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Ireland. Berlin: Springer; 2002. p. 182-91.

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Cancer-Pain.org [Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

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CONTENTS

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EDITORIAL

COVID-19: ROLE OF VARIOUS PHARMACOLOGICAL AGENTS

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Introduction

The current pandemic is caused by COVID-19, which first emerged in Wuhan, China, in late 2019. Considered as a highly contagious disease it has affected many countries with global average mortality rate being 4.6% (1). There have been ongoing efforts to develop effective treatment modalities for this dreaded pandemic. Currently, no specific therapies against SARS-CoV-2 infection exist, and a series of pharmacological agents have been repurposed with negative to inconclusive evidence available (2). These are briefly described below.

SARS-CoV-2, an ssRNA (single-stranded RNA) enveloped virus, binds to the ACE2 (angiotensin-converting enzyme 2) receptor on the cell surface. After binding, it enters inside the cell. Inside the cell, the virus synthesizes RNA and structural proteins leading to the release of viral particles. The following table (**Table 1**) summarizes the mechanism of action of major pharmacologic agents for COVID-19 (3).

Table 1: Proposed mechanism of action of drugs used against Covid 19

Drugs	Mechanism of action
Hydroxychloroquine sulphate / Chloroquine phosphate	Inhibition of ACE-2 present on cell surface for virus entry (by reduction of glycosylation in the enzyme), inhibition of release of viral particles into intra-cellular space, and anti-inflammatory effect (inhibition of interleukin-6, tumour necrosis factor, aberrant interferon, and other pro-inflammatory cytokines that cause lung injury leading to acute respiratory distress syndrome).
Lopinavir/ritonavir	3CL protease enzyme
Ribavirin	
Umifenovir	S protein/ACE2, membrane fusion inhibitor

Favipiravir	RNA polymerase inhibitor
Remdesivir	
Tocilizumab	IL-6 inhibition- reduction in cytokine storm
Ivermectin and Doxycycline	Inhibits ACE2 and prevent viral entry in to the host cells. Ivermectin also binds with NSP3, NSP10, NSP15 and NSP16 which helps virus in escaping from host immune system.
Dexamethasone	Reduction in lug injury and cytokine storm by inhibition of multiple inflammatory mediators

Antimalarial drugs (Chloroquine and Hydroxychloroquine)

A recent systematic review analyzed the therapeutic efficacy data of 17 studies including 8071 participants (4). The authors concluded the findings as follows: as very low quality evidence suggests an increased risk of mortality and adverse event with HCQ plus Azithromycin combination (not HCQ alone); caution should be exercised while prescribing this combination for treatment of hospitalized adults with COVID-19 infection. Good quality, multi-centric RCTs (including both hospitalized and non-hospitalized patients) are required for any firm recommendation to be made during the ongoing pandemic. The conclusion regarding prophylactic effect is not clear (5), and ICMR recommends that healthcare workers may continue to take HCQ till they have the risk of exposure. The dose suggested by ICMR in this regard is 400 mg BD on day 1 followed by weekly 400 mg after food.

Lopinavir/Ritonavir

A recent systematic review concluded that, the benefit-risk profile in severe COVID-19 cannot be considered positive until further efficacy and effectiveness data become available (6).

Ribavirin

A systematic review found inconclusive results in 26 of the 30 studies reviewed, with 4 studies demonstrating possible harm due to adverse effects including hematologic and liver toxicity (7).

Umifenovir (Arbidol)

A recent systematic review concluded unclear benefit, and advised to wait for till more data on safety and effectiveness becomes available (8).

Remdesivir

A recent systematic review concluded that there may be a favourable benefit-risk profile for remdesivir in severe COVID-19 infection, and further data on benefits would strengthen this evaluation (9). There is limited safety data for remdesivir, which should be obtained in further studies. However there is concern that it may not be better than antimalarial drugs (HCQ/CQ), may have more side effects, and is a highly costly treatment (10).

Favipiravir

In earlier data the drug is found to demonstrate a favourable safety profile though, safety concerns still remains regarding hyperuricaemia, teratogenicity and QTc prolongation. Given the limitations of the evidence and unresolved safety concerns, caution is warranted in the widespread use of favipiravir against pandemic COVID-19 (11).

Dexamethasone

A recent large RCT from UK (Recovery Trial)

including 2104 patients concluded that in patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support (12).

Tocilizumab

A recent systematic review concluded that based on low-quality evidence, there is no conclusive evidence that tocilizumab would provide any additional benefit to patients with severe COVID-19. Therefore, further recommendation of tocilizumab for COVID-19 cases should be halted until high-quality evidence from randomized controlled trials is made available (13).

Convalescent plasma or hyperimmune immunoglobulin

The authors of the Cochrane review are very uncertain whether convalescent plasma is beneficial for people admitted to hospital with COVID-19. There is only very low-certainty evidence for safety of convalescent plasma for COVID-19. There are 98 ongoing studies evaluating convalescent plasma and hyperimmune immunoglobulin, of which 50 are RCTs. The authors will continue to update this review periodically. These updates may show different results to those reported here (14).

Conclusions

To conclude, there is no good quality evidence for any of these pharmacological agents in the treatment of Covid 19 infection. As many RCTs are ongoing, we expect the picture to be clearer in due course. Till that time, these drugs should be used with caution.

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Competing interest -None

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REVIEW ARTICLE

NEONATAL HYPOGLYCEMIA

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ABSTRACT

Hypoglycemia in newborn stands as a very much treatable event. It can be transitional, and in first few hours of life Physiological. Compounded with other factors leading to less supply of alternate fuel to the brain it can cause neuro-developmental delay in later life. Taking into consideration of 'At Risk' neonates with blood glucose a 'safe range' approach for therapy has been postulated. The variation of the normal range and the presence or absence of symptoms makes the decision difficult but due to the treatability of the condition and the sequelae without adequate therapy gives special consideration to the less frequent malady.

Key words: Hypoglycemia, infants, preterm, neuro-development, treatment, prevention.

Introduction

GHypoglycemia in new born is said to be present when serum glucose level are significantly lower than the range in post-natal age matched normal infants. A value less than two standard deviation (SD) with matched healthy controls is an acceptable guide (1). But no absolute value can be taken to define clinically significant hypoglycemia. The drop in blood glucose after birth is common in healthy neonates, and is termed "Transitional Hypoglycemia". It resolves within 48 hours after birth. If it continues beyond this period, then it is pathological (2). The long term effect of low glucose concentration depends upon the ability to use alternate fuels for metabolism in the brain. Though healthy premature infants have a low glucose level, yet both pre-mature and full term infants are at risk for serious neuro-developmental deficit from equally low levels. This risk is related to the depth and duration of hypoglycaemia (3). Compounded to the fact, the situation is treatable, and an adequate intervention at appropriate time gives cent percent dividend. Therefore apart from a rigid definition a "safe range" approach have been adopted (4). The so called normal ranges are presumably dependent upon the infant's size, gestation, clinical conditions, availability of energy sources and ongoing energy demands. Definition of hypoglycemia should be flexible enough to encompass all these groups. As features of hypoglycemia are noted in a wide range of blood sugar, the safe range approach was considered from different angles.

Use of normal range

In normal new born, the blood glucose level is 80% of the maternal blood due to high consumption of glucose in the fetus with placental barrier. The gradient is 80% in the last trimester of pregnancy (5). Breast fed babies have blood glucose concentration from 1.5 to 5.3 mmol/L (1 mmol = 18 mg) compared to formula fed babies with a range of 2.5 to 6.2 mmol/L (6). Hypoglycemia can be fatal if gone undetected. Many studies have taken a level > 2.6 mmol/L as the safe range to guide therapy (7). Blood sugar in term breast fed neonates is rarely <2.5 mmol/L after 24 hours of age. Because of the concern of possible neuro-developmental sequelae (8), most authorities recommend any value of blood glucose <55 mg/dL in neonates should be viewed with suspicion (9). The whole blood glucose is 10 to 15 % lower than serum or plasma glucose concentration.

