RISK FACTORS FOR SEVERE AND/OR PERSISTENT DISEASE

**Table 1.1. Is there a relationship between severe or persistent diarrhea and etiology?**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study**  **type** | **Period of observation** | **QoS** | **Country** | **In/Out**  **Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU n/N** | **ITT** | **Outcomes measures** | **RCT n** | **Effect**  **measure** | **Effect**  **size**  **(95% CI)** | **Comments** |
| Shai S, 2013 | Surveillance system | Between April 2009 and March 2011 | + | Germany | Inpatients | N= 130 children younger than 17 years with very severe RV gastroenteritis (101 were verified) | — | Survey on hospital discharge data | — | — | No | No. of severe RV gastroenteritis (N° nosocomial) | — | Number | 17/101 | RV infection can have a life-threatening course |
| Incidence of very severe RV diarrhea in children  less than 5 years of age; | Incidence rates | 1.2/100,000/year  ( 0.9–1.4/100,000) |
| Valentini D, 2013 | Prospective cohort study | March 2010 to April 2011 | + | Italy | Inpatients | N=232 between 1 month and 16 years of age admitted for AGE | — | Collection of clinical data and stool samples | Coinfections vs Monoinfections | 232/275 | No | Max. no of diarrhea stools/24 h (≥6) | — | OR (95%CI) | 8.79 (3.32;23.28) p <0.001 | Coinfection with different pathogens is associated with a more severe course of symptoms |
| Duration of diarrhea (days) (≥5) | 3.81 (1.47;9.86) p= 0.006 |
| Duration of vomiting (days) (≥3) | 7.11 (2.74;18.42) p<0.001 |
| Fever (≥38°) | 17.78 (2.32;136.17) p=0.006 |
| Severe dehydration (%) | 28.70 (3.04;270.6) p=0.003 |
| Friesema IH, 2012 | Case-control study | May 2008 to November 2009 | + | The Netherlands | Inpatients | N=144 (+63 controls) children 0 -15 yr (73% being <2 yr), admitted for severe AGE | — | Collection of clinical data and stool samples | Diarrhea vs not diarrhea | 143/144 | No | Pathogens isolated from children (0-1yr) hospitalized with gastroenteritis (N=51) | — | Rates | Virus: 50/51(98%) [RV 65%, Adeno 31%, NV 23%]; Bacteria 12/51 (23%) [Campylobacter 4%, EPEC 16%, EAEC 4%]; Parasites 0% | Importance of viral pathogens, especially RV, in hospitalizations of children with gastroenteritis. |
| Pathogens isolated from children (1-2yr) hospitalized with gastroenteritis (N=23) | Rates | Virus: 21/23(91%) [RV 70%, Adeno 13%, NV 10%]; Bacteria 7/23 (30%) [Salmonella 10%, EPEC 13%]; Parasites 10% |
| Pathogens isolated from children (2-4yr) hospitalized with gastroenteritis (N=16) | Rates | Virus: 7/16 (44%) [RV 31%, Adeno 12%, NV 7%]; Bacteria 8/16 (50%) [Salmonella 31%]; Parasites 31% |
| Pathogens isolated from children (>4yr) hospitalized with gastroenteritis (N=6) | Rates | Virus: 1/6 (17%) [RV 17%]; Bacteria 4/6 (67%) [Salmonella 50%]; Parasites 20% |
| Consumption of eggs | OR (95%CI) | 4.25; (1.06–17.06) p<0.05 |
| Consumption of fish | OR (95%CI) | 0.08; (0.01–0.97) p<0.05 |
| Oldak E, 2012 | Prospective cohort study | July 2009 and June 2010 | + | Poland | Inpatients | N=242 children <5yr of age admitted for AGE | — | Collection of clinical data and stool samples | RV vs NV infections | 242/242 | Yes | Isolation of pathogens | — | Rates | RV 51/242 (21.1%) vs NV 35/242 (14.5%) | NV are a relevant cause of acute, community acquired gastroenteritis in Polish children |
| Duration of diarrhea (≥6 days) | Rates | RV 11/51 (21.6%) vs NV 4/35 (11.4%)p= 0.17 |
| Severity score (severe) | Rates | RV 22/51 (43%) vs NV 5/35 (14.3%) p<0.01 |
| Ogilvie I, 2012 | Scoping review | — | — | Western Europe | Inpatients | 76 studies from 16 countries on European children <5 yr of age with community-acquired and nosocomial diarrhea | — | — | Community acquired vs Nosocomial diarrhea | — | — | Patients with severe nosocomial RVGE in France, Italy, Spain and the UK | 2 (n=3734; n=251) | Rates (%) | 42.6% | RV gastroenteritis is a common disease associated with significant morbidity and costs across Western Europe |
| Patients with severe nosocomial RVGE in Austria, Germany, and Switzerland | Rates (%) | 24.4%, 30.2% and 40% |
| Severe dehydration in children with community-acquired vs nosocomial gastroenteritis | 2 (Ireland n=663; Sweden n=984) | Rates (%) | 80% vs 55% (Ireland) 10.8% vs 0.8% (Sweden) |
| Mortality due to nosocomial RVGE (< vs > 12mo) | 1(n=10,990) | Incidence rates | 0.74 per 100,000 vs 0.16 per 100,000 |
| Lorrot M, 2011 | Prospective cohort study | November 2001 to May 2004 | + | France | Inpatients | N=457 children 0-15 yr of age admitted for severe AGE (Patients with chronic diarrhea >10 days were excluded) | — | Collection of clinical data and stool samples | RV vs NV infections | 457/457 | Yes | Isolation of pathogens (0-6mo) N=177 | — | Rates | RV 77 (43.5%) NV 15 (8.5%) Bacteria 8 (4%) | NV are the second leading causative agent of gastroenteritis in hospitalized young children and such infections are less severe than those caused by RV |
| Isolation of pathogens (6-12mo) N=106 | Rates | RV 63 (59.4%) NV 10 (9.4%)Bacteria 2 (2%) |
| Isolation of pathogens (12-24mo) N=102 | Rates | RV 59 (57.8%) NV 8 (7.8%) Bacteria 4 (4%) |
| Isolation of pathogens (24-60mo) N=49 | Rates | RV 22 (44.9%) NV 3 (6.1%) Bacteria 6 (12%) |
| Isolation of pathogens (>60mo) N=23 | Rates | RV 4 (17.4%) NV 2 (8.7%) Bacteria 5 (20%) |
| Length of hospitalization (days) (RV vs NV) | Median ± SD | 3.02 (1.54) 1.85 (1.03) p<0.001 |
| Severity score (Vesikari) RV vs NV | Median ± SD | 12.6 (2.92) 10.47 (2.83) p<0.001 |
| Intravenous rehydration (%) RV vs NV (N=261, mixed infections excluded) | Rates | 172 (77.13%) 21 (55.26%) p=0.005 |
| Mrukowicz JZ, 1999\* | Retrospective cohort study | 1994-96 | + | Poland | Inpatients | N=953 children hospitalized for AGE | — | Hospital discharge data | RV vs not RV | — | — | Severe clinical conditions (Vesikari score >11) in children with RV associated diarrhea | — | Rates | 94% (61.6% of cases younger than five years) p<0.001 | RV is a leading aetiological agent of severe gastroenteritis in young children in Poland and that the burden of this infection is significant (1999) |
| Duration of hospitalization (days) | Median ± SD | 9.5 d (+/-9.8 d) |
| \*Ogilvie 2011 (systematic review) cited this study and concluded that data on the burden of RVGE in terms of mortality, morbidity and economic burden is limited for Central and Eastern Europe. | | | | | | | | | | | | | | | | |
| Rimoldi SG, 2011 | Prospective cohort study | January 2008 to October 2009 | + | Italy | Inpatients | N=273 children, suffering from acute gastroenteritis, in the age range from 0 to 222 mo | — | Clinical data and stool samples | Different viruses-associated diarrhea | — | — | Severe clinical conditions (Vesikari score) in children 1-18mo with diarrhea | — | Median ± SD | RV 2.9±2.8 vs NV 3.1±3.5 Boca 11.5±4.5 Adeno 0.2 (Adeno vs others p<0.001) | The severity of AdV-associated infection was lower than for NoV, HRV and HBoV. |
| Gimenez-Sanchez F, 2010 | Prospective cohort study | January, February and March of 2006 | + | Spain | Inpatients | N=1192 children <5yr of age | — | Clinical data and stool samples | RV (n = 584) vs not RV (n = 503) | — | — | Severe clinical conditions (Merck scale) in children <5yr with diarrhea | — | Median ± SD | 14.2 (3.8) vs 11.0 (4.2) p<0.001 | RV is the primary causal agent of AGE in children under the age of 2 years in Spain and that it produces a more severe manifestation |
| Severe clinical conditions (Merck scale) in children <5yr with diarrhea | Rates | 30% vs 12% p<0.001 |
| Severe dehydration (degree >6%) | Rates | 51 (20.2%) 10 (11%) NS |
| Wiegering V, 2011 | Retrospective cohort study | April 1, 2005 to May 31, 2008 | + | Germany | Inpatients | 650 charts of children with AGE. 262 (43.8%) had RV, 188 (31.4%) NV, 58 (9.7%) AV, 47(7.9%) Salmonella. | — | — | Comparisons between all viral infections and Salmonella infection | — | — | Duration of diarrhea (all viral vs Salmonella) | — | Mean number ±SD | 3.4±0.1 vs 6.1±0.4, p<0.001 | Children with viral infection had significanlty more respiratory associated symptoms and vomiting, but less episodes of diarrhea and total duration of diarrhea when compared to children with Salmonella infection. |
| Diarrhea events (all viral vs Salmonella) | mean number ±SD | 3.8±0.1 vs 10.4±0.5, p<0.001 |
| Vomiting events (all viral vs Samonella) | mean number ±SD | 2.6±0.2 vs 1±0.4, p<0.001 |
| Airway inflammation score (all viral vs Salmonella) | mean number ±SD | 1.8±0.1 vs 0.6±0.3; p<0.001 |
| Gastroenteritis score (all viral vs Samonella and RV vs AV and NV) | mean number ±SD | All viral 12.7±0.1 vs Salmonella 13.4±0.5, p=NS; RV 13.5± 0.2 vs AV and NV 11.9± 0.2 and 11.5±0.4 , p<0.001 |
| Muhsen K, 2009 | MA | 1970s through 2009 | ++ | Developing countries | Inpatients and Outpatients | N=17030 mostly <6yr of age (1 case-control study 0-14 yr; 1 case-control study all ages); 13 case-control studies and 2 cohort studies | — | Detailed clinical history and laboratory investigations | Acute vs persistent diarrhea vs controls | — | — | Association between Giardia Lamblia and PD | 4 case-control, 1 cohort study | OR (95%CI) | 3.18 (1.50-6.76) p<0.0001 | G. lamblia was not associated with acute diarrhea. However, limited data suggest that initialGiardia infections in early infancy may be positively associated with diarrhea. Meta-analysis of 5 persistent diarrhea studies showed a positive link with Giardia |
| Association between Giardia Lamblia and AD | OR (95%CI) | 0.60 (0.38-0.94) p=0.03 |
| Abba K, 2009 | Systematic review | Search date: May 20, 2008 (none after 2000) | ++ | Developing countries | Inpatients and Outpatients | N=3832 children <6yr of age | — | Sample stools | Persistent Diarrhea vs no diarrhea | — | — | RV |  | Weighted mean percentage | PD 5% vs no diarrhea 3% | There is no evidence that any particular pathogen or type of pathogen is associated with persistent diarrhea in children under the age of six in low and middle income countries. There is therefore no evidence to justify routine antimicrobial use for children with persistent diarrhea of unknown cause, in keeping with current guidelines. |
| Enteric Adenovirus |  | Weighted mean percentage | PD 5% vs no diarrhea 1% |
| Campylobacter |  | Weighted mean percentage | PD 6% vs no diarrhea 8% |
| Shigella | 7 (680 cases and 1021 controls) | Weighted mean percentage | PD 4% vs no diarrhea 2% |
| Salmonella | 6 (510 cases and 857 controls) | Weighted mean percentage | PD 4% vs no diarrhea 0% |
| Vibrio Cholerae | 3 (405 cases and 813 controls) | Weighted mean percentage | PD 0% vs no diarrhea 1% |
| EPEC | 7 (550 cases and 604 controls) | Weighted mean percentage | PD 41% vs no diarrhea 30% |
| EHEC | 2 (143cases and 143 controls) | Weighted mean percentage | PD 0% vs no diarrhea 0% |
| Giardia | 8 (688cases and 1062 controls) | Weighted mean percentage | PD 10% vs no diarrhea 7% |
| Cryptosporidium | 0 |  |  |
| Entamoeba histolytica | 5 (688 cases and 1063 controls) | Weighted mean percentage | PD 2% vs no diarrhea 3% |
| Ochoa TJ, 2009 | Prospective cohort study | September-2006 and December-2007 | + | Perù | Outpatients | N=1034 children from 2 to 12 months of age | Controls were selected randomly\* | A field worker visited control children at home to collect stool samples. A field worker visited children with diarrhea at home at least once a week until the episode ended. | Diarrhea vs not diarrhea | 992/1034 | No | Duration of diarrhea in accordance to age\* | — | Mean±SD | 7.1 ± 6.1 (children < 6mo) vs 4.9 ± 3.8 (children ≥ 6mo) | Persistent diarrhea was more frequent in infants < 6mo of age. No specific bacterial species was associated with persistent diarrhea |
| Persistent diarrhea\*\* | Rates | 13.5% (children < 6mo) vs 3.6% (children ≥ 6mo) |
| Isolation of EAEC in stool coltures in children with persistent diarrhea | Rates | 14.1% (12/85) |
| Isolation of EPEC in stool coltures in children with persistent diarrhea | Rates | 7.9% (3/38) |
| Isolation of DAEC in stool coltures in children with persistent diarrhea | Rates | 15% (3/20) |
| Isolation of ETEC in stool coltures in children with persistent diarrhea | Rates | 18.8% (3/16) |
| Isolation of Campylobacter in stool coltures in children with persistent diarrhea | Rates | 2.9% (3/103) |
| Isolation of Roatvirus in stool coltures in children with persistent diarrhea | Rates | 1.2% (1/85) |
| Isolation of mixed pathogens in children with persistent diarrhea | Rates | 3.7% (4/109) |
| \*not specified how  \*\*diarrhea lasting > 14 days was considered persistent | | | | | | | | | | | | | | | | |
| Rivera FP, 2010 | Prospective cohort study | 26 months (September 2006-July 2008) | + | Perù | Outpatients | N=1873 (1129 cases and 744 controls) children 2-24 months of age | — | Collection of stool samples | Diarrhea vs not diarrhea | NO | No | Clinical and epidemiological characteristics of ETEC diarrhea | — | Rates | Isolated ETEC strains in cases (60/1129; 5.3%) and controls (32/744 ; 4.3%) | The duration of diarrhea caused by ETEC-LT strains tended to be longer (up to 24 days). |
| Persistent diarrhea\* (single ETEC strain, N=38): 11% |
| Persistent diarrhea (all ETEC isolates N=60): 8% |
| Presence of ST (heat-stable toxin) and LT (heat-labile toxin) | Rates | Persistent diarrhea (ETEC-LT strain, N=31): 6% |
| Persistent diarrhea (ETEC-ST isolates N=15): 0%\* |
| \*diarrhea lasting > 14 days was considered persistent | | | | | | | | | | | | | | | | |
| Moore SR, 2010 | Prospective cohort study | 127 months (August 1989-March 2000) | ++ | Brazil | Outpatients | N=414 children ≤ 5 years of age and newborns between August 1989 and March 2000 | — | Nurses visit home of each newborn child 3 times a week for the first 45 mo. Then twice a week. Children with diarrhea were visited daily | Diarrhea vs not diarrhea | 414/414 | Yes | Isolation of Cryptosporidium species in stool coltures | — | Rates | 12/98 (12.2%) vs 15/289 (5.2%) | Shigella and Cryptosporidium are significantly associated with prolonged episodes\* of diarrhea, and both of them are related with growth faltering, especially in tropical and developing regions. Ascaris and multiple pathogens were found to be more frequent in controls than in children with persistent diarrhea\*\*, due to a possible mitigating effect on the duration of intestinal infections by altering immune response. |
| Isolation of Ascaris species in stool coltures | Rates | 7/132 (5.3%) vs 61/442 (13.8%) |
| Isolation of bacteria in stool coltures (all species) | Rates | 16/132 (12.1%) vs 8/442 (1.8%) |
| Isolation of Shigella species in stool coltures | Rates | 6/132 (4.5%) vs 5/440 (1.1%) |
| Fecal Leukocytes | Rates | 67/132 (50.8%) vs 28/442 (6.3%) |
| Lactoferrin | Rates | 27/35 (77.1%) vs 47/95 (49.5%) |
| Multiple pathogens | Rates | 26/98 (26.5%) vs 82/194 (40.7%) |
| \*Prolonged diarrhea= 7-13th day  \*\*Diarrhea lasting > 14 days was considered persistent | | | | | | | | | | | | | | | | |
| Allison GM, 2011 | Case-control study | — | + | Bangladesh | Inpatients | N=92 children from 15 days to 60 mo of age with diarrhea (46 controls with negative stool coltures for Cryptosporidium; subsequently 7 controls were founf positive for PCR and were thus considered cases) | — | Detailed clinical history and laboratory investigations | Positive for Cryptosp. vs Negative for Cryptosp. | 50/92 (33 cases) - 3 weeks | No | N° of persistent diarrhea\* (Cases vs controls) | — | Rates | 37% (18/47) vs 0% (0/39) | In Bangladesh, where cryptosporidiosis is endemic, it is associated with persistent diarrhea\*. Although the dominant antibody response appears to be targeted to conserved peptide epitopes of g15, antibody responses to polymorphic, species- or subtype specific epitopes may also occur. These findings have implications for development of gp15 as a putative vaccine candidate |
| Antibody (IgG) levels to Cryptosporidium parvum gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | 68 [28; 110] vs 4 [0; 10] |
| Antibody (IgM) levels to Cryptosporidium parvum gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | −29 [–97; 13] vs 0 [–; 0] |
| Antibody (IgA) levels to Cryptosporidium parvum gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | 83 [19; 243] vs 40 [3; 61] |
| Antibody (IgG) levels to Cryptosporidium hominis gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | 62 [19; 124] vs 0 [–7; 7] |
| Antibody (IgM) levels to Cryptosporidium hominis gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | 2 [–20; 20] vs 0 [–7; –8] |
| Antibody (IgA) levels to Cryptosporidium hominis gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | 50 [10; 138] vs 4 [–1; 24] |
| \*Diarrhea lasting > 14 days was considered persistent | | | | | | | | | | | | | | | | |

AGE= Acute gastroenteritis; AV= Adenovirus; DAEC= diffusely adherent *Escherichia coli*; EAEC=Enteroaggregative *Escherichia coli*; EPEC=enteropathogenic *Escherichia coli*; ETEC= Enterotoxigenic *Escherichia coli*; LT=heat-labile toxin; NV= Norovirus; OR=odd ratio; QoS=Quality of Study; RV=Rotavirus; RVGE= Rotavirus gastroenteritis; SD=standard deviation; ST= heat-stable toxin.

