The Child and Newborn

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Editorial

It is with a sense of disappointment that I write this editorial. It seems as if we are struggling for survival. There is always a dearth of articles for our journal. To circumvent this problem , it was decided at the Executive Body meeting that every EB member would contribute at least one article per year. It was not too much to expect from our respected members who are quite active academically . But this is not happening. As a result , we are unable to bring out our journal regularly .

A request was made to all members of our association to write something- either a query, clarification or interesting case or experience. Except for Dr. Basudeb Patra of Hoogly Branch, nobody responded. I convey my gratitude and congratulations to Dr. Patra for the same. Articles do not come spontaneously , they have to be begged for, except in a few instances.

Though it is true that publication in a non-indexed journal will not fetch any points for academic elevation , it is also true that if we support our own journal for a few years , we will have an indexed journal where we can easily publish our articles , without having to face rejection by some journals which are more often than not, biased, and have lots of requirements for even posting one article. I am sorry if some of you do not agree with my views but this is a fact.

This journal took its roots with Respected (late) Tapan da and Prof. Dilip Mukherjee with financial support from Nestle in 1994. From the very beginning, I was associated with the journal and contributed articles. With the help of Ms Arati Arora, a Nestle medical representative , we persuaded the company to sponsor the initial few issues of the journal, before the IMS Act barred us from accepting their sponsorship . It makes me really sad to see this journal facing survival issues.

It has come to my notice that some Paediatrics journals have started being published from our State. I suggest that we have one strong and meaningful journal published from our State rather than several, with smaller membership. I request our honourable members to volunteer their names for editorial board membership.

I hope this editorial will wake up our members and stir them to action so that we can have regular issues of The Child and Newborn ; thus helping to get it indexed. The photograph on cover page represents the state of our journal.

Dr (Prof) Atul Kumar Gupta
Editor in chief

Original Article

G6PD Deficiency With It's Relation To Malaria In The Eastern Indian Pediatric Population

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Abstract:

Background : *Glucose-6-phosphate-dehydrogenase (G6PD) deficiency is an X-linked genetic defect predominant among the tribal population. . Deficiency of this enzyme is highly polymorphic in those areas where malaria is/has been endemic. .*

Introduction : *Malaria is a national health problem. In india, patients with G6PD deficiency presents with sudden hemolysis after antimalarial therapy. Females can thus be homozygously / heterozygously deficient. Heterozygously-deficient women have a mixed population of erythrocytes, owing to random inactivation of one of the two X chromosomes, known as lyonization. One of the erythrocyte populations is G6PD deficient; the other has normal G6PD function.*

Materials & Methods : *The cytochemical assay is a test in which G6PD activity causes staining of the individual erythrocyte by converting exogenous G6P and $NADP^+$. The percentage of stained and unstained cells can be determined by light microscopy.*

Results : *We have taken 80 patients, out of which 13 patients were found to be suffering from G6PD deficiency & 16 patients are suffering from malaria.*

Discussion : *The major clinical manifestations of this disorder are drug induced haemolytic anaemia and/or neonatal jaundice and a small proportion of G6PD deficient individuals have chronic non-spherocytic haemolytic anaemia. It is believed that this disorder is selected due to malarial endemicity in many regions of the country.*

Conclusion : *G6PD deficiency in our region highlights the need to undertake systematic studies on G6PD deficiency in the Indian tribal population. G6PD deficiency increases in areas which were endemic for malaria.*

Keywords: *Deficiency, G6PD, malaria, tribes*

Background :

It is believed that the tribal people, who constitute 8.6 per cent of the total population (2011 census of India), are the original inhabitants of India. Glucose-6-phosphate-dehydrogenase (G6PD) deficiency is an X-linked genetic defect, affecting around 400 million people worldwide and is characterized by considerable biochemical and molecular heterogeneity. Deficiency of this enzyme is highly polymorphic in those areas where malaria is/has been endemic. G6PD deficiency was reported from India more than 50 years ago. G6PD deficiency is the most common human enzyme defect[10].

Introduction :

Glucose is the main source of energy for the red cell, which is metabolized by two major routes; the glycolytic pathway and the hexose monophosphate (HMP) shunt. Glucose-6-phosphate-dehydrogenase (G6PD) is an X-linked enzyme that catalyses the first step in the HMP pathway of glucose metabolism and it produces NADPH, which is required for the maintenance of reduced glutathione (GSH). GSH is essential for protecting red cells from oxidative damage. Hence, this enzyme is important in red cell metabolism and its deficiency renders the red cell extremely vulnerable to any kind of oxidative stress[1].

In India, malaria is a national health problem and anti-malarial drugs used leads to sudden hemolysis in cases of G6PD-deficient individuals, and hence it is of great concern in some populations where this deficiency is high. G6PD deficiency, an X-linked disorder. Females can thus be homozygously deficient or heterozygously deficient, whereas males are hemizygously deficient. Heterozygously-deficient women have a mixed population of erythrocytes, owing to random

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inactivation of one of the two X chromosomes, known as lyonization. One of the erythrocyte populations is G6PD deficient; the other has normal G6PD function[13].

G6PD deficiency is an example of balanced polymorphism, in which high rate of mortality caused by this disorder is offset by the protection that it offers against Plasmodium falciparum malaria. Alleles of the G6PD gene that encode a deficient enzyme attain high frequencies in areas where malaria is or has been endemic. It is believed that this disorder is selected due to malarial endemicity in many regions of the country. A correlation was found between high prevalence of malaria due to *P. falciparum* and incidence of G6PD deficiency[12].

A higher incidence of G6PD deficiency is seen in tropical and subtropical zones of the world. Molecular analysis has revealed that each population has a characteristic profile of deficient variants. The G6PD A- variant is mainly found in African populations while G6PD Mediterranean variant is predominant throughout the Mediterranean region, Middle East and India.

Detection of G6PD Deficiency :

There are several tests that can be used for the detection of G6PD deficiency, but only a few tests diagnose G6PD deficiency in heterozygous women reliably. DNA tests can be used for the diagnosis of G6PD deficiency. In these extremely reliable tests, primers are used to check whether the G6PD gene contains a mutation. They can be used for the diagnosis of homozygously, hemizygously, and heterozygously-deficient patients but have the great disadvantage that only one mutation can be analyzed with one primer. At present, 140 mutations are known, and the DNA sequences of these mutations have to be known before primers can be designed. It is unlikely that rare or new mutations will be found with DNA tests. At the moment, DNA tests can only be used for screening of prevalent mutations, for example G6PD A-. Moreover, DNA tests are expensive and require sophisticated equipment, which makes them unsuitable for diagnosis on a large scale and impossible to apply in third-world countries[2].

Tests based on the measurement of the NADPH production capacity of G6PD can be used for the diagnosis of all mutations. The most frequently used tests that measure NADPH production are the fluorescent spot test, the spectrophotometric assay, and the cytochemical assay. The tests are based on the formation of fluorescence (the fluorescent spot test and the spectrophotometric assay) or color (cytochemical assay). NADPH fluoresces when it is excited with light of a wavelength of 340 nm, whereas NADP+ does not, and NADPH converts colorless tetrazolium salt into colored formazan, whereas NADP+ does not. The Brilliant Cresyl Blue (BCB) dye test, based on the reduction of BCB to a colorless state by NADPH, was previously a commonly used test but has largely been replaced by the fluorescent spot test. In some tests, the BCB is replaced by dichlorophenol indophenol[15].

Materials and Methods :

The study was conducted in patients attending the OPDs of Pediatrics, Medicine and Clinical Hematology from March 2016 to June 2017. The clinical history was collected, routine investigations (Complete Blood Count and Retic count) were advised at the same time specialized tests like G6PD estimation, hemoglobin electrophoresis and ICT/QBC were also advised. We have taken 80 patients for the study, those who are not suffering from sickle cell anaemia, tuberculosis and other infectious diseases except malaria. The regions from which the patients came were also noted.

The diagnosis of red cell enzyme deficiency usually depends on the demonstration of decreased enzyme activity either through a quantitative assay or a screening test. There are several methods available for the diagnosis of G6PD deficiency. However, fluorescent spot test and dichlorophenol indophenol (DPIP) decolourisation method were found to be useful and suitable for routine use. The fluorescent spot test is based on the fluorescence of NADPH which has been generated by G6PD while in the DPIP dye decolourisation method; presence of G6PD in red cells is detected by the decolourisation of the dye within a specified time. It has an advantage over fluorescent spot test in that the heterozygotes can be easily detected and a large number of samples can be processed together at the same time. It is the method of choice along with quantitation of enzyme while screening large population[22]. Quantitation of enzyme activity involves the measurement of reduction of NADP to NADPH spectrophotometrically in the presence of G6P and haemolysate[3].

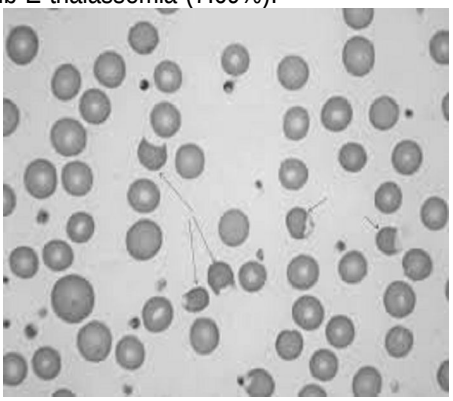
In our laboratory, we do the test by cytochemical assay. In this test, G6PD activity causes staining of the individual erythrocyte by converting exogenous G6P and $NADP^+$. Unstained erythrocytes have little or no G6PD activity. The percentage of stained and unstained cells can be determined by light microscopy. Leakage of colored end products from healthy erythrocytes into the medium and unstained cells makes the test unreliable, but optimization of the staining procedure improves the reliability of the test. Leakage of the colored end product is largely prevented[8].

The cytochemical assay is based on the reduction of water-soluble colorless tetranitro blue tetrazolium via the electron carrier 1-methoxyphenazine methosulfate, in its water-insoluble dark-colored formazan by NADPH. Dark-purple granules are present in erythrocytes that contain G6PD activity, whereas G6PD-deficient erythrocytes remain unstained.

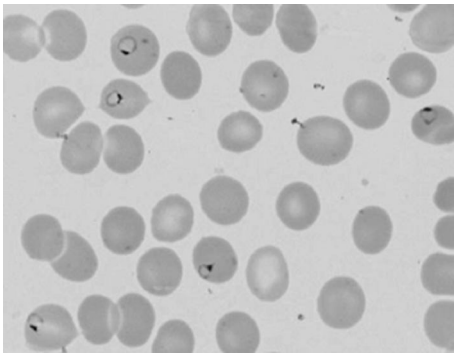
The cytochemical assay is reliable for detection of hemizygously, homozygously, and heterozygously-deficient patients because it shows G6PD activity in individual erythrocytes. When the percentage of stained and unstained cells has to be determined manually, at least 1000 erythrocytes have to be included in each count to estimate G6PD deficiency. Formazan crystals in erythrocytes quench the autofluorescence of erythrocytes. Therefore, cells that lack G6PD activity, and thus do not contain formazan crystals, show strong autofluorescence. The more formazan crystals are present in cells, the less fluorescence can be observed. On this basis, percentages of stained and unstained cells can be determined objectively. Reagents : Sodium nitrite - 0.18mol/l, Incubation medium - 9g/l NaCl, 4ml ; 50 g/l glucose, 1.0ml ; 0.3mol/l phosphate buffer, pH 7.0, 2.0ml ; 0.11 g/l Nile blue sulphate, 1.0ml ; water 2.0ml, MTT tetrazolium - 5 g/l of 3-(4,5-dimethyl-thiazolyl-1-2)-2,5 diphenyltetrazolium bromide in 9 g/l NaCl, Hypotonic saline - 6 g/l NaCl. Procedure : Venous blood is collected in ACD. Test should be carried out within 8hrs of collection and the blood should be kept at 40C until it is tested. Then the blood is centrifuged at 40C for 20mins at 1200-1500g. Supernatent is discarded. 0.5ml of of the packed red cells is added to 9ml of 9g/l NaCl and 0.5ml of sodium nitrite solution contained in a 15ml glass centrifuge tube. It is incubated at 370C for 20mins. Then again it is centrifuged at 40C for 15mins at approx. 500g. The supernatent fluid id again discarded without disturbing the buffy coat and the uppermost layer of red cells. The cells are washe4d 3times in cold saline. After the last wash, the buffy coat is removed, packed cells are mixed well and 50µl of it is transfered into a glass tube containing 1ml of incubation medium. Suspension is incubated undisturbed at 370C for 30mins. 0.2ml of MTT tetrazolium solution is added, shaken gently and incubated at 370C for 1hr. cells are resuspended thoroughly. 1drop of suspended cells and 1 drop of hypotonic saline is placed on a glass slide, mixed well and covered with a coverslip. Interpretation : When G6PD activity is normal, all the red cells are stained. In G6PD hemizygotes, the majority of the red cells are unstained. In heterozygotes mosaicism is usually seen, usually 40%-60% of the cells are unstained, but the proportion may be much less and in extreme cases only as few as 2%-3% may be unstained[4].

