Treatment of acute diarrhoea : update of guidelines based on a critical interuniversity assessment of medications and current practices

D. Urbain[1], J. Belaiche[2], M. De Vos[3], R. Fiasse[4], M. Hiele[5], S. Huijghebaert[6], F. Jacobs[7], H. Malonne[8], P. Speelman[9], A. Van Gompel[10], A. Van Gossum[11], E. Van Wijngaerden[12]

(1) Department of Gastroenterology, Free University of Brussels (VUB) ; (2) Department of Gastroenterology, University Hospital Medical Center (CHU) Sart-Tilman, Liège ; (3) Department of Gastroenterology, Gent University (RUG) ; (4) Department of Gastroenterology, Catholic University of Louvain (UCL), Brussels ; (5) Catholic University of Leuven (KUL) ; (6) PhD. Pharm., Pharmaceutical Sciences Consultant, La Hulpe ; (7) Department of Infectious Diseases, Free University of Brussels (ULB) ; (8) Department of Pharmacology, Free University of Brussels (ULB) ; (9) Department of Infectious Diseases, AMC, Amsterdam (Netherlands) ; (10) Department of Gastroenterology, Institute of Tropical Medicine, Antwerp ; (11) Department of Gastroenterology, Free University of Brussels (ULB) ; (12) Department of Infectious Diseases, Catholic University of Leuven (KUL).

Abstract

Further to a thorough analysis of the problem of acute diarrhoea and the therapeutic options, recommendations were defined following a multidisciplinary approach. These guidelines take into account the reality of frequent self-medication. They further differ as a function of age (children, primarily treated by ORS and for whom self-medication is not advised versus adults who can self-medicate), symptoms (uncomplicated diarrhoea versus dysentery) and location where the diarrhoea is contracted (at home or when travelling). (Acta gastroenterol. belg., **2003**, 66, **218-226**).

Key words : acute diarrhoea, treatment, guidelines, oral rehydration, diet, probiotic, loperamide, antibiotic.

Introduction

Acute diarrhoea is defined as a sudden abnormal increase in liquid consistency and frequency of bowel movements. It is usually self-limiting but it can also result in serious inconvenience to the patient and in the case of a child, be a major concern for parents. An effective and reassuring approach to the problem is desirable (1). Guidelines, however, frequently propose divergent recommendations, with a sole exception : the position of oral rehydration solutions (ORS) as the primary and essential treatment in infant diarrhoea. This recommendation is supported both by the World Health Organisation (WHO) and paediatric associations worldwide, such as the American Association of Paediatrics (AAP) and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (2-6).

Discrepancies in recommendations mainly apply to dietary measures, need to medicate and therapeutic options. They may arise from different risk-benefit interpretations and perceptions. With respect to the dietary management of diarrhoea, fasting, diets and special milk formula are still popular, despite the evidence in paediatric diarrhoea that early resumption of normal feeding leads to faster recovery and the latter recommendation by the WHO, AAP and ESPGHAN (4-7). Further, medication for diarrhoea is often discouraged and postponed until after 2 days of diarrhoea suffering (8,9). Such an approach is justified in children, in whom the risk-benefit of drugs in general is uncertain, and in adults suffering a short-lasting bout of diarrhoea for less than 24 hours. It is more difficult to understand in adults with disabling symptoms. Acute diarrhoea presents with physically impairing symptoms such as cramping, abdominal pain or pressure and urgency. Adult patients moreover experience social dysfunction and fear social embarrassment. There are thus reasons to help the patient, if symptoms are impairing. When compared to headache, another common ailment, for which it is socially and medically accepted to provide immediate symptom relief, diarrhoea carries a heavy social stigma.