**1.2. Is there a relationship between host-related factors and risk of severe or persistent diarrhea?**

**Table 1.2.1. Risk factor: younger age**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Period of observation** | **QoS** | **Country** | **In/Out Patients** | **Population** | **Intervention** | **Comparison** | **FU n/N** | **ITT** | **Outcomes measures** | **Effect measure** | **Effect size** | **Comments** |
| Friesema IH, 2012 | Case-control study | May 2008 to November 2009 | + | The Netherlands | Inpatients | N=144 (+63 controls) children 0 -15 yr (73% being <2 yr), admitted for severe AGE | Collection of clinical data and stool samples | Diarrhea vs not diarrhea | 143/144 | No | Pathogens isolated from children (0-1yr) hospitalized with gastroenteritis (N=51) | Rates | Virus: 50/51(98%) [RV 65%, Adeno 31%, NV 23%]; Bacteria 12/51 (23%) [Campylobacter 4%, EPEC 16%, EAEC 4%]; Parasites 0% | Importance of viral pathogens, especially RV, in hospitalizated children with gastroenteritis |
| Pathogens isolated from children (1-2yr) hospitalized with gastroenteritis (N=23) | Rates | Virus: 21/23(91%) [RV 70%, Adeno 13%, NV 10%]; Bacteria 7/23 (30%) [Salmonella 10%, EPEC 13%]; Parasites 10% |
| Pathogens isolated from children (2-4yr) hospitalized with gastroenteritis (N=16) | Rates | Virus: 7/16 (44%) [RV 31%, Adeno 12%, NV 7%]; Bacteria 8/16 (50%) [Salmonella 31%]; Parasites 31% |
| Pathogens isolated from children (>4yr) hospitalized with gastroenteritis (N=6) | Rates | Virus: 1/6 (17%) [RV 17%]; Bacteria 4/6 (67%) [Salmonella 50%]; Parasites 20% |
| Lorrot M, 2011 | Prospective cohort study | November 2001 to May 2004 | + | France | Inpatients | N=457 children 0-15 yr of age admitted for severe AGE (Patients with chronic diarrhea >10 days were excluded) | Collection of clinical data and stool samples | Comparing children basing on clinical conditions and age | 457/457 | Yes | Isolation of pathogens (0-6mo) N=177 | Rates | RV 77 (43.5%) NV 15 (8.5%) Bacteria 8 (4%) | Main role of RV in hospitalized gastroenteritis among Frenchchildren less than 2 years of age |
| Isolation of pathogens (6-12mo) N=106 | Rates | RV 63 (59.4%) NV 10 (9.4%)Bacteria 2 (2%) |
| Isolation of pathogens (12-24mo) N=102 | Rates | RV 59 (57.8%) NV 8 (7.8%) Bacteria 4 (4%) |
| Isolation of pathogens (24-60mo) N=49 | Rates | RV 22 (44.9%) NV 3 (6.1%) Bacteria 6 (12%) |
| Isolation of pathogens (>60mo) N=23 | Rates | RV 4 (17.4%) NV 2 (8.7%) Bacteria 5 (20%) |
| Lenght of hospitalization (days) in children 0-6 mo (RV vs NV) | Median ± SD | RV 3.26 (±1.84) NV 2.17 (±1.06) p=0.0293 |
| Lenght of hospitalization (days) in children 6-24 mo (RV vs NV) | Median ± SD | RV 2.90 (±1.39) NV 1.78 (±1.06) p=0.0013 |
| Lenght of hospitalization (days) in children >24mo (RV vs NV) | Median ± SD | RV 2.85 (±1.26) NV 1.2 (±0.45) p=0.0078 3.02 |
| Lenght of hospitalization (days) (RV vs NV) | Median ± SD | 3.02 (1.54) 1.85 (1.03) p<0.001 |
| Severity score (Vesikari) in children 0-6 mo (RV vs NV) | Median ± SD | NS |
| Severity score (Vesikari) in children 6-24 mo (RV vs NV) | Median ± SD | 13.48 (±2.54) 11.39 (±3.05) p<0.002 |
| Severity score (Vesikari) in children 24 mo (RV vs NV) | Median ± SD | 12.88 (±2.94) 8.8 (±2.28) p=0.007 |
| Intravenous rehydration (%) in children 0-6mo; RV vs NV (N=261, mixed infections excluded) | Rates | NS |
| Intravenous rehydration (%) in children 6-24mo; RV vs NV (N=261, mixed infections excluded) | Rates | 107 (87.7%) 12 (66.67%) p=0.031 |
| Intravenous rehydration (%) RV vs NV (N=261, mixed infections excluded) | Rates | NS |
| Moore SR, 2010 | Prospective cohort study | 127 months (August 1989-March 2000) | ++ | Brazil | Outpatients | N=414 children ≤ 5 years of age and newborns between August 1989 and March 2000 | Nurses visit home of each newborn child 3 times a week for the first 45 mo. Then twice a week. Children with diarrhea were visited daily | Diarrhea vs not diarrhea | 414/414 | Yes | Age-specific attack rates | Rates | Total, AD, and PD all peaked at 6-12 months of age (5.15, 4.22, and 0.68 episodes per child-year, respectively). | Infants with Prolonged diarrhea have a higher risk of developing PD in later childhood. \* |
| Children with PD who experienced also ProD episode; children in the first year of life | Rates | 57/71 (80.3%); 30/57 (52.6%) |
| Risk to develop PD in children who experienced ProD in their first year of life | OR | 2.2, 95% CI; [1.32-3.54], P=0.002 |
| \*Prolonged diarrhea= 7-13th day, diarrhea lasting > 14 days was considered persistent | | | | | | | | | | | | | | |
| Pathela P, 2006 | Prospective cohort study | 1993-1996 | + | Bangladesh | Outpatients | N= 252 children < 5yr of age | Door-to-door census conducted by community health workers | Age groups | 244/252 | YES | Risk to develop PD (n° episodes per child year) in children 0-5 mo | Incidence Rates | 0.4 (45); p < 0.001 | Significant differences between 0 /5-month age groups and all other age groups |
| Risk to develop PD in children 18-23 mo | OR (95%CI) | 0.59 (0.48 /0.73); p<0.001 | When adjustment for other covariates was done, the relative odds of diarrhea in the older age groups were lower compared to the youngest age group. |
| Pereira AL, 2007 | Case-control study | Not specified | + | Brasil | Inpatients | N=261 (134 cases and 127 controls) ≤ 5 years of age; controls were defined as children who did not present with diarrhea in the 4 weeks before sample collection | Collection of stool samples | Acute vs persistent diarrhea vs controls | — | YES | Detection of EAEC virulance markers in fecal samples | Rates | CVD432+ : Acute (11.1%) Persistent (23.9%%) Controls (9.7%) in children < 12 mo of age vs Acute (6.7%) Persistent (20.9%) Controls (12.7%) in children > 12 mo of age | The age-stratified analyses showed that different CVD432-related genotypes were associated with persistent diarrhea in the 2 groups studied. CVD432+ strains were associated with persistent diarrhea in children <12 months of age, whereas, inchildren >12 months of age, the genotype associated with protracteddiarrhea was CVD432+EAST1+ |
| Detection of EAEC specific genotypes in fecal samples | Rates | CVD432+ : Acute (6.8%) Persistent (15.2%%) Controls (3.8%) in children < 12 mo of age vs Acute (3.8%) Persistent (9.3%) Controls (8.1%) in children > 12 mo of age |
| Rates | EAST1+ : diarrhea (13%) and controls (4%) in children 6-12 mo of age vs diarrhea (8.2%) and controls (4.2%) in children < 6 mo of age |
| Mukhopadhyay C, 2007 | Case-control study | 71 months (April 1998-March 2004) | + | Nepal | Inpatients | N=508 < 5 years of age (253 children with persistent diarrhea, 155 with acute diarrhea and 100 controls) | Collection of stool samples | Persistent diarrhea vs acute diarrhea vs controls\* | — | NO | Rates of intestinal protozoal infections in age groups (6-11; 12-23; 24-35; 36-60) | Rates | 13.8%, 19.3%, 25.2%, and 33.2% | In each age group, the rate of infection was significantly higher than the previous age group. |
| \*diarrhea lasting > 14 days was considered persistent | | | | | | | | | | | | | | |
| Moyo SJ, 2007 | Prospective cross-sectional study | December 2005 to February 2006. | + | Tanzania | Inpatients | N=218 children <5yr of age, admitted for acute/persistent diarrhea | Detailed clinical history and laboratory investigations | Age groups | — | YES | Detection of EAEC strains in children with acute/persistent diarrhea | Rates | EAEC: 0-6mo 27.5%; 7-12mo 15.6%; 13-24 6%; 25-60mo 7.4% | EAEC and EPEC were significantly more prevalent among the age group 0–6 months |
| Detection of EPEC strains in children with acute/persistent diarrhea | Rates | EPEC: 0-6mo 13.7%; 7-12mo 3%; 13-24 3%; 25-60mo 0% |
| Ochoa TJ, 2009 | Prospective cohort study | September-2006 to December-2007 | + | Perù | Outpatients | N=1034 children from 2 to 12 months of age | A field worker visited control children at home to collect stool samples. A field worker visited children with diarrhea at home at least once a week until the episode ended. | Diarrhea vs not diarrhea | 992/1034 | NO | Duration of diarrhea in accordance to age | Mean±SD | 7.1 ± 6.1 (children < 6mo) vs 4.9 ± 3.8 (children ≥ 6mo); p< 0.0001 | Persistent diarrhea was more frequent in infants < 6mo of age.\*\* |
| Persistent diarrhea | Rates | 13.5% (children < 6mo) vs 3.6% (children ≥ 6mo); p< 0.0001 |
| Passive surveillance diarrhea incidence, episodes/child/year | Incidence Rates | 1.26 (children < 6 mo) vs 0.85 (children ≥ 6mo); p=0.0018 |
| Isolation of RV in children with persistent diarrhea <6mo and ≥ 6mo of age | Rates | 24/434 (5.9%) vs 137/530 (28.1%) |
| \*not specified how \*\*diarrhea lasting > 14 days was considered persistent | | | | | | | | | | | | | | |
| Rivera FP, 2010 | Prospective cohort study | 26 months (September 2006-July 2008) | + | Perù | Outpatients | N=1873 (1129 cases and 744 controls) children 2-24 months of age | Collection of stool samples | Diarrhea vs not diarrhea | — | NO | Clinical and epidemiological characteristics of ETEC diarrhea | Rates | Isolated ETEC strains in cases (3.4%) and controls 1.2%) < 12 mo of age vs cases (14.5%) and controls (8.4%) > 12 mo of age | The incidence of ETEC diarrhea in our sample was significantly more frequent in children > 12 months of age than in younger children\* |
| \*diarrhea lasting > 14 days was considered persistent | | | | | | | | | | | | | | |
| Umamaheswari B, 2010 | Case-control study | 17 mo, November 2000-April 2002 | + | India | Inpatients | N=120 children from 1 mo. to 10 yr. of age with persistent\* or acute diarrhea | Detailed clinical history and laboratory investigations | Persistent vs acute diarrhea | 55/120 - 3 months | YES | Children with PD and AD < 1yr | Rates | PD 30/60(50%) vs AD 37/60 (61.7%) | Persistent diarrhea was more frequent in infants <5yr of age\* |
| Children with PD and AD 1-5yr | Rates | PD 29/60(48.4%) vs AD 22/60 (36.7%) |
| Children with PD and AD >5yr | Rates | PD 1/60(1.6%) vs AD 1/60 (1.6%) |
| Children with PD who died (all <5yr of age) | Rates | 5/60 (8.3%) |
| \*diarrhea lasting > 14 days was considered persistent | | | | | | | | | | | | | | |
| Sutra S, 2012 | Cross-sectional study | 2011 | + | Thailand | Inpatients | Children < 5yr of age | The authors investigated the number of OPD visits (756,552; 1:5 ), IPD (124,403 admissions; 1:30) | — | — | Yes | Persistent diarrhea | N° of episodes and rates | 202 episodes (1.6 per 1,000 admissions) | age, sepsis, anemia, chronic diseases, malnutrition and HIV are related to persistent diarrhea |
| Risk factors related to PD | Multivariate analysis | age, sepsis, anemia, chronic diseases, malnutrition and HIV. |
| Strand TA, 2012 | Prospective cohort study | June 1998 to September 2000 | + | Nepal | Outpatients | N=335 children 6-35 mo of age | Study physicians undertook the initial interview and clinical examination, while trained field workers visited the homes for follow-up every fifth day until recovery | — | 334/335 | — | Risk of persistent diarrhea in children 6-11 mo of age | OR (95%CI) | 17.0 (3.5, 83.1) | The odds of prolonged illness was 9.3-fold higher if a child was not breastfed, this effect was not modified by age. This is an argument for recommending breastfeeding, also beyond infancy in populations where childhood diarrhea is common. |
| Risk of persistent diarrhea in not breast fed children | OR (95%CI) | 9.3 (2.4, 35.7) |

AD= Acute diarrhea; AGE= Acute gastroenteritis; EAEC=Enteroaggregative *Escherichia coli*; EPEC=enteropathogenic *Escherichia coli*; ETEC= Enterotoxigenic *Escherichia coli*; NV= Norovirus; PD= Persistent diarrhea; ProD= Prolonged diarrhea; QoS=Quality of Study; RV=Rotavirus; SD=standard deviation.

**Table 1.2.2. Risk factor: Feeding practice**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Period of observation** | **QoS** | **Country** | **In/Out Patients** | **Population** | **Intervention** | **Comparison** | **FU n/N** | **ITT** | **Outcomes measures** | **Effect measure** | **Effect size** | **Comments** |
| Morales E, 2012 | Population-based cohort | 2 years | + | Spain | Outpatients | 580 children (131 never breastfed, 75 brestfed for less 2 m, 97 for 2-4m, 215 for 4-6 m, 62 for more than 6 m) | Active surveillance and evaluation of risk of Wheezing, PRTIs, atopic eczema and gastroenteritis |  |  | No | Incidence of AGE from birth to 6 months and 7-14 months and incidence or recurrent AGE | OR (95%CI) | Risk of AGE 4-6m = 0.34 (0.18-0.64) Risk of recurrency 4-6m= 0.37 (0.17-0.77) | Risk of gastroenteritis in other age ranges seems to be not significantly reduced by brestfeeding. |
| Moore SR, 2010 | Prospective cohort study | 127 months (August 1989-March 2000) | ++ | Brazil | Outpatients | N=414 children ≤ 5 years of age and newborns between August 1989 and March 2000 | Nurses visit home of each newborn child 3 times a week for the first 45 mo. Then twice a week. Children with diarrhea were visited daily | Diarrhea vs not diarrhea | 414/414 | Yes | Age at weaning from exclusive breastfeeding | Linear correlation | positive correlation with age at first ProD episode (Spearman's ρ=0.309; P=0.005) | early weaning was associated with earlier onset of Prolonged diarrhea\* |
| \*Prolonged diarrhea= 7-13th day | | | | | | | | | | | | | | |
| Morrow AL, 2005 | Prospective cohort study | 1988–1991 | + | US | Outpatients | N=93 children up to 2yr of age and their mothers | Mother–infant pairs were followed from birth up to 2 y postpartum with weekly collection of infant stool and infant feedingand illness data | Groups (low, intermediate, high) of specific and total 1,2-linked milk oligosaccharides (mmol/L) | 93/93 | Yes | Consumption of high levels of 2 -FL as a percentage of milk oligosaccharide (protection against Campylobacter) | Poisson regression | p= 0.004 | Breast-feeding conveys natural anti-infective compounds tothe child and is the most effective intervention currentlyknown for preventing morbidity and mortality, caused byinfectious disease in young children |
| Consumption of high levels of LDFH-I as a percentage of milk oligosaccharide (protection against Calicivirus) | Poisson regression | p= 0.012 |
| Consumption of high levels of total 2-linked oligosaccharide as a percentage of milk oligosaccharide (protection against severe diarrhea) | Poisson regression | p<0.0001 |
| Content of 2-linked oligosaccharides in children whocontracted ST-associated diarrhea while breast-feeding | Means±SD | Children with diarrhea and ST-coli infection: 3.9 ± 0.7 SE (n = 4); children without diarrhea infected by ST-coli (7.6 ± 1.0, n= 43); uninfected controls (7.5 ± 1.0,n = 46) (P <0.01) |
| Manger MS, 2011 | Prospective cohort study | February 1998-September 2000 | + | India | Outpatients | N=2296 children 6-30 mo of age | Detailed clinical history and laboratory investigations | — | 2296/2296 | Yes | Risk for PD in breast-fed children | OR (95%CI) | 0.56 (0.37, 0.83) p= 0.004 | Breast feeding is protective against PD |
| Allison GM, 2011 | Case-control study | — | + | Bangladesh | Inpatients | N=92 children from 15 days to 60 mo of age with diarrhea (46 controls with negative stool coltures for Cryptosporidium; subsequently 7 controls were found positive for PCR and were thus considered cases) | Detailed clinical history and laboratory investigations | Positive for Cryptosp. vs Negative for Cryptosp. | 50/92 (33 cases) - 3 weeks | No | N° of persistent diarrhea\* (Cases vs controls) | Rates | 37% (18/47) vs 0% (0/39) | In Bangladesh, where cryptosporidiosis is endemic, it is associated with persistent diarrhea. Although the dominant antibody response appears to be targeted to conserved peptide epitopes of g15, antibody responses to polymorphic, species- or subtype specific epitopes may also occur. These findings have implications for development of gp15 as a putative vaccine candidate\* |
| Antibody (IgG) levels to Cryptosporidium parvum gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | 68 [28; 110] vs 4 [0; 10] |
| Antibody (IgM) levels to Cryptosporidium parvum gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | −29 [–97; 13] vs 0 [–; 0] |
| Antibody (IgA) levels to Cryptosporidium parvum gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | 83 [19; 243] vs 40 [3; 61] |
| Antibody (IgG) levels to Cryptosporidium hominis gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | 62 [19; 124] vs 0 [–7; 7] |
| Antibody (IgM) levels to Cryptosporidium hominis gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | 2 [–20; 20] vs 0 [–7; –8] |
| Antibody (IgA) levels to Cryptosporidium hominis gp15 (Initial-follow-up period) | Median [25th-75th percentiles] | 50 [10; 138] vs 4 [–1; 24] |
| \*diarrhea lasting > 14 days was considered persistent | | | | | | | | | | | | | | |

AGE= acute gastroenteritis; PD= Persistent diarrhea; ProD= Prolonged diarrhea; QoS=Quality of Study.

**Table 1.2.3. Chronic diseases and Immune deficits**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Period of observation** | **QoS** | **Country** | **In/Out Patients** | **Population** | **Intervention** | **Comparison** | **FU n/N** | **ITT** | **Outcomes measures** | **RCT n** | **Effect measure** | **Effect size** | **Comments** |
| Sugata K, 2012 | Prospective cohort study | Between September 2004 and February 2007 | +/- | Japan | Inpatients | N= 62 pediatric recipients at the time of HSCT, weekly for 3 or 4 months post  transplant | Collection of recorded clinical data and serum samples | HSCT recipients vs immunocompetent RV gastroenteritis patients | — | No | Levels of RV antigenemia | — | mean number ±SD | 0.22 ± 0.19 vs 0.49 ± 0.18, P = 0.0011 | Although the duration of antigenemia was clearly longer in HSCT patients than in immunocompetent RV gastroenteritis patients, the levels of viral antigen were not as high. |
| HLA mismatch vs matched | HLA matching | OR (95%CI) | 9.44 (1.09–82.11) p=0.024 |
| Pascarella F, 2009 | Retrospective, single-center, observational,  case-control study | between January 2005 and  December 2007 | +/- | Italy | Inpatients | N= 193 patients aged 18 months to 18 years (81 affected by IBD or with an history of diarrhea and abdominal pain and 112 controls) who were admitted | Collection of recorded clinical data and stool samples | IBD vs no IBD | — | No | Positive C difficile stool test results, n (%) | — | Rates | 20 (24.7) vs 10 (8.9) p=0.004 | The present study has demonstrated a higher prevalence of C difficile infection in a pediatric population with IBD compared with  one without IBD. |
| Nylund CM, 2011 | Retrospective cohort study | Years 1997, 2000, 2003, and 2006 | + | US | Inpatients | N= 10474454 children hospitalized (0.2% cases of clostridium infection) | Collection of hospital discharge data from national database | Comorbidity vs no comorbidity | — | No | Inflammatory  bowel disease | — | OR (95%CI) | 11.42 (10.16-12.83) | Clostridium difficile is emerging as a major agent of severe diarrhea in children with chronic conditions |
| Solid organ transplant | 4.53 (3.92-5.24) |
| HIV infection | 1.36 (1.04-1.79) |
| Hematopoietic stem cell  transplantation | 3.31 (2.87-3.82) |
| Neoplastic disease | 3.10 (2.89-3.31) |
| Fungal infection | 2.71 (2.39-3.07) |
| Cystic fibrosis | 2.65 (2.22-3.17) |
| Pancreatitis | 2.86 (2.41-3.39) |
| Hematologic disorders | 2.50 (2.34-2.66) |
| Gastrostomy | 2.00 (1.67-2.39) |
| Liver disease | 2.04 (1.80-2.32) |
| Malnutrition | 2.39 (2.14-2.67) |
| Renal disease | 2.09 (1.99-2.19) |
| Systemic lupus  erythematosus |
| 2.06 (1.58-2.68) |
| Bandin F, 2009 | Retrospective case series study | January 2006 to December 2008 | - | France | Inpatients | N=199 children who received renal transplantation | Collection of recorded clinical data and stool samples | (1) infectious diarrhea , (2) secondary to immunosuppressant treatment (3) unclassified diarrhea. | — | No | Etiologic group of reported diarrheal episodes (N=64) | — | Rates | Infectious 38/64 (59%), Immuno 14/64 (22%), Not classified 12/64 (19%) | Need to have a high index of suspicion for cryptosporidiosis in pediatric renal transplant patients who present with diarrhea. The routine stool evaluations for parasites may not identify Cryptosporidium. |
| Cryptosporidium in infectious diarrheal episodes | Rates | 7/38 (18%) |
| Henke-Gendo C, 2009 | Retrospective cohort study | 1 January 2005 to 30 June 2008 | + | Germany | Inpatients | N=75 patients of all ages receiving high-level immunosuppressive drug therapy with calcineurin inhibitors | Collection of recorded clinical data and stool samples | Comparing levels of NV excretions | — | Yes | Immunosoppression as a risk factor | — | OR (95%CI) | 9.19 (2.86–29.47) p<0.0001 | Highly immunosuppressed patients as well as young children fail to eliminate NV infection and shed the virus at high loads for a long period of time. |
| Transplant recipient as a risk factor | OR (95%CI) | 7.49 (2.06–28.32) p<0.001 |
| Age < 3yr as a risk factor | OR (95%CI) | 4.36 (1.23–15.85) p<0.008 |
| Bok K, 2012 | Review | 2012 | + | High and low income countries | Inpatients | Immunocompromised patients (all ages) with persistent diarrhea | — | — | — | — | — | — | — | — | NVs are increasingly recognized as an important cause of chronic gastroenteritis in immunocompromised patients, as reflected by the growing number of clinical case reports |
| Kaiser P, 2012 | Retrospective study | 1 October 2002 to 31 May 2008 | ++ | Germany | Inpatients | 6884 children < 5 years, 4880 RV positive and 2118 RV negative. | — | — | — | — | Underlying Cardiac disease(RV pos vs RV neg) | — | Number (%) | 32 (1.5%) vs 89 (3.2%), p<0.001 | The higher proportion of cardiac patients in the RV− group is due to multiple Clostridium infections in the cardiac wards in Giessen, where 56 of the 62 Clostridium infections (partially mixed infections) in the entire study group were observed (90.3%) |
| Underlying Neurologic disease (RV pos vs RV neg) | Number (%) | 37 (1.7%) vs 79 (2.9%), p=0.013 |
| Underlying Metabolic disease (RV pos vs RV neg) | Number (%) | 21 (1%) vs 46 (1.7%), p=0.47 |
| Bhutta ZA, 2008 | Systematic review |  | + | Low-income countries | Inpatients and Outpatients | Hospitalized and not hospitalized children ≤ 5 years of age with diarrhea (Perù, Brasil, USA, Bangladesh, Haiti, England) | — | — | — | — | Increase of risf for malnutrition at 24mo of age with each diarrheal episode | Black, Lancet 2008 (cross-sectional study in 3 World region - Asia, Africa and Latin America) | OR (95%CI) | 4% with each diarrheal episode  OR 1.04 (1.0–1.08; p < 0.03) | It is not possible to determine the population-attributable fraction of stunting and undernutrition that may be related to PD |
| — | Lebenthal, New York Raven Press; 1984 |  |  | Prolonged small intestinal mucosa injuries has been named as a central mechanism in the pathophysiology of PD, but we must discriminatebetween persisting infective colonization with enteropathyand a postinfective enteropathy that fails to heal or heals slowly |
| Mor SM, 2009 | Prospective cohort study | from November 2002 through May 2003 | + | Uganda | Inpatients | N=243 children ≤ yr of age with Persistent diarrhea | Collection of recorded clinical data and stool samples | Microsporidiosis in children with and without concurrent cryptosporidiosis and HIV | 224/243 | No | Microsporidiosis in children with concurrent cryptosporidiosis | — | OR (95%CI) | 78.3 (30.8–199.1) p < 0.0001 | microsporidian fungus Enterocytozoonbieneusi is associated with lower rates of weight gainin children in Uganda with persistent diarrhea. This relationshipremained after controlling for HIV and concurrent cryptosporidiosis. |
| Microsporidiosis in children with concurrent HIV | OR (95%CI) | 41.8 (18.3–95.4) p<0.001 |
| Microsporidiosis in children with concurrent HIV and cryptosporidiosis | OR (95%CI) | 153.0 (43.1–543.5) p<0.001 |
| Microsporidiosis in wasted children | OR (95%CI) | 2.1 (1.2–3.7) p= 0.013 |
| Microsporidiosis in underweight children | OR (95%CI) | 1.2 (0.7–2.2)p= 0.525 |
| Microsporidiosis in stunted children | OR (95%CI) | 1.2 (0.7–2.2)p= 0.508 |
| Idris NS, 2010 | Prospective cross-sectional study | April 2008 to February 2009 | + | Indonesia | Inpatients | N=42 children aged 6mo.-18 yrs , with persistent and/or recurrent diarrhea and had at least one of the following conditions: HIV infection, malignancy, severe malnutrition, on immunosuppressive therapy for a minimum of four weeks, or primary immunodeficiency. | Collection of recorded clinical data and stool samples | Comparing rates of intestinal parasites infections between groups | 38/42 | Yes | Immunocompromised state and presence of parasites infection | — | Rates | HIV 16/42 (42%); Malignancy 4/42 (9%); Severe malnutrition (NO HIV) 3/42 (7%); Immunosuppressive therapy 1/42 (2%) | The prevalence of intestinal parasitic infection among immunocompromised children with persistent and/or recurrent diarrhea was moderately high. The main groups affected were toddlers and preschoolers as well as those children infected with HIV who were not on antiretroviral therapy or with low CD4 counts. |
| Umamaheswari B, 2010 | Case-control study | 17 mo, November 2000-April 2002 | + | India | Inpatients | N=120 children from 1 mo. to 10 yr. of age with persistent or acute diarrhea | Detailed clinical history and laboratory investigations | Persistent vs acute diarrhea | 55/120 - 3 months | YES | Children with PD and prior antibiotic use | — | Rates | 43/60 (72.2%) | Protein energy malnutrition, vitamin A deficiency and prior antibiotic use were the risk factors for PD.\* |
| OR (95%CI) | 5.28 (2.01–13.74) p = 0.0003 |
| Children with PD and steroid use | Rates | 8/60 (13.3%) |
| OR (95%CI) | 4.46 (0.82-31.9) p = 0.048 |
| Children with PD and anemia | Rates | 48/60 (80%) |
| OR (95%CI) | 3.74 (1.55-9.15) p = 0.002 |
| Children with PD and vitamin A deficiency | Rates | 24/60 (40%) |
| OR (95%CI) | 4.28 (1.29–14.09) p = 0.012 |
| Children with PD and Z-score WFH <-2 | Rates | 35/60 (58.3%) |
| OR (95%CI) | 1.66 (1.0–2.77) p = 0.04 |
| \*diarrhea lasting > 14 days was considered persistent | | | | | | | | | | | | | | | |
| Al Jarousha AM, 2011 | Case-control study | February 2006-January 2007 | + | Palestine | Inpatients | N= 465 children aged up to 12 yrs (165 controls) | Detailed clinical history and laboratory investigations | Diarrhea vs not diarrhea | — | Yes | Risk for PD in malnourished children |  | OR (95%CI) | 8.57 (3.98–18.44)p <0.001 | Malnutrition is a risk factor for PD |
| Das SK, 2012 | Case-control study | 1991-2010 | ++ | Bangladesh | Inpatients | N= 3776 children < 5yr of age with PD (944) and AD (2832) | Detailed clinical history and laboratory investigations | Persistent vs acute diarrhea | — | Yes | Children with PD who had wasting syndrome | — | OR (95%CI) | (36/294) OR 1.62 (1.18, 2.21) p<0.01 | Malnutrition remains a risk factor for PD |
| Sutra S, 2012 | Cross-sectional study | 2011 | + | Thailand | Inpatients | Children < 5yr of age | The authors investigated the number of OPD visits (756,552; 1:5 ), IPD (124,403 admissions; 1:30) | — | — | Yes | Persistent diarrhea | — | N° of episodes and rates | 202 episodes (1.6 per 1,000 admissions) | age, sepsis, anemia, chronic diseases, malnutrition and HIV are related to persistent diarrhea |
| Risk factors related to PD | Multivariate analysis | age, sepsis, anemia, chronic diseases, malnutrition and HIV. |
| Manger MS, 2011 | Prospective cohort study | February 1998-September 2000 | + | India | Outpatients | N=2296 children 6-30 mo of age | Detailed clinical history and laboratory investigations | — | 2296/2296 | Yes | Risk for PD in children with folate plasma concentrations < 25th percentile | — | OR (95%CI) | 1.77 (1.14, 2.75) p = 0.01 | Poor folate status was an independent predictor of persistent diarrhea in this population |

