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Letter from President's Desk

It is my proud privilege to lead the Academy of Pediatrics, Uttar Pradesh, as President for the year 2019.

AOP, U.P. is an outstanding institution of higher learning working consistently for upliftment of child- health in our State.

The thrust this year is on Adolescent health in our state of Uttar Pradesh. There are 253 million adolescents in the age group 10-19 years in India and the health situation of this age group is a key determinant of India's overall health. Adolescents require proper nutrition, education, counseling and guidance to ensure their transition into physically & mentally healthy adults.

The Presidential Action Plan "TENS TO TEENS" has been launched in UP PEDICON 2018 where 31 passionate adolescent health ambassadors trained themselves in Teen Counselling and Teen Mental Health.

I sincerely urge all members of AOP U. P. to take up the cause of the Adolescent Child as an integral part of social work & academic pursuits in the year 2019.

I wish our pediatric fraternity a very happy Janmashtami and successful year ahead.

Dr Piyali Bhattacharya

REVIEW ARTICLE

Role of Complementary Foods and Micronutrient in Improving Iron Status in Infants and Children

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Past President, I.A.P. (UP State), Past President NNF (UP State)
&
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INTRODUCTION

Medical knowledge on the subject of pediatric nutrition, growth and development is increasing rapidly, particularly in relation to epidemiological, biochemical and clinical aspect. Several of these advances have direct bearing and practical implication for the practitioners of health care in developing world.

In children, nutrition, growth and development are intricately interrelated and aberrations of one aspect tend to significantly influence the other. Optimum nutrition is essential for child survival and quality of survival. The word 'Nutrition' is derived from 'Nutricus', which means to suckle at the breast.

Breast feeding is as old as civilization and is the most natural and ideal food for infants, and it is also species. Though babies may thrive on breast milk alone during first 6 months of life, it is essential to prevent growth faltering after 6 months, which is done by introduction of complementary foods (weaning), the systemic process of introduction of suitable food at the right time in addition to mothers milk in order to provide needed nutrients to the baby. Infact, Infant complementary feeding is the second step for self existence. Most of the children fall into the pit of malnutrition during the weaning and post weaning phase and some even succumb to it. Jelliffe has suggested a three plank protein bridge or bridge of complementary feeding to carry the children across pit of malnutrition during liquid to solid transition (K.E. Elizabeth).

Breast-fed infants and young children need complementary foods with a very high nutrient density (particularly for iron and zinc), especially at ages 6–12 mo. However, in low-income countries, their diet is usually dominated by cereal-based porridges with low nutrient density and poor mineral bioavailability.

The period of transition from exclusive breastfeeding to consuming a wide range of foods in addition to breast milk is considered the period of complementary feeding, generally between 6 and 24 mo of age. This 18-mo interval is the largest part of the ''1000 days'' encompassing pregnancy and the first 2 years after birth, now viewed as the key window of opportunity for preventing undernutrition and its long-term adverse consequences. In disadvantaged populations, considerable growth faltering occurs between 6 and 24 mo of age, and there is often a high incidence of infection, which increases nutritional needs. Thus, ensuring adequate nutrition during the period of complementary feeding is a major global health priority. However, meeting nutritional needs during this age interval is challenging. (Kathryn G, 2013). Globally, millions of children suffer from micronutrient deficiencies and as stated by UNICEF, few children are getting the nutrition they need to survive, grow and develop.

Importance of micronutrient in human health:

Challenges to ensuring adequate nutrition at 6-24 months of age - Children <2 y of age have high nutrient needs to support growth and development, yet breast-fed infants typically consume relatively small amounts of foods other than breast milk. As a result, complementary foods need to be high in nutrient density, i.e., the amount of each nutrient per 100 kcal of food. Iron and zinc are generally the most problematic nutrients during the period of complementary feeding, largely because their concentrations in human milk are low relative to needs. Because average expected energy intake from complementary foods is lowest at 6–8 mo [;200 kcal/d, assuming the average breastmilk intake observed in developing countries], the minimum target nutrient densities in those foods tend to be highest for that age range (e.g., 4.5 mg iron/100 kcal and 1.14 mg zinc/100 kcal). Target nutrient densities are lower for breast-fed infants at 9–11 mo than at 6–8 mo, because average expected intake from complementary foods increases to ;300 kcal/d at 9–11 mo. Expected energy intake from complementary foods increases further to ;550 kcal/d at 12–23 mo, while at the same time the need for iron is lower, than during infancy and the need for zinc stays the same. As a result, the minimum iron and zinc densities of

complementary foods are considerably lower in the second year of life (1.0 and 0.46 mg/100 kcal, respectively) than in the first year. Thus, the greatest challenge for meeting micronutrient needs of breast-fed children typically occurs during the second 6 mo of life. (Kathryn G, 2013)

Infants need complementary foods with much higher nutrient density than is required for adult diets. For example, per 100 kcal of food, a breast-fed infant at 6–8 mo needs 9 times as much iron and 4 times as much zinc as an adult male [who needs 0.5 mg iron and 0.26 mg zinc/100 kcal based on 2700 kcal/d and recommended intakes of iron and zinc]. Thus, infants should receive the most nutrient-rich foods available in the household, yet often the opposite is the case in low-income countries where infants are typically fed nutrient-poor, watery porridges.

Most common micronutrient deficiencies (MND)

Atleast 50% of children aged 6 month to 5 years suffer from one or more micronutrient deficiencies. About 155 million are stunted and 52 million children are wasted (Global Nutrition Report).

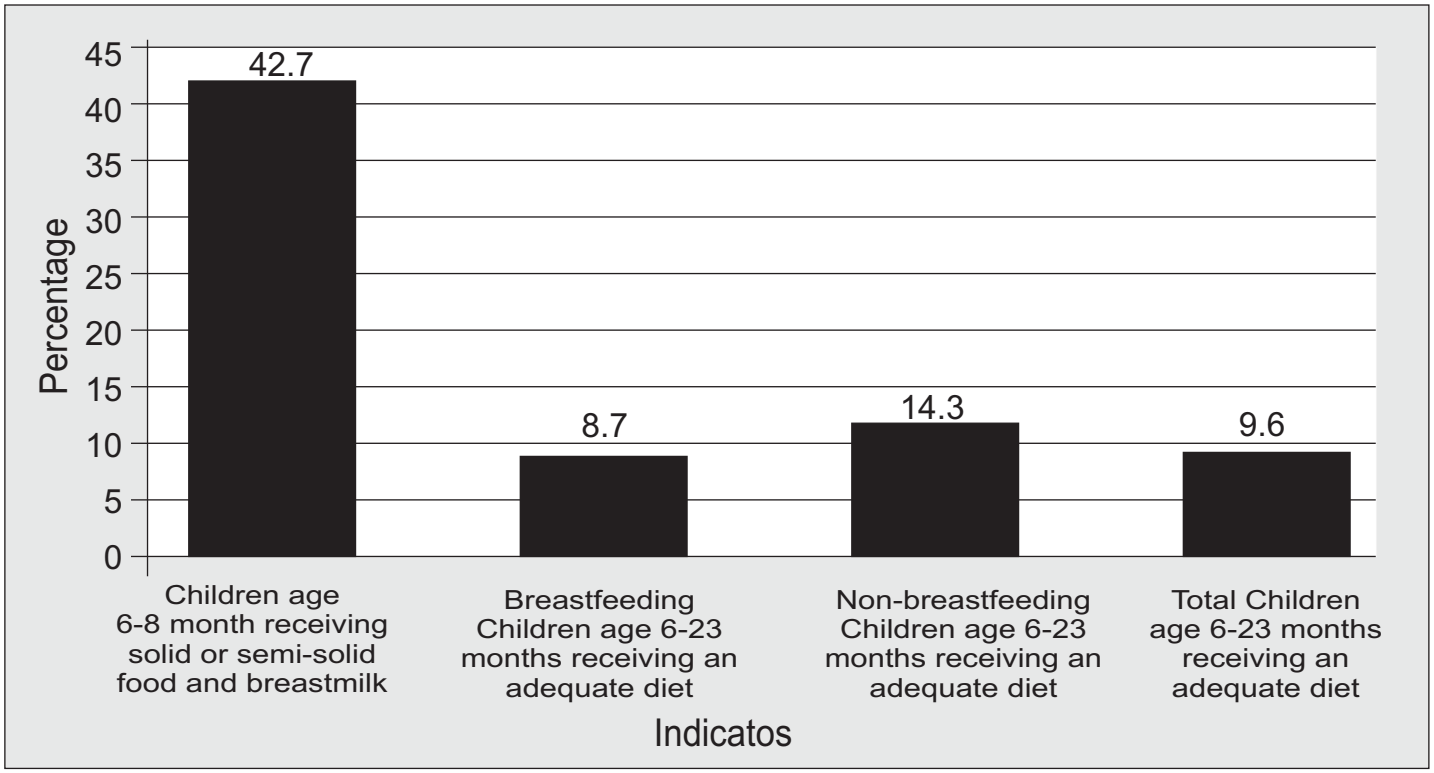
Micronutrient malnutrition (Hidden Hunger)

Hidden hunger is defined as deficiencies in essential micronutrients (vitamins and minerals) in individuals which negatively impact or health, cognition, function, survival and economic development. India is one of the top 20 countries with a high Hidden Hunger score and is home to 1/3rd of global micronutrient deficient population. (Muthayya S et al, 2013)

Status of complementary feeding in India

The proportion of children in India, who are not fed with appropriate complementary feeding practices like timely initiation at 6 months; consuming appropriate number of variety of food groups (i.e. three or ore food groups for breastfed children and four or more food groups for nonbreastfed children); and minimum frequency of feeding (i.e. feed solid or semisolid food at least twice a day for infants of 6-8 months, 3 or more times for other breastfed children, and 4 or more times for nonbreastfed children) is very large. Data from the rapid survey on children (2013-14) are depicted in figure :

Fig – 1 : India – Complementary feeding indicators
Source : NFHS (2015-16). http://rchiips.org/NFHS/pdf/NFHS4/India.pdf



It is evident that in India, complementary foods are not introduced to 49.5% infants at appropriate time (6-8 months), minimum dietary diversity is available to only 19.9% children between 6 months and 23 months and 63.7% are not fed with minimum frequency required. Coupled with the fact that more than half of infants are not exclusively breastfed during first 6 months, suboptimal complementary feeding contributes significantly to child undernutrition in India.

NFHS-4 (2015-16) shows the complementary feeding practices in different parts of country, with children in Southern states (Tamilnadu (TN), Karnataka and Andhra Pradesh (AP)) on complementary food to the extent of 81.2% (TN), as against just 42.6% in Haryana and a dismal rate of just 26.7% in U.P.

