | Pristine Organics | 483 kcal, Protein: 12.5g, Fat: 25g, CHO: 52g (Above 3 y: Metanutrition Tyros-2)  |
|   | TYR Gel; 6 mo to 10 y<br>TYR Express; above 3 y                  | Nestle (Vitafo)   | TYR gel : 339 kcal, Protein: 41.7 g, Fat: 0.05 g, CHO: 42.9 g 297 kcal, Protein: 60 g, Fat: 0.2 g, CHO: 13.7 g. Contains soya.   |

Contd....

Web Table II continued

| Metabolic disease/<br>Dietary intervention  | Products/ Age recommended  | Company                                       | Remarks (Nutrients/100 gm)   |
|---|--|---|--|
| Homocystinuria<br>(HCU)/<br>Diet – Methionine free  | Milupa HOM-1 Mixt<br>Anamix infant HCU Form; below 1 y<br>Hominex-1; below 3 y                               | Nutricia<br>Abbott Healthcare                 | Milupa HOM-1: 302 kcal, Protein: 50 g, Fat: 0 g, CHO: 25.6 g<br>(Above 1 y: Milupa HOM 2-prima Mixt)<br>Hominex-1 (Per 100 mL): 72 kcal, Protein: 2 g, Fat: 3 g, CHO: 8 g,<br>(Above 3 y: Hominex-2)   |
|   | Metanutrition HCY-1;<br>Below 3 y  | Pristine Organics                             | 483 kcal, Protein Eq: 12.5g, Fat: 25 g, CHO: 52 g<br>(Above 3 y: Metanutrition HCY 2)  |
|   | HCU Gel; Above 3 y<br>6 mo to 10 y: HCU Express  | Nestle (Vitafo)                               | 339 kcal, Protein Eq: 41.7 g, Fat: 0.05 g, CHO: 42.9 g, 297 kcal,<br>Protein: 60 g, Fat: 0.2 g, CHO: 13.7 g. Contains soya.  |
| Maple syrup urine<br>disease (MSUD)/<br>Diet – Leucine,<br>Isoleucine and Valine free   | Milupa MSUD-1 Mixt<br>Anamix Infant MSUD Form; below 1 y<br>Ketonex-1<br>Below 3 y                           | Nutricia<br>Abbott                            | Milupa MSUD-1: 302 kcal, Protein: 50 g, Fat: 0 g, CHO: 25.6 g<br>(Above 1 y: Milupa MSUD-2 prima Mixt)<br>Ketonex-1 (Per 100mL): 72 kcal, Protein: 2 g, Fat: 3 g, CHO: 8 g<br>(above 3 y: Ketonex-2)   |
|   | BCAD-1, below 1 y<br>Metanutrition MSUD-1 below 3 y  | Mead Johnson<br>Pristine Organics             | 500 kcal, Protein: 16.2 g, Fat: 26 g, CHO: 51 g. Iron fortified<br>483 kcal, Protein: 12.5 g, Fat: 25 g, CHO: 52 g (above 3 y<br>Metanutrition MSUD-2)   |
|   | MSUD Gel; 6 mo to 10 yrs<br>MSUD Express; above 3 y  | Nestle (Vitafo)                               | 339 kcal, Protein: 41.7 g, Fat: 0.05 g, CHO: 42.9 g, 297 kcal, Protein Eq:<br>60 g, Fat: 0.2 g, CHO: 13.7 g. Contains soya.  |
| Methylmalonic acidemia<br>and Propionic acidemia<br>(MMA/PA)/<br>Diet – Methionine and Valine -<br>Free and Isoleucine and<br>Threonine -Low/free | Milupa OS-1 Mixt<br>Anamix Infant MMA/PPA; below 1 y<br>OA 1; below 1 y<br>Metanutrition MMA/PA-1; below 3 y | Nutricia<br>Mead Johnson<br>Pristine Organics | Milupa OS-1: 286 kcal, Protein Eq: 50 g, Fat: 0 g, CHO: 21.5 g<br>(above 1 y: Milupa OS 2 - Prima Mixt)  |
|   | MMA/PA Gel; 6 mo to 10 y<br>MMA/PAExpress above 3 y  | Nestle (Vitafo)                               | 500 kcal, Protein: 15.7 g, Fat: 26 g, CHO: 51 g<br>483 kcal, Protein: 12.5 g, Fat: 25 g, CHO: 52 g (above 3 y:<br>Metanutrition MMA/PA-2)  |
| Isovaleric acidemia (IVA)/<br>Diet – Leucine free   | Milupa LEU-1 Mixt.<br>Anamix infant IVA Form; below 1 y<br>I-Valex-1; below 3 y                              | Nutricia<br>Abbott                            | 339 kcal, Protein Eq: 41.7 g, Fat: 0.05 g, CHO: 42.9 g, 297 kcal,<br>Protein Eq: 60 g, Fat: 0.2 g, CHO: 13.7 g. Contains soya<br>Milupa LEU-1: 286 kcal, Protein : 50 g, Fat: 0 g, CHO: 21.5 g<br>(Above 1 y: Milupa LEU 2-prima Mixt)<br>I-Valex-1 (Per 100 mL): 72 kcal, Protein: 2 g, Fat: 3 g, CHO: 8 g,<br>(above 3 y: I-Valex-2) |
|   | Metanutrition IVA-1; below 3 y   | Pristine Organics                             | 483 kcal, Protein: 12.5 g, Fat: 25 g, CHO: 52 g<br>(Above 3 y: Metanutrition IVA-2)  |

Contd....

Web Table II continued

| <i>Metabolic disease/<br/>Dietary intervention</i>  | <i>Products/ Age recommended</i>   | <i>Company</i>   | <i>Remarks (Nutrients/100 gm)</i>  |
|---|--|--|--|
| Glutaric acidemia<br>Type I (GA I)  | Milupa GA-1 Mixt<br>Anamix infant GA I Form; below 1 y   | Nutricia   | Milupa GA-1: 290 kcal, Protein: 50 g, Fat: 0 g, CHO: 22.4 g (above 1 y; Milupa GA2-prima Mixt)   |
| Diet – Lysine free and<br>Tryptophan - Low/free   | Glutarex-1; below 3 y<br><br>Metanutrition GA-1; below 3 y   | Abbott Healthcare<br><br>Pristine Organics                         | Glutarex (Per 100 mL): 72 kcal, Protein: 2 g, Fat: 3 g, CHO: 8 g, (above 3 y; Glutarex-2)<br>483 kcal Protein: 12.5 g, Fat: 25g, CHO: 52 g. (Above 3 y; Metanutrition GA-2)  |
| Hyperlysinemia/<br>Diet – Lysine free   | GA 1 Gel6; mo to 10 y<br>GA 1 Express; above 3 y<br>Milupa LYS-1 Mixt; below 1 y   | Nestle (Vitaflo)<br><br>Nutricia                                   | 339 kcal, Protein: 41.7 g, Fat: 0.05 g, CHO: 42.9 g 297 kcal, Protein: 60 g, Fat: 0.2 g, CHO: 13.7 g. Contains soya<br>290 kcal, Protein : 50g, Fat: 0 g, CHO: 22.4 g May use in pyridoxine dependent epilepsy in infants (Above 1 y: Milupa LYS 2-prima Mixt)     |
| Non-ketotic hyper<br>glycinemia (Glycine<br>encephalopathy);/<br>Diet – Protein free,<br>dietary intervention<br>limited role | Milupa Basic – p; Infants<br>Metanutrition HLP; Any age<br>Pro-Phree; Infants/toddlers                                   | Nutricia<br>Pristine Organics<br>Abbott Healthcare                 | 536 kcal Protein Eq: 0g, Fat: 32 g, CHO: 62 g<br>535 kcal, Protein: 0 g, Fat: 25 g, CHO: 70 g<br>Per 100 mL: 77 kcal, Protein Eq: 0 g, Fat: 4 g, CHO: 10 g.  |
| *Protein and Aminoacid<br>free formulas   | Milupa Basic-p; infants<br>Pro-Phree; infants/toddlers<br>PFD; toddler young children<br>Metanutrition AAMD-1; below 3 y | Nutricia<br>Abbott Healthcare<br>Mead Johnson<br>Pristine Organics | 536 kcal Protein Eq: 0 g Fat: 32 g, CHO: 62 g<br>Per 100 mL: 77 kcal, Protein: 0 g, Fat: 4 g, CHO: 10 g.<br>530 kcal, Protein: 0 g, Fat: 32 g, CHO: 60 g.<br>Metanutrition AAMD-1: 385 kcal, Protein: 0 g, Fat: 5 g, CHO: 85 g<br>(above 3 y Metanutrition AAMD-2) |

*CHO: Carbohydrate; AA: Aminoacids; Gel (Vitaflo, Nestle) - Concentrated powdered protein which when mixed up with water is easily made to a smooth, semisolid consistency. Available as pre-measured sachet, 10 gm Protein Eq per sachet. Suitable from 6 months to 10 years of age. Available for PKU, TYR, MSUD, HCU, MMA/PA and GA I; Trio (Vitaflo, Nestle) – Powdered protein substitute. Contains milk and soya. Suitable from 1 year of age. Available for UCD and PKU; Express (Vitaflo, Nestle) – Powdered protein substitute. Available as pre-weighed sachets, 15 gm protein equivalent. Contains soya. Suitable from 3 years of age. Available for PKU, TYR, MSUD, HCU, MMA/PA and GA I; Gel, Trio and Express contain essential and non-essential aminoacids (but excluding the offending aminoacids), carbohydrate, vitamins, minerals and trace element; Mixtures (Mixt) should be taken mixed with calculated amount of food or drink. Formula (Form) can be used as a supplementary feed upto 3 yrs; \*Recommended as emergency regimen in sick patients with suspected Amino acidemias, Organic acidurias, Urea cycle disorders.*

**Web Table III Formulas for Lipid Metabolism Disorders**

| <i>Diseases/diet intervention</i>                  | <i>Products</i>  | <i>Company</i>       | <i>Remarks (Nutrients/100 g)</i>  |
|--|--|----------------------|---|
| Lipid Metabolism disorders (LMD)/<br>diet: Low fat | Milupa Basic-f; Infants/toddlers   | Nutricia             | 374 kcal, Protein: 14 g, Fat: <0.5 g, CHO: 79 g.  |
|  | Monogen; Infants/ children   | Nutricia             | 420 kcal, Protein: 12.5 g (Whey based), Fat: 11 g, (MCT 84%), CHO: 68 g.  |
|  | ProViMin; Infants/ children  | Abbott               | Per 100 mL: 62.6 kcal, Protein: 14.6 g (Casein based), Fat: 0.3 g, CHO: 0.4 g.  |
|  | Metanutrition LD (Lipid disorders);<br>Infants/children                                | Pristine<br>Organics | 462 kcal, Protein Eq: 12.5 g, Fat: 20 g, CHO: 58 g.<br>MCT 80%.   |
|  | Metanutrition LCHAD (Long chain<br>hydroxyacyl-CoA dehydrogenase);<br>Infants/children | Pristine<br>Organics | 520 kcal, Protein: 12.5 g, Fat: 30 g, CHO: 50 g.<br>Long chain triglycerides (LCT) free. Indicated in<br>LCHAD deficiency |

*\*\* LMD include Fatty acid oxidation disorder, Severe cholestais, Intestinal lymphangiectasia, Abeta/Hypobetalipoproteinemia, Chylothorax, Malabsorption and Maldigestion of fats. Formula for these should be individualized and chosen in consultation with a specialist.*

## An Infant with Severe Anemia and Hypoalbuminemia

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We discuss the case of a two-month-old girl admitted with complaints of progressive pallor, generalized body swelling and pale colored stool since the neonatal period. On examination, severe pallor, chubby cheeks and moderate hepatomegaly were noted. Investigations revealed isolated anemia, transaminitis, conjugated hyperbilirubinemia, prolonged prothrombin time and hyperlipidemia. She died due to severe sepsis, shock, and pulmonary hemorrhage. An autopsy revealed characteristic histopathology findings of cystic fibrosis in the liver, lungs, and pancreas. Genetic analysis performed on autopsy tissue was positive for F508del compound heterozygous (WT/F508del) mutation, confirming the diagnosis of cystic fibrosis.

**Keywords:** Autopsy, Cholestatic jaundice, Cystic Fibrosis.

### CLINICAL PROTOCOL

*History:* A two-month-old girl, a product of non-consanguineous marriage, presented with complaints of gradually increasing generalized body swelling starting from the age of 15-20 days. It was associated with progressive pallor, for which she had received one packed red blood cell (PRBC) transfusion at 1½ month of age. Since one month of age, she had passed 8-10 pale-colored semisolid stools per day. She also had fast breathing for 15 days prior to admission. There was no history of jaundice, high colored urine, bleeding from any site, mucus in stool, lethargy, poor feeding, irritability, seizures, and encephalopathy. She was born at term gestation with a birthweight of 2.3 kg and was admitted in the intensive care unit for five days in view of abdominal distension and respiratory distress since birth. She passed meconium at the end of day 2 of life, following which abdominal distension resolved. The baby was exclusively breastfed, immunized for age and developmentally normal for age. The elder sibling had a tracheo-esophageal fistula and had died on day two of life.

*Clinical examination:* At admission, she was alert and active with a heart rate of 128/min, respiratory rate of 58/min, good volume pulses, normal capillary refill time, and 100% oxygen saturation on room air. She had severe pallor and anasarca. She weighed 3.5 kg (-4.28 Z) and the occipitofrontal circumference was 34.1 cm (-4.51 Z). The baby had very prominent chubby cheeks. Respiratory system examination showed bilateral basal crepitations. The abdomen was distended with liver being palpable 6

cm below right costal margin and 3 cm below the left costal margin in the midclavicular line (span 9-10 cm), soft-to-firm in consistency, non-tender, with ill-defined borders. The spleen was not palpable. Examination of cardiovascular system and central nervous system was normal. Fundus examination did not show any chorioretinitis or cherry red spot.

*Laboratory investigations:* She had normocytic normochromic anemia (haemoglobin 6.5 g/dL), leukocytosis (white cell count 34,360/μL, differential counts (53% polymorphs), normal platelet count, transaminitis (alanine aminotransferase – 79 IU/L and aspartate aminotransferase – 367 IU/L), cholestatic jaundice (total bilirubin – 4 mg/dL, direct – 3.3 mg/dL), severe hypoalbuminemia (1.5 g/dL), deranged coagulation profile (prothrombin time – 20.9 seconds, activated thromboplastin time – 44.6 seconds) and hyperlipidemia (total cholesterol – 255 mg/dL, triglyceride – 289 mg/dL) and a high C-reactive protein (33.6 mg/L). Arterial blood gas analysis revealed respiratory alkalosis. She also had persistent hyponatremia (126 mEq/L) and hypochloremia (93 mEq/L). Chest radiograph, stool examination, immunoglobulin profile (IgG- 346 mg/dl, IgA- 51 mg/dL), and T-cell subset assay (CD3+= 55.43%, CD 19+= 32.34%, CD56+=4.84%, CD3+ CD56+=0.46%) were normal. Blood sugar was 96 mg/dL and serum ammonia was 225.8 μmol/L. Urinary aminoacidogram could not be done. Human immunodeficiency virus, cytomegalovirus, and toxoplasma serology were negative. Ultrasound abdomen showed hepatomegaly with normal liver echotexture. The cranial ultrasound did not show any structural

malformation or calcification. The blood culture sent at presentation was sterile; however, repeat blood culture sent on day 4 grew *Staphylococcus hominis* (sensitive to ciprofloxacin, clindamycin, teicoplanin and vancomycin; oxacillin and erythromycin).

*Course management:* The infant received intravenous cefotaxime, cholestatic regimen [1] and PRBC transfusion. On day 3 of hospital stay, she had one episode of fresh blood in stool along with deranged coagulation profile; therefore, fresh frozen plasma was transfused. However, on the next day she worsened further in the form of tachycardia, poor pulses, and prolonged capillary refill time, for which antibiotics were empirically upgraded to vancomycin, meropenem and amphotericin B. Fluid bolus and inotropic support was given for the shock. On day 5 of hospital stay, she had further cardiorespiratory worsening for which she was intubated and kept on manual intermittent positive pressure respiration. On the same day she developed hypocalcemia and hypokalemia requiring correction. She deteriorated further and received intravenous immunoglobulin, multiple fluid boluses and inotropes (dopamine, dobutamine, and adrenaline). However, she had worsening of shock and hypoxemia followed by massive pulmonary haemorrhage leading to cardiac arrest and death on day 5 of hospital stay.

*Unit's final diagnosis:* Glycogen storage disorder with refractory septic shock and pulmonary hemorrhage.