Results :

Out of total 80 patients, patients suffering from G6PD deficiency are 13 patients (16.25%) and from malaria are 16 patients (20%). Out of 13 patients suffering from G6PD defiency, 5 patients are having malaria (38.46%), among these 1 patient is having ß thalassemia trait (7.69%) and 1 patient is having Hb E thalassemia (7.69%).



Bite Cells & Helmet Cells



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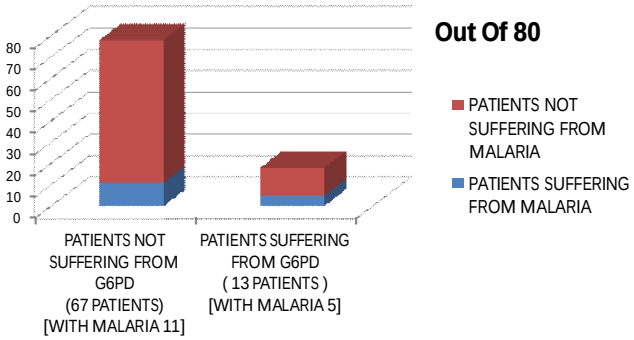
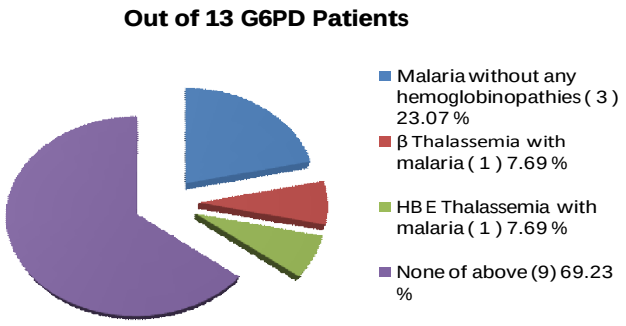
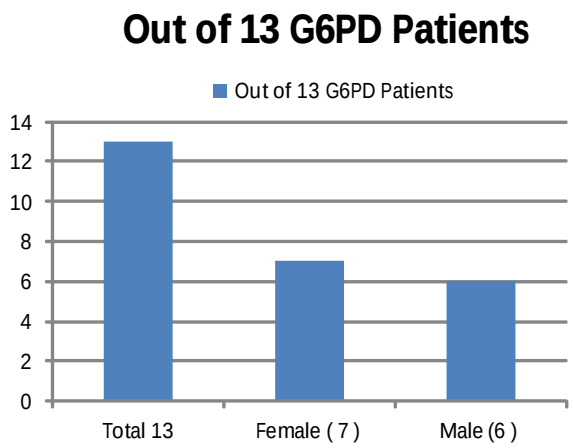
AGE GROUPS	TOTAL PATIENTS	G6PD DEFICIENCY	MALARIA		HEMOGLOBIN ELECTROPHORESIS
			POSITIVE	NEGATIVE	
<1yr.	32 (40%)	3 (9.37%)	1 (3.125%)	31 (96.87%)	Normal Hemoglobin Pattern
1-5yrs.	37 (46.25%)	7 (18.91%)	12 (32.43%)	25 (67.57%)	1 HbE thalassemia
6-18yrs.	11 (13.75%)	2 (18.18%)	3 (27.27%)	8 (72.72%)	1 βthalassemia trait

Study was done on 80 patients from March 2016 to June 2017







Demographic	G6PD Status		p-Value	OR(95%CI)
	G6PD Deficiency	Normal		
Male	7	27	0.379*	1.716
Female	6	40		

*Comparison of the two groups using the Fisher's exact test

Demographic	G6PD Status among malaria patients		p-Value	OR(95%CI)
	G6PD Deficiency	Normal		
Male	2	5	1.000*	0.811
Female	3	6		

*Comparison of the two groups using the Fisher's exact test

Discussion :

Out of 13 patients suffering from G6PD deficiency, 7 patients are female (53.84%) and 6 patients are male (46.15%). 12 patients (92.31%) out of 13 are less than 6yrs of age. 70% of the patients are from the tribal regions like Phulbani, Boudh, Kalahandi and Keonjhar.

The major clinical manifestations of this disorder are drug induced haemolytic anaemia and/or neonatal jaundice and a small proportion of G6PD deficient individuals have chronic non-spherocytic haemolytic anaemia. It is believed that this disorder is selected due to malarial endemicity in many regions of the country[5].

Classification :

The World Health Organization classifies G6PD genetic variants into five classes, the first three of which are deficiency states[14].

(a) Class I: Severe deficiency (<10% activity) with chronic (nonspherocytic) hemolytic anemia.

(b) Class II: Severe deficiency (<10% activity), with intermittent hemolysis.

(c) Class III: Mild deficiency (10-60% activity), hemolysis with stressors only.

(d) Class IV: Non-deficient variant, no clinical sequelae

(e) Class V: Increased enzyme activity, no clinical sequelae

Class I defects are probably caused by mutations in the region of the enzyme where NADP+ or G6P binds. The genetic background of the other classes is unknown. Class I deficiencies are rare and can be severe enough to cause transfusion dependency. Patients in this class usually suffer from chronic non-spherocytic hemolytic anemia. Erythrocytes of these patients have a considerably shorter lifespan then healthy erythrocytes, even when they are not exposed to oxidative stress. G6PD deficiency renders the erythrocytes susceptible to damage from stress encountered in the circulation[6].

Nonetheless, patients with class II, III, or IV mutations are usually asymptomatic. Class III deficiencies are the most prevalent defects. Hemolysis due to stress is self-limiting in this class. Only the older erythrocytes lack sufficient active G6PD to counteract oxidative stress episodes. Class II deficiencies are usually asymptomatic as well, but both young and old erythrocytes are susceptible to oxidative stress. Hemolysis in this class is more severe and not self-limiting. Hemolysis stops after removal of the stress-causing agent.

Malaria And G6PD Deficiency :

Acute and chronic malaria can cause anemia. When severe G6PD deficiency complicates malaria infection, treatment with primaquine or dapsone can lead to life-threatening acute intravascular hemolysis followed by anemia and acute renal failure. Primaquine and dapsone are not very frequently used in malaria therapy, but recently, proposed a role for primaquine in a combination therapy with artemisinin derivatives for the treatment of Plasmodium falciparum. When this strategy becomes standard treatment, many G6PD-deficient individuals could experience a hemolytic crisis: the high prevalence of G6PD deficiency in malaria-endemic areas, where 300–500 million people are infected annually with malaria, implies that many patients that are treated for malaria with an artemisinin–primaquine combination will suffer (severely) from the treatment because of oxidative stress in their G6PD-deficient erythrocytes. To prevent this, patients should be tested for G6PD deficiency before treatment with these anti-malaria drugs[7].

The combination of G6PD deficiency and ß thalassemia trait has been found to cause a significant increase in MCV which however remains below normal range. Association of G6PD deficiency with thalassemia should get more attention due to increased hemolysis as the patients with the latter condition are treated with regular blood tranfusions or bone marrow transplantation[9].

Conclusion :

This is a burden on the National Health programme and highlights the need to undertake systematic studies on G6PD deficiency in the Indian tribal population. As my study shows >90% of the affected children are <6yrs, newborn screening of G6PD deficiency is necessary specially in tribal population. There is a consensus agreement that the health status of tribal populations is very poor and is even worse among the primitive tribes because of their isolation as they reside in remote areas where malaria is or has been endemic. Therefore, it is recommended that the vulnerable tribal communities should be screened before administering the oxidative drugs if screening is not done in the newborn period[11]. In my study the sample size was small and the tests for categorization (molecular study) for G6PD should have been done.

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Antimicrobial Prophylaxis

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Antimicrobial prophylaxis (AP) is commonly used by clinicians for the prevention of numerous infectious diseases. Antimicrobial prophylaxis can be used effectively to prevent infection, but its use should be limited to specific, well-accepted indications to avoid excess cost,toxicity, and antimicrobial resistance. Antimicrobial prophylaxis may be considered primary (prevention of an initial infection) or secondary (prevention of the recurrence or reactivation of an infection), or it may also be administered to prevent infection by eliminating a colonizing organism. Perioperative antimicrobial prophylaxis is recommended for various surgical procedures to prevent surgical site infections. Optimal antimicrobial agents for prophylaxis should be bactericidal, nontoxic, inexpensive, and active against the typical pathogens that can cause infection. Prophylaxis is theoretically more effective when a single pathogen is targeted. In general, the greater the number of targeted pathogens, the less effective, the more toxic, and the more expensive the regimen becomes. Ideally, prophylaxis should be administered at the time of exposure to the potential pathogen. If exposure is prolonged or continuous, prophylaxis become less effective and less desirable.

Points to be considered while prescribing:

1. The severity of the disease to be prevented: it is a major consideration. Potentially fatal infections (e.g., meningococcemia) or infections that result in high morbidity (e. g., endocarditis) are justifiably targeted. Prophylaxis usually is not required for minor illness (e.g. cuts, abrasions).
2. The site of infection: adequate concentrations of antimicrobials should be achieved readily at the site. The organs that are highly vascular and have no barriers where as infections in restricted compartments (e.g. middle ear) or those that involve prosthetic materials may require special considerations.

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Points to be considered while selecting the antimicrobial agent:

1. The antimicrobial agent should be narrow spectrum, easy to administer, well tolerated, has minimal side effects and should be least expensive.
2. The agent which requires less frequent administration will be more effective as it can have better patient compliance. When prophylaxis can be achieved effectively with a single administration of the antimicrobial agent, prophylaxis is likely to be ideal and will be more compliant.

Non surgical antimicrobial prophylaxis:

Rheumatic Fever – Rheumatic fever (RF), which is associated with tonsillo-pharyngitis caused by the group *A ß-hemolytic streptococci,* may result in carditis with or without valvulopathy. Primary prevention of RF involves prompt and appropriate antibiotic treatment of group A ß-hemolytic streptococcal pharyngitis with a penicillin (drug of choice) or alternative antibiotic. Continuous secondary AP prevents recurrent episodes of RF, which could otherwise lead to worsening of the severity of rheumatic heart disease that developed after the initial attack or the development of rheumatic carditis in those who did not develop carditis with the initial RF episode. Penicillins are the antibiotics of choice for secondary prophylaxis for RF, and intramuscular penicillin is superior to oral penicillins. Macrolides (eg, erythromycin, clarithromycin, azithromycin) should be reserved for patients who are allergic to both penicillin and sulfa antibiotics.

Primary prevention

For primary prevention of RF penicillin is the drug of choice and is highly effective. Those patients who are allergic to penicillins alternative antibiotics can be prescribed. The acceptable regimens for treatment of acute group A streptococcal infections (i.e., primary prevention) are provided in Table1. Even when treatment is started as long as 9 days

after the onset of acute illness, penicillin effectively prevents primary attacks of rheumatic fever.Intramuscular Benzathine penicillin G is preferred to oral penicillin, particularly for patients who are unlikely to complete a 10-day course of oral therapy.