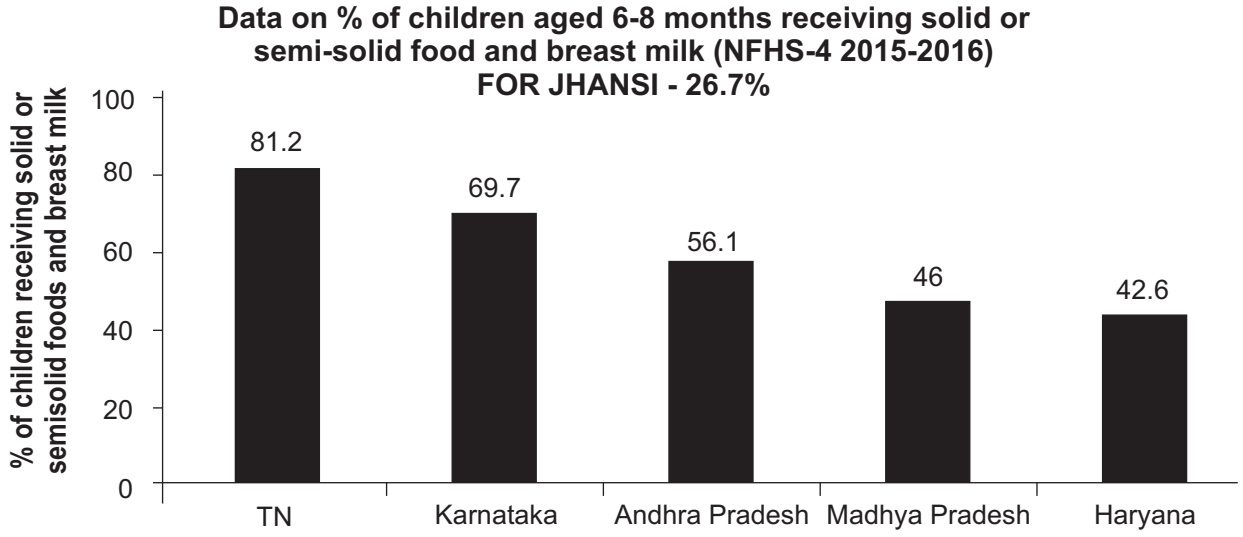


Fig – 2 – Complementary feeding practices in India : Far From Satisfactory (NFHS- 4 Data)

Complementary feeding "A critical window for improving iron status (nutrition Gap)

Term babies who are thriving on exclusive breast feeding do not need supplements, but after 6 months there is depletion of iron stores, increased post natal requirements and low iron intake from milk evolved with decreased milk secretion from mothers which leads to decreased zinc intake, which is a necessity for growth. When actual nutrient densities of typical complementary foods are compared with the target nutrient densities, protein density is generally adequate but several micronutrients are ''problem nutrients''. In developing countries, the usual problem nutrients, include, iron and zinc, and other nutrients may also be low depending on the types of foods consumed (e.g., riboflavin, niacin, thiamin, folate, vitamin B-6, vitamin B-12, calcium, vitamin A, vitamin C, and vitamin E) or the water and/or soil content (e.g., iodine, selenium).

Complementary feeding after 6 months, along with breast feeding provides adequate iron and zinc, which improves iron and zinc status and thereby improves neuro cognitive development and immune function and height for age Z score and decreased stunting.

Nutrient gap for iron is widest

This chart of WHO regarding complementary feeding reveals iron nutrient gap to be 94%, which has to be fulfilled by complementary food.

Iron Gap

Full term infants are born with adequate iron store and get some iron in breastfed milk, thus do not require additional iron for first 6 months of life. After 6 months of life, breastmilk iron is grossly inadequate and most of iron demand needs to be met with complementary foods. This is important to provide iron rich foods to children during this period to fill iron gap. Iron rich foods include green leafy vegetables, legumes, dried fruits, meat, fish and poultry products. Bioavailability of iron from plant foods is not optimum, addition of fruits rich in vitamin C increases the absorption of iron from plant foods. It is important to note that with increasing age (6-24 months), requirement for iron decreases.

Fig – 3-A: Iron need and supply in infants and young children

Source : Complementary feeding – family foods for breastfed children, WHO, 2000

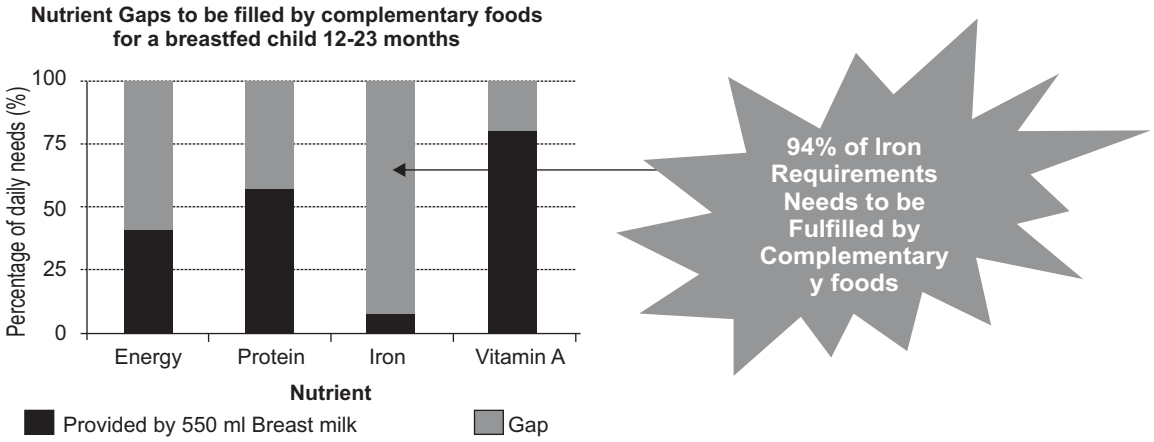
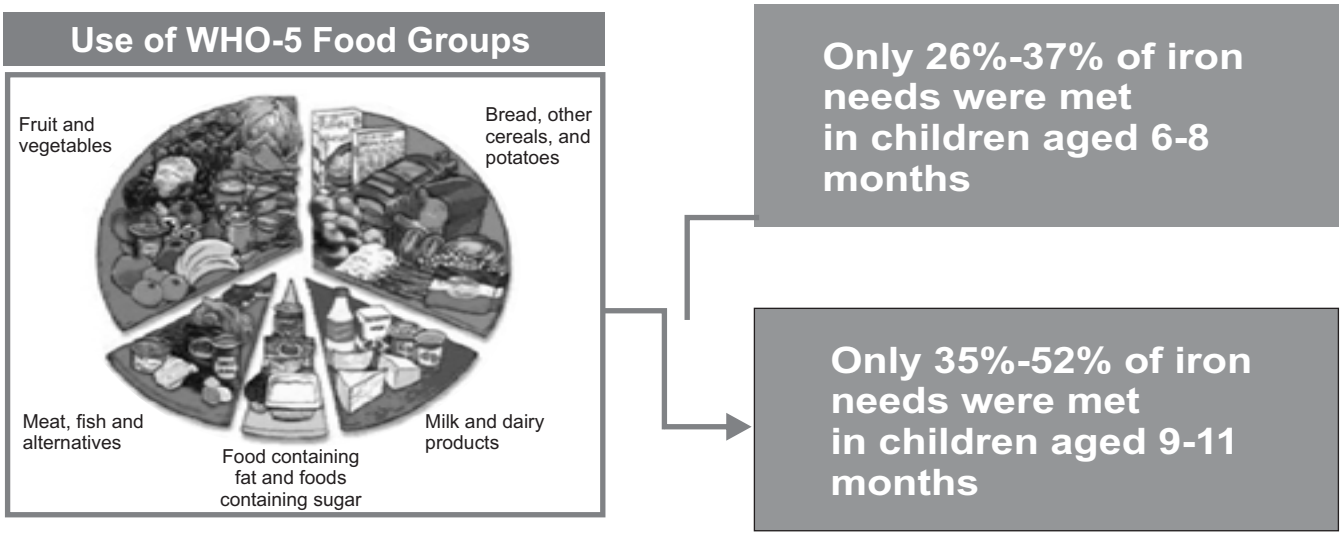


Fig – 3-B – Nutrition Gap for Iron is the widest

WHO, 2001

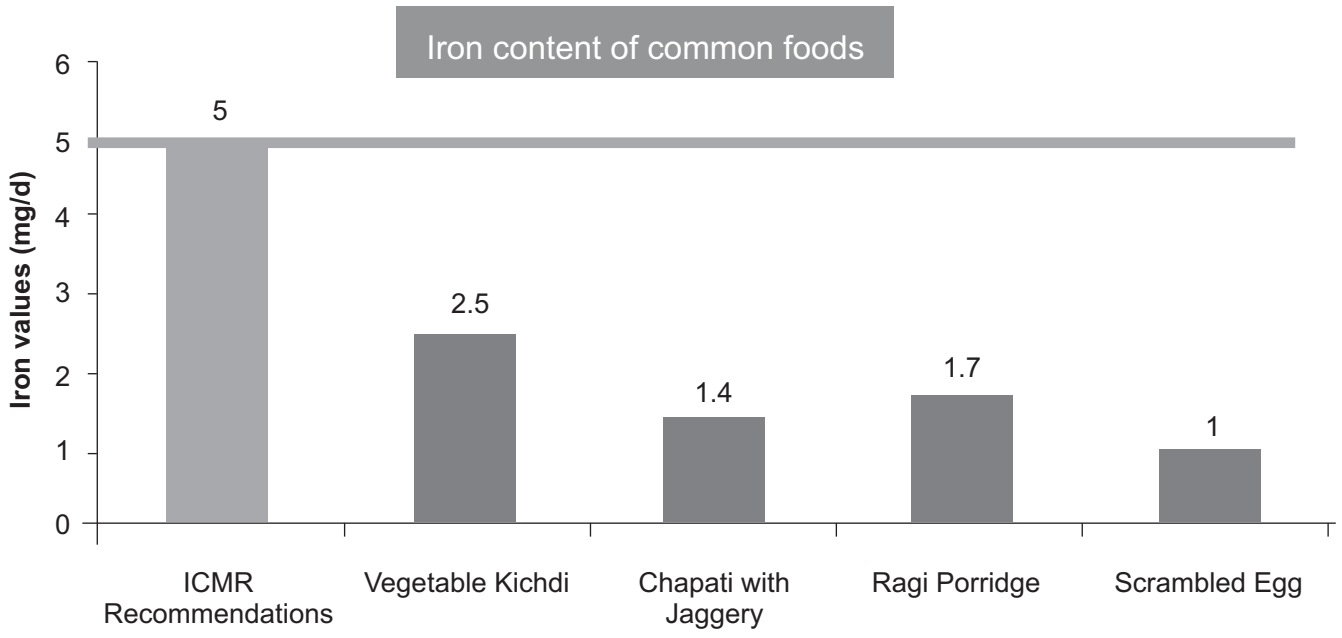
Plessow et al (2015) reported 49.5% of IDA in 5-23 month old and 39.9% in 24-58 months children. The prevalence of IDA is not only limited to children living in poor and rural areas, it is also seen in those living in healthy urban households.