Safe range approach

There is not a specific plasma glucose concentration or duration of hypoglycemia that can predict permanent neurological injury in high risk infants (10). In absence of a concrete defined level for diagnosis, an operational threshold has been advocated (11,12). A number of studies in at risk term, preterm, and small for gestational age (SGA) infants have suggested an association of blood glucose level <2.6 mmol/L with short and long term neurological sequelae. Data from infants of diabetic mother (IDM) suggest that long term outcome may be negatively affected at glucose levels from <1.1 mmol/L to 2.8 mmol/L (13). Unfortunately, given the wide range of normal blood glucose levels found in newborns, and the varieties of causes of low blood glucose, cohort and case control studies could not determine, whether low blood glucose is the direct cause of an adverse outcome or simply an associated finding. Most neonates compensate for physiologic hypoglycemia by producing alternative fuels including ketone bodies which are released from fat (14). No studies have shown that treating transiently low blood glucose levels results in better short term or long term outcome compared with no treatment, in fact there is no evidence at all that hypoglycemic infants with no clinical signs benefit from treatment (15,16). Clinical trial of abolition of symptoms with administration of glucose stands as the best option to define hypoglycemia. But the benefit of the intervention to the short and long term risks is not well defined.

Glucose homeostasis

The fetus has a continuous supply of glucose through the placenta. Because of the free access without barrier the blood glucose of the mother and fetus are equal. After birth the blood glucose immediately falls to 70% to 80% of maternal blood and the lowest is around 3 hours after birth. With compensatory mechanisms it rises again. Glucose and oxygen are the main metabolic substrates of mature brain, but the neonatal brain can use alternative metabolic fuels like Ketones and Lactate. That is why the brain may be able to function normally or near normally despite very low levels of blood glucose. Profound neurologic compromise and irreversible damage occur if the brain is deprived of glucose and alternative metabolic substrates.

Constant maternal glucose supply is interrupted with cord ligation which is followed by an endocrine stress response, and is characterized by a huge catecholamine response of 3 to 10 times, increase in plasma glucagon of 3 to 5 times and a plasma cortisol surge. These endocrine changes are essential for hepatic glycogenolysis, gluconeogenesis, and lipolysis (17). Glycogenolysis occurs mostly in liver from where 90% of glucose store is converted to glucose with 2 hour starting just after cord clamping. Gluconeogenesis produces glucose from amino-acids (alanine in particular), lactate, pyruvate, and glycerol. They enter at different points in glucose metabolic pathway (EM pathway). It starts at 2 hours after birth, peaks at 12 hours. Lipolysis,

glycerol is mobilized from adipose tissue and can be directly utilized in gluconeogenesis. Other products like fatty acids and triglycerides derived from the process are metabolized to ketone bodies which may directly be utilized by the brain for energy production. Alternative substrates, glucose oxidation supports 70% of brain energy need, ketone bodies and lactate are important alternatives. Hepatic ketogenesis is limited within first hour of birth. From 12 hours, lipolytic ketogenesis is maximum, which continues for 2 to 3 days (18). All these events are described in **Figure 1**.

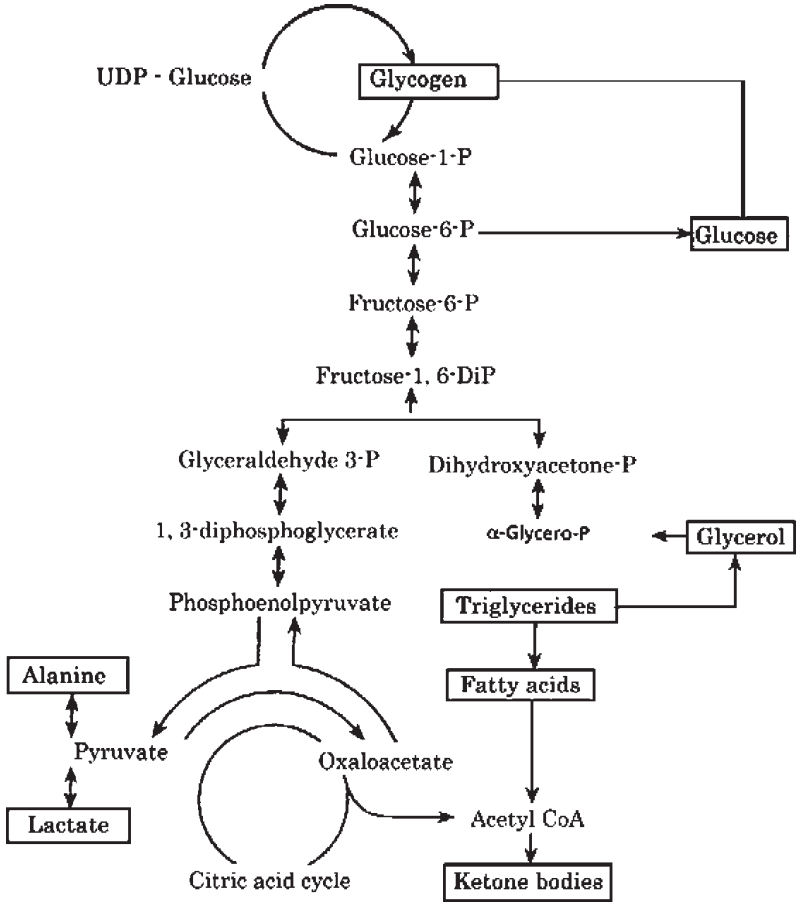

Figure 1: Alternate pathways of glucose production during hyp[oglycemia.

Measurement of blood glucose

It is essential to measure blood glucose rapidly and accurately in high risk neonates (19). A variety of techniques have been developed. The bedside determination employs capillary whole blood, and the laboratory more likely gives serum glucose value which is 10-15% more than the whole blood samples. The bed side strip test utilizes "glucose oxidase" method. At lower levels of glucose the reliability is less. However, it can be accepted as a reasonable screening test and with low levels therapy can be instituted keeping a sample for laboratory evaluation. The modern strip tests claim to be reasonably reliable.

Pathology in brain due to hypoglycaemia

The most consistent performance of severe hypoglycemia is acute phase occipital-posterior cortical

edema with atrophy in the chronic phase (20). It can be manifest as haemorrhage or infraction. Basal ganglia and thalamus can also be involved. Energy metabolic disorder during hypoglycemia can lead to brain cell softening, swelling, necrosis, gyrus atrophy or white mater demyelination.

Neonates at high risk for hypoglycaemia

Normal blood glucose levels are maintained by gluconeogenesis. Neonatal hypoglycemia most commonly occurs in infants with altered gluconeogenesis brought about by excess insulin production, altered counter-regulatory hormone production, inborn errors of glucose and amino-acid metabolism or an inadequate substrate supply. Classically these states occur in infants of diabetic mothers, small for gestational age (LGA), preterm infants, large for gestational age (LGA) infants, and late preterm (21). Some doubts have been raised as to whether LGA infants who are not IDMs are truly at risk.

Causes of neonatal hypoglycemia

These are mentioned below (9,22,23).

A. Hyper-insulinism: In this group the insulin production is high with normal or low substrate supply.
   - ✓ Persistant hyperinsulinemic hypoglycemia of Infancy (PHHI)
   - ✓ Infants of Diabetic mother (IDMs)
   - ✓ Infants of mothers having gestational diabetis.
   - ✓ Erythroblastosis fetalis
   - ✓ Beckwith Weidmann Syndrome
   - ✓ Familial hyperinsulinemic hypoglycemia (Nesidioblastosis)
   - ✓ Rapid tapering of higher glucose infusion.
   - ✓ Maternal therapy with beta-agonists (terbutaline, isoxsuprine, salbutamol), chlorpropamide & possibly benzothiazides.

