Diarrhea in neonatal intensive care unit

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AIM: To investigate the frequency, etiology, and current management strategies for diarrhea in newborn.

METHODS: Retrospective, nationwide study involving 5801 subjects observed in neonatal intensive care units during 3 years. The main anamnesis and demographic characteristics, etiology and characteristics of diarrhea, nutritional and therapeutic management, clinical outcomes were evaluated.

RESULTS: Thirty-nine cases of diarrhea (36 acute, 3 chronic) were identified. The occurrence rate of diarrhea was 6.72 per 1000 hospitalized newborn. Etiology was defined in 29 of 39 newborn (74.3%): food allergy (20.5%), gastrointestinal infections (17.9%), antibiotic-associated diarrhea (12.8%), congenital defects of ion transport (5.1%), withdrawal syndrome (5.1%), Hirschsprung’s disease (2.5%), parenteral diarrhea (2.5%), cystic fibrosis (2.5%), and metabolic disorders (2.5%). Three patients died due to complications related to diarrhea (7.7%). In 19 of 39 patients (48.7%), rehydration was performed exclusively by the enteral route.

CONCLUSION: Diarrhea in neonates is a challenging clinical condition due to the possible heterogeneous etiologies and severe outcomes. Specific guidelines are advocated in order to optimize management of diarrhea in this particular setting.

Key words: Chronic diarrhea; Congenital diarrhea; Food allergy; Oral rehydration solution; Rotavirus

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INTRODUCTION

Diarrhea and neonatal age are two major factors responsible for pediatric mortality worldwide\(^1,2\). The neonate has increased susceptibility to complications related to diarrhea due to immaturity of the systems that regulate fluid homeostasis and immunologic response\(^3\). Early diagnosis and timely treatment are crucial because diarrhea in neonates may rapidly lead to life-threatening dehydration and malnutrition\(^4,5\). Clinical and epidemiologic studies defining severity and etiology are needed in order
to improve diagnostic and therapeutic approaches for neonatal diarrhea. Starting with these considerations, the Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP), on behalf of the Italian Society of Neonatology (SIN), designed a nationwide study aimed at investigating the frequency, etiology, clinical features, nutritional management, therapeutic approach, and outcomes of diarrhea observed in hospitalized neonates.

MATERIALS AND METHODS

A multicenter, retrospective study was planned. The study design and aims were presented and discussed during two meetings of the SIGENP and the SIN. We invited the participation of the chiefs of neonatal intensive care units (NICUs) of urban children’s hospitals, university medical centers or large community hospitals, observing at least 100 newborns per year and having the following diagnostic facilities: determination of fecal electrolyte concentrations, full microbiological examination, food allergy tests, gastrointestinal endoscopy and histology, metabolic tests and genetic counselling. The neonologists operating in the participating centers were invited to review the data of 3 consecutive years (i.e. 2000-2002). Inclusion criteria were: (1) age at hospitalization ≤ 28 d; (2) gestational age at birth ≥ 24 wk; (3) clinical chart and hospital records available for review; and (4) presence of diarrhea, defined on the basis of increased frequency and watery consistency of stools along with dehydration. This definition, which was adopted in a previous study of neonates[4], is in accordance with the traditional definition employed in pediatric gastroenterology[5] and to the more recent guidelines for the management of acute gastroenteritis of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/European Society for Paediatric Infectious Diseases (ESPID)[6]. Data were recorded in a specific reporting form made up of 5 sections: (1) demographic characteristics: sex, gestational age, birth weight, age at hospitalization and at diarrhea onset; (2) anamnesis: intrauterine growth restriction, polyhydramnios, risk for allergy according to American Academy of Pediatrics (AAP) guidelines[7], familiarity for chronic diseases including diarrhea, surgery, diet before diarrhea onset; (3) characteristics of diarrhea: number of bowel movements, stool consistency, presence of blood and mucus in the stools, severity of dehydration, complications, development of chronic diseases, diarrhea duration and presence of other intestinal or extra-intestinal symptoms; (4) etiology of diarrhea; and (5) nutritional and therapeutic management, clinical outcomes.

To better define the study population and to establish the diarrhea occurrence rate, the number of hospital admissions and the main demographic characteristics of all subjects observed during the study period, in each participating NICU, were also evaluated. Diarrhea was classified as acute or chronic if it lasted < 14 d or > 14 d, respectively, according to the definition of the World Health Organization[8,9]. The study protocol was approved by the Ethics Committee of our institution. No competing interest was declared by the investigators involved in the study.