Fig – 3-C– Commonly eaten foods leave a nutrient gap



Dewety KG, J. Nutr, 2013

Fig – 4 – Iron deficit in common complementary Indian foods compared to recommendation (ICMR 2010)



ICMR recommended RDA for Iron of 5mg/dl in young children aged 6-12 months is clearly not met by common complementary foods (2010) (Figure – 4).

Food fortification way forward to bridge nutrient gap – Anaemia

Sazawel S et al (2014) has reported an increase of 1.29gm/dl of Hb with complementary foods as against 0.23gm/dl without fortification. This tantamounts to 67% reduction in Anaemia in children with fortification, as against only 22% with no fortification.

Pletro and Detzel (2016) have estimated that the current consumption level of fortified food have already reduced the burden of IDA by $1.4 billion and 0.6 million DALYS equivalent to 1 life span per hr.

Key Messages

·India is home to 1/3rd of the global micronutrient deficient population.

·Iron deficiency in infants and young children impacts cognition, learning, memory and immunity.

·Nutrient gap for iron is the largest during transition from breastfeeding to complementary feeding.

·Commonly available complementary foods may not bridge all the nutrient gaps, particularly those of iron in infants.

Food fortification is an assured means of addressing micronutrient deficiencies, especially that of iron in infants and young children.

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REVIEW ARTICLE

Study of mean micronutrient level in children with nutritional anemia and correlation with different demographical profile

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ABSTRACT

Objectives : To study mean micronutrient levels in children of nutritional anemia having Iron, Folate, and Vitamin B12 deficiency.

Materials and Methods: This cross sectional study was done in Department of Pediatrics, Sarojini Naidu Medical College, Agra in collaboration with Institute of Genomics and Integrative Biology, New Delhi. Children of age 6 months to 14 years admitted having signs and symptoms of anemia were included in study. Sample size calculated was 157. Each case was subjected to CBC, GBP, serum iron, ferritin, folate and vitamin B12 level estimation. Data was analysed using unpaired t test, ANOVA and chi square test.

Result: Out of 672 children, 157 children with clinical feature of anemia were enrolled in study. Among these 157 children, 52.87% were male. Percent proportion of anemia was highest among toddlers (27.39%) and lowest in adolescent (10.83%). The maximum cases were of urban area (65.6%) and middle socioeconomic status (47.13%). Most of the children were undernurished/underweight (60.4%). Mean iron level was significantly low in female children, children of rural areas, low socioeconomic status and malnutrition/underweight. Mean folate and vitamin B12 levels were also low but not statistically significant. Mixed iron, folate and B12 deficiency was found in 48.41%, 30.57% and 22.93% cases respectively. In 24.20% cases no deficiencies was found and were classified as anemia due to some unspecified causes.

Conclusion: Nutritional deficiency anemia is contributing to a large proportion of anemic patients. More intensified programmes are needed specially for female children, children of rural areas, low socioeconomic status and malnutrition/underweight.

INTRODUCTION :

According to WHO, anemia is a widespread public health problem with major consequences for human health as well as social and economic development. [1] Anemia, is functionally defined as an insufficient RBC mass to adequately deliver oxygen to peripheral tissues. WHO published a data in 2015 on "global prevalence of Anemia 2011", according to which anemia affects 273.2 Million children of age 6 months to 59 months, which corresponds to 42.6 % of the total population of the children [2]. Nutritional deficiencies are the primary cause of anemia. Anemias of nutritional origin are acquired problems caused by diets that lack sufficient quantity of bioavailable essential hematopoietic nutrients to meet the need for hemoglobin and red blood cell synthesis [3]. Forty two percent of the cases of anemia in children are attributable to Iron deficiency. According to data from "Global Prevalence of Anemia 2011" India has a mean haemoglobin concentration of 10.6g/dl in children of age 6 month to 59 month ,which already comes under the category of mild anemia[2]. WHO and UNICEF therefore re-emphasize the urgent need to combat anemia and stress the

importance of recognizing its multifactorial etiology for developing effective control programmes. [1] The aim of this study was to evaluate Iron, Vitamin B12 and Folate deficiency in children with anemia. The objectives were to study mean micronutrient levels in children of nutritional anemia having Iron, Folate, and Vitamin B12 deficiency.

MATERIAL AND METHODS: This cross sectional study was done in Department of Pediatrics, S.N. Medical College, Agra in collaboration with Institute of Genomics and Integrative Biology, New Delhi.

Children of age 6 months to 14 years admitted in department of paediatrics, having signs and symptoms of anemia were included in the study. The sample size was calculated using the formula 4 X %PREVALENCE X (100 - % PREVALENCE) / (d2). Prevalence was obtained from national family health survey-3 (NFHS 3) data of Uttar Pradesh, which was 73.9%. 'd' is the 'allowable error of prevalence' which was taken as 10%. Sample size calculated was 157 and the samples were collected from November 2014 to March 2015. This study was approved by ethical committee of the institute. Subjects were included in the study after taking informed consent from the parents/guardian.

In study we excluded the children who had received Iron, folate, vitamin B12 therapy, blood transfusion in immediate past, patients diagnosed with other pathological anemia and seriously sick children. After taking detailed history and clininal examination, 5 ml of blood sample was collected through venepuncture and the samples was divided into two parts, E.D.T.A sample were subjected to complete blood count (CBC) and general blood picture (GBP), and the serum samples were stored at -200 degree celsius in cryovials for the estimation of serum iron, ferritin, folate and vitamin B12 and were later sent to the Institute of Genomics and Integrative Biology by maintaining the cold chain. Iron estimation was done using colorimetric method with ferrozine without deproteinization. Ferritin estimation was done by particle enhanced immunoturbidimetric assay. Vitamin B12 estimation was based on competitive test principle using intrinsic factor specific for vitamin B12. Folate assay based on a competitive test principle using natural folate binding protein (FBP) specific for folate. Cut of value for serum Iron, Ferritin, Folate and Vitamin B12 are 30 microgram/dl, 15 ng/ml, 5.0 ng/ml and 200 pg/ml respectively.[4,5.6] If the serum samples were not having any deficiency of Iron, ferritin, folate and vitamin B12 were diagnosed as anemia due to some unspecified causes. We had implied the Student unpaired t test and analysis of variance (ANOVA) for quantitative data and chi square test for qualitative data analysis.

RESULTS: A total of 672 children of age group 6 months to 14 years were admitted in our department from November 2014 to March 2015. Out of these, 157 children with clinical feature suggestive of anemia were included in the study. Socio-demographic profiles of these patients have been shown in Table.1. Among these 157 children, 52.87% were male and 47.13% were female. The percent proportion of anemia was more among toddlers (27.39%) and lowest among adolescent (10.83%). The cases belonged to urban areas were 65.6% as compared to 34.4% of rural area. Maximum cases belonged to middle (47.13%) and lower (35.67%) socioeconomic status as per Kuppuswamy's grading. When the nutritional status was studied, we found maximum cases belonged to severe (31.84%) followed by moderate (28.66%) and mild (19.05%) grade of undernutrition or underweight as per W.H.O classification of malnutrition/ underweight. Out of all anemic cases, 57.96% cases were of moderate grade of anemia, 38.21% were of severe and 3.82% were of mild grade of anemia. In general blood picture maximum were of microcytic hypochromic (31.85%) followed by macrocytic hypochromic (24.20%), dimorphic (23.57%) and normocytic normochromic (20.83%).

Iron deficiency was present in 90% of the cases having microcytic and 83.7% cases of dimorphic general blood picture. Folate deficiency was observed in 47.37% cases of macrocytic general blood picture and 40.54% cases of dimorphic general blood picture. Maximum Vitamin B12 deficiency was found in dimorphic (48.65%) followed by macrocytic (36.84%), normocytic (25%) and microcytic (16%) general blood picture cases. Percent proportions of different demographic profile of anemia according to micronutrient deficiency were as depicted in Table no 1.

Mean micronutrient levels were not significantly correlated with any of the age subgroup. Iron and ferritin was significantly low in females as compared to males. Folate and vitamin B12 were also low in females but not statistically significant. The mean micronutrient levels (iron, ferritin, Folate and vitamin B12) were low in rural population when compared to urban, but the deficiency was significant only for iron and not for other micronutrients. Iron levels were significantly reduced in the patient of low socioeconomic class. Ferritin, folate and Vitamin B12 were low in patient of low socioeconomic class when compared to middle and high socioeconomic class but was not statistically significant. Mean micronutrient levels for iron were significantly low in various grades of malnutrition/ underweight. Mean micronutrient levels for ferritin, folate and vitamin B12 were also low in the different grades of malnutrition/ underweight compared to normal nutrition but

statistically not significant (Table.2).

Out of 157 anemic cases, 50(31.85%) had pure iron deficiency, 19(12.10%) had pure folate deficiency and 17(10.83%) had pure vitamin B12 deficiency. In mixed form of anemia, iron plus folate, folate plus Vitamin B12 and iron plus B12 contributed to 14(8.92%), 7(4.46%) and 4(2.55%) cases respectively. In 8(5.10%) cases there was combined deficiency of all three micronutrient (Iron, folate and Vitamin B12). 48.41% had pure or mixed iron deficiency, 30.57% had pure or mixed folate deficiency and 22.93% had pure or mixed Vitamin B12 deficiency. In 38(24.20%) cases no deficiency was found and such cases were classified as anemia due to some unspecified causes. Etiologies of anemia in 157 children along with 95% confidence interval were as depicted in table no 3.

DISCUSSION: Anemia is a significant public health problem with major consequences for human health and socio-economic development. Anemia is an indicator of poor nutrition and poor health. Developing countries carry the most significant burden of the reported cases of anemia whose etiology is often multifactorial.[7]

In our study maximum cases belonged to toddler, school going and preschool age children. The numbers of cases in these different age groups were near about same. Adolescent contributed about 10.83% of cases. There was decrease in prevalence of anemia as age increases and these findings were similar to the study done by Rajaratnam.J et al in Tamilnadu.[8] This was probably due to reason that early age group children were maximally dependenton their care providers for their nutrition.

In present study, males were slightly more than females. This is similar to the study done by Gomber.S et al.[9] Iron and ferritin levels were significantly low in female along with low level of folate and vitamin B12, it can be because of poor attitude towards female child health and nutrition in our society.

In this study almost two third of cases belonged to urban area. Health care facilities are usually easily accessible in urban areas and this can be attributed to the increase in the number of urban patients. This is in accordance with several studies done in the past.[10,11,12,13]

Mean micronutrient levels were compared between urban and rural subgroups. Rural population has statistically significant deficiency of iron. Though the levels of ferritin, Vitamin B12, and folate were also low in rural population but the difference was not statistically significant. This can be attributed to the poor nutritional care in the rural population.

In our study anemia was more prevalent among cases of middle and low socioeconomic status. Several studies done in south east Asia also showed similar results.[14,15,16,17]

Prevalence of anemia was graded on the basis of specific nutrient deficiencies in different socioeconomic group and it was found that iron deficiency anemia was more in low and middle socioeconomic status. Cobalamine and folate deficiency was also more prevalent in the low and middle socioeconomic status groups.

