Hospital management of children with acute gastroenteritis

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Purpose of review
Acute gastroenteritis (AGE) is a major cause of ED visits, hospitalizations, and prescription of investigations, drugs, and changes in diet. Several guidelines on management have been produced.

Recent findings
There is new information on different rehydration protocols, use of antiemetics, and antidiarrheal drugs that could reduce the burden of AGE. The need of intravenous (i.v.) rehydration is the main cause of hospital admission yet a standardized rehydration scheme is not available. Rehydration therapy through nasogastric tube is better than i.v. rehydration, in children with moderate-severe dehydration. Ultrarapid rehydration has been proposed by enteric or i.v. route to reduce the time in hospital and costs. However, reduced rehydration times are associated with high readmission rates and side effects. Antiemetics may reduce the need of i.v. rehydration because of vomiting and the number of hospital admissions. However, the main antiemetic, ondansetron, has been loaded with a warning for potentially severe side effects. Selected antidiarrheal drugs could reduce the length of stay, but data on their use in inpatients are still not conclusive.

Summary
Inappropriate medical interventions are still common in the hospital setting and have a high impact on costs. A validated management is still needed in inpatients.

Keywords
acute diarrhea, acute gastroenteritis, hospital, rehydration

INTRODUCTION

Acute gastroenteritis (AGE) has a high spectrum of severity whose hallmark is dehydration, which requires replacement of fluids usually through oral route [1]. The effectiveness of oral rehydration solution (ORS) in children with mild-to-moderate dehydration has been demonstrated by a Cochrane meta-analysis showing no clinical differences between oral and parenteral rehydration therapy in children with AGE [2]. However, failure of oral rehydration is the main indication to hospital admission and to receive enteral or intravenous rehydration therapy (IVT) [3,4]. However, the majority of articles on AGE management do not specifically address the problem of inpatients management and the recommendations for intravenous (i.v.) rehydration are poorly standardized. However, the National Institute for Health and Clinical Excellence [5] and more recently the Cincinnati Children's Hospital [6▪▪], specifically provided i.v. rehydration protocols, indications to laboratory investigations and criteria for hospital discharge.

The purpose of this review is to discuss when and how a child with acute diarrhea should receive i.v. rehydration, the indications to enteral rehydration and laboratory tests and finally to summarize recent evidence for active treatment of AGE in the inpatient setting.

INDICATIONS TO HOSPITAL ADMISSION FOR ACUTE GASTROENTERITIS

Indications to hospital admission for acute gastroenteritis are based on opinion of experts. Hospital admission is recommended in case of severe dehydration, shock, failure of oral rehydration therapy

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KEY POINTS

- Reliable data are available mostly for outpatients and indications for inpatients are mostly based on opinion and indirect data.
- Standard indications for nasogastric/i.v. rehydration and their schemes are not available.
- Antiemetics are largely used and effective, but there are issues on their safety.
- Drugs used in outpatients could be used in inpatients also with good results, but the ideal drug for diarrhea is still to be identified.

(ORT), severe vomiting, neurological symptoms, inability of caregivers to manage the problem, and in case of surgical condition is considered ([3,6▪▪,7,8▪]; Table 1). Generally, these conditions do not allow ORT and require i.v. rehydration. Interestingly since implementation of rotavirus immunization, a marked reduction in hospitalizations has been observed with a parallel reduction of costs [9▪▪].

INDICATIONS TO LABORATORY AND MICROBIOLOGICAL INVESTIGATIONS

AGE does not usually require stool microbiological investigations. Most children have a viral cause and in addition bacterial or protozoal agents generally do not require antimicrobial treatment. Stool cultures should be considered in case of persistent diarrhea, when antimicrobial treatment is considered (e.g. in immune-compromised children, in septic or toxic children or children with dysentery), in case of an outbreak or if the child has recently been abroad.

