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## Is Rotavirus Breaking Through Another Glass Ceiling? (Sharing Is Caring)

	
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### ABSTRACT

Rotavirus is a highly contagious virus. Diarrhea is dangerous. Vomiting is a hallmark of rotavirus disease. It is the leading cause of death in children below 5 years. It is both preventable and treatable in general, rotavirus infections are more severe than are those caused by other viral gastrointestinal agents. Gastroenteritis, which is also known as stomach flu, and cause an inflammation of the gastrointestinal tract. There are winter epidemics in developed countries, particularly in nurseries. Epidemic vomiting disease has been described first in 1929 and was named "winter vomiting disease" Rotavirus, a common cause of stomach flu in kids also affects adults. Vomiting, dehydration, and hospitalization occur in patients infected with rotavirus.



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## INTRODUCTION

Rotaviruses were the single most important cause of severe infantile gastroenteritis worldwide. (1) Each year, approximately 760,000 children die from severe dehydrating diarrhea in developing countries (2). Depending on the severity of diarrhea, treatment consists of oral rehydration, during which the child is given extra water to drink that contains small amounts of salt and sugar. Some infections are serious enough to warrant hospitalization where fluids are given by intravenous drip or nasogastric tube, and the child's electrolytes and blood sugar are monitored. Antibiotics are not recommended (3). The uneven distribution of Rotavirus mortality is staggering among the developing countries more than 65% of the global deaths caused by rotavirus occur in 11 countries in Asia and Africa, where an estimated 345000 children under the age of 5 years die each year.(4) Rotavirus primarily infects mature enterocytes located in the middle and upper villous epithelium(5). Rotavirus specific IgA antibodies on the enteric mucosal surface on through to mediate protective immunity. Infection with one serotype provides serotype-specific (homotypic) protection and repeated infections lead to partial cross serotype(heterotypic) protection. Thus, serotype does not appear to be the sole determinant in providing protective immunity. (6) The early appearance of virus stools of some neonates indicates that infection probably was acquired at delivery.

Virus can be detected on the first or second day of life in many infected infants(7)Infection in newborn children, although common, is often associated with the mild or asymptomatic disease; the most severe symptoms tend to occur in children six months to two years of age, the elderly, and those with compromised or absent immune system functions. Due to immunity acquired in childhood, most adults are not susceptible to rotavirus; gastroenteritis in adults usually has a cause other than rotavirus, but asymptomatic infections in adults may maintain the transmission of infection in the community (8). Rotavirus was also found in large numbers in stool specimens negative stain electron microscopy and significant antibody titer rises were shown between acute and convalescent sera from children with acute gastroenteritis by immune electron microscopy. (9) Rotavirus infection occurs throughout life. Multiple rotavirus infections commonly occur during infancy and early childhood. The first rotavirus infection typically results in the most severe disease outcome, although infection in the neonatal the period often tends to be asymptomatic subsequent rotavirus infections, irrespective of infecting serotypes are associated with a milder disease or may

even be asymptomatic (10). The most important factors influencing the incidence of rotavirus diarrhea in a nursery are the proximity to other newborns and the frequency of hand washings (11). Early signs of illness, such as lethargy, irritability, vomiting, and poor feeding, usually, are followed in a few hours by the passage of watery yellow or green stools free of blood but sometimes containing mucus (12). The diarrhea is caused by multiple activities of the virus. Malabsorption occurs because of the destruction of gut cells called enterocytes. The toxic rotavirus protein NSP4 induces age- and calcium ion-dependent chloride secretion disrupts SGLT1 transporter-mediated reabsorption of water, apparently reduces the activity of brush-border membrane disaccharidases, and possibly activates the calcium ion-dependent secretory reflexes of the enteric nervous system (13). Rotavirus gastroenteritis caused almost 400,000 infant deaths every year before the implementation of neonatal vaccination programs (14). Natural history studies suggest that a single infection with rotavirus provides a solid immunity and that it improves with each subsequent infection (15).