Mean micronutrient levels were also compared in different socioeconomic status. Mean iron level was significantly low in low socioeconomic status, though the mean micronutrient level of ferritin, folate and B12 were also low in the low socioeconomic status but were not statistically significant. This is supported by the study on adolescent girls in Korea, where there was a relationship between household income and ferritin levels for iron deficiency anemia[18].

In our study 80.25% anemic cases had some grade of malnutrition/ underweight and only 19.75% of cases had normal nutrition. This was in accordance with study done in Northern Himalayan state of India and Bihar where anemic cases were suffered from different grades of malnutrition/underweight.[19,15,20]

Mean micronutrient levels were noted in the different grades of malnutrition/ underweight and it was found that mean micronutrient level for iron was significantly low in different grades of malnutrition/underweight compared to children with normal nutritional status. The levels of ferritin, folate and Vitamin B12 were also low in different grades of malnutrition/underweight but difference was not statistically significant.

Among 157 anemic cases studied, prevalence of moderate anemia was highest followed by severe and mild. Similar results were found in other studies done in past.[21,22] The reason behind this could be that these studies included only hospitalised cases.

In present study maximum percentage of cases were of microcytic hypochromic general blood picture (31.85%) followed by macrocytic (24.20%), dimorphic (23.57%) and normocytic normochromic blood picture (20.38%). The study was similar to other studies done in past in which they found that in maximum cases general blood picture was of microcytic hypochromic type.[21,22].

In the present study pure or mixed iron deficiency had the highest prevalence (48.41%). Prevalence of iron deficiency was commonest in studies done in past.[9,23,24,25] Pure or mixed folate deficiency was around 30.57% and contributed to the second most common cause of nutritional deficiency anemia and this

was in accordance with Mamabolo. L.R et al[26] who found folate deficiency anemia was the second most common cause of nutritional deficiency anemia. In present study vitamin B12 or cobalamine (22.93%) deficiency was least common cause of nutritional deficiency anemia. The study was similar to other studies in which they found vitamin B12 deficiency was the least common cause of anemia[26,27,28]. Variation in the causes of anemia and micronutrient levels in different studies may be contributed to either selection of age group or demographical and geographical reasons.

Children with unspecified anemia (24.20%) in whom no deficiency of iron, folate and vitamin B12 was found, maximum number belonged to high and middle socioeconomic status had moderate to severe grade of anemia and normocytic normochromic blood picture. This may be due to coexisting disease such as malaria, worm infestation, hemoglobinopathies and intake of hematinics, any undiagnosed chronic disease, hemolytic disorders, thyroid disorders, liver disorders and renal disorders.

Conclusion: Nutritional deficiency anemia is still contributing a large proportion of the anemic patients. In spite of large scale supplementation with iron and folate, the deficiency of these micronutrient as reflected from the mean micronutrient levels, are still prevalent, so the strengthening of same is required. Vitamin B12 deficiency is also common in pediatric age group. Large proportion of the pediatric population is still vegetarian so supplementation and fortification of vitamin B12 is also required to reduce the prevalence of anemia.

TABLE.1 Demographic profile and micronutrient deficiency in Children with anemia.

DEMOGRAPHICAL FACTORS		N=157(%)	Iron deficiency N=76	Folate Deficiency N=48	VitaminB12 deficiency N= 36
AGE GROUP	INFANT	18(11.47%)	6(7.89%)	4(8.33%)	6(16.67%)
	TODDLER	43(27.39%)	23(30.26%)	14(29.17%)	8(22.22%)
	PRE-SCHOOL	38(24.20%)	19(25%)	12(25%)	10(27.78%)
	SCHOOL-GOING	41(26.11%)	20(26.32%)	10(20.83%)	9(25%)
	ADOLESCENT	17(10.83%)	8(10.53%)	8(16.67%)	3(8.33%)
SEX	MALE	83 (52.87%)	43(56.58%)	24(50%)	21(58.33%)
	FEMALE	74(47.13%)	33(43.42%)	24(50%)	15(41.67%)
RESIDENCY	URBAN	103(65.6%)	33(43.42%)	18(37.50%)	10(27.78%)
	RURAL	54 (34.4%)	43(56.58%)	30((62.50%)	26(72.22%)
SOCIOECONOMIC STATUS	UPPER	27 (17.20%)	3(3.95%)	5(10.42%)	5(13.89%)
	MIDDLE	74(47.13%)	33(43.42%)	16(33.33%)	18(50%)
	LOWER	56(35.67%)	40(52.63%)	27(56.25%)	13(36.11%)
UNDERWEIGHT/ UNDERNUTRITION	MILD	31 (19.75%)	1519.74	5(10.42%)	6(16.67%)
	MODERATE	45(28.66%)	2228.95	18(37.5%)	14(38.89%)
	SEVERE	50(31.84%)	3444.74	19(39.58%)	11(30.55%)
	NORMAL	31(19.75%)	56.58	6(12.5%)	5(13.89%)
GRADES OFANEMIA	MILD	6 (3.82%)	3(50%)	2(33.33%)	1(16.67%)
	MODERATE	91 (57.96%)	47(51.65%)	28(30.77%)	23(25.27%)
	SEVERE	60 (38.21%)	26(43.33%)	18(30%)	12(20%)
GENERAL BLOOD PICTURE	MICROCYTIC HYPOCHROMIC	50(31.85%)	45 (90%)	0	8 (16%)
	MACROCYTIC HYPOCHROMIC	38(24.20%)	0	18 (47.37%)	14 (36.84%)
	DIMORPHIC	37 (23.57%)	31 (83.78%)	15 (40.54%)	18 (48.65%)
	NORMOCYTIC NORMOCHROMIC	32 (20.83%)	0	3 (9.38%)	8 (25%)

TABLE. 2 Mean micronutrient level and their correlation with demographic profile

DEMOGRAPHICAL FACTORS		IRON DEFICIENCY ANEMIA				FOLATE DEFICIENCY ANEMIA		VITAMIN B12 DEFICIENCY ANEMIA	
		Iron Mean ± SD (mg/L)	P VALUE	Ferritin Mean ± SD (mcg/dl)	P VALUE	Folate Mean ± SD (mcg/L)	P VALUE	B12 Mean ± SD (pg/ml)	P VALUE
AGE GROUP	Infant	0.19±0.1	0.333	19.79±32.56	0.682	3.41±1.72	0.088	54.84±23.50	0.284
	Toddler	0.15±0.08		7.29±4.68		3.91±2.83		55.08±24.34	
	Pre- school	0.32±0.51		33.30±120.18		3.64±1.57		44.69±21.34	
	School-going	0.19±0.09		10.43±10.51		3.75±1.16		52.17±26.63	
	Adolescent	0.18±0.10		8.38±5.11		4.02±2.44		48.11±16.78	
SEX	MALE	0.25±0.16	0.0094	21.18±81.74	0.0001	4.22±2.44	0.1253	51.59±20.32	0.8861
	FEMALE	0.18±0.17		9.28±8.66		3.31±1.46		50.43±25.87	
RESIDENCY	URBAN	0.19±0.10	0.0415	10.33±22.3	0.4916	3.03±1.66	0.0674	58.44±62.44	0.6776
	RURAL	0.25±0.14		13.32±12.33		4.07±2.15		67.85±51.34	
SOCIO ECONOMIC STATUS	UPPER	0.27±0.05	0.031	20.84±4.05	0.956	4.04±1.52	0.079	48.41±18.18	0.976
	MIDDLE	0.23±0.08		10.35±15.44		3.86±0.94		46.36±22.10	
	LOWER	0.19±0.07		9.87±83.03		2.53±2.52		45.80±25.03	
NUTRITION STATUS UNDER-WEIGHT OR UNDER-NUTRITION	MILD	0.18±0.09	0.006	12.90±22.37	0.486	3.48±1.39	0.603	62.40±28.37	0.516
	MODERATE	0.17±0.18		10.38±111.93		3.45±1.56		52.64±20.20	
	SEVERE	0.12±0.08		7.93±4.65		3.23±2.76		49.52±25.16	
	NORMAL	0.32±0.08		14.33±3.82		4.55±0.72		64.20±8.35	

TABLE.3 Etiological distribution of anemia in study group.

TYPE OF ANEMIA	Number of children {N=157(%)}	95% Confidence interval (%)
Pure Iron deficiency	50(31.85%)	24.16-40.54
Pure Folate deficiency	19(12.10%)	9.24-15.34
Pure Vitamin B12 deficiency	17(10.83%)	9.12-13.45
Iron plus Folate deficiency	14(8.92%)	7.01-10.45
Folate plus Vitamin B12 deficiency	7(4.46%)	3.55-5.45
Iron plus B12 Deficiency	4(2.55%)	1.22-6.45
Iron plus Folate plus Vitamin B12 deficiency	8(5.10%)	3.67-5.96
Unspecified	38(24.20%)	15.78-38.87
Total	157(100%)	

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REVIEW ARTICLE

Optimizing Bone Health in Children: Endocrinology and Micronutrient Influences

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Abstract

Paediatric bone health is the most important modifiable determinant of long term skeletal health in adulthood. Various modifiable and non-modifiable factors determine the actual bone mass in adulthood. Bone mineralisation starts in utero, with maximum calcium accretion in third trimester. Thereafter, peak bone mass is achieved by the end of 2nd decade. Nearly, half of the adult bone mass is accrued in adolescent years, with one-fourth of it occurring around peak height velocity during puberty. Hence, it is of immense importance to optimize bone health during childhood.Also, in extreme old age, osteoporosis and osteopenia significantly affects quality of life and serious fractures, hence, should be prevented. Pediatricians are in an ideal position to monitor and assess calcium status during childhood, identifying deficient intakes that can lead to fractures and future issues with osteopenia and osteoporosis. This article discusses in brief various factors in determining bone health in children and its optimisation.

Key Words: Vitamin D, Calcium, Sex steroids, Peak Bone mass

Introduction

A good bone health is essential for people of all age group as it provides structural and mechanical support to our body and helps us stay healthy and independent in long term. 1 As childhood and young adulthood are the bone building years, promoting good bone health in the early life ensures good skeletal health in advancing age also. Establishing bone health in childhood reduces the likelihood of fractures and prevents development of mineral deficiency disease such as osteoporosis in adulthood.2,3

Bone is a structural unit of the skeletal system which forms the framework of our body3. Bone is composed of the following:

- Collagen fibers3
- Bone cells: osteoblasts, osteocytes, osteoclasts, stromal, and hematopoietic cells1
- Bone minerals: calcium (mostly as hydroxyapatite) and phosphates4

Eighty percentage of adult skeleton is formed of dense outer part called cortical bone while 20% is made of network of trabecular bone enveloped by cortical bone. Factors responsible for the bone loss mostly affect trabecular bone. 4

Bone Development, modeling and remodeling

The basic skeletal formation, development and mineralization occur during embryonic age only. After the birth subsequent changes in bone shape, size and mass occurs during bone modeling process. The process is associated with increase bone mass.1 There is 40-times increase in bone mineral content (BMC) from birth to adulthood. About 90% of peak bone mass is achieved at the age of 18 years. 3 The human skeleton is renewed throughout life by the process called bone remodeling or bone metabolism.1

The process of bone modeling and remodeling is accomplished by the action of osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells).1, 4 Genes, hormones, nutrition, and physical activity play an important role in achieving peak bone mass.5

Factors affecting bone health

There are several factors which affect bone health where some are non-modifiable like genetics, gender and ethnicity while others are modifiable such as hormonal status, nutrition, mineral deficiency, physical activity, and other lifestyle related factors.3

Various factors that influences bone health are:

Non-modifiable factors:

Genetics: Bone mineral density (BMD) has some hereditary link although no particular gene contributing in bone health has been determined. BMD varies with population where black women demonstrate higher bone mass compare to their white or Asian counterpart.3

Gender: The influence of gender on BMD has also been

noticed in several studies. Women have lower bone mass as compare to Men, also many mother–child studies demonstrated close relation between mother–daughter BMD than mother–son BMD.2,3

Ethnicity: Black woman have higher bone mass than white Non-Hispanic woman or Asian woman3.