## DISCUSSION

*Clinical discussant:* We have a two-month-old girl presenting with severe pallor, anasarca, pale stool, chubby cheeks, failure to thrive, microcephaly, moderate hepatomegaly, transaminitis, cholestatic jaundice, and hyperlipidemia. She had isolated normocytic normochromic anemia, with deranged coagulation profile and required two blood transfusions during the initial two months of life. This case can be analyzed with respect to underlying disease and the pre-terminal events. The primary analysis suggests multi-system disease with predominant hepatic involvement. There are many causes of isolated hepatomegaly with the above findings. Of these, intrauterine infections (TORCH), hemophagocytic syndrome and metabolic/storage disorders can present like this child. Intrauterine infections (particularly CMV and toxoplasma) are unlikely in the absence of splenomegaly, thrombocytopenia, chorioretinitis, hepatic, and cerebral calcification. Moreover, the serology for CMV and toxoplasma was negative. Hemophagocytic syndrome is also unlikely in the absence of fever, splenomegaly, and bicytopenia. The NK cell activity was also normal. The possible storage/

metabolic disorders can be glycogen storage disorder (GSD), lipid storage disorder (Gaucher and Niemann-Pick disease), iron storage (neonatal hemochromatosis due to gestational alloimmune liver disease, GALD), alpha-1 antitrypsin deficiency, galactosemia, cystic fibrosis (CF), and citrin deficiency. However, in the absence of splenomegaly, thrombocytopenia, cardiac malformation, and cherry-red spot; lipid storage disorders are less likely. GALD is less likely as it starts from fetal life itself and frequently present in the early neonatal period with prematurity, acute hepatic failure, very high bilirubin, hydrops, and renal failure. Alpha -1 antitrypsin deficiency can have similar presentation, but lack of respiratory symptoms, splenomegaly, and chubby cheeks make it less likely. Presence of chubby cheeks and lack of significant coagulopathy are against galactosemia. The rest of the metabolic disorders (GSD, citrin deficiency and CF) are strong possibilities. Among GSDs; type I, III, VI, and IX have a predominant hepatic presentation with moderate hepatomegaly, but only GSD type I can lead to severe anemia at this age. However, the presence of significant microcephaly, severe hypoalbuminemia, prolonged PT/APTT and lack of hypoglycemia even in extreme sickness is against GSD type I.

Citrin deficiency has a wide spectrum and can present in infancy as Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) and/or Failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD) [2]. The classical features of citrin deficiency are low birth weight, intrauterine growth restriction, microcephaly, chubby cheeks due to excessive lipid deposition, hepatomegaly, neonatal cholestasis, features of liver failure and hemolytic anemia. They also have mild hyperammonemia, hyperlipidemia, increased alpha-fetoprotein, and fatty liver. Diagnosis is based on abnormal newborn screen (aminoaciduria) followed by genetic analysis. All the features in the index case are consistent with the citrin deficiency except, normocytic anemia, hyponatremia, hypochloremia, and pulmonary symptoms. However, chubby cheeks with predominant hepatic manifestations are classical of GSD and citrin deficiency. Since GSD is less likely in this case, citrin deficiency may be considered as a strong differential diagnosis.

Cystic fibrosis-associated liver disease (CFLD) can present in early infancy with features of hepatomegaly, cholestasis, transaminitis, dyslipidemia, and severe anemia along with hypoalbuminemia. Severe anemia can be the first sign of cystic fibrosis in 7-10 % of infants with cystic fibrosis and the concomitant presence of severe hypoalbuminemia makes it more likely [3]. The anemia of CF is normocytic normochromic and may precede several



months of respiratory symptoms. The index case also has delayed passage of meconium along with hyponatremia and hypochloremia, further favoring the diagnosis of CF. However, the presence of chubby cheeks and normal liver echotexture is not consistent with CF. Overall, citrin deficiency and CF are the most likely clinical differential diagnosis in the index case. The prominence of chubby cheeks strongly favors citrin deficiency. However, disregarding chubby cheeks, the clinical picture is consistent with CF.

In terminal stages, the infant had severe sepsis (most likely of bacterial origin) characterized by increasing CRP, high leukocyte count, and decreasing platelets. She developed refractory septic shock leading to multiorgan dysfunction and subsequently died.

*Chairperson:* As per the clinical experience of the unit; which is most common among GSD, Citrin deficiency, and CF?

*Pediatric gastroenterologist 1:* During hospitalisation, GSD was our first possibility. However, on retrospective analysis of the biochemical profile (AST much higher than ALT, dyslipidemia, lack of hypoglycemia and lactic acidosis) in the presence of very prominent chubby cheeks developing over two months, citrin deficiency seems more likely. Citrin deficiency has been described over the last few years, primarily from Japan and South East Asia. It is perceived to be rare, though not uncommon. However, it is unlikely that this case will have a definite histopathological picture of citrin deficiency. In our experience, GSD is the most common clinical condition. However, recently we were able to diagnose a few cases of citrin deficiency too. The children with citrin deficiency generally do well and improve over a period of time. This child died because of sepsis, not of citrin deficiency *per se*.

*Pediatric pulmonologist:* There was delayed passage of meconium with some component of diarrhea. This child is a classic picture of cystic fibrosis. The chubby cheeks may be due to hypoalbuminemia and edema which may give a false impression of good nourishment.

*Neonatologist:* In CF, we expect a low level of cholesterol, whereas the cholesterol was significantly elevated in this case.

*Pediatric Gastroenterologist 1:* Galactosemia is a mimicker of citrin deficiency. However, the chubby cheeks and lack of significant coagulopathy are strongly against it.

*Pediatric Neurologist 1:* Niemann pick type C can present like hydrops fetalis in early infancy. Tyrosinemia can also have a similar presentation.

*Pediatric Gastroenterologist 2:* Lack of splenomegaly and thrombocytopenia are against Niemann pick type C. In tyrosinemia, the prominent features are severe coagulopathy and fulminant hepatic failure, which was not seen in this case. I would like to keep the possibility of a congenital disorder of glycosylation (CDG) type Ib/Ih.

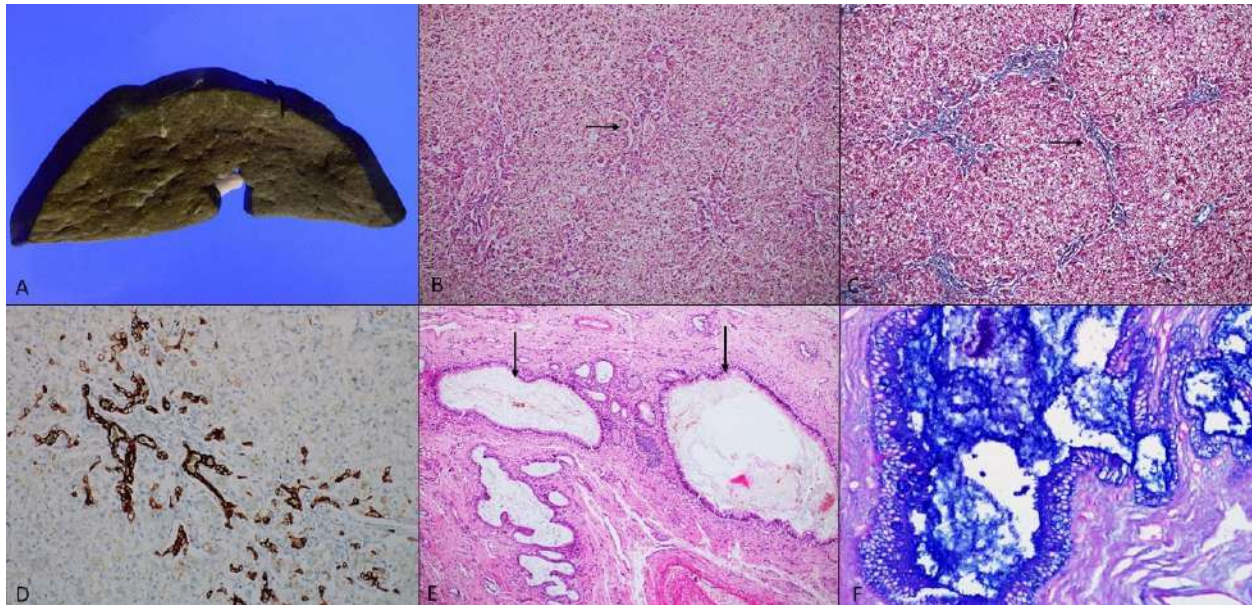
*Pediatric Neurologist 2:* Severe anemia at an early age is not usual in storage disorders. Therefore, it must be due to the marrow involvement and Pearson marrow-pancreas syndrome can be considered as a differential diagnosis. CDG also has similar features along with abnormal fat distribution.

## PATHOLOGY PROTOCOL

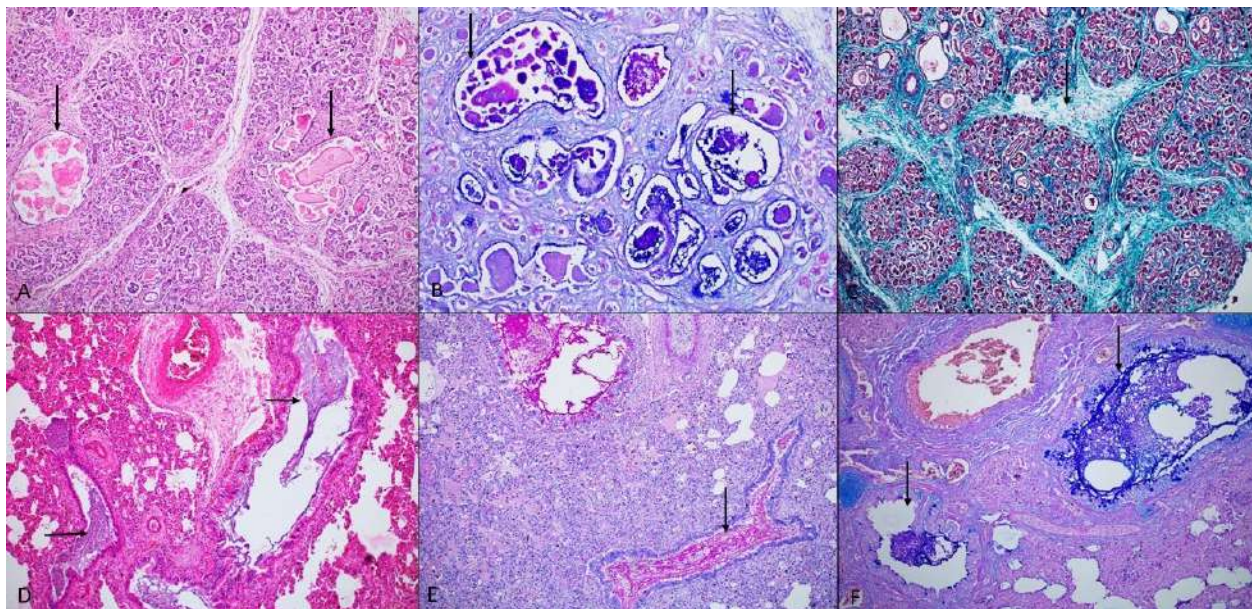
A complete autopsy was performed in the index case. There was 50 ml straw-coloured fluid in the pleural and peritoneal cavity.

Liver weighed 226 g and was slightly enlarged, soft, and bile stained (**Fig. 1**). Gall bladder was normal in size and the extrahepatic biliary tree was patent. Microscopically, the liver showed expansion of the portal tracts with mild fibrosis and extensive bile ductular proliferation. There was a focal porto-portal bridging, producing focal biliary cirrhosis. There was extensive macrovesicular steatosis, along with intrahepatocytic and intracanalicular cholestasis, producing feathery degeneration of the hepatocytes (**Fig. 1 b-d**). However, there were no PAS-positive diastase resistant inclusions in the hepatocytes. Larger bile ducts and bile ducts at porta hepatis were markedly dilated and filled with inspissated secretions. These inspissated secretions were Periodic-Acid-Schiff (PAS) positive, diastase-resistant and strongly positive for the alcian blue, indicating mucinous nature. The biliary epithelium showed evidence of mucinous metaplasia. Similar inspissated secretions were also seen in peribiliary glands (**Fig. 1 e-f**). The pancreas was firm in consistency. It showed marked dilatation of the ducts filled with inspissated secretions. There was marked intra and interlobular fibrosis with loss of acini, and focal lymphomononuclear infiltrate (**Fig. 2 a-c**). Spleen (12 g) showed normal white and red pulp. Stomach, esophagus, small intestine, and large intestine were grossly unremarkable. There were no inspissated secretions. Perl stain did not reveal any evidence of excess iron deposition in liver, spleen or pancreas.

Lung weighed 95 g and the bilateral pleura were dull. Bilateral lower lobes were consolidated. There was extensive hemorrhagic discoloration of both lungs (left > right). Sections of the lungs showed dilated bronchioles, filled with inspissated secretions. Inspissated secretions



**FIG. 1** (a) Gross photograph of liver shows extensive bile staining. (b) Liver shows irregular portal tracts (black arrow), with macrovesicular steatosis and cholestasis (hematoxylin and eosin,  $\times 100$ ). (c) Masson's trichrome highlights irregular portal fibrosis with occasional porto portal bridging (black arrow) ( $\times 100$ ). (d) Bile ductular proliferation is highlighted by cytokeratin 7 (immunohistochemistry,  $\times 200$ ). (e) Section from porta of liver shows marked dilatation of larger bile ducts, filled with inspissated secretions (black arrow) (hematoxylin and eosin,  $\times 100$ ). (f) Alcian blue-Periodic acid Schiff stain highlights the inspissated secretions and mucinous metaplasia of the biliary epithelium ( $\times 400$ ).



**FIG. 2** (a) Pancreas shows dilated ducts with inspissated secretions (black arrows) and parenchymal fibrosis (hematoxylin and eosin,  $\times 100$ ). (b) Alcian blue-Periodic acid Schiff stain highlights the inspissated secretions in the pancreatic ducts (black arrows) ( $\times 100$ ). (c) Masson's trichrome stain highlights inter and intralobular fibrosis in pancreas (black arrows) ( $\times 100$ ). (d) Section from lung shows dilated bronchioles filled with inspissated secretions (black arrows) (hematoxylin and eosin,  $\times 100$ ), which is highlighted by (e) periodic acid Schiff ( $\times 100$ ) and (f) Alcian blue stain ( $\times 100$ ).

were also seen in the main bronchus (**Fig. 2 d-f**). The subepithelial glands were hypertrophied and showed inspissated secretions. In addition, lungs showed exuberant capillary proliferation in the alveolar septa, with the capillaries infiltrating the wall of the pulmonary arteries, producing pulmonary capillary hemangiomatosis. Extensive fresh pulmonary hemorrhage was noted. Also, there was evidence of bronchopneumonia with diffuse alveolar damage.

Heart (25 g) showed normal chambers and valves. Kidneys (46 g) showed normal fetal lobulations. Microscopic examination did not reveal any pathology. Brain (491 g) showed normal sulci and gyri. No gross or microscopic pathology was seen. Bone marrow was normocellular for age and showed marked erythroid hyperplasia. Other hematopoietic lineages were adequately represented. Thymus showed extensive cystic degeneration of the Hassel corpuscles likely due to stress-induced involution.

*Genetic mutations in the CFTR gene:* Peripheral blood was collected at autopsy and was subjected to *CFTR* gene mutation by the mass array. A limited *CFTR* gene panel was examined and showed F508del compound heterozygous (WT/F508del) mutation. Mass array performed for *FIC 2* and *3* genes did not reveal any mutation.

Final autopsy diagnosis:

- Cystic fibrosis involving lung, pancreas, and liver (F508del compound heterozygous)
- Bronchopneumonia with diffuse alveolar damage
- Pulmonary capillary hemangiomatosis
- Pulmonary hemorrhage
- Erythroid hyperplasia of bone marrow

*Pediatric Pulmonologist:* The histopathology shown here is the classical book picture of cystic fibrosis. This mutation is likely a compound heterozygote and they do not have a very good phenotypic-genotypic correlation. The parents should also be evaluated for the mutation. If we would have suspected in the antemortem period, the course would have been different and treatment can be offered in earlier stages.

*Pediatric Gastroenterologist 1:* The clinical picture was not very classical of CF. Even if we would have done an antemortem percutaneous liver biopsy, the conclusive diagnosis was unlikely. The focal biliary cirrhosis is a very nonspecific finding and is seen in myriad conditions. Even sweat chloride testing is not feasible at this age. Therefore, it is very difficult to make an antemortem

diagnosis of CF at such an early age. The classical features appear during adolescence only.

*Pathologist 1:* The pulmonary capillary hyperplasia shown in histopathology is a reactive finding and is commonly observed during infancy. It should not be confused with the pulmonary capillary hemangiomatosis (PCH), which is a diagnosis of exclusion. PCH should show infiltration of pleura, septa, veins, and the vessel wall. Moreover, in PCH, the capillaries form a nodule and show multiple layers. Therefore, here it was just a reactive pulmonary capillary hyperplasia.

*Pediatric Pulmonologist:* PCH is also known to occur in CF when they develop pulmonary artery hypertension. There is hypersecretion of VEGF that leads to this finding in CF.