Statistical analysis

Patients were classified according to the duration of diarrhea into the acute and chronic groups. For continuous variables, the t-test for equality of means was used. For categorical variables, the χ² test and Fisher’s exact test were used. Possible correlations between the duration of diarrhea and gestational age, birth weight, sex, number of bowel movements, antibiotic use, age at diagnosis and severity of dehydration were investigated by linear regression analysis. The level of significance for all statistical tests was 2-sided P < 0.05. Statistical analysis was performed using SPSS software (Version 14.0 for Windows, SPSS Inc., Chicago, IL, USA).

RESULTS

Sixteen NICUs were invited to participate in the study and 7 accepted. The clinical charts of 5801 cases were reviewed, and 39 cases of diarrhea were reported. The occurrence rate of diarrhea was estimated at 6.72 per 1000 hospitalized newborn. The number of cases observed during the study period was: 12 in the first, 14 in the second and 13 in the third year of the study. Diarrhea was the main cause of hospital admission in 14 of 39 subjects (35.9%). Diarrhea was classified as acute in 36 patients (92.3%) and chronic in 3 neonates (7.7%). The etiology of diarrhea was identified in 29 of 39 patients (74.3%) (Table 1).

A diagnosis of cow’s milk allergy (CMA) was reported in 8 cases. Five of these cases were considered to be at risk for allergic diseases according to the AAP definitions[10]. In patients with CMA, diarrhea was associated with eczema or vomiting in 6 and in 5 subjects, respectively. Specific IgE titers against milk proteins were positive in 6 of 8 patients (> 5.0 kU/L)[11]. In each case of CMA, the diagnosis was confirmed by observation when an antigen elimination diet with an extensively hydrolyzed casein formula (Nutramigen®, Mead-Johnson Nutritional, Italy) resulted in symptomatic improvement, and the reintroduction of cow’s milk after 4 wk caused symptoms to reappear. An open food challenge was performed in 5 of 8 subjects during hospitalization in consultation with a pediatric allergy specialist, and in 3 of 8 patients after discharge, in a tertiary Center of Pediatric Gastroenterology and Food Allergy.

Seven patients were classified as having intestinal infection according to the results of microbiological analysis. The microorganisms responsible for diarrhea are reported in Table 1. One patient initially classified as having gastrointestinal infection had a familial history of immunodeficiency and a clinical course characterized by growth delay, recurrent opportunistic infections, lymphopenia, associated with defective cellular and humoral immune responses. In this case, molecular analysis...
confirmed the clinical diagnosis of adenosine deaminase deficiency (OMIM 608958)\(^{[12]}\).

Five babies presented with antibiotic-associated diarrhea. The microbiological analysis, including the search for *Clostridium difficile*, was negative in all these subjects.

According to clinical findings and the results of molecular analysis, two patients received a diagnosis of congenital diarrheal disorders (OMIM 251850): one with glucose-galactose malabsorption (OMIM 182380); and one with congenital chloride diarrhea (OMIM 214700)\(^{[13]}\).

Neonatal withdrawal syndrome-induced diarrhea was reported in 2 subjects from mothers with a history of drug abuse (heroin and methadone) during pregnancy.\(^{[14]}\). One case of Hirschsprung’s disease was diagnosed according to the clinical history (no passage of meconium in the first 72 h of life, bloating of the abdomen) and the results of diagnostic tests, including rectal manometry, barium enema, and rectal biopsies\(^{[15]}\). This patient had diarrhea as a consequence of severe enterocolitis requiring broad-spectrum antibiotic therapy. Parenteral diarrhea induced by extra-intestinal infection caused by *Klebsiella pneumoniae*-induced urinary infection was reported in one full-term baby during the first week of life. In this patient, diarrhea started before antibiotic treatment, all microbiological evaluations on stools were negative, and diarrhea improved rapidly when the urinary infection disappeared. For one subject with a familial history of cystic fibrosis (CF), intrauterine growth retardation, and chronic diarrhea, a final diagnosis of CF was achieved by a sweat test and was confirmed by the identification of a CFTR AF508 mutation, at the age of 4 mo\(^{[16]}\). A urea defect cycle was diagnosed in one patient by the presence of diarrhea together with metabolic acidosis, hyperammonemia and protein load intolerance\(^{[17]}\).

The main anamnestic and demographic characteristics of the neonates with diarrhea are shown in Table 2. Symptoms associated with diarrhea are reported in Table 3. The
onset. After diarrhea onset, breast milk was continued in 3 subjects, temporarily withdrawn (24 h) in 2, and definitively suspended in 4 of 9 newborn.