Modifiable factors:

Hormones : Many hormones such as sex steroids, glucocorticoids, growth hormones and IGF-1 have key role in bone health. Estrogen helps in maintain BMD in female. Its deficiency can cause increased bone resorption and increases the risk of fracture in women. Growth hormone, testosterone and IGF-1 stimulate bone formation while opposite is promoted by glucocorticoids.3

Nutrition: The qualitative and quantitative nutritional supply at all stages right from fetal life to adolescence determines the bone health in children.2

Prenatal: During fetal stage nutritional requirement like vitamin D and calcium are meet through only maternal source. Thus nutritional deficiency in mother affects the health of her baby. As in case of deficiency of Vitamin D in mother during pregnancy, her baby is born with vitamin D deficiency and poor bone health. However, deficiency of calcium during pregnancy has little or no effect on child bone health in a term baby. This could be due to active transport of calcium through placenta. On the other hand, premature babies are deficient in calcium stores and are prone to develop osteopenia of prematurity, hence, they need regular calcium and vitamin D supplementation2.

Early childhood:

Sub optimal level of calcium and vitamin D intake results in lower bone mass in children. Calcium is the major component of bone mineral. It is essential for achieving peak bone mass. 2Vitamin D is essential for the absorption and utilization of calcium by the body. Only 10% to 15% of calcium is absorbedin absence of vitamin D. 3 Deficiency of vitamin D leads to the development of rickets in young children whereas increases the risk of fracture in older children, teenagers and adults.3

Risk of Vitamin D deficiency is also high in children with liver or renal insufficiency and diseases, on certain medications like anticonvulsant, antifungal, antiretroviral and glucocorticoids. 3 Also studies have shown that vitamin D deficiency is common in children who suffer fractures in childhood.6

Sunlight is the major source of vitamin D. Our skin synthesizes vitamin D when expose to UV B rays (290 to 315 nm) from sunlight.[3]

Late childhood and adolescence:

Undernourishment during childhood and teenage results in reduced bone formation and growth and affects overall health. Its deficiency can cause osteomalacia in the children of this age group.3

Physical activity or exercise

Some kind of physical activity increases bone formation, growth and augments bone strength in children and teenagers. 2 Activities like such as jogging, walking, jumping, running, basketball, gymnastic, and dancing are good for bone health in children and adolescents.3

Other lifestyle factors:

Obesity, smoking, alcohol consumption, caffeine, soda consumption and poor food habits such as diet low in protein or high in sodium all contribute to poor bone as well as overall health in children, teens, and adults. 2, 3 Lifestyle changes such assedentary behavior and growing indoor culture among children is also a big reason for development of vitamin D deficiency in children.7

Prevention of Vitamin D and Calcium Deficiency in Children and Adolescents.

As both calcium and vitamin D are essential for good bone health, their deficiency will have negative impact on bone health.7

Vitamin D

About 90% of vitamin D is obtained through synthesis by skin on sunlight exposure. 6 Sunlight is the ultimate source of vitamin D. Skin exposure to sunlight for up to 15 min twice or thrice a week synthesizes approximately 3000IU of vitamin D. However people with darker skin tone require 3 to 5 times longer exposure to sunlight.3

Dietary sources of vitamin D are fewer namely cod liver oil, fortified foods and fishes such as sardines, tuna, and salmon. Normal levels are >20 ng/ml, 12-20 ng/ml is insufficient and less than 12 ng/ml is deficient.3

Skin synthesizes maximum amount of vitamin D between 10:00am to 3:00pm in the day time in the spring, summer and fall.[3]

Calcium

Approximately 99% of calcium is found in skeleton. It is transported through gut via both active and passive transport. Active transport is mediated via vitamin D and its metabolites. The primary source of calcium for neonates is breast milk or formula milk. For children above 1-year dietary sources are also available such as milk and dairy products, legumes, green leafy vegetables,

fruits, nuts and cereals. 3 Teenagers and older children have higher dietary calcium requirement in order to sustain bone growth.2

Calcium and vitamin D present in breast milk is not sufficient to meet the requirement of growing newborn. Hence calcium and vitamin D supplement is imperative to meet the need of growing body.7

Each 240mL of milk serving provides about 300 mg of calcium.[3]

Indian Academy of Pediatrics (IAP) Guidelines has recommendations for prevention and treatment of vitamin D and calcium deficiency presented below in the table7:

Age	Vitamin D (IU/day)		Calcium(mg/day)	
	Prevention	Treatment	Prevention	Treatment
Premature infants	400	1000	Intake of 150–200 mg/kg per day	175–200 mg/kg per day (max)
New born (<1 month)	400	2000	200 mg/day	500 mg/day
Infants (1–12 months)	400	2000	250–500 mg/day	500 mg/day
Children (1–18 years)	600	3000–6000	600–800 mg/day	600–800 mg/day
At risk children	400–1000	According to age group	According to age group	According to age group

After treatment of vitamin D/Calcium deficiency, a minimum of 3 months daily maintenance treatment should be given.

Role of Healthcare Providers

Healthcare provider has prime role to play in promoting good bone health in children. He should counsel the children about the effect of malnutrition on health and encouraging them for the following 3 :

- increased dietary consumption of calcium and vitamin D,
- to take nutritional supplement,
- perform require amount of physical exercise daily

Conclusion

Both calcium and vitamin D are essential for good bone health. Their deficiency will have negative impact on bone health. 7 Proper nutrition along with exercise is important for good skeletal health during growing years as well as in later life.2

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Diagnosing Pediatric NAFLD

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ABSTRACT

NAFLD; Non alcoholic fatty liver disease is accumulation of excessive fat in liver. It progress to inflammation and cirrhosis. Ethnic differences and clinical heterogeneity regarding NAFLD is well known. More children are getting diagnosed. Multiple factors are involved in pathology of NAFLD. This review focuses on diagnosis of NAFLD children based on available guidelines and literature. Clinical approach to NAFLD is suggested.

Key words:

NAFLD: Non alcoholic fatty liver disease; ALT: Alanine Transaminase; Steatosis Index; Fibrosis Index; Liver biopsy;

USFLI SCORE: ultrasonographic fatty liver indicator; MRI – PDFF: Magnetic Resonance Imaging - Proton density fat fraction

Non alcoholic fatty liver disease (NAFLD) is accumulation of excessive fat in liver. It progress to inflammation and cirrhosis. Ethnic differences and clinical heterogeneity regarding NAFLD is well known. More children are getting diagnosed. Multiple factors are involved in pathology of NAFLD. This review focuses on diagnosis of NAFLD children based on available guidelines and literature. Clinical approach to NAFLD is suggested.

Is it NAFLD?

Non alcoholic fatty liver is rare in children less than 3 years. In Children between 3-10 years other causes of fatty liver should be ruled out prior considering diagnosis of NAFLD. Children above 10 years with central adiposity, elevated body mass index; clinical signs of insulin resistance, positive family history of co-morbid metabolic pathology is the classical setting for diagnosis of NAFLD. Sedentary life styles do contribute to the diagnosis. Obvious liver failure, conjugated jaundice, large hepatosplenomegaly rarely presents as NAFLD [1].

Metabolic diseases [1] like ornithine transcarbamylase deficiency can present as micro-vesicular steatosis. Citrin deficiency, hepatic form of glycogenosis, hereditary, fructose intolerance, congenital disorder or glycosylation, cholesterol ester-storage disease should be suspected in differential diagnosis. The non-classical presentation in clinical signs and atypical age group would help in diagnosis. Children with abetalipoproteinemia and hypobetalipoproteinemia can develop abnormal accumulation of fat in liver. Other differential diagnoses are cystic fibrosis, celiac disease and mal-nutrition which can present as fatty liver or hepatic steatosis. Endocrinopathies [1] like hypothyroidism and hypothalamic diseases are suspected with associated clinical signs and symptoms. Genetic disorders like Down's syndrome and turner syndrome have non alcoholic fatty liver as frequent co morbidity. Auto immune hepatitis can present in conjugation with steato-hepatitis. HIV infected children can have steatosis. Drugs [1] like Long term steroids, methotrexate, tetracycline, aminodarone, nucleoside analogues, aspirin, antiretroviral drugs are few of important drugs causing fatty liver. Diagnosis of NAFLD needs through clinical evaluation, ruling out co-morbid clinical conditions and appropriate drug history.

Secondary NAFLD is suspected in non-obese children with elevated ALT (>2 x upper limit) which is persistent for 6 months even after life style intervention [2]. Secondary NAFLD sometimes is called as Lean NAFLD. Lipodystrophy and alternative diagnosis due to genetic and congenital conditions should be ruled out. Monogenic causes of chronic liver disease like fatty acid oxidation defects, peroxisomal disorder, lysosomal storage disease should be considered in non over-weight and very young children as per AASLD guideline [3]. NASPGHAN guideline gives strength – 1, level of evidence – A for recommending to exclude alternative etiologies for evaluating hepatic steatosis [4].

Clinical diagnosis of NAFLD:

Most children with hepatic steatosis are asymptomatic. There may be non-specific abdominal pain, malaise or fatigue. Mild hepatomegaly can be appreciated .Acanthosis nigricans, raised waist circumference are accompanying clinical signs in some cases with NAFLD [5,6,7] .Waist circumference and waist to height ratio provide an estimate for adiposity. Clinical history of obstructive sleep apnea should raise suspicion of lean NAFLD [8].

Biochemical investigations:

The best screening test recommended by NASPGHAN for diagnosis NAFLD is ALT (strength – 1, evidence – B) but it has limitation [4]. ALT can be elevated in many hepatic disorders. Persistent elevated ALT for more than 3 months twice the upper limit of normal should direct one to investigate for NAFLD or other causes (strength – 1, level C) .Furthermore if ALT > 80 U/l the likelyhood of significant liver disease is higher. (strength -2, evidence C). Normal ALT does not exclude liver steatosis or its progression to cirrhosis as per ESPGHAN guideline [5]. The AST: ALT ratio > 1; directs towards increasing fibrosis [9].