*Clinical discussant:* Everything was consistent with CF, but the chubby cheeks took us away from it; likely these were a manifestation of severe hypoalbuminemia.

*Pathology discussant:* The histopathology shown here is very characteristic of reactive pulmonary capillary hemangiomatosis, which can be associated with cystic fibrosis and various metabolic liver diseases.

*Pathologist 2:* Even if we would have done an antemortem liver biopsy, the diagnosis was unlikely. Here we have a whole liver, so we could show classical findings. In suspected CF, we should always look for changes in Brunner gland in the duodenum.

*Pathologist 3:* Liver biopsy plays an important role in the work-up of infantile cholestasis. Although, it may not be diagnostic in all cases, it provides important information to exclude other conditions presenting as infantile cholestasis such as congenital hepatic fibrosis, extrahepatic biliary atresia, progressive familial intrahepatic cholestasis or paucity of intrahepatic bile duct.

## DISCUSSION

Cystic fibrosis is one of the commonest life-limiting autosomal recessive monogenic disorders. Initially thought to be affecting the Caucasians only, its presence is pan-ethnic [4]. It is caused by mutations in the *CFTR* (*cystic fibrosis transmembrane conductance regulator*) gene. Till now, more than 1500 mutations have been described in CF, of which the deletion of phenylalanine at codon 508 ( $\delta F508$ ) is the commonest. Different mutations have varying genotypic effects on *CFTR* function and can result in different phenotypic expression of the disease [5,6]. The manifestations of CF may begin in early infancy itself in the form of delayed passage of meconium, meconium ileus, recurrent loose stool, malabsorption, cholestatic jaundice and failure to

thrive. Later they have recurrent respiratory infections, features of malabsorption and involvement of many other organ systems, namely endocrine, hepatobiliary and reproductive system [7].

CFLD, the liver involvement in cystic fibrosis can be found in infancy in 13%-17% cases of cystic fibrosis [8,9]. The presentation of CFLD may vary from asymptomatic transaminitis to prolonged cholestasis, hepatomegaly, and severe liver dysfunction [8]. The diagnostic criteria of CFLD comprises either a positive histopathological test (focal or multilobular biliary cirrhosis) or presence of at least two of the following criteria, evaluated at least twice a year: (i) Hepatomegaly (>2 cm below the costal margin in the midclavicular line) confirmed by ultrasound test; (ii) abnormal elevation of liver enzymes; and (iii) positive ultrasound findings (increased echogenicity of liver parenchyma, tuberosities, irregular edges and splenomegaly) [8,10]. Pulmonary complications are the predominant cause of morbidity and mortality in CF. CFLD is an evolving paradigm and is believed to be the third commonest cause of mortality in patients with CF [8].

The symptoms evolve over time, and in early infancy, anemia may be the first clinical presentation of CF [3]. These infants typically have normocytic normochromic anemia secondary to multiple etiologies like iron deficiency, chronic inflammation, vitamin E deficiency, ineffective erythropoiesis, and ongoing micro-bleeding. The anemia is often accompanied by hypoalbuminemia [11]. The severity of hypoalbuminemia can be used as a marker of severity of respiratory morbidities in later life [12]. These two manifestations can precede respiratory symptoms for many months [3]. Therefore, the concomitant presence of severe anemia and hypoalbuminemia in early infancy should raise the possibility of CF.

To establish the diagnosis of CF, sweat chloride estimation is the first test to be done, followed by *CFTR* genetic analysis, and *CFTR* physiologic tests. All individuals diagnosed with CF should have a sweat test and a *CFTR* genetic analysis performed [13]. However, in neonates and early infancy, the sweat chloride test is difficult to perform due to logistic issues; therefore the reliance is more towards the genetic analysis (*CFTR* mutation panel).

F508del is the commonest *CFTR* gene mutation in the Western population, up to the tune of 80% of all tested alleles. However, this mutation is much less commonly observed in Asian and Indian patients [14,15]. Thus, a limited mutation analysis may not be able to provide a genetic diagnosis of CF, and we may need complete *CF* gene sequencing for the confirmation of the diagnosis.

In the index case, the antemortem diagnosis could not be made, but post-mortem histopathology along with positive mutation is diagnostic of cystic fibrosis.

*Contributors:* JK: clinical protocol discussant, reviewed the literature and drafted the manuscript; DC: pathology protocol discussant, reviewed the literature and edited the manuscript; SL: treating unit consultant, provided critical inputs in the draft of the manuscript, and edited the manuscript; PK: substantial inputs in analysis of the case, critically reviewed and edited the manuscript. All the authors approved the final version of the manuscript.

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*Ethics statement:* The authors certify that the family was informed about the final diagnosis, and appropriate counselling provided.

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**Annexure I**

*Name of Discussants* (In the sequence they appear in the manuscript)

*Clinical Discussant* : Jogender Kumar

*Chairperson* : KL Gupta

*Pediatric Gastroenterologist 1* : Sadhna BLal

*Pediatric Pulmonologist* : Meenu Singh

*Neonatologist* : Sourabh Dutta

*Pediatric Neurologist 1* : Renu Suthar

*Pediatric Gastroenterologist 2* : G. Vybhav Venkatesh

*Pediatric Neurologist 2* : Arundhati B Mukherjee

*Pathologist 1* : Kirti Gupta

*Pathology discussant* : Debajyoti Chatterjee

*Pathologist 2* : Kim Vaiphei

*Pathologist 3* : Uma Nahar

**ERRATUM**

Please note following corrections in the article titled "Early Outcomes of Neonatal Cardiac Surgery in India" published in *Indian Pediatr.* 2020;57:129-32.

In Table III, third row, the unit of age should be 'day' in place of 'month.'

Appropriate corrections have already been done in the web version at <http://www.indianpediatrics.net/feb2020/129.pdf>.

## Global Strategy on Digital Health

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Digital technology has been a revolutionary foray in education, industry, research and recently, healthcare. Digital health encompasses various aspects of technology like information and communication, mobile health, data-recording and telemedicine. There has been an exponential and unregulated increase in digital health services in last few years which have raised concerns over data privacy, ethical standards and quality of services. The World Health Organization recently released the global strategy on digital health as a visionary document that provides a framework for countries to implement and expand digital health services. The following update briefly highlights the salient features of the update.

**Keywords:** eHealth strategy, Health system, Public health, Technology.

Digital technology has been a recent and innovative addition to healthcare. Healthcare delivery faces problems of high burden of infections and non-communicable diseases, dearth of human resource, inequitable distribution of healthcare, lack of personalized care and limited preparedness for emergencies in both developed and underdeveloped countries. Advances in technology have improved communication, patient outreach facilities and access to medical information. Patients have emerged as consumers and doctors as service providers, where patients now play a more participatory role in healthcare decisions. Patient-centered healthcare prompted research and development of technology, which paved way for digitalization in health care. The Sustainable development goals envision for universal access to quality healthcare with financial risk protection, which can be achieved through use of technology in a cost-effective manner [1]. A resolution was passed in May, 2018 at the 71<sup>st</sup> World Health Assembly to develop digital technology for the advancement of health of the people of the world by identifying the relevant digital services and prioritizing their use, so as to promote equitable and universal access to health for all [2].

Digital health has many facets including e-health, mobile-health (m-health), medical informatics and telemedicine. Its role has been diversified beyond just electronic data recording to telemedicine, which gives accessible and cost-effective virtual access to doctors, teleradiology for improved image interpretation, real-time data reporting, and use of mobile based applications for healthcare and therapeutics [3].

The World health organization recently announced Global strategy on digital health 2020-2024 with the vision to “improve health for everyone, everywhere by accelerating the adoption of appropriate digital health [4].” It redefines digital health to “the field of knowledge and practice associated with any aspect of adopting digital technologies to improve health, from inception to operation,” thus making it more comprehensive [4]. The strategy is aimed to facilitate countries to optimize the use of digital healthcare technology in a sustainable, equitable, accessible and scalable manner such that it enables patients to manage their health better, develop improved communication with healthcare providers and help countries monitor impact of the health policies for further improvement. Its key objectives and framework for action are shown in **Box I**. The Global Strategy also emphasizes the need to develop inter-sectoral coordination to integrate financial, organizational, human, and technology resources for best utilization of digital services.

In future, digihealth is expected to help more efficient utilization of resources to improve patient care. The National eHealth strategy toolkit formulated by WHO can help the countries integrate information and technology in their health care systems [5].

### STATUS IN INDIA

Few digital health missions already adopted by Government of India include Mother and child tracking system, hospital information system, drugs and vaccines distribution system and ASHA-Soft (an online portal by Government of Rajasthan for capturing beneficiary

### Box I Global Strategy on Digital Health 2020-24

#### Objectives

- Engage stakeholders on a shared global agenda on digital health.
- Build and consolidate global digital health capacity that reflects national needs.
- Commit and engage stakeholders to advance digital health in every country.
- Improve measurement, monitoring, research and practice in digital health.

#### Framework for action

- **Commit:** To identify the stakeholders and make them responsible. 'Champion' countries to be identified which can share their experiences about digital health and guide other stakeholders.
- **Catalyse:** To accelerate the process of developing and implementing digital health technology after a needs assessment. To facilitate collaboration between countries with common interests and create a roadmap for cooperation in development of technology and related services.
- **Measure:** To monitor for safety and effectiveness of technology with key indicators and targets. This will be able to identify redundancy and suggest further improvements.
- **Increment and iterate:** To assess the status of activities and collaborations for future recommendations and optimization.

Source: World Health Organization. *Global Strategy on Digital Health, 2020-2024* [4].

information for each ASHA and managing her incentives accordingly) [6]. In connivance with the technology reform, India set up the National health portal to provide access to medical information with integrated services like online registration system, details of nearest health facility, information, education and communication material, personalized health records, mHealth, tele-medicine, eRaktKosh and information about AYUSH/naturopathy/spirituality services [7]. The Ministry of Health and Family Welfare released the National digital health blueprint in April, 2019 [8] under the vision of National health policy, 2017. The document is an action plan to help achieve digitalization of health records at district level, maintain registries for important diseases and link primary health care services with referral care services. The other key components include creation of unique digital health ID, supply chain management for drugs, payment gateways, and provision for standards and regulations within the operating framework regarding patient safety, quality of services, privacy and data security.

Indian academy of pediatrics (IAP) has also recently launched the digital health platform in the year 2020, known as dIAP [9]. The key components include use of technology for professional education and capacity-building of pediatricians through online videos, webinars, and reference scientific content, and a personalized patient education platform that is reliable and updated for ready reference.

### CHALLENGES

Even though Digital Health seems to be a promising modality, it brings with it few challenges. Medical information can be misinterpreted by patients when acquired over casual web portals and unreliable online resources [10]. Medical devices can report data hacking and loss of data, which raises concerns over data safety and privacy [11]. The sole use of a digital platform for healthcare delivery lacks personal touch and trust in doctor-patient relationship. Lack of training of human resource in application usage and interpretation of technology also poses a threat to ethical practicing standards [11]. The implementation of digital health services will require good governance to ensure data privacy, and efficient management of available resources, while maintaining highest possible societal and ethical standards [12].

A review of 34 published studies on health governance interventions reported that strategies which used authentication of information, provided for accessibility of data for communication, and auditing with quality assurance of technology, were found supportive [13]. The European public health alliance recommended involvement of the end-user during development and implementation of digital health (person-centered care) to improve practical applicability of technology, emphasized involvement of primary and secondary health services including pharmacies, and suggested that digital health be positioned as a supplement to traditional healthcare,

instead of its alternative [14]. Similar hurdles will have to be identified and tackled during implementation of the proposed National digital health mission in India.

Digital health holds promise to be a revolutionary paradigm in improving information, education, communication, health monitoring, diagnostics and data handling. The Global strategy by WHO provides a framework for countries to develop, implement and collaborate these services in the best interest of consumers. The National Digital Health Mission can help create and deliver the most suitable personalized digital health ecosystem for India.

*Contributors:* AD: conceived the idea. Both AD and DD were involved in preparing the manuscript, and have read and approved the contents of the manuscript.

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## EVENT

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□ Nineteenth ICMR Course in Medical Genetics & Genetic Counseling: Pedigree to Genome  
17-29 August, 2020.

**Contact:** Dr. Shubha Phadke, Department of Medical Genetics, SGPGIMS, Lucknow.

shubharaophadke@gmail.com; [www.sgpgi.ac.in/conf/ICMR%20Course%202020.pdf](http://www.sgpgi.ac.in/conf/ICMR%20Course%202020.pdf)



## Ethambutol: The Turtle of the Fifty Year Race!

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As we come closer to achieve the Sustainable development goal of ending tuberculosis (TB) by 2030 [1], it is time to relook on the journey of one of the earliest discovered and effective anti-tubercular drug with a low potential for resistance – Ethambutol. This bacteriostatic drug was discovered in 1961 at the time when the then triple therapy (isoniazid, streptomycin, para-amino salicylic acid) was starting to get overpowered by resistant organisms, rising incidence of TB, and multiple side-effects [2,3].

### PAST

Almost fifty years back, Patwardhan, *et al.* [2] concluded that ethambutol-isoniazid (INH) combination was effective in treatment of primary childhood TB [2]. This conclusion was based their study on 60 children, 6 months to 5 years age, diagnosed with primary tuberculosis. The study compared three regimens: INH alone; streptomycin-INH combination; and ethambutol-INH combination. INH was dosed at 15-20 mg/kg in two divided doses whereas ethambutol was started at 25mg/kg, later reduced to 15 mg/kg as symptoms improved. Both the drugs were given for a period of one year. Streptomycin was given at 40-50 mg/kg intramuscular daily for 6 weeks followed by alternate day for next 6 weeks. Children were then followed upto 2 years. Significant clinical improvement was noted in all three groups, maximum being in streptomycin-INH group. Radiological clearing was earliest in the ethambutol-INH group. Recurrence was noted more often in children receiving INH alone or those receiving ethambutol-INH when the dose of ethambutol was decreased to 15 mg/kg. At that time INH alone was widely used and resistance rates had started rising; rates were reported to be 16% in primary cases and almost 49% in previously treated cases [2]. Streptomycin resistance was also high – varying from 14% in primary cases to 46% in secondary cases.

On the other hand, ethambutol was a less used, newer drug showing comparable efficacy, ease of oral administration and low rates of resistance. In the same year, another study in the journal by Mankodi, *et al.* [3] concluded that ethambutol is an effective bacteriostatic drug to be used as an adjuvant to INH in children who were poor responders or had failed triple drug standard therapy. The study included 16 children diagnosed with TB but unresponsive to streptomycin, INH or para-amino salicylic acid (PAS). These children were treated with ethambutol-INH combination for 8-18 months. Ethambutol was given as 25 mg/kg daily for 3 months and then 15 mg/kg daily for rest of the therapy duration along with INH at 20 mg/kg daily. Almost 80% of the cases (13/16)



showed good response. Most children showed clinical improvement in first six months. Adverse effects, noted to be disc edema and thyroid enlargement, were minimal and reversible.

### PRESENT

Fifty years later, ethambutol continues to be one of the standard drugs in TB management, now given in combination with INH, rifampicin and pyrazinamide. With the latest guidelines, the drug is now part of both intensive phase and continuation phase of treatment [4,5]. The most significant side effects that need clinical monitoring are optic neuritis and altered color vision. Pre-treatment check and immediate cessation of drug at onset of symptoms remains the key. Ethambutol has a clear dose-related efficacy and toxicity as a result of which appropriate dosing has always been a topic for research. In the last fifty years, many more studies were conducted. In a major study from India published in 1991, Seth, *et al.* [6] studied the visual evoked responses (VER) of children between 3-13 years who were treated with ethambutol at 20 mg/kg given for tuberculosis. They could not find any

greater risk of ethambutol induced optic damage as compared to adults. In another review by Graham, *et al.* [7] in 1998, more than fifteen studies were analyzed for ethambutol toxicity in children. They once again concluded that the risk associated with ethambutol is minimal if given in appropriate doses. Serum concentrations of ethambutol in children have been reported to be lesser than adults when given at the same dose [7,8]. Finally, World Health Organization in 2006 [9] reviewed all the published literature on dosage, toxicity and pharmacokinetics in which they found that ethambutol in combination with INH shows better response when given at 25 mg/kg as compared to 15 mg/kg suggesting a dose-related efficacy [10]. They also found that ocular toxicity was again dose-related and occurred mostly above 50 mg/kg in adults. The pharmacokinetics of the drug showed that the peak serum ethambutol levels in children at the same dose were lesser than adults making them less susceptible to side-effects. Considering all the above facts, they standardized the daily dose of ethambutol in children to 20 mg/kg (range 15-25 mg/kg). Another Indian study published in 2016 [11] suggested that the two hour serum levels of ethambutol were low in more than 50% of the study population at a mean dose of 21.7 mg/kg further putting in doubt if a still higher dose is actually needed.