A reason to withhold medication has been the opinion that diarrhoea functions as a defence mechanism to eliminate pathogens and therefore should not be treated with an antidiarrhoeal that will modify intestinal secretions and motility (10,11). The data used to support this notion are scarce (12) and have recently been judged unconvincing (1). Also our panel could not confirm such rationale after in-depth analysis of these data, consideration of the different mechanisms involved in diarrhoea (13,14), and evaluation of clinical studies with the antidiarrhoeal loperamide in acute infectious diarrhoea (15-19). The current therapeutic options for acute diarrhoea were reviewed by this panel, and their risk-benefit profile, resulting from published clinical evidence, product labelling and current medical expertise, is summarised in the tables of this publication.

Patients with diarrhoea very often treat themselves. Two thirds of the medications for diarrhoea in Belgium are dispensed without a prescription (20). Therefore it is important that the risk groups for which medical advice is mandatory are properly defined. Education of the self-medicating adult patient and clear instructions to the caring parent are warranted. In view of differences in risks, tolerability and efficacy of therapeutic approaches

Correspondence to : Prof. Dr. D. Urbain, Department of Gastroenterology, VUB, Laerbeeklaan 101, B-1090 Brussels. E-mail : Gasund@az.vub.ac.be.

Table 1. — **Signs of dehydration**

General	Signs of severe dehydration > 10% in babies
– A general weak condition (difficult standing on feet) – Dry mucous membrane – Confusion – Reduced consciousness or drowsiness – Reduced skin turgor (sticky skin, having lost its tension when taken between thumb and forefinger)	– High temperature, but absence of sweating – Crying without tears – Cessation of urination – Weakness and decreased alertness

between children and adults, their respective management is discussed separately in this article. Management specific to the elderly is not discussed.

I. Treatment of children

The term 'children' is defined here as the age group from 0 to 4 years. This age group is extremely susceptible to dehydration (Table 1). The infant group up to age six months, in particular, requires special attention. Older children (above 4 years) and adolescents are less susceptible to dehydration. Treatment in children therefore will focus in the first place on oral rehydration (2,3). The rapid reestablishment of normal feeding has also been found to play an important role in the process of recovery (4,5).

ORS

– Various ORS are available in pharmacies. They contain an optimal ratio of sugar (glucose) and electrolytes (salts) in order to stimulate the sodium-glucose co-transport in the small intestine and the resultant absorption of water. Some ORS contain also amino acids stimulating the amino acid-glucose co-transport. These solutions, taken orally, are as effective as parenteral infusions in rehydrating the body during secretory diarrhoea. All commercial ORS powders are very similar in electrolyte-sugar composition and osmolarity, some are rice-based (21,22). Soparyx®, for instance, contains rice powder, so that it has a slightly higher calorific value and a lower osmolarity than the other ORS. It is however not advised under the age of one year, because it contains aspartame, an artificial sweetener with allergizing potential. In general, ORS are hypocaloric : it is thus important to encourage parents to resume the child's normal feeds as soon as possible (2,3).
– It is important to dissolve the ORS powder in the correct amount of water, specified in the package insert. Too little water will make the fluid hyperosmotic, which may exacerbate diarrhoea, by dragging more body water in the intestine. Vice versa, when ORS is too much diluted, there is insufficient stimulation of the sodium-glucose transport for efficient hydration. Commercial powders are superior to homemade ORS because mistakes can easily be made when 'teaspoons' of salt and sugar are measured out (23,24). An excessive amount of salt can lead to hypernatremia (a sensation of thirst, drowsiness, weakness, irritability developing into muscular contractions, epilepsy and coma). The preparation of homemade ORS is therefore not recommended unless in emergency situations, for want of something better. If ORS powder in line with the recommendations of the WHO/paediatric associations, is not commercially available, ORS can be prepared by mixing 20 g glucose or 40 g saccharose (8 pieces of sugar of 5 g) with 3.5 g NaCl (salt : ¾ of a coffee spoon) and 1.5 g potassium chloride (a glass of orange juice or 2 bananas) for 1 litre of water (to be cooked in cholera-endemic areas). However, such preparation should not be routinely recommended. Commercial ORS are better in quality and entail fewer risks for the infant. ORS are also more efficient in hydrating the infant than commercially available sugar-containing beverages, such as Coca-Cola® or soft drinks (relatively few electrolytes, much sugar) and rice water (too few carbomonohydrates).