The clinical outcomes of diarrhea are reported in Table 4. Three deaths were reported among the 39 subjects (7.7%). Patients affected by adenosine deaminase deficiency, CF, and Hirschsprung’s disease died due to complications related to fatal systemic infections at 1, 12 and 7 mo of life, respectively.

**DISCUSSION**

This is the first systematic study describing diarrhea in patients hospitalized in the NICU in an industrialized country and outside outbreak conditions. The results of our investigation showed that, in this particular setting, diarrhea is a relatively uncommon but insidious condition underlying a broad spectrum of illnesses. The list of diseases and mechanisms responsible for diarrhea in neonates is large and the number of possible etiologies is higher when compared to older pediatric patients. In recent years, new diseases have been described (i.e. enteric anen, cystic fibrosis, and Hirschsprung’s disease) and Hirschsprung’s disease died due to complications related to fatal systemic infections at 1, 12 and 7 mo of life, respectively.

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**COMMENTS**

**Background**

Diarrhea represents a major condition responsible for pediatric mortality worldwide. The onset of neonatal diarrhea may rapidly lead to life threatening dehydration and malnutrition. Thus, early diagnosis and timely treatment are both crucial in the management of diarrhea in neonates. Clinical and epidemiologic studies defining severity and etiology are needed in order to improve diagnostic and therapeutic approaches for the management of neonatal diarrhea.

**Research frontiers**

This study showed that neonatal diarrheal diseases are challenging clinical conditions due to their heterogeneous etiology and possible severe outcomes. The list of diseases and mechanisms responsible for diarrhea in neonates is large and the number of possible etiologies is higher compared with older pediatric patients. Specific guidelines for the management of diarrheal disorders in neonates are advocated.

**Table 4  Severity of dehydration, modalities of rehydration and clinical outcomes n (%)**

|                      | Acute       | Chronic     |
|----------------------|-------------|-------------|
| Number of patients   | 36          | 3           |
| Degree of dehydration|             |             |
| Severe dehydration   | 5 (13.9%)   | 2 (66.7%)   |
| Rehydration modalities|             |             |
| Exclusively oral rehydration | 18 (50.0%) | 1 (33.3%)   |
| Exclusively parenteral rehydration | 2 (5.6%)  | 1 (33.3%)   |
| Oral plus parenteral rehydration | 16 (44.4%) | 1 (33.3%)   |
| Clinical outcomes    |             |             |
| Duration of diarrhea | 5.7 ± 2.5   | 44.3 ± 6.7  |
| Electrolyte abnormalities | 8 (22.2%) | 2 (66.7%)   |
| Deaths               | 2 (5.5%)    | 1 (33.3%)   |

*P < 0.05. Data are expressed as mean ± SD when not specified.
**Innovations and breakthroughs**

This is the first systematic study describing diarrhea in patients hospitalized in the neonatal intensive care unit in an industrialized country and outside outbreak conditions. The results of the authors’ investigation showed that, in this particular setting, diarrhea is a relatively uncommon but insidious condition underlying a broad spectrum of illnesses.

**Applications**

This research opens the way for new investigations in the area of diarrheal diseases with neonatal onset. The authors believe that these studies will help neonatologists to prevent diarrhea from becoming a severe clinical condition, and to recognize and correctly manage rare chronic cases who need the assistance of a specialized team dedicated to their long-term treatment.

**Terminology**

A neonatal intensive care unit, usually abbreviated to NICU, is a unit of a hospital specializing in the care of ill or premature newborn infants.

**Peer review**

This well-written informative and innovative manuscript convincingly shows that neonatal diarrheal diseases are challenging clinical conditions because of the heterogeneous etiology and possible severe outcomes. This study will help neonatologists to prevent diarrhea from becoming a severe clinical condition.