The drug is also valued for the protection it offers to other companion drugs against development of drug resistance. In the first national anti TB drug resistance survey in 2016 [12], primary and secondary TB cases showed highest resistance to INH and lowest to ethambutol (primary cases: INH-11.1%, pyrazinamide-6.9%, streptomycin-6.9%, ethambutol-2.3%; secondary cases: INH-25.1%, pyrazinamide-8.8%, streptomycin-13.3%, ethambutol-7.0%). In the same survey, resistance to ethambutol in MDR-TB was 46.98%. As per the RNTCP updated pediatric guidelines for drug resistant TB, the drug continues to be used in intensive and continuation phase of mono/poly - drug resistant TB, shorter MDR-TB regime and MDR/RR TB without additional resistance to fluoroquinolones and/or second line injectable drugs [5]. For the conventional long MDR TB regime, it is now placed in category C; used as an add-on drug. With the latest WHO 2019 update on drug resistant TB, the drug continues to be part of complete therapy for INH resistant TB and as one of the add on drugs for MDR TB [13].

## CONCLUSION

As we move from Revised National Tuberculosis Control Program (RNTCP) to National Tuberculosis Elimination Program (NTEP), ethambutol has come a long way. To start as drug of choice in cases resistant to then TB drugs few decades back, it still continues to be one of the drugs in MDR-TB besides being an essential drug for complete regimen in non-resistant cases.

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## Correct Antemortem Diagnosis of Pneumonia in Children With Fatal Illnesses

This retrospective study analyzed the level of concordance between clinical and autopsy diagnosis of pneumonia over a 3-year period. Utilizing the Goldman classification, the concordance rate was found to be 37.5%. Major discrepancies (Class I and II) were found in 25% cases, and minor discrepancies (Class III and IV) in 37.5% cases.

**Keywords:** Autopsy, Medical audit, Risk factors, Viral pneumonia.

We conducted a retrospective study to analyze the level of concordance between clinical and autopsy diagnosis of pneumonia in children. A secondary objective of the study was to assess if known risk factors associated with mortality due to pneumonia were mentioned in their clinical case records.

Over a 3-year period (January, 2012 to December, 2014), 88 children were confirmed to have pneumonia on autopsy study. Their median (IQR) age was 10.5 (45) months (49 males). Detailed histopathological examination identified etiology of the pneumonia as viral in 42 (47.7%), bacterial in 27 (30.7%), bacterial and viral in 18 (20.4%), and fungal in one (1.1%) child.

Utilizing the Goldman classification [1], our analyses revealed that in only 33 (37.5%) cases the ante mortem diagnosis of pneumonia (including its etiology) was also confirmed on autopsy to be directly related to death (Class V). In only one child the discrepancy was major (Class I) wherein had the correct diagnosis been made clinically, it would have changed patient management and might have resulted in cure or prolonged survival. This case was a 1-year-old girl with severe acute malnutrition admitted with history of fever for 21 days. Her chest radiograph revealed a bronchopneumonia which was treated with broad-spectrum antibiotics. She died after a 7.5 day stay in hospital in spite of intensive care and mechanical ventilator support. Her post-mortem examination revealed fungal (*Aspergillus*) bronchopneumonia.

In 21 (23.9%) cases, the discrepancy was major (Class II) but the missed diagnosis of pneumonia would not have altered treatment or survival. Of these 21 cases, in 18

(20.4%) cases the patient had already been empirically started on oral antibiotics by a private practitioner (with or without oseltamivir) for a few days before being referred to our institute. The remaining 3 (3.4%) cases had been brought directly to our emergency department. All 21 cases were critically ill and received appropriate resuscitative management, but had succumbed before a chest radiograph could be done.

In 31 (35.2%) cases, the discrepancy was minor (Class III) and the missed diagnosis of pneumonia was not directly related to death but related to the terminal disease process (e.g. septicemia, meningitis, congenital heart disease). In two (2.3%) cases, the discrepancy was minor (Class IV) and the missed diagnosis of pneumonia was not directly related to death nor to the terminal disease process (e.g. fulminant hepatitis, leukemia, encephalitis).

Known risk factors associated with fatal outcomes of childhood pneumonia observed in majority of our cases included: age less than 1 year in 49 (55.7%) [2-4], moderate and severe acute malnutrition in 55 (62.5%) [3-5], belonging to lower socioeconomic status in 70 (79.5%) [5-6], and prior complaints before hospitalization of inability to feed in 58 (65.9%) [2], and altered sensorium in 55 (62.5%) [4]. Small sample size precluded subgroup analysis of the data.

Our study reaffirms the importance of autopsy in hospital practice. Risk factors observed may help identify cases of pneumonia with a predilection for a poor outcome.

*Contributors:* SK, PV, PS: involved in study design and implementation; LK, PS: collected data; SK, PV, LK, PS: discussed core ideas and interpretation of data; SK: searched the literature and drafted the manuscript; PV, LK, PS: critically reviewed the manuscript; SK: will act as guarantor for this paper. All authors have approved the final manuscript.

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## B-type Natriuretic peptide Levels and Outcome in Children With Severe Acute Malnutrition With Co-morbidity

We studied the ability of B-type natriuretic peptide (BNP) in predicting mortality among 86 in-patients with severe acute malnutrition presenting with co-morbidity, and found that cut-off level of BNP  $\geq 201$  pg/mL in Receiver operating characteristics curve [AU-ROC 0.96 (95% CI 0.92, 1.003,  $P < 0.0001$ )] had high discriminative ability to distinguish between survivors and non-survivors.

**Keywords:** *Cardiac failure, Mortality, Under-nutrition.*

Pneumonia presenting with respiratory failure is associated with heart failure, even in healthy children without cardiac risks, and high mortality [1]. However, risk of mortality and cardiac morbidity is further increased in pneumonia occurring in children with severe acute malnutrition (SAM). The accuracy of diagnosing heart failure in children with presenting with respiratory distress is difficult clinically, as signs of heart failure are subtle and mimic the features of SAM. Prior studies revealed increased levels of BNP in pneumonia complicated with heart failure which returned to lower levels with control of heart failure [2,3]. However, there is paucity of data on BNP levels in children with SAM with pneumonia. Present study, aims to identify levels BNP that predict mortality in children with SAM with co-morbidities.

This case-control study was conducted from September, 2016 to May, 2018 in a tertiary care hospital in Northern India. Consecutive children, aged 6 to 60 months fulfilling the WHO criteria of SAM were enrolled as cases [4]. Age- and sex-matched children of age group

6 to 60 months with weight for length/height  $> 1SD$ , and mid upper arm circumference  $> 13.5$  cm and without pitting edema were recruited as controls from well-baby clinic of the department of pediatrics. The study was approved by the Institutional ethics committee, and informed consent was obtained from the parents before the study. Detailed history, clinical examination, socio-demographic variables, anthropometry, laboratory results, diagnosis and outcome were recorded on pre-designed form.

Co-morbidity was defined as presence of one or more additional conditions co-occurring in SAM children. Tachypnea was defined as respiratory rate  $> 50$ /minute in 6-12 months children and more than 40/minute in children 13-60 months. Tachycardia was defined as pulse rate  $> 160$ /minute in children up to one year and more than 140/minute in children 13-60 months [4]. Clinical heart failure was defined as the presence of tachycardia, tachypnea, triple rhythm, tender hepatomegaly and engorged jugular veins [5]. Biochemically heart failure was defined as BNP levels  $> 300$  pg/mL [6]. Investigations included arterial blood gas analysis, serum electrolytes, calcium, serum albumin, blood sugar, X-ray chest, and any other as per indication. The Alere Triage Cardio 3 panel was used to estimate levels of BNP in SAM children and age- and sex-matched healthy children as per manufacture's guidelines.

For sample size calculation, we measured BNP levels in 16 children with SAM and found that mean (SD) BNP level was 22.6 (25.27) and ranged from 1.8 to 103 pg/mL. Considering  $\leq 100$  pg/mL as normal levels, and assuming 20% increase in BNP levels in SAM children with co-morbidity, with power of study as 90% and with alpha error of 0.05, a sample size of 75 SAM children with SAM was required.

Data were analyzed by using SPSS (version 16.0). The Receiver operating characteristic (ROC) curve analysis was performed to obtain the area under the curve (AUC)

as well as the recommended cut-off point. Sensitivity, specificity, positive predictive value, and negative predictive value was calculated.

Of the 86 children (65.1% males), the mean (SD) age of study population were 28.8 (15.2) months and edematous children constitute 60.4% of cases. Thirty-two (37.2%) presented with tachycardia, 53 (61.6%) tachypnea, 31 (36%) with hypoxia (SpO<sub>2</sub> <90%), and 18 (20.9%) with hypotension. The co-morbidities were pneumonia 52 (60.4%), acute diarrhea 54 (62.7%), and meningitis 18 (20.9%). Nine (10.4%) children died and rest were discharged from hospital. SAM children dying in hospital were more likely to have tachycardia and hypotension ( $P<0.001$ ). Among those dying in hospital, 7 presented with septic shock and 9 had pneumonia with diarrhea. Of the 86 children, 32 had BNP levels  $>100\text{pg/mL}$  and among increased BNP levels, 25 children had tachycardia. The median (IQR) value of BNP in SAM children was 88 (31,117.5) pg/mL, in healthy control children it was 14 (11.23, 18.62) pg/mL and in SAM children without co-morbidity it was 14.5 (11.3, 25.18) pg/mL. There was no difference observed in median (IQR) BNP levels between edematous and non-edematous children [87 (26,111) vs 88 (28,109),  $P=0.69$ ]. There was a significant difference in BNP levels between children who survived and those died, with respect to edema, tachycardia, tachypnea, and hypoxia (**Table I**). AU-ROC curve revealed a cut-off levels of BNP  $\geq 201\text{ pg/mL}$  to discriminate between survivors and non-survivors and this value had sensitivity of 100%, specificity of 90.9%, positive predictive value of 56.2%, negative predictive value of 100%, and accuracy of 91.8%. AU-ROC curve was 0.96 (95% CI 0.92, 1.003,  $P<0.001$ ) (**Fig. 1**).

Among clinical signs tachycardia had area under curve, 0.88 (95% CI 0.76, 1.002,  $P<0.001$ ), revealing a cut-off levels of BNP  $\geq 201\text{ pg/mL}$  to discriminate between survivors and non-survivors and this value had sensitivity of 100% and specificity of 69.6%.

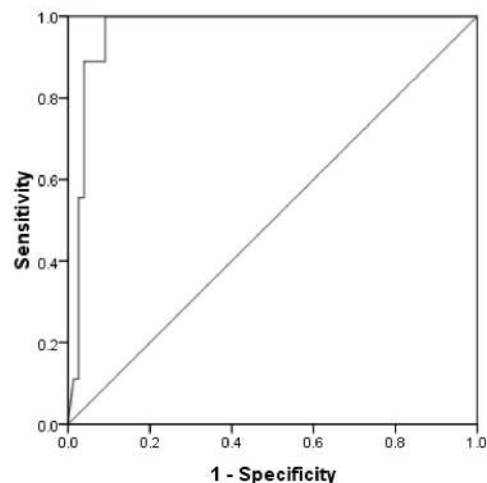
The main finding of the present study is that BNP levels increase significantly in pneumonia with heart failure in children with SAM, and a cut-off levels  $\geq 201\text{ pg/mL}$  has the ability to differentiate between surviving children and those dying in hospital. Similar observations have been reported previously [2,7]. The increased levels of BNP in pneumonia with heart failure are because of stimulation of sympathetic nervous system, pro-inflammatory cytokines, and further compounded by cardiac dysfunction [8]. There was no difference between healthy controls and children with SAM without co-morbidity, signifying that increased BNP levels may be because of co-morbidity in children with SAM. The

present study showed that early clinically recognizable parameters like tachycardia in heart failure and shock has good discriminative ability to differentiate between survivors and non-survivors at cut-off levels of BNP  $\geq 201\text{ pg/mL}$ . Echocardiography demonstrated cardiac dysfunction correlates with BNP levels, and a cut-off level  $\geq 140\text{ pg/mL}$  in children with moderate heart failure is associated with a higher risk for death [9]. A single BNP cutoff value of  $100\text{ pg/mL}$  had of an accuracy of 83% for differentiating cardiac dyspnea from non-cardiac dyspnea in adults [10]. However, in children, a single BNP assay prior to treatment with values  $>550\text{ ng/L}$  may indicate the presence of CCF in a child with pneumonia, this might be because of lower age group in study cohort by Sadoh, *et al* [7], as age has impact on BNP levels. In the present study, lower cut-off of BNP to predict mortality may be because of least variability of BNP levels in age group of 1-5 years.

We had few limitations in our study, as we could not correlate the levels of BNP with ventricular functions of heart and the cardiac mass. Our study in an Indian setup, adds to the growing evidence all over the world that in inconclusive clinical state of heart failure in pneumonia, subtle features of heart failure and the BNP levels  $\geq 201\text{ pg/mL}$  with tachycardia in SAM children warrants the clinicians to suspect and manage heart failure appropriately.

**Contributors:** DK: acquisition of data, analysis and interpretation; SKR: concept, design, drafting of the manuscript, critical analysis.

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**Fig.1** Receiver operating characteristic curve for BNP levels to predict the death of hospitalized children with SAM. The area under the curve was 0.96 (95% CI, 0.92 to 1.003,  $P<0.001$ ) for a level of  $\geq 201\text{ pg/mL}$ .

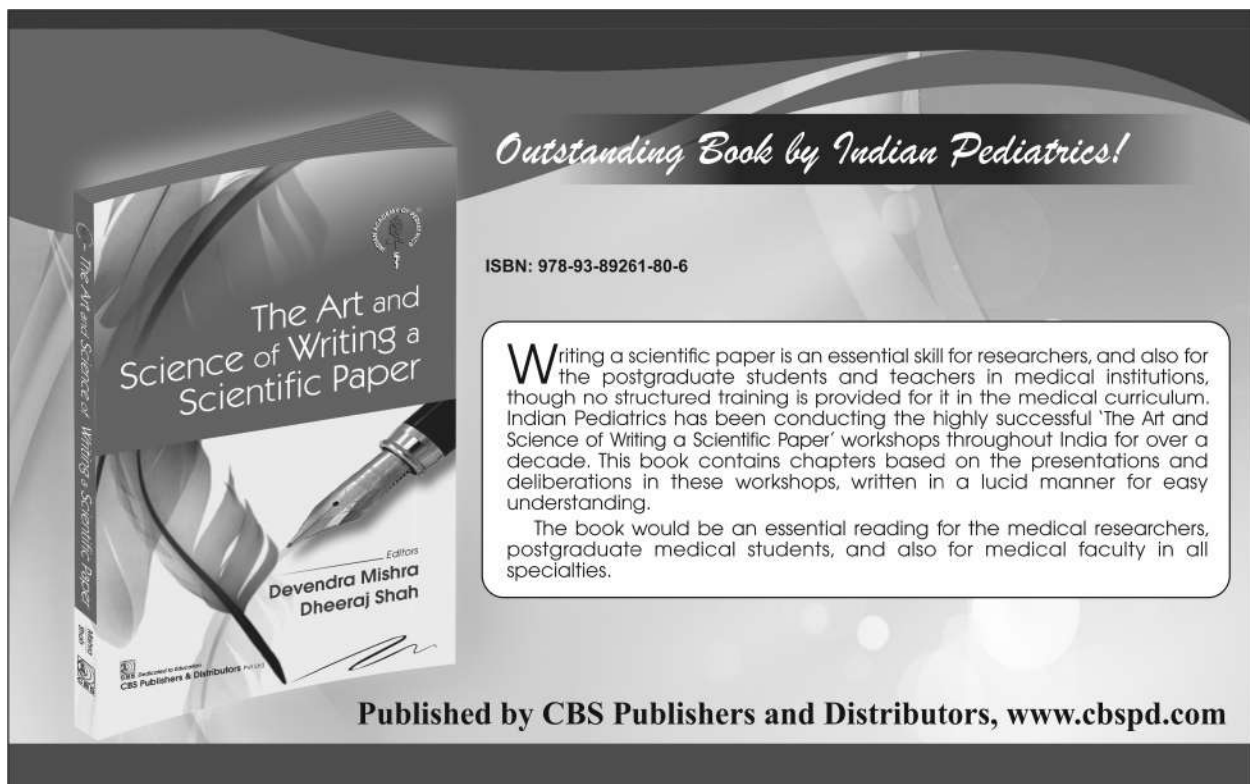
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**Web Table I B-type Natriuretic Peptide Levels Among Inpatients With Severe Acute Malnutrition (N=86)**

| <i>Variables</i>                         |            |                        | <i>BNP levels (pg/mL), median (IQR)</i> |                       | <i>P value</i> |
|--|------------|------------------------|---|-----------------------|----------------|
|  | <i>No.</i> | <i>Survived (n=77)</i> | <i>No.</i>                              | <i>Died (n=9)</i>     |                |
| SAM children                             | 77         | 79 (27,106)            | 9                                       | 667 (453,931.5)       | <0.001         |
| Edematous                                | 50         | 78.5 (22.75,101.5)     | 5                                       | 689.2 (508.5,1050)    | <0.001         |
| Non- edematous                           | 27         | 86 (33,101)            | 4                                       | 561.5 (273.75,832)    | 0.001          |
| Tachycardia                              | 23         | 112 (90,256)           | 9                                       | 667 (453,931.5)       | <0.001         |
| Hypotension                              | 9          | 256 (161.5,786.5)      | 9                                       | 667 (453,931.5)       | 0.13           |
| Tachypnea                                | 46         | 86.5 (22.75,109)       | 7                                       | 689 (456,667)         | <0.001         |
| Hypoxia (SpO <sub>2</sub> <90%)          | 23         | 80 (23.5,100)          | 8                                       | 678.1 (479.25,953.75) | <0.001         |
| <i>Heart failure* (n=17)</i>             |            |                        |   |                       |                |
| Clinical                                 | 3          | 223 (189,256)          | 3                                       | 67(213,689.2)         | 0.40           |
| Biochemical <sup>#</sup> (BNP>300 pg/mL) | 5          | 590 (332,1053)         | 8                                       | 678.1(483.75,953.75)  | 0.71           |

\*Median (IQR) BNP in heart failure, 567(293,931.5); <sup>#</sup>includes both clinical and biochemical heart failure.