General recommendations for the physicians and parents

Doctors can best give following advice to parents :

– It is important to monitor the child closely. Infants can soon get better, but their condition can also deteriorate rapidly. Especially the baby who vomits and frequently passes watery stools, should raise concerns because of the high risk of rapid dehydration : 80% of the infant's body weight consists of fluid ; furthermore, the renal capacity to concentrate urine is much lower. It is recommended that the physician closely monitors the course of the disease in babies with severe diarrhoea (e.g. with vomiting and 8-10 bowel movements). Such infants, or infants exhibiting slight signs of dehydration on initial examination, are best be reexamined by the attending physician within 12 hours. Hospitalisation is indicated in the case of severe dehydration (Table 1).
– As per consensus by the WHO, the ESPGHAN and the AAP,[2,4,5,6] treatment targets oral rehydration of the child (Table 2). Care should be taken not to overhydrate. As soon as the fluid balance is restored, the child's natural craving to drink ORS will diminish. The child can then go back to normal bottle-feeding,

Table 2. — **Characteristics of ORS (oral rehydration solutions)** (2,3,9,13,21-23,44)

Properties	Clinical efficacy	Safety / Comments
Stimulate water absorption via activation of sodium-glucose co-transport	– Very effective in hydration – As effective as parenteral hydration – Rice-based ORS : also effective in reducing stool output by about one third only in "cholera", but not in "non-cholera" diarrhoea (21,22).	– Essential in infants and young children (2,3) – Can be home made (for banal diarrhoea), but commercially available ORS powders are preferred (if too much electrolytes, risk of hypernatremia with thirst and shock) (23) – Adults : soups or sweetened drinks combined with light carbohydrate-rich meals usually suffice (44)

Table 3. — **Features of fasting, diet and normal feeding** (4,5)

Properties	Clinical efficacy	Safety / Comments
Fasting / diet : presumed benefits (1) : – Less stimulation of gastrocolic reflex – Carrots, rice, banana : stool-binding – Logical if nausea, vomiting Early reintroduction of feeding provides : – Essential nutrients (carbohydrates, amino acids and fatty acids) and – Calories (energy) For regeneration of the gut wall and recovery	– No proven efficacy of diet (no studies), unless in diarrhoea due to food intolerance – Accelerated recovery with early resumption of normal feed (both in malnourished and normal children) ; diarrhoea duration reduced by half a day (4,5,24) – No data in adults on effect of early normal refeeding	Current recommendation (1,4,5,9) : – In children (WHO, ESPGHAN, AAP) : early reintroduction of usual milk feed (no dilution of milk or special formulas) – In general : guidance of food intake by appetite and intake of normal food (light balanced meals)

alternated with ORS, following vomiting or passage of liquid stools. The early resumption of normal feeding is important to fasten recovery (4,5) (See Table 3 and also 'Rapid resumption of normal feeding').

– Symptoms in the child that should prompt parents to seek medical help without delay are (Table 2) : high temperature but absence of sweating, crying without tears, cessation of urination, or weakness and decreased alertness. These are signs of severe dehydration (> 10%) and they call for immediate treatment. Attempts are frequently made to determine the presence of dehydration on the basis of the baby's weight. This is not so evident, because the precise weight of the baby just before the onset of the diarrhoea is most often not known.

As a general rule, medication should not be used to treat diarrhoea in young children. This recommendation is the result of evidence-based analysis of trials of acute diarrhoea in children (24,25,26), and the consensus by the WHO and the paediatric associations (AAP and ESPGHAN) (2,5,6). All focus should be on the primary therapy, which is hydration with ORS, and on good feeding practices, which provide benefit in reducing diarrhoea duration (2,4,5,6). The evidence of efficacy of existing medications for diarrhoea in infants is considered to be insufficient, and/or may expose young infants to the risks of potentially serious adverse events.