Secondary prevention

Continuous antibiotic administration is indicated in patients at risk for development of disease after having infection with *group A streptococcus* or for those children with congenital or acquired cardiac disease who are at risk for development of recurrent attack of rheumatic fever, even after those infections that are asymptomatic or in those symptomatic infections that are treated optimally. Continuous prophylaxis is recommended for patients with a well-documented history of rheumatic fever (including cases manifested solely by Sydenham chorea) and for those with definite evidence of rheumatic heart disease. Such prophylaxis should be initiated as soon as acute rheumatic fever or rheumatic heart disease is diagnosed. A full therapeutic course of penicillin or other effective regimen should be given first to patients with acute rheumatic fever to eradicate residual *group A streptococcus.* An injection of 1,200,000 U of Benzathine penicillin G every 4 weeks is the recommended regimen for secondary prevention in most circumstances. In special circumstance, or in certain high-risk individuals, such as patients with residual rheumatic carditis, administration of Benzathine penicillin G every 3 weeks is justified and recommended. Long – acting penicillin is of value in patients with a high risk of having a recurrence of rheumatic fever, especially those with rheumatic heart disease, in whom recurrence is very serious.

Success of oral prophylaxis (penicillin V or sulfadiazine) depends primarily on the patient's adherence to prescribed regimens. Even with optimal adherence of the patient, the risk of having a recurrence is higher in individuals receiving oral prophylaxis than in those receiving intramuscular Benzathine penicillin G.

Antimicrobial prophylaxis should be continued until 10 years has elapsed since the last rheumatic fever attack or the age of 21 years, whichever is longer for patients with carditis without valvular disease. (Table 2.)Prophylaxis should be continued in patients even after prosthetic valve replacement surgery. Antibiotic suppression for the prevention of RF is not adequate for infective endocarditis (IE) prophylaxis before dental procedures.

As such sulfonamides are not effective in the eradication of group A streptococcus, they do prevent development of infection. For patients who are allergic to penicillin and sulfisoxazole, erythromycin is recommended. No data have been published about the use of other penicillins, macrolides or cephalosporins for the secondary prevention of rheumatic fever, but the American Academy of pediatrics has stated that clarithromycin for 10 days or azithromycin for 5 days is

Table 1 : Antimicrobial prophylaxis for prevention of Rheumatic Fever:

Agent	Dose	Mode	Duration
Primary Prevention:			
Benzathine Penicillin G	600,000 U for pt < 27 Kg 1,200,000 U for pt >27 kg	IM	Once
Penicillin V	Children: 250mg 2-3 times daily	Orally	10days
	Adolescents: 500 mg 2-3 times	Orally	10 days
For Allergic to Penicillin			
Erythromycin	40 mg/kg/day 2-4 times daily	Orally	10 days
Secondary Prevention:			
Benzathine Penicillin G	1,200,000 U every 3-4 wks	IM	see text
Penicillin V	250 mg twice daily	Orally	see text
Sulfadiazine	0.5 g once daily for pt <27 kg	Orally	see text
	1 g daily for pt >27 kg	Orally	see text
For Allergic Individuals:			
Erythromycin	250 mg twice daily	Orally	see text

Table 2. Duration of Secondary Rheumatic Fever Prophylaxis*

Category	Duration
Rheumatic fever with carditis and residual heart disease (persistent valvular disease)	10 years or until 40 years of age (whichever is longer), sometimes lifelong prophylaxis
Rheumatic fever with carditis but no residual heart disease (no valvular disease)	10 years or until 21 years of age (whichever is longer)
Rheumatic fever without carditis	5 years or until 21 years of age (whichever is longer)

*Adapted from the American Heart Association.

adequate for secondary prevention.

Bacterial Endocarditis:

In USA in 2007, recommendations for antimicrobial prophylaxis were changed significantly from previous guidelines in 1997. The logical reasons behind these changes were:

1. Endocarditis much more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremia caused by dental, gastrointestinal tract, or genitourinary procedure
2. Prophylaxis may prevent an exceedingly small number of (if any) cases of endocarditis in individuals who undergo any procedure and the risk of adverse reactions to antibiotics probably exceed the benefit in any form of prophylactic treatment.
3. Maintenance of oral health and hygiene may reduce the incidence of bacteremia from daily activities and is important than prophylaxis for a dental procedure to reduce the risk of endocarditis.

Table -3, Cardiac conditions associated with highest risk

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair.
- A history of Previous infectious endocarditis.
- Congenital heart disease.
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired CHD with prosthetic material or devise inserted during the first 6 months after the procedure
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device
- Cardiac transplantation recipients who develop valvulopathy

From year 2007 the antimicrobial prophylaxis for endocarditis is recommended only for the high risk cardiac conditions. Cardiac conditions associated with the highest risk are as listed above in Table 3.

- **Recommendations for dental procedures :** For patients with high risk conditions, all dental procedures that involve manipulation of gingival tissues or the periapical region of teeth or perforation of the oral mucosa are reasonable for administration of dental prophylaxis. Events and procedures such as routine anesthetic injections through noninfected tissues, taking dental orthodontic brackets, shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa do not require prophylaxis. The recommended for regimens for oral parenteral antibiotic are as listed in Table 4 are for all dental procedures for which dental prophylaxis is reasonable for persons with high risk conditions.
- **Recommendations for respiratory procedures:** Recommendations are only for procedures that involve the incision or incisional biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy. Therefore, prophylaxis is not recommended for broncoscopy unless an incision of the respiratory tract is to be made. An antimicrobial regimen that includes coverage of viridians group streptococci can be selected from Table 4.
- **Recommendations for gastrointestinal/ genitourinary procedures :** When using prophylaxis for high risk procedures of the gastrointestinal or genitourinary tract, consideration of the possible involvement of enterococcal organisms must be considered as well as the inclusion of mixed infections with aerobic and anaerobic gram negative and gram positive organisms. However, only enterococci are frequent causes of endocarditis. For patients with infections of the gastrointestinal or genitourinary tract who may have intermittent or sustained enterococcal bacteremia or for those who receive antibiotic therapy to prevent wound infections or sepsis associated with a gastrointestinal or genitourinary tract procedure, it is

reasonable to include an agent active against enterococci, such as penicillin, piperacillin, or vancomycin. Similarly for patients with high risk conditions listed in Table 3 antibiotic therapy to eradicate the infection from the urine prior to surgery is reasonable for those who are scheduled for an elective cystoscopy or other urinary tract manipulation who have an enterococcal urinary tract infection or colonization. Amoxicillin or ampicillin is the preferred agent for enterococci, but vancomycin may be used in those intolerant of b-lactam antibiotics.

Procedures on infected skin, skin structure, or musculoskeletal tissues are likely to cause endocarditis. Therefore, for children with high risk cardiac conditions, a therapeutic regimen administered for treatment of the infection should contain an agent active against *staphylocci* and *B – hemolytic* streptococci, such as an antistaphylococcal penicillin or cephalosporin. Vancomycin or clindamycin may be administered to children unable to tolerate B – lactam antibiotics or those who are known or suspected to be infected with a *methicillin-resistant strain of staphylococcus* (MRSA).

Recurrent Urinary Tract Infection:

About 30-50% children suffering from UTI can have recurrent UTIs and most of the recurrences of infection takes place within 3 months after the initial episode, 80% of recurrence is new infections caused by different colonic species that have become resistant to recently administered antibiotics. The recurrence rate is not altered by extending the duration of treatment.

About 30-50 % children suffering from UTI have been found to have underlying vesicoureteral reflux and is in direct proportion with number of UTI episodes and inversely to age. Children who have three or more UTIs in a 12 month period may benefit from suppressive antibiotic therapy for as long as 6 months to allow repair of intrinsic bladder defense mechanisms. In children with anatomic defects or reflex, suppressive therapy may be needed for as long as the underlying defect exists.

Appropriate prophylactic agents should result in low serum but high urinary levels of the medication, have minimal effect on fecal flora, be well tolerated, and be inexpensive. Useful agents for prophylaxis in children with normal renal function are trimethoprim-sulfamethoxazole (TMP – SMX). Nitrofurantoin, and nalidixic acid.

- TMP-SMX can be given at 2mg of TMP and 10mg of SMX per kilogram in a single daily dose or at 5mg of TMP and 25mg of SMX per kilogram twice a week. TMP has additional unique characteristic of diffusing into vaginal and urethral fluids, thereby decreasing colonization with members of the *enterobacteriaceae* and diminishing ascending re-infection.
- Nitrofurantoin is recommended at 1 to 2 mg/kg, taken each night. It has been used effectively as prophylaxis for recurrent UTIs in infants and children.
- More recently, various cephalosprins and amoxicillin clavulanic acid have been used as prophylactic agents with good results especially in infants less than 6 months of age. Prophylactic agents are best administered as a single dose at bed time.

Prophylaxis for UTIs may reduce the incidence of UTIs by up to 50% in children with nocturnal continence. No studies of prophylaxis in children without nocturnal continence have shown efficacy, and prophylactic regimens employing broad

Table 4, Prophylactic antimicrobial regimens for dental, respiratory, GIT & GUT Procedures:

Situations	Agents	Regimen: Single Dose 30-60 minutes Before procedure
Oral	Amoxicillin	50 mg/kg
Unable to take oral medications	Ampicillin *or*	50 mg/kg IV / IM
	Cefazoline or ceftriaxone	50 mg/kg IV / IM
Allergic to Penicillins		
Oral	Cephalexin *or*	50 mg/kg
	Clindamycin *or*	20 mg/kg
	Azithro or Clarithro	15 mg/kg
Unable to take oral	Cefazoline or Ceftriaxone	50 mg/kg IV / IM
	Or Clindamycin	20 mg/kg IV / IM

–spectrum antibiotics (e.g., amoxicillin, cephalexim) are associated with emergence of recurrent infections caused by antibiotic resistant organisms such as *pseudomonas aeruginosa.*

Recurrent Otitis Media :

Acute otitis media is one of the most common infections in infants and children and has a tendency to recur, particularly during the first few years of life. Antimicrobial prophylaxis currently is recommended for a child who has three or more episode in 6 month or four episodes within a year, with the last episode occurring during the previous 6 months. Patients who are most likely to benefit from prophylaxis include those younger than 2 years and those in out of home Childcare. Prophylaxis is directed against the most common potential pathogens that cause otitis media: *Streptococcus pneumonia, Moraxella* Catarrhalis, and *Nontypeable haemophilus* influenza. Amoxicillin, at a dose of 20mg/kg, or sulfisoxazole, at a dose of 50mg/kg, may be given orally each evening for a period of 3 to 6 months or during the winter months.

Post-exposure prophylaxis

Meningococcal Infections

Close contacts of patients with invasive disease caused by *Neisseria meningitides* (meningococcemia, meningitis, or both) are at higher risk for acquisition of infection. Close contacts include household members, day care center staff, and any person directly exposed to an infected person's oral secretions. Chemoprophylaxis should be administered as soon as possible preferably within 24 hours of identification of the index case.

- The antibiotic of choice in most instances is rifampin. The recommended regimen is 10 mg/kg (maximum, 600mg) every 12 hours for a total of four doses in 2 days. Rifampin prophylaxis has several shortcomings; it fails to eradicate N. meningitides in 10-20 % of pharyngeal carriers and is not recommended for pregnant women.
- During an outbreak, a single intramuscular injection of ceftriaxone was significantly more effective than rifampin in eradicating *meningococci* at 1 week (97% versus 75%) and at 2 weeks (97% versus 81%) after prophylaxis. ceftriaxone administered as a single intramuscular dose (125mg for children younger than15 years and 250mg for adults) now is recommended as an acceptable for prophylaxis. Ceftriaxone has the advantages of ease of administration, possibly greater efficacy, and safety in pregnancy.
- For high risk contacts 18 years of age or older, a single 500mg oral dose of ciprofloxacin is a third option for meningococcal prophylaxis.