Healthy enterocytes secrete lactase into the small intestine; milk intolerance due to lactase deficiency is a symptom of rotavirus infection, which can persist for weeks. A recurrence of mild diarrhea often follows the reintroduction of milk into the child's diet, due to bacterial fermentation of the disaccharide lactose in the gut (16). The influence of cell-mediated immunity is less clearly understood but is probably related both to recovery from infection and to protection against subsequent disease (17). Diagnosis of infection with rotavirus normally follows a diagnosis of gastroenteritis as the cause of severe diarrhea. Most children admitted to hospital with gastroenteritis are tested for rotavirus A. Specific diagnosis of infection with rotavirus A is made by finding the virus in the child's stool by enzyme immunoassay. There are several licensed test kits on the market which are sensitive, specific and detect all serotypes of rotavirus A (18). Although rotavirus causes severe diarrhea in numerous species, including humans, the mechanisms responsible have not been determined and may be due to multiple factors. Rotavirus replicates extensively in epithelial cells of the small intestine and is released in large numbers into the intestinal lumen. The damage caused by multiplication in the epithelial cells causes impairment of the absorption of water and electrolytes from the lumen, leading to diarrhea which is followed by dehydration. However other mechanisms have also been proposed, including viral non-structural protein NSP4 acting as enterotoxin (19).

The infection triggers a humoral and cell-mediated immune response at the mucosal level and the virus is normally cleared within a week. However, infection in the immunodeficient child may persist with severe chronic diarrhea associated with rotavirus excretion that can last many months (20).

## **HISTORY**

Viruses with morphological features, later associated with rotaviruses were observed first by electron microscopy in 1963 in intestinal tissues and rectal swab specimens from mice and monkeys.

These agents called epizootic diarrhea of infant mice virus and simian agent 11 respectively that had a wheel-like appearance. Hence they have later designated Rotaviruses from Latin word for the wheel (21).

In 1943, Jacob Light and Horace Hodes proved that a filterable agent in the feces of children with infectious diarrhea also caused scours (livestock diarrhea) in cattle. (22) Three decades later, preserved samples of the agent were shown to be rotavirus. In the intervening years, a virus in mice was shown to be related to the virus causing scours. In 1973, Ruth Bishop and colleagues described related viruses found in children with gastroenteritis. (23)

In 1974, Thomas Henry Flewett suggested the name *rotavirus* after observing that, when viewed through an electron microscope, a rotavirus particle looks like a wheel (*rota* in Latin)(24) the name was officially recognized by the International Committee on Taxonomy of Viruses four years later. In 1976, related viruses were described in several other species of animals. These viruses, all causing acute gastroenteritis, were recognized as a collective pathogen affecting humans and animals worldwide. Rotavirus serotypes were first described in 1980(25) and in the following year, rotavirus from humans was first grown in cell cultures derived from monkey kidneys, by adding trypsin (an enzyme found in the duodenum of mammals and now known to be essential for rotavirus to replicate) to the culture medium. (26) The ability to grow rotavirus in culture accelerated the pace of research, and by the mid-1980s the first candidate vaccines were being evaluated (27).

In 1998, a rotavirus vaccine was licensed for use in the United States. Clinical trials in the United States, Finland, and Venezuela had found it to be 80 to 100% effective at preventing severe diarrhea caused by rotavirus A, and researchers had detected no statistically

significant serious adverse effects.(28) The manufacturer, however, withdrew it from the market in 1999, after it was discovered that the vaccine may have contributed to an increased risk for intussusception, a type of bowel obstruction, in one of every 12,000 vaccinated infants.(29) The experience provoked intense debate about the relative risks and benefits of a rotavirus vaccine.(30) In 2006, two new vaccines against rotavirus A infection were shown to be safe and effective in children, and on June 2009 the World Health Organization recommended that rotavirus vaccination be included in all national immunization programs to provide protection against this virus.(31)

In 1980 particles that were indistinguishable morphologically from established Rotavirus strains but lacked the common group Antigen were discovered in pigs(32)The development of Rota Virus vaccines has been a major priority because of the high burden of disease and cost-effectiveness analysis have shown that a rotavirus immunization program would be cost-effective from the perspective of society and health care system(33)Rota Shield Rheuses/human reassortant vaccine approved in 1998 by the US. Rotarix, a human attenuated vaccine approved in 2004 by Mexico. Rotateq, Bovine/human vaccine approved in 2006 by The US.

Later Rorix TM (human attenuated vaccine, approved in 2008 by the US.

### **SIGNIFICANT GAP IN RESEARCH**

Rotavirus is the most common cause of dehydrating diarrhea in children in the USA and worldwide and infants nearly every child in the first few years of life.