HSCT=haemopoietic stem cell transplantation; IBD=Inflammatory bowel disease; NV= Norovirus; PD=Persistent diarrhea; QoS=Quality of Study; RV=Rotavirus.

**Table 1.3. Is there a relationship between the child’s clinical conditions and risk of severe or persistent diarrhea?**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Period of observation** | **QoS** | **Country** | **In/Out**  **Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU n/N** | **ITT** | **Outcomes measures** | **Effect measure** | **Effect size (95% CI)** | **Comments** |
| Verrotti A, 2009 | Systematic Review | 1993-2007 | + | Japan, UK, Taiwan | Inpatients | N=368 children <5 yr of age with mild RV gastroenteritis | \_ | \_ | \_ | \_ | \_ | Incidence of afebrile seizures  following RV gastroenteritis | Rates (%) | 2.1–6.4% | Benign afebrile seizures, not related to severe dehydration or electrolyte imbalance, have been associated with RV gastroenteritis |
| Chan CM, 2011 | Retrospective study |  | + | Hong-Kong | Inpatients | N=405 children between 1mo. and 6yr of age with acute gastroenteritis (232 with RV infection and 173 with NV infection) | \_ | \_ | RV vs NV infection | \_ | \_ | Maximun body temperature (RV vs NV) | Mean ± SD | 38.56 ± 1.01 vs 37.65 ± 0.78; p<0.001 | Children with RV infection had higher temperature and more diarrhea episodes, while more blood-stained stools and afebrile seizures were noted in the NV group |
| Presence of diarrhea | Rates (%) | 96% vs 84%; p<0.001 |
| Presence of bloody diarrhea | Rates (%) | 1% vs 5%;p=0.035 |
| C-reactive protein mg/L | Mean ± SD | 11.04 ± 18.18 vs 8.83 ± 16.96; p= 0.002 |
| Sodium mmol/L | Mean ± SD | 138.31 ± 3.20 vs 139.38 ± 2.92; p<0.001 |
| Length of stay (days) | Mean ± SD | 3.89 ± 1.83 vs 3.60 ± 1.67; p=0.049 |
| Presence of afebrile seizure | Rates (%) | 1% vs 9%; p<0.001 |
| Fasheh Youssef W, 2011 | Case-series | \_ |  |  |  |  |  |  |  |  |  | Isolation of RV | Number (%) | 11/28 (39) | Afebrile convulsion during mild gastroenteritis is a banal symptom with good prognosis |
| Isolation of Salmonella | 1/28 (4) |
| Day TG, 2012 | Case-series | \_ |  |  |  |  |  |  |  |  |  | \_ | \_ | \_ | First reported cluster of children presenting with neurological symptoms and stool virology positive for RV |
| Shai S, 2013 | Surveillance system | Between April 2009 and March 2011 |  |  |  |  |  |  |  |  |  | Cases of severe hypernatremia (>155mEq/L) between community-acquired gastroenteritis | Number | 26/84 | Although the incidence is relatively low compared  with all RV cases, significant RV morbidity could be identified |  |
| Cases of severe hyponatremia (<125mEq/L) between community-acquired gastroenteritis | 10/84 |
| Cases of encephalopathy between community-acquired gastroenteritis | 58/84 |
| Cases of deaths between community-acquired gastroenteritis | 3/84 |
| Shkalim V, 2012 | Retrospective comparative study | — | +/- | Israel | Inpatients | 17 otherwise healthy children aged 2-36 months with non-typhoid Salmonella and bacteremia | — | — | Cases were compared to 17 age-matched children with non-typhoid salmonella gastroenteritis | — | — | Toxic appearence (cases vs controls) | frequency (%) | 4(24%) vs 1(6%), p=0.002 | Toxic appearence and convulsions on admission were more common among children with non-typhoid Salmonella and bacteremia if compared to those with Salmonella AGE. |
| Convulsions (cases vs controls) | frequency (%) | 3(19%) vs 0, p=0.002 |
| Payne DC, 2008 | Surveillance system | January 1, 2006 to June 30, 2006 | + | USA | Inpatients, ED patients and outpatients | 516 children (181 inpatients, 201 ED and 134 outpatients). 44% with RV diarrhea. | — | — | RV positive and RV negative patients | — | — | Frequency of vomiting (RV pos vs RV neg) | frequency | 95% vs 79%, p<0.001 | Children with RV infection presented more frequently with vomiting, fever and lethargy compared to children with non RV infection. |
| Fever (RV pos vs RV neg) | frequency | 78% vs 63%, p=0.001 |
| Lethargy (RV pos vs RV neg) | frequency | 53% vs 27%, p<0.001 |
| Kaiser P, 2012 | Retrospective study | 1 October 2002 to 3 May 2008 | +/- | Germany | Inpatients | 6884 children < 5 years, 4880 RV positive and 2118 RV negative. | — | — | — | — | — | Respiratory Infections Rate (RV pos vs RV neg) | Number (%) | 648 (30.6%) vs 1,112 (40.2%), p<0.001 | Hypernatremia is a specifc complication of RV positive AGE |
| Abdominal symptoms (RV pos vs RV neg) | Number (%) | 23 (1.1%) vs 118 (4.2%), p<0.001 |
| Neurological symptoms (RV pos vs RV neg) | Number (%) | 50 (2.4%) vs 138 (5%), p<0.001 |
| Metabolic disorders (RV pos vs RV neg) | Number (%) | 85 (4%) vs 56 (2%), p<0.001 |
| Hypertonic dehydration | Number (%) | 49 (2.3%) vs 15 (0.5%), p<0.001 |
| Ansaldi F, 2008 | Prospective Cohort study | April 2005–April 2006 | +/- | Italy | Outpatients | 3611 children < 5 years surveyed by 10 primary pediatricians; 684 with AGE | — | — | RV positive and RV negative patients | — | — | Fever (RV pos vs RV neg) | frequency | 56.2% vs 31.8%, p<0.01 | Children with RV infection had significantly more fever and dehydration than RV negative patients. No difference in number of stools, blood in stools andabdominal pain. |
| Dehydration (RV pos vs RV neg) | frequency | 18.7% vs 9.7%, p<0.01 |
| Risk of RV AGE in patients with fever | OR(95% CI) | 2.6 (1.8-3.7), p<0.01 |
| Risk of RV AGE in patients with dehydration | OR(95% CI) | 1.8 (1.1-3), p=0.02 |
| Chisti MJ, 2011 | Prospective Cohort study | September-December 2007 | +/- | Bangladesh | Inpatients | 258 children <5yr of age admitted for severe diarrhea | — | — | Children who died vs children who survived | — | — | Absent peripheral pulse even after complete rehydration | OR(95% CI) | 10.9 (2.1-56.8), p < 0.01 | the absence of peripheral pulses even after full rehydration, severe malnutrition, hypoxaemia, lobar pneumonia and hypernatraemia are independent predictors of death |
| Severe malnutrition | OR(95% CI) | 7.9 (1.8-34.8), p < 0.01 |
| Hypoxaemia | OR(95% CI) | 8.5 (1.0-75.0), p = 0.05 |
| Radiological lobar pneumonia | OR(95% CI) | 17.8 (3.7-84.5), p < 0.01 |
| Hypernatraemia | OR(95% CI) | 15.8 (3.0-81.8), p < 0.01 |

AGE=Acute gastroenteritis; NV= Norovirus; OR=odds ratio; QoS=Quality of Study; RV=Rotavirus.

**1.4. Is there a relationship between setting or socio-economic factors and risk of severe or persistent diarrhea?**

**Table 1.4.1. Hospitalization**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Period of observation** | **QoS** | **Country** | **In/Out**  **Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU n/N** | **ITT** | **Outcomes measures** | **RCT n** | **Effect measure** | **Effect size (95% CI)** | **Comments** |
| Waisbourd-Zinman O, 2011 | Prospective Cohort study | Between 2003 and 2006 | +/- | Israel | Inpatients | N= 2287 children RV AGE (1931 community acquired 356 Nosocomial) | — | Weekly surveillance  of the microbiologic laboratory for hospitalized children  with positive fecal RV antigen | Community acquired vs nosocomial | — | — | Percentage of nosocomial RV AGE in children treated in full compliance with hand hygiene | — | Correlation | P <.0001 | Nosocomial cases can be easily prevented by adherence to hand hygiene measures |
| Waisbourd-Zinman O, 2009 | Prospective Cohort study | From January 1, 2003 to December 31,  2006 | +/- | Israel | Inpatients | N=356 children with Nosocomial-RV AGE | — | Collection of clinical data | — | — | — | Children with Nosocomial-RV AGE ≤ 2 years | — | Number (%) | 320/356 (90%) | The risk of nosocomial diarrhea is related to young age |
| Wildi-Runge S, 2009 | Retrospective cohort study | January 2002 to March 2006 | +/- | Switzerland | Inpatients | N=590 children <3yr of age hospitalized for RV acute gastroenteritis | — | — | Community acquired vs Nosocomial diarrhea | — | — | Persistent Diarrhea (>5days) Community (23.6%) vs Nosocomial (18%) | — | OR (95%CI) | 1.3 (0.6–3.0), p=0.46 | Nosocomial cases tended to be less severe than those acquired in the community |
| Vomiting events (>2/day) Community (78%) vs Nosocomial (35%) | OR (95%CI) | 5.3 (2.6–10.8), p< 0.001 |
| Dehydration (>5% of weight loss) Community (85%) vs Nosocomial (35%) | OR (95%CI) | 11.3 (5.7–22.4), p <0.001 |
| Wiegering V, 2011 | Retrospective cohort study | April 1, 2005 to May 31, 2008 | + | Germany | Inpatients | 650 charts of children with AGE. 262 (43.8%) had RV, 188 (31.4%) NV, 58 (9.7%) Adenovirus, 47(7.9%) Salmonella. | — | — | Community acquired vs Nosocomial diarrhea | — | — | Gastroenteritis score (Community acquired vs Nosocomial infections): pulmonary symptoms | — | mean number ±SD | 1.5±0.2 vs 3.6±0.3, p<0.001 | The underlying disease which led to admission, predominantly airway infections, explains the high respiratory symptoms score |
| Gastroenteritis score (Community acquired vs Nosocomial infections): gastrointestinal symptoms | mean number ±SD | 13±0.1 vs 9.8±0.2 , p<0.001 |
| Garcia-Basteiro AL, 2011 | Cross-sectional study | 2003-2008 | + | Spain | Inpatients | N=3265 children < 5 years of age admitted for RV-AGE | — | — | Community acquired vs Nosocomial diarrhea | — | — | Nosocomial RV-AGE | — | Rates (%) | 892/3265 (27%) | Children under 12 months old appear to be at higher risk of acquiring nosocomial RV gastroenteritis than older children |
| Annual incidence of presumed nosocomial RV-AGE per 1000 hospitalizations | Mean Incidence rate (95%CI) | 2.5 cases per 1,000 (2.0 to 2.8) |
| Age of hospitalized children with RV-AGE (nosocomial vs community acquired) (mo) | Mean ±SD | 5.08±9.4 vs 7.6±10.1 |
| Gleizes O, 2006 | Review | — | + | France, Germany, Italy, Poland, Spain and the United Kingdom | Inpatients | Children with a diagnosis of Nosocomial RV-AGE | — | — | Community acquired vs Nosocomial diarrhea | — | — | Nosocomial/Community acquired RV in children <5yr of age | — | Ratio | France: 0.61 ; Germany 1.04; Poland: 0.64; Spain: 0.96; UK: 0.76 |  |
| Asymptomatic manifestations of Nosocomial RV infection in children <3mo of age | Rates (%) | 18-39% |  |
| RV-infected health-care workers taking care of children with community-acquired RV-AGE | Rates (%) | 76–78% | The main vectors of transmission are contaminated (mostly uninfected) health care workers |
| Duration of hospital stay (days) Nosocomial vs Community-acquired AGE | Mean difference | France: +5d; Italy: +1.7d; Poland: +5.9; Spain: +1.8; UK +4 | The rate of NV infection can rise to 70% if patients stay hospitalized for 6 days |
| Age of hospitalized children with RV-AGE (nosocomial vs community acquired) (0-5 mo) | Rates (%) | 48% vs 20% |  |
| Age of hospitalized children with RV-AGE (nosocomial vs community acquired) (6-11 mo) | Rates (%) | 26% vs 30% |
| Age of hospitalized children with RV-AGE (nosocomial vs community acquired) (12-23 mo) | Rates (%) | 19% vs 28% |
| Age of hospitalized children with RV-AGE (nosocomial vs community acquired) (24-59 mo) | Rates (%) | 7% vs 22% |
| Nosocomial diarrhea requiring rehospitalization | Rates (%) | 2 and 13% |
| Ogilvie I, 2012 | Scoping review | — | — | Western Europe | Inpatients | 76 studies from 16 countries on European children <5 yr of age with community-acquired and nosocomial diarrhea | — | — | Community acquired vs Nosocomial diarrhea | — | — | Patients with severe nosocomial RVGE in France, Italy, Spain and the UK | 2 (n=3734; n=251) | Rates (%) | 42.6% | RV gastroenteritis is a common disease associated with significant morbidity and costs across Western Europe |
| Patients with severe nosocomial RVGE in Austria, Germany, and Switzerland | Rates (%) | 24.4%, 30.2% and 40% |
| Severe dehydration in children with community-acquired vs nosocomial gastroenteritis | 2 (Ireland n=663; Sweden n=984) | Rates (%) | 80% vs 55% (Ireland) 10.8% vs 0.8% (Sweden) |
| Mortality due to nosocomial RVGE (< vs > 12mo) | 1(n=10,990) | Incidence rates | 0.74 per 100,000 vs 0.16 per 100,000 |

AGE= acute gastroenteritis; NV= Norovirus; OR=odds ratio; QoS=Quality of Study; RV=Rotavirus; RVGE= Rotavirus gastroenteritis.

**Table 1.4.2. Socioeconomic factors**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Period of observation** | **QoS** | **Country** | **In/OutPatients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU n/N** | **ITT** | **Outcomes measures** | **Effect measure** | **Effect size (95% CI)** | **Comments** |
| Pockett RD, 2011 | Retrospective cohort study | 1st April 2009 and 31st March 2010 | +/- | UK | Inpatients | N=1334 children ≤5 yr of age with RV-AGE | — | — | Correlation with deprivation rank | — | — | Variation of hospital admissions' rates in relation to the decrease of a deprivation ranking | Rates | from 0.346 to 0.287 per 10,000 (p < 0.001) | Hospital admissions increased as deprivation increased\* |
| \*Index of Multiple Deprivation (IMD) 2007 for England | | | | | | | | | | | | | | | |
| Kyle RG, 2011 | Retrospective study | — | + | UK | Inpatients (ED) | 24,481 children under 15 years admitted to ED for breathing difficulty, fever or diarrhoea during 2007/2008. | — | — | — | — | — | Index of Multiple Deprivation | Sperman rho | 0.31, p=0.09 | There were no statistically significant relationships between the ED admission rate of children admitted for diarrhoea and the Index multiple derivation and its single indicators. |
| overcrowding | Sperman rho | 0.21, p=0.267 |
| houses in poor condition | Sperman rho | 0.11, p=0.543 |
| air quality | Sperman rho | 0.16, p=0.387 |
| homelessness | Sperman rho | 0.14, p=0.439 |

AGE= acute gastroenteritis; ED=emergency department; QoS=Quality of Study; RV=Rotavirus.

**Table 1.4.3. Day care attendance**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Period of observation** | **QoS** | **Country** | **In/Out**  **Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU n/N** | **ITT** | **Outcomes measures** | **RCT n** | **Effect measure** | **Effect size** | **Comments** |
| Sandora TJ, 2005 | RCT | — | + | USA | Outpatients | N= 292 families with children aged < 5yr | Computered permuted-blocks design with random block sizes | Supply of alcohol-based hand sanitizer to use at home | Controls | 281/292 | Yes | Gastrointestinal-Illness transmission (treated vs controls) | — | IRR  (95% CI) | 0.41 (0.19–0.90) p=.03 | This intervention significantly reduced the transmission of GI illnesses in the homes of families with children who were enrolled in out-of-home child care. |
| Kotch JB, 2007 | RCT | September 2002 to January 2003 | + | USA | Outpatients | N=388 infants and toddlers attending child-care centers (23 matched-paired centers) | Appropriate | Installation of diaper-changing, hand-washing, and food-preparation equipment | Controls | 388/388 | No | Child Diarrhea Frequency per 100 Child-Days (treated vs controls) | — | Incident rates | 0.90 vs 1.58 (p<0.001) | High-quality equipment is associated with significantly fewer episodes of diarrhea among children and fewer sick days among staff. |
| % of Days Child Ill per 100 Child-Days (treated vs controls) | Incident rates | 4.0 vs 5.0 (p<0.001) |
| % of Days Caregiver Absent because of Illness (treated vs controls) | Incident rates | 0.77 vs 1.73 (p<0.001) |
| Grimprel E, 2010 | Surveillance study | December 2006 and May 2007 | + | France | Outpatients | N=371 children aged <3yr attending child-care centers | — | — | — | — | No | Cases of RVGE per 100,000 person-days | — | Incidence rate (95%CI) | 46.7 (26.7-75.8) | RV can easily spread in a day care setting |
| Age-distribution of children with RV-AGE | Rates (%) | 0-11 mo: 50%; 12-23mo: 37%; >24mo: 13% |

AGE= Acute gastroenteritis; GI=Gastrointestinal; QoS=Quality of Study; RV=Rotavirus; RVGE=Rotavirus gastroenteritis.

CLINICAL EVALUATION AND DISEASE SEVERITY

**Table 2.1. What are the indications for a medical visit?**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Period of observation** | **QoS** | **Country** | **In/Out Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU n/N** | **ITT** | **Outcomes measures** | **GL n** | **Effect**  **measure** | **Effect**  **size**  **(95% CI)** | **Comments** |
| Williams DJ, 2012 | Retrospective surveillance system | May 1, 2004 to April 30, 2007  May 1, 2007 to April 30, 2010 | + | US | Outpatients | N= 19731 AGE-related calls | — | Vanderbilt Telephone Triage Program | Postlicensure period (2007–2010)) vs Prevaccine period (2004–2007 | — | — | AGE-related Call Proportions After RV Vaccine Licensure (RV Season) | — | IRR (95% CI) | 0.72 (0.67–0.78) | A telephone consultation can be appropriate in the management of uncomplicated cases of AGE |
| van den Berg J, 2011 | Systematic review | 2011 | ++ | Europe, USA, Canada | Outpatients | N=8 guidelines | — | Assess the quality of international CPG for the management of acute diarrhea in children in high income countries with the Appraisal of Guidelines, Research and Evaluation (AGREE) instrument | — | — | — | Indication to medical visit: Young age | n=4 | Consensus (n/N) and Consistency (Y/N) of the recommendation | 3/4; Y | Not recommended by ESPGHAN, to be included\* |
| Indication to medical visit: High Output --> 6 diarrheal stool in 24 h, or > 3 vomits in 24 h or watery diarrhea > 6 times a day > 3 days (<2 years: > 1 day) | Consensus (n/N) and Consistency (Y/N) of the recommendation | 4/4; Y |
| Indication to medical visit: Persistent vomiting or >2 vomits/24h | Consensus (n/N) and Consistency (Y/N) of the recommendation | 3/4; Y |
| Indication to medical visit: Reported signs of severe dehydration\* | Consensus (n/N) and Consistency (Y/N) of the recommendation | 3/4; Y\* |
| Indication to medical visit: Signs of severe cause for diarrhea/underlying disease | Consensus (n/N) and Consistency (Y/N) of the recommendation | 4/4; Y |
| \*Consistency of recommendations: If more than 50% of these guidelines made an identical recommendation, it was considered consistent | | | | | | | | | | | | | | | | |

AGE= acute gastroenteritis; CPG=Clinical practice guidelines; ESPGHAN= European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; QoS=Quality of Study; RV=Rotavirus.