Pertussis

Prompt administration of erythromycin or other approved macrolide drug to those in close contact with a case of pertussis is effective in limiting secondary transmission. Close contacts are household members, attendees of childcare facilities, and other individuals who are in contact with the index case for 4 hours or more a day. Chemoprophylaxis is recommended irrespective of age or vaccination status because immunity after receiving pertussis immunization is not absolute and may not prevent development of infection.

- For erythromycin the recommended dose is 40 to 50 mg/kg/day (maximum, 2g/day) to be given orally in four divided doses for 14 days.
- For clarithromycin, 15 mg/kg, up to a maximum of 1.0g, divided twice daily for 7 days,
- Azithromycin at standard doses (10 mg/kg the first day, up to a maximum of 500 mg, followed by 5 mg/kg, up to a maximum of 250 mg, each of the days 2 through 4 have been shown to be as effective as erythromycin and are much better tolerated than is erythromycin
- Individuals who are allergic to erythromycin or macrolides or those who cannot tolerate their side effects may be given TMP – SMX, although the efficacy of this regimen has not been documented. The dose is 8 mg/kg day (TMP) and 40 mg/kg/day (SMX) orally in two divided doses for 14 days.

Tuberculosis

The three goals of preventive therapy for tuberculosis are (1) to prevent asymptomatic (latent) infections from progressing to clinical (active) disease, (2) to prevent recurrence of past disease, and (3) to prevent initial infection in individuals who have negative tuberculin skin test results. Chemoprophylaxis is given in an attempt to prevent the establishment of infection, and the recipient is protected only as long as antituberculous therapy is continued.

Whom to offer chemoprophylaxis?

- All asymptomatic contacts (< 6 years) of a smear positive case, after ruling out active disease
- HIV infected children with known exposure to an infectious TB case or are TST positive (>=5 mm induration) but have no active TB disease
- All TST positive children who are receiving immunosuppressive therapy
- A child born to mother who was diagnosed to have TB in pregnancy after congenital TB has been ruled out

The recommended molecule is isoniazid in dose of 10 mg/kg/day as a single daily dose for total 6 month. However if mother has MDR TB,no chemoprophylaxis is to be offered to new born baby.

Host targeted prophylaxis

Asplenia:

The spleen plays an important role in the primary defense against bacteria that gain access to the circulation and has an active role in phagocytosis, is a major source of T lymphocytes, and produces IgM antibodies, complement, opsonins, and tuftsin (a phagocytosis promoting tetrapeptide). Asplenia may be congenital or acquired. Asplenic individuals often have over whelming fatal septicemia and increased frequency of meningitis.Fatality from sepsis in splenectomized individuals is 200 times more common than that in the normal population.

The risk for development of sepsis is greatest in patients who have under gone splenectomy for underlying immunologic or reticuloendothelial disorders, and risk is lowest in children after splenectomy for trauma. In all categories, the risk is highest in young infants and children, The period of heightened susceptibility to infection is the initial 1 to 2 years after splenectomy..

Overall, 80% of post splenectomy infections are caused by bacteria with capsular polysaccharides, particularly *S. pneumoniae* and *H. influenzae. Although N. meningitis* also has a polysaccharide capsule, lack of terminal components of complement constitute the greater risk for development of infection, and whether the incidence of sepsis is higher in persons with asplenia is unclear. However, because overwhelming meningococcal sepsis has been reported in patients with asplenia, it is reasonable to include these patients at risk.

To reduce the likelihood of serious infections after splencetomy, several measures are advisable.

- Perform Splenectomy only when it is absolutely indicated.
- If possible, delay the surgical intervention until the child is 5 or 6 years of age.
- *Vaccination with pneumococcal vaccines* : For children with congenital high risk conditions, pneumococcal polysaccharide protein conjugate vaccines, children > 2years old under going splenectomy can be offered multivalent pneumococcal polysaccharide vaccine 2 years, ideally 2 weeks before the splenectomy is performed.
- *Vaccination against H. influenzae type b and N. meningitides types A, C, Y, and W -135* with the appropriate polysaccharide or polysaccharide protein conjugate vaccine recommended for use in children should be provided.
- For antibiotic prophylaxis, penicillin is the agent of choice. Penicillin V given twice daily (125mg twice daily for children younger than 5 years; 250mg twice daily for children older than 5 years) significantly decreases the frequency of invasive pneumococcal infection. Erythromycin and TMP-SMX are alternative options in patients with documented hypersensitivity to penicillin. The duration of prophylactic coverage remains controversial; current practice is to provide penicillin prophylaxis indefinitely in immunocompromised patients.

HEMOGLOBINOPATHIES

Children with sickle cell anemia have functional asplenia and that is the primary reason for susceptibility to pneumococcal infection in children with sickle cell anemia. These children are at risk for development of overwhelming infection (septicemia and meningitis) by encapsulated bacteria, including *S. Pneumoniae, H. influenza type b*, and rarely, *N. meningitis. S. Pneumoniae* is the most important and frequent cause of septicemia and meningitis in these patients. The risk is particularly high in children younger than 3 years. A trend toward increase frequency of invasive disease in the first 2 to 5 years after splenectomy also has been noted. Unlike very young children, school age children are found to be less vulnerable to pneumococcal invasive infection, even though they remain functionally asplenic.

The efficacy of penicillin prophylaxis in preventing pneumococcal infection in infants and young children with sickle cell disease has been well documented in several reports. The recommended dose of penicillin V is 125mg twice daily in children younger than 3 years and 250mg twice daily in children 5 years or older.

Surgical prophylaxis : Wound infections are the commonest hospital-acquired infections in surgical patients.They result in increased antibiotic usage, increased costs and prolonged hospitalisation.Appropriate antibiotic prophylaxis can reduce the risk of postoperative wound infections, but additional antibiotic use also increases the selective pressure favouring the emergence of antimicrobial resistance. Judicious use of antibiotics in the hospital environment is therefore essential.

Surgical antibiotic prophylaxis is defined as the use of antibiotics to prevent infections at the surgical site. It must be clearly distinguished from pre-emptive use of antibiotics to treat early infection, for example perforated appendix, even though infection may not be clinically apparent.

Principles of surgical antibiotic prophylaxis

- Decide if prophylaxis is appropriate
- Determine the bacterial flora most likely to cause postoperative infection (not every species needs to be covered)
- Choose an antibiotic, based on the steps above, with the narrowest antibacterial spectrum required
- Choose the less expensive drug if two drugs are otherwise of equal antibacterial spectrum, efficacy, toxicity, and ease of administration
- Administer dose at the right time
- Administer antibiotics for a short period (one dose if surgery of four hours duration or less)
- Avoid antibiotics likely to be of use in the treatment of serious sepsis
- Do not use antibiotic prophylaxis to overcome poor surgical technique
- Review antibiotic prophylaxis protocols regularly as both cost and hospital antibiotic resistance patterns may change

Indications for surgical antibiotic prophylaxis

A classification system which ranks procedures according to their potential risk for infectious complications has greatly facilitated the study of surgical antibiotic prophylaxis. This system ranks procedures as:

- clean
- clean-contaminated
- contaminated.

Choice of antibiotic:The choice of the antibiotic for prophylaxis is based on several factors. Always ask the patient about a prior history of antibiotic allergy, as beta-lactams are the commonest type of antibiotics used in prophylaxis. It is important to select an antibiotic with the narrowest antibacterial spectrum required, to reduce the emergence of multi-resistant pathogens. The use of 'third generation' cephalosporins such as ceftriaxone and cefotaxime should therefore be avoided in surgical prophylaxis.

Route and timing of antibiotic administration: Prophylactic antibiotics are usually given intravenously as a bolus on induction of anaesthesia to ensure adequate tissue concentrations at the time of surgical incision. This timing of dosing is particularly important for most beta-lactams which have relatively short half-lives. Vancomycin has to be infused over one hour so it must be started earlier so the infusion finishes just before induction.

Intramuscular antibiotics are less commonly used than intravenous antibiotics. They are typically given at the time of pre-medication so that peak tissue levels are attained at the most critical time, the time of surgical incision. Oral or rectal antibiotics need to be given earlier to ensure adequate tissue concentrations during surgery. Metronidazole suppositories are commonly used in bowel surgery and must be given 2-4 hours before it begins. Topical antibiotics are not recommended, with the exceptions of ophthalmic or burns surgery.

Duration of antibiotic administration

If the operation lasts four hours or less, one antibiotic dose is usually sufficient. In prolonged surgery of greater than four hours, further antibiotic doses may be required to maintain the concentration, particularly if the antibiotic has a short half-life. Continuing antibiotic prophylaxis until surgical drains have been removed is illogical and also of unproven benefit.

Table 5, Classification of surgical Procedures according to risk

Type of Surgery	Definition	Examples	Indication for surgical antibiotic prophylaxis
Clean surgery	Healthy skin incised Mucossa of respiratory, alimentary, genitorinary tract and oropharyngeal cavity not traversed	Herniorrhaphy, mastectomy, cosmetic surgery	Not recommended
	Insertion of prosthesis or artificial device	Hip replacement, heart valve	Recommended
Cean-contaminated	Respiratory, alimentary or genitourinary tract is penetrated under controlled conditions without unusual	Laryngectomy, uncomplicated appendicectomy, chpolecystectomy transurethral resection of prostate gland	Recommended
Contaminated	Macroscopic soiling of operative field	Large bowel resection, biliary or genitourinary tract surgery with infected bile or urine	Strongly recommended

Role of Zinc in Pediatric Diarrhea

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Abstract

Zinc supplementation is a critical new intervention for treating diarrheal episodes in children. Recent studies suggest that administration of zinc along with new low osmolarity oral rehydration solutions / salts (ORS), can reduce the duration and severity of diarrheal episodes for up to three months. The World Health Organization (WHO) and UNICEF recommend daily 20 mg zinc supplements for 10 – 14 days for children with acute diarrhea, and 10 mg per day for infants under six months old, to curtail the severity of the episode and prevent further occurrences in the ensuing -two to three months, thereby decreasing the morbidity considerably. This article reviews the available evidence on the efficacy and safety of zinc supplementation in pediatric diarrhea and convincingly concludes that zinc supplementation has a beneficial impact on the disease outcome.

Keywords*: Acute diarrhea, oral rehydration solutions/salts, zinc salts.*

Introduction

Acute diarrhea remains a leading cause of childhood deaths despite the undeniable success of oral rehydration therapy (ORT). Worldwide, diarrheal diseases are the leading cause of pediatric morbidity and mortality, with 1.5 billion episodes and 1.5 - 2.5 million deaths estimated annually among children below five years of age[1,2]. In developing countries, the scenario is worse due to infection, malnutrition, and illiteracy. One out of every five children who die of diarrhea worldwide is an Indian. Daily around 1,000 children die of diarrhea in India, which means 41 children lose their lives every hour[3]. Giving oral fluids using an oral rehydration solution (ORS) saves children's lives, but does not seem to have any effect on the length of time the children suffer with diarrhea.

Hence, new revised recommendations have been formulated by the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF), in collaboration with the United States Agency for International Development (USAID) and other experts. It recommends zinc salt along with low osmolarity ORS, with reduced levels of glucose and salt, during acute diarrhea, which reduces the duration and severity of the episode; and zinc supplementation given for 10-14 days lowers the incidence of diarrhea in the following two to three months[4].

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Despite the evidence of benefit, there has been little progress on the widespread introduction of low osmolarity ORS and zinc for the treatment of diarrhea. Many countries have changed diarrhea management policies to include low osmolarity ORS and zinc, but there is a gap between policy change and effective program implementation, with very few children currently being appropriately treated[5]. Although the Government of India has initiated the provision of zinc in addition to low osmolarity ORS through the public health system, under the National Rural Health Mission, a survey conducted by UNICEF in India documented less than 1% prescriptions for zinc. One of the main reasons for this is the lack of knowledge and awareness among the care providers on how to implement the existing cost-effective interventions. The challenge is to achieve a greater coverage of these interventions in resource poor settings[6].