Electrolyte abnormalities may develop, although usually they are not severe. Hypernatremia and hyponatremia may occur, although isonatremic dehydration is the most common form. Selected children may have hypoglycemia and some may present metabolic acidosis, but their incidence is low. Furthermore, the accuracy of available tests in detecting severity of dehydration is not established. The laboratory test that best correlates with dehydration is serum bicarbonate [10]. Blood tests are not routinely needed, but serum potassium, sodium, urea and creatinine, and serum bicarbonate should be considered for children severely

Table 1. Indications to visit or emergency/hospital admission according to available guidelines

Criteria for medical visit	Europe 2008 [3]	Australia 2008[a] [7]	United States 2011 [6▪▪]	South Africa 2012 [8▪]
Age below 2 months	+			
Persistent fever after 24 h of ORT				+
The child refuses to drink		+		+
Reduction of urinary output		+		+
High volume diarrhea	+	+		
Diarrhea persisting more than 1 week				+
Persistent vomiting that does not allow oral rehydration	+	+		+
Vomiting associated with abdominal distention and pain				+
Mucous or bloody diarrhea		+		+
Severe stomachache		+		
Lethargic, restless or irritable		+		+
Severe underlying diseases (i.e. diabetes and renal failure)	+			
Social or logistical concerns		+		
Criteria for ED and/or hospital admission	**Europe 2008 [3]**	**Australia 2008[a] [7]**	**United States 2011 [6▪▪]**	**South Africa 2012[b] [8▪]**
Severe dehydration and/or shock	+	+	+	+
Oral rehydration failure	+	+	+	+
Intractable vomiting	+		+	+
Neurological abnormalities (lethargy, seizures, etc)	+			+
Suspected surgical conditions	+			
Social or logistical concerns	+	+	+	

[a]All the indications to medical consultation represent a criteria for ED visit if physician is not available within few hours [7].
[b]Indications to hospital admission are extrapolated from criteria for intravenous rehydration [8▪].

dehydrated or in whom i.v. rehydration is required. However, in the absence of risk-benefit indications, ordering laboratory tests based on clinical judgment may be superior to routine screening [6▪▪]. Despite this, a recent survey showed that 40–60% of enrolled physicians require laboratory tests in moderately dehydrated patients [11▪].

REHYDRATION THERAPY

Rehydration may be provided through oral, enteral (through nasogastric tube; NGT), and i.v. route according to the severity of dehydration and the conditions of the child. In the hospital setting, the last two options are typically considered.

Rehydration through nasogastric tube

A Cochrane review compared the efficacy of IVT in 17 trials with oral or nasogastric rehydration [2]. In eight of 17 trials, rehydration was given through NGT alone or in combination with ORT. There were no differences in the rehydration failure, incidence of hyponatremia, hypernatremia, mean duration of diarrhea, weight gain, or total fluid intake in children on ORT or IVT. Children on ORT had a significantly shorter stay in hospital and a lower risk of phlebitis [2]. A meta-analysis showed that NGT rehydration is associated with reduced risk of electrolyte imbalances, cerebral edema, phlebitis compared with i.v. rehydration. Rehydration through NGT is a valid alternative to IVT with equal efficacy, less adverse events and reduces the length of hospital stay [12].

Current guidelines concluded that rehydration should be provided through NGT if children are unable to drink it or if they have persistent vomit. The American Academy of Pediatrics recommends rapid (over 4 h) NGT rehydration for treatment of children with moderate dehydration. This regimen offers several benefits including a shorter stay in the hospital and less disruption of the family routine compared with the standard regimen. A prospective, randomized, clinical trial compared two different regimens of nasogastric rehydration: the standard nasogastric regimen (SNR) (replace fluids over 24 h) and the rapid nasogastric regimen (RNR) (100 ml/kg of rehydration solution administered over 4 h) [13▪]. The results showed no significant difference in the primary treatment failure defined as an additional loss of more than 2% of weight at any time during the rehydration period. Furthermore, no differences in the secondary treatment failures defined as inability to tolerate NGT, persistent vomiting, need of i.v. rehydration, persistent signs of moderate dehydration, need of nasogastric fluids beyond 24 h, were observed between the two groups at 4–6 h after beginning of rehydration therapy. At 24 h and 7 days after the admission, a higher proportion of secondary treatment failures in the RNR group compared with the SNR group was observed.