## Neonatal Appendicitis with Cow Milk Protein Allergy

Appendicitis is rare in the neonatal period. A 6-week-old baby presented with fulminant appendicitis. At the age of 6 months, the infant was diagnosed with Cow milk protein allergy. Association between CMPA and appendicitis was a rare association in our case, showing that CMPA can have a wide spectrum of gastrointestinal involvement.

**Keywords:** Mesenteric abscess, Neonatal sepsis.

Appendicitis is rare in the neonatal or post neonatal period with incidence reported as 0.04% to 0.2 % in premature males [2]. A 6-week-old baby presented with complaints of frank blood in stool, diarrhea, and fever since 7 days. The child was afebrile, feeding well and was occasionally irritable but consolable on carrying and feeding. Abdominal examination was normal. Stool routine examination done on day 2 showed 8-10 red blood cells and 6-8 pus cells, and stool culture had no growth. Ultrasonography (USG) abdomen done on day 2 was normal. Child was started on oral cefixime, but as symptoms persisted, child was admitted and treated with intravenous ceftriaxone and amikacin. On day 7, child developed fever and three episodes of bilious vomiting. Hemoglobin was 7 g/dL and total leucocyte count was 39000 per mm<sup>3</sup> with 90 % neutrophils and CRP of 162 µg/dL. Repeat USG of the abdomen now showed four liver abscesses, largest measuring 1.9×1.1cm and remaining small, subcentimeter sized. Ultrasonography showed a doubtful mass in the pelvis without vascularity and mixed echogenicity, measuring 5×4.3×3.1 cm, which was confirmed on computed tomography of abdomen to be a mesenteric collection measuring 4.9×2.6×2.4 cm with irregular margin, in close proximity to the ileum with air speckles inside suggesting possibility of intestinal perforation and mesenteric abscess.

Surgical exploration revealed that appendix was badly inflamed and infected, tip had sloughed off with perforation. The ileal loop which was close to the appendix was stuck to its wall and had also perforated with a mesenteric abscess. Appendectomy was done with resection anastomoses of the inflamed ileal loop. The remaining intestine was normal and there was no Meckel diverticulum. Histopathology showed appendicitis and ileal serosal inflammation. The Nitroblue-tetrazolium

(NBT) test for chronic granulomatous disease and Lymphocyte subset assay were normal.

The intra-operative findings were considered to be not commonly associated with the symptom of frank blood in stool. Hence, possibility of coexisting pathologies like Cow milk protein allergy (CMPA), polyp, and early inflammatory bowel disease (IBD) was kept in mind. The child recovered well after surgery. Feeds (soy protein formula) were started on day 3 and gradually increased to full feeds by day 6. Complete blood count on day 7 was normal. Day 10 USG showed complete resolution of liver abscesses and normal abdominal findings. Child was discharged on day 10 on soy-based milk formula and there was no recurrence of symptoms till 6 months age.

At 6 months, two weeks after introduction of weaning food (containing milk protein), child started passing fresh blood in stool again. On elimination of this food the symptoms disappeared in one week. IgE specific for cow's milk was reported negative. Fecal calprotectin was 423 mg/kg (normal ≤50). However, it is a non-specific marker of inflammation in the intestine and may be elevated in IBD as well as CMPA. It has also been used to evaluate efficacy of elimination diet in CMPA [1]. Hence, a colonoscopy/ biopsy was planned to confirm etiology. Colonoscopy showed scattered nodules all over colon and terminal ileum, no sites of bleed and no signs of IBD like ulcers or skip lesions. Microscopy revealed many eosinophils in the lamina propria suggesting CMPA. Thus, the diagnosis of non IgE-mediated CMPA was confirmed. At 9 months of age, off cow's milk in any form, child is doing well.

In the neonatal or post-natal period, appendicitis presents as irritability, bilious vomiting, fever, leukocytosis like non-specific signs and symptoms. It is generally not known to cause frank blood in stools. So we assume that the symptom of frank blood in stools seen in our case was because of the underlying CMPA, which was confirmed later at 6 months of age as the criteria needed for making the diagnosis was met *i.e.*, through allergen elimination and challenge.

CMPA has a wide spectrum of gastrointestinal involvement. The alarm symptoms are macroscopic blood loss in stool causing anemia, failure to thrive, breathing difficulty, anaphylaxis, and severe exudative urticaria. If any of these symptoms occur and cannot be explained by another cause, CMPA may be considered a potential



diagnosis. In most cases with suspected CMPA, the diagnosis needs to be confirmed or excluded by an allergen elimination and challenge procedure [3]. This can be performed as open, single-, or double-blind challenge. Serum specific IgE, skin prick test and radio-allergosorbent assay are some of the tests available for IgE mediated CMPA. No confirmatory laboratory test is available for non IgE-mediated CMPA. Nevertheless, an oral challenge test is necessary in most cases to confirm an adverse reaction to cow's milk protein and then to make a diagnosis of CMPA. A biopsy is not needed to confirm the diagnosis unless there are very severe or overlapping symptoms.

Non IgE-mediated food allergies are known to be associated with enterocolitis syndrome (Food protein-induced enterocolitis), enteropathy, enteritis, proctitis and proctocolitis [4]. Neonatal appendicitis, as noted in this child, is a rare finding, and needs to be recognized as another manifestation of the wide spectrum of presentation of CMPA.

*Contributors:* AS: analyzed the case, drafted the manuscript, collected references; JM: analyzed the case and operated on the case.

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## Consumptive Hypothyroidism Due to Diffuse Hepatic Hemangiomas Treated With Propranolol Therapy

Infantile hepatic hemangioma (IHH)-related consumptive hypothyroidism is rare and occurs as a result of excess thyroid hormone inactivating enzyme, type-3 iodothyronine deiodinase. We present an infant with IHH-related hypothyroidism, in whom treatment with propranolol led to regression of tumor and subsequent euthyroid status.

**Keywords:** *Liothyronine, Management, Type 3 deiodinase.*

Consumptive hypothyroidism is a complication of infantile hepatic hemangioma (IHH) caused by increased expression of type-3 deiodinase enzyme in the tumor tissue. This enzyme causes increased degradation of T4 and T3 to reverse T3 (inactive metabolite). When this exceeds the rate of synthesis of these hormones, a state of hypothyroidism ensues. Definitive therapy for the hemangioma and reduction in tumor burden leads to resolution of hypothyroidism. We describe a child who presented with severe hypothyroidism secondary to consumption by an IHH.

A 3-month-old female baby presented with severe constipation for the past one month. Parents also complained of dullness, poor cry and abdominal distention. There was no history of poor feeding, umbilical hernia or jaundice. The child had been born at term to a primigravida mother with a birth-weight of 2.2 kg. Her weight at presentation was 4.5 kg (−2 SD) and length 55 cm (−2 to −3 SD). Physical examination revealed pallor, depressed nasal bridge and macroglossia. Her abdomen was distended and liver palpable 6 cm below the costal margin. She had an ejection systolic murmur. The thyroid gland was normally palpable.

An abdominal ultrasound revealed multiple hypoechoic lesions in the liver. Contrast-enhanced CT scan showed these lesions to have early enhancement with persistence in delayed phase consistent with a diagnosis of IHH (**Fig. 1 a**). The child was not found to have any cutaneous hemangiomas. Thyroid function tests showed high TSH >75 mIU/L (0.57–5.54), low-normal FT4 14.6 pmol/L (60-160) and low T3 <0.62 nmol/L (1.3-2.8) (**Web Table I**). Thyroid ultrasound showed a eutopically located gland and thyroid scan showed normal radionuclide uptake. Reverse T3 levels were raised (607 ng/dL, normal range 10-50) pointing towards peripheral consumption of thyroid hormone. She was

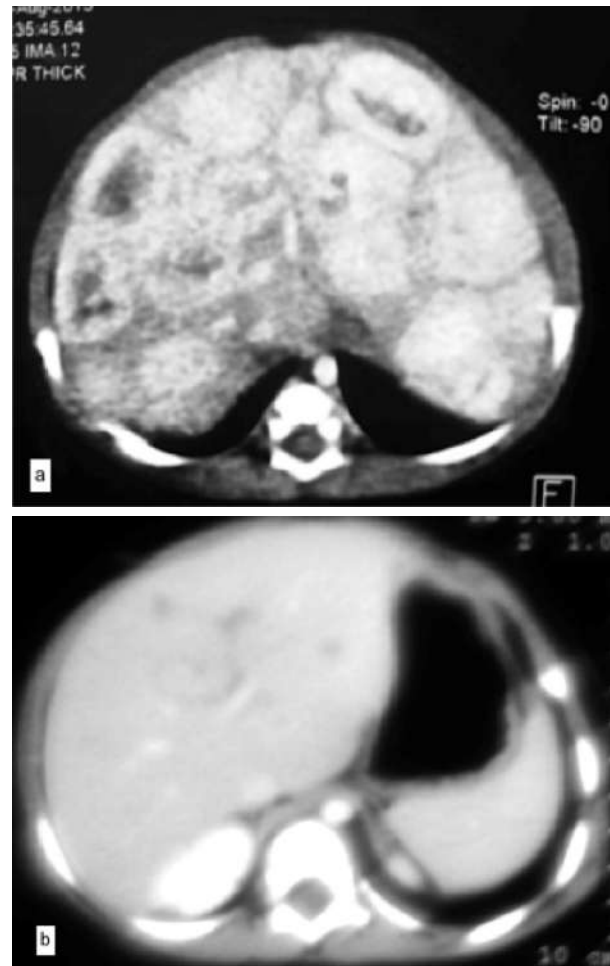
treated with oral levothyroxine 50 µg (11 µg/kg/day). However, even after two weeks, TSH remained high. Therefore, thyroxine dose was further increased. For the hemangioma, child was started on prednisolone at the dose of 2mg/kg/d. When even after 2 weeks of therapy ultrasound did not show any reduction in size of the lesion, interferon α (6 mu/m<sup>2</sup>/day alternate day) was added. During this period the child also developed congestive cardiac failure, which was treated with digoxin and furosemide.

TSH persisted to be high even on 112.5 µg (22.5 µg/kg/day) of levothyroxine necessitating further increase in the dose to 150 µg. As the child was requiring such high doses of LT4, oral liothyronine (T3) preparation (Bitiron) was added at a dose of 12.5 µg twice a day (**Table I**). On this dose the child remained stable with normalization of thyroid function. As ultrasound of the abdomen did not reveal any significant reduction of the tumour mass on interferon alpha therapy, it was discontinued and propranolol was started (2 mg/kg/d). Over the next 3 months, there was significant reduction in tumor size and in her thyroxine requirements. Her cardiac status also improved. There was no bradycardia or hypotension during therapy.

Liothyronine could be tapered and stopped after 5 months. After 10 months of propranolol treatment, repeat CT imaging showed complete resolution of tumor and propranolol was stopped (**Fig. 1b**). Thyroxine doses were tapered and finally stopped at the age of 21 months. (**Table I**). On follow-up until the age of two years the child remained euthyroid, with age appropriate developmental milestones, and normal liver appearance on ultrasound scans.

In IHH with consumptive hypothyroidism, supra-physiological doses of thyroxine are required to counteract the deactivation of T4 by the D3 deiodinase. As untreated or inadequately treated hypothyroidism in the first year of life can have severe consequences, like impaired neurodevelopmental outcome, aggressive treatment of babies with consumptive hypothyroidism is mandated. Most children respond to high doses of thyroxine, though addition of liothyronine to the treatment regimen has been reported to help in normalization of T3 levels and earlier restoration of euthyroidism [1]. Combined therapy may be useful in challenging cases where there is high rate of consumption of thyroid hormones.

Definitive therapy for hypothyroidism is treatment of IHH. Traditionally high dose corticosteroids have been the first line therapy [2]. However, steroids can have adverse effects and also increase the thyroid hormone



**Fig. 1** (a) Contrast-enhanced computed tomograph of abdomen in venous phase showing diffuse involvement of liver by hemangiomas, (b) Post-propranolol therapy showing complete resolution of hemangiomas.

requirement by inducing type-3 deiodinase activity and impair T4 to T3 conversion leading to further worsening of thyroid function. Second line therapy consisted of vincristine, interferon and cyclophosphamide [2]. Intractable cases need hepatic artery embolization, segmental resection or liver transplantation.

Propranolol was first suggested as therapy for cutaneous hemangiomas in 2008 and since then has been used for IHH as well with recent data showing a complete response in >90% patients [3-5]. Some of the proposed mechanisms of action include vasoconstriction, decreased renin production, inhibition of angiogenesis, and stimulation of apoptosis [5]. Adverse effects of the drug may be bronchospasm, bradycardia, hypotension, and hypoglycemia [3]. However, our patient did not demonstrate any of the above complications and rather showed resolution of cardiac failure.

**Table I Trend of Thyroid Profile and Thyroid Hormone Requirements in the Index Case**

| Age (mo)     | Weight (Kg.) | TSH (mIU/L) | T <sub>4</sub> (nmol/L) | T <sub>3</sub> (nmol/l) | Levothyroxine dose (mcg) | T <sub>3</sub> dose (mcg) | Treatment For IHH |
|--------------|--------------|-------------|-------------------------|-------------------------|--------------------------|---------------------------|-------------------|
| 3            |              | >75         | FT <sub>4</sub> -14.8   | <0.62 (pmol/L)          | -                        | -                         |                   |
| 4            | 4.1          | -           | 110                     | 0.72                    | 75                       | -                         | Prednisolone      |
| 5            |              | 26.1        | 230                     | -                       | 112.5                    |                           | Prednisolone      |
| + Interferon |              |             |                         |                         |                          |                           |                   |
| 6            | 5            | 0.44        | 116                     | <0.62                   | 150                      | 25                        | Propranolol       |
| 7            |              | 0.15        | 149                     | <0.62                   | 100                      | 25                        |                   |
| 8            |              | <0.01       | 136                     | 2.51                    | 75                       | 12.5                      |                   |
| 9            |              | 0.02        | 149                     | 2.66                    | 50                       | 12.5                      |                   |
| 11           |              | 0.068       | 101                     | 2.8                     | 37.5                     | 12.5                      |                   |
| 15           |              | 0.05        | 133                     | 2.65                    | 25                       | Stopped                   |                   |
| 16           |              | 0.52        | 88                      | 3.1                     | 18.75                    | -                         | Stopped           |
| 18           | 10           | 1.7         | 126                     | 3.1                     | 12.5                     | -                         |                   |
| 21           |              | 0.97        | 100                     | 1.5                     | Stopped                  | -                         |                   |
| 23           |              | 1.5         | 89                      | 2.8                     | -                        | -                         |                   |

Normal ranges: TSH:0.57-5.54 mIU/L, T<sub>4</sub>: 60-160 nmol/L, T<sub>3</sub>:1.3-2.8 nmol/L, FT<sub>4</sub>: 14-31 pmol/L; TSH: Thyroid stimulating hormone.

Propranolol should possibly be offered as first line therapy to infants with diffuse IHH, especially those with hypothyroidism, as rapid normalization of thyroid function is highly desirable to ensure normal neurodevelopment.

*Contributors:* All authors were involved in case-management and manuscript preparation, and approved the final version of manuscript. All authors agree to be accountable for all aspects related to the study.

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## Wernicke Encephalopathy and Lactic Acidosis in Thiamine Deficiency

Thiamine deficiency can cause encephalopathy (Wernicke) and lactic acidosis. Herein we report a 6-year-old girl on total parenteral nutrition (TPN) who developed lactic acidosis and neurological symptoms due to improper vitamin replacement, which responded to thiamine injection. The MRI brain findings were not typical for Wernicke encephalopathy.