**2.2. Is there any clinical feature that may suggest a bacterial versus viral etiology of diarrhea?**

**Table 2.2.1. Bacterial versus viral**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **QoS** | **Country** | **In/Out Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU** | **ITT** | **Outcomes measures** | **Effect measure** | **Effect size (95% CI)** | **Comments** |
| Wiegering V, 2011 | Retrospective cohort study | + | Germany | Inpatients | 650 charts of children with AGE reviewed between 2005 and 2008. 262 (43.8%) had RV, 188 (31.4%) NV, 58 (9.7%) Adenovirus, 47(7.9%) Salmonella. | \_ | \_ | Comparisons between all viral infections and Salmonella infection | \_ | \_ | Respiratory symptoms score (all viral vs Salmonella) | mean score (0-6)±SD | 1.8±0.1 vs 0.6±0.3, p<0.001 | Children with viral infection had significantly more respiratory associated symptoms and vomiting, but less episodes of diarrhea and total duration of diarrhea when compared to children with Salmonella infection. |
| Duration of diarrhea (all viral vs Salmonella) | mean number ±SD | 3.4±0.1 vs 6.1±0.4, p<0.001 |
| Diarrhea events (all viral vs Salmonella) | mean number ±SD | 3.8±0.1 vs 10.4±0.5, p<0.001 |
| Vomiting events (all viral vs Samonella) | mean number ±SD | 2.6±0.2 vs 1±0.4, p<0.001 |
| Comparisons between viral infections: RV vs NV vs Adenovirus | \_ | \_ | Duration of diarrhea (RV vs NV vs AV) | mean number ±SD | **4.1±0.2** vs 2.7±0.2 vs 3.4±0.3, p<0.001 | Children with RV infection had significantly higher severity scores, more diarrheal events and long-lasting diarrhea. In contrast NV infection had more vomiting events. |
| Diarrhea events (RV vs NV vs AV) | mean number ±SD | **4.4±0.2** vs 3.2±0.2 vs 3.4±0.4, p<0.001 |
| Vomiting events (RV vs NV vs AV) | mean number ±SD | 2.4±0.2 vs **3.2±0.2** vs 1.6±0.3, p=0.05 |
| Gastroenteritis score (RV vs NV vs AV) | mean score (0-15)±SD | **13.5±0.2** vs 11.9±0.2 vs 11.5±0.4, p<0.001 |
| Payne DC, 2008 | Surveillance system | + | USA | Inpatients, ED patients and outpatients | 516 children (181 inpatients, 201 ED and 134 outpatients). 44% with RV diarrhea. | \_ | \_ | RV positive and RV negative patients | \_ | \_ | Fever (RV pos vs RV neg) | frequency | 78% vs 63%, p=0.001 | Children with RV infection presented more frequently with vomiting, fever and lethargy compared to children with non RV infection. |
| Lethargy (RV pos vs RV neg) | frequency | 53% vs 27%, p<0.001 |
| Narkeviciute I, 2008 | Retrospective study | +/- | Lithuania | Inpatients | Random retrospective selection of 140 charts of children < 3y with NV (70) and RV (70) infection. | Random selection of charts; no allocation to any intervention | \_ | RV vs NV infection | \_ | \_ | High grade fever (BT> 38°C) (RV vs NV) | frequency | 81% vs 48%, p<0.0001 | RV infection presents more likely with fever, usually high grade (>38°) and frequent diarrheal episodes (>7/d). NV AGE is commonly characterized by the presence of vomiting (71% more than 4episodes/d) and in 1/5 of cases without diarrhea |
| Frequency of fever (RV vs NV) | frequency | 97% vs 66%, p<0.0001 |
| Diarrhea >7 episodes/d (RV vs NV) | frequency | 42% vs 12%, p<0.0001 |
| Vomiting > 4/d (RV vs NV) | frequency | 49% vs 71%, p=0.01 |
| Children without diarrhea (RV vs NV) | frequency | 4% vs 19%, p=0.01 |
| Ansaldi F, 2008 | Prospective Cohort study | +/- | Italy | Outpatients | 3611 children < 5 years surveyed by 10 primary pediatricians; 684 with AGE | \_ | \_ | RV positive and RV negative patients | \_ | \_ | Fever (RV pos vs RV neg) | frequency | 56.2% vs 31.8%, p<0.01 | Children with RV infection had significantly more fever and dehydration than RV negative patients. No difference in number of stools, blood in stools and abdominal pain. |
| Dehydration (RV pos vs RV neg) | frequency | 18.7% vs 9.7%, p<0.01 |
| Risk of RV AGE in patients with fever | OR(95% CI) | 2.6 (1.8-3.7), p<0.01 |
| Risk of RV AGE in patients with dehydration | OR(95% CI) | 1.8 (1.1-3), p=0.02 |
| Ghorashi Z, 2010 | Case-control study | +/- | Iran | Inpatients | 49 cases with convulsion due to AGE (in absence of electrolyte imbalance) and 51 controls with AGE but without convulsions | \_ | \_ | \_ | \_ | \_ | Frequency of Shigellosis (cases vs controls) | frequency | 8 vs 2, p=0.014 | The frequency of Shigellosis in the case group was significantly higher than in the control group. |
|
|
|
|
| Chen SM, 2012 | Prospective Cohort study | + | Taiwan | Inpatients | 168 children (1.2 - 4.7 years) admitted for AGE. 30 with RV, 25 NV, 26 Salmonella (SA). | \_ | \_ | \_ | \_ | \_ | Maximum number of diarrheal episodes/d (RV vs NV vs SA) | Median (IQR) | RV 6(4-9.5) vs NV 4 (3-6.25) vs **SA 8(6-10)**, p<0.001 | Children with Salmonellosis demonstrated higher fever, bloody diarrhea and more diarrheal episodes when compared to RV and NV positive patients. |
| Maxiumun number of vomiting episodes/d (RV vs NV vs SA) | Median (IQR) | RV 4 (2-7) vs NV 2.5 (1-5.2) vs **SA 1 (1-2)**, p<0.001 |
| Fever > 38°C (RV vs NV vs SA) | Frequency (%) | RV 36 (87.8%) vs NV 13 (38.2%) vs **SA 29 (100%)**, p<0.001 |
| Maximun body temperature (RV vs NV vs SA) | Median (IQR) | RV 38.8 (38.4 -39) vs NV 37.9 (37.2-38.7) vs **SA 39.1 (38.9-39.6)**, p<0.001 |
| Stool occult blood | Frequency (%) | RV 16 (39%) vs NV 8 (23.5%) vs **SA 18 (62.1%)**, p<0.001 |
| Kaiser P, 2012 | Retrospective study |  | Germany | Inpatients | 6884 children < 5 years, 4880 RV positive and 2118 RV negative. | \_ | \_ | \_ | \_ | \_ | Respiratory Infections Rate (RV pos vs RV neg) | Number (%) | 648 (30.6%) vs 1,112 (40.2%), p<0.001 | Hypernatremia is a specific complication of RV positive AGE |
| Abdominal symptoms (RV pos vs RV neg) | Number (%) | 23 (1.1%) vs 118 (4.2%), p<0.001 |
| Neurological symptoms (RV pos vs RV neg) | Number (%) | 50 (2.4%) vs 138 (5%), p<0.001 |
| Metabolic disorders (RV pos vs RV neg) | Number (%) | 85 (4%) vs 56 (2%), p<0.001 |
| Hypertonic dehydration | Number (%) | 49 (2.3%) vs 15 (0.5%), p<0.001 |

AGE= acute gastroenteritis; NV=Norovirus; QoS=Quality of Study; RV=Rotavirus.

**Table 2.2.2. Systemic Involvement**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **QoS** | **Country** | **In/Out Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU** | **ITT** | **Outcomes measures** | **Effect measure** | **Effect size (95% CI)** | **Comments** |
| Shkalim V, 2012 | Retrospective comparative study | +/- | Israel | Inpatients | 17 otherwise healthy children aged 2-36 months with non-typhoid Salmonella and bacteremia | \_ | \_ | Cases were compared to 17 age-matched children with non-typhoid salmonella gastroenteritis | \_ | \_ | Toxic appearence (cases vs controls) | frequency (%) | 4(24%) vs 1(6%), p=0.002 | Toxic appearence and convulsions on admission were more common among children with non-typhoid Salmonella and bacteremia if compared to those with Salmonella AGE. |
| Convulsions (cases vs controls) | frequency (%) | 3(19%) vs 0, p=0.002 |

AGE=acute gastroenteritis; QoS=Quality of Study.

**2.3 How is dehydration assessed?**

**Table 2.3.1. Clinical dehydration scale**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study design** | **Country** | **Aim** | **Setting** | **N** | **Age range** | **Inclusion criteria** | **Outcome measures** | **Results/conclusions** |
| Friedman JN, 2004 | Prospective cohort study | Canada | To develop a clinical dehydration scale for use in children <3 y of age. | ED | 137 | 1-36 mo (median: 18 mo) | GE | Urine output; general appearance; eyes; mucous membranes (tongue); tears; respiratory rates; heart rate. | ‘Clinicians and researchers may consider this four-item, 8-point rating scale, developed using formal measurement methodology, as an alternative to scales developed ad hoc.’ |
| Goldman RD, 2008 | Prospective cohort study | Canada | To validate the CDS with a new cohort of patients with AGE. | Tertiary care ED | 205 | 1 mo -5 y (22.4 ± 14.9 mo) | Symptoms of AGE | Length of stay, proportion of children receiving intravenous rehydration; proportion of children with abnormal serum pH values or bicarbonate levels. | The CDS was valuable in predicting a longer length of stay and the need for intravenous rehydration in children with symptoms of AGE. |
| Bailey B, 2010 | Prospective cohort study | Canada | To validate the CDS for children with gastroenteritis in a different ED from where it was initially derived and validated. | Tertiary care ED | 150 | 1 mo – 5 y | Vomiting and/or diarrhea | Primary: the association between the CDS for children and the length of stay in ED after being seen by the attending physician. | The CDS is a good predictor of (1) length of stay in the ED after being seen by a physician; (2) perceived need for IV rehydration; (3) utilization of laboratory blood tests. |
| Gravel J, 2010 | Prospective cohort study | Switzerland, Canada | To validate the association between the CDS and markers of dehydration in children aged 1 mo to 5 y visiting ED for vomiting and/or diarrhea. | ED | 219 | 1 mo -5 y (mean age: 22 ± 14 mo;  range 4 mo to 4 y) | Vomiting and/or diarrhea | Primary: the percentage of dehydration calculated by the difference in weight at first evaluation and after recovery.  Secondary: proportion of blood test measurements, intravenous use, hospitalization, and inter-rater agreement. | ‘CDS categories correlate well with markers of dehydration four young children complaining of vomiting and/or diarrhea in the ED.’ |
| Kinlin LM, 2012 | Prospective cohort study | Canada | To evaluate the reliability and validity of the CDS in a cohort of children with gastroenteritis and evidence of dehydration. | Tertiary ED | 226 | ≥3 mo | GE and dehydration requiring intravenous rehydration | Reliablity (by comparing the scores assigned independently by a trained research nurse and a physician).  Validity (by using parameters reflective of disease severity: weight gain; baseline laboratory results; willingness of the physician to discharge the patient; hospitalization; length of stay). | ‘In children administered intravenous rehydration, the CDS was characterized by moderate interobserver reliability and weak associations with objective measures of disease severity. These data do not support its use as a tool to dictate the need for intravenous rehydration or to predict clinical course.’ |
| Pringle K, 2011 | Prospective cohort study | Rwanda | To determine whether the WHO scale, the Gorelick scale and the CDS scales can accurately assess dehydration status in children when performed by nurses or GP in a low-income country. | Hospital | 49 | <15 y (but analysis limited to children fitting within the predefined age ranges for each of the scales) | Diarrhea and/or vomiting | Sensitivity; specificity. | ‘In this sample of children, the WHO scale, Gorelick scale, and CDS did not provide an accurate assessment of dehydration status when used by GP and nurses in a developing world setting’. |
| Pruvost I, 2013 | Prospective cohort study | France | To estimate the value of post-illness weight gain prospectively as a gold standard for acute weight loss  in a larger population. | Tertiary ED | 293 | 1 to 24 months of age | Acute diarrhea, and daily weight  surveillance for 7 days following the ED visit, were included | Pearson correlation between post-illness and theoretical weight | The correlation between post-illness and theoretical weight was excellent (0.978), but  bootstrapped linear regression analysis showed that post-illness weight underestimated theoretical weight by 0.48 kg. These data suggest that post-illness weight is of little value as a gold standard to determine the true level of dehydration |

CDS=clinical dehydration scale; ED=emergency department; WHO=World Health Organization.

**Table 2.3.2. Severity scores**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study design** | **Country** | **Aim** | **Setting** | **N** | **Age range** | **Inclusion criteria** | **Outcome measures** | **Results/conclusions** |
| Schnadower D, 2013 | Prospective cohort study | US | To evaluate the reliability, construct validity, and generalizability  of the Modified Vesikari Score by studying its characteristics in a network of pediatric  EDs in the United States | ED | 282 | Between 91 days and 48 months of age) | AGE | Reliability, construct validity, and generalizability  of the Modified Vesikari Score | ‘The Modified Vesikari Score effectively measures global severity of disease and  performs similarly in varying populations within the US health care system. Its characteristics support its use in multisite outpatient clinical trials.’ |
| Ruuska T, 1990 | Prospective cohort study | Finland | To assess the use of the classical Vesikari score for clinical severity of diarrhoeal episodes | Hospital | 336 | 24-32 months of age | AGE | Severity of symptoms between RV e non-RV AGE | Using this system, the mean severity score for the 65 episodes of RV diarrhoea was 11.0 +/- 3.7 as compared to 5.6 +/- 3.2 for the 183 episodes of non-RV diarrhoea (p<0.001). |

AGE= acute gastroenteritis; ED=emergency department; RV=Rotavirus**.**

**Table 2.3.3. Clinical and laboratory assessment**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study design** | **Country** | **Aim** | **Setting** | **N** | **Age range** | **Inclusion criteria** | **Outcome measures** | **Results/conclusions** |
| Parkin PC, 2010 | Data were  collected prospectively; however the analysis was  post hoc. | Canada | To evaluate clinical and laboratory assessment (serum bicarbonate and venous pH) of dehydration severity in children. | ED | 93 | 1-36 mo | AGE | For a clinical score of 0, the LR+ 2.2 (0.9-5.3);  For a clinical score of 1 to 4, the LR+ was 1.3 (0.90-1.74);  For a clinical score of 5 to 8, the LR+ was 5.2 (2.2-12.8);  For a venous pH <7.32, the LR+ was 7.2 (2.4-21.9);  For serum bicarbonate <18 mmol/L, the LR+ was 11.6 (3.5-38.0). | Clinicians may find it useful to incorporate the Clinical Dehydration Scale and laboratory measures into clinical decision-making algorithms to assess dehydration severity in children with acute gastroenteritis. |

AGE= acute gastroenteritis; ED=emergency department; LR=likelihood ratio.

**Table 2.3.4. Standardized Scoring System**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study design** | **Country** | **Aim** | **Setting** | **N** | **Age range** | **Inclusion criteria** | **Outcome measures** | **Results/conclusions** |
| Roland D, 2010 | Prospective observational study | Australia | To determine if scoring system based on standardized clinical signs would reduce the variability between doctors’ assessment of dehydration. | ED | 100 | 1 mo-12 y (median 24 mo) | GE | Estimated percentage dehydration. Agreement between raters. | The clinical scoring system used did not reduce the variability of assessment of dehydration |

ED=emergency department; GE=gastroenteritis.

**Table 2.3.5. Ultrasound**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study design** | **Country** | **Aim** | **Setting** | **N** | **Age range** | **Inclusion criteria** | **Outcome measures** | **Results/conclusions** |
| Chen L, 2007 | Prospective observational study | US | To compare the IVC and Ao diameters ratio of dehydrated children with controls and to compare the IVC/Ao ratio before and after IV rehydration in children with dehydration. | ED | 72 | 6 mo-16 y | Subjects with evidence of dehydration plus matched controls | IVC/Ao ratio | The ratio of inferior vena cava diameter is lower in children with clinical dehydration. It increases with administration of IV fluid boluses. |
| Chen L, 2010 | Prospective observational study | US | To validate the use of bedside ultrasound measurement of IVC/Ao diameter by investigating whether IVC/Ao ratio correlated with dehydration in children with AGE.  To investigate the inter-rater variability of the IVC/Ao measurements. | ED | 112 | 6 mo-18 y | GE | Sensitivity, specificity, likelihood ratios, area under the receiver operator characteristic curves. | IVC to Ao diameter was a marginally accurate measurement of acute weight loss in children with dehydration from gastroenteritis |
| Levine AC, 2010 | Prospective cohort study | Rwanda | To determine the test characteristics for two different ultrasound measures of severe dehydration in children (Ao to IVC) ratio and IVC inspiratory collapse and the WHO dehydration scale. | ED | 73 | 1 mo-10 y | Diarrhea and/or vomiting | Sensitivity, specificity, likelihood ratios, area under the receiver operator characteristic curves. | Ao to IVC and IVC inspiratory collaps. Ultrasound if the aorta/IVC ratio can be used to identify severe dehydration in children presenting with acute diarrhea. |

AGE= acute gastroenteritis; Ao=aorta; ED=emergency department. IVC=inferior vena cava; WHO=World Health Organization.

**Table 2.3.6. Hand-held bladder ultrasound**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study design** | **Country** | **Aim** | **Setting** | **N** | **Age range** | **Inclusion criteria** | **Outcome measures** | **Results/conclusions** |
| Enright K, 2010 | Prospective observational study | UK | To evaluate the utility of a hand-held bladder ultrasound scanner in monitoring urine production in children attending the emergency department with suspected dehydration. | Tertiary ED | 45 | 4 mo – 10 y | Possible dehydration | Primary: the ability to document the hourly rate of urine production for each child, using the hand-held bladder scanner.  Secondary: the relationship between the measured urine production and clinical features of dehydration, patient disposal and rehydration therapy. | Serial bladder ultrasound scanning using a hand-held device is a convenient non-invasive and objective adjunct in the management of suspected dehydration in ED. |

ED=emergency department;

**Table 2.3.7. Digital videography to measure capillary refill time**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study design** | **Country** | **Aim** | **Setting** | **N** | **Age range** | **Inclusion criteria** | **Outcome measures** | **Results/conclusions** |
| Shavit I, 2006 | Prospective cohort study | Canada | To determine whether digitally measured capillary-refill time assesses the presence of significant dehydration (≥5%) in young children with GE more accurately than conventional capillary refill and overall clinical assessment. | Tertiary ED | 83 | 1 mo – 5 y | Gastroenteritis judged to be at least mildly dehydrated. | Sensitivity, specificity, likelihood ratios, area under the receiver operator characteristic curves. | Digitally measured capillary-refill time more accurately predicts significant dehydration (≥5%) in young children with GE than overall clinical assessment. |

ED=emergency department; GE=gastroenteritis.

**Table 2.3.8. Bioelectric impedance**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study design** | **Country** | **Aim** | **Setting** | **N** | **Age range** | **Inclusion criteria** | **Outcome measures** | **Results/conclusions** |
| Dunkelmann L, 2012 | Case series | Switzerland | To compare a bioimpedance device to the validated clinical score for the determination of the degree of dehydration in children with AGE. |  | 26 | 0.5 to 10 y | AGE | The subgroup of children with mild dehydration (n=14) had significantly lower Ω50 compared to the subgroup of children with moderate/severe dehydration (n=12), p=0.003. | Possible usefulness of bioelectric impedance for the assessment of dehydration. |

AGE= acute gastroenteritis;

**Table 2.3.9. Plasma water**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study design** | **Country** | **Aim** | **Setting** | **N** | **Age range** | **Inclusion criteria** | **Outcome measures** | **Results/conclusions** |
| Plaisier A, 2010 | Prospective cohort study | The Netherlands | To evaluate plasma water as a diagnostic tool in the assessment of dehydration in children with AGE admitted to hospital with moderate to severe dehydration. | ED | 101 | Up to 12 y | AGE and dehydration | Plasma water did not correlate with the percentage of weight loss. | There is insufficient evidence to justify the use of plasma water as a diagnostic tool in the assessment of dehydration in children with AGE. |

AGE=acute gastroenteritis; ED=emergency department; GE=gastroenteritis.