The incidence of rotavirus infections is highest in children between the ages of 6 and 24 months but the age may be lower in less developed countries(34)Adults, including elderly patients, also are susceptible to re-infection, which can cause mild and sometimes severe disease in children with symptoms, the onset often is abrupt, with fever and vomiting followed by explosive, watery diarrhea. Vomiting may precede diarrhea in approximately half the cases.

Stools are non-bloody and generally lack fecal leucocytes, but mucus may be found in 20%. Fever occurs in rotavirus illness, with estimates of between 45 and 84% of the population (35)In another study, one-fourth of the patients infected with rotavirus presented with

hypernatremia dehydration. Numerous reports associate respiratory symptoms like cough, pharyngitis, otitis media, and pneumonia.

Other clinical manifestations associated either etiologically or incidentally with a rotavirus infection have been described and include encephalitis and meningitis(36) In one study, scientists reported that the retarded differentiation of uninfected enterocytes that migrated at an accelerated rate from the crypts, after the virus had invaded villus cells was responsible for absorptive abnormalities. In one study, it is observed that the destruction of the villus tip cells cause carbohydrate malabsorption and osmotic diarrhea(37).

### **MAJOR ADVANCES AND DISCOVERIES**

Of interest, Rotavirus antigen recently has been reported to be found also in the blood of immunocompetent children with confirmed rotavirus gastroenteritis. There are currently five groups(A to E) and evidence to establish three additional groups (F to H) Only groups A to C have been associated with human diseases, and most known cases of rotavirus gastroenteritis(38).

### **WHERE THE RESEARCH GO NEXT?**

Rotavirus is very contagious, with as little as one tissue culture infectious dose able to cause illness in a fully susceptible hos. The virus is very stable in the environment and is shed in a very large amount in feces.

Rotavirus generally transmitted by the fecal-oral route. Oral administration of rotavirus-positive stool material induced diarrheal illness and viral shedding in adult volunteers. The early appearance of the virus in stools of some neonates indicates that infection probably was acquired at delivery.

Virus particles can be detected on the first or second day of life in many infected infants. By day 3 or 4 most infected infants who will shed virus, with or without signs of illness, are doing so(39) Isolation of less common types seems to be more frequent among neonates with nosocomial rotavirus infections.

There are numerous reports of nosocomial and daycare center rotavirus gastroenteritis outbreaks, which attests to the ease with which this agent spreads through a hospital or institutional setting(40).

## **CURRENT DEBATE**

Most of the people are unable to afford to purchase the vaccine because of the high cost. In advanced countries like the USA, rotavirus vaccination is controversy. People discouraged the vaccine, as it is attenuated.

Though children have taken the vaccination, still, some are getting the disease as the vaccination is not giving full protection, In Finland, rotavirus infection was most common in children <5 years of age before vaccine introduction, but after vaccine introduction, it is most common in unvaccinated children between 6 and 16 years of age and changes in the seasonal pattern of rotavirus disease. Nitazoxanide inhibits the replication of rotavirus by interfering with viral morphogenesis.

## **VACCINATION**

Development of rota vaccines began in the early 1980s. The development of rota vaccines has been a major priority because of the high burden of disease, and cost-effectiveness analyses have shown that a rotavirus immunization program would be cost-effective from the perspective of society and the health care system.

Rotashield, an oral formulation of a simian-human quadrivalent reassortant vaccine, was recommended for use in children in a three-dose regimen to be received at 2,4, and 6 month age. There are four important vaccines currently available. They are as follows:

Rotateq,(Merk) Rotarix (GlaxoSmithKline), LLR (Lanzhou Institute of biological products) which is licensed only in China, and 116E (BBIL) Rotatex is pentavalent live oral human-bovine reassortant (WC3)A three-dose series is given between the ages of 6-32 weeks, ensuring at least 4 weeks between vaccines. This vaccine is licensed by the FDA Australia, Canada, the EU and Mexico, several countries in Asia and Latin America. It is not available in India.

Rotarix is human attenuated. It is approved in July 2004 by Mexico.RotaShield, Rhesus/human reassortant. This is approved by the US in August 1998.LLR (Lanzhou Institute of biological products. This vaccine is Monovalent live oral lamb LLR strain.It is Monovalent serotype of P(12G(10) Group A rotavirus vaccine. This is licensed by the

Chinese regulatory authority. It is available only in China.116E(BBIL). This vaccine is in the trail.

This is Monovalent live oral naturally attenuated neonatal strain. This vaccine is phase 111 trials completed. The Rota Teq and Rotarix have undergone safety studies and have been found to be safe for use in children of 9 years ago.