Thiamine acts as a co-enzyme for decarboxylation and transketolase reactions. Blood pyruvate and lactate can increase in thiamine deprivation [1]. Wernicke encephalopathy is a neurological complication of thiamine deficiency characterized by nystagmus, ophthalmoplegia, ataxia, and confusion. It is mostly reported in chronic alcoholic adults and in few pediatric patients with other etiologies [2].

A 6-year-old girl was referred for encephalopathy, tachycardia and lactic acidosis. She was diagnosed with megacystis microcolon intestinal hypoperistalsis syndrome and had previously undergone several surgeries including total colectomy and subtotal ileum resection. She was admitted for six months with dehydration, electrolyte imbalance, poor oral intake and was receiving total parenteral nutrition (TPN) since then. She had developed encephalopathy and blurred vision three days back and, tachycardia and lactic acidosis several hours before admission to the intensive care unit.

On admission, the heart rate was 145/min, blood pressure was 100/65 mmHg with normal capillary refill time and no edema. She was lethargic, with Glasgow coma scale of ten. Neurological examination showed nystagmus and ankle clonus. Rest of the tendon reflexes and sensory system were normal.

Preliminary laboratory examination showed hemoglobin 9.7 g/dL, white cell count  $10 \times 10^3$  cells/ $\mu$ L, aspartate transaminase 108 U/L, alkaline phosphatase 352 U/L, serum procalcitonin 1.42 ng/mL, CRP 9.5 mg/L and lactic acidosis (pH 7.32,  $PCO_2$  26.6 mmHg,  $HCO_3$  15.9 mmol/L, lactate 7.3 mmol/L). Chest X-ray showed normal heart size and echocardiography was normal for systolic function (ejection fraction 65%). Her thyroid function test was normal.

Septic shock was diagnosed in the presence of fever, indwelling catheter for TPN and positive blood culture for gram-positive bacteria. Intravenous meropenem and

teicoplanin were started empirically. Norepinephrine was added after fluid bolus but later discontinued as she progressively developed tachycardia and high blood pressure, and lactate increased to 13 mmol/L. It was noticed that she had not received water-soluble multivitamin infusion (MVI) due to a hospital-wide shortage for the last one month. Oral multivitamins were not substituted as physicians were unaware of the situation due to an electronic order system error. Thiamine 100 mg was administered intramuscularly. Lactate level decreased to 2 mmol/L within the first hour and tachycardia resolved within 12 hours. Magnetic resonance imaging (MRI) of brain showed diffusion restriction and signal increase on T2 weighted images in bilateral temporal, frontal and parietal cortex, corpus striatum, pons, and medulla oblongata. On the second day of thiamine treatment, her mental status improved, she became responsive to verbal stimuli and nystagmus disappeared. However, clonus persisted. Thiamine replacement (100 mg/day intramuscular) was continued for 14 days in addition to MVI in TPN.

Wernicke's encephalopathy is an acute neurological disorder due to thiamine deficiency. The mental deterioration and cardiovascular instability in the index patient were due to thiamine deficiency as neurological symptoms started one month after MVI shortage and improved after initiation of thiamine replacement. She recovered with neurological sequela due to delayed replacement of thiamine.

The typical radiological finding of Wernicke encephalopathy is symmetric hyperintensities on T2 weighted MRI in the thalamus, mamillary bodies, periaqueductal gray matter, and tectal plate [3]. Atypical cases with cortical involvement are reported similar to index patient [4].

Thiamine deficiency may cause lactic acidosis which is rapidly reversible by vitamin replacement. Cases with profound lactic acidosis traced to thiamine deficiency were reported during a nationwide shortage of intravenous multivitamins in the United States in 1997 [5]. Erythrocyte transketolase activity and thiamine pyrophosphate effect tests were not available to us. However, the dramatic regression of neurological symptoms and lactic acidosis after thiamine replacement was suggestive of thiamine deficiency.

Clinical suspicion of thiamine deficiency might be life-saving, treatment should be started as early as possible before laboratory confirmation. In case of unexplained, refractory lactic acidosis, thiamine deficiency should always be considered in the differential diagnosis.

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## Post-traumatic Pseudoaneurysm of Hepatic Artery: An Unusual Cause of Upper Gastrointestinal Bleeding

Pseudoaneurysm of hepatic artery with upper gastrointestinal bleeding is a rare but life-threatening complication of blunt trauma to the abdomen. An 8-year-old child with this condition was treated successfully with percutaneous coil embolization of the pseudoaneurysm.

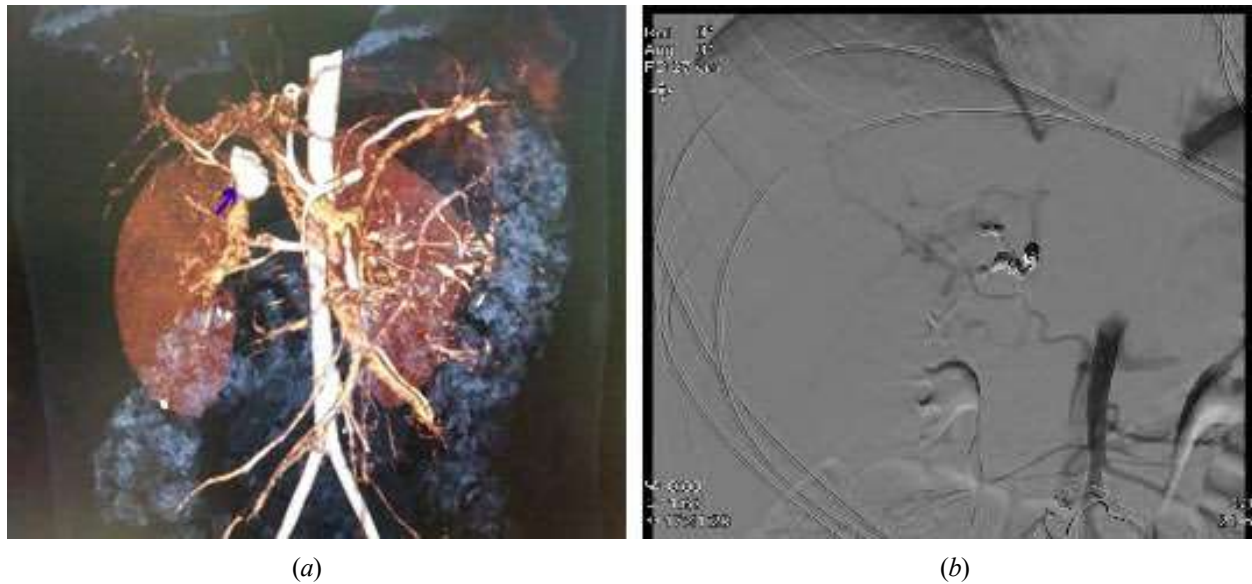
**Keywords:** *Arterial injury, Management, Trauma.*

Pseudoaneurysm of any artery develops due to collection of blood between its two outer layers, the tunica media and the tunica adventitia. It is in contrast with the true aneurysm which involves all three layers of the wall of an artery. Among children sustaining traumatic injuries, 21% have abdominal injuries [1,2]. Rarely, the blunt trauma of the abdomen may be complicated by development of pseudoaneurysm of hepatic artery, which may rupture inside biliary tract, leading to life-threatening complication of hemobilia. Classical signs of hemobilia consist of upper abdominal pain, upper gastrointestinal hemorrhage and jaundice, called Quincke triad. All these three signs are present in only 22% of cases, whereas only upper gastrointestinal bleeding is present in 42% of cases [3].

An 8-year-old child presented in our emergency department with complaint of pain abdomen for 15 days and hematemesis and melena for 10 days. The pain abdomen started when he was punched in his abdomen

by one of his schoolmates. He took analgesics for his pain abdomen. There was no history of fever, rash or any bleeding diathesis. He was pale and had tachycardia at admission. There was no history of fever, rashes or any bleeding diathesis. Blood pressure was 113/70 mmHg and there was no petechial/purpuric rash. He was given normal saline bolus and intravenous pantoprazole followed by whole blood transfusion. Blood investigations revealed low hemoglobin (4.8 g/100 mL) with normal leucocyte counts, liver enzymes and renal function tests; International normalized ratio was 0.95. Ultrasonography abdomen done outside had revealed a 9 mm calculus in gall bladder neck. Upper gastrointestinal endoscopy, which had been done prior to coming to our hospital, had documented erosion of mucosa of antrum and pylorus with blood and blood clot inside stomach. Blood was also seen coming out from ampulla of Vater and an impression of erosive gastritis and hemobilia had been reported. The child continued to have hematemesis after admission. A computed tomography (CT) angiography of the abdomen was done which revealed a pseudoaneurysm of the right hepatic artery (**Fig. 1a**). Percutaneous coil occlusion of the right hepatic artery was done through the ipsilateral femoral artery (**Fig. 1b**), and the hematemesis stopped thereafter. He continued to have intermittent colicky pain abdomen post procedure also, which persisted along with melena, till sixth day of admission. The child became completely asymptomatic on seventh day of admission, when he was discharged. He was asymptomatic, without any pallor, and with normal liver function test on follow up after one month.

Approximately 1.7% of children sustaining blunt



**FIG. 1** (a) Pseudoaneurysm of right hepatic artery in CT-angiography (arrow), (b) Coil embolization of the pseudoaneurysm of right hepatic artery.

trauma to the abdomen develop pseudoaneurysm of hepatic artery and most of the pseudoaneurysm of the hepatic artery are associated with the higher grades of liver injury [4]. Other causes of pseudoaneurysm of hepatic artery include surgical procedures like cholecystectomy or percutaneous procedures and endoscopic procedures like cholangiopancreatography, liver biopsy and drainage of liver abscess [5]. Pseudoaneurysm may produce mass symptoms and local pain or the situation may be further complicated by rupture of the pseudoaneurysm. Rupture of the pseudoaneurysm occurs within days to weeks after the injury. When the pseudoaneurysm ruptures inside the biliary system, it leads to haemobilia and life threatening upper gastrointestinal bleeding. Ultrasonography may demonstrate pseudoaneurysm as a sac like structure with blood flow within it, but its sensitivity is low (37%) although it has a high specificity (100%). Contrast enhanced ultrasonography has been shown to have high sensitivity (75%) and specificity (100%) [6]. Endoscopy may also detect hemobilia resulting from rupture of pseudoaneurysm by demonstrating blood coming out from papilla of Vater, but it also carries a low sensitivity. CT angiography is investigation of choice for pseudoaneurysm of hepatic artery. It provides a precise location of the pseudoaneurysm and delineates the involved blood vessel.

Percutaneous arterial embolization is highly effective in controlling arterial bleeding in hemobilia [7]. Success of endovascular management at experienced centres

approaches 100% [8]. In a series of 176 children sustaining liver injury, 3 (1.7%) had developed pseudoaneurysm of hepatic artery [4]. Two of them experienced life-threatening bleeding, both at 10 days after injury. This was controlled by angiographic embolization in one and by laparotomy in other. One asymptomatic patient underwent successful embolization of a large pseudoaneurysm, seven days after injury [4]. Hepatic necrosis, gall bladder ischemia, biliary fistula and hepatic abscess are known complications of this procedure. Surgical intervention is rarely necessary, and it is usually reserved for failed percutaneous embolization. However, it is first line of management if pseudoaneurysm is infected or if it is compressing other vascular structures. On follow-up of such children with coil embolization of hepatic artery, clinical jaundice and liver function test derangement should be looked for.

In conclusion, an upper gastrointestinal bleeding associated with abdominal trauma could be due to hemobilia due to ruptured pseudoaneurysm of hepatic artery. It may lead to life threatening hematemesis, hence prompt recognition of this condition by CT angiography and its management is important.

*Contributors:* AP: drafted the manuscript, collected clinical details; SK: was involved in doing percutaneous coil occlusion of pseudoaneurysm of the patient in case report; Abhiranjana P: did the literature search related to the topic; PK: reviewed the article and suggested editing. All authors reviewed article before final submission.

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## Congenital Linkage of Lacrimation with Micturition: A Wiring Defect or Just a Spillover?

Association of lacrimation and micturition is rarely reported in the medical literature. It has been hypothesized that abnormal parasympathetic connections occur between the lacrimal nucleus and the pontine micturition center, which give rise to this finding. Here we report a 5-year-old girl who presented with tearing from both eyes whenever she passed urine.

**Keywords:** *Lacrimal apparatus, Parasympathetic Nervous system, Pons reflex.*

Lacrimation and the act of micturition are both under the control of the parasympathetic nervous system. Despite being so similar in their control they never go together except if emotion is attached, like pain. Lacrimation associated with painless act of micturition has been earlier mentioned in few case reports [1-3]. Here we report a young girl with this finding.

A 5-year-old girl visited the outpatient pediatric clinic in June, 2019 with complaint of tearing from both eyes during micturition, without any associated pain or discomfort. This phenomenon was witnessed by the treating doctors also. The child was delivered at full term and had achieved all milestones at appropriate age including bowel-bladder control. There was no history of a similar phenomenon occurring in near or distant family

members. The examination of the external genitalia and eyes was normal. Urine analysis and ultrasound of the urinary tract were also normal. This abnormal lacrimation got resolved with injection atropine (0.25 mg intravenous bolus just before the act of micturition).

The child was advised to pass urine frequently without the urge of micturition. Lesser amount of bladder stimulation decreased the parasympathetic activity and tearing. With this bladder regime, she reported a decrease in the tearing. The parents were counseled about the benign nature of this phenomenon as it probably represented an abnormal neural connection.

Tears relate to emotions as disparate as pain, sadness, anger, frustration, happiness, and religious aspiration. Tears may be rarely attributed to a neurological disorder or disease like the syndrome of crocodile tears. In the index case, tears were linked to urination without any emotional connection.

The central nervous control of micturition is a complex arrangement between the higher centers, the pons and the spinal cord [4]. The Pontine micturition center (PMC) acts as a switch in the micturition reflex pathway and coordinates the activity of the bladder and the urethral sphincter [5]. This center receives input from a higher center situated in the medial pre-frontal cortex (mPFC). The supra-spinal control of bladder and orchestration of micturition is also done by the central-autonomic-network (CAN) [6]. Like the PMC, the function of the lacrimal nuclei

is also modulated by the higher centers namely the limbic system and/or CAN (medial pre-frontal cortex is a part of CAN) which controls the emotional tearing, and the trigeminal nucleus which controls the reflex tearing. No direct connection between PMC and the lacrimal nucleus (LN) has been documented till date to explain involuntary/non-emotional tearing in association with the act of micturition.

Bowler, *et al.* [1] hypothesized that abnormal parasympathetic connections occur between the lacrimal nucleus and the PMC which are responsible for this finding. We offer two hypotheses as the neuro-physiological basis of this phenomenon. First, it is possible that some of the mPFC neurons which were destined to synapse with the PMC inadvertently synapsed with the lacrimal nucleus leading to reflex co-activation as both receive input from the medial pre-frontal cortex. Second, lacrimal reflex and micturition reflex are both controlled by autonomic parasympathetic system which can lead to simultaneous neuronal discharges. However, in the absence of functional images, no conclusion could be drawn.

Clinicians should be aware of this phenomenon, its benign nature, and that it is at best a aberrancy and not a disease.

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## Late onset Job syndrome With Growth Retardation

A 9-year-old girl presented with severe eczematous lesions and multiple infections since age of 6 year with growth retardation and raised serum IgE levels, suggestive of Job syndrome. The unusual late onset of clinical manifestations of the disease is highlighted.

**Keywords:** *Hyper IgE syndrome, Recurrent infection, Eczema.*

Job syndrome or hyper-IgE syndrome is characterized by eczema, recurrent skin and pulmonary infection, and elevated serum IgE levels (>2000 IU/mL) [1]. It is mostly sporadic with an incidence of one in 500,000 and has an early onset in life [1]. We report a child with uneventful early childhood and disease onset at 6 years of age.

A 9-year-old girl, product of a non-consanguineous marriage, presented with history of scaling over scalp and itchy red lesions with oozing and pus discharge in the inguinal region, trunk and lower limbs for past 4 months. There was history of discharge from the right ear and the

left eye for past 2 months. The child was treated for tubercular cervical lymphadenitis two years ago. Subsequently child developed repeated episodes of bronchitis and wheezing. Birth and developmental history of the child were uneventful. Her growth parameters were apparently normal till 6 years of age. The siblings were all healthy and there were no similar complaints in parents or close relatives. On examination, the child had hypertelorism, broad and flat nose with increased inter alar distance. Her height was 121 cm (3rd – 10th percentile) and weight 20 kg (3rd – 10th percentile). There were thick adherent yellowish greasy scales all over scalp with sparsening of hair, hemorrhagic crusts and serous exudate over few areas. Left eye showed mucopurulent discharge, crusting and erythema of eyelid margins with matting of eyelashes. Left ear had features of chronic otitis media. Trunk, buttocks and lower limbs showed scaling and erythema along with foul smelling purulent discharge from the erosion over the inguinal folds. Vulvovaginal candidiasis and chronic paronychia of right thumb and left index finger were present. Cervical lymph nodes were enlarged. Skeletal examination revealed scoliosis in dorsolumbar spine. No dental



abnormalities were noted and intelligence quotient was normal for age.