B. Decreased stores –
   - ✓ Prematures
   - ✓ Intra uterine growth retardation: Smaller of the discordant tweens (by more than 25%) is severely affected. Apart from low glycogen stores in the liver they appear to have decreased gluconeogenesis, free fatty acid oxidation, cortisol production, high insulin level and reduced epinephrine production in response to hypoglycemia.
   - ✓ Increased Metabolic demands: sick infants may develop hypoglycemia due to increase in caloric need in comparison to the store in the body. Prematures with disease develop hypoglycemic symptoms early. Contributing causes are: prematures infants with respiratory distress syndrome, shock, sepsis, hypothermia, perinatal asphyxia, congenital cyanotic heart disease, abrupt Interruption of IV fluids with high glucose concentration and exchange transfusion, and polycythemia.
   - ✓ Genetic and Endocrine deficiencies: they are rare causes in neonates. These include: carbohydrate metabolism defects (Galactosemia, Glycogen storage disease and fructose intolerance), endocrine deficiency – adrenal deficiency, hypothalamic deficiency, and congenital hypopituitarism, and defect in aminoacid metabolism (Maple syrup urine disease, propionic acidemia, methyl malonic acidemia, and Tyrosinemia).

Clinical manifestations

Because the clinical presentations overlap with other diseases it is difficult to assess the exact incidence of hypoglycaemia (9,19,23,24). It probably varies from 1 to 3 per 1000 live births and affects about 5 to 15% of growth restricted infants. In approximate order of frequency symptoms include: Jitteriness or tremors, apathy, episodes of cyanosis, convulsions, intermittent apneic spells or tachypnea, weak or high pitched cry,

limpness or lethargy, difficulty in feeding, eye rolling, and episodes of sweating (though rare), sudden pallor, hypothermia or cardiac failure/arrest. Sometimes neonates may not have any symptoms. The non-specific nature of the symptoms makes it mandatory to take blood glucose level and administer glucose in therapeutic doses. Good response confirms hypoglycemia.

Differential diagnosis

Because of the commonness in clinical manifestation the following should be borne in mind.

- ✓ Sepsis and meningitis
- ✓ Central nervous system anomalies (intracranial bleed, edema or infection).
- ✓ Perinatal asphyxia.
- ✓ Apnea of prematurity.
- ✓ Congestive cardiac failure and polycythemia
- ✓ Maternal drug withdrawal
- ✓ Metabolic abnormalities: Hypocalcemia, Hypomagnesemia.

When 'at risk' infants should be screened

Due to the interruption of maternal-fetal flux of glucose at birth blood sugar level in neonate starts falling during the 1st or 2nd hour of birth reaching a natural through before rising again. The value of screening well babies at this time is limited. Williams complied a review of neonatal hypoglycemia, had recommended infants at risk be screened at 4 to 6 hours of age, asserting that no studies demonstrate harm from a few hours of asymptomatic hypoglycaemia (25,26).

Cohort studies demonstrated IDMs frequently experience asymptomatic hypoglycemia by 1 hour of age supporting earlier screening in this population. It is found that the average time LGA neonates experience low blood glucose level was 2.9 hours with a range from 0.8 to 8.5 hours. Preterm SGA infants experienced the same at 6.1 hours with range of 0.8 to 34.2 hours. Keeping the longest time is consideration one can infer LGA and IDM infants usually get hypoglycemia within 12 hours of birth. Screening beyond this period is not required if the blood glucose level is maintained at 2.6 mmol/L or higher (27). However, the preterm SGA infants are vulnerable up to 36 hours of age particularly if regular feeds or IV fluids are not established. Therefore screening can be discontinued at 36 hours in these neonates with establishment of feed and if blood glucose is maintained at 2.6 mmol/L or higher. Based on the assumption that brief periods of asymptomatic hypoglycemia are benign, it is recommended that screening be initiated in at risk babies at 2 hours of age (after an initial feed) and should be continued until the period of risk is considered to be over.

Screening for Neonatal hypoglycaemia

Traditionally, blood glucose has been conveniently measured on capillary samples using chemical strips or bed side glucometers, as a substitute for formal laboratory analysis (28). Unfortunately, it is not very reliable at low glucose levels. In addition there is variability between different types of samples used. Plasma glucose is higher than whole blood glucose (9), stored blood gives lower levels which is proportionate to the delay in processing. There is also difference between capillary and venous blood sampling. However, the newer techniques of determination from capillary blood give dependable result with advancement of technology. However, as a working principle screening can be done with glucometers and if level is found low requiring intervention a venous sample should be processed in the Laboratory, the result of which should be made available early. Little more glucose is not going to do much harm if administered and discontinued under supervision.

Intervention level of blood glucose (3,8,15,29)

- ✓ Symptomatic hypoglycemia – Symptomatic hypoglycemia results in neuronal injury and mental retardation, making urgent intervention

mandatory in sick new borns. The proposed cut-off at 2.6 mmol/L in at risk infants is recommended. Beyond this level the symptoms are unlikely to be due to hypoglycemia.

- ✓ Asymptomatic Hypoglycemia – Long term follow up of SGA preterm infants with blood glucose less than 2.6 mmol/L demonstrated a association of hypoglycemia with lower head circumference and lower developmental score (30). Follow up of IDMs with asymptomatic hypoglycemia with blood glucose <1.5 mmol/L showed minimal neurological dysfunction (31). Taking all these into account a concept of operational threshold has been proposed. The glucose concentration of 2 mmol/L has been taken as the threshold glucose value that requires action and 2.6 mmol/L is the target level to which interventions are aimed at. At risk babies who repeatedly have blood glucose levels of less than 2.6mmol/L despite subsequent feeding should be considered for IV therapy.
- ✓ Screening Frequency – Blood glucose screening may be performed at 2 hours of age in at risk neonates. It should be repeated every 3 to 6 hours. In IDMs and LGA it should be discontinued after 12 hours if blood glucose becomes stable at 2.6 mmol/L or higher. In SGA and Preterm infants it is to be continued up to 36 hours. It is reasonable to screen once or twice in the second day of life to ensure the blood glucose level remains >2.6 mmol/L. If there is no feeding concern and the infant is well it should discontinued at 36 hours.

Treatment (4,7,9,29)

Essentially there are two sets of approaches. The first supports increased energy intake either orally or intravenously and the second supports increased mobilization of energy stores using counter regulatory hormones such as glucagon or corticosteroids. The urgency and nature of interventions depend upon the presence of symptoms like convulsion/no convulsion and severity of hypoglycemia.

Asymptomatic hypoglycemia:

a) At risk asymptomatic newborns should be encouraged to take frequent breast feeding. It should be started within ½ hour to 1 hour after birth and continued 2 hourly. In case of hypoglycaemia, feeding should be as soon and as frequent as possible with repeated glucose measurement (31).

b) There is some evidence to suggest that increased carbohydrate intake prevents low glucose levels in healthy term infants. Routine supplementation of dextrose water reduces the likelihood of hypoglycemia. In neonates who could not suck at breast, expressed breast milk orally by cup and spoon or by gavage will help. To the Breast milk or formula extra glucose can be added. In situation of enteral feeding, blood sugar should be checked after 60 minutes to ensure response.

c) If enteral feeding is not effective and plasma glucose level declines to <2.6 mmol/L in preterms and < 2 mmol/L in term infants, intravenous (IV) glucose infusion should be started at the rate of 4-6 mg of glucose/kg/minute. Please remember 80 ml/kg/day of 10% dextrose provide 5.5 mg/kg/minute. Breast feeding can be continued as colostrum gives less volume load.

Symptomatic Hypoglycemia:

a) Symptomatic neonates without seizure: When symptoms other than seizures are present an intravenous bolus of 200 mg/kg (2ml/kg) of 10% dextrose will be effective in elevating and stabilizing blood glucose level. It should be followed by IV infusion of 10% dextrose solution to provide 4-6 mg/kg/minute which will keep the blood glucose level at > 2.6 mmol/L.

b) Symptomatic neonates with Seizure: When seizure exists with defined hypoglycemia IV infusion of 4 ml/kg of 10% dextrose should be done and it should be followed by infusion of 8 mg/kg/minute of dextrose. Blood sugar level should be checked every 30 minutes. If not controlled the glucose concentration should be raised step wise from 10% to 12.5% or higher. The IV infusion should be not be > 120 ml/kg/day as it will cause over hydration and hyponatraemia.

c) Resistant and persistent hypoglycemia: In spite of high concentration of IV glucose if hypoglycemia is not controlled it is called resistant hypoglycemia. When hypoglycemia persists beyond 1 week it is called persistent hypoglycemia. Both require further investigation for pharmacological causes or pancreatic pathology. In hyperinsulinemic states Diazoxide, 2-5 mg/kg/dose 8 hourly can be given orally if glucose transfusion fails. Glucagon by intravenous bolus of 0.1 mg to 0.3 mg/kg or infusion of 10 - 20 µg/kg/hour has been observed to raise bold glucose and prevent recurrent episodes of hypoglycemia in term and preterm infants with adequate glycogen store. Hydrocortisone 10 mg/kg/day in two divided doses helps but data are limited for its use. Dexamethasone 0.25 mg/kg intravenously can be given every 12 hourly as an alternative to hydrocortisone. Octreotide can be used if no response to Diazoxide in a dose of 7-12 µg/kg/day with a maximum of 40 µg/kg/day subcutaneously every 4-6 hours or can be given by continuous intravenous drip. Throughout therapy the oral and IV intake should not exceed 100 ml/kg/day to avoid hypervolemia and hyponatremia. Breast feeding is to be encouraged due to low volume with high calorie in first few days.