## **DIAGNOSIS**

Plasma electrolytes, urea, creatinine, and glucose should be checked. If antibiotics are started, a blood culture should be taken(41) Rotavirus fecal antigen detection test is used for the diagnosis of enteric infection caused by rotavirus.

This the test may be ordered for patients usually young children, who present with a sudden onset of watery diarrhea, which often preceded by vomiting. The unpreserved stool is submitted for testing. Rotavirus antigen in the stool is detected by immunologic techniques using rotavirus-specific antibodies. Since 1973, many assays have been developed for the detection rotavirus in stools, although at present solid-phase immunoassay and RT-PCR-based assays are the primary diagnostic tools.

Specimens from the first to the 4<sup>th</sup> day of illness are optimal for virus detection using traditional assays(ELISA)shedding can continue for three weeks, depending on the duration of symptoms and maybe detected longer by RT-PCR. The method of choice in many laboratories is ELISA, because it is sensitive, does not require specialized equipment, is available commercially invalidated formats is relatively inexpensive and often has a built-in control for non-specific reactions.

Other methods of viral detection, such as counterimmunophoresis, gel electrophoresis of rotavirus RNA, reverse passive hemagglutination assay(RPHA), and latex agglutination, have been used in the past. A variety of generally sensitive and specific commercial kits for rotavirus detection is now available primarily using some form of ELISA solid-phase immunoassay format.

Enzyme immunoassays have also been developed in research laboratories for detection of group B or Group C rotavirus and for measurement of antibodies directed against these viruses. A dot blot hybridization assay for detection of rotaviruses was developed based on in



situ hybridizations of labeled rotavirus ssRNA transcripts to heat-denatured rotavirus RNA immobilized on a nitrocellulose membrane. The method is highly specific, yielding results concordant with those obtained with other tests such as EM, ds RNA detection, and ELISA. In a comparative study of ELISA and dot hybridization for the detection of rotavirus in various dilutions of fecal specimens, the dot hybridization method was 10 to 100 times more sensitive than the confirmatory ELISA but much less practical and has not been generally employed since RT-PCR based assays became available.

## **MANAGEMENT**

The primary goal of therapy is the restoration and maintenance of fluid and electrolyte balance.

Despite the documented defect in carbohydrate digestion with rotavirus diarrhea, rehydration often can be accompanied by glucose-electrolyte solutions given orally<sup>(42)</sup>. Intravenous fluids may be needed in neonates who are severely dehydrated, who have ileus or who refuse to feed. Persistent or recurrent diarrhea after the introduction of milk-based formulas or human milk warrants investigation for secondary carbohydrate or milk protein intolerance. Several studies have shown that breastfeeding protects against symptomatic rotavirus infection<sup>(43)</sup>. A study also found that breastfeeding was protective against hospitalization for acute gastroenteritis caused by rotavirus in infants younger than 6 months.

Supporting the role of human milk in protection against rotavirus is a study demonstrating those infants who received human milk with higher concentrations of the glycoprotein lactadherin were more likely to have asymptomatic rotavirus infections compared with those receiving milk with lower concentrations<sup>(44)</sup>.

## **CONCLUSION**

The disease burden of rotavirus is substantial, and the economic burden from infection in infants and children is a threat worldwide.

Rotavirus vaccination is a cost-effective measure to prevent rotavirus infection. Rotavirus diarrhea is considered to be a vaccine-preventable disease based on recent successful outcomes in children in developed countries.