Serum IgE level was elevated [4624 IU/ml (0-175 IU/mL)], hemogram revealed eosinophilia (7%), and chest X-ray showed calcified opacities in the left hilum and the right paratracheal region suggestive of healed pulmonary tuberculosis. Thyroid function tests, serum cortisol, vitamin D and parathyroid hormone levels were normal. Pus culture showed *Staphylococcus aureus*. Needle cytology from cervical lymph nodes revealed reactive lymph node hyperplasia. She received topical antibiotics and oral and topical antifungals. Her skin lesions resolved in two weeks and scalp scales cleared over a period of one month with hair growth.

Most patients of Job syndrome present early in life with severe skin and lung infections [1,2]. Sporadic and autosomal dominant Hyper IgE syndrome have additional features like scoliosis, retained primary teeth, hyper extensibility and moderate eosinophilia. Autosomal recessive form lacks these features and presents with recurrent viral infections and severe eosinophilia [1]. The index patient probably had the sporadic form.

Most cases that have been reported so far had a very early onset of disease [1-3]. Wu, *et al.* [3] reported onset of disease before two years in 85.7% of patients. Antoniadis, *et al.* [4] reported an overlap of Job syndrome and Dubowitz syndrome unlike the index

patient who had no particular features of Dubowitz syndrome to explain her growth retardation. Investigations to rule out on endocrine cause were also normal. Repeated immunological stimulation, infections and prolonged drug intake could be a reason for her growth retardation. We report this case to highlight that Job syndrome should be kept as a differential in patients presenting late with multiple infections and growth retardation.

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## Subsultus Tendinum in a Child with Typhoid Fever

A 5-year-old male child with blood culture confirmed typhoid fever presented with twitching over the left scapular region. Contrast computerized tomography and electroencephalogram were normal. Following treatment with azithromycin and clonazepam, the twitching subsided. Subsultus tendinum, a rare neurological complication of typhoid fever, resolves spontaneously with treatment.

**Keywords:** Enteric fever, Movement disorder, Neurological complications.

Neurological complications, including Guillain-Barre syndrome and acute transverse myelitis [1,2] following typhoid fever have been reported from typhoid endemic settings. We report a rare complication of subsultus tendinum (an involuntary twitching of the muscles of the limbs) in a young boy with blood culture-confirmed typhoid fever.

A 5-year-old boy, residing in a semi-urban settlement of Vellore town, presented to the community clinic in the area with a history of three days of fever associated with sore throat, malaise, cough, nausea, and headache. The highest temperature recorded during the episode was 103.8 °F. As a part of the SEFI (Surveillance for Enteric Fever in India) protocol, a blood culture is performed for all study children who present with three or more days of fever, and hence the child's blood culture was sent to the laboratory [3]. Blood culture grew *Salmonella enterica* serovar Typhi. Following the culture result, oral azithromycin (20 mg/kg body weight) was initiated and continued for 10 days.

Fever abated on the third day following the initiation of azithromycin. Four days following fever defervescence, the child was brought back with pain in the left side of the neck and shoulder spreading down to the scapular region, with no swelling, warmth or tenderness. Two days later, the child developed twitching movements over the left shoulder and scapular region

which increased over the next few days and was observed even while the child was asleep. There was an associated worsening of pain in the left neck and shoulder. There was no history of seizures, abnormal movements or loss of consciousness. There was no history of seizures in the family. His general and systemic examination including a complete neurological examination was normal except for the persistent twitching over his left shoulder and scapular regions. His investigations showed serum creatinine (0.39 mg/dL) and sodium (138 mmol/L) to be within the normal range. Given the persistent twitching, he was suspected to have *epilepsia partialis continua*. However, MRI of the brain with contrast and EEG were normal. He was evaluated by a pediatric neurologist and was started on clonazepam at a dosage of 0.25 mg twice daily. The twitching movements continued to persist during sleep; however, with decreased intensity and frequency. The twitching persisted for five weeks from the onset of his symptoms and then subsided. He was followed up again at eight weeks and 20 weeks after discharge, and was asymptomatic. In view of this clinical course, a diagnosis of subsultus tendinum complicating typhoid fever was made.

The burden of typhoid fever continues to remain high in India, especially in the pediatric population [4]. Complications that ensue following an episode of enteric fever are protean including neurological conditions [5]. These neurological complications can present as delirium, drowsiness, seizures, tremors, chorea, cranial nerve palsies, and even blindness. However, sparse literature mentions subsultus tendinum as a complication of typhoid fever in children. It is defined as the involuntary twitching of muscles, typically of fingers and wrists, and is classically described as one of the components of 'typhoid state', that occurs rarely in association with typhoid fever and occasionally with typhus fever and other bacteremias. Typhoid state is defined as a febrile state of semi-consciousness accompanied by delirium [6]. Typhoid state can be associated with carphology, which is the picking of clothes and floccillation, the state of picking at imaginary objects with the patient often found motionless and exhausted [6]. Subsultus tendinum has also been described along with the typhoid state. In this child, the twitching was not associated with delirium and it involved the muscles around the shoulder girdle rather

than the fingers or wrists. Hence, we propose that subsultus tendinum need not present with the typical 'typhoid state', but can rarely present as localized twitching of the skeletal muscles around the limb-girdle, even without delirium. The condition may persist for a few weeks, and abates gradually with the treatment of typhoid fever. It is not clear if anti-seizure medication is mandated in this situation; however, it can be supportive in relieving the symptoms temporarily, with timely and appropriate anti-microbial therapy being the mainstay of management.

*Contributors:* KNS,MS: designed the concept and overviewed literature, collected the case details and prepared the initial draft; PDM,MT: managed the patient and supervised the draft; JJ: supervised and reviewed the draft; WR: supervised the draft and overall guarantor of the authenticity of the case. The final manuscript was approved by all the authors.

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## Infantile Beri Beri: The Mizoram Experience

In the land where the bamboo flowers, and where the population is just over 10 lakhs, is the small North-Eastern state of Mizoram, from where we would like to share our experience with infantile beriberi and how we handled it.

In the last couple of years, from the months of August-September to around February-March, we used to get very sick infants aged mostly 6 weeks to about 3 to 4 months of age. The babies usually came with complaints of lethargy, drowsiness, groaning, poor feeding, sometimes with high shrill cries and sometimes with rapid breathing – fever was noticeably absent. Most were hospital-born with uneventful birth history. Their mothers had regular antenatal checkups and were receiving iron/ folic acid and calcium tablets till before and after delivery. All the babies were on exclusive breast feed. These babies were mainly from low socio-economic status families.

At first, our line of treatment was on the lines of infection/sepsis. But in spite of giving all the best antibiotics and all supportive measures, we kept losing these infants. When bird flu H1N1 cases were reported from these South East Asia and India, we thought it might be a viral cause and used Oseltamivir suspensions for such sick infants, but to no avail. We contacted National Institute of Virology (NIV), Pune for detailed virological analysis, but there was no response. Our diagnoses for these infants varied from septicemia, viral encephalitis, right heart failure (as echocardiographic findings showed pulmonary artery hypertension, tricuspid regurgitation, and right heart dilatation) [1], acute respiratory distress, shock *etc* as the final end stage presentation. These deaths were an important component of the Infant mortality rate (IMR) in Mizoram.

In December, 2014, having run out of options, we started giving vitamin B-complex infusion (Vitneurin, Beplex) along with the usual antibiotics and supportive care to these infants. Following that practice, there was a dramatic change in the outcome of these infants, and no more babies that came with these symptoms died in our hospital after that period (**Fig. 1**). We concluded that we were dealing with infantile beriberi, and giving a bolus of

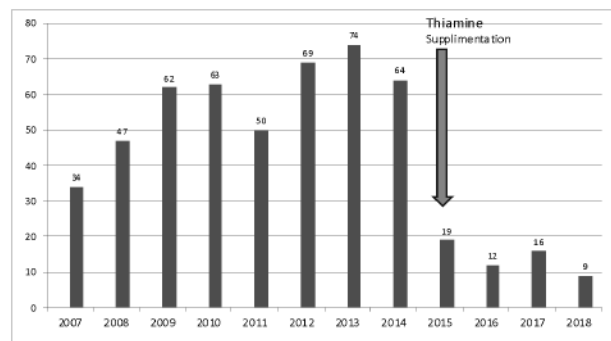
thiamine infusion and seeing the clinical response is the best diagnostic method [2].

We presented our findings to the Department of Health and Family Welfare of Mizoram (NHM) in Aizawl in March, 2015. Convinced by our observations, a government order was issued for all post-partum mothers to be given vitamin B complex tablets from their time of delivery till their babies were six months of age. These vitamin B complex tablets were to be dispensed from the institution of delivery (District hospitals, PHCs, Sub Centers) to last till their child's first vaccination. Further, vitamin B complex tablets were to be dispensed from sub-centers on vaccination days.

The actions taken by the government health authorities led to a marked decline in new cases of infantile beriberi in the State of Mizoram. From 2015 onwards, these cases just dried-up and the infant deaths dropped, possibly also contributing to the lowering of infant mortality rate of Mizoram.

Although, we did not find any literature on universal B-complex supplementation for postpartum mothers, it was better than waiting for infants to develop beriberi.

We now know that thiamine deficiency is rampant in Mizoram. These infants who died or came with the illness were mostly low socio-economic families, the mothers were regular pan chewers, and infants were on exclusive breast feeds. The risk of beriberi is known to increase in individuals who consume a diet high in thiaminase-rich foods (*eg*, raw freshwater fish or shellfish, ferns), a diet high in anti-thiamine factors (*eg*, tea, coffee, betel nuts), or both [3]. Since betel nuts cause depletion in vitamin B1



**Fig. 1** Infant mortality at Synod Hospital, Durtlang before and after routine thiamine supplementation in the post-partum period.

stores and with a poor nutritional intake, babies born to these mothers have a very poor chance of survival. Breastfed infants whose mothers have thiamine deficiency develop an infantile form of beriberi [4]. Providing iron and calcium tablets to mothers does not help, if the mother is thiamine-deficient [5].

Since supplementation for pregnant women in India is only oral calcium, iron and folic acid, it would be prudent to additionally provide vitamin B1, B6 and B12. This would go a long way in saving the lives of infant born to thiamine-deficient mothers without additional infrastructure and manpower inputs.

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## All is not well

It was the day of festival of lights. But an unfortunate toddler was stuck in darkness in the depths of an unclosed abandoned borewell near his home at Nadukattupatti in Trichy district of Tamil Nadu. Public, media, politicians, fire personnel and all the paraphernalia were around. But the child's life could not be saved. Even before this tragedy ended, another toddler from Tuticorin drowned in a water filled barrel at home. Paradoxically, her parents were watching the live coverage of the rescue operations of the borewell boy. Chennai was not far behind. A cracker burst incidence lead to loss of vision in a child who was a bystander. These examples are just tip of the iceberg and there could be several other unaccounted stray incidents in the community. Is the concept of prevention restricted only to textbooks of preventive medicine?

The major thrust area in child health is infections and non-communicable diseases; however, accidents in and around the home environment silently add to the under-five mortality. Water scarcity is an important basic problem giving rise to more borewells and water barrels. The above accidents were preventable. The abandoned borewell and water barrel should have been covered. The parents should have watched the toddler and not the television. Eyes should have been covered with goggles when bursting crackers.

Anticipatory guidance should be given by the

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healthcare provider to assist parents or guardians to prevent accidents during expected growth and development of their children. It is specific to the age of the child, and includes information about the benefits of healthy lifestyles and practices towards injury and disease prevention. Common examples include reminding about foreign body aspiration when pincer grasp develops; keeping kerosene, button batteries and pills away from the reach of toddlers; using appropriate footwear and bicycle helmets and decreasing screen time and avoiding junk food for school children and adolescents. Engineering at home, school and roads should focus on child safety. A multi-pronged approach using legislation, safety technology, improving the built-environment, anticipatory guidance by healthcare providers, and education of caregivers is necessary to decrease and prevent injuries in the twenty-first century [1,2]. The government and society should wake up and ensure that all is well with all children.

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## Formulation and Reporting of Guidelines: Providing More Information Will Make Them Better

The recently published consensus guidelines for immunization of children with cancer in India [1] address an important ‘felt-need’ of the practicing pediatricians. It has been stated in the article that these guidelines were in the making since 2014 and were finalized in 2018. Based on the list of references cited, it appears that although the experts have considered various guidelines published till 2018, they have only reviewed original data generated till 2014. Since the guidelines have been published in December 2019, it would have been better if original studies, especially the Indian ones, published till 2019 were reviewed and considered while making the recommendations. It was also desirable to provide information regarding the quality of evidence supporting every recommendation and the strength of each recommendation. This would have helped healthcare providers in making appropriate informed decisions with greater confidence. It may be noted that the Infectious Disease Society of America guidelines that the authors have referred to, provide such information for each recommendation [2].

In the interest of enhancing confidence in such guidelines, it is necessary that the experts formulating these provide greater details of the methodology used for arriving at the recommendations (including the search strategy and process, evidence selection criteria, process of evaluation of the quality of evidence, procedure for formulating recommendations, use of external review and quality assurance process). A gist of these procedural details can be published in the published guidelines, and comprehensive methodological details can be put up at the organization’s website. This will enhance the transparency in the system of making recommendations and will also allow a critical appraisal of the judgments made while formulating the guidelines [3].

With a view to ensure comprehensive reporting, the editors of *Indian Pediatrics* encourage authors to adhere to relevant guidelines (eg. CONSORT guidelines and STROBE guidelines, etc) while writing research articles [4]. They can extend this principle to reporting recommendations and practice guidelines by encouraging the expert groups to adhere to AGREE Checklist [5] or the RIGHT statement [6], while formulating and reporting recommendations. This will promote trans-

parency, allow critical appraisal and assure the readers about the evidence-base of the recommendations made.

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### AUTHORS’ REPLY

We thank the reader for his interest in the guideline on immunization of children treated with chemotherapy [1]. We agree that five years (2014-2019) was a long time for this guideline to develop from inception of the idea to publication; however, despite the lag time, the published version was updated immediately pre-publication in line with the Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP) 2018-2019 immunization recommendations [2] (which in itself is updated based on current evidence) based on pre-approval review by the ACVIP itself.

We also acknowledge that it is essential to detail the methodology of guideline development and grade the strength of recommendations based on the level of evidence. A companion article with more detailed review of literature and gradation of available evidence was previously submitted to this journal along with the guidelines, and is currently under review for publication in a different journal. When considered together, the companion article should be able to complement the published guidelines, so as to fulfill many of the items mentioned in the AGREE 2016 checklist [3].

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## Mauriac Syndrome in a Young Child with Diabetes

Mauriac syndrome is a rare complication of type 1 diabetes mellitus, usually reported in adolescents with poor glycemic control. It is characterized by hepatomegaly due to glycogen deposition, growth failure and delayed puberty [1]. Often these children have cushingoid facies, elevated liver enzymes and dyslipidemia in the form of increased cholesterol and triglyceride level in blood [2].

A two-year-old girl, diagnosed with type 1 diabetes six months back, presented with severe diabetic ketoacidosis. She had been advised split-mix regime but had poor compliance with the treatment. On examination, she had tachypnea, growth failure (weight and height <-2 SD for age), cushingoid facies, distended abdomen, and hepatomegaly (span 10 cm).

Investigations showed elevated blood glucose of 506 mg/dL, severe ketoacidosis (blood pH 6.98) ketonuria, HbA1c 11.5g/dL, high serum triglycerides (207mg/dL) and serum total cholesterol levels (192 mg/dL), elevated hepatic transaminase (AST 183 U/L, ALT 196 U/L), and normal antinuclear antibodies, thyroid function tests and anti-tissue transglutaminase levels. Ultrasound of abdomen showed normal echotexture of liver and normal intrahepatic biliary radicles. Ketoacidosis was managed as per standard protocol, and she was discharged on subcutaneous isophane and regular insulin. There was normalization of hepatomegaly and elevated liver enzymes after two months and liver biopsy was deferred. Mauriac syndrome was considered as the most probable explanation for liver dysfunction in this child.

There are anecdotal case reports of mutation in *PHKG2*, which is the catalytic subunit of the enzyme

glycogen phosphorylase kinase. Hepatomegaly is a cardinal feature of Mauriac syndrome present in the majority, which occurs due to hepatic glycogen deposition due to the facilitated glucose diffusion across the hepatocytes [3]. The possible mechanisms for growth failure in Mauriac syndrome are inadequate tissue glucose availability, reduced circulating IGF-I level, and a relative growth hormone-resistant state [4]. The cushingoid features probably occur due to secondary hyperadrenocorticism. Short acting insulin regimens and brittle glycemic control are predisposing factors in these children for this rare complication. Most children with Mauriac syndrome are reported during adolescence. To the best of our knowledge, the youngest case of this syndrome reported earlier was aged three years [5]. Clinicians should suspect it in any child with uncontrolled diabetes and hepatic dysfunction. Identification of this syndrome indicates poor disease control, which can guide further management.