Mechanism of Action of Zinc in Diarrhea

The physiological effect of zinc on intestinal ion transport has not yet been established thoroughly. Therefore, the fundamental information of the mechanism by which zinc may be effective in improving diarrhea is needed. A very recent publication has established that zinc inhibits cAMP-induced, chloride-dependent fluid secretion by inhibiting basolateral potassium (K) channels, in /in-vitro/ studies with rat ileum. This study has also shown the specificity of Zn to cAMP-activated K channels, because zinc did not block the calcium

(Ca)-mediated K channels. As this study was not performed in Zn-deficient animals, it provides evidence that Zn is probably effective in the absence of Zn deficiency[7]. Zinc also improves the absorption of water and electrolytes, improves regeneration of the intestinal epithelium, increases the levels of brush border enzymes, and enhances the immune response, allowing for a better clearance of the pathogens[9]. Another report has recently provided evidence that zinc inhibits toxin-induced cholera, but not Escherichia coli heat-stable, enterotoxin-induced, ion secretion in cultured Caco-2 cells[10]. Thus, Zinc plays an important role in modulating the host resistance to infectious agents and reduces the risk, severity, and duration of diarrheal diseases. It also plays a critical role in metallo-enzymes, polyribosomes, and the cell membrane and cellular function, giving credence to the belief that it plays a central role in cellular growth and in the function of the immune system[11].

Pharmacokinetics of Zinc in Diarrhea[12]

Absorption :

The molecular weight of elemental zinc is 65.37 and zinc sulfate is 287.5. Crude zinc sulfate is also known as white Vitriol. Each gram of zinc sulfate represents 3.5 millimoles of Zn. Its solubility is 1 in 0.6 ml of water and it is insoluble in alcohol. Zinc and its salts are poorly absorbed from the gastrointestinal tract (GIT) (only 20 to 30%), duodenum, and ileum. Endogenous zinc is reabsorbed in the ileum and colon, creating enterohepatic circulation.

Distribution :

After absorption zinc is bound to protein metallothionein in the intestines. Zinc is widely distributed throughout the body. It is primarily stored in RBCs, WBCs, Muscles, Bones, Skin, Kidneys, Liver, Pancreas, Retina, and Prostate. The extent of binding is 60 - 70% to plasma albumin, 30 - 40% to alpha 2 macroglobulins or transferrin and 1% to amino acids like histidine and cysteine. Peak plasma concentration occurs in approximately two hours.

Elimination :

Zinc is excreted mainly in the feces (90%) and only traces are found in the urine, as the kidney plays a small role in regulating the body Zn content.

Convincing evidence for the clinical importance of zinc has come from the randomized controlled trials (RCTs) evaluating the impact of zinc supplementation during acute and persistent diarrhea.

Zinc supplements reduce the severity and duration of diarrhea

A study tested the hypothesis that daily supplementation of zinc had an effect on the clinical course of acute diarrhea, that is, frequency of stool, stool amount, and duration of acute diarrhea, in 117 children, of age six to fifty-nine months. Reduction in stool frequency per day was found to be 62% in the zinc-supplemented group and 26% reduction was found in the placebo-supplemented group, with an obvious difference of 36% between the two groups from day 1 to day 3 and day 5, which was found to be statistically significant. Similarly, a significant difference was observed for reduction in amount of stool per day from day 1 to day 3 and day 5, with an obvious difference of 45% between the study groups[13]. A meta-analysis of 12 studies examined the impact of zinc supplements on the management of acute diarrhea, 11 of which showed a reduction in the duration of the diarrheal episode. In eight of these, the reduction was statistically significant. Five of these studies also collected data on stool volume and frequency, and found that zinc supplements reduced stool output and frequency. The data showed that zinc supplementation had a significant and beneficial impact on the clinical course of acute diarrhea, reducing both its duration and severity[4]. Another meta-analysis of 18 trials with 6165 enrolled participants showed that in acute diarrhea, zinc resulted in a shorter diarrhea duration (MD -- 12.27 hours, 95% CI -23.02 to -1.52 hours; 2741 children, nine trials), and less diarrhea by day three (RR 0.69, 95% CI 0.59 to 0.81; 1073 children, two trials), day five (RR 0.55, 95% CI 0.32 to 0.95; 346 children, two trials), and day seven (RR 0.71, 95% CI 0.52 to 0.98; 4087 children, seven trials). Zinc also reduced the duration of persistent diarrhea (MD -15.84 hours, 95% CI - 25.43 to - 6.24 hours; 529 children, five trials). Few trials reported the severity, but the results were inconsistent[14].

The results of a recent systematic review suggest that zinc supplementation reduced the mean duration of acute diarrhea by approximately 20%, and persistent diarrhea by 15 – 30%, but had no significant effect on stool frequency or stool output. There was a high degree of statistically significant heterogeneity across the published studies for the effects of zinc supplementation on mean diarrheal duration and risk of vomiting following the administration of zinc[15].

Zinc supplementation in prevention of acute and persistent diarrhea

Studies evaluating the effect of zinc supplementation on diarrheal diseases found a preventive and long-lasting impact. These showed that 10 mg to 20 mg of zinc per day, for 10 – 14

days, reduced the number of episodes of diarrhea in 2 – 3 months after the supplementation[4,16]. The WHO and UNICEF, therefore, recommend 20 mg zinc supplements daily, for 10 – 14 days, for children with acute diarrhea, and 10 mg per day for infants under six months of age, to curtail the severity of the episode and prevent further occurrences in the ensuing 2-3 months.

Zinc supplementation in the treatment of persistent diarrhea

An RCT in 40 infants (6 - 18 months old) with persistent diarrhea (greater than two weeks' duration) evaluated the effect of oral zinc supplementation. It concluded that in persistent diarrhea there was depletion of zinc with the progression of the disease and oral zinc administration improved the zinc status[17].

A pooled analysis of four RCTs has been reported on the effects of supplementary oral zinc in children, under the age of five, with persistent diarrhea. The Cox survival regression analysis was used to evaluate the overall effect of zinc on the continuation of diarrhea and possible differential effects in the subgroups. Zinc-supplemented children with persistent diarrhea had a 24% lower probability of continuing diarrhea (95% CI: 9%, 37%) and a 42% lower rate of treatment failure or death (95% CI: 10%, 63%) than those in the control group[18].

Zinc supplementation in the treatment and prevention of bloody diarrhea

Studies conducted during acute shigellosis showed that zinc therapy was associated with enhanced antigen-specific antibody responses. The bactericidal antibody titers against Shigella increased the proportions of B cells and plasma cells, as also higher lymphocyte proliferation responses in the peripheral circulation, during the early convalescent phase of shigellosis. For all these reasons, it is clear that zinc supplementation should be given as an adjunct to antimicrobial (AM) treatment in bloody diarrhea[19].

Zinc supplementation and cost-effectiveness

A study analyzed the incremental costs, effects, and cost-effectiveness when zinc was used as an adjunct therapy to the standard treatment of acute childhood diarrhea, including dysentery, and reassessed the cost-effectiveness of standard case management with ORS. The probabilistic cost-effectiveness analysis was performed using a Monte-Carlo simulation technique and the potential impacts of uncertainty in single parameters were explored with one-way sensitivity analyses. In this study, the ORS was found to be less cost-effective than was previously thought. The use of zinc as an adjunct therapy, however, significantly improved the cost-effectiveness of the standard management of diarrhea for dysenteric as well as non-dysenteric illnesses[20].

Zinc supplementation and irrational use of antimicrobials

Excessive use of antimicrobials (AMs) for diarrhea is a major contributing factor toward increasing rates of AM-resistance in developing countries. A study of AM use in a rural area of Bangladesh found that 26% of the purchased medicines were AMs, which were most frequently purchased for children aged 0 – 4 years to use for diarrhea. A community-based controlled trial was conducted in Bangladesh where there were 30 service areas (clusters), around the Matlab Treatment Center, each with about 200 children between the ages of 3 and 59 months, who were randomly allocated to intervention or comparison areas. All children between the ages of 3 and 59 months were included in the study. The significant reduction in AM use and related behavior in the intervention group demonstrated that the benefits of zinc supplementation extend well beyond reducing childhood morbidity and mortality. Zinc supplementation for diarrhea with education programs, in addition to ORT, can reduce inappropriate AM use that leads to resistant pathogens[21].

Recommended dose of zinc in diarrhea[22]

Elemental zinc is used orally, as an adjunct to ORT in acute diarrhea, in infants (under six months): 10 mg daily for 10 – 14 days; and in children (six months - five years): 20 mg daily for 10 - 14 days.

How to administer zinc salt?[22]

Zinc sulfate, acetate, and gluconate are all acceptable zinc salt formulations, of which zinc sulfate is low-cost, efficacious, safe, and therefore, optimal for the national program. Zinc sulfate tablets may be dispersed in breast milk, in oral rehydration solutions, or in water on a small spoon; older children may chew the tablets or swallow them with water. Zinc sulfate dispersible tablet is also available in the market, containing 20 mg of elemental zinc. Pediatric zinc sulfate tablets are also available.

Drug Interaction[22,24]

If zinc is given concomitantly with the following, drug interaction may occur. Phytate, which is present in staple foods like cereals, corn, and rice, decreases zinc absorption from composite meals. Experiments /in vitro/ have shown that zinc is precipitated by phosphate and phytate at pH values close to those of the intestinal lumen.Dairy products and brown bread decrease zinc absorption. Coffee also inhibits zinc absorption.

Iron supplements inhibit absorption of Zn and therefore Zn supplements are administered two hours before iron supplements. Penicillamine and other chelators reduce absorption of Zn. Calcium salts reduce absorption of zinc. Oral Tetracyclines reduce absorption of Zn, and hence, Zn supplements are administered two hours before tetracyclines. Amino acids, such as histidine and methionine, and other low-molecular-weight ions, such as EDTA and organic acids (e.g., citrate), enhance zinc absorption. Zn inhibits copper absorption from the intestine. Thiazide diuretics increase urinary excretion of Zn. Zinc reduces absorption of Ciprofloxacin, Levofloxacin, and Ofloxacin. Absorption of both zinc salts and ferrous salts will reduce if used concomitantly.

Side effects of zinc supplementation

To date there have been no reports of severe adverse reactions from any form of zinc supplementation used in the treatment of diarrhea. A zinc dose of 40 mg has been approved as being safe to use by the Food and Drug Administration (FDA), and a zinc dosage of more than this can pose certain risks. Too much zinc will probably interfere with the metabolism and absorption of other essential minerals in the body, especially iron, magnesium, and copper, reduce the body's immune function, and reduce the HDL level. Oral zinc sulfate supplements can also cause side effects such as stomach upset, heartburn, and nausea. Rare side effects include fever, sore throat, mouth sores, weakness, and fatigue. Trials have included more than 8,500 children who participated in efficacy trials in both the placebo and zinc study arms, with nearly 12,000 child-years of observation, from one large effectiveness trial. No differences in adverse reactions based on the different zinc salts (sulfate, acetate, and gluconate) were noted in the supplementation trials. One trial reported higher vomiting in the zinc versus the control group, when zinc was given with multiple micronutrients, but not when given alone. The copper status has been evaluated in four trials. Three of these have not found a difference in the serum copper status after supplementation. However, one trial did find a significant trend of decreased copper level when comparing zinc-supplemented children with non-zinc supplemented children. However, these children were malnourished with persistent diarrhea at baseline. Overall, there is no substantial evidence of short-term zinc supplementation for the treatment of diarrhea adversely affecting the copper status[25].

Recommendations

The Indian Academy of Pediatrics, WHO, and UNICEF have already endorsed the use of zinc as a supplement to ORS in the management of diarrhea. A dosage of 20 mg of elemental zinc per day has been shown to be effective and safe in age group six months -to five years. Administration of zinc is recommended through a primary healthcare.