Serum uric acid is important investigation in considering diagnosis of NAFLD. Higher serum uric acid is noted with hepatic steatosis in children [10]. The risk of developing NAFLD increases with increase in GGT levels [11]. High GGT in NAFLD is associated with liver fibrosis

[12]. One of the best independent predictive risk factor for diagnosis NAFLD in obese children is fasting serum insulin > 18.9 u/ml [13]. Insulin resistance and high serum triglyceride are additional risk factor for NAFLD [5]. HOMA – IR provides an estimate for insulin resistance. It has its limitation in metabolic conditions.[14] The 4.9 cut-off value for HOMA-IR is associated with severe steatosis in obese children with a 100% negative predictive value and a 33% positive predictive value in studies.[14]

Other non invasive biomarkers are studied in children with NAFLD [15]. More validation studies are required as per AASLD and NASPGHAN and ESPGHAN guidelines. In atypical lean or secondary [2] NAFLD cases; other causes for hepatic steatosis should be ruled out viz Hbsag, GGT, IgA, IgA TTG(Tissue transglutaminase), serum CPK, serum ceruloplasmin, autoimmune markers. Sr.TSH should be done to rule out hypothyroidism. Lipid profile would rule out co-morbid dyslipidemia. Mean ALT of child over follow up of 96 weeks and percentage of change of ALT from base line to 96 weeks are noted to be significant predictors of NAFLD.ALT > 60 at baseline and mean ALT < 62-77 U/lt over time predicted improvement in NA5H [16]. NICE guideline considered using enhanced liver fibrosis test (ELF) in children diagnosed with NAFLD. ELF score > 10.50 suggest advance liver fibrosis and early referral to specialist. If ELF < 10.51, children should be retested every 2 years [17]. During follow up HOMA – IR might help to identify patient at risk of fibrosis progression.

Genetic signature of NAFLD:

PNPLA3 single nucleotide polymorphic is associated with portal pattern of steatosis, inflammation and fibrosis [18]. Another study identified that PNPLA3 , TM6SF2T alleles have more than threefold higher risk of NAFLD than non carriers [19]. The mutated PNPLA3I 148M variant attached to surface of lipid droplets reduces the cleavage of triglyceride leading to lipid retention in hepatocyte and hepatic steatosis [20]. The genetic risk score based on combination of variants and clinical risk factors improves prediction of NAFLD in obese children by 5.2% as compared to clinical factor alone [21].

Metabolic signature of NAFLD:

The lipid lipoprotein profile in NAFLD is characterised by increased extremely large to small VLDL. Triglyceride remnant cholesterol and saturated fatty acid concentrates of glycoprotein acetyls are also increased which suggest chronic inflammation [22]. Saturated fatty acids, palmitic acid, myristic acid in saliva are increased in paediatric obesity related liver disease. Higher level of salivary pyroglutamic acid is suggested biomarker of increasing severity of NAFLD [23]. Steroid metabolities are also altered in non-syndromic childhood obesity. Urine 5 alphar eductase, 21 hydroxylase activity are increased while 11beta HSD1 activity, DHEA is reduced in NAFLD. These findings reflected lesser hepatic recycling of cortisone to cortisol which is compensated by increased adrenal cortisol leading to higher gluco-corticoid metabolites and lower mineralo-corticoid metabolites [24]. It is also called as steroid metabolic signature of liver disease in childhood obesity.

Microbiome signature of NAFLD:

NAFLD children have altered intestinal flora. The proportion of actinomycetes is lower and proportion of thermus is higher in NAFLD group at level of phylum. At the level of genus the proportion of bacteroids and bifidobacterium in NAFLD children is lower while the proportion of prevotella is higher. This is supposed to alter lipid metabolic pathway leading to NAFLD [25].

Intestinal dysbiosis is also confirmed in analysis of fecal microbiomes of children with NAFLD. NAFLD children have lower diversity of microbiome in the gut. High prevotella is associated with fibrosis. Genes involved in

flagellar assembly are enriched in patient with fibrosis [26]. Small intestinal bacterial over growth also affects insulin level and NAFLD [27].

Genetic, metabolic & microbiome signature of NAFLD are newer approaches to study and diagnose NAFLD. The need for studies across different ethnicity is must for further validation.

Newer biomarkers of NAFLD:

NAFLD liver fat score ,fatty liver index and hepatic steatosis index need further validation confirmatiory studies.4 Combined paediatric NAFLD fibrosis index and enhanced liver fibrosis score are proposed to be accurate in children with NAFLD [4,5]. ESPGHAN, NASPGHAN, AASLD recommends more studies to confirm the role of biomarkers in children with NAFLD. NICE guideline considers ELF test for NAFLD liver fibrosis. A Brief overview of clinically significant test is described here with.

PNFI [28] paediatric NAFLD fibrosis index using age, waist circumference and triglycride can be use in place of liver biopsy to rule in liver fibrosis. PNFI > 9 has positive predictive value of 98.5%. Enhanced liver fibrosis (ELF) test [29] is proposed for screening progressive fibrosis. It uses hyaluronic acid, aminoterminal propeptide type III collagen (PIINP) and tissue inhibitor of metalloprotienase (TIMP – 1). Combination of PNFI & ELF [30] is also used to predict presence of fibrosis. PNFI < 3.47 rule out liver fibrosis. PNFI > 9 can rule in liver fibrosis. If PNFI is 3.47 to 8.99 then ELF score is used. ELF < 8.49 can rule out fibrosis.

Paediatric study for validation for fibrosis - 4 (FIB – 4) is noted to be insensitive [31]. AST / ALT ratio, APRI, NFS have poor accuracy. BARD score is not evaluated for detecting mild – moderate fibrosis .It has also poor accuracy. ELF test is the test with high accuracy buts its costly and needs kit from manufactures which make it difficult to access. PNFI and PNES are complex with poor-moderate accuracy [32].

Low neuregulin 4 level, adipokine in NAFLD is considered to be diagnostic. Elevated neuregulin 4 is associated with decreased risk of NAFLD [33]. Another adipokine chemerin is noted be a suitable biomarker of liver steatosis [34]. Leptin / adiponectin ratio is also raised in children with NAFLD [35]. Hepatokines are produced by liver regulating glucose and lipid metabolism like FGF – 21 is significantly noted to be higher in NAFLD [36].

Liver biopsy:

As per AASLD guideline liver biopsy should be done in children suspected NAFLD in whom diagnosis is unclear and there is the possibility of multiple diagnosis or before starting hepatotoxic medical therapy. While NASPGHAN guideline considered Liver biopsy in patient with increased risk of NASH and /or advanced fibrosis, ALT > 80 U/lt, splenomegaly and AST / ALT > 1, panhypopituitarism, type 2 DM (strength I, evidence B). ESPGHAN guidline accepted the indication to do liver biopsy as follow: to exclude other treatable diseases, in case of clinically advanced disease, before pharmacological / surgical treatment, as a part of intervention protocol or clinical research trial, < 10 years of age, family h/o severe NAFLD.

Histopathology of liver biopsy in children particularly prepubertal boys show more steatosis less ballooning and more portal based inflammation and fibrosis, commonly described as type II NASH [32]. The diagnosis of NAFLD is established when an atleast 5% of hepatocytes present with micro or macro-vesicular steatosis

[37]. Two widely accepted and validation methods for scoring and staging the pathologic lesion of NAFLD are NASHCRN proposed score (NAFLD activity score) [38] and score by the European fatty liver inhibition of progression (SAF score) [39] Paediatric NAFLD histological scores strongly correlate with presence of NASH [40].

Imaging for NAFLD:

Ultrasonography (USG): It is the first line imaging modality for diagnosis of NAFLD. Ultrasound for fatty liver is safe, inexpensive test, but plain ultrasound cannot quantify steatosis or fibrosis. It is useful to rule out other pathologies, but it has poor specificity as per NASPGHAN and ESPGHAN guideline. NICE guideline uses USG for screening purpose. Increased brightness of the liver compared to adjacent right kidney or spleen indicates hepatic steatosis [41]. USG score more than or equal to 2 by saverymuttu [42] score, has high pool specificity of 96% and sensitivity of 52%. The mean sensitivity [43] of USG for steatosis identification range from 73-90%. Controlled attenuation parameter (CAP) is used to assess presence of hepatic steatosis by using shear wave propagation. It is used in transient elastography; fibroscan CAP value > 24 1 dB/m) suggest steatosis [44]. CAP value estimation has limitation in obese [44] children. Liver stiffness measurement by fibro-scan > 5.5 Kpa is useful to diagnose hepatic fibrosis. [45] More validation studies are needed.

Magnetic Resonance Imaging (MRI) : It is not cost effective but can help in diagnosing steatosis and fibrosis .Proton density fat fraction(PDFF) by MRI is an objective test for quantification of liver steatosis [46]. MRI – PDFF

allows fat mapping of entire liver. HMR spectroscopy measures concentration of lipids in small area of interest in liver [47]. More paediatric specific research is indicated.

Newer tests like non invasive semi quantitative ultrasonography fatty liver indicator are studied in paediatric NAFLD. USFLI SCORE more than 2 is diagnostic of NAFLD [48]. USFLI score >6 has positive predicative value of 71% sensitivity of 75% and specificity of 63% for predicting hepatitis in children with NAFLD. [49]

Field of artificial intelligence integrating radiologic bio-images with genomic data and its correlation with liver biopsy would improve diagnosing NAFLD in future.

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CASE REPORT

Nephrotic Syndrome in a child with horse shoe kidney

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BACKGROUND: Pediatric patient with horse shoe kidney developing steroid resistant nephrotic syndrome is uncommon.

CASE CHARACTERISTICS: Ten year old boy with horse shoe kidney and infrequently relapsing nephrotic syndrome developed resistance to steroid treatment.

OUTCOME: Child responded to Tacrolimus.

MESSAGE: Although rare but horse shoe kidney may be associated with steroid resistant nephrotic syndrome.

Introduction : Horse shoe kidney (HSK) is a common congenital anomaly of genito-urinary system, occurring in about 0.25% of the population [1]. Urinary tract infection, hydronephrosis, renal calculi and tumors of the renal pelvis are known complications of HSK [2]. However its association with infrequently relapsing nephrotic syndrome progressing to late onset steroid resistant nephrotic syndrome (SRNS) has not been reported earlier, to our knowledge, especially in a pediatric patient. We report a case of child with HSK developing SRNS.

CASE DESCRIPTION: A ten year old boy presented to our emergency department with anasarca for three days. He had history of onset of nephrotic syndrome at the age of four years for which he was treated with steroids. Later he behaved as infrequently relapsing nephrotic syndrome. Incidental ultrasonography(USG) done at seven years of age showed HSK which was supported by dimercaptosuccinic acid(DMSA) scan. There was absence of any scars. Micturating cystourethrogram done at the time showed no reflux.