Despite the evidence of safety and efficacy, NGT rehydration regimen continues to be poorly applied in clinical practice, perhaps because placing a NGT is considered more invasive than IVT. These concerns need to be balanced against the i.v. complications such as phlebitis or cellulitis.

Intravenous rehydration

The indications to IVT generally overlap the indications to hospital admission. Guidelines recommend i.v. rehydration in case of severe dehydration and/or in case of oral rehydration failure. The recent evidence-based guidelines from Cincinnati Children's Hospital [6▪▪] recommend i.v. therapy, if there is a severe dehydration or if it is impossible to replace the estimated deficit fluids using oral solution alone.

Intravenous rehydration consists in the administration of an isotonic crystalloid solution without dextrose as an i.v. bolus of 20 ml/kg followed by a continuous infusion of dextrose – containing crystalloid solution if prolonged hydration is required. Intravenous rehydration should be started with isotonic fluid (normal saline) because this is more effective in reducing the risk of hyponatremia than hypotonic fluids (half normal saline with 5% dextrose) [14]. Isotonic Ringer lactate is associated with a better outcome from shock compared with hypotonic fluids in children with severe malnutrition and hypovolemia [15]. The Cincinnati Children's Hospital guidelines [6▪▪] recommend to start IVT with a bolus of 20 ml/kg of normal saline over 30–60 min followed by a maintenance volume of half normal saline with 5% dextrose to replace losses and maintain hydration. Despite the lack of evidence of efficacy, in the last years a rapid rehydration scheme (40–60 ml/kg normal saline bolus over 60 min) has been gradually incorporated into clinical practice with the aim to obtain a reduction of symptoms, an improvement of appetite, and a reduction of hospital stay and of global costs of AGE. A survey of North American physicians, specialized in pediatric emergency, found that several regimens are used [16▪▪]. In a recent clinical trial comparing two different i.v. schemes, the tolerance to the administration of 50 ml/kg in 1 h was similar to that of 50 ml/kg in 3 h, but it was associated to earlier discharge from emergency department (ED) [17]. A recent trial comparing the effect of boluses of 20–40 ml/kg of 5% albumin solution or 0.9% saline solution or no bolus in critically ill African children,

showed that both bolus-fluid resuscitation, compared with no bolus regimen, increased the absolute risk of death at 48 h by 3.3%. These data, although obtained in clinical conditions other than AGE, suggest that there may be severe risks associated to rapid rehydration regimens [18▪▪]. In order to evaluate the efficacy of rapid rehydration for AGE-induced dehydration, a randomized blinded comparative trial was conducted in children in whom oral rehydration failed and i.v. rehydration was required [19▪▪]. Children randomly received a 20 ml/kg (standard) or 60 ml/kg (rapid) of 0.9% saline infusion over 60 min followed by 5% dextrose in 0.9% saline at maintenance rate. Clinical dehydration scores, vital signs, and adverse events were recorded every 30 min for a total of 4 h. No difference in the percentage of children rehydrated after 2 h was observed between the two groups (36% in rapid rehydration group vs. 29% in standard rehydration group). There was no difference in the rates of prolonged treatment, mean dehydration scores, repeat visits to emergency, adequate oral intake. However, the median time to discharge was significantly longer in the rapid compared with the standard group (6.3 vs. 5.0 h; $P = 0.03$) and children receiving rapid i.v. rehydration were more commonly admitted to the hospital. The authors concluded that none of the outcomes support the use of rapid i.v. rehydration and that there was a trend toward worse outcomes in these children. This data strongly indicate that the routine use of i.v. rapid rehydration should be prescribed cautiously.

PHARMACOLOGIC TREATMENT

Only few of the many drugs proposed for AGE have proof of efficacy in preventing complications and in reducing hospital admission, duration of symptoms and the length of stay in hospital setting (Table 2).