– For instance, effects of probiotics have been documented in a few trials such as with *Saccharomyces boulardii*, *Lactobacillus casei GG* and *Lactobacillus acidophilus*, but the benefits are usually limited (see Table 4) to young children having rotavirus diarrhoea ; the doses are generally high (often higher than commercially available) (27,28,29,30).
– Adsorbents (table 5) have stool-thickening properties. There is no conclusive evidence available today that these agents reduce the duration of diarrhoea or stool frequency. One study showed some effect at doses higher than registered (31). Disadvantages include adsorption of nutrients, enzymes and other medications, such as antibiotics in the gut.
– Loperamide is not recommended to treat acute diarrhoea in young children : risks of adverse events in the young outweigh its benefits (Table 6) (2,4-6,24-26). It is contra-indicated below 2 years (32). If used in children below 6 years, caution is to be exerted : it should be exclusively under medical supervision, correctly dosed in function of the child's bodyweight and flexibly administered (only if and as long as the child passes loose stools). Cautious dosage is required because of the risk of adverse events such as ileus following overdosing in the case of too highly dosed or too frequent administration (33).
– Also antibiotics should not be used routinely (34). Apart from the fact that childhood diarrhoea is often viral (not responding to antibiotics), reasons for proposing very restricted use include resistance, adverse events and inefficacy in uncomplicated infectious diarrhoea (35,36). The exception is severe invasive diarrhoea/dysentery (body temperature > 38.5°C and bloody stools) or prolonged diarrhoea : the antibiotic is to be selected in function of the identified micro-organism. Also during a travel, their empirical use in children is not recommended, unless in the case of desperate condition during a travel in the tropics at places where medical help is not accessible (see self-medication). Following reports on a deleterious effect of antibiotics on bloody diarrhoea due to haemorrhagic E. coli (evolution to haemolytic-uraemic

Table 4. — Probiotics (mainly *Lactobacillus ssp. and Saccharomyces boulardii*) (27-30,41,45-47, 49,50)

Properties	Clinical efficacy	Safety / Comments
Experimental (46,46,48,46,49,50) : – Disaccharidase activity (also confirmed in human upon chronic intake) – Stimulation of the immune system – Production of bacteriostatins – Competition for bacterial adhesion – Beneficial changes in bacterial flora (confirmed in human at high doses) – Antisecretory / anti-protease activity against some toxins *(Saccharomyces boulardii)*.	– Depends on strain and age – Acute diarrhoea : 1) limited effect in children (mainly rotavirus diarrhoea) with *Saccharomyces boulardii, Lactobacillus acidophilus, casei GG* and *reuteri* [generally highly dosed] : no significant effects during first 48 hours ; one stool less on day 3 or/and 4 ; duration of diarrhoea reduced by half a day to less than 1 day ; 2) no effects documented in adults within the first 24 or 48 hours (27-30,47,49,50) – Acute travellers' diarrhoea : no proven efficacy (protection considered insufficient in the case of prophylaxis) (41,45) – Antibiotic associated diarrhoea : 1) in children : no documentation of efficacy in placebo-controlled trials ; 2) in adults : no efficacy in acute condition, but effective for prophylaxis, mainly at high (not registered) dosages (47,50)	Considered well tolerated. Occasional adverse events (57) : – bloating, meteorism. Rare adverse events : – bacteremia, resistance/plasmid transfer, induced artritis (by cell mebrane components of killed bacteria) (*Lactobaccillus ssp.*) (49) – fungicemia (*Saccharomyces boulardii*, in immunodepressed, at intravenous line) (50,57) – skin reactions and Quincke oedema (*Saccharomyces boulardii*) (57) Use in children not recommended by WHO, AAP, or ESPGHAN (2,5,6)