**REFERENCES**

1. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS. How many child deaths can we prevent this year? *Lancet* 2003; 362: 65–71
2. Kosek M, Bern C, Guerrant RL. The global burden of diarrheal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ* 2003; 81: 197–204
3. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, Bauer CR, Donovan EF, Korones SB, L impart AK, Lemons JA, Oh W, Papile LA, Shankaran S, Stevenson DK, Tyson JE, Poole WK. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol* 2007; 196: 147.e1–147.e8
4. Parkash J, Das N. Pattern of admissions to neonatal unit. *J Coll Physicians Surg Pak* 2005; 15: 341–344
5. Sherman PM, Mitchell DJ, Cutz E. Neonatal enteropathies: defining the causes of protracted diarrhea of infancy. *J Pediatr Gastroenterol Nutr* 2004; 38: 16–26
6. Baiqui AH, Black RE, Yunus M, Hoque AR, Chowdhury HR, Sack RB. Methodological issues in diarrheal diseases epidemiology: definition of diarrhoeal episodes. *Int J Epidemiol* 1991; 20: 1057–1063
7. Guarino A, Albano F, Ashkenazi S, Gentrel D, Hoekstra JH, Shamir R, Szajewska H. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe. *J Pediatr Gastroenterol Nutr* 2008; 46 Suppl 2: S81-S122
8. Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atop disease in infants and children: the role of maternal dietary restriction, breast-feeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008; 121: 183–191
9. WHO, DDC. Persistent diarrhea in children. Geneva: WHO, 1985
10. WHO. The treatment of diarrhea: a manual for physicians and other senior health workers. Geneva: WHO, 2005: WHO/CDC/SER/80.2
11. Miceli Sopo S, Radzik D, Calvani M. The predictive value of specific immunoglobulin E levels for the first diagnosis of cow’s milk allergy. A critical analysis of pediatric literature. *Pediatr Allergy Immunol* 2007; 18: 575-582
12. Nyhan WL. Disorders of purine and pyrimidine metabolism. *Med Genet Metab* 2005; 86: 25–33
13. Berni Canani R, Cirillo P, Terrin G. Chronic and intractable diarrhoea. In: Guandalini S, editor. Essential pediatric gastroenterology, hepatology, and nutrition. New York: McGraw-Hill, 2005; 25–46
14. Kuschei C, Managing drug withdrawal in the newborn infant. *Semin Fetal Neonatal Med* 2007; 12: 127–133
15. de Lorigi F, Boeckxstaens GE, Benninga MA. Symptomatology, pathophysiology, diagnostic work-up, and treatment of Hirschsprung disease in infancy and childhood. *Curr Gastroenterol Rep* 2007; 9: 245–253
16. Minasian C, McCullah A, Bush A. Cystic fibrosis in neonates and infants. *Early Hum Dev* 2005; 81: 997-1004
17. Brosilow SW, Horwich AL. Urea cycle disorders. In: Scriber CR, Beaudet AL, Sly WS, Vale DT, editors. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill, 2001; 1909-1963
18. Fontana M, Zuin G, Pancheri P, Fusco FC, Tamburini A, Berni Canani R. Costs associated with outpatient diarrhoea in infants and toddlers: a nationwide study of the Italian Society of Paediatric Gastroenterology and Hepatology (SIGEPI). *Dig Liver Dis* 2004; 36: 523-527
19. Guandalini S. Acute Diarrhea. In: Guandalini S, editor. Essential Pediatric Gastroenterology, Hepatology and Nutrition. New York: McGraw-Hill, 2005: 15-23
20. Wang J, Cortina G, Wu SV, Tran R, Cho JH, Tsai MJ, Bailey TJ, Tamrakar M, Ament ME, Turem WR, Hill ID, Vargas JH, Gershuny C, Farmer DG, Reyon L, Martin MG. Mutant neurogenin-3 in congenital malabsorptive diarrhea. *N Engl J Med* 2006; 355: 270–280
21. Asher MI, Montefort S, Bjørkstøl B, Lai CK, Strachan DP, Weiland SK, Williams H. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368: 753-763
22. Host A, Koletzko B, Drehborg S, Muraro A, Wahn U, Agger P, Bresson JL, Hernell O, Lafolere H, Michaelson KF, Micheli JL, Rigo J, Weaver L, Heymans H, Strobæl S, Vandenpla J. Dietary products used in infants for treatment and prevention of food allergy. Joint Statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committee on Hypoallergenic Formula and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition. *Arch Dis Child* 1999; 81: 80–84
23. Zuppa AA, Cota F, Barberi S, De Luca D, Visintini F, Tororolo G. Antimicrobial strategies in the neonatal period in the prevention of allergies. *Pediatr Med Chir* 2002; 24: 45-52
24. Gleizes O, Desselberger U, Tatochkeno V, Rodrigo C, Salinan M, Mezner Z, Giaquinto C, Grimpel E. Nosocomial rotavirus infection in European countries: a review of the epidemiology, severity and economic burden of hospital-acquired rotavirus disease. *Paediatr Infect Dis J* 2006; 25: S12-S21
25. Elliott EF. Acute gastroenteritis in children. *BMJ* 2007; 334: 35-40
26. Thomas PD, Forbes A, Green J, Howdle P, Long R, Playford R, Sheridan M, Stevens R, Valori R, Walters J, Addison GM, Hill P, Brydon G. Guidelines for the investigation of chronic diarrhoea, 2nd edition. *Gut* 2003; 52 Suppl 5: v1-v15

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