Prognosis (8,11)

Prognosis is good in asymptomatic hypoglycemia of short duration. Recurrence is 10 to 15%. Abrupt discontinuation of IV therapy before good tolerance to oral feed predisposes for recurrence. Severe prolonged symptomatic hypoglycemia is associated with neurologic sequelae, neuro-developmental and intellectual function delay in later age (32). Symptomatic SGA infants with hyperinsulinemic hypoglycaemia and IDMs have a poorer prognosis for subsequent normal intellectual development than asymptomatic infants.

Conclusions

Hypoglycemia in neonates is not very uncommon especially in SGA, Preterm LGA and IDMs. Its link with future intellectual handicap and easy methods of management renders an important position to this less conspicuous disease. Though healthy newborn can stand blood glucose level of 1.8mmol/L in the first few hours without difficulty, yet adverse short and long term outcomes my result from levels <2.6mmol/L in those who are at risk. In symptomatic and persistent hypoglycaemia, a negative outcome is almost certain. Screening and intervention is therefore felt mandatory in early detection and treatment of infants at risk.

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Competing interest -None

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REVIEW ARTICLE

TRANSIENT HYPOTHYROIDISM IN THE NEWBORN: WHETHER TO TREAT AND HOW LONG TO TREAT

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ABSTRACT

Transient CH is a temporary abnormality of thyroid function identified after birth which reverts back to normal after varying period of time and may or may not require lifelong replacement therapy. Incidence of transient hypothyroidism varies in different regions, depending on the basis of newborn screening tests (NBS) or abnormal follow up confirmatory result at 3 years of age. From among the cases diagnosed as CH, as much as 17% - 40% was later found to be transient CH cases. Transient CH may be due to factors primarily affecting the thyroid such as iodine deficiency or excess, maternal thyroid-stimulating hormone receptor (TSHR) antibodies, prematurity, maternal ingestion of antithyroid drugs, maternal or neonatal iodine exposure, DUOX 2 (dual oxidase 2) mutations and hepatic hemangiomas. In vast majority of infants, the classic signs and symptoms of CH are not visible immediately after birth due to temporary protection by maternal thyroxine. Large scale implementation of NBS is primarily responsible for early detection and management of hypothyroidism in the newborn, thereby preventing intellectual disability to a great extent. In this review a rational and evidence based approach has been presented to take a decision regarding management of transient CH.

Key words: Hypothyroidism, infants, neuro-development, treatment, newborn screening.

Introduction

Congenital hypothyroidsm is the most common cause of preventable mental retardation and intellectual disability (1).Thyroid hormone plays an important role in the development of brain during the first 2 to 3 years of life. Majority of newborns do not manifest clinical Signs and Symptoms of deficiency until the age of 3 months either due to transplacental passage of maternal thyroid hormone or some residual thyroid function (2). Congenital hypothyroidism (CH) has been classified as permanent CH (sustained thyroid deficiency throughout life necessitating lifelong treatment), transient CH (temporary phase of thyroid deficiency detected at the time of birth, later improving to normal thyroid levels

usually in few months) and Syndromic hypothyroidism (where CH is associated with reduced function of other organs) (3). Transient hypothyroxinemia of prematurity (THOP) is defined as deficiency of thyroid hormone [low thyroxine (T4) accompanied by weak or absent TSH surge after birth in preterm infants]. For the last three decades newborn screening (NBS) for CH is practised in many countries. The inclusion of NBS is strongly advocated by the Indian Academy of Pediatrics (IAP) in India's public health policy (4). Of late Rashtriya Bal Swasthya Karyakrama (RBSK) under the umbrella of NHM, has incorporated detection of CH in its public health policy in India.

Epidemiology

After the introduction of NBS the incidence of CH has markedly increased globally. The overall incidence ranges from 1:3000 to 1:4000 of live-births worldwide as per data in 1975. In 2011, another study reported CH prevalence to be approximately 1:2000 to 1:3000. The exact incidence of CH in India is not known. However an Indian study (including 40,000 neonates), reported the incidence to be 1:2640 (6). A study by ICMR (Indian Council of Medical Research) reported the incidence to be 1:1130 (7). A study from CMC Vellore over a period of 18 years reported a rate of 1:1204 (8). The transient CH case rate was found to be 6.5%. A study in NBS programme in Michigan, USA reported the prevalence of transient CH to be around 24-36% of confirmed CH cases (9).

Patho-physiology of transient hypothyroidism

The fetal thyroid starts to concentrate iodine around 10 weeks of gestational period and to secrete thyroxine (T4) and triidothyronine (T3) around 12 weeks. These two hormones increase gradually throughout gestation. Maternal thyroid function is modulated significantly by placental oestrogen and HCG production leading to Thyroid Binding Globulin (TBG),T4 and T3 in the maternal circulation thereby increasing thyroid function (10). Placenta acts as a potential barrier for maternal TSH transfer causing inactivation of majority of maternal T4 and thus effecting insignificant impact on the growing fetus. Although in early gestational period small amounts of maternal thyroid hormone cross the placental barrier, fetal thyroid develops independent of maternal thyroid function. The fetus has a limited need for thyroid hormones as it remains in a state of anabolism normally. The need for thyroid hormones is ensured by inactivation of thyroid hormones produced by the fetal thyroid gland by converting these into sulphated moieties by action of mono-deiodinases (MDI) especially MDI-3 expressed by the placenta. Maturation of the hypothalamic-pituitary-thyroid (HPT) axis starts functioning around 20 weeks and is complete close to term only (11). The neonatal thyroid gland is required post-natally to ensure a constant supply of thyroid hormones to ensure thermogenesis and support development of other organs like central nervous system. The preterm infant with an immature HPT axis and limited capacity of generating bioactive thyroid hormone witnesses a dip in thyroid hormone around one week of age (12). In sick preterm infants where a poorly functioning HPT axis is unable to produce enough TSH in response to low T4 and T3, this decrease is exaggerated, thereby leading to a relative deficiency. This relationship is responsible for the majority of transient CH witnessed in many neonates (10).