Laboratory examination of urine rendered (++++) proteinuria and 24 hours urine protein excretion was 4g/day. Urine microscopy and culture was insignificant. Blood tests showed following results: 10g/dl hemoglobin, total protein 4.27g/dl, serum albumin 2.04g/dl, blood urea 15.4mg/dl, plasma creatinine 0.7mg/dl, total cholesterol 262mg/dl, sodium 154mEq/l, potassium 3.5mEq/l. Taking his past history into account, diagnosis of relapse of nephrotic syndrome was made. Prednisolone was started at 2mg/kg/day along with enalapril at 0.37mg/kg/day. However despite four weeks of daily steroid he did not attain remission and was labeled as late onset SRNS. Although edema reduced but his total protein was 4.8g/dl and serum albumin was 2.2g/dl. HSK is considered a major contraindication to renal biopsy owing to the anomalous and unpredictable location of the internal renal structures and because it often straddles the aorta [3]. Hence renal biopsy was not done in this patient.

Tacrolimus at 0.1mg/kg/day was started with alternate day steroid. The child went into remission after four weeks of Tacrolimus. He is still in remission continuing Tacrolimus for last four months and his alternate day steroid is being tapered.

DISCUSSION: HSK occurs in 1 in 400-800 births[4]. It is frequently associated with anomalies of other systems in which genetic factors may be common in their etiologies like musculoskeletal, cardiovascular, gastrointestinal and certain neurological conditions [5].

International Study of Kidney Disease in Children defines SRNS as: No urinary remission within 4 weeks of prednisolone therapy at 60mg/m2/day (2mg/kg/day). SRNS constitutes about 10-20% of pediatric NS cases. Although number of agents with variable efficacy is available for these patients but still their management is difficult [6]. Any stress and functional impairment, as well as podocyte loss, may compromise the filtration barrier and lead to proteinuria. Continuing podocyte loss may be critical below a certain thresh hold, which is estimated as a loss of more than 20%[7]. Once sclerotic lesions are established, a point of no return for theses lesions is reached and the defect becomes somewhat resistant to any kind of pharmacological treatment. The side effect of treatment with immunosuppressive agents in these patients

complicates the unremitting nature of the disease and the progression of the renal damage due to it.

There are only few reports of HSK associated with proteinuria. And occurrence of nephrotic range proteinuria with HSK has been reported in some adult patients only[8,9].

Vesico ureteric reflux(VUR) which could lead to FSGS is a clinical condition commonly associated with HSK. Can this post-VUR FSGS lead to nephrotic syndrome? Continuous injury to the renal parenchyma leading to unremitting inflammation and resistant scarring of the renal tissue may theoretically explain post VUR nephrotic syndrome[8]. However in the case reported, VUR was ruled out so this theory does not hold true here.

In cases it is believed that HSK predisposes glomerular disease because it facilitates immune complex deposition[9]. There is evidence from many clinical observations that a circulating factor targets the kidney, leading to proteinuria and glomerular sclerotic lesions. Although nature of this factor is yet to be confirmed but work on the Savin factor seems promising[10]. Does HSK have any special predilection for such deposit leading to glomerular injury is presently under investigation?

In one of the cases of HSK reported, renal adeno carcinoma was associated with HSK. Nephrotic syndrome in this case was due to FSGS secondary to hyper filtration which evolves towards chronic renal failure[9].

The question remains whether glomerulopathy is idiopathic or associated with the anatomic anomaly. There is insufficient evidence to conclude that there is a causal relationship between HSK & SRNS. Because sometimes routine USG misses the diagnosis of HSK, exact incidence can be higher than the numbers reported in literature. However as HSK is the most common anomaly of genitourinary system, it is believed that the concurrence of these two conditions may be sporadic and more common than the incident reported.

More cases will be necessary to determine whether there is any causal relationship between nephrotic syndrome and HSK or is it a mere co-incidence. More importantly it needs to be determined whether HSK leads to any predisposition towards steroid resistance.

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JOURNAL WATCH

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1. Making a Genetic Diagnosis in a Level IV Neonatal Intensive Care Unit

Population: Who, When, How, and at What Cost? Kayleigh A et al

DOI:https://doi.org/10.1016/j.jpeds.2019.05.054

Objective: To investigate the prevalence of genetic disease and its economic impact in a level IV neonatal intensive care unit (NICU) by identifying and describing diseases diagnosed, genetic testing methodologies used, timing of diagnosis, length of NICU stay, and charges for NICU care.

Study design: A retrospective chart review of patients admitted to a level IV NICU from 2013 to 2014 (n = 1327) was undertaken and data collected up to 2 years of age from the electronic medical record.

Results: In total, 117 patients (9%) received 120 genetic diagnoses using a variety of methodologies. A significant minority of diagnoses, 36%, were made after NICU discharge and 41% were made after 28 days of age. Patients receiving a genetic diagnosis had significantly longer mean lengths of stay (46 days vs 29.1 days; P < .01) and costlier mean charges ($598 712 vs $352 102; P < .01) for their NICU care. The NICU stay charge difference to care for a newborn with a genetic condition was on average $246 610 in excess of that for a patient without a genetic diagnosis, resulting in more than $28 000 000 in excess charges to care for all patients with genetic conditions in a single NICU over a 2-year period.

Conclusions: Given the high prevalence of genetic disease in this population and the documented higher cost of care, shortening the time to diagnosis and targeting therapeutic interventions for this population could make a significant impact on neonatal care in level IV NICUs.

2. Restricted fluid bolus volume in early septic shock: results of the Fluids in Shock pilot trial. Inwald DP et al.

http://dx.doi.org/10.1136/archdischild-2018-314924

Objective: To determine the feasibility of Fluids in Shock, a randomized controlled trial (RCT) of restricted fluid bolus volume (10 mL/kg) versus recommended practice (20 mL/kg).

Design : Nine-month pilot RCT with embedded mixed-method perspectives study.

Setting: 13 hospitals in England.

Patients : Children presenting to emergency departments with suspected infection and shock after 20 mL/kg fluid.

Interventions : Patients were randomly allocated (1:1) to further 10 or 20 mL/kg fluid boluses every 15 min for up to 4 hours if still in shock.

Main outcome measures : These were based on progression criteria, including recruitment and retention, protocol adherence, separation, potential trial outcome measures, and parent and staff perspectives.

Results : Seventy-five participants were randomized; two were withdrawn. 23 (59%) of 39 in the 10 mL/kg arm and 25 (74%) of 34 in the 20 mL/kg arm required a single trial bolus before the shock resolved. 79% of boluses were delivered per protocol in the 10 mL/kg arm and 55% in the 20 mL/kg arm. The volume of study bolus fluid after 4 hours was 44% lower in the 10 mL/kg group (mean 14.5 vs 27.5 mL/kg). The Paediatric Index of Mortality-2 score was 2.1 (IQR 1.6–2.7) in the 10 mL/kg group and 2.0 (IQR 1.6–2.5) in the 20 mL/kg group. There were no deaths. Length of hospital stay, paediatric intensive care unit (PICU) admissions and PICU-free days at 30 days did not differ significantly between the groups. In the perspectives study, the trial was generally supported, although some problems with protocol adherence were described.

Conclusions : Participants were not as unwell as expected. A larger trial is not feasible in its current design in the UK.

3. Use of a Probiotic to Enhance Iron Absorption in a Randomized Trial of Pediatric Patients Presenting with Iron Deficiency. Gerald M et al.

DOI: https://doi.org/10.1016/j.jpeds.2018.12.026

Objective: To evaluate the efficacy of low dose ferrous sulfate for the treatment of iron deficiency and if the probiotic Lactobacillus plantarum 299v (LP299v) enhances treatment.

Study design: This randomized, double-blinded, controlled trial of the treatment of iron deficiency in children compared the use of low-dose ferrous sulfate (1-3 mg/kg/day), with or without probiotic (LP299v).

Results: Serum ferritin level increased in all children from a baseline of 23.7 ng/mL to 45.4 ng/mL after 6-8

weeks of treatment. There was no significant difference in the increase in serum ferritin in children taking the probiotic LP299v compared with controls (23.2 vs 20.0 ng/mL, respectively). Additionally, an increase in ferritin level was not significantly associated with probiotic use when controlling for other factors, including child weight and dosing. Overall, the treatments were well-tolerated, with mild side effects.

Conclusions : Treatment with low-dose ferrous sulfate is well-tolerated and effective in correcting iron deficiency in children. However, the probiotic LP299v did not enhance treatment. Further attention should examine the dose–response effect in children, including an alternate day dosing schedule.

4.Randomized clinical trial of high concentration versus titrated oxygen use in pediatric asthma. Patel B et al.

https://doi.org/10.1002/ppul.24329

Objective: To compare the effects of high concentration to titrated oxygen therapy (HCOT) on transcutaneous carbon dioxide (PtCO2) level in pediatric asthma exacerbation. Titrated oxygen therapy (TOT) in acute asthma will avoid a rise in PtCO 2 in the pediatric population.

Method: The study design is a prospective, randomized, clinical trial comparing HCOT (maintain SpO2 92-95%) while being treated for asthma exacerbation in the emergency department (ED). Inclusion criteria: 2 to 18 years, previously diagnosed asthma with acute exacerbation (asthma score >5). PtCO2 and asthma scores were measured at 0, 20, 40, 60 minutes and then every 30 minutes until disposition decision. The primary outcome was a change in PtCO 2. Secondary outcomes were admission rate and change in asthma score.

Results: A total of 96 patients were enrolled in the study with a mean age of 8.27 years; 49 in HCOT and 47 in the TOT group. The 0 minute PtCO2 was similar (35.33 + 3.88 HCOT vs 36.66 + 4.69 TOT, P = 0.13); whereas, the 60 minutes PtCO 2 was higher in the HCOT (38.08 + 5.11 HCOT vs 35.51 + 4.57 TOT, P = 0.01). The asthma score was similar at 0 minute (7.55 + 1.34 HCOT vs 7.30 + 1.18 TOT, P = 0.33); whereas, the 60 minutes asthma score was lower in the TOT (4.71 + 1.38 HCOT vs 3.57 + 1.25 TOT, P = 0.0001). The rate of admission to the hospital was 40.5% in HCOT vs 25.5% in the TOT (P = 0.088).

Conclusions: HCOT in pediatric asthma exacerbation leads to significantly higher carbon dioxide levels, which increases asthma scores and trends towards the increasing rate of admission. Larger studies are needed to explore this association.

5. The bowel movement characteristics of exclusively breastfed and exclusively formula fed infants differ during the first three months of life. Moretti E et al.

https://doi.org/10.1111/apa.14620

Aim: Breastfed infants pass more stools and more liquid stools than formula fed infants and some have no bowel movements or infrequent stools for several days or weeks. We compared exclusively breastfed and exclusively formula fed infants for the first three months.

Methods: This study of 118 infants was carried out in the maternity ward of the Lille University Jeanne de Flandre Hospital, France, in 2015. The outcomes were the number and consistency of stools and the prevalence of infrequent stools.