## REFERENCES

1. Parashar UD, Burton A, Lanata C, et al. Global mortality associated with rotavirus disease among children in 2004. *J. Infect. Dis.* 2009;200 (suppl1)S9-15
2. Tate JE, Burton AH, Boström-Pinto C, et al. 2008. An estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of Universal rotavirus vaccination programs. A systemic review and meta-analysis. *Lancet. Infect. Dis* 2012;12;136-41
3. Patel MM, Tate JE, Selvarangan R, et al. (2007). "Routine laboratory testing data for surveillance of rotavirus hospitalizations to evaluate the impact of vaccination". *Pediatr. Infect. Dis. J.* **26**(10): 914–9. doi:10.1097/INF.0b013e31812e52fd. PMID 17901797.
4. Naghipour M, Nakagomi T, Nakagomi O, Issues with reducing the Rotavirus associated mortality by vaccination in developing countries. *Vaccines* 2008,26;3236-41
5. Graham DY, Estes MK. Comparison of methods for immunocytochemical detection of rotavirus infections. *Infect. Immune* 1979,26;686,
6. Ward RL. Rotavirus vaccines. How they work or don't work. *Expert Rev. Mol. Med* 2008,10;5. Hunter tropical medicine and emerging infectious diseases
7. Murphy AM, Albrey MB, Crew EB, Rotavirus infections in neonates. *Lancet* 2;1149,1879
8. Hardy DB (1987). "Epidemiology of rotavirus infection in adults". *Rev. Infect. Dis.* **9** (3): 461–9. doi:10.1093/clinids/9.3.461. PMID 3037675
9. Kapikian AZ, Kim HW, Wyatt RG et al. Reo virus-like agent in stools, association with infantile diarrhea and development of serologic tests. *Science* 1974;185;1049-53
10. Bishop RF, Barnes GL, Capriani E, et al. Clinical immunity after neonatal rotavirus infection. A prospective longitudinal study in young children. *N. Engl. J. Med.* 1983,309;72-6
11. Bishop RF, Cameron, Veenstra AA, et al. Diarrhea and Rotavirus infection associated with differing regimens for postnatal care of newborn babies. *J. Clin. Microbiol.*
12. Tallet S, Mac Kenzie C, Middleton P et al. Clinical. Laboratory and epidemiologic features of a viral gastroenteritis in infants and children. *Paediatrics* 60;217,1977
13. Gregorini, L; Marco, J; Bernies, M; Cassagneau, B; Pomidossi, G; Anguissola, GB; Fajadet, J (Apr 15, 1997). "The alpha-1 adrenergic blocking agent urapidil counteracts post rotational atherectomy "elastic recoil" where nitrates have failed". *The American Journal of Cardiology.* **79** (8): 1100–3. DOI:10.1016/S0002-9149(97)00053-2. PMID 9114772
14. Parashar UD, Himmelman, Bresse JS, et al. Global illness and deaths caused by Rotavirus disease in children. *emerg. infec. Disc.* 9;565,2003
15. Velazquez FR, Matson DO, Calva JJ, et al, Rotavirus infections in infants as protection against subsequent infections. *N. Eng. J. Med.* 1996;335;1022-8
16. Arya SC (1984). "Rotaviral infection and intestinal lactase level". *J. Infect. Dis.* **150** (5): 791. doi:10.1093/infdis/150.5.791. PMID 6436397
17. Green KY, Taniguchi K, Mackow ER, et al. Homotypic epitope-specific antibody responses in adult and infant rotavirus vaccines; implications for vaccine development. *J. Infect. Dis* 1990,161;667-79
18. Ward RL, Mechanisms of protection against rotavirus in humans and mice. *J. Infect. Dis* 1996;174(suppl);S51-8
19. Ref. Bali JM, Tian. Zeng CQ. et al. Age-dependent diarrhea induced by rotavirus. Non-structural glycoprotein. *Science* 1996,5;272;104-4
20. Saulsbury FT, Wienkelstein JA, Yolken RH. Chronic rotavirus infection in immunodeficiency. *J. Pediatr.* 1980,97;61-5
21. Mary Allen Staat, Monica Malone, Meneel, David Bernstein, Chapter 172 pp 2176-2178,
22. Light JS, Hodes HL (1943). "Studies on epidemic diarrhea of the new-born: Isolation of a Filtrable Agent Causing Diarrhea in Calves". *Am. J. Public Health Nations Health.* **33** (12): 1451–4. doi:10.2105/AJPH.33.12.1451. PMC 1527675. PMID 18015921.
23. Woode GN, Bridger JC, Jones JM, Flewett TH, Davies HA, Davis HA, White GB (1 September 1976). "Morphological and antigenic relationships between viruses (rotaviruses) from acute gastroenteritis in children, calves, piglets, mice, and foals" (PDF). *Infect. Immun.* **14** (3): 804–10. PMC 420956. PMID 965097.