Antiemetics

Vomiting is probably the main indirect cause of hospital admission. However, the therapy for vomiting remains controversial. None of the currently available guidelines suggests a routine use of antiemetics in children with AGE [3–5,6▪▪,7,8▪], but emerging evidence indicates that selected antiemetics may help in oral rehydration delivery, and reduce i.v. rehydration and hospital admissions.

The use of ondansetron, a selective (5-HT3) serotonin antagonist, is progressively increasing [20▪] to the point that American Pediatric Emergency Medicine Physicians indicated ondansetron as the drug of choice in vomiting patients with AGE [16▪▪].

A recent systematic review, including seven trials and more than 1000 patients, provided

Table 2. Effects by antidiarrheal drugs in hospital setting and their level of evidence

Antidiarrheal drug	Dose	Effect on duration of hospitalization	Other outcome measures	Best level of evidence available
Lactobacillus rhamnosus GG (LGG)	10^{10} CFU per day	Reduction of LOS[b] for rotaviral diarrhea; Trend toward reduction fo LOS, but not conclusive evidence for other etiologies	Duration of diarrhea; Risk of protracted diarrhea; Duration of hospitalization	Meta-analysis
S. boulardii	200–500 mg per day (about 4–10 × 10^9 CFU)	Reduction of LOS of about 1 day	Duration of diarrhea; Risk of protracted diarrhea; Duration of hospitalization	Meta-analysis (Few studies consider LOS)
Racecadotril	1.1,5 mg/kg TID	Not assessed	Stool output; Duration of diarrhea	Systematic review; Meta-analysis[a]
Zinc	10 mg <6 months of age; 20 mg >6 months of age	Not assessed	Duration of diarrhea; Stool output; Risk of hospitalization; Death	Meta-analysis
Smectite	3 g <1 year of age; 6 g 1–2 years of age; 6–12 g >2 years of age	Not assessed	Duration of diarrhea; Risk of protracted diarrhea; Number of stools	Meta-analysis
Oral administration of immunoglobulins	200–300 mg/kg per day	Reduction of LOS for rotaviral diarrhea in at-risk children or in severe conditions	Intake of oral fluids; Duration of intravenous rehydration; Resolution of diarrheal symptoms	Controlled studies

[a]No clear distinction between in- and out-patients effect size.
[b]Length of stay.

evidence in support of ondansetron as adjunct therapy in case of mild-moderate dehydration [21▪▪].

A single oral dose (0.15–0.3 mg/kg) of ondansetron controlled vomiting and reduced hospitalization rates [risk ratio (RR) 0.40, 95% CI 0.19–0.83, $P = 0.01$] and i.v. fluids need (RR 0.57, 95% CI 0.42–0.76, $P = 0.0002$, NNT = 6) when administered in EDs [21▪▪]. This intervention may be highly cost-effective [22].

In a 5-year retrospective study, the increased use of ondansetron (from 1 to 18%) was associated with a reduction of i.v. rehydration (from 26 to 14%, $P < 0.001$), length of stay in ED (8.6 ± 3.4 to 5.9 ± 2.8 h, $P = 0.03$) and return visits (18–13% $P = 0.008$) [20▪].

Major concerns on antiemetics prescription have been historically related to the potential side effects. A Cochrane review only reported few cases of increased diarrhea secondary to ondansetron administration [21▪▪]. Nevertheless, in September 2011, the US Food and Drug Administration (FDA) released a warning on the use of ondansetron in patients with underlying heart conditions, such as congenital long QT syndrome, heart failure, and bradyarrhythmias [23]. This was based on case reports of QT prolongation after ondansetron administration in adults [24] and children [25]. However, in addition to heart conditions, the FDA extended the warning to patients predisposed to hypokalemia and hypomagnesemia, or taking medications that may lead to QT prolongation. Abnormalities in electrolyte serum levels may be frequent in AGE, which opens a burning question on a routine use of ondansetron to prevent the need of i.v. rehydration and hospitalization in the light of some (low) risk of (potentially severe) side effects.