For maximum impact on diarrheal diseases, zinc and ORS should be made available at the community level. Community-based programs increase the use of zinc and the introduction of zinc increases the use of ORS in the same communities

The revitalization of community-health workers with a reach into the least fortunate communities will be critical to achieving the targeted coverage rates. In addition, incorporating the private sector, the medical and non-medical sectors, and the formal and informal sectors, may help reach additional segments of the population.

Conclusion

Oral zinc administration provides substantial benefit in the reduction of stool output, frequency, and duration, combined with safety, efficacy, and affordability in acute diarrhea. Thus, it can be concluded that oral zinc supplementation is a simple and effective therapeutic intervention in the management of acute diarrhea.

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Announcement

Role of Probiotics in Paediatrics

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The Greek term Probiotic means 'for life'. According to WHO,Probiotics are 'live microorganism which, when administered in adequate amounts, confer a health benefit on the host' [1] *. Probiotics can be consumed as medicinal supplement or modified food.*

Background

Human gut and microbial ecosystem :

Human gut is a natural reservoir for numerous species of microorganisms. Largest part of microorganisms is located in lumen. They function as virtual organ system.

Occurrence of many diseases both intestinal and non intestinal, can be related to dysregulation or interference with early development of intestinal mucosal defence system. This can be Atopic (Asthma , Eczema, Allergic Rhinitis) or Autoimmune (multiple sclerosis, Type 1DM, IBD) .

Factors influencing intestinal colonization :

Natural colonization at birth is a rule. It is influenced by route of delivery, early feeding pattern, gestational age and consumption of antimicrobial drugs during perinatal period.

After normal delivery, pattern of bacterial colonization varies according to age

(a) At 48 hours of age – Breast fed and formula fed have similar organisms

(b) By 7 days of age – 2/3rd formula fed infants and 22% breast fed infants have *bacteroides fragilis*

(c) End of 1st month – breast fed infants predominantly have *bifidobacteria*

Predominantly/formula fed infants have bacteroides and bifidobacteria equally.

After Caeserian section, there is increased colonization of *Klebsiella, Enterobactor and Clostridia.*

The composition of intestinal microflora does not change significantly after infancy[2]. 500 different bacterial species contribute to adult colonic microflora – among them 99% is accounted for by 30-40 species

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Historical aspects

1818 – Lister isolated lactic acid bacilli (LAB) from rancid milk and subsequently it was isolated from gut

1857 – Louis Pasteuer first credited for discovering LAB (lactic acid bacilli) – he proposed use of non pathogenic bacteria to control pathogenic bacteria.

1889 – Henry Tissier discovered *Bifidobacterium spp*.

1900 – Discovery of *Lactobacillus acidophilus*

1906 – Henry Tissier first promoted probiotics for therapeutic relief of intestinal Disorders. *Bacillus bifidum* communis was isolated and recommended for use in infantile diarrhea.

Beginning of 20th century - Dr. E Metchnikoff published book Prolongation of Life. He Postulated that the growth of lactic acid bacteria in the intestines displaced the harmful disease causing organisms, reduced the production of toxins and thus improved health

1917 – Alfred Nissle isolated *E. coli* and employed it in acute intestinal infection as a non lab probiotic (Mutaflor – *Escerichia coli* Nissle 1917)

Originally *Saccharomyses boulardii* was derived from lychee and mangosteen fruit by Henri Boulard, a French scientist in 1923.He discovered this strain of yeast during his trip to Indonesia. During his stay he was faced with disease conditions affecting the locals, one of which was diarrhea, he discovered that most locals drank tea (from lychee and mangosten) to stop it

1996 – WHO recommended use of probiotics through food, supplements or both for health benefits. Important probiotic strains – these includes both bacteria and fungi

Bacteria – Lactobacilli (*L.acidophilus, L.rhamnosus GG*),

Lactococci (*L.lactis*), *Bifidobacterium, Streptococcus thermophilus, Bacillus subtilis* and *E.Coli strain nissle.*

Fungi - *Saccharomyces boulardii* and *Saccharomyces cerevisiae.*

What are Prebiotics, Synbiotics and Postbiotics

Prebiotics are nondigestible food ingredient that selectively stimulates growth of one or more Probiotics e.g. lactulose .

Synbiotics are a combination of both Prebiotics and Probiotics for synergistic effect e.g. *lactobacilius* + Inulin.

Breast Milk should be regarded as containing Synbiotics, because it is rich in Prebiotic oligosaccaride and probiotic *Lactic acid bacillus, Bifidobacteria.*

Postbiotics are metabolic byproduct generated by probiotic bacteria that influence biological function.

Criteria for earning label 'probiotic' includes

(a) It should be of human origin

(b) Non pathogenic

(c) Should be safe

(d) Should be resistant to gastric, bile and pancreatic digestion

(c) Have property of adherence to and colonization of enterocyte

(d) Production of antimicrobial substance

(e) Favourable immunomodulation properties

(f) Ability to influence metabolic activities

Mechanism of action of Probiotics

(a) Maintenance of appropriate host – microbe interactions and pathogen exclusion

(b) Mucus secretion from goblet cells

(c) Modulation of epithelial barrier function

(d) Production of antimicrobial factors

(e) Activation of host adaptive immune system

Adverse Reactions

But they are not always safe. There are occasional reports of serious infections in Preterm, Immunocompromised and Indwelling catheter or other medical device. WHO, FAO recommend centralized product monitoring .

Best studied and therapeutically effective probiotic strains

These are *L. rhamnosus GG (LGG)* and *Saccharomyces boulardi* followed by *B.lactis* and *S.thermophilus*[3].

A probiotic strain should be chosen as per individual needs – age, indication, length of supplementation required.Usually powder or liquid formulation is preferred[3]

Optimum dose

L Rhamnosus GG

5-40 billion colony forming units (CFU)/Day in 1-2 divided dose

S. Boulardii

250-500mg/day for 5-7 days[3]

Specificity of probiotics in disease states

(a) *L.rhamnosus* reduce prevalence of atopic dermatitis by 2 years age

(b) *L.rhamnosus GG* and *S.boulardii* most effective agent in treatment of acute diarrhea and antibiotic associated diarrhea

(c) VBSL#3 (mixture of 3 different strains at high concentration) effective in ulcerative colitis, now in Irritable bowel syndrom in children too.

(d) *Lactobacillus casei ,Lactobacillus reuteri ,Lactobacillus rhamnosus* and *Bifidobacterium lactis* are moderately useful for management of common infections in children attending day care

Use of Probiotics

Probiotics in GI disorders

Diarrheal Diseases

Mechanisms of probiotics in infectious diarrhea includes:

(a) Restoration of beneficial intestinal flora

(b) Enhancement of epithelial barrier function and host protective immunity (down regulation of pro inflamatory cytokines and up regulation of antiinflamatory cytokines)

(c) Production of antibacterial factors like bacteriocins

Prevention of acute infectious Diarrhea :

Modest benefit of giving probiotics in prevention of acute GIT infections in healthy infants and children (According to results of published RCTs)

Treatment of acute infectious Diarrhea :

There is therapeutic benefit of probiotics in children with acute infectious diarrhea (according to well conducted RCTs in healthy children in developed countries)

Probiotics reduce :

(a) no. of diarrheal stools

(b) duration of diarrhea

They are more effective when given early in the course of diarrhea

Most helpful for otherwise healthy infants and young children

with watery diarrhea secondary to viral gastroenteritis but not invasive bacterial infections

Antibiotic associated diarrhea (AAD) :

Concurrent daily administration of probiotics may well counter the disruption of the host microbiota with emergence of Clostridium difficiale caused by antibiotics (ampicillin oral), preventing Clostridium difficiale associated diarrhea or antibiotic associated diarrhea. For preventing AAD because of risk factors - *L Rhamnosus GG* and *S Boulardii* is recommended. For preventing Clostridium difficiale associated diarrhea - *S Boulardii* is recommended[4] .

Necrotizing enterocolitis :

Probiotics have beneficial effects in prevention of NEC in preterm and LBW infants by reduction of incidence and decrease in severity[5].

But for routine use of probiotics in premature infants - there are certain unresolved issues like what is/are most effective probiotic, A standard dose or strain of probiotic is not established ,Infant formula is not strictly regulated and no available formula with a probiotic designed for preterm neonates .

Irritable Bowel Syndrome :

IBS patients may benefit from use of probiotics like VSL3. It results in decrease in Bloating, Abdominal pain and Colonic transit[6].

Lactobacillus Rhamnosus Strain (LGG) significantly reduces frequency and severity of abdominal pain in children with IBS[7].

H.Pylori infection :

Probiotics inhibit attachment of H. Pylori to gastric mucosa. It helps in eradication of infection when administered as a component of therapeutic regimen (*s.boulardii* +triple therapy).

Evidence from limited studies are both favorable and unfavorable.

Constipation :

Bifidobacterum brave is recently reported to be effective in management of childhood constipation[8].

Inflamatory Bowel Disease :

Ulcerative colitis - *E.coli Nissle Strain* may be equivalent to mesalazine in managing remission

Crohn's disease - No evidence to suggest that probiotics are beneficial for maintenance of remission

Lactose Intolerance :

Streptococcus Thermophilus and *Lactob. Delbruckii subsp.bulgaricus* improves lactose digestion and reduces symptoms.

Probiotics in non GI disorders

Allergy :

Probiotics reduce intensity or even fully resolve manifestation of Atopic Dermatitis(AD). Administration of *L.rhamnosus strain* GG reduces incidence of AD in at risk children during first 2 year of life, specially in patients with positive skin prick test and high IgE level[9].

Administration of probiotics postnatally (to infant) may extend the benefit upto 4-5 years. Combined pre and direct infant postnatal supplementation has demonstrated most consistent effects[10].

Immunocompromised states and immunologic disorders

Certain probiotics may play an important role in immunoregulation, thereby preventing RTI or at least reducing frequency and intensity

Obesity :

Perinatal probiotic intervention may safeguard against development of overweight and obesity in first 2 years of life[11]

Infections :

Upper Respiratory Tract Infections may be prevented and to some extent Urinary Tract Infections, HIV and surgical infections.

Liver disease :

Limited evidence of beneficial effect of probiotics in cirrhosis (VSL #3) and minimal hepatic encephalopathy (mixture of bioactive fiber of glucan, inulin, pectin and resident starch)[12,13]

Neurologic Disorders :

Signals are sent from the intestine to the brain. These signals can be modulated by a dietary change.

Regular consumption of probiotic containing yoghurt shows altered activity of brain regions that control central processing of emotions and sensation

Wound healing in surgery :

Probiotics may be of benefit in wound healing and prevention of infection before and after surgery.

Fermented milks were used to help healing of wounds and to fight infection before antiseptics and antibiotics were available. In animal studies, *L.fermentum RC-14* and proteins produced by these organisms were shown to prevent severe *staphylococcus aureus* surgical implant infection.

Infant Formulas with probiotics

Some infant formulas contain limited amount of added free nucleotides (7-20mg/dl). Nucleotides do not fit the exact definition of probiotics – they are probiotic like agents having immunomodulating and direct intestinal biological properties.

Human milk have variable amount of oligosaccharides (14g/l) as well as free nucleotides (upto 20% on NPN).

But there is insufficient data to recommend routine use of probiotic and/or prebiotic supplemented formula according to ESPGHAN committee on the group.

Safety issues and adverse drug reactions

By and large probiotics are very safe but occasionally GI upset (diarrhea, constipation, abdominal bloating), skin rash and headache are reported. These are due to liberation of toxin by harmful gut bacteria that probiotics try to kill.

Excessive Drainage Syndrome – results from consumption of too much probiotics like eating large amount of yoghurt or overdose of supplement. Manifestations include Constipation, headache and bloating.

There is risk of sepsis in immunocompromised subjects.