24. Flewett TH, Woode GN (1978). "The rotaviruses". *Arch. Virol.* **57** (1): 1–23. doi:10.1007/BF01315633. PMID 77663.
25. Flewett TH, Bryden AS, Davies H, Woode GN, Bridger JC, Derrick JM (1974). "Relation between viruses from acute gastroenteritis of children and newborn calves". *Lancet.* **2** (7872): 61–3. doi:10.1016/S0140-6736(74)91631-6. PMID 4137164.
26. Matthews RE (1979). "Third report of the International Committee on Taxonomy of Viruses. Classification and nomenclature of viruses". *Intervirology.* **12** (3–5): 129–296. doi:10.1159/000149081. PMC 5586817. PMID 43850.
27. Beards GM, Brown DW (March 1988). "The antigenic diversity of rotaviruses: significance to epidemiology and vaccine strategies". *European Journal of Epidemiology.* **4** (1): 1–11. doi:10.1007/BF00152685. PMID 2833405.
28. Urasawa T, Urasawa S, Taniguchi K (1981). "Sequential passages of human rotavirus in MA-104 cells". *Microbiol. Immunol.* **25** (10): 1025–35. doi:10.1111/j.1348-0421.1981.tb00109.x. PMID 6273696.
29. Rotavirus vaccine for the prevention of rotavirus gastroenteritis among children. Recommendations of the Advisory Committee on Immunization Practices (ACIP)". *MMWR Recomm Rep.* **48** (RR-2): 1–20. 1999. PMID 10219046.
30. Kapikian AZ (2001). A rotavirus vaccine for prevention of severe diarrhoea of infants and young children: development, utilization and withdrawal. Novartis Found. Symp. Novartis Foundation Symposia. **238**. pp. 153–71, discussion 171–9. doi:10.1002/0470846534.ch10. ISBN 9780470846537. PMID 11444025.
31. Dennehy PH (2008). "Rotavirus vaccines: an overview". *Clin. Microbiol. Rev.* **21** (1): 198–208. doi:10.1128/CMR.00029-07. PMC 2223838. PMID 18202442.
32. Cherry, Harrison, Kaplon, Steinbach, Hotez, Feigen and Cherry's Textbook of pediatric infectious disease 7th Ed. Elsevier 2014
33. Widdowson MA, Steele D, Voidani J, et al, Global Rotavirus surveillance. Determining the need and measuring the impact of Rotavirus vaccines. *J. Infect. Dis.* 2009(Suppl)S1-8
34. Iturriza-Gomara M, Clarke I, Desselberger U, et al. seroepidemiology group C rotavirus infection in England and Wales *Eur. J. Epidemiol* 1953,595,2004.
35. Uhnoo, I, Olding-Stenkvis E, and Kreuger A, Clinical features of acute gastroenteritis associated with rotavirus, enteric adenoviruses, and bacteria. *Arch. Dis. Child.* 61;732-738, 1986
36. Yoshida A, Kawamoto T, Tanaka R, et al. Rotavirus encephalitis. Detection of virus genomic RNA in the CSF of the child. *Paediatr. Infect. Dis. J.* 14;914-916, 1995.
37. Graham DY, Sackman JW, and Estes, MK, Pathogenesis of rotavirus-induced diarrhea. Preliminary studies in miniature swine piglet. *Gig. Dis. Sci* 29;1028-1035. 1984
38. David M. Knipe, Peter M. Howley, Jeffrey Cohen, Diane E, Griffin. Robert A, Lamb, Malcolm A, Martin Vincent R, Racanillo, Bernard, Roizman, Fields virology 6th Edition, Vol-2, 2013
39. Madeley CR, Cosgrove BP, Bell EJ, Stool viruses in babies in Glasgow. 2. Investigation of normal newborns in hospital. *I. Hyg.* 81;285, 1978
40. Herruzo R, Omenaca F, Garcia S S, et al. Identification of risk factors associated with nosocomial infection by rotavirus P4G2, in a neonatal unit of tertiary care hospital *Clin. Microbiol. Infect* 15;280, 2009
41. Tom Lissaure, Graham Clayden, Illustrated textbook of Paediatrics, 4th Ed, Mosby, Elsevier, 2012.
42. Black RE, Merson MH, Taylor PR, et al, Glucose vs sucrose in oral rehydration solutions for infants and young children with rotavirus-associated diarrhea. *Paedi.* 67;79, 1981
43. Newburg DS, Peterson J, A, Ruiz-Palaciou GM, et al, Role of breast milk lactadherin in protection against symptomatic rotavirus infection. *Lancet*, 351;1160-1164, 1998
44. (Dennehy PE, Cortese MM, Begue RE, et al, A case-control study to determine risk factors for hospitalization for rotavirus gastroenteritis in US, children. *Paediatr. Infect. Dis. J.* 25;1123-1131, 2006)