Etiology

1. Iodine deficiency:- Iodine is an essential element for production of thyroid hormone, containing 59% of T3 and 65% of T4. During pregnancy fetal iodine store is dependent upon the maternal iodine status and post-natally on the iodine content of human milk or formula milk. India is now considered an iodine deficient country with pockets of iodine deficiency (13), though it is more common in Europe due to

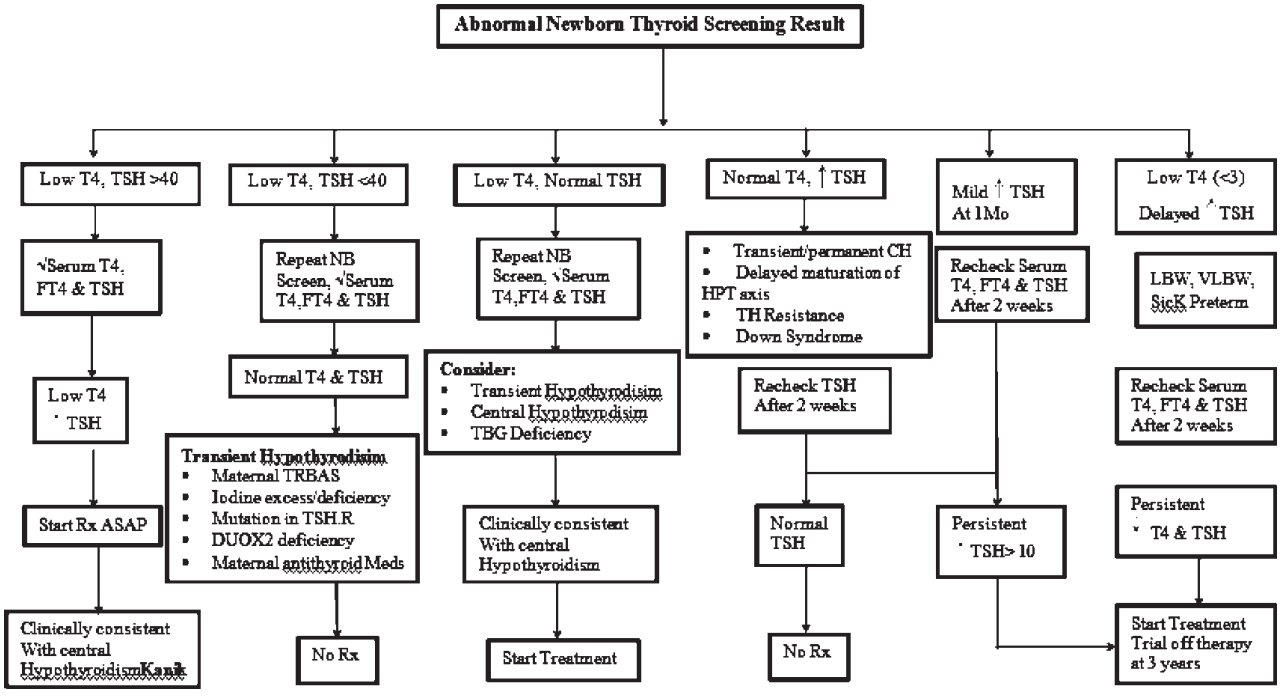
iodine deficiency in maternal diet. Neonatal TSH status is indicative of iodine status of the population. The premature infants are especially at risk of hypothyroidism due to iodine deficiency because of their in-utero thyroidal stores and immaturity of the hypothalamic pituitary axis for thyroid hormone production and less ability for converting T4 to metabolically active T3. Deficiency of other elements, selenium and iron affects neurologic development and thyroidal response to iodine supplementation (14). More amount of iodine is required in the extra uterine environment to maintain a positive iodine balance in these infants than term infants. So in areas of iodine deficiency infants show transient hypothyroidism in the first weeks after birth.

2. Maternal TSH Receptor Blocking Antibodies:- These develop in women suffering from Autoimmune thyroid diseases like Graves, Chronic Lymphocytic Thyroiditis, and Acquired hypothyroidism, DUOX2 enzyme mutations. Trans-placental passage of these antibodies can cause transient blockage of thyroid function in neonates thereby producing transient hypothyroidism (15-17). The half life of these antibodies is around 3-4 weeks and they disappear completely by 3-6 months. This type of hypothyroidism closely resembles thyroid agenesis even though it is transient (16).
3. Maternal anti thyroid drugs:- Trans-placental passage of anti-thyroid drugs like Propylthiouracil or Methimazole can reduce fetal thyroid hormone production for a few days to 2 weeks from birth. Intra uterine thyroid replacement may be warranted as this may develop fetal respiratory distress. The neonatal goiter and hypothyroidism normalises in a few days time and most often the TSH level will be normal (18,19).
4. DUOX2 mutations:- DUOX 2 is required for production of hydrogen peroxide, required by thyroid peroxidise for thyroid hormone synthesis. Monoallelic mutations result in transient hypothyroidism (20). The presence of coexistent iodine deficiency may alter the phenotype of such congenital defects.
5. Iodine excess:- Iodine excess, just like iodine deficiency, can cause transient hypothyroidism especially in premature infants. This is because of the inability of infants' thyroid gland to tackle the excess thyroidal iodine uptake due to exposure to an iodine load. This exposure may be fetal or neonatal. Maternal use of Amiodarone during pregnancy can cause transient hypothyroidism in newborns. The resolution occurs around 5 months but adverse neurological outcomes may still occur (21,22). Use of antiseptic compounds in pregnancy, ingestion of excessive iodine containing nutritional supplements and Amnio-fetography with iodine containing contrast can also cause transient hypothyroidism (23,24). Neonatal exposure to excess iodine use can also cause hypothyroidism due to Wolf-Chaikoff effect especially in premature babies. These infants get exposed to high doses of iodine due to usage of iodine containing antiseptics for umbilical and peripherally inserted central catheter lines (25,26).
6. Hepatic hemangiomas:- Large amounts of type 3-iodothyronine deiodinase, produced by congenital large hemangiomas cause a consumptive type of hypothyroidism. Serum T4 levels are low, TSH and reverse T3 levels are high. So to maintain an euthyroid state high doses of thyroxine are required. Involution or surgical treatment of hemangiomas cause resolution of hypothyroidism (27,28).
7. Transient hypothyroxinemia of prematurity (THOP):- It occurs in preterm infants after birth due to a weak or absent TSH surge. The incidence increases with

decreasing gestational age (29). A recent study in Netherlands demonstrated no relationship between THOP and future neuro-developmental defect (30).

Newborn Screening (NBS)

The most screening test for CH is initial measurement of TSH. Sample can be collected from cord blood or after the age of 24 hour but best window period is 48-72 hours. Blood sample is usually collected by heel prick spotted on filter paper, then dried and sent for TSH analysis. The European Society for Pediatric Endocrinology (ESPE) guidelines (2014) advised repeat screening in preterm neonates with gestational age <37 weeks, low birth weight and very low birth weight neonates, ill neonates admitted to the NICU, multiple births and in babies whose sample is collected in first 24 hours. The second screening sample should be collected at 2 weeks of age or 2 weeks of first sample (31). In India, majority of the screening programmes are conducted between 2nd and 5th day of birth, to minimise false positive high values (unless placental or cord blood is used) due to the physiological neonatal surge in TSH (within 30 minutes of birth) (32). The cut off values between the NBS programmes vary because it largely depends on timing of sample collection to define cut-offs. In a recent study conducted in India, authors recommended that a cut off of e"20 mIU/l for capillary TSH screening beyond 24 hours of life is optimal in the Indian setting and repeat sampling is advised is advised in newborns with initial TSH value between 10-20 mIU/l (33). An algorithm is provided (**Figure 1**).