DIAGNOSTIC WORKUP

**Table 3.1. Is There Any Reliable Hematological Marker of Bacterial Diarrhea?**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Type of Study** | **Country** | **Inpatient Outpatient** | **Follow-up n/N** | **Population** | **Intervention** | **Comparison** | **Outcome measures** | **Results /Effect size** | **Risk of Bias** | **Source of Funding** | **Conclusions and Comments** |
| Wiegering V, 2011 | Retrospective  Apr 2005 to May 2008 | Germany | Inpatient | Not reported | 650/1157 children with pathogen proven AGE  Age  22d-17.9y  (mean 2.4y) | NA | Clinical score to differentiate between different etiologies | Etiology  Duration of diarrhea  Laboratory and other hematologic markers | **Etiology:**  84.9% viral  7.9% Salmonella  7.2% multiple agents  **Duration of diarrhea:**  All viral 3.4±0.1 days  Salmonella 6.1±0.4 days  (p<0.001)  **CRP**  Viral AGE 1.2±0.1  Salmonella AGE 6.9±0.4  (p<0.001)  **ESR**  Viral AGE 15±0.8  Salmonella AGE 27±2.2  (p<0.001) | NA | None | RV was the commonest cause of viral AGE and Salmonella the commonest cause of bacterial AGE  Children with bacterial AGE were older, had a more severe clinical course, significantly longer duration and significantly more elevated inflammatory markers  These parameters may make possible to differentiate between viral and bacterial AGE |
| Marcus N, 2007 | Prospective  Convenient sample  Aug 2002 to  Feb 2003 | Israel | Outpatient  ER | 7-12 days (med 2.4) | 75 children  AGE  Age 4d - 17y  44 children included  Bacterial 8/44 (18%)  Viral AGE 36/44 (82%) | NA | Bacterial vs  Viral AGE | Validity and feasibility of QR-CRP in diagnosis of bacterial vs viral AGE | **QR-CRP (mg/L), mean±SD**  Bacterial 22.3.8±150.3  Viral 30±50  (P<0.001)  **QR-CRP ≥ 24.5 mg/L**  OR 1.49 (95%CI 1.13-1.90  PPV 70%, NPV 97%  **QR-CRP ≥ 95 mg/L**  OR 1.49 (95%CI 1.13-1.90  PPV 91.7%, NPV 87% | NA | QR-CRP assay kit was provided by Orion  DiagnosFinland | CRP levels of 95mg/L or more within 48 hours of presentation had a high sensitivity and specificity for predicting culture-confirmed bacterial AGE |
| Chen SM, 2012 | Prospective  March 2008 to  Jan 2009 | Taiwan | Inpatients | NA | 168 children  AGE  Age 4m- 14y  Pathogens identified in 123/168  82 viral AGE  36 bacterial AGE  IL-6, IL-10 assayed:  55 viral AGE 26 *Salmonel*  11 healthy controls | NA | Bacterial vs  Viral AGE | Diagnostic performance  IL-6, IL-10,  ANC, CRP  RV vs  NV  Viral vs bacterial AGE | RV vs Salmonella  **ANC, mm3**  8075 (4225-13407) vs  4444 (3118-5867)  P= 0.004  **CRP, mg/dl**  0.62 (0.3-1.59) vs  6.42 (3.06-12.25)  P≤ 0.001  **IL-6, IL-10 (p<0.001)**  **RV vs NV**  AUC±SE (95% CI)  **IL-6** 0.663±0.075(0.515±0.81)  P=0.039  **IL-10**  0.710±0.69 (0.574-0.84)  P= 0.008 | NA | Chung Shan Hospital  (CSH 97A-03) | IL-10 exhibited a significant high level in the acute phase of RV and NV AGE in children and showed a significant discriminating ability between the two most common viral pathogens |
| Korczowski B, 2004 | Prospective | Poland | Inpatients | NA | 129 children diarrhea  37 systemic infections  36 bacterial AGE  43 RV AGE  13 IBD | NA | Different etiologies of diarrhea | Performance of PCT compared to CRP | **PCT> 5ng/ml**  100% systemic infections  61% bacterial AGE  7% RV AGE  23% IBD  **CRP> 2mg/dl**  89% systemic infections  61% bacterial AGE  19% RV AGE  46% IBD | NA | None declared | In this study PCT was a more reliable marker than CRP of systemic bacterial infection in children with diarrhea. PCT was more specific but less sensitive in the differentiation of bacterial and non-bacterial etiology of inflammation. |

AGE= acute gastroenteritis; ANC=absolute neutrophil count; AUC=area under the curve; IL-6=interleukin 6; IL-10=interleukin 10; CI=confidence interval; CRP=C-reactive protein; NPV=negative predictive value; NV=norovirus; OR=odds ratio; PCT=procalcitonin; PPV=positive predictive value; QR-CRP=quick-read C-reactive protein; RV= rotavirus; SE=sensitivity; SP=specificity.

**Table 3.2. Stool markers for identification of bacterial diarrhea**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Type of Study** | **Country** | **Inpatient Outpatient** | **Follow-up n/N** | **Population** | **Intervention** | **Comparison** | **Outcome measures** | **Results /Effect size** | **Risk of Bias** | **Source of Funding** | **Conclusions and Comments** |
| Sykora J, 2010 | Prospective | Czech Republic | Inpatients and Outpatient | NA | 66 children AGE  Age 1-36m  34 bacterial  32 viral  25 unknown  41 healthy controls | NA | BGA  vs  VGE | Reference fCP in healthy children  Performance of fCP in bacterial vs viral AGE | **fCP**  BGA 219.9µg/g (119-350)  P<0.001 vs VGE/ control  VGE 49.3µg/g (8.8-131.1)  Controls 26.5µg/g (14.9-55)  **fCP≥103.9 µg/g**  AUC 0.95 (CI 0.89-0.98)  **CRP≥16.9mg/ml**  AUC 0.87 (0.83-0.96)  **WBC≥9.5X103**  AUC 0.77 (0.69-0.82)  **ESR≥15MM/H**  AUC 0.84 (0.79-0.89)  AUC fCP vs CRP, p<0.05  AUC fCP vs WBC, p<0.001  AUC fCP vs ESR, p<0.01  AUC fCP vs IL-6, p<0.001 | NA | None declared | fCP is a valuable, non-invasive and esily measured laboratory test  fCP is variable and is age dependent in children <3 years  fCP was superior to clinical symptoms (fever, stool frequency and vomiting ) and laboratory (CRP, WBC) in the diagnosis of bacterial AGE. |
| Opintan JA, 2010 | Prospective Cross-sectional  Aug 2007 to May 2008 | Ghana | Outpatient | NA | Children<5y  170 AGE  104 controls without diarrhea | NA | Well nourish vs  Malnurished | Etiology of bacterial AGE  Fecal lactoferrin in AGE vs controls | Bacterial agents isolated  161/170 AGE  80/104 controls  EAEC isolated  145/170 diarrhea  79/84 controls without diarrhea  f-Lactoferrin, µg/ml  Children with diarrhea, n=143  1658.9±204.2  Control without diarrhea, n=84  935.5±194.4  P=0.019 | NA | Ghana University and  Pfizer-funds  Virginia University  US | EAEC and cryptosporidium were the most common agents isolated in children with and without diarrhea in this study in children < 5 years from Ghana  Fecal lactoferrin was significantly elevated in children with diarrhea |
| Chen CC, 2011 | Prospective  Cross-sectional  Sept 2008 to May 2010 | Taiwan | Inpatient | NA | 117 children  Age 3.23y  (3m-10y) | NA | Clinical severity of infectious diarrhea  (Vesikari and Clark scores) | Fecal lactoferrin as marker of severity of AGE | **AGE etiology**  41/117 RV  28/41 NV  31/117 Salmonella  17/117 Campylobacter  **f-Lactoferrin, µg/g**  RV 2.82±1.27  NV 3.16±1.18  Salmonells 11.17±2.73  (p<0.05 vs viral)  Campylobacter 10.32±2.9  (p<0.05 vs viral)  **f-Lactoferrin, µg/g**  Severe AGE 11.32±3.29  P<0.05 vs moderate AGE  P<0.05 vs mild AGE  Moderate 3.77±2.08  Mild 1.51±1.36 | NA | Chung Shan Hospital  Grants | Fecal lactoferrin is a non-invasive marker able to predict bacterial vs viral infection, and the relative values may be associated with the severity of AGE, corresponding to Vesikari and Clark scores |

AGE=acute gastroenteritis; AUC=area under the curve; BGA=bacterial acute gastroenteritis; CRP=C-reactive protein; EAEC=enteroaggregative E coli; fCP=fecal calprotectin; NV=norovirus; RV=rotavirus; VGE= viral acute gastroenteritis.

**Table 3.3. Does Any Biochemical Test Change the Approach to the Child With Gastroenteritis? (Biochemistry)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Type of Study** | **Country** | **Inpatient**  **Outpatient** | **Follow-up**  **n/N** | **Population** | **Intervention** | **Comparison** | **Outcome measures** | **Results /Effect size** | **Risk of Bias** | **Source of Funding** | **Conclusions and Comments** |
| Hayajneh WA, 2010 | Prospective  Cross-sectional  Jan 2007 to May 2007 | Jordan | Inpatient | NA | 251 children  AGE  Dehydration  Severe 9%  Mild 91% | NA | Dehydration severity | Clinical and laboratory associations with severity of dehydration | **Severe vs mild dehydration:**  **More hyperNa**  52% vs 3%, p<0.001  **More hyperK**  17% vs 3%, p<0.001  **Less isoNa**  39% vs 95%, p<0.001  **Mean urea,mmol/L**  16.2 vs 5.5, p<0.001  **Mean creatinine,µmol/L**  69 vs 38, p<0.001  **Mean glucose, mmol/L**  5.9 vs 4.7, p<0.001  **AUC urea**  0.991 (95%CI 0.98-1.001)  P<0.001  **AUC Natrium**  0.862 (95% CI 0.74-0.97)  P<0.001  **AUC creatinine**  0.850 (95%CI 0.75-0.94)  P<0.001  **AUC Kalium**  0.69 (CI 95% 0.55-0.82)  P<0.006  **AUC glucose**  0.684 (CI 95% 0.57-0.79)  P<0.007 | NA | None declared | Historical and clinical characteristics in this cohort did not correlate with the degree of dehydration  Serum urea, creatinine, sodium, potassium and glucose were independently correlated with the degree of dehydration.  Serum urea performed best  The results from this study are in conflict with the results from previous studies and AAP and ESPGHAN guidelines |
| Steiner MJ, 2007 | Prospective cohort study  Convenience sample | USA | Outpatient ER | Variable | 74/79  Children AGE  Age 17.3m  (3-36m) | NA | Presence of dehydration | Urine specific gravity, urine ketones and output during rehydration | **Urine specific gravity** correlation with % dehydration  r=-0.06, p=0.64  **Urine ketone levels** correlation with % dehydration  r=0.08, p=0.52  **Urine output during** rehydration  correlation with % dehydration  r=0.01, p=0.96 | NA | None declared | Elevated urine specific gravity and urine ketones , low urine output were not useful diagnostic tests for the identification of dehydration during the initial assessment of children with AGE |

AAP=American Academy of Pediatrics; AGE=acute gastroenteritis; AUC=area under the curve; CI=confidence interval; ER=Emergency room; ESPGHAN= European Society for Paediatric Gastroenterology, Hepatology, and Nutrition.

HOSPITAL MANAGEMENT

**Table 4.1. What are the indications for hospitalization?**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **QoS** | **Country** | **In/Out**  **Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU** | **ITT** | **Outcomes measures** | **Effect measure** | **Effect size**  **(95% CI)** | **Comments** |
| Pockett RD, 2011 | Retrospective cohort study | +/- | UK | Inpatients | N=1334 children ≤5 yr of age with RV-AGE | — | — | Correlation with deprivation rank | — | — | Variation of hospital admissions' rates in relation to the decrease of a deprivation ranking\* | Rates | from 0.346 to 0.287 per 10,000 (p < 0.001) | Hospital admissions increased as deprivation increased\* |  |  |
| \*Index of Multiple Deprivation (IMD) 2007 for England | | | | | | | | | | | | | | |  |  |
| Kyle RG, 2011 | Retrospective study | + | UK | Inpatients (ED) | 24,481 children under 15 years admitted to ED for breathing difficulty, fever or diarrhoea during 2007/2008. | No | No | No | \_ | \_ | Index of Multiple Deprivation | Sperman rho | 0.31, p=0.09 | There were no statistically significant relationships between the ED admission rate of children admitted for diarrhoea and the Index multiple derivation and its single indicators. |
| overcrowding | Sperman rho | 0.21, p=0.267 |
| houses in poor condition | Sperman rho | 0.11, p=0.543 |
| air quality | Sperman rho | 0.16, p=0.387 |
| homelessness | Sperman rho | 0.14, p=0.439 |
| Freedman SB, 2011 | Prospective cohort study | + | Canada | Inpatients (ED) | 647 children 3-48 months admitted to 11 different ED. Exclusion: children already enrolled in other studies or families that were unavailable/unable to complete telephone follow-up | No | No | No | 398/446 (89%) | \_ | proportion of children treated with IV rehydration | number and % | 149/647 (23%, range 6-66%) | The use of IV rehydration varied dramatically among different institutions. IV rehydration at the index visit was significantly associated with the institution providing care and was not associated with a reduction in the need for follow-up care |
| risk of readmission after IV therapy in target visit vs no IV therapy | rate | 20% vs 9%, p=0.002 |
| Volume of IV fluids | range and variation | 15-87 ml/kg, p=0.003 |
| Predictors of IV rehydration: | | |
| institution location | OR (95%CI) | 3.0 (1.8 –5.0) |
| vomiting bile or blood | OR (95%CI) | 2.6 (1.2–5.5) |
| previous physician visit | OR (95%CI) | 1.7 (1.0–2.7) |
| n° vomiting in 24 hours | OR (95%CI) | 1.1 (1.0 –1.1) per additional episode |

AGE=acute gastroenteritis; ED=Emergency department; OR=odds ratio; QoS=Quality of Study; RV=rotavirus.

**Table 4.2. What hygiene and isolation precautions are indicated for a child with AGE?**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study**  **type** | **QoS** | **Country** | **In/Out**  **Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU** | **ITT** | **Outcomes measures** | **Effect measure** | **Effect size (95% CI)** | **Comments** |
| Valentini D, 2013 | Prospective cohort study | + | Italy | Inpatients | N=232 between 1 month and 16 years of age admitted for AGE | — | Collection of clinical data and stool samples | Coinfections vs Monoinfections | 232/275 | — | Max. no of diarrhea stools/24 h (≥6) | OR (95%CI) | 8.79 (3.32;23.28) p <0.001 | Coinfection with different pathogens is associated with a more severe course of symptoms |
| Duration of diarrhea (days) (≥5) | 3.81 (1.47;9.86) p= 0.006 |
| Duration of vomiting (days) (≥3) | 7.11 (2.74;18.42) p<0.001 |
| Fever (≥38°) | 17.78 (2.32;136.17) p=0.006 |
| Severe dehydration (%) | 28.70 (3.04;270.6) p=0.003 |

AGE=acute gastroenteritis; OR=odds ratio.

**Table 4.3. What are the indications for nasogastric rehydration?**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **QoS** | **Country** | **In/Out Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU** | **ITT** | **Outcomes measures** | **RCT n** | **Effect measure** | **Effect size**  **(95% CI)** | **Comments** |
| Freedman SB, 2012 | Prospective cross-sectional study | + | Canada | Inpatients (ED) | N=434 children aged 3-48 months with AGE; N=113 health care providers | — | Phase1: caregivers were asked to complete a survey on nasogastric rehydration (vs IV). Phase 2: data recorded. Phase 3: health-care providers completed a survey | IV rehydration | — | — | Caregivers who did not believe that IV/NG insertion is easy (NG group vs IV group) |  | Rates | 77% vs 59% (p<0.001) | Most health care providers are unfamiliar with the use of NG rehydration and this treatment choice is in keeping with caregivers desires |
| Caregivers who did not believe that IV/NG rehydration will replenish fluids (NG group vs IV group) | Rates | 11% vs 3% (p<0.001) |
| Estimated pain with IV/NG insertion according to caregivers ‘perception (0=no pain 100= worst possible pain) (NG group vs IV group) | Interquartiles | 80(60-100) vs 70(50-90); p<0.001 |
| Estimated pain with NG insertion according to health-care providers (0=no pain 100= worst possible pain) (Nurses vs Medical staff vs Fellows) | Median±SD | 64±18 vs 52±25 vs 50±16; p=0.007 |
| Estimated percentage of vomiting in children rehydrated with NG according to health-care providers (Nurses vs Medical staff vs Fellows) | Median±SD | 24±19 vs 11±11 vs 22±20; p=0.001 |
| Estimated percentage of shorter ED stay in children rehydrated with NG according to health-care providers (Nurses vs Medical staff vs Fellows) | Rates | 38% vs 56% vs 75%; p<0.001 |
|  | MA (17 RCTs) | ++ | High income (USA, Australia, Finland) and low income (Puerto Rico, Egypt, Mexico, Iran, Afghanistan, Colombia, Peru) | Inpatients and Outpatients | N=1811 (most trials included children from 3mo to 5y) | — | ORT orally or via NGT (40-50 ml/kg administered in 3-6 h) | IV therapy | — | — | Failure to rehydrate | 18(1811) | Weighted mean difference (95%CI) | 0.04 (0.01 to 0.07) | see GL |
| Weight gain (g) at discharge | 6 (369) | Weighted mean difference (95%CI) | -26 (-207 to 154) NS |
| Percent weight gain (g) at discharge | 5 (767) | Weighted mean difference (95%CI) | -0.26 (-1.56 to 1.05) NS |
| Length of hospital stay | 6 (526) | Weighted mean difference (95%CI) | -1.2 (-2.38 to -0.02) ↓ |
| Incidence of hyponatremia | 2 (248) |  | NS |
| Incidence of hypernatremia | 10 (1062) | Weighted mean difference (95%CI) | 0.0 (-0.01 to 0.01) NS |
| Duration of diarrhea (h) | 8 (960) | Weighted mean difference (95%CI) | -5.9 (-12.7 to -0.89) ↓ |
| Total fluid intake (ml/kg) at 6h | 8 (985) | Weighted mean difference (95%CI) | 32.1 (-26.7 to 90.9) NS |
| Total fluid intake (ml/kg) at 24h | 7 (835) | Weighted mean difference (95%CI) | 73.45 (-31.8 to 178.7) NS |
| Phlebytis |  |  | More often with IVT |
| Paralytic ileus |  |  | More often with ORS but NS |
| Varavithya W, 1978 | RCT | - | Thailand | Inpatients | N= 22, 4–17 months of age, moderate dehydration | NO | Nasogastric Rehydration (150 mL/kg/day - 10–20 mL/kg/h for 2 h, then a costant rate over 22 h) | IV rehydration with 5% dextrose 0.3% Na+ (150 mL/kg/day - 10-20 mL/kg/h for 2h, then a costant rate over 22h) | 22/22 | Yes | Weight gain | — |  | Similar weight gain, oral intake, and improvement in laboratory test results between groups; sodium and osmolarity returned to normal without complications in both groups\*\* |  |
| Stool loss |
| Oral intake |
| Blood Sodium |
| Osmolarity |
| Serum specific gravity |
| Hidayat S, 1988 | RCT | - | Indonesia | Inpatients | N=75 , 1–59 months of age, severe dehydration (WHO) | NO | Nasogastric rehydration (WHO standard ORS) 40 ml/kg in the first hour, 30 ml/kg in the second, 20 ml/kg in the third and fourth hours | IV rehydration: lactated Ringer's solution (40 mL/kg X 1h, then 30 mL/kg X 1h, then 20 mL/kg X 2h) | 75/75 | Yes | Weight gain | — | Rates | No difference\*\* |  |
| Hourly assessment of degree of dehydration | Rates | No difference\*\* |
| 4-h assessment of degree of dehydration | Rates | No difference\*\* |
| Mean hospital stay | Mean difference | No difference\*\* |
| Duration of vomiting | Mean difference | No difference\*\* |
| Pignatelli S, 2000 | Prospective cohort study | + | Burkina Faso | Inpatients | N=4131 < 5y of age with acute diarrhea and severe dehydration | — | Nasogastric rehydration (50-100 mL/kg/day for the first 10 kg of weight and 25 to 50 mL/kg per day for the remaining) | — | — | Yes | Increased weight at 4-5 h (%) | — | Rates | 3717/4131 (90%); p<.001 | Safe and effective in the treatment and prevention of dehydration in developing countries |
| Longer period of infusion (%) |  | Rates | 413/4131 (10%) |
| Powell CV, 2011 | Non-inferiority RCT | + | Australia | Inpatients (ED) | N=254 , 6-72 months of age, moderate degree of dehydration (Gorelick) | Appropriate | Rapid Nasogastric Rehydration (100 ml/kg ORS in 4 h) | Standard Nasogastric Rehydration (according to the % of weight loss) | 207/254 | NO | Additional loss of >2% compared with admission weight |  | Rates Difference (95%CI) | 2.6% (-5.3% to 10.5%); p=0.524 | No differences between groups (Rapid in 4h vs 24 hours) in terms of efficacy and safety. However, even if RNR administered in ED could reduce the need of hospitalization, discharge failed in about one fourth of patients. Limits: ITT is missing; 21/254 patients were lost at FU and no reason provided; single-blinding |
|  |  |  |  |
| Inability to tolerate the insertion of NGT |  | Rates (95%CI) | 0.8% (0-2.4) vs 1.8% (0-4.4); p=0.51 |
| Persistent vomiting |  | Rates (95%CI) | 5%(1.0-9.0) vs 2.8%V(0-5.9%); p=0.38 |
| Commencement of IV rehydration |  | Rates (95%CI) | 5.9% (2.9-11.7) vs 4.9% (2.0-10.3); p=0.66 |
| Continued signs of moderate dehydration (>3 clinical signs) |  | Rates (95%CI) | 18.4%v(11.4-25.4) vs 28.4% (19.6-37.2) p=0.08 |
| Need for NGT fluids beyond 24 hours (SNR only) |  | Rates (95%CI) | 9.2% (3.7-14.7) |
| \*\*Rouhani | | | | | | | | | | | | | | | |

AGE=acute gastroenteritis; ED=emergency department; IV=Intravenous; NG=Nasogastric; NGT=Nasogastric tube; NS= Not significant; ORS= Oral Rehydration Solution; QoS=Quality of Study; RNR=rapid nasogastric rehydration; SNR=standard nasogastric rehydration.