Antiemetic drugs alternative to ondansetron are limited; domperidone is a widely used drug with little evidence of efficacy [26]. A randomized controlled trial assessing the efficacy of ondansetron and domperidone compared with placebo in children admitted to EDs for AGE is currently ongoing in Italy [27▪].

A recent trial in Qatar showed no difference between ondansetron and metoclopramide in cessation of vomiting, length of stay, and side effects [28▪]. On the basis of these results, it was suggested that metoclopramide could represent an effective and cost-sparing alternative to ondansetron for persistent vomiting in poor countries. Considering the severe side effects reported for metoclopramide, this proposal raises concerns in terms of safety, mainly in developing areas where surveillance and accurate follow-up are limited.

Indications are, therefore, strongly needed on the use of antiemetics in AGE.

Antidiarrheal drugs

The simple replacement of lost fluids does not shorten the course of diarrhea and different approaches have been proposed to reduce duration and severity of diarrhea in hospitalized children, such as antimotility/antiperistaltic drugs, antesecretory, absorbents, and antimicrobial treatments.

Probiotics

These are recognized as first-line therapy for AGE in adjunct to rehydration [29], based on a demonstrated effect in reducing the duration of diarrhea by about 24 h, the risk of diarrhea lasting at least 4 days and the stool frequency on day 2 [30▪]. An analysis on hospitalized children also showed a significant effect of probiotics on duration of diarrhea (mean difference −20.90 h 95% CI −31.44 to −10.35) [30▪].

As the beneficial effects of probiotics are strain related, pooling data on different strains is inappropriate.

Lactobacillus rhamnosus GG [LGG] and *Saccharomyces boulardii* are the two strains, with consistent evidence of efficacy. LGG is the recommended treatment in evidence-based guidelines [3,6▪▪]. It also reduced the duration of hospitalization in previous meta-analysis [31].

Two recent double-blind RCTs, were conducted on *S. boulardii* in children hospitalized in low-income areas.

The first was carried out in two Brazilian hospitals and showed a reduction of diarrhea duration within 72 h from its onset. This reduction was significant in children with rotavirus infection (RR 0.45, 95% CI 0.28–0.74), but not in nonrotaviral diarrheal episodes [32▪].

The second study, performed on a small Bolivian population with rotaviral infection, compared the effect of *S. boulardii* and a mix of probiotics containing lactobacilli, bifidobacteria and *S. boulardii* with placebo. The authors reported a modest but significant effect of *S. boulardii* on the duration of diarrhea that was not observed with the combined probiotic product [33▪]. A new strain (DSM 17938) of *Lactobacillus reuteri* was tested in 70 children hospitalized with mild-to-moderate diarrhea [34,35▪]. *L. reuteri* reduced the duration of diarrhea (2.1 ± 1.7 vs. 3.3 ± 2.1 days, $P < 0.03$) and the prevalence of children with diarrheal stools at day 2 (55 vs. 81%, $P < 0.02$) and day 3 (46 vs. 73%, $P < 0.03$).

Guidelines produced in developing countries do not recommend probiotics in children with AGE [36] and their administration is currently considered as a common violation to recommendations [37▪].

This discrepancy between different geographic settings is essentially due to the limited evidence of

efficacy available in developing areas wherein cause of diarrhea, availability of fluids/water and probably alimentary habits may limit probiotic efficacy.

Racecadotril

Racecadotril, an enkephalinase inhibitor, is not approved by US FDA and data comes from European countries and developing areas [38▪▪]. In a recent meta-analysis including nine RCTs and more than 1300 inpatients and outpatients, racecadotril was effective in reducing diarrhea duration and stool output. The effect was independent from dehydration, rotavirus positivity and country [39▪▪].

A deterministic and probabilistic sensitivity analysis on the economic impact of racecadotril showed a reduction in the hospital expenses related to AGE event by about £380 due to primary care reconsultation and secondary referral [40▪].

Other antidiarrheal drugs

Zinc supplementation is recommended as universal treatment for acute diarrhea in childhood [3], based on several clinical trials and meta-analysis [41–43]. Efficacy is unclear in nonmalnourished children [44▪,45], but a clear efficacy has been shown in children severely malnourished [41].