Results: At three months, 84 infants remained and we compared 40 who were exclusively breastfed and 13 who were exclusively formula fed. Daily stool frequency was significantly higher in the breastfed than formula fed infants during the first (4.9 ± 1.7 vs. 2.3 ± 1.6, $p < 0.001$) and second (3.2 ± 1.6 vs. 1.6 ± 1.5, $p = 0.003$) months. Stools were more liquid in the breastfed infants during the first three months. Infrequent stools occurred in 28% of breastfed and 8% of formula fed infants at least once. ($p = 0.25$).

Conclusion: Exclusively breastfed infants produced more stools than exclusively formula fed infants during the first two months and more liquid stools during the first three. Infrequent stools were 3.5 times more likely in the breastfed infants.

6. Association of Atopic Dermatitis with Sleep Quality in Children. Faustine D et al

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Objective: To determine whether children with active AD have impaired sleep duration and quality at multiple time points throughout childhood and whether disease severity affects sleep outcomes.

Design, Setting, and Participants: This longitudinal cohort study used data of children enrolled in the Avon Longitudinal Study of Parents and Children, a population-based birth cohort in Avon, United Kingdom. Participants were children (N = 13◉988) alive at 1 year and followed up with repeated measures of self-reported AD and sleep through 16 years of age. This study was based on data collected from 1990 to 2008. Data analysis was performed from June 2017 to June 2018.

Main Outcomes and Measures: Standardized measure of sleep duration and composite measure of sleep quality, including nighttime awakenings, early morning awakenings, difficulty falling asleep, and nightmares, were repeated at multiple time points between 2 and 16 years of age.

Results: The study sample comprised 13◎988 children (7220 male [51.6%]) followed up for a median (interquartile range [IQR]) duration of 11 (5-14) years. Of this total, 4938 children (35.3%) met the definition of having atopic dermatitis between 2 and 16 years of age. Total sleep duration was similar between children with active AD and without AD at all ages, and the average estimated difference across childhood was a clinically negligible difference of 2 minutes less per day for children with AD (95% CI, −4 to 0 minutes). In contrast, children with active AD were more likely to report worse sleep quality at all-time points, with a nearly 50% higher odds of experiencing more sleep-quality disturbances (adjusted odds ratio [aOR], 1.48; 95% CI, 1.33 to 1.66). Children with more severe active disease (quite bad or very bad AD: aOR, 1.68; 95% CI, 1.42 to 1.98) and with comorbid asthma or allergic rhinitis (aOR, 1.79; 95% CI, 1.54 to 2.09) had worse sleep quality. However, even children with mild AD (OR, 1.40; 95% CI, 1.27 to 1.54) or inactive AD (OR, 1.41; 95% CI, 1.28 to 1.55) had statistically significantly increased odds of impaired sleep quality.

Conclusions and Relevance: Atopic dermatitis appeared to be associated with impaired sleep quality throughout childhood; thus, it is suggested that clinicians should consider sleep quality among all children with AD, especially those with comorbid asthma or allergic rhinitis and severe disease, and that interventions to improve sleep quality are needed.

7.Development of a Core Outcome Set for Infant Gastroesophageal Reflux Disease.Singendon K et al. JPGN. 68(5):655-661, May 2019.

doi: 10.1097/MPG.0000000000002245ZZ

Objective: In therapeutic trials for infant gastroesophageal reflux disease (GERD), ways to define GERD and measure and report study outcomes vary widely. The aim of this study was to develop a core outcome set (COS) for infant GERD

Methods: The COS was developed using the Delphi technique, adhering to the Outcome Measures in Rheumatology Initiative 2.0 recommendations. Healthcare professionals (HCPs) (predominantly pediatric gastroenterologists and general pediatricians) and parents of infants (age 0–12 months) with GERD, listed up to 5 primary goals of therapy from their perspective and up to 5 persistent signs or symptoms that would signify inadequate treatment. Outcomes mentioned by >10% of participants were included in 2 shortlists. Next, HCPs and parents rated and prioritized outcomes on these shortlists. Outcomes with the highest rank formed the draft COS. The final COS was created after 2 consensus meetings between an expert panel and patient representatives.

Results: In total, 125 of 165 HCPs (76%) and 139 of 143 parents (97%) of infants with GERD completed the first phase. The second phase was completed by 83 of 139 HCPs (60%) and 127 of 142 different parents (89%). Outcomes of these phases were discussed during the consensus meetings and a 9-item COS was formed: "Adequate Growth," "Adequate Relief," "Adverse events,", "Crying," "Evidence of Esophagitis," "Feeding Difficulties," "Hematemesis," "No Escalation of Therapy," and "Sleep Problems."

Conclusions: We developed a COS for infant GERD consisting of 9 items that should minimally be measured in future therapeutic trials to decrease study heterogeneity and ease comparability of results.

8.Antimicrobial-impregnated central venous catheters for prevention of neonatal bloodstream infection (PREVAIL): an open-label, parallel-group, pragmatic, randomised controlled trial. Gilbert et al. Lancet Child Adolesc Health 2019; 3: 381–90 Published Online April 27, 2019

http://dx.doi.org/10.1016/S2352-4642(19)30114-2

Background: Bloodstream infection is associated with high mortality and serious morbidity in preterm babies. Evidence from clinical trials shows that antimicrobial-impregnated central venous catheters (CVCs) reduce catheterrelated bloodstream infection in adults and children receiving intensive care, but there is a paucity of similar evidence for babies receiving neonatal intensive care.

Methods: This open-label, parallel-group, pragmatic, randomised controlled trial was done in 18 neonatal intensive care units in England. Newborn babies who needed a peripherally inserted CVC (PICC) were allocated randomly (1:1) to receive either a PICC impregnated with miconazole and rifampicin or a standard (non-antimicrobial-impregnated) PICC. Random allocation was done with a web-based program, which was centrally controlled to ensure allocation concealment. Randomisation sequences were computer-

generated in random blocks of two and four, and stratified by site. Masking of clinicians to PICC allocation was impractical because rifampicin caused brown staining of the antimicrobial-impregnated PICC. However, participant inclusion in analyses and occurrence of outcome events were determined following an analysis plan that was specified before individuals saw the unblinded data. The primary outcome was the time from random allocation to first microbiologically confirmed bloodstream or cerebrospinal fluid (CSF) infection between 24 h after randomisation and 48 h after PICC removal or death. We analysed outcome data according to the intention-to-treat principle. We excluded babies for whom a PICC was not inserted from safety analyses, as these analyses were done with groups defined by the PICC used. This trial is registered with ISRCTN, number 81931394.

Findings: Between Aug 12, 2015, and Jan 11, 2017, we randomly assigned 861 babies (754 [88%] born before 32 weeks of gestation) to receive an antimicrobial-impregnated PICC (430 babies) or standard PICC (431 babies). The median time to PICC removal was 8·20 days (IQR 4·77–12·13) in the antimicrobial-impregnated PICC group versus 7·86 days (5·00–12·53) days in the standard PICC group (hazard ratio [HR] 1·03, 95% CI 0·89–1·18, p=0·73), with 46 (11%) of 430 babies versus 44 (10%) of 431 babies having a microbiologically confirmed bloodstream or CSF infection. The time from random allocation to first bloodstream or CSF infection was similar between the two groups (HR 1·11, 95% CI 0·73–1·67, p=0·63). Secondary outcomes relating to infection, rifampicin resistance in positive blood or CSF cultures, mortality, clinical outcomes at neonatal unit discharge, and time to PICC removal were similar between the two groups, although rifampicin resistance in positive cultures of PICC tips was higher in the antimicrobial-impregnated PICC group (relative risk 3·51, 95% CI 1·16–10·57, p=0·018). 60 adverse events were reported from 49 (13%) patients in the antimicrobial-impregnated PICC group and 50 events from 45 (10%) babies in the standard PICC group.

Interpretation: We found no evidence of benefit or harm associated with miconazole and rifampicin-impregnated PICCs compared with standard PICCs for newborn babies. Future research should focus on other types of antimicrobial impregnation of PICCs and alternative approaches for preventing infection.

9.Eichenwald EC and AAP committee on fetus and newborn. Diagnosis and Management of Gastroesophageal Reflux in Preterm Infants. Pediatrics. 2018;142(1):e20181061

DOI: 10.1542/peds.2018-1061

Highlights of the guidelines are as follows. GER is a normal developmental phenomenon that will resolve with maturation. Signs commonly ascribed to GER in preterm infants include feeding intolerance or aversion, poor weight gain, frequent regurgitation, apnea, and desaturation bradycardia and behavioral signs, including irritability and perceived postprandial discomfort. These signs will usually improve with time without treatment. There is poor data on worsening lung disease attributable to GER and micro aspiration in mechanically ventilated preterm infants. Left lateral body position, head elevation, and feeding regimen manipulation, have not been shown to reduce clinically assessed signs of GER in the preterm infant. Supine positioning on a flat and firm surface and avoidance of commercial devices designed to maintain head elevation in the crib, should be paramount importance in practice. Drugs should be used sparingly, if at all, in preterm infants.

10. Progression of Celiac Disease in Children With Antibodies Against Tissue Transglutaminase and Normal Duodenal Architecture Auricchio, R. et al. Gastroenterology, article in press

DOI: https://doi.org/10.1053/j.gastro.2019.04.004

Potential celiac disease is characterized by positive results from serologic tests for tissue transglutaminase antibodies (anti-TG2) but normal duodenal architecture (Marsh stages 0–1). Which patients would progress to overt celiac and which would need observation is a matter of debate. This study highlights on this issue much pending issue.

This is a prospective study of 280 children (ages 2–18 years) in Italy with suspected celiac disease. Enrolled patients have 2 consecutive positive results from tests for anti-TG2, tested positive for the endomysial antibody (anti-EMA), have total serum levels of IgA in the normal range, normal duodenal architecture (Marsh stages 0–1) in 5 biopsies, and HLA DQ2- or DQ8-positive haplotypes. Follow up period is 12 years (range, 18–150 months; median 60 months). Serologic tests and clinical analyses are done in the study every 6 months and a small bowel biopsy was taken every 2 years. A multivariate analysis of clinical, genetic, and histologic data to identify factors associated with progression to villous atrophy is done. The study has a largest cohort of potential celiac disease

patients with the longest follow up. Immunohistochemical staining of duodenal biopsy for CD3+, TCRγδ+, and CD25+cells and presence of extracellular deposits of anti-TG2 IgA is done.

42 of 280 children (15%) developed villous atrophy. 89 children (32%) no longer tested positive for anti-TG2 or anti-EMA on follow up. The cumulative incidence of progression to villous atrophy is 43% at 12 years on gluten consumption. Data suggest that prescribing indistinctly to all potential celiac disease patients a GFD(Gluten free diet) would be an overtreatment. Younger patient at diagnosis has a greater chance to remain "potential". Factors most strongly associated with development of villous atrophy are numbers of γδ intraepithelial lymphocyte cells followed by age and homozygosity for the HLA DQB1*02. Lower numbers of γδ positive cells in the intestinal epithelium have been noted to be protective. Marsh 0 lesions at diagnosis on histopathology have less progression to villous atrophy. HLA effect is age specific and is not generalized and needs further research.

NOTES