**4.4. What are the indications for intravenous rehydration?**

**Table 4.4.1 Composition**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **QoS** | **Country** | **In/Out**  **Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU** | **ITT** | **Outcome measures** | **Effect measure** | **Effect size**  **(95% CI)** | **Comments** |
| Neville KA, 2006 | RCT | + | Australia | Inpatients (ED) | 124 children with AGE (62 per group). Exclusion criteria: Renal or pulmonary disease, abnormal ADH secretion, ADH active drugs, pituitary/hypotalamic disease. | Not clearly described | IV rehydration with 0.45% saline in 2.5% dextrose (N/2) | IV rehydration with 0.9% saline in 2.5% dextrose (NS) | 102/124 | Not clear | Change in [Na] mmol/L in hyponatremic patients (N/2 vs NS) | mean (SD) | 0.4 (1.7) vs 2.4 (2.0), p=0.003 | Hypotonic saline solutions exacerbate the tendency to develop dilutional hyponatremia while isotonic solutions are protective. The maximum decrease in [Na] was of 6mmol/L in the 2 patients treated with rapid hypotonic rehydration |
| Change in [Na] mmol/L in normonatremic patients (N/2 vs NS) | mean (SD) | -2.3 (2.2) vs +0.8 (2.4), p<0.001 |
| [Na] decrease > 2 mmol/L in hyponatremic patients (N/2 vs NS) | prevalence | 13% vs 0% |
| [Na] decrease > 2 mmol/L in normonatremic patients (N/2 vs NS) | prevalence | 51% vs 13% |
| Hanna M, 2010 | Retrospective study | +/- | USA | Inpatients | 141 records of patients admitted for AGE having at least two registration of serum electrolytes. | \_ | 10-40 ml/kg fluids containing 5% dextrose in 0.2, 0.3 or 0.45 % saline. | \_ | \_ | \_ | Development of hyponatremia | prevalence | 18/97 (18,5%) | 18,5% developed a mild hyponatremia (Na 133,4±0,9 mEq/L) |
| Han JJ, 2009 | RCT | +/- | Korea | Inpatients | 33 **neonates** with acidosis secondary to AGE (Ph<7.25 or BE-15). In addition to interventions, all patients received maintenance with 5% dexstrose and NaCl 20 mEq/L, correction of acidosis and potassium supplementation. | Not clearly described | 10 ml/kg of 5% Albumin | 10 ml/kg of 0.9% normal saline | 33/33 | Not reported | Weight gain (Albumin vs normal saline) | mean % of weight gain±SD | 5.08±6.33 vs 5.67±5.73, p=NS | No differences either in the pH, BE and HCO3 levels, in the body weight and weight gain 4 days after treatment or in the length of hospital stay. |
| Length of stay (Albumin vs normal saline) | mean days±SD | 8.13±3.23 vs 9.36±4.16, p=NS |
| Persistence of acidosis after 3 h rehydration | rate | 80% vs 61.1%, p=NS |
| Levy JA, 2007 | Case-control study | +/- | USA | Inpatients (ED) | 56 cases and 112 controls arriving at the ED for dehydration due to AGE. Cases were those children requiring return visit with admission | \_ | \_ | \_ | \_ | \_ | Risk of return visit with admission for children receiving no dextrose-containing fluids | OR [95%CI] | 3.9 [1.8 to 8.7] | children who received more IV **dextrose** independently from fluid amount, were less likely to have a return visit requiring admission. |
| Risk of return visit with admission for children receiving no dextrose-containing fluids, according to fluid amounts | OR [95%CI] | <500 mg/kg=3.0 [1.6 to 5.8] <750 mg/kg=3.7 [1.7 to 8.1] <1000 mg/kg= 5 [1.7 to 14.9] |
| Hoorn EJ, 2004 | Observational study |  | Canada | Inpatients | 40 children who had a hospital-acquired hyponatremia (Na<136 mmol/L) compared with non-hyponatremic patients who had at least 2 [Na] evaluation during their stay (1:3 ratio) | \_ | \_ | \_ | \_ | \_ | Electrolyte free water received (cases vs controls) |  | 2±2 vs 1±1, p=0.001 | Cases received 3-fold more elecrolyte free water than controls and had a greater positive fluid balance than the control group (P=0.02). No significant differences related to the underlying disease. |
| Saba TG, 2011 | RCT | + | Canada | Inpatients | 59 children (34 surgical and 25 medical, **NO AGE**) aged 3 months to 18 years admitted to ED for medical or surgical problems. Exclusion criteria: electhrolyte alterations, neurological, cardiac or renal illness, edema and diuretic drugs use. | Adequate | IV rehydration with 0.9% Saline in 5% dextrose (Isotonic) | IV rehydration with 0.45% saline in 5% dextrose (Hypotonic) | 12/25 medical and 25/34 surgical patients | not performed | Rate of change in [Na] | median [IQR] | 0.20[0.03 to 0.4] vs 0.08[-0.15 to 0.16] | The absolute change in [Na] was greater for 0.9% saline group compared with the 0.45% group (+3mmol/L vs +1 mmol/L), but not statistically significant |
| Number of patients with decrease in [Na] | number (%) | 3 (19%) vs 5 (24%) |
| Hyponatremia [Na<136] | number (%) | 1(6%) vs 1 (5%) |
| Hypernatemia [Na>145] |  |  |
| Yung M, 2009 | 4 arms RCT | +/- | Australia | Inpatients (PICU) | 50 children admitted to PICU for different reasons (37 surgery, 15 of them ventilated). **NO AGE** | Adequate | Rehydration with 0.9% saline (Isotonic). Subdivision in two groups 1. full maintenance regimen and 2. restricted fluids | Rehydration with 4% dextrose and 0.18% saline (hyposmolar). Subdivision in two groups 1. full maintenance regimen and 2. restricted fluids | 50/50 | not performed | Overall [Na] fall | mean mmol/L | 2.3 (+ 4.0) | The change in [Na] was significantly affected by fluid type (P = 0.0063) but not fluid rate (P = 0.12). Among surgical patients, there were significantly greater falls in mean [Na] for hyposmolar compared with isosmolar fluids: 4.4 (1.9, 6.8) mmol/L, P = 0.0009 |
| [Na] fall difference (hypotonic vs isotonic) | difference (95%CI) in mmol/L | 3.0 (0.8–5.1), p=0.006 |
| [Na] fall difference full (maintenance vs restricted) | difference (95%CI) in mmol/L | 1.6 (-0.7, 3.9), p=NS |
| Akech SO, 2010 | Phase II RCT | + | Africa | Inpatients | children with severe malnutrition and shock, septic shock **BUT Not DUE TO AGE** . |  |  |  |  |  |  |  |  | Isotonic fluids were associated with modest improvement when compared to half-strength Darrow's in 5% dextrose |

ADH=Antidiuretic hormone; AGE=acute gastroenteritis; ED=emergency department; IV= intravenous; QoS=Quality of Study SD=standard deviation.

**Table 4.4.2. Regimen**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **QoS** | **Country** | **In/Out**  **Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU** | **ITT** | **Outcomes** | **Outcome measure** | **Effect size**  **(95% CI)** | **Comments** |
| Freedman SB, 2013 | Overview of 4 systematic reviews of RCTs (3 cochrane reviews) | ++ | High and middle income | In and outpatients | 95 unique randomized controlled trials (N=12478)  87 randomized controlled trials included subjects < 18 years (N = 10 954) | All studies included in the review were RCTs | Oral rehydration | IV rehydration | - | - | Length of stay (6 trials = 526 patients) | Mean difference | −1.20 (−2.38 to −0.02) |  |
| Complication (phlebitis) | Risk difference | −0.02 (−0.04 to −0.01) |
| Freedman SB, 2013 | RCT | + | Canada | Inpatients (ED) | 224 children (114 intervention group vs 110 control group) aged 3 months-11 years with dehydration (CDS>3) due to AGE and no response to ORT. **Exclusion criteria**: underlying chronic diseases. | Adequate | IV rehydration with **60 ml/kg** 0.9% saline solution in **1 h** followed by 5% dextrose in 0.9% saline at a maintenance rate. | IV rehydration with **20 ml/kg** 0.9% saline solution in **1 h** followed by 5% dextrose in 0.9% saline at a maintenance rate. |  | Yes | Change in sodium levels (mEq/L) (60mL/Kg vs 20 mL/Kg) | Mean±SD | 1.6±2.4 vs 0.9±2.2 (p=0.04) | Large volume IV fluids does not promote the development oh hyponatraemia |
| Sodium decrease ≥2 mEq/L from 0-4 h | Rates | 8/112 (7%) vs 17/105 (16%); (p=0.04) |
| Sodium increase ≥2 mEq/L from 0-4 h | Rates | 59/112 (53%) vs 39/105 (37%); (p=0.02) |
| Freedman SB, 2011 | RCT | + | Canada | Inpatients (ED) | 226 children (114 intervention group vs 112 control group) aged 3 months-11 years with dehydration (CDS>3) due to AGE and no response to ORT. **Exclusion criteria**: underlying chronic dieases. | Adequate | IV rehydration with **60 ml/kg** 0.9% saline solution in **1 h** followed by 5% dextrose in 0.9% saline at a maintenance rate. | IV rehydration with **20 ml/kg** 0.9% saline solution in **1 h** followed by 5% dextrose in 0.9% saline at a maintenance rate. |  | Yes | Rehydration (CDS<1) within 2 hours after treatment | absolute difference (95%CI), NNT | 6.5% (CI 5.7% to 18.7%, p=0.32) NNT=15 | Children were moderately dehydrated. No difference in major outcomes between the two treatment arms was found. No relevant benefit of the rapid rehydration regimen. **Time to discharge** was slightly higher in rapid dehydration group although it did not achieve significance settled at 0.01 (6.3 h vs 5 h, **p=0.03**) |
| Prolonged IV treatment | absolute difference (95%CI) | 8.9% (CI 21% to -5%, p=0.19) |
| Clinical dehydration scores | rate | p=0.96 |
| Time to discharge | mean time (h) | 6.3 h vs 5 h (p=0.03) |
| Physician comfort to discharge within 4 hours (Rapid vs standard group) | 5 point Likert scale | 61(54) vs 74 (66), p=0.06 |
|
| Nager AL, 2010 | RCT | + | USA | Inpatients (ED) | 88 children aged 3-36 months with moderate dehydration due to AGE. **Exclusion criteria**: electrolyte alteration, severe dehydration/shock, surgical conditions. | Adequate | IV rehydration with 50 ml/kg 0.9% saline in **1 h** | IV rehydration with 50 ml/kg 0.9% saline in **3 h** | 88/88 | No | mean weight (g) gain (% of weight), rapid vs standard group | Mean (%) | 474 (4.2%) vs 408 (3.8%), p=0.34 | Early discharge for cases (2 h vs 4 h). No difference between the two groups for all the outcomes. |
| Return visits | Frequency (95%CI) | 15.6%(6.5 to 29.5) rapid vs 14% (5.3 to 28), p=0.99 |
| Electrolyte alteration | single values | NS difference |
| Freedman SB, 2011 | Prospective cohort study | + | Canada | Inpatients (ED) | 647 children 3-48 months admitted to 11 different EDs. **Exclusion criteria**: children already enrolled in other studies or families that were unavailable/unable to complete telephone follow-up | No | No | No | 398/446 (89%) | \_ | proportion of children treated with IV rehydration | number and % | 149/647 (23%, range 6-66%) | The use of IV rehydration varied dramatically among different institutions. The volume of IV fluids administered also varied according to site (P .003), with a range between 15 and 87 ml/kg). |
| Frequency of readmission in patients undergoing IV therapy vs no IV therapy | rate | 20% vs 9%, p=0.002 |
| Volume of IV fluids | range and variation | 15 -87 ml/kg, p=0.003 |
| **Predictors of IV rehydration:** | | |
| institution location | OR (95%CI) | 3.0 (1.8 –5.0) |
| bilious or bloody vomiting | OR (95%CI) | 2.6 (1.2–5.5) |
| previous physician visit | OR (95%CI) | 1.7 (1.0–2.7) |
| n° vomiting in 24 h | OR (95%CI) | 1.1 (1.0 –1.1) per additional episode |
| Moineau G, 1990 | Prospective Cohort study | - | Canada | Inpatients (ED) | 17 children with isonatremic mild-to-moderate dehydration due to AGE, aged 1-6 years | No | 30 ml/kg 3.3% dextrose + 0.3% saline over 3 h | \_ | 17/17 | no |  |  |  | No patients required hospitalization. Only one patient required a new course of rapid IV rehydration. |
| Spandorfer PR, 2005 | RCT | + | USA | Inpatients (ED) | 73 children (ORT 36 vs IV 37) aged < 3 years (mean age 15 m) with moderate dehydration (Gorelick score) secondary to AGE. **Exclusion criteria**: hypotention, diarrhea > 5 d, chronic illnesses, malnutrition | Adequate | Oral rehydration with 50 ml/Kg (for dehydration score 3,4,5) or 75 ml/Kg (for score >6) hyposmolar ORS | IV rehydration with 2 bolus of 20ml/Kg saline solution in 1 h. Then oral rehydration for 3 h | 67/73 (3 ORT, 3 IVT) | yes | Success of treatment at 4 hours (defined as resolution of dehydration, weight gain, correction of urine output, absence of severe emesis) | percentage of responders and risk difference | ORT 55.6% vs IV 56.8%, RD= -1.2% [95%CI -24% to 21.6%] | Initiating treatment with ORT was quicker than with IVT. ORT gained less weight than IVT |
|
| Time to initiate therapy | time and difference [95%CI] | ORT 15 min vs IV 36 min, RD 21.2 [CI 10.3 to 32.1] |
| Improvement of dehydration after 2 h | % of responders and difference | ORT 78.8% vs IV 80%, RD -1.2% [95%CI -20.5% to 18%] |
| Hospitalization rate | rate | ORT 30.1% vs IV 48.7%, RD -18.1% [-40.1% to 4%] |
| Phin SJ, 2003 | Prospective study with historical controls | +/- | Australia | Inpatients (ED) | 145 children aged 6 months to 16 years, with AGE < 48h prospectively enrolled, 170 historic controls. **Exclusion criteria:** bloody stools, bilious vomiting, chronic medical conditions. | \_ | Pathway including oral administration of fluids in 1 h followed by 20 ml/kg/h of 0.45% + 2.5% dextrose or Gastrolyte per NGT. | Hystoric pathway, IV rehydration over 24 h and NGT rarely used. | \_ | \_ | discharge in 8 h (mild dehydration) | rate | 61.3% vs 72.7%, p=NS | rapid rehydration in children moderately dehydrated is effective in reducing admission rate and lengths of stay in ED |
| discharge in 8 h (moderate dehydration) | rate | 44.2% vs 3.7%, p<0.001 |
| admission rate (mild dehydration) | rate | 26.9% vs 25.9%, p=NS |
| admission rate (moderate dehydration) | rate | 55.8% vs 96.3%, p<0.001 |
| procedure rate (mild dehydration) | rate | 62.4% vs 23.9%, p<0.001 |
| procedure rate (moderate dehydration) | rate | 94.2% vs 88.9%, p=NS |
| Reid SR, 1996 | Prospective cohort study |  | USA | Inpatients (ED) | 58 patients aged 6 months to 13 years (median age 22 months) with moderate dehydration | \_ | 20-30 ml/kg isotonic cristalloid solution IV in 1-2 h followed by 30-90 ml of ORT | \_ | \_ | \_ |  |  |  | All patients demonstrated improvement of hydration degree. 28% did not tolerate ORT and were admitted to continue IVT. No complications were registered during IVT. |

AGE=acute gastroenteritis; ED=emergency department; IVT=Intravenous therapy; NGT=Nasogastric tube; ORS= Oral Rehydration Solution; ORT=Oral rehydration therapy; QoS=Quality of Study.

**Table 4.4.3. Treatment of hypernatremia**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **QoS** | **Country** | **In/Out Patients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU** | **ITT** | **Outcomes measures** | **Effect measure** | **Effect size (95% CI)** | **Comments** |
| El-Bayoumi MA, 2012 | Retrospective study | + | Egypt | Inpatients (PICU) | 48 children (mean age 21.8 m) with AGE and hypernatremic dehydration [Na]>150 (mean 163 mmol/L). **Exclusion criteria**: renal failure and diseases | \_ | **No Intervention.** Rehydration regimen: Fluid bolus of 20ml/kg 0.9% saline in 20 min followed by 48h infusion of 25-50 ml/kg/day of 0.9% saline in 5% dextrose. Velocity was 4 ml/kg/h first 10 Kg, 2 ml/kg/h 10-20 kg and 1ml/kg/h above 20 kg. | \_ | \_ | \_ | risk of mortality in children receiving > 40 ml/kg initial fluid bolus | OR (95%CI) | 3.3 (1.5 to 7.2) | Serum Na should be lowered slowly with rate of 0.5mEq/L/h. No difference in [Na] between children who presented seizures and not. |
| risk of seizures | rate | 6.3% |
| Hourly delta of Na 0-6 h | mean delta (mEq/L/h) | 0.58 seizures vs 0.52 not (p=0.08) |
| Hourly delta of Na 0-24 h | mean delta (mEq/L/h) | 0.65 seizures vs 0.51 not (p=0.02) |
| Hourly delta of Na 6-24 h | mean delta (mEq/L/h) | 0.63 seizures vs 0.51 not (p=0.037) |
| Robertson G, 2007 | Retrospective study |  | South Africa | Inpatients (PICU) | 57 children with hypernatremia (Na>145, meadian 165 mmol/L) | \_ | **No intervention**: Maintenance according to Holliday-Segar + 50 ml/kg/day for moderately dehydrated children and 100 ml/kg/day for severely dehydrated with half Darrow's Dexstrose (5% dexstrose and 61 mEq/L Na) | \_ | \_ | \_ | Median rate of Na fall | velocity mmol/L/h | 0.6 | The majority of children in this study received a hypotonic IV infusion containing 61 mmol/L sodium. Although univariate analysis demonstrated a non-significant trend towards a more rapid fall in serum sodium in children who received solutions containing <61 mmol/L of sodium, this was not associated with a difference in outcome. |
| Incidence of seizures (fall <0.6 group vs >0.6 mmol/L/h group) |  | p=0.43 |
| Incidence of adverse event (fall <0.6 group vs >0.6 mmol/L/h group) |  | p=0.31 |
| Mortality | Percentage | 7% |
| Sharifi J, 1985 | RCT | +/- | Iran | Inpatients (PICU) | 470 children aged 1-18 months admitted for severe AGE | Not appropriately described | NGT rehydration 40 ml/kg/h (max 400 ml/h) ORS for 6 h followed by maintenance per os or NGT with hypotonic ORS | IV 20-30 ml/Kg/h Ringer Solution followed by maintenance fluids for 48 h |  | No | Seizures in hypernatremic patients treated with NGT vs IV rehydration | rate (%) | 2/34 (6%) vs 6/24 (25%), p=0.05 | ORT through NGT is successful in treating severe dehydration due to AGE and superior to IV therapy in reducing the complications associated with the treatment of hypernatremia. Methodological limitations: protocol, randomization and allocation concealment not described. |

AGE=acute gastroenteritis; NGT=Nasogastric tube; ORS=oral rehydration solution; QoS=Quality of Study.

**Table 4.5. When to discharge a child admitted because of gastroenteritis**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **QoS** | **Country** | **In/OutPatients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU** | **ITT** | **Outcomes measures** | **Effect measure** | **Effect size (95% CI)** | **Comments** |
| Patel B, 2009 | Intervention study | +/- | US | ED | Patients aged 3 months to 18 years with | No | Written discharge instructions reinforced verbally by the bilingual discharge facilitator | Standard discharge group vs intervention group | \_ | No | Recall of 7 warning signs and symptoms assessed 24 to 48 hours after the ED visit (English speakers) | Mean (95%CI) | 3.5 (3.26-3.78) vs 4.1 (3.83-4.43) | Verbal reinforcement of written discharge instructions by a bilingual DF improves parental recall of discharge instructions for gastroenteritis. |
| Recall of 7 warning signs and symptoms assessed 24 to 48 hours after the ED visit (Spanish speakers) | Mean (95%CI) | 3 (2.67-3.36) vs 4.5 (4.18-4.88) |
| Callery P, 2010 | Retrospective | + | UK | Inpatients (ED) | All children under 15 years of age discharged following emergency admission for breathing difficulty, feverish illness and/or diarrhea during 2005/2006 (n=20,354) or 2006/2007 (n=23,018) | No | No | No | No | No | Rate of readmission after same day discharge | | | The total number of admissions to hospital in the year was associated with its readmission rate (Kendall's tau(b)=0.71, p=0.002). Variations between hospitals suggest that other factors can also affect readmission rates. |
| Overall | Kendall's tau | 0,61, p=0,007 |
| Respiratory illnesses | Kendall's tau | 0,83, p<0,001 |
| Feverish illnesses | Kendall's tau | 0,50, p=0,023 |
| Acute diarrhea | Kendall's tau | 0,37, p=0,098 |

DF= discharge facilitator; ED=emergency department; QoS=Quality of Study.

**Table 4.6. Can any therapeutic intervention reduce the length of hospital stay?**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **QoS** | **Country** | **In/OutPatients** | **Population** | **Randomization** | **Intervention** | **Comparison** | **FU** | **ITT** | **Outcomes measures** | **RCT (n/N)** | **Effect measure** | **Effect size (95% CI)** | **Comments** |
| Dupont C, 2009 | RCT | + | Peru and Malaysia | Outpatients and Inpatients | N=602 (1-36 mo) | DB | Smectite (6-12 g) | Placebo. | - | Yes | Duration of diarrhea (hours) | - | - | - | Peru: lower 72-hour cumulative stool output (P=0.032); shorter duration of diarrhea (P=0.001).  Malaysia: lower 72-hour stool output (P=0.007); shorter duration of diarrhea (P=0.001). |
| Mujawar QM, 2012 | RCT | +/- | India | ED | N=117 (2-5 y) with AGE. | Single blinded | Diosmectite (4.5 g/d for 5 d) | no intervention | - | - | Duration of diarrhea | - | - | - | Shorter time for resolution of diarrhea (P<0.001). |
| Lehert P, 2011 | MA | ++ | high- or middle-income countries | Outpatients and Inpatients | (9 RCTs, n=1384, 1 mo- 15 y) | Heterogeneous | Racecadotril (typically 1.5 mg/kg TID) | placebo or equivalent (in particular, kaolin-pectin) | - | - | Patients with recovery defined as patients with a diarrhea duration of less than 2 days | 9 | HR (95%CI) | 2.04 (1.85 to 2.32)P<0.001 | Proven effective in reducing the duration of symptoms in children with AGE |
| Macgillivray S, 2013 | MA | ++ | high- or middle-income countries | Inpatients (1 outpatient) | N= 2973 children aged two months to 59  Months (29 RCT) | Heterogeneous | Lactose-free milk, milk products, or foodstuffs | Lactose-containing milk, milk products, or foodstuffs | - | Yes | Duration of diarrhea (hours) | 16/29 | Mean difference (range) | -17.77(25.32 to 10.21) vs (28.8 to 230) | In young children with acute diarrhea who are not predominantly breast-fed, change to a lactose-free diet may result in earlier resolution  of acute diarrhea and reduce treatment failure. Diluting lactose-containing formulas may also have some beneﬁts but further trials are  required to have conﬁdence in this ﬁnding. However data were different in outpatients setting. |
| Treatment failure | 18/29 | Relative effect  (95% CI) | 0.52  (0.39 to 0.68) |
| Need for hospitalization | 1/29 | Relative effect  (95% CI) | 0.79  (0.09 to 6.65) |
| Szajewska H, 2013 | MA | ++ | High income (Europe) and low income | In and outpatients | N= 2963  patients (1603 in the experimental group and 1360 in  the control group) 🡪 15 studies | 5 unclear | Daily  doses of LGG ranging from 1.2 x 108 CFU to 2 x 1012 CFU in addition  to rehydration therapy | Placebo (10) | \_ | Yes | Duration of diarrhea in days. (High dose and low dose). | 12/15 | Mean (95%CI) | –1.11 [–1.91, –0.31] and –0.90 [–2.50, 0.69] | LGG reduces the duration of diarrhea either in terms of days and hospitalization |
| Duration of diarrhea in days. Setting (Europe and non-Europe). | 11/15 | Mean (95%CI) | –1.27 [–2.04, –0.49]and –0.87 [–1.81, 0.08] |
| Hospitalization in days. | 4/15 | Mean (95%CI) | –1.42 [–3.05, 0.21] |
| Dinleyici EC, 2012 | MA | ++ | high- or middle-income countries | Inpatients | 13 RCTs | Heterogeneous | *S boulardii* | Placebo or no intervention | Yes | Yes | Duration of hospitalization | n=449 | Mean difference (95%CI) | -0.84 (-1.14 to -0.54) | administration of this probiotic strain may reduce the duration of hospitalization in inpatient children |
| Freedman SB, 2013 | Overview of 4 systematic reviews of RCTs (3 cochrane reviews) | ++ | High and middle income | In and outpatients | 95 unique randomized controlled trials (N=12478)  87 randomized controlled trials included subjects < 18 years (N = 10 954) | All studies included in the review were RCTs | Probiotics | Oral rehydration | - | - | Length of stay | 10 trials = 1932 patients | Mean difference | −1.12 (−1.16 to −0.38) |  |
| Piescik-Lech M, 2013 | RCT | + |  |  |  |  | LGG (6 x 109) plus scmectite | LGG plus Placebo | 81/87 | Yes | Duration of intravenous therapy after randomization,  days | - | Median (range) | 1 (0–1) vs 1 (0–3) p=0.02 | LGG plus smectite and  LGG alone are equally effective for treating young children  with AGE. Combined use of the two interventions is not  justified. |
| Duration of hospitalization after randomization,  days |  | No difference |
| Vomiting, number |  | No difference |
| Need for hospitalization | Number (%) | No difference |
| Rautenberg TA, 2012 | cost utility analysis | + | UK | Outpatients | 10 individual studies, 2 SR and 2 MA | - | Racecadotril + ORS | ORS | - | - | Total incremental QALY gain |  | Probabilistic sensitivity analysis | +0.0008 | Considering the best  available evidence, racecadotril is cost effective in the treatment of AGE in children |
| Drug cost | Cost results | £12.17 vs £3.03 |
| Primary care |  | £51.12 vs £62.64 |
| Secondary care |  | £40.20 vs £416.82 |
| Adverse events |  | £0.35 vs £0.46 |
| Total mean cost per patient |  | £103.84 vs £482.95 |

AGE=acute gastroenteritis; LGG= Lactobacillus rhamnosus GG; ORS=Oral rehydration solution; QALY=quality adjusted life year.