Zinc-enriched ORS did not show similar efficacy in a recent trial in Indian inpatients [46▪]. A randomized placebo-controlled trial assessing the efficacy of a 14-days oral zinc supplementation in US inpatients and outpatients children is currently ongoing at the Boston Children's Hospital. The length of stay is the main outcome measure (clinicaltrials.gov NCT01198587).

Smectite is a natural clay with effects on permeability, cytokine production and electrolyte secretion, able to reduce duration of diarrhea and stool volumes.

A controlled trial, involving about 100 Indian children, showed a significant reduction of diarrhea duration of about 18 h [47▪].

A further option to be considered in severe and/or immunocompromised patients or in severe AGE episodes is oral administration of immunoglobulins [48,49]. This approach seems highly indicated for children in severe conditions with viral diarrhea. Oral administration of a hyperimmune immunoglobulin preparation produced from hens immunized against human rotavirus (anti HRV IgY, 500 mg × 4 per day) showed a significant effect on rotavirus excretion ($P = 0.05$), duration of diarrhea ($P = 0.01$), duration of i.v. rehydration ($P = 0.03$) and ORS needed ($P = 0.004$) [50▪]. As almost all the patients (92%) in the trial had, together with the rotavirus infection, a second enteric noncholera pathogen, the authors speculated that the product may improve the clinical outcomes also in patients with mixed enteric infections.

Florescu *et al.* [51▪] proposed the oral administration human immunoglobulins, for norovirus enteritis in a small population of patients that underwent bone marrow or solid organ transplantation or chemotherapy. A trend toward resolution of diarrhea and stool output was observed after 7 days from the onset of symptoms, although no benefits were found on the length of stay and hospital costs.

Antibiotics

Antibiotics are not routinely recommended in pediatric AGE [3] and they may increase costs, prolong diarrheal episodes, and contribute to spreading antibiotic resistance [52]. A quality care improvement approach with a multifaceted intervention led to a weak reduction of inappropriate antibiotic prescription in children with AGE in Kenya [53▪].

In developing areas where antibiotics are largely used to manage AGE, antibiotic resistance is becoming a common problem [54,55▪,56] and new molecules are being tested.

Vinh *et al.* [57▪] recently tested the efficacy of a 3-day course of gatifloxacin compared with the WHO standard treatment with ciprofloxacin for shigellosis in hospitalized children with no significant difference between the two antibiotics in terms of treatment failure (about 10%) and resolution of symptoms.

CONCLUSION

Several guidelines on the management of AGE in children are available, of good quality and similar in their indications [58▪▪]. Their application should limit the high number of inappropriate interventions that are common in hospital settings and could significantly reduce hospital costs [59]. Children admitted to ED with mild-to-moderate dehydration often receive i.v. fluids and unnecessary laboratory tests. However, protocols to rehydrate children with AGE are needed. The rapid/ultrarapid rehydration schemes may be loaded with electrolyte imbalances and have no clear advantages compared with standard rehydration. The main advantage is an early discharge with the reduction of the ED overcrowding, however, children treated with rapid i.v. rehydration are often readmitted to the ED. Several studies support the use of antiemetics in ED to prevent hospitalization, but recently the FDA released a warning on the use of ondansetron in patients with underlying heart conditions and electrolyte disorders. Finally, although AGE is a self-limiting disease, several efforts are ongoing to find the 'ideal drug' for treatment of acute diarrhea.

Acknowledgements

None.

Conflicts of interest

The authors have no conflict of interest to be declared.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 93–94).

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This trial performed on about 3000 children with shock and life-threatening infections who live in resource-limited areas, studied the role and effects of three different fluid resuscitation schemes including (5% albumin-bolus or 0.9% saline-bolus) or not (controls) administration of bolus. Authors demonstrated that fluid boluses significantly increased 48-h mortality in critically ill children with impaired perfusion. Children with AGE were excluded, but the results reported in that trial could have a significant impact on clinical management of severely dehydrated children, mainly in low-income countries.

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