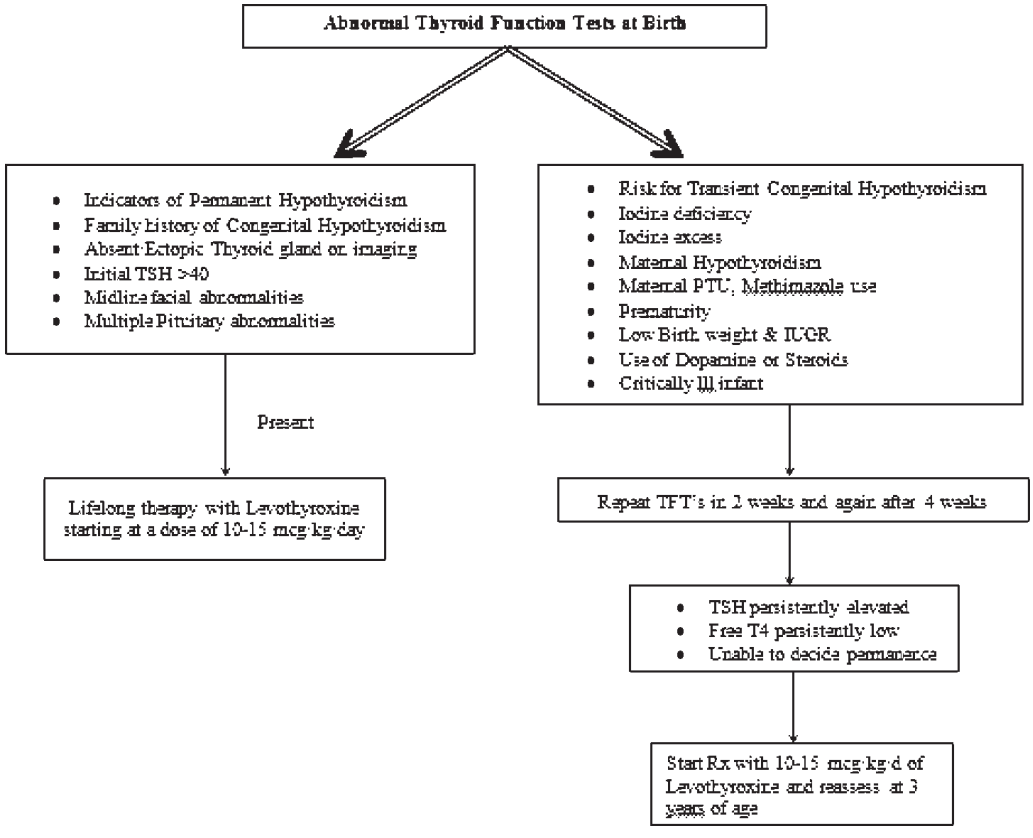
Clinical features

Clinical differentiation between permanent and transient forms of CH in the newborn period is very difficult. The classic clinical symptoms and signs of CH are usually absent in the newborn period in the vast majority of infants. Presence of an ectopic thyroid gland, absent thyroid gland by ultrasound, an initial TSH of more than 100 mIU/l and multiple pituitary hormone deficiencies clinically confirms the permanent nature of CH. In the absence of clinical clues, if risk factors like iodine

deficiency, peri-natal iodine exposure, history of maternal hyperthyroidism or its treatment, prematurity, low birth weight, malnutrition and use of drugs like steroids and dopamine are present, the possibility of transient CH should be considered (34). However the classic features of CH include large anterior and posterior fontanel, prolonged physiological jaundice, relatively narrow forehead, depressed nasal bridge, large tongue, puffy eyelids, thick, dry and cold skin, long abundant coarse hair, bradycardia, hypotension with narrow pulse pressure, abdominal distension, anaemia, umbilical hernia and hypo-reflexia (35).

Management

Thyroid function test including TSH and free T4 decides the mode and course of treatment. Figures 2 and 3 provide an algorithm of suggested approach of treatment of both permanent and transient CH. High TSH and low free T4 value in serum confirms the diagnosis of primary hypothyroidism and warrants immediate treatment with levothyroxine with an initial dose of 10-15 µg/kg/day. Levothyroxine should be administered orally. As liquid formulations are not available, tablet should be crushed and administered via small spoon with a few ml of water or breast milk. Normal free T4 or total T4 concentration indicates subclinical hypothyroidism. The newborns with marginally elevated TSH (6-10 mIU/L) should be meticulously monitored and serum TSH and free T4 be re-estimated in a week. In case of serum TSH not remaining in normal level by 4-6 weeks of age, treatment with thyroxine should be initiated. Low free T4 with low or normal TSH concentration indicates Central hypothyroidism. If TSH is only estimated this form of hypothyroidism is not detected but these cases require treatment with thyroxine. An algorithm is provided (**Figure 2**).



Complications

Transient CH if untreated may lead to severe long term consequences and morbidity. Due to lack of imaging modalities and problems in interpretation, the cause of transient CH cannot be diagnosed in all centres. Also majority of centres do not have the facility to perform genetic tests to differentiate between permanent and transient CH. Persistent elevation of TSH beyond 4 weeks of age is detrimental for brain development. In population with higher incidence of autosomal recessive diseases, lack of iodine supplementation and lack of prenatal care and testing, specific approach is recommended. The high cost of taking care of one affected infant will far outweigh the cost of treatment up to 3 years and cost of relatively cheap laboratory follow up tests. If a case is missed, the chance of detection of it being a permanent or transient CH in later life is almost impossible. Therefore, in the event of low FT4 or TSH more than 5 mIU/L on serial testing within the first month of life, the infant should be started with thyroxine until 3 years of age to protect brain development. Therapy should be aimed at ensuring normal growth and development by keeping Total T4 or FT4 serum concentration level in the upper half of the reference range during infancy and serum TSH range in the optimal range of 0.5-2.0 mIU/L (36). ISPAE guidelines 2018 also recommend initiation of Levothyroxine at 10-15 µg/kg/day in the neonatal period (37). Serum FT4/T4 is measured at 2 week, TSH and T4/FT4 at 1 month, then 2 monthly till 6 months, 3 monthly from 6 months-3 years. Babies with the possibility of transient CH should be re-evaluated at the age of 3 years to assess the need for lifelong therapy. Also the CMC Vellore study advocated treating transient CH cases till 2.5-3 years (38). Over treatment with thyroxine also poses short term and long term adverse outcomes. Short term risks include tachycardia, excessive nervousness and disturbed sleep pattern which may be eliminated by dosage adjustment. The long term risks include bone age advancement, learning difficulties, hyperactive behaviour, osteoporosis and premature craniosynostosis (38).

Treatment of THOP

The Cochrane review does not recommend use of prophylactic thyroid hormone in preterm neonates for reduction of neonatal morbidity and mortality or improvement of neurodevelopmental outcome (39). A recent multicentre randomised clinical trial in Japan demonstrated no beneficial effect at 3 years of age after thyroxine supplementation in VLBW infants with THOP (40). Recent studies have recommended that the course of CH is transient in nature and cessation of treatment with Thyroxine is possible even before 3 years of age. Therefore a specific guideline regarding the follow up and re-evaluation of transient CH especially in preterm babies needs to be formulated.

Prognosis

Early diagnosis and treatment of babies with CH, possible due to wide NBS programmes, have reduced the severe neuro-developmental impairments. The timing of starting of thyroxine supplementation is crucial and determines the outcome. Review of studies comparing Thyroxine supplementation at earlier periods (12-30 days of life) versus later periods (>30 days of life) demonstrated that infants treated earlier have higher 15.7 IQ points than the other group (41).

Conclusions

At present there is no specific guideline by AAP, ESPE and ISPAE to treat preterm babies with CH and with the current guideline majority of preterm infants where the hypothyroidism is most likely transient are treated for 3 years. Thyroid function abnormalities should be interpreted with caution in neonates keeping in view of adverse outcomes of both under treatment and over treatment. In the event of absence of firm evidence of

permanent CH, if treatment is started with ground of suspicion, reassessment must be performed at 3 years of age. Further studies and specific guidelines are needed for identification, treatment and follow up for transient CH.

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PERSPECTIVE

MEMORABLE JOURNEY OF IMMUNIZATION IN INDIA

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ABSTRACT

Immunization is a proven tool for controlling and eliminating life-threatening infectious diseases and is estimated to avert 20 lakh deaths each year. It is one of the most cost-effective health investments, with proven strategies that make it accessible to even the most hard-to-reach and vulnerable populations. It has clearly defined target groups; it can be delivered effectively through outreach activities. I have described the immunization jounrney in India in this paper.

Introduction

Immunization is a proven tool for controlling and eliminating life-threatening infectious diseases and is estimated to avert 20 lakh deaths each year (1). It is one of the most cost-effective health investments, with proven strategies that make it accessible to even the most hard-to-reach and vulnerable populations. It has clearly defined target groups; it can be delivered effectively through outreach activities. The challenges faced in delivering lifesaving vaccines to the targeted beneficiaries need to be addressed from the existing knowledge on immunology and learning from the past. This review documents the history of vaccines and vaccination in India with an objective to derive lessons for policy direction to expand the benefits of vaccination in the country.

History

A brief historical perspective on smallpox disease and preventive efforts since antiquity is followed by an overview of 19th century efforts to replace variolation by vaccination, setting up of a few vaccine institutes, cholera vaccine trial and the discovery of plague vaccine.