TREATMENT

**Table 5.1. Rehydration**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Intervention** | | **Randomization** | **Allocation concealment** | **Blinding** | **ITT analysis** | **Population** | **Main results**  **(experimental group *vs.* control group)** |
| Santucci KA, 1998 | Frozen solution (FS) (Revital-ICE, PTS Labs, Deerfield, Ill) vs conventional glucose electrolyte solution (CS) | | Prospective controlled crossover trial. | | | | N=91 (6 months to 13 years of age) children with AGE seen in pediatric ED | Children with mild or moderate dehydration are more likely to tolerate FS than CS. Conventional solution failures crossed over to FS had a greater tolerance rate than the reverse. |
| Freedman SB, 2012 | **ORS with improved taste** | 2 sucralose-sweetened ORSs *vs.* rice syrup solid ORS | Adequate | Adequate | DB | + | N=66 (5-10 y), healthy children | Sucralose-sweetened ORSs significantly more palatable (P<0.001). |
| Diez-Gandia A, 2010 | 4 ORSs (cola, strawberry, fruit, neutral) | Adequate | No | Single-blinded | Yes | N=116 (6-9 y), healthy children | Preference for cola (rated as good or really good by 87.9%) and strawberry flavor (62.1%). |
| Piescik-Lech M, 2012 | Apple taste ORS *vs.* regular taste ORS | Adequate | Adequate | DB | No (ACA) | N=130 (4-48 mo) children with AGE | Similar resolution of signs of dehydration (P=0.28), adequate weight gain (P=0.48), urine production at 24 h (P=0.95). |
| Wadhwa N, 2011 | **ORS with zinc** | ORS with *vs.* ORSwithout zinc (40 mg/L) | Adequate | Adequate | DB | Yes | N=500 (boys, 1-35 mo) | Similar stool output (P=0.25); no difference or reduction in recovery time (HR 1.06, 95%CI 0.88 to 1.27). |
| Passariello A, 2011 | **ORS with zinc and prebiotics** | ORS with zinc (1 mmol/L) & prebiotics *vs.* standard ORS | Adequate | Adequate | SB | Yes | N=119 (3-36 mo) | Higher resolution of diarrhea at 72 h (P=0.01); reduced number of daily outputs at 24 h (P=0.002). |
| Gregorio GV, 2009 | **ORS with polymers** | Polymer-based ORS *vs.* glucose-based ORS | Of the 34 trials, the methods used to generate the allocation sequence were adequate (computer-generated or random-numbers table) in 24 trials and unclear in the remaining 10 trials. Less than half of the trials (12) used an adequate method to conceal allocation. The method was unclear in the other 22 trials.  Blinding of the participants, providers, and assessors was only done in three trials. Blinding was difficult or impossible in most trials because of the difference in the appearance of the ORS formulation after reconstitution.  All but two trials included an adequate (> 90%) number of randomized participants in the analysis. The number was assessed as inadequate in two trials. | | | | MA (34 RCTs, n=4214; 27 RCTs in children) | Fewer unscheduled intravenous infusions in the polymer-based ORS group compared with glucose-based ORS (ORS ≥ 310 and ≤ 270 groups combined) (RR 0.75, 95% CI 0.59 to 0.95; 2235 participants, 19 trials).  Wheat-based ORS resulted in lower total stool output in the first 24 hours compared with ORS ≤ 270 (MD -119.85 g/kg, SD -114.73 to -124.97; 129 participants, 2 trials). Adverse effects were similar for polymer-based ORS and glucose-based ORS. |
| Alam NH, 2011 | **ORS with L-isoleucine** | ORS with *vs.* ORS without L-isoleucine (2 g/L) | Adequate | Adequate | DB | Yes | N=50 (boys, 6-36 mo) | Reduced stool output on day 3 (P=0.03); smaller ORS intake on day 1 (P=0.04); similar duration of diarrhea (P=0.96). |
| Abdulrhman et al. 2010 \* | **ORS with honey** | ORS with *vs.* ORS without honey |  |  |  |  | N=100 (aged approx. 1.3 y) | Reduction in vomiting (P<0.001) and diarrhea frequency (P<0.05). |
| \*Article not entirely accessed | | | | | | | | |
| Esteban Carretero J, 2009 | Gelatin tannate + ORS | Gelatin tannate + ORS vs ORS alone | No – observational study | - | - | No | 239 children aged 3 months to 12 years with AGE (mean age 2.3 y) | Stool decrease index ORS  -0.1894 vs ORS + gelatin tannate -0.6023 (p<0.0001). The two groups of treatment differ at baseline with controls having more stools per day. |

AGE=acute gastroenteritis; ORS=Oral rehydration solution.

**Table 5.2. Nutritional management**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Type of Study** | **Country** | **In/Out**  **Patients** | **FU n/N** | **Population** | **Intervention** | **Comparison** | **Outcome measures** | **Results /Effect size** | **Risk of Bias** | | | | **Source of Funding** | **Conclusions and Comments** |
| **Randomization** | **Allocation Concealment** | **Blinding** | **ITT** |
| Gregorio GV, 2011 | Systematic review | 16 countries Europe, USA, Africa, Asia | 10 trials Inpatient 2 trials Outpatient | Variable | 12 trials, 1226 children AGE 0-5 years 724 early 502 late refeeding | Early refeeding < 12h vs Late refeeding >12h Different feedings | Efficacy and Adverse effects | Primary: Duration of diarrhea (7 Secondary: Stool output Weight gain IV fluids Vomiting | **Early vs Late Refeeding**  **Duration of diarrhea** 7/12 trials, 685 particip MD -6.90 h,CI -18.70 to 4.91 **Unscheduled IV fluids** 6/12 trials, 813 particip RR 0.87, CI 0.48 to -1.59 **Stool output 24-48h** 3/12 trials No difference **Weight gain after 24h** 3/12 trials No difference **Vomiting** 5/12, 456 participants RR 1.16, CI 0.72 to 1.86 | All studies were RCT | Yes – 2 studies Unclear -10 studies | No – 11 studies Yes – 1 study, single blinding | Yes, for all outcomes – 5 trials Yes, for some outcomes – 7 trials | Different sources: Industry Academic WHO | The present meta-analysis did not provide evidence that early refeeding increases unscheduled use of IV fluids, episodes of vomiting, and development of persistent diarrhea. The results support existing practice of early refeeding during or after start of rehydration of patients. No conclusion could be made regarding the duration of diarrhea. |
| Saneian H, 2012 | Prospective controlled trial Jan 2009 to Aug 2009 | Iran | Outpatient | 7 days | 71 Children AGE Mean age 7.1±3.7m 1-24 months Formula fed | Refeeding with Lactose-free vs Lactose containing formula | Advantages of refeeding lactose-free formula | Time to relief from diarrhea | **Diarrhea relief, days** Lactose-free vs lactose 1.7±0.7 vs 2.6±0.7 95%CI 1.5 to 3.9, p<0.001 P<0.001 | No | NA | NA | Not reported | Isfahan University Grant | Early administration of lactose-free formula for formula fed children presenting with AGE can result in a more rapid relief of diarrhea However there were baseline differences between the groups (more days with diarrhea in the intervention group,p=0.047, more severe dehydration in the control, p=0.015) |
| Rabbani GH, 2009 | DB-RCT Sept 2004 to May 2005 | Bangladesh | Inpatient |  | 73 Children Shigella AGE 6-60m All treated Ciprofloxacin | Cooked green addition of banana (GB) 250g/L in children with Shigellosis | Effect on diarrhea severity | Success rate | **Effect of GB on stools:** Reduction of volume Reduction of numbers/d Clearance of blood, mucus Reduction of fever Reduction of ORS volume **GB vs control Clinical success** 85.3% vs 66.7%, p=0.001 **Clinical failure** 14.7% vs 33.6%, p= 0.05 | Yes- computer generated random number | Yes-Investigators and patients | Yes- Investigators and patients | Not reported | None declared | GB diet improved clinical severity of childhood Shigellosis and can use as a simple and useful adjunct for dietary management of AGE Shigellosis |
| Macgillivray S, 2013 | MA | ++ | high- or middle-income countries | Inpatients (1 outpatient) | N= 2973 children aged two months to 59 Months (29 RCT) | Lactose-free milk, milk products, or foodstuffs | Lactose-containing milk, milk products, or foodstuffs | Duration of diarrhea (hours) | Mean difference (range): -17.77 (25.32 to 10.21) vs (28.8 to 230) | Yes | Heterogeneous | Heterogeneous | Yes | University of Dundee, UK. Hull York Medical School and NIHR Centre for Reviews and Dissemination, University of York, UK. Tenovus Scotland, UK. | In young children with acute diarrhea who are not predominantly breast-fed, change to a lactose-free diet may result in earlier resolution of acute diarrhea and reduce treatment failure. Diluting lactose-containing formulas may also have some beneﬁts but further trials are required to have conﬁdence in this ﬁnding. However data were different in outpatients setting. |
| Treatment failure | Relative effect  (95% CI) 0.52  (0.39 to 0.68) |  |  |  |  |
| Need for hospitalization | Relative effect  (95% CI) 0.79  (0.09 to 6.65) |  |  |  |  |

AGE=acute gastroenteritis; NIHR=National Institute for Health Research; ORS=Oral rehydration solution.

**Table 5.3. Pharmacological Therapy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Intervention** | | **Randomization** | **Allocation concealment** | **Blinding** | **ITT analysis** | **Population** | **Main results**  **(experimental group *vs.* control group)** |
| Freedman SB, 2013 | **Antiemetics** | Ondansetron *vs.* placebo. | All studies included in the review were RCTs | | | | 95 unique randomized controlled trials (N=12478)  87 randomized controlled trials included subjects < 18 years (N = 10 954) | Rate of admission to hospital (during ED stay) 🡪 Relative Risk and NNT: 0.40 (0.19 to 0.83),  NNT= 17 (13-60).  Rate of IV rehydration (during ED stay) 🡪 Relative Risk and NNT: 0.41 (0.29 to 0.59),  NNT= 5 (4-8).  Revisit rate 🡪 ewlative risk: 0.09 (0.66 to 1.79) |
| DeCamp LR, 2008 | Ondansetron (oral: 2-8 mg; 1.6-4 mg; IV: 0.15-0.3 mg/kg) *vs.* placebo. | Validity assessment was undertaken using two scales and a summary score was calculated. The two scales used were the Downs and Black checklist (maximum score 31) and the Delphi List (maximum score 9). Validity assessment was undertaken by two independent reviewers. | | | | MA (6 RCTs, n=745, 1 mo-12 y with vomiting and AGE) | Reduced risk of persistent vomiting (RR 0.45, 95% CI 0.33 to 0.62; NNT 5); reduced need for IV therapy (RR 0.41, 95% CI 0.28 to 0.62, NNT 5); and reduced risk of immediate hospital admission (RR 0.52, 95% CI 0.27 to 0.95, NNT 14). Increased diarrheal episodes (3 RCTs, data not pooled). No effect on return to care (RR 1.34, 95% CI 0.77 to 2.35). |
| Carter B, 2012 | Ondansetron (oral: 2-8 mg; IV: 0.15-0.3 mg/kg) *vs.* placebo | Quality of the evidence (GRADE) as assessed by the authors – low to moderate (depending on the outcome) due to design limitation (risk of bias) and/or inconsistency due to possible change of effect of intervention over time and inconsistent follow up. | | | | MA (7 RCTs, n=760, <18 y with vomiting and AGE) | Increased cessation of vomiting: (oral administration: 4 RCTs, RR 1.44, 95% CI 1.29 to 1.61; IV administration: 3 RCTs, RR 2.01, 95% CI 1.49 to 2.71; NNT 3). Reduced need for IV therapy: (oral administration, 4 RCTs, RR 0.41, 95% CI 0.29 to 0.59; NNT 5). Increased number of episodes of diarrhea (P<0.05). |
| Gouin S, 2012 | Dimenhydrinate (oral: dosage of 1 mg/kg per dose every 6 hours for 4 doses, with a maximum dose of 200 mg/day) *vs* placebo | Adequate | Adequate | DB | No | N=152 (76 cases and 76 controls) | The prescription of oral dimenhydrinate did not significantly decrease the frequency of vomiting in children with acute gastroenteritis compared with placebo. |
| Kita F, 2012 | Domperidone plus ORS *vs* ORS alone | Adequate | | | | N=56 (24controls) | It appears that domperidone in combination with ORT in the treatment of acute gastroenteritis does not reduce vomiting in the early period. |
| Lehert P, 2011 | **Racecadotril** | Racecadotril (typically 1.5 mg/kg TID) *vs.* placebo or equivalent (in particular, kaolin-pectin) | The methodological quality of each study was assessed using  Chalmers scale (including sequence generation, allocation concealment, adequacy of blinding and handling of incomplete outcome data). Included studies were of various methodological quality. | | | | MA (9 RCTs, n=1384, 1 mo- 15 y) | Higher proportion of patients with recovery defined as patients with a diarrhea duration of less than 2 days (HR 2.04, 95%CI 1.85 to 2.32; P<0.001).  Reduced mean stool output in inpatients (HR 0.59, 95%CI 0.51 to 0.74; P<0.001).  Reduced mean number of diarrheal stools in outpatients (HR 0.63, 95%CI 0.51 to 0.74; P<0.001). |
| Dupont C, 2009 | **Smectite** | Smectite (6-12 g) *vs.* placebo. | Adequate | Unclear | DB | Per protocol analysis | N=602 (1-36 mo) | Peru: lower 72-hour cumulative stool output (P=0.032); shorter duration of diarrhea (P=0.001).  Malaysia: lower 72-hour stool output (P=0.007); shorter duration of diarrhea (P=0.001). |
| Mujawar QM, 2012 | Diosmectite (4.5 g/d for 5 d)  *vs.* no intervention | Adequate | Unclear | Single blinded | ? | N=117 (2-5 y) with AGE. | Shorter time for resolution of diarrhea (P<0.001). |
| Patro B, 2008 | **Zinc** | Zinc *vs.* placebo or zinc in other dose or no intervention | Key criteria assessed included the adequacy of allocation concealment, blinding (investigators, participants, outcome assessors and data analysts), ITT analysis and completeness of follow‐up. Study quality was reported to be high. | | | | MA (18 RCTs, n=11,180 with AGE, <5y) | Reduced duration of diarrhea (13 RCTs, n=5643, MD -0.7 day; 95% CI -0.97 to -0.40).  Reduced the risk of diarrhea lasting >7days (8 RCTs, n=5769, RR 0.71; 95% CI 0.53–0.96).  Increased chance of vomiting (5 RCTs, n=3156, RR 1.2; 95% CI 1.05–1.4). |
| Patel A, 2010 | Zinc *vs.* placebo or no intervention | No report of the formal assessment of the risk of bias in included trials. | | | | MA (26 RCTs, n=20,480) | Shorter duration of diarrhea (19 RCTs; n=8957; shortened by 19.7%; 95% CI 11.9% to 27.4%).  Increased chance of vomiting (10 RCTs; n=6779; OR 2.13; 95%CI 1.37-3.31).  No effect on stool frequency and stool output. |
| Lazzerini M, 2012 | Zinc *vs.* placebo | Quality of the evidence (GRADE) as assessed by the authors – very low (death; hospitalization); low (duration of diarrhea all trials); moderate (diarrhea on day 7); high (duration of diarrhea in trials limited to children with signs of moderate malnutrition; adverse events). | | | | MA (24 RCTs, n=9128, age 1 mo- 5 y) | Reduced duration of diarrhea in children > 6 mo (MD -10 h; 95%CI -21.12 to 0.25).  Reduced duration of diarrhea in malnourished children (MD -27 h; 95%CI -14.7 to -39). |
| Allen SJ, 2010 | **Probiotics**  **(as a group)** | Probiotics *vs.* placebo or no intervention. | The methodological quality (i.e. generation of allocation sequence, allocation concealment, blinding, and loss to follow) varied considerably. Twenty-three studies were considered adequate  for generation of the allocation sequence, 15 for concealment of allocation, 35 for blinding and 45 for loss to follow up. Ten studies were adequate for all of the four methodological quality assessment  parameters and five studies were inadequate for all four parameters. | | | | MA (63 RCTs, n=8014) | Reduced duration of diarrhea (35 RCTs, n=4555; MD -25 h; 95% CI 16 to 34); reduced risk of diarrhea lasting ≥4 days (29 RCTs, n=2853, RR 0.41, 95% CI 0.32 to 0.53). |
| Allen SJ, 2010 | ***Lactobacillus* GG** | *Lactobacillus* GG *vs.* placebo or no intervention | See above | | | | MA, 11 RCTs, n=2072 | Reduced duration of diarrhea (MD -26.69; 95%CI -40.5 to -12.88), mean stool frequency on day 2 (6 RCTs, n=1335; MD -0.76, 95%CI -1.32 to -0.2), and the risk of diarrhea lasting ≥4 days (4 RCTs, n=572; RR 0.59, 95%CI 0.40 to 0.87). |
| Szajewska H, 2013 | ***Lactobacillus* GG** | Daily doses of LGG ranging from 1.2 x 108 CFU to 2 x 1012 CFU in addition to rehydration therapy vs Placebo | The methodological quality of the studies (generation of randomization, allocation concealment, blinding, ITT analysis, and completness to follow-up) varied. | | | | MA, N= 2963  patients (1603 in the experimental group and 1360 in  the control group) 🡪 15 studies | Lactobacillus GG reduces the duration of diarrhea either in terms of days and hospitalization |
| Allen SJ, 2010 | ***Saccharomyces boulardii*** | *S boulardii* *vs.* placebo or no intervention | See above | | | | MA (10 RCTs, n=860) | Reduced risk of diarrhea lasting ≥4 d (6 RCTs, n=606, RR 0.37; 95% CI 0.21 to 0.65; NNT 3, 95% CI 2-3). |
| Szajewska H, 2009 | *S boulardii* *vs.* placebo or no intervention | The methodological quality of the trials varied. | | | | MA (9 RCTs, n=1117) | Reduced duration of diarrhea (7 RCTs, n=944, MD 1.08 d, 95%CI -1.64 to -0.53 |
| Dinleyici EC, 2012 | *S boulardii vs.* placebo or no intervention | All included trials had a number of methodological limitations; however, >80% of the studies have follow-up and ITT analysis. Small sample sizes in some of the trials. | | | | MA (13 RCTs) | Reduced duration of diarrhea (11 RCTs, n=1306; MD -0.99 d (-1.4 to -0.58).  Diarrhea on day 3 (9 RCTs, n= 1128; RR 0.52; 95% CI 0.42 to 0.65)  Duration of hospitalization (n=449; MD -0.84 d (-1.14 to -0.54) |
| Riaz M, 2012 | *S boulardii vs.* placebo | Unclear | Unclear | DB | No (ACA) | N=108 (3-59 mo) | Reduced duration of diarrhea (P=0.03)  Shorter time of appearance of first semi- formed stool (P=0.008). |
| Correa NB, 2011 | *S boulardii* *vs.* placebo | Adequate | Unclear | DB | No  (ACA) | N=176 (6-48 mo) | Reduced frequency of diarrhea at day 2 (P<0.01).  Reduced frequency of diarrhea at day 3 (P<0.01). |
| Chmielewska A, 2008 | ***L. reuteri* ATCC 5573** | *L. reuteri* ATCC 5573 *vs.* placebo | The methodological quality of the studies (generation of randomization, allocation concealment, blinding, ITT analysis, and completeness to follow-up) varied. | | | | MA (2 RCTs, n=106) | Reduced duration of diarrhea (MD -25 h; 95%CI-39.4 to -10.9).  Reduced risk of diarrhea on day 1 (RR 0.88; 95%CI 0.8 to 0.99), on day 2 (RR 0.6; 95%CI 0.4 to 0.8), on day 3 (RR 0.45; 95%CI 0.3 to 0.8), and on day 4 (RR 0.36; 95%CI 0.1 to 0.7). |
| Francavilla R, 2012 | ***L. reuteri* DSM 17938** | *L. reuteri* DSM 17938 *vs.* placebo | Adequate | Unclear | DB | Yes | N=74 (6-36 mo) | Reduced duration of watery diarrhea (P<0.03).  Smaller number of patients with persistent diarrhea on day 2 (P<0.01) and on day 3 (P<0.03).  Lower relapse rate (P<0.03). |
| Piescik-Lech M, 2013 | ***LGG (6 x 109) plus scmectite*** | LGG (6 x 109) plus scmectite vs LGG plus Placebo | Adequate | Adequate | DB | Yes | N=88 children (44 treated and 44 controls) aged 4 to 60 months | LGG plus smectite and  LGG alone are equally effective for treating young children  with AGE. Combined use of the two interventions is not  justified. |
| Vandenplas Y, 2011 | **Synbiotics** | 5 probiotic strains & fructooligosaccharides *vs.* placebo | Adequate | Adequate | DB | Yes | N=111 (1-186 mo) | Reduced duration of diarrhea [3 days (IQR 2-4) *vs.* 4 days (IQR 4-5); P<0.005]. |
| Passariello A, 2012 | *L. paracasei* B21060 plus arabinogalactan and xilooligosaccharides *vs.* placebo | Adequate | Adequate | DB | Yes | N=107 (3-36 mo) | Higher rate of resolution of diarrhea at 72 hours (P=0.005).  Reduced duration of diarrhea (P=0.04).  Reduced number of daily stool outputs from 48 to 72 hours after treatment (P=0.005). |
| Teran CG, 2009 | **Nitazoxanide** | Nitazoxanide 15 mg/kg/d for 3 days *vs.* placebo | Adequate | Unclear | SB | No (ACA) | N=75 (1-24 mo) | Reduced duration of diarrhea (52.9±27.7 *vs.* 74.6±26.6 h; MD -21.7 h, 95% CI -34.74 to -8.66).  Reduced duration of hospitalization (81.8±30.8 *vs.* 100.9±27.3; MD -19.1 h; 95% CI -33.27 to -4.93). |

AGE=acute gastroenteritis; ACA=available-case-analysis; CI=confidence interval; ED=Emergency department; HR=hazard ratio; IV=intravenous; LGG= Lactobacillus rhamnosus GG; MA=meta-analysis; MD=mean difference; OR=odds ratio; ORS=oral rehydration solution; ORT=oral rehydration treatment; RR=risk ratio; TID= three times a day.