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## Measles Immunization: Worth Considering Containment Strategy for SARS-CoV-2 Global Outbreak

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Data on individuals aged 18 years and under reported by the World Health Organization (WHO) China Joint Mission on COVID-19 suggest that there is a relatively low attack rate in this age group (2.4% of all reported cases). These observations are in agreement with epidemiological pattern of 2003 Coronavirus SARS-CoV outbreak when 8,098 cases of SARS were diagnosed worldwide and only <5% of all cases were diagnosed in patients <18 years of age [1]. 2012 MERS-Coronavirus outbreak reported few cases of MERS-CoV in children and it remained mainly a disease of adults [2].

Measles Mumps Rubella (MMR) vaccine has been thought to protect against other viral causes of respiratory diseases as well. Although satisfactory immune response is elicited upto 10 years after the MMR immunization, there is reduction in both the measles seropositivity rates and the measles antibody geometric mean concentrations [3]. An Italian study reported that significant proportion of subjects immunized for measles do not show a protective IgG titers even 10 years after vaccination [4].

Spike (S) of coronavirus and Hemagglutinin (H) of measles virus have a critical involvement in receptor recognition, as well as virus attachment and entry. The H of measles virus plays a crucial role in success of measles vaccine and the S protein of coronavirus is the most promising and studied candidate antigen for SARS-CoV vaccine development. It is the major target for neutralizing antibodies in human patients and in animal models. These

similarities in structural construct may play a role in eliciting immune response against coronavirus in a child previously immunized against measles.

Age-related declining immunogenicity of measles vaccine, possible structural and functional similarities between measles virus and SARS-CoV-2, sparing of young population from the clinically symptomatic cohort, and importantly, no other plausible immunological explanation of COVID-19 being a predominantly adult age group disease warrants serious probing of measles vaccine as a containment strategy during this ongoing pandemic. Measles vaccination carries a number of advantages: highly efficient, safe, easily manufactured at large scale, vaccine strains are genetically stable, measles does not recombine or integrate genetic material, vaccine does not persist or diffuse, mass booster doses can be given to both pediatric and adult population, and it presents an economical option that can be evaluated swiftly in times of crisis.

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### **Radiological Findings of Covid-19 Infection**

A review of the radiological features of the novel Corona virus infection has recently been published. In the various reports published so far it appears that initial chest CT findings are abnormal in 86% of cases. In fact, a small series of 5 suspected patients in whom the initial swab test for the virus was negative, early abnormalities on CT chest were helpful in making the diagnosis.

The characteristic features on chest radiography are bilateral, peripheral, basal predominant either patchy consolidation or ground glass appearance. A study of CT findings in 41 patients with the COVID-19 infection found that sick patients who required ICU care had patchy consolidation while the less sick patients had a ground glass appearance. Pleural effusions, cavitation, pulmonary nodules and lymphadenopathy usually imply superimposed bacterial infection. Early CT findings (0-4 days) may be normal in around 17%. In the mid-term (5-14 days), the lung lesions gradually progress. During the peak, there may be a crazy pavement pattern seen on CT chest. Clearance starts after 14 days but may not be complete even upto 26 days.

Compared to patients with SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome), in COVID-19 infections there were more bilateral involvement of the lungs whereas it was often initially unilateral in SARS and MERS.

With the rapid spread of the COVID-19 around the world it would be prudent for all physicians to be prepared to identify this disease early.  
*(Am J Roentgen 19 February 2020)*

### **Corticosteroids in Covid-19 Pneumonia**

Physicians from the Chinese Thoracic Society have developed an expert consensus statement on the use of corticosteroids in the 2019 novel Corona viral pneumonia. This was developed urgently *via* online meetings and email correspondence by physicians actively involved in the treatment of the COVID-19 patients.

They have cautioned rightly that corticosteroids are a double edged weapon to be used with caution. They have laid four guidelines for its use. First the benefits and harm for every individual patient has to be carefully analyzed. Second they may be used with care in critically ill patients. The dosage should be low: less than 0.5-1 mg/kg/day of methyl prednisolone, and duration should be short*i.e.*, less than or equal to 7 days. For patients with underlying hypoxemia due to previous disease or previously on corticosteroid, further use of steroid should be cautious.

The mechanism of use is purported to be an inhibition of the overwhelming inflammation and cytokine mediated lung injury.  
*(The Lancet 11 February 2020)*

### **Tackling Covid 19 With Technology**

China's response to the COVID 19 epidemic is being termed "*perhaps the most ambitious, agile and aggressive disease containment effort in history.*" What is remarkable is the imaginative use of technology. A case in point is a COVID app which can inform a person if he has been in contact with a confirmed case of the infection using flight and train data. The government has a platform which allows employers to detect if any of their employees may have been in close contact with an infected person using their national identification number. Telecom operators are sharing location data to identify contacts of infected persons. In Hangzhou, citizens have been given a health QR code marked as either green (safe to travel), orange (7 days of quarantine) or red (14 days of quarantine). In Sichuan province, in remote areas and where doctors are overburdened, artificial intelligence is being used to read CT chest reports for early identification of COVID 19 infections. In some areas, to reduce risk of infections, autonomous vehicles with "contactless deliveries" are being utilized to provide food and medicines.

In this brave new world, we are sailing in uncharted territory and history is being written every day.  
*(The Hindu 6 March 2020)*

### **FDA Assigns Boxed Warning To Montelukast**

Montelukast was approved for use for prophylaxis in childhood asthma above 1 year, for perennial allergic rhinitis above 6 months, seasonal allergic rhinitis above 2 years and exercise induced asthma above 6 years. However, since 2009, there have been reports of neuropsychiatric adverse effects with this drug. Around 16% of children above 1 year using montelukast reportedly stopped it due to neuropsychiatric side effects. These included irritability, aggression and sleep disturbances. Onset of symptoms was early (median, 7 days) and symptoms resolved quickly on stopping (mean, 2 days).

Citizen Groups have cited major problems like suicidal ideation, tremors and depression. The FDA, after various reviews, has now added a boxed warning which advises doctors to avoid using montelukast for minor symptoms especially allergic rhinitis.  
*(fda.gov 4 March 2020)*

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**Low-dose ofatumumab for multidrug-resistant nephrotic syndrome in children: A randomized placebo-controlled trial** (*Pediatr Nephrol.* 2020 Jan 28. doi: 10.1007/s00467-020-04481-y)

Children with multidrug-resistant nephrotic syndrome (MRNS) are exposed to drug toxicity and have increased risk of kidney disease progression. In small case series, the fully humanized anti-CD20 antibody ofatumumab (OFA) has been shown to have some benefits. In this double-blind randomized placebo-controlled trial, children who had been resistant to a combination of calcineurin inhibitors (CNI) and steroids, with or without mycophenolate mofetil (MMF) or rituximab, were randomized to receive single infusion OFA (1500 mg/1.73 m<sup>2</sup>) or normal saline. The authors assessed complete or partial remission of proteinuria after 3, 6 and 12 months, as well as progression to end-stage kidney disease. After 13 of the planned 50 children (25%) were randomized, the data monitoring board recommended study termination for futility. All 13 children remained nephrotic. Renal function worsened in 5 children (2 in Intervention arm, 3 in Placebo arm) who required renal replacement therapy during the study period. To conclude, OFA given in one single infusion of 1500 mg/1.73 m<sup>2</sup> doses does not induce remission in MRNS. The search for an effective management strategy in this group of children continues.

**Crescentic glomerulonephritis in children** (*Pediatr Nephrol.* 2020 Feb 12. doi: 10.1007/s00467-019-04436-y)

There is paucity of information regarding crescentic glomerulonephritis (cGN), the most frequent immunologic cause of acute kidney injury in children. In this study, over a period of 16 years, the authors retrospectively analyzed the data in 60 pediatric patients diagnosed with cGN. The underlying diseases were immune complex GN (45, 75%), including IgA nephropathy (19, 42%), lupus nephritis (10, 22%), Henoch-Schonlein purpura nephritis (7, 16%) and post-infectious GN (7, 16%); ANCA-associated pauci-immune GN (10, 17%), and anti-glomerular basement-membrane GN (1, 1.7%). Patient CKD stages at time of diagnosis and at a median of 362 days (range 237-425) were CKD I:  $n = 13/n = 29$ , CKD II:  $n = 15/n = 9$ , CKD III:  $n = 16/n = 7$ , CKD IV:  $n = 3/n = 3$ , CKD V:  $n = 13/n = 5$ , respectively. Forty-eight/60 children were treated with  $\geq 5$  methylprednisolone pulses and 53 patients received oral pre-dnisolone in combination with mycophenolate mofetil, cyclosporine A, and/or cyclophosphamide, rituximab, azathioprine, tacrolimus, and plasmapheresis/immunoadsorption. Overall, the treatment success was dependent on early diagnosis and aggressive therapy, as well as on the percentage of crescentic glomeruli on renal biopsy and on the underlying type of cGN. CsA and MMF seemed to be effective alternatives to cyclophosphamide.

**Kidney and blood pressure abnormalities 6 years after acute kidney injury in critically ill children: A prospective cohort study** (*Pediatr Res.* 2020 Jan 2. doi: 10.1038/s41390-019-0737-5)

Acute kidney injury (AKI) in pediatric intensive care unit (PICU) children may be associated with long-term chronic kidney disease or hypertension. This study was conducted to study the association between renal sequelae (low estimated glomerular filtration rate (eGFR) or albuminuria) and blood pressure (BP) consistent with pre-hypertension or hypertension, 6 years after PICU admission. This was a longitudinal study of children admitted to two Canadian PICUs (January, 2005-December, 2011). Of 277 children, 25% had AKI. AKI and stage 2/3 AKI were associated with 2.2- and 6.6-fold higher adjusted odds, respectively, for the 6-year outcomes. Applying new hypertension guidelines attenuated associations; stage 2/3 AKI was associated with 4.5-fold higher adjusted odds for 6-year CKD signs or elevated BP. The study concluded that kidney and blood pressure abnormalities are common 6 years after PICU admission and associated with AKI. Other risk factors must be elucidated to develop follow-up recommendations and reduce cardiovascular risk.

**Change in dyslipidemia with declining glomerular filtration rate and increasing proteinuria in children with chronic kidney disease** (*Clin J Am Soc Nephrol.* 2019;14:1711-18)

Dyslipidemia, a risk factor for cardiovascular disease, is common in chronic kidney disease (CKD) but its change over time and how that change is influenced by concurrent progression of CKD have not been previously described. A total of 508 children with CKD had 2-6 lipid measurements each, with a median (IQR) follow-up time of 4 (2.1-6.0) years. Longitudinal increases in proteinuria were independently associated with significant concomitant increases in non-HDL cholesterol [nonglomerular: 4.9 (3.4-6.4) mg/dL; glomerular: 8.5 (6.0-11.1) mg/dL] and triglycerides [nonglomerular: 3% (0.8%-6%); glomerular: 5% (0.6%-9%)]. Decreases in GFR over follow-up were significantly associated with concomitant decreases of HDL cholesterol in children with nonglomerular CKD (-1.2 mg/dL; IQR, -2.1 to -0.4 mg/dL) and increases of non-HDL cholesterol in children with glomerular CKD (3.9 mg/dL; IQR, 1.4-6.5 mg/dL). The study concluded that dyslipidemia is a common and persistent complication in children with CKD and it worsens in proportion to declining GFR, worsening proteinuria, and increasing body mass index.

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<sup>^</sup> Meningococcal Vxs global IMS data

Reference : 1. S.A. Halperin et al., Vaccine 28 (2010), 7865–7872 2. Lalwani S, et al. Int J Infect Dis. 2015;38:36-42 3. GSK data on file- Sales summary- May 2019

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For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

Abbreviated Prescribing Information of MENVEO (Meningococcal Group A, C, W-135 and Y Conjugate Vaccine Ph. Eur.)

**ACTIVE INGREDIENT:** Each reconstituted dose (0.5ml) contains: 10 µg Meningococcal group A oligosaccharide conjugated to 16.7-33.3 µg CRM197, 5 µg Meningococcal group C oligosaccharide conjugated to 7.1-12.5 µg CRM197, 5 µg Meningococcal group W-135 oligosaccharide conjugated to 3.3-8.3 µg CRM197, 5 µg Meningococcal group Y oligosaccharide conjugated to 5.6-10 µg CRM197. **Therapeutic Indication:** Active immunization of children (from 2 years of age), adolescents and adults to prevent invasive meningococcal disease caused by *Neisseria meningitidis* groups A, C, W-135 and Y. **Toxicology:** Children (> 2 years of age), adolescents and adults administered as a single dose (0.5 ml). Older people: Limited data in aged 56-65. No data in aged >65 years. **Booster vaccination:** May be given in subjects vaccinated with same, either conjugated or unconjugated polysaccharide meningococcal vaccine. **Need and timing of booster dose to be based on national recommendations.** Children under 2 years of age: Safety and efficacy not established. **Method of Administration:** Intramuscular injection, preferably in deltoid muscle. **Contraindications:** Hypersensitivity to any active substance, excipient or diphtheria toxoid (CRM197), or life-threatening reaction after administration of vaccine with similar components. **Postpone in acute severe febrile illness.** **Minor infection not a contraindication.** **Special Warnings and Precautions:** Take all precautions for prevention of allergic or other reaction. **Appropriate medical treatment and supervision should be readily available in case of rare anaphylactic reaction.** **Anxiety-related reactions (vasovagal reactions, syncope, hyperventilation or stress-related reactions)** may occur; ensure procedure to avoid injury from fainting. **Should not be administered intravascularly.** **Not protect against serogroups of *N. meningitidis* not included in vaccine.** **May not elicit protective immune response in all vaccines.** **Waning of serum bactericidal antibody titres against serogroup A seen in studies: clinical relevance unknown.** **If individual at risk of exposure to Men A: consider booster dose.** **No data on use as post-exposure prophylaxis.** **Vaccination in immunocompromised individuals may not result appropriate protective antibody response.** **Increased risk of invasive disease in individuals with familial complement deficiencies and treatments that inhibit terminal complement activation (for example, eculizumab).** **Evaluate risk-benefit in persons at risk of hematoma following intramuscular injection.** **Interaction with Other Medicinal Products and Other Forms of Interactions:** Can be given concomitantly with hepatitis A and/or B, yellow fever, typhoid fever (Vi polysaccharide), Japanese encephalitis and rabies. **Administer concomitant vaccines at separate injection sites (preferably contralateral).** **Adolescents (11-18 years of age):** Can be co-administered with Tetanus, Reduced Diphtheria and Acellular Pertussis Vaccine. **Adsorbed (Tdap) alone or Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant (HPV).** **Lower W-135 seroresponse on administration of MENVEO one month after Tdap; clinical relevance unknown.** **Children (2-10 years of age):** No data on concomitantly administration with other childhood vaccines. **Co-administration with other vaccines not studied.** **Administer concomitant vaccines at separate injection sites, preferably contralateral.** **Effects on Ability to Drive and Use Machines:** Dizziness very rarely reported, may temporarily affect ability to drive or use machines. **Undesirable Effects: Clinical Trial Data: A)** Subjects aged 2-10 years: Very common (> 1/10): sleepiness, headache, irritability, malaise, injection site pain, erythema (≤50 mm), induration (≤50 mm) Common (≥ 1/100 to <1/10): eating disorder, nausea, vomiting, diarrhea, rash, myalgia, arthralgia, injection site erythema (>50mm), induration (>50mm), chills, fever >38°C Uncommon (≥1/1,000 to <1/100): injection site pruritus B) Subjects aged 11 to 65 years: Very common (> 1/10): headache, nausea, myalgia, injection site pain, erythema (≤50 mm), induration (≤50 mm), malaise Common (≥1/100 to <1/10): rash, arthralgia, injection site erythema (>50 mm), induration (>50 mm), fever >38°C, chills Uncommon (≥ 1/1,000 to <1/100): dizziness, injection site pruritus **Post-marketing experience (all age groups):** hypersensitivity including anaphylaxis, tonic convulsion, fibrillar convulsion, syncope, vertigo, injection site cellulitis, injection site swelling, including extensive swelling of the injected limb. **Version: MEN/PI/IN updated 6-Sep-2019.**

Registered medical practitioners can refer company website <http://india-pharma.gsk.com/en-in/products/prescribing-information/> for full Product Information.

Please report adverse events with any GSK product to the company at [india.pharmacovigilance@gsk.com](mailto:india.pharmacovigilance@gsk.com).

Menveo® is a registered trademark of GSK group of companies.

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