The early twentieth century witnessed the challenges in expansion of smallpox vaccination, typhoid vaccine trial in Indian army personnel, and setting up of vaccine institutes in almost each of the then Indian States. In the post-independence period, the BCG vaccine laboratory and other national institutes were established; a number of private vaccine manufacturers came up, besides the continuation of smallpox eradication effort till the country became smallpox free in 1977. The Expanded Programme of Immunization (EPI) (1978) and then Universal Immunization Programme (UIP) (1985) were launched in India (1).

India is a vast country with difficult geographical terrain with natural calamities occurring every year and having various socioeconomic and literacy rate in various

states. This is reflected in health delivery system. Vaccine preventable diseases still continue to be among 5 major killers in U5 children in India. For reduction of U5-mortality routine immunization coverage has to be increased to more than 80 to 90% in all states.

Our UIP is one of the largest immunization programs in the world. The preventive efforts from diseases were practiced in India, the reluctance; opposition and a slow acceptance of vaccination have been the characteristic of vaccination history in the country. The operational challenges keep the coverage inequitable in the country. The lessons from the past events have been analysed and interpreted and thus previous 6 antigens gradually became 12 antigens.

The journey so far

The intervening events since UIP till India being declared polio free in 2014 have been described (1-7).

1985	: UIP contain vaccines against 6 vaccine preventable diseases
2002	: Hep B Vaccine piloted
2006	: Live JE introduced
2010	: 2nd Dose Measles introduced
2010 to 2014	: Hep B scaled up nation wide
2011 to 2015	: Pentavalent vaccine introduced
2013	: 2nd dose JE introduced
2015	: IPV introduced
2015 to 2016	: Pentavalent scaled up in entire country
2015	: Maternal & neonatal tetanus elimination
2015	: Mission Indradhanush (MI) launched
2016	: Rotavirus vaccine introduced
2016	: Switch from tOPV to bOPV
2017	: MR, JE expanded to many new endemic districts, PCV
2017	: Intensified Mission Indradhanush (IMI)

Conclusions

Really journey of immunization in INDIA is tortuous with full of hurdles thus imbibing a great lesson for better immunization schedule in our country. There has been initiative to develop indigenous low cost conjugate pneumococcal & Typhoid conjugate vaccine. Every child in the country should receive basic vaccines as per GOVT. of INDIA schedule and these are available free of cost at all health centres in INDIA. As per CDC no child should die from VPD. We the paediatricians so called stakeholders of child health let us join our hand to hand to mobilize all children for RI thus preventing millions of death and building a healthy nation.

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Conflicts of interest – None

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PERSONAL VIEWPOINT

STAY HOME, STAY HEALTHY - DURING COVID -19

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ABSTRACT

The COVID-19 pandemic has forced us to stay home which means less social interactions and less exercise. This can have a negative effect on our health. As we know health of an individual has two dimensions - physical health and mental health. We must keep both of them at their best during this crisis. In this paper, I have described some TIPS to stay healthy amid Covid -19, which is helpful for children, adolescents and young adults.

Background

The COVID-19 pandemic has forced us to stay home which means less social interactions and less exercise (1). This can have a negative effect on our health. As we know health of an individual has two dimensions - physical health and mental health. We must keep both of them at their best during this crisis (2,3). So, how to keep ourselves healthy during this pandemic ? Here are some TIPS to stay healthy amid Covid -19 (1-5).

Physical health

1. Diet:

Eating a healthy diet is very important during the COVID-19 pandemic (1,3). Good nutrition can affect our body's ability to prevent, fight and recover from infections. We must keep in mind that no foods or dietary supplements can prevent or cure COVID-19 infection, but healthy diets are important for supporting immune systems (6).

(a) Add variety to daily diet

- ✓ Whole grains - wheat, maize and rice, legumes like lentils and beans, plenty of fresh fruit and vegetables.
- ✓ Foods from animal sources (e.g. meat, fish, eggs and milk) - eggs are best.
- ✓ Taking non-vegetarian diet is not a risk factor for catching covid-19.
- ✓ Unprocessed maize, millet, oats, wheat and brown rice must be chosen over processed for reason well known to all. They are rich in valuable fibre and can help you feel full for longer.
- ✓ For snacks, raw vegetables, fresh fruit, and unsalted nuts are recommended.

(b) Cut back on salt

- ✓ Limit salt intake to 5 grams (equivalent to a teaspoon) a day.

(c) Tips

- ✓ Say no to Chinese recipe at home so that sauces and condiments (like soy sauce, stock or fish sauce) use can be avoided.
- ✓ Remove the salt shaker from the table.
- ✓ Exclude pickle, pappad from menu.
- ✓ Try Salad without salt
- ✓ If fond of pakhala, a famous odiya dish during summer, don't add salt to it.
- ✓ Above all regular salt may be replaced by black salt (rock salt), well available everywhere (table salt has many additives).

(d) Eat moderate amounts of fats and oils

- ✓ Replace butter, ghee with healthier fats like olive, soy, sunflower or rice bran oil for cooking (soy oil is the cheapest & healthy), mustard oil is also a better alternative & widely used.
- ✓ Choose white meat like poultry and fish which are generally lower in fats than red meat.
- ✓ Select low-fat or reduced-fat versions of milk and dairy products.
- ✓ Avoid processed, baked and fried foods that contain industrially produced trans-fat.(also they have high salt content)
- ✓ Try steaming or boiling instead of frying food when cooking.

(e) Limit sugar intake

- ✓ Drink plenty of water.
- ✓ Limit intake of sweets and sugary drinks – this includes not only cold drinks, fizzy drinks but also fruit juices , milk based drinks, challah (a very widely used drink made of dahi must be also avoided as it has high salt content)
- ✓ Choose fresh fruits instead of sweet snacks such as cookies, cakes and chocolate.
- ✓ Avoid giving sugary foods to children.
- ✓ Salt and sugars should not be added to complementary foods.

(f) Keys to safe food

- ✓ Keep clean
- ✓ Separate raw and cooked
- ✓ Cook thoroughly
- ✓ Keep food at safe temperatures
- ✓ Use safe water and raw materials

2. Breastfeed babies and young children (<2 years)

- ✓ Breast milk is the ideal food for infants.
- ✓ It is safe, clean and contains antibodies which help protect against many common childhood illnesses.
- ✓ Women with COVID-19 can breast feed the baby but should take appropriate infection prevention and control measures.
- ✓ From 6 months of age- continue breast feeding along with complementary feeding with no added salt or sugar.

Infection prevention and control measures for a mother with COVID-19 who breast feed the baby or practice skin-to-skin contact.

- ✓ Mother must wear a medical mask.
- ✓ If she does not have a mask, she should still be encouraged to continue breastfeeding and providing breast milk as the benefits of breastfeeding outweigh the potential risks of transmission of the virus.
- ✓ Mother if Sneezing and coughing, should be educated to perform proper cough etiquette ie- sneezing or coughing into a tissue and immediately disposing of the tissue.
- ✓ Performing frequent hand hygiene especially before and after holding the baby, with soap and water or alcohol hand rub if available.

- ✓ Avoid talking while breastfeeding the baby as droplets can be produced while talking.

Staying fit during lockdown

The COVID-19 pandemic has compelled many of us to stay at home and sitting down more than we usually do. It's hard for a lot of us to do the sort of exercise we normally do. It's even harder for people who don't usually do a lot of physical exercise. WHO's "Be Active campaign" aims to help people do just that, also to have some fun at the same time (7-9).

- ✓ Just taking a short break from sitting, by doing 3-4 minutes of light intensity physical movement, such as walking or stretching, will help ease your muscles and improve blood circulation and muscle activity.
- ✓ Regular physical activity benefits both the body and mind. It can reduce high blood pressure, help manage weight and reduce the risk of heart disease, stroke, type 2 diabetes, and various cancers - all conditions that can increase susceptibility to COVID-19.
- ✓ It also improves bone and muscle strength and increases balance, flexibility and fitness. For older people, activities that improve balance help to prevent falls and injuries.

Regular physical activity can help give our days a routine and be a way to stay in contact with family and friends. It's also good for our mental health, reducing the risk of depression, cognitive decline, and delays the onset of dementia, and improves overall feelings

WHO has recommendations on the amount of physical activity people of all ages should do to benefit their health and wellbeing (1).