New Developments

(a) Probiotics in particular *L.reuteri* appear effective for reducing infantile colic

(b) Genetically engineered probiotics (Turboprobiotics) have been developed to deliver active compounds

(c) Research is underway to evaluate role in regulating BP, lowering cholesterol and reducing obesity in adulthood

Probiotics in clinical practice: should we use or not

Probiotics are one of the most commonly used medicines in Paediatric Gastroenterology practice. But there are some worries

(a) No clear local and international legislation on use of probiotics

(b) Most of tested products are not in conformity with guidelines

(c) Safety concern

(d) Commercial availability of recommended probiotics

(e) They are not uniform- same strain wouldn't be effective for different clinical condition

(f) Probiotics are supplements and not substitutes for treatment

(g) Increasing dose doesn't always solve purpose

(h) Combining probiotics is not a healthy practice without understanding consequences

(i) Dietary food and probiotics interaction should also be considered

(j) Conditions in which utility is being examined are obesity, infections and neurological disorders

(k) Besides risk of sepsis in immunocompromised subjects, probiotics raise the issue of safety concern in terminally ill subjects, preterm infants and subjects with indwelling catheters

Take home message

(a) Probiotics are friendly bacteria/fungi that usually are beneficial to the host when available in adequate quantity

(b) Probiotics contribute to development of intestinal immune system

(c) The best studied probiotics are *Lactobacillus rhamnosus GG, S. boulardi, B. lactis* and *S.thermophilus.*

(d) Good evidence of usefulness in diarrhea, IBD, IBS and allergy (AD), equivocal evidence in NEC, *H.pylori,* constipation

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Newborn Screening Hearing Screening Early Hearing Detection and Intervention (EHDI)

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Hearing impairment is the most frequent sensory impairment with significant social, psychological, and emotional implications. Late diagnosis and intervention can result in poor speech and language, cognitive and intellectual development. Poor future literacy skills, disrupted family relations, problems with long term self esteem , mental health and employment opportunities are other added complications of this handicap. Identification of hearing loss by six months of age, followed by appropriate intervention is the most effective strategy for normal development of speech and language in deaf and hard of hearing infants and toddlers[1].

Common reasons for late diagnosis are some common myths and belief among people about deafness along with the lack of awareness .

Satisfying prerequisites of the neonatal hearing screening , the target should be to identify all moderate or greater bilateral permanent congenital hearing loss. Moreover, it is this degree that causes significant delays in language development and academic achievement which can be effectively treated by providing amplification, advice and support to the family[2].

Application of universal neonatal hearing screening programme is possible only by government intiative. Unfortunately, with the present infrastructure and huge other health care issues and burden, this appears to be a difficult task in near future. However, a practical and approachable high risk baby(Table- 2) screening can lead us to pick up at least 45-55%of the cases.

Table-1 below for common misconceptions held by the public about hearing loss, its identification in infants and the clinical facts.

Misconception	Clinical Fact
Parents will know if their child has a hearing loss by the time their child is aged 2-3 months.	The average age at which children are found to have a hearing loss is 2-3 years. Children with mild-to-moderate hearing loss are often not identified until 4 years of age.
Parents can identify a hearing loss by clapping their hands behind the child's head.	Children can compensate for a hearing loss. They use visual cues, such as shadows or parental expressions and reactions, or they may feel the breeze caused by the motion of the hands.
The high risk register is all that is needed to identify children with hearing loss.	The register actually misses approximately 50% of all children with hearing loss which have no identifiable cause..
Hearing loss does not occur often enough to justify the use of universal screening programs.	Hearing loss affects approximately 2-4 per 1000 live births, and it has been estimated to be one of the most common congenital anomalies.
Screening tests are not reliable and cause too many infants to be referred to specialists.	Proper timing and strategy if used can lower the referral rates to as low as 5-7%.
There is no rush to identify a hearing loss. The loss does not need to be identified until a child is aged 2-3 years.	Children identified when they are older than 6 months can have speech and language delays. Children identified when they are younger than 6 months do not have these delays and are equal to their hearing peers in terms of speech and language.
Children younger than 12 months cannot be fitted with hearing aids.	Children younger than 3 months can be fitted with and benefit from amplification aids.

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Table-2

- Any speech and language delay specially with parental concern or suspicion for Childs responses to sounds.
- Any type of meningitis or meningoencephalitis.
- Hyperbilirubenemia with exchange transfusion.
- Congenital intrauterine infections specially Rubella, CMV and Toxoplasmosis.
- Craniofacial syndromes.
- Cases of adoption

In recent times various neonatal screening procedures and protocols are followed depending on the risk category of the referred baby (Table -3 and 4). The positive predictive value of these procedures can be increased when done in combination[3].

Successfully identifying hearing impaired infants at birth through newborn hearing screening without effective follow up that includes rescreening, diagnostic evaluation, and appropriate early intervention, defeats the purpose of any screening programme. For this reason it is important to divert some attention from hearing screening goals and to ensure timely and effective follow up of identified deaf babies and infants.

Detection of Permanent Congenital Hearing loss of infancy(PCHI) by objective neonatal screening procedures have gathered a lot of criticism that the condition may any way have come to light without screening. A controlled trial in United Kingdom identified 93% of babies reported to be deaf before 6 months of age were picked up with neonatal screen as opposed to 17 % without the screen[4].

Continuing evolution of the pattern of postnatal care and of screening technology may alter the available options for the precise method of neonatal screening but, in practice, effectively managed screen delivery and early patient centered treatment are more likely to affect outcome. We can now look forward to better language development with all its secondary benefits for these children and their families in near future.

Screening procedures (Table -3): Should satisfy the prerequisites of any screening programme.

Type of Test	Response	Interpretation Subjective or Objective	Sensitivity and Specificity
Behavioural observation	Change in behaviour to loud sounds in terms of ye blink, eye widening, Startling.	subjective	60-70%
Oto Accoutic emissions (OAE)	Pass or Fail result with graphs	Objective	80-85%
Automated Auditory Brainstem responses(AABR)	Age and gestation specific wave V interpretation at thresholds levels	subjective	85-95%
Auditory Steady state Responses (ASSR)	Graphical and electrophysiological audiometery	Objective	75-80%
Parental questionnaire and checklist of sounds	Observation of babies age appropriate responses to loud and soft sounds	subjective	60-70%

Screening Protocols(Table -4):

Type of test;	Population type:
• NICU babies (more then 5 days of stay in NICU irrespective of the reason) OAE (Oto acoustic emissions) and AABR (Automated Auditory brainstem responses) both. • Well babies (normal babies on post natal ward) Only OAE AABR done only if OAE is fail.	• Universal for each and every single baby born in the area conducting screening procedure. • Target for babies who fall in high risk category here incidence of hearing loss is 6-8/1000. • Optional where choice if left on the parents.

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BERA or ABR Testing

BERA or ABR Testing

Auditory brainstem response (ABR) audiometry is a neurologic test of auditory brainstem function in response to auditory (click) stimuli. First described by Jewett and Williston in 1971, ABR audiometry is the most common application of auditory evoked responses.

ABR audiometry refers to an evoked potential generated by a brief click or tone pip transmitted from an acoustic transducer in the form of an insert earphone or headphone. The elicited waveform response is measured by surface electrodes typically placed at the vertex of the scalp and ear lobes. The amplitude (microvoltage) of the signal is averaged and charted against the time (millisecond), much like an EEG. The waveform peaks are labeled I-VII. These waveforms normally occur within a 10-millisecond time period after a click stimulus presented at high intensities (70-90 dB normal hearing level [nHL]). (See image below.)

Normal auditory brainstem response (ABR) audiometry waveform response.

Although the ABR provides information regarding auditory function and hearing sensitivity, it is not a substitute for a formal hearing evaluation, and results should be used in conjunction with behavioral audiometry whenever possible.

This mnemonic helps when remembering the ascending order of structures that corresponds to each waveform in an auditory brainstem response (ABR) tracing:

- E COLI

Mnemonic

- E: eighth nerve action potential (wave I)
- C: cochlear nucleus (wave II)
- O: olivary complex (superior) (wave III)
- L: lateral lemniscus (wave IV)
- I: inferior colliculus (wave V)
- Origin of VI and VII waves not very clear possibly thalami medial geniculate body

(source: radiopedia .Org and medscape)

World Breastfeeding Week –2017

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Introduction:

World Breastfeeding Week is observed all over the world during 1-7 August every year. The purpose is to give an additional thrust to breastfeeding activities and to remind people everywhere this is something that ought to be nurtured always. The first World Breastfeeding Week (WBW) was held in 1992 ; so this year we have just celebrated the 25th WBW.

Objectives.

1. To protect breastfeeding from conflicts of interest.
2. To promote breastfeeding to the public through appropriate information.
3. To support breastfeeding by strengthening the efforts of all stakeholders.

The theme for this year is: *Sustaining Breastfeeding-Building Alliances Without Conflicts of Interest.* What it means, in a nutshell, is, to work together to Protect, Promote and Support breastfeeding, a pledge, taken by the member states of the UNICEF and WHO, and other world health bodies in 1989[1].

To sustain breastfeeding, it must be protected, promoted, and supported.

Protecting Breastfeeding.

Who from, and how, do we protect breastfeeding? Here is where "conflict of interest" comes in. Anyone, (be it an individual, a group, an organisation or a company) whose ideas, actions, words or intentions are detrimental/contrary to optimal infant feeding and child health, has a conflict of interest.

In this context, we are mainly concerned with the infant milk producing companies and whoever falls under their influence.

In our country we have an excellent tool to protect breastfeeding. This is the Infant Milk Substitutes Act (The IMS Act). One of the provisions of this act is that no company, producing infant milk substitutes, feeding bottles or infant foods may bestow any favour/incentive, eg. gifts (in cash or kind), sponsoring of conferences, trips, entertainment and so on, to any individual or group of individuals, for the purpose of promoting their products. Advertising in any guise is also prohibited. But, this Act is more often violated than followed. There may be several reasons for this: lack of awareness, difficulty in resisting the glitter and glamour of the incentives offered by the companies, inability to recognize the actual intention behind the façade of an event, e.g. a poster competition for health workers, donation of educational material or scientific equipment, are one or two amongst many. It must be borne in mind that the main, interest of a business house is to promote its product. So, it is upto each individual health worker, members and also groups of the community to be aware of the violations of the IMS ACT and protect child health.

Promoting Breastfeeding.

According to the joint statement by the UN Special Rapporteurs[2] on the Right to Food, Right to Health, the Working Group on Discrimination against Women in law and practice, and the Committee on the Rights of the Child in order to promote, protect and support breastfeeding states "Breastfeeding is a human rights issue both for the child and the mother. Children have the right to life, survival and development……of which breastfeeding must be considered an integral component, as well as safe and nutritious foods. Women have the right to accurate, unbiased information needed to make an informed choice about breastfeeding……" The statement also emphasizes the right of women to good quality health services including reproductive health, right to maternity protection, and, for successful breastfeeding, right to an environment conducive to breastfeeding in the work place and in public.

Mothers, families and the public have a right to correct information about optimal infant feeding. It is the responsibility of professionals and the administration to ensure that this information reaches all strata of society. This can be done by

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various means: putting up posters and notices in healthcare facilities, holding seminars and CMEs, in-service training programmes; information can also be disseminated through news media, hoardings, distribution of pamphlets, holding talks for school and college students and those of other educational establishments. These are only some of the avenues that can be explored.

The advantages of breastfeeding and the grave consequences of artificial feeding must always be clearly explained.

Supporting Breastfeeding .

Today, the term "Breastfeeding" is not only confined to exclusive breastfeeding for 6 months but also includes the addition of adequate and appropriate complementary foods with continued breastfeeding. Hence, to mean both, we generally use the term, "Infant and Young Child Feeding" or IYCF.

As a backdrop to this year's theme we have the Millenium Development Goals, giving us a chance to bring together various sectors of society, services and administration to strengthen breastfeeding.

In the year 2000 the member countries of the UN set themselves 8 goals to improve the quality of life and the environment. These goals include:

Eliminate poverty.