Table 5. — Adsorbents (1,31,48)

Properties	Clinical efficacy	Safety / Comments
– Adsorb water – Bind, thicken stools – Experimentally : *in vitro* absorption of viruses and toxins ; *in vivo* efficacy documented by pre-treatment only – Experimentally : protective effects on the mucous barrier	– Efficacy documented at higher than registered dose in acute infant diarrhoea (shorter duration, less stools) (31) – No adequate documentation of good efficacy in placebo-controlled studies in adult acute diarrhoea (1,48)	– Well tolerated, sometimes constipation – Can adsorb other medications (antibiotics) : if to be taken concurrently, intake of the medications to be separated by 2 hours – Use in young children not recommended by WHO, ESPGHAN and AAP (2,5,6)

syndrome), even a contraindication for use of antibiotics in residential bloody diarrhoea has been proposed, unless after exclusion of this pathogen (37). Also use of nifuroxazide is highly questionable in children : 1) there is no published evidence of efficacy in children, 2) resistance to this agents has been reported and a recent study in adults did not confirm efficacy (38,39).

Rapid resumption of normal feeding :

Fasting or restriction of food and full avoidance of fat is no longer recommended. It has been shown that early feeding and resumption of normal food does not prolong diarrhoea, but fastens recovery in the child by about half a day (4,5,6,24) (Table 3)

– According to the recommendations of the WHO and the ESPGHAN, the infant should be rehydrated during the first 3-4 hours, followed immediately by the normal milk at full concentration to provide the child with the necessary calories for recovery (2,3,7). After each soft or watery stool, ORS is given again. In practice, this is sometimes difficult (for instance, in day care centres). It frequently results in postponement of early realimentation by 12, or as much as 24 hours. Frequently, bottle-feed is diluted or lactose-free milk is given. These practices are however not optimal. In fact, the use of lactose-free formulae in the majority of children appears to be unjustified (7). The use of milk at full lactose concentration is encouraged in order to provide the child with sufficient energy for recovery. Lactose contents in feeds should only be reduced in the case that diarrhoea worsens on reintroduction of milk, after checking the stools for acidity and presence of > 0.5% reducing substances suggestive of lactose intolerance (6,7).
– Fat intake should not be restricted but be kept normal. A frequent cause of persisting diarrhoea after a phase of acute diarrhoea is giving the child a completely fat-free diet. Mothers are often obsessive about avoiding all fat in their child's food because the stools often look worse after fat intake. Reintroduction of fat in the child's feed can lead to full recovery within two days.
– Despite the benefits for the child, many European paediatricians appear not to comply with the feeding guidelines by the WHO, AAP and ESPGHAN and still burden parents of young children with buying special formulas and unnecessary medications for acute diarrhoea (6,40). Some doctors also prescribe probiotics to relieve or prevent antibiotic-induced diarrhoea in infants, yet there is little, if any documentation for such practices in children, or for their benefit over the classical recommendation of yoghurt supplementation (no placebo-controlled trials in children retrievable from Medline or reviews on probiotics) (46,47,49,50).

Table 6. — Loperamide (15-19,32,33,38,45,59-62)

Properties	Clinical efficacy	Safety / Comments

– Antisecretory properties (58) :
  – experimentally and in human (also at therapeutic dosages)
  – via opiate and non-opiate mediated mechanisms (Ca^{2+}-antagonism, calmodulin, sodium chloride co-transport)
– In normal subjects : after a single intake of 4 mg, no inhibitory effect on small intestinal motility or gut transit ; only slowing of gut transit upon repetitive dosing (59,60)
– In diarrhoea patients : flexible dosing "normalises" gut transit (61)
	– Fast symptomatic relief of acute, non-dysenteric diarrhoea and travellers' diarrhoea (less stools and cramps, shorter diarrhoea duration) (15-19,32,38,45)
	– Combined with an antibiotic : better symptomatic