(a) Infants under 1 year of age
- ✓ All infants should be physically active several times a day - engage them in simple games (age appropriate), help them learn new games too.
- ✓ For those not yet mobile, this includes at least 30 minutes in prone position (tummy time), as floor-based play, spread throughout the day while awake.

(b) Children under 5 years of age
- ✓ All young children should spend at least 180 minutes a day in a variety of physical activities at any intensity.
- ✓ 3-4 year old children should spend at least 60 minutes of this time in moderate- to vigorous-intensity physical activity

(c) Children and adolescents aged 5-17 years
- ✓ All children and adolescents should do at least 60 minutes a day of moderate to vigorous-intensity physical activity
- ✓ This should include activities that strengthen muscle and bone, at least 3 days per week
- ✓ Doing more than 60 minutes of physical activity daily will provide additional health benefits

Mental Health

Restriction of movement as part of efforts to reduce the number of people infected with COVID-19, we are making huge changes to our daily routines (2).

New realities

- ✓ Work from home,
- ✓ Temporary unemployment,
- ✓ Home-schooling of children,
- ✓ Lack of physical contact with other family members, friends and colleagues
- ✓ Adapting to lifestyle changes and managing the fear of contracting the virus and worry about people close to us who are particularly vulnerable, are challenging for all of us.
- ✓ They can be particularly difficult for people with mental health conditions.

Tips for better mental health during lockdown

(a) Keep informed.

- ✓ Listen to advice and recommendations from national, state & local authorities.
- ✓ Follow trusted news channels, such as local and national TV, radio and keep up-to-date with the latest news from @WHO on social media.
- ✓ Avoid fake news.

(b) Minimize newsfeeds.

- ✓ Reduce screen time – more TV viewing, more anxiousness & more distress. But to remain updated, seek the latest information at specific times of the day, once or twice a day if needed.

(c) Social contact is important

- ✓ Keep in regular contact with people close to you by telephone and online channels.

(d) Have a routine- make one

- ✓ Get up and go to bed at similar times every day.
- ✓ Keep up with personal hygiene.
- ✓ Eat healthy meals at regular times.
- ✓ Exercise regularly.
- ✓ Allocate time for working and time for resting.
- ✓ Make time for doing things you enjoy.

I. Screen time: be aware of how much time you spend in front of a screen every day. Make sure that you take regular breaks from on-screen activities.

II. Video games: while video games can be a way to relax, it can be tempting to spend much more time on them than usual

III. Social media: use your social media accounts to promote positive & hope stories: correct misinformation wherever you see it.

IV. Help others: if you are able to, offer support to people in your community.

Fight social stigma (a mental stress creator)

Whole world is now engulfed by COVID-19 (7). Everyday a sense of fear & insecurity building up occurs within each & every person. This pandemic has virtually snatched the happiness & peace from our inner self. No medicine, vaccine is in the far horizon, This is a definitely a challenge for survival of mankind. COVID -19 has provoked a lot of social stigma & discrimination. Because of its highly contagious nature, people getting infected are facing a lot of stigma in the society. This creates a lot of mental stress in Covid patients & also in their relatives. Some Do s & Don't s to fight stigma;

- ✓ DO talk about covid-19.
- ✓ DON'T attach area, ethnicity, and religion to this disease.
- ✓ DO talk about people who have covid -19 or may have covid-19. Talk about those who died of the deadly disease.
- ✓ DON'T refer to people as covid -19 cases or victims. Don't talk about people transmitting covid-19 or infecting others, be empathetic to them, encourage them to come forward for testing, encourage them to fight against the disease. Don't talk about people spreading the virus as it implies intentional transmission & assigns blame.
- ✓ DO speak & share accurate information about the risk of covid-19.
- ✓ DON'T share rumour that are not confirmed or language that spreads fear.
- ✓ DO talk positively & emphasize the effectiveness of preventive measures.
- ✓ DON'T emphasize or dwell on the negative or threatening message.
- ✓ DO good: use your social media account to spread facts & solidarity.

Fear is a normal reaction in situations of

uncertainty. But sometimes fear is expressed in ways which hurt others.

- ✓ Be kind. Don't discriminate against people because of your fears of the spread of COVID-19.
- ✓ Don't discriminate against people who you think may have Covid.
- ✓ Don't discriminate against health workers. Health workers deserve our respect and gratitude.
- ✓ COVID-19 has affected people from many countries. Don't attribute it to any specific group.

How to reduce stress in children (10)

- ✓ Maintain familiar routines as much as possible, or modify according to child's need.
- ✓ Discuss the new Covid with the children in an honest way, using age-appropriate language.
- ✓ Support children with at-home learning and make sure time is set aside for play.
- ✓ Help children find positive ways to express feelings such as fear and sadness. Sometimes engaging in a creative activity, such as playing or drawing, can help with this process.
- ✓ Help children stay in contact with friends and family members through telephone and online channels.
- ✓ Make sure that children have time away from screens every day and spend time doing off-line activities too. Do something creative: draw a picture, write a poem, and build something. Bake a cake. Sing or dance, or play in your garden, if possible.
- ✓ Try & ensure children do not spend significantly more time than usual on video games.

Conclusions

The COVID-19 pandemic has forced us to stay home which means less social interactions and less exercise. This can have a negative effect on our health. As we know health of an individual has two dimensions - physical health and mental health. We must keep both of them at their best during this crisis. The TIPS described here would help children, adolescents and young adults during the pandemic.

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Conflicts of interest – None

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PERSONAL VIEWPOINT

DISCHARGE STANDARDS AND FOLLOW -UP PLAN FOR COVID -19 PATIENTS

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ABSTRACT

World Health Organization (WHO) is regularly publishing guidelines on the clinical management, and discharging criteria for patients since the onset of COVID-19 pandemic. As new research data is emerging, the management and discharge criteria of COVID-19 patients are also going periodic revision. In this perspective, I have discussed the discharge criteria of these groups of patients. We have to remember that it may change with time as the pandemic continues.

Background

Starting from the onset of COVID-19 pandemic, World Health Organization (WHO) has been publishing guidelines on the clinical management, and discharging criteria for patients (1). It has to be remembered that patients may still test positive for COVID-19 by RT-PCR for many weeks even after symptoms have resolved. These patients are not likely to be infectious, and may not transmit it to another person. Below mentioned is some guidance regarding discharge and follow-up of children with COVID-19 infection. We have to remember that it may change with time as the pandemic continues.

Discharge standards:

a) Body temperature remains normal for at least 3 days.
b) Significant Improvement of Respiratory symptoms.
c) The COVID -19 RT–PCR negative twice consecutively (sampling interval more than 24 hrs).
d) Lung imaging shows obvious improvement in lesions.
e) There are no co-morbidities or complications which require hospitalization.
f) SpO2 >92% in room air.
g) Discharge approved by multi-disciplinary medical team

Medications after discharge:

Symptomatic treatment can be continuing if the child has mild cough or poor appetite (2).

Home isolation:

Children with COVID-19 must continue two weeks of isolation after discharge like adult (3). Recommended home isolation conditions are:

a) Independent living area with good ventilation and frequent disinfection.
b) Avoid contacting with other children and elderly people and people with weak immunity.
c) Patient and their family member must wear mask and frequently wash their hands.
d) Body temperature should be taken twice a day (in the morning and evening) and pay close attention to any change in patient's condition.

Follow up:

A specialized doctor should be arranged for each discharged patient's follow-up. The first follow up should be made within 48hrs after discharge. The outpatient follow-up will be carried out on 1st week, 2nd week, and 1 month after the discharge. Examination includes CBC with serum ferritin, LFT with LDH, KFT, PFT in >5yrs of age, Lung CT & nucleic acid test of sputum and stool should be reviewed according to the patient's condition. Follow-up phone calls should be made at 3 and 6 months after discharge if patient couldn't turn up (4,5).

Management of patients tested positive again after discharge:

There are very few cases reported to be positive after discharge in adult not yet recorded in case of children (4,5). For these patients:

a) Isolation according to COVID – 19 protocols.
b) Start of same treatment as before.

Conclusions

The present data on discharge policy can be followed till new data is available.

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