Eliminate hunger.

Control diseases e.g. HIV/AIDS, malaria, etc.

Provide quality education.

Prevent environmental degradation.

Prevent discrimination against women.

These goals have to be achieved by 2030.

The above 8 goals have now evolved to 17 Sustainable Development Goals (SDGs)[3] –by 2030. Goal 3 lays special stress on health; all the others are either directly or indirectly related to health. Some of these goals especially focus on maternity protection, agriculture including animal husbandry and fishery, economic growth, clean water and sanitation, peace and justice amongst others. If we study these goals, we will find that infant feeding is directly or indirectly related most of these goals.

The state of IYCF in our country is far from satisfactory. The NFHS4 (2015-2016) data shows: Early initiation of breastfeeding-41.6% with institutional deliveries being 78%.

Exclusive breastfeeding – 55%.

Children 6-8months of age receiving solid food with breastmilk -42.7% (NFHS3-52.6%).

Breastfed children upto 23 months receiving an adequate diet- 8.7%.

Most mothers, especially first-time and young mothers who bottle-fed a previous child, need a lot of support and encouragement during the first few weeks. We have to remember that help may not be readily available at home for these mothers. Most grandmothers of today were bottle-feeders of yesterday. So they have little or no experience about breastfeeding. Also, it must be understood that breastfeeding is not the sole responsibility of the mother or the family. Lalitpur in Uttar Pradesh[4] has shown us what can be achieved at the community level through trained peer counseling and mother support groups. This is an example that can be replicated elsewhere.

Conclusion:

Supporting breastfeeding is in the interest of a community-at present and in the future. Therefore all sections of society, in their own interest need to take an active part in supporting breastfeeding and infant feeding.

If the SDGs are to be achieved by 2030, no one can work alone; yet each must do his/her best. We have to build partnerships and converge our efforts to be successful.

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Case Report

Adams Oliver Syndrome

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Abstract

Adams-Oliver syndrome (AOS) is a congenital condition characterized by aplasia cutis congenita, transverse limb defects, and cutis marmorata telangiectatica. AOS can also be associated with extensive lethal anomalies of internal organs, including the central nervous, cardiopulmonary, gastrointestinal, and genitourinary systems. Generally, the more severe these interrelated anomalies are, the poorer the prognosis. We report a case of AOS with typical skin defects only, and no internal organ anomalies.

Introduction

Adams-Oliver syndrome (AOS) is a rare congenital anomaly complex characterized by aplasia cutis congenita in the vertex area, terminal transverse defects of the limbs, and cutis marmorata telangiectatica congenita (CMTC). As this syndrome has severe forms of expression, including central nervous system abnormalities, cardiovascular disease, and gastrointestinal malformations, patients with this syndrome usually die within several weeks. To the best of our knowledge, no report yet has discussed the lifespan of AOS patients.

Case Report

A one day old male newborn presented with a hairless atrophic scalp patch (fig 1), shortening of the fingers and toes, syndactyly of the 2nd and 3rd finger of right hand(fig 2), total absence of fingers of left hand (fig 3) and talipes equinovarus of both right and left foot (fig 4). He was born as a term baby by normal vaginal delivery with uneventful perinatal period. Mother had no history of teratogenic drug intake, infections or radiation exposure during the pregnancy. There was no familial history of AOS, mental retardation or CNS abnormalities. The scalp had a well-demarcated 10×12 cm hairless atrophic patch at its vertex. Histopathological examination of the scalp lesion revealed rete ridge flattening, collagen bundle thickening in the dermis, and the loss of appendages. No abnormalities were noted on brain computed tomography (CT) or on chest x-ray. The combination of aplasia cutis congenita and skeletal defects of the extremities resulted in a diagnosis of AOS.

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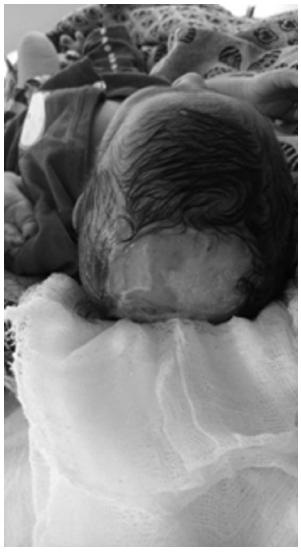

Fig 1

Fig 2

Fig 3

Fig 4

Discussion

AOS is a congenital disease characterized by aplasia cutis congenita, transverse limb defects, and CMTC[1,2]. It was initially described in 1945 by Adams and Oliver. The disease largely has an autosomal dominant mode of inheritance, although autosomal recessive and sporadic modes often occur [3,4]. Our patient had no family history of congenital scalp or limb defects. Therefore, this case was likely a sporadic one.

The limb defects, the most common feature of this disease, are usually asymmetric. The lower limbs are more susceptible than the upper limbs. The range of involvement includes brachydactyly, syndactyly, agenesis of fingernails or toe nails, loss of the terminal phalanges or even more severe defects such as the complete absence of a finger, toe, hand, foot, or limb[5,6]. Our patient had shortening of the fingers and toes, syndactyly of the 2nd and 3rd fingers of right hand, and total absence of fingers of left hand, and talipes equinovarus of both feet. Scalp defects are the second most frequent finding in AOS. The scalp lesions occasionally extend through the skull deformities. Our patient exhibited only a scalp defect and skull thinning. The lesion was confirmed as aplasia cutis congenita upon histopathological examination. Other associated defects include CMTC, central nervous system and cardiovascular malformations, accessory nipples, microphthalmia, and cleft lip[7,8].

Although the exact pathogenesis of AOS remains unknown, vascular impairment during embryogenesis has been proposed as a possible mechanism. In order to identify the genetic cause of AOS, Verdycket al[9] evaluated a family with 10 affected individuals over four generations. However, they failed to find any disease-causing mutations.

Various expressions of AOS have been reported. If a newborn presents with aplasia cutis congenita and limb defects, detailed evaluation of the central nervous system has to be done and investigated for cardiovascular, gastrointestinal, and genitourinary malformations.

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Request

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Case Report

Recurrent Rhinosinusitis and Epistaxis : A Case Report

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Abstract:

Recurrent rhino sinusitis with epistaxis is a common disorder among children and young adults. We report an unusual cause, intranasal supernumerary tooth causing recurrent sinusitis and epistaxis.

Key words : *ectopic tooth , supernumerary teeth , recurrent rhinosinusits , epistaxis*

Case report:

A 13 years old female patient showed up to our OPD with recurrent right sided nasal obstruction, intermittent headache, which was more dominant in the mornings. She also complained about foul smelling nasal discharge since last 14 days. There were recurrent episodes of epistaxis in the past. Neurological examinations were normal. No local tenderness was present. Her throat was mildly erythematous; no significant postnasal discharge (PND) was detectable at the time of examination. Rhinological examination revealed a white hard mass, surrounded with granulation tissue which was difficult to remove in OPD. She was referred for a CT scan; that demonstrated a radiopaque mass located in the right nasal cavity between the inferior turbinate and the nasal Septum (fig 1). She was advised for removal of FB under GA which came out to be an ectopic tooth (fig 2).

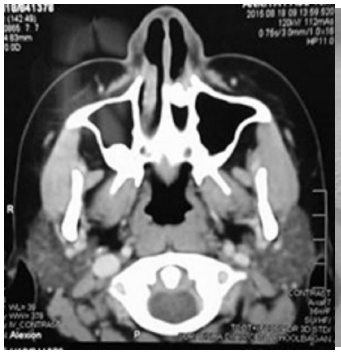

Fig 1

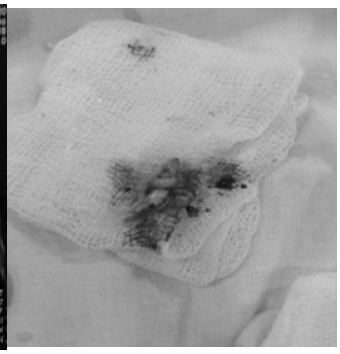

Fig 2

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Discussion:

The incidence of supernumerary teeth generally affects 0.1–1% of the population. The most common location is the upper incisor area, known as mesiodens. The presence of one or more teeth into the nasal cavity may be either the consequence of an aberration of the regular dentition or can be supernumerary[1,2]. The etiology of intranasal teeth is not clear; potential causes include cleft palate, maxillofacial trauma, Gardner's syndrome and cleidocranial dysostosis. None of these factors were identified in the described case. In fact idiopathic eruption of a supernumerary tooth into the nasal cavity forms a separate entity, where biological and genetic mechanisms remain largely unexplored.

Irrespective of their origin, nasal teeth can cause facial pain, epistaxis, nasal obstruction, paranasal sinusitis, nasal septum deviations, nasal septal abscess and oro- nasal fistula [2,4]. Intranasal teeth may be also asymptomatic and may be incidentally recognized during routine examination[3]. Differential diagnoses should be considered, such as a foreign body, rhinolith, tumor, osteoma, odontoma or a cystic lesion. Radiographs help to differentiate between these possibilities and in particular computed tomography is a very useful means that allows to confirm the diagnosis and to facilitate surgical planning[4,5] . Once diagnosed the supernumerary nasal tooth should be extracted to avoid future complications. The most common surgical techniques include the transnasal and transpalatal approaches.

The best time to remove the tooth is after the roots of the permanent teeth have completely formed, to avoid injury during their development[6,7] .

Conclusion :

Nasal teeth results from the ectopic eruption of supernumerary teeth and may cause a variety of symptoms and complications. A child with recurrent rhinosinusitis , nasal discharge or epistaxis where a foreign body as a cause has been ruled out, a high index of suspicion should be there for nasal teeth. Their clinical and radiologic presentation is so characteristic that their diagnosis is not difficult. CT scan is helpful in planning their treatment.

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Answer to Photo Quiz

Williams Syndrome

This girl is showing typical "elfin" facies of William syndrome with short upturned nose, flat nasal bridge, long philtrum, flat malar area, wide mouth, full lips, dental malocclusion, micrognathia, and periorbital fullnes.

The genetic analysis showed deletion at 7q11.23 (elastin gene). She demonstrated over friendliness with mild mental retardation and hyperactivity

There was no history of hypercalcemia and echocardiography was normal.

Williams syndrome is a developmental disorder that affects many parts of the body. This condition is characterized by mild to moderate intellectual disability or learning problems, unique personality characteristics, distinctive facial features, and heart and blood vessel (cardiovascular) problems.

People with Williams syndrome typically have difficulty with visual-spatial tasks such as drawing and assembling puzzles, but they tend to do well on tasks that involve spoken language, music, and learning by repetition (rote memorization). Affected individuals have outgoing, engaging personalities and tend to take an extreme interest in other people. Attention deficit disorder (ADD), problems with anxiety, and phobias are common among people with this disorder.

Young children with Williams syndrome have distinctive facial features including a broad forehead, a short nose with a broad tip, full cheeks, and a wide mouth with full lips. Many affected people have dental problems such as teeth that are small, widely spaced, crooked, or missing. In older children and adults, the face appears longer and more gaunt.

A form of cardiovascular disease called supravalvular aortic stenosis (SVAS) occurs frequently in people with Williams syndrome. Supravalvular aortic stenosis is a narrowing of the large blood vessel that carries blood from the heart to the rest of the body (the aorta). If this condition is not treated, the aortic narrowing can lead to shortness of breath, chest pain, and heart failure. Other problems with the heart and blood vessels, including high blood pressure (hypertension), have also been reported in people with Williams syndrome.

Additional signs and symptoms of Williams syndrome include abnormalities of connective tissue (tissue that supports the body's joints and organs) such as joint problems and soft, loose skin. Affected people may also have increased calcium levels in the blood (hypercalcemia) in infancy, developmental delays, problems with coordination, and short stature. Medical problems involving the eyes and vision, the digestive tract, and the urinary system are also possible.

Source : Pediatric Picture tests - The Pediatric Website www.pediatricwesite.com - pedtests accessed on December 2017