**5.4. Anti-infective therapy**

**Table 5.4.1. Pathogen-based approach: Shigella gastroenteritis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Population** | **Intervention** | **Comparison** | **Outcome** |
| Vinh H, 2011 | RCT, open-label  Allocation concealment | 494 hospitalized children with dysentery (107 with confirmed shigellosis) | Gatifloxacin 10mg/kg/d (single dose), for 3 days | Ciprofloxacin 30mg/kg/d (bid), for 3 days | Similar duration of symptoms (95 vs 93 hs) and clinical failure rates |
| Christopher PR, 2010 | Meta-analysis | 1748 children and adults with Shigella dysentery | 16 controlled trials of antibiotics for Shigella dysentery | Placebo or comparative antibiotics | Appropriate antimicrobial therapy shotened the duration of Shigella dysentery  Insufficient evidence to support superior efficacy of any class of antibiotics |
| Boumghar-Bourtchai L, 2008 | Case series | 50 children, mostly hospitalized, with shigellosis, during an outbreak | Identification of plasmid-mediated macrolide resistance | - | Macrolide-resistant S. Sonnei in France |
| Centers for Disease Control and Prevention (CDC), 2012 | Report of an outbreak | 43 cases of suspected shigellosis, 14 confirmed S. sonnei | Clinical and laboratory investigation | - | Plasmid-mediated azithronycin resistance (MIC>16 mcg/ml),  Single clone by PFGE |
| Centers for Disease Control and Prevention (CDC), 2010 | Case series | 2 hospitalized children and an adult with clinical shigellosis | Descriptive antibiotic resistance | - | Reprt from the US of S.flexneri 2a resistant to cefriaxone and ciprofloxacin |
| Vrints M, 2009 | Descriptive | 7307 Shigella isolates (children and adults) in Belgium  During 1990-2007 | Descriptive antibiotic resistance | - | Very high resistance to ampicillin and TMP-SMX  Resistance to nalidixic acid (12.8%); no resistance to ciprofloxacin |
| Shiferaw B, 2012 | Descriptive | 1376 Shigella isolates (children and adults) in the US  During 2000-2010 | Descriptive antibiotic resistance | - | High resistance to ampicillin and TMP-SMX  Low resistance to nalidixic acid (2%) and ciprofloxacin (0.5%) |
| Haltalin KC, 1967 | Double-blind  RCT  Allocation concealment | 52 children hospitalized  With Shigella GE | Ampicllin vs sulfadiazine vs placebo | Length of symptoms and  Fecal excretion | Ampicillin (vs placebo) shortened the duratin of diarrhea by 45%  (3.3 d vs 6), of fever by 50% (1.3 vs 2.6) and excretion by 60% (2 vs %) |
| Basualdo W, 2003 | Open-label  RCT  Allocation concealment | 182 children with bloody diarrhea of whom 75 had shigellosis, mostly S. flexneri | Azithromycin (12 and then 6 mg/d) vs cefixime (8mg/d), both for 5 d | Length of symptoms and  Fecal excretion, clinical and bacteriologic relapse during 1w after end of therapy | Azithro vs cefixime: clinical success 93% vs 78%, clinical failure 2 vs 7 children, legth of diarrhea 2.5 vs 3.9 d, bacterial eradication 93% vs 59% (p<0.01, 95% CO 1.7-69.7), clinical relapse 1 child in azithro group, bacteriologic relapse 1 vs 2 patients |
| Ashkenazi S, 1993 | Double-blind  RCT  Allocation concealment | 102 children with inflammatory diarrhea, of whom 79 had shigellosis, mostly S. sonnei | Cefixime (8 mg/kg/d, bid vs T-S, 5d | Length of symptoms and  Fecal excretion | Better clinical and bacteriological efficacy of cefixime, mainly because 32/39 treated with T-S were resistant to it. Bacteriologic eradication by cefixime was 78% (sub-optimal ) |
| Miron D, 2004 | Non-randomized controlled study during outbreak | 29 children with S. sonnei | Azithromycin 10mg/kg for 3 d vs nalidixic acid 55mg/kg/d qid for 5 d | Length of symptoms and  Fecal excretion | Better efficacy of azithromycin: clinical response 100% vs 65%, p<0.01, bacterilogic response 100% vs 72%, p=0/012 |
| Varsano I, 1991 | Open  RCT | 49 children with severe dysentery, of whom 40 had shigellosis, mostly S. sonnei | Ceftriaxone 50mg/kg/d, IV then IM vs ampicillin 100mg/kg/d, IV then PO, both for 5d | Length of symptoms and  Fecal excretion, relapse rates | Better efficacy of ceftriaxone: diarrhea 2.5 vs 6.8 d (p<0.005), bacterial eradication 100% vs 60% (p<0.001), bacteriologic relapse 0 vs 40% (p<0.001) |
| Eidlitz-Marcus T, 1993 | Open  RCT | 40 children with shigellosis, mostly S. sonnei | Ceftriaxone 50mg/kg/d, IV then IM 5d vs 2d | Length of symptoms and  Fecal excretion | No difference between 2 and 5 days |
| Salam MA, 1988 | Double-blind  RCT | 9o children with dysentery, of whom 74 had shigellosis, mostly S. dysenteriae and S. sonnei | Nalidixic acid 55 mg/kg/d vs ampicillin 100 mg/kg/d, both for 5d | Length of symptoms and  Fecal excretion | Nalidixic acid and Ampicillin effective, when the isolate susceptible to Ampicillin. Clinical response 81% vs 77%, Bacteriologic response 100% for both groups on d 3, but the response after 1d was better (38% vs 12%) |
| Bennish ML, 2006 | Review of 7 studies and follow up of 20 children prospectively | 378 patients with S. dysenteriae, 250 children, 128 adults | Appropriate antibiotic therapy | Rate of the HUS complication, fecal Stx level | Low risk of developing HUS with therapy( 0.0026), early antibiotics reduces fecal Stx levels |
| Leibovitz E, 2000 | Double-blind RCT | 221 children with invasive diarrhea, 73 with shigellosis | Ciprofloxacin PO 20mg/kg/d bid vs IM ceftriaxone 50/mg/kg, both 3d | Length of symptoms and  Fecal excretion | No differences in the clinical or bacteriologic response. No joint problems related to cipro treatmet for 3 d |
| Prado D, 1992 | RCT | 93 children with dysentery, of whom 22 had shigellosis or EIEC | Ceftibuten 9 mg/kg/d vs T-S 10-50mg/kg/d  Both bid, for 5d | Length of symptoms and  Fecal excretion | Similar clinical and bacteriologic responses unless the pathogen was resistant to T-S |
| DuPont HL, 2001 | Double-blind  RCT | 187 adults with traveler’s diarrhea, 9 with Shigella, no studt in children | Rifaximin 400 mgX2/d vs Ciprofloxacin 500 mgX2/d, both for 3 d | Length of symptoms and  Fecal excretion | Similar clinical and bacterial efficay. But: only 9 Shigella, 64 ETEC; no studies in children |

AGE=acute gastroenteritis; ED=Emergency department; EIEC=enteroinvasive E. coli; ETEC=enterotoxigenic E. coli; HUS=hemolytic-uremic syndrome; IM=intramuscular; IV=Intravenous; LGG=Lactobacillus rhamnosus GG; ORS=Oral rehydration solution; ORT=Oral rehydration treatment; PO=Oral; Stx=Shiga toxin; TID= three times a day; T-S=trimethoprim-sulfamethoxazole.

**Table 5.4.2. Pathogen-based approach: Salmonella (non-typhoidal) gastroenteritis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Population** | **Intervention** | **Comparison** | **Outcome** |
| Onwuezobe IA, 2012 | Systematic Review  of RCTs  1980-8/2012 | 12 trials identified  Including 767 patients with Salmonella gastroenteritis, of whom 258 were children | Antibiotics vs placebo or no antibiotics | Clinical and bacteriologic responses, relapse, adverse effects | No significant differences in length of diarrhea or fever between any antibiotic regimen and placebo. Antibiotics result in more negative cultures during the 1st week of treatment, but more cases of positive cultures after 3 weeks. Relapse more frequent in those receiving antibiotics. Adverse effects more common with antibiotics |
| Shkalim V, 2012 | Descriptive study | 17 children with non-typoidal Salmonella bacteremia during 1995-2010 | - | - | Salmonella bacteremia was associated with toxic appearance and convulsions (17%) and occurred in children older than 3 months |
| Chiu CH, 1999 | Open-label RCT  Allocation concealment | 42 children with Salmonella GE | Azithromycin 10mg/kg/d vs cefixime 10mg/kg/d bid, both for 5 days vs no antibiotics | Clinical and bacteriologic responses | Duration of diarrhea or fever not affected by antibiotics. No effects of antibiotics on fecal eradication |
| Sirinavin S, 2003 | Open-label RCT | 265 asymptomatic carriers of Salmonella | Norfloxacin 400 mgx2/d vs Azithromycin 500 mg/d, both for 5 days, vs placebo | Fecal eradication: stool cultures on days 7, 30, 60, 90. | Antibiotic regimens had no significant effect vs placebo on fecal eradication, and was associated with development of antibiotic resistance |

**Table 5.4.3. Pathogen-based approach: Campylobacter gastroenteritis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Population** | **Intervention** | **Comparison** | **Outcome** |
| Vukelic D, 2010 | RCT  Assessor-blind  Allocation concealment | 120 children (<12 y) with Campylobacter enterocolitis | Single dose (20 or 30 mg/kg) azithromycin | 1. Erythromycin for 5 days 2. No antibiotics | 1. Erythromycin was not better than no antibiotics 2. A single dose of azithromycin, 30 mg/kg, was superior to no antibiotics and to erythromycin 3. All antibiotic regimens had 100% bacteriologic cure |
| Ternhag A, 2007 | Meta-analysis | 11 double-blind RCTs | Antibiotics vs no treatment or placebo | Clinical and bacteriologic outcome | Antibiotics reduced the duration of intestinal symptoms by a mean of 1.3 days |
| Salazar-Lindo E, 1986 | Double-blind RCT  Allocation concealment | 170 children 3-60 mo with acute dysentery, of whom 30 had Campylobacter jejuni  Treatment started within 5 days of diarrhea | Erythromycin 50mg/kg/d qid for 5 days vs placebo | Clinical and bacteriologic responses | Treatment failure clinically 0% vs 42% (p<0.01), diarrhea after 2d 0% vs 64% (p<0.05), normal stools after 5 d 7% vs 50% (p<0.02), shorter excretion of the pathogen. Clinical and bacteriologic efficacy documented with the **early treatment, for dysenteric Campy GE and with a dose of 50mg/kg/d** |
| Williams MD, 1989 | Open-label  RCT  Allocation concealment | 20 children (>6m) and 23 adults with acute (<72h) inflammatory diarrhea were enrolled.  21 were C. Jejuni positive | Erythromycin 50mg/kg/d tid vs TMP-SMX, both for 5 days | Clinical and bacteriologic responses | In those with Campy GE: eryhromycin was bacterilogical efficacious – fecal eradication on d3 was 100% vs 10% (p<0.002) and on d5 100% vs 20% (p<0.001). Clinically, no significant effect on mean days of diarrhea, mean stools per day and mean symptom score |
| Pai CH, 1983 | Open-label  RCT | 27 children with confirmed Campy GE | Erythromycin 40mg/kg/d qid for 7 days vs no treatment  Nean diarrhea before treatment: 5.5 vs 6.4d!!! | Clinical and bacteriologic responses  relapse | Duration of diarrhea (3.2 vs 3.8) or fever  Bacterial shedding: 2 vs 16.8 d (p<0.05)  Relapse: 6.7% vs 25% |
| Ashkenazi S, 1987 | Intervention during a DCC outbreak | Ongoing outbreak of Campy GE in a DCC,  22 children | Erythromycin 50mg/kg/d qid  For 7 days | Fecal eradication, outbreak course. | The ongoing outbreak stopped |

DCC=day-care center; D=day; GE=gastroenteritis.

**Table 5.4.4. Pathogen-based approach: E. coli, cholera, others gastroenteritis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Population** | **Intervention** | **Comparison** | **Outcome** |
| Kaushik JS, 2010 | RCT  Allocation concealment | 180 hospitalized children with confirmed cholera diarrhea | Azithromycin, single 20/mg/kg dose | Ciprofloxacin, single 20mg/kg dose | Azithromycin superior: clinical efficacy 95% vs 71%, bacteriologic efficacy 100% vs 96%, duration of diarrhea 55 vs 72 h and vibrio excretion 35 vs 52 h and less IV fluid needed (3491 vs 4705 ml. |
| Wong CS, 2012 | Case-control study | 259 children with O157:H7 diarrhea | Antibiotics | No antibiotics | HUS rate: 36% with antibiotics vs 12% without (p=0.001) |
| Geerdes-Fenge HF, 2013 | Case-control study | 24 patients with EHEC (O104:H4) diarrhea | Ciprofloxacin | Other or no antibiotics | HUS rate: 40% with ciprofloxacin vs 89% without ciprofloxacin (p=0.043) |
| Trehan I, 2009 | RCT  Double-blind  Allocation concealment | 144 ambulatory children aged 3-5 years with tropical enteropathy | PO rifaximin for 7 days | Placebo | No beneficial effect of rifaximin, "suggesting that small-bowel bacterial over growth in not an important etiology in this condition |
| Hu Y, 2012 | Meta-analysis | 4 RCTs including 502 participants | PO rifaximin | Placebo | Rifaximin reduced significantly the rate of non-invasive E. coli (mainly ETEC) diarrhea |
| Safdar N, 2002 | Meta-analysis  O157:H7 and HUS | 26 publications were identified; 9 fulfilled the criteria for inclusion in the analysis  Only one randomized, the others prospective cohort or retrospective case-control studies | Antibiotic therapy of E. Coli O157:H7 and the risk of HUS | Risk of developing HUS | A total of 1121 patients with E. coli O157:H7 enteritis were analyzed, of whom 175 developed HUS.  Various antibiotics were used  The odds ratio was 1.15 (95% CI 0.79-1/68)  Recommended a prospective large RCT |
| Proulx F, 1992 | Open-label  RCT | 47 children with E. coli O157:H7 enteritis  Randomization 7.4 days after the onset of diarrhea | T-S for 5 d vs no antibiotics | Length of symptoms and  Fecal excretion, risk of developing HUS | Antibiotics (vs no treatment) did not affect the resolution of clinical symptoms or bacterial eradication. The risk of HUS was 9% vs 16% |
| Oberhelman RA, 1987 | Double-blind  RCT | 141 children with acute diarrhea, of whom 31 had enterotoxigenic E. coli | TMP-SMX for 5 d vs placebo | Length of symptoms and  fecal excretion | IN children with ETEC: significant (p<0.01) improvement in the clinical symptoms with antibiotics and in bacteriological efficacy |
| Ericsson CD, 1987 | Double-blind  RCT | 191 adults with travelers diarrhea were enrolled, of whom 73 had ETEC | Ciprofloxacin or T-S or placebo for 5 days | Length of symptoms and  Fecal excretion, relapse | Clinical efficacy of both antibiotics: average h of diarrhea were 33, 26, and 84 (p<0.001). Bacteriologic efficacy also documented: fecal eradication rates were 100%, 100% and 71% |
| Adachi JA, 2003 | Double-blind  RCT | 217 adults with traveler’s diarrhea, of whom 110 had ETEC | Azithromycin 100 mg vs levofloxacin 500 mgd | Length of symptoms and  Fecal excretion | Similar clinical efficacy of azithromycin and levofloxacin: duration of diarrhea 22.3 vs 21.5 h. Bacteriologic eradication 55% vs 61% |
| Infante RM, 2004 | Double-blind  RCT | Adults with traveler’s diarrhea caused by EaggEC | PO rifaximin vs placebo | Length of symptoms | Shorter duration of diarrhea with rifaximin: 22 vs 72 hours, (p=0.03) |
| Thoren A, 1980 | Open-label  RCT  Allocation concealment | 49 infants with EPEC diarrhea | Mecillinam vs T-S vs placebo | Length of symptoms and  Fecal excretion | Better clinical response with both antimicrobial agents: 79% vs 73% vs 7% (p<o.001). Bacteriologic response: 53% for both antibiotic groups vs 0% (p<o.001). |

EPEC=enteropathogenic *Escherichia coli*; ETEC= Enterotoxigenic *Escherichia coli*; HUS=hemolytic-uremic syndrome; T-S=trimethoprim-sulfamethoxazole.

**Table 5.4.5. Antimicrobial therapy of parasite-induced gastroenteritis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **Population** | **Intervention** | **Comparison** | **Outcome** |
| Vandenberg O, 2012 | Prospective cohort study | 130 children (3mo-3yr) attending a day-care center in Brussels | Collection of stool samples over | - | Our study underscores the need to rule out Cryptosporidium etiology in a diarrheal outbreak in a DCC. Rapid implementation of infection control measures can most likely halt the spread of infection |
| Granados CE, 2012 | MA (19 RCTs) | 1817 patients (1441 children) with giardiasis infection | Albendazole (400 mg once daily for five to 10 days) | metronidazole (250 mg to 500 mg three times daily for five to 10 days) | Studies were generally small, with poor methods reporting. Albendazole may be of similar effectiveness to metronidazole, may have fewer side effects, and has the advantage of a simplified regimen. |
| Escobedo AA, 2008 | Controlled trial | 166 children infected with G. lamblia, with those of | tinidazole, given as a single dose of 50 mg/kg. (63 completed the study) | nitazoxanide, given at a dose of 7.5 mg/kg twice a day for 3 days.  (74 completed the study) | Cure rate: G. lamblia not found in both post-treatment samples: 90.5% Tinidazole vs 78.4% Nitazoxanide (P<0.05) |
| Canete R, 2012 | Double-blind, randomized, controlled trial | 150 Adults patients had a confirmed symptomatic G. duodenalis mono-infection | Albendazole, 400 mg/daily for 5 days (75 pts) | Metronidazole 250 x3/die for 5 days (75 pts) | Cure rate: 82,6% vs 85,3 %, p>0.05 . Side effects : bitter taste, headache, vomiting and dizziness significantly higher in the Mentronidazole group. Abdominal pain significantly higher in Albendazole group |

DCC=day-care center.

**Table 5.4.6 Antiviral treatment**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study type** | **QoS** | **Country** | **In/Out**  **Patients** | **Population** | **Randomization** | **Blinding** | **Allocation concealment** | **Intervention** | **Comparison** | **FU** | **ITT** | **Outcomes measures** | **Effect measure** | **Effect size (95% CI)** | **Comments** |
| Guarino A, 1994 | RCT | + | Italy | Inpatients | N=98 children with acute gastroenteritis | Appropriate | Double-blinded | Not clear | Single oral dose of 300 mg/kg body weight of human serum immunoglobulin | Placebo | 98/98 | Yes | Mean duration of diarrhea (h) | Number | 76 vs 131 (p<0.01) | Consistent evidence demonstrated that oral administration of immunoglobulin (300 mg/kg) may be beneficial for rotaviral infection and is associated with a faster recovery from acute diarrhea |
| Viral excretion (h) | Number | 114 vs 180 (p<0.01) |
| Hospital stay (h) | - | \*reduced in treated chilren |
| Sarker SA, 1998 | RCT | + | Bangladesh | Inpatients | N=85 male infants and children aged 4 to 24 months with a history of acute watery diarrhea | Appropriate | Double-blinded | Appropriate | Immunoglobulin from immunized bovine colostrum (10 g in 20ml of water in 4 divided doses for 4 days) | Placebo | 80/85 | No | Stool rate (grams/kg/day) | Mean±SD | Day 1 (P = 0.006), Day 2 (0.006) and Day 3 (0.02) |
| Intake of ORS (ml/kg/day) | Mean±SD | 281±30 vs 410±39; p<0.001 |
| Stool frequency (number/days 1-4) | Number | 29 vs 42; p=0.007 |
| Number of days required for RV ELISA-negative stool (days) | Mean±SD | 1.5 vs. 2.9, P < 0.001 |
| Duration of diarrhea after initiation of therapy (h) | Mean±SD | 72.6±38.9 vs 96.4±46.7; p=0.0016 |
| Rahman S, 2012 | RCT | + | Myanmar | Inpatients | N=54 infants and children aged between 2 and 36months with acute watery diarrhea and dehydration | Appropriate | Double-blinded | Appropriate | Rotamix IgY four times daily for 8 consecutive days in addition to rehydration therapy | Placebo | 52/54 | Yes | Intake of ORS (ml) | Mean±SD | 699.3±111.1 vs. 919.1±171.31, p=0.004 | Oral administration of IgY could improve clinical outcomes (ORS intake, and duration of IV administration, of diarrhea, and of RV clearance), even for patients with mixed (RV and non-RV) enteric infections, and is a potentially useful adjunct to general supportive therapy in pediatric patients |
| Mean duration of intravenous ﬂuid administration (days) | Mean | 5 vs 8; p=0.03 |
| No. of stools/day (day 2) | Mean±SD | 6.7±4.3 vs 10.2±8.8 (p=0.03) |
| Total duration of diarrhea from day of admission (h) | Mean±SD | 135.3±42.0 vs 185.5±41.7; p=0.01 |
| Florescu DF, 2011 | Case-control study | + | USA | Inpatients | N=24 immunocompromised patients (16 children) diagnosed with NV gastroenteritis | - | - | - | 25 mg/kg of oral human immunoglobulin administered every six h for a total of eight doses in adjunct to standard therapy | Controls | - | - | Resolution of diarrhea | OR | 65.3; p=0.008 | Oral immunoglobulin treatment has been proposed for NV enteritis. Resolution of diarrhea and decreased stool output were observed at 7 days, but no benefit was found for length of hospital stay or hospital cost |
| Stool output seven days after treatment (mL/kg/day) | Mean | -22.15 vs -10.20; p=0.009 |

NV=Norovirus; OR=odds ratio; ORS=Oral rehydration solution; QoS=Quality of Study; RV=Rotavirus.

**Table 5.4. Nitazoxanide**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Intervention** | **Randomization** | **Allocation concealment** | **Blinding** | **ITT analysis** | **Population** | **Main results**  **(experimental group *vs.* control group)** |
| Teran CG, 2009 | Nitazoxanide 15 mg/kg/d for 3 days *vs.* placebo | Adequate | Unclear | SB | No (ACA) | N=75 (1-24 mo) | Reduced duration of diarrhea (52.9±27.7 *vs.* 74.6±26.6 h; MD -21.7 h, 95% CI -34.74 to -8.66).  Reduced duration of hospitalization (81.8±30.8 *vs.* 100.9±27.3; MD -19.1 h; 95% CI -33.27 to -4.93). |

ACA=available case analysis; CI=confidence interval; MD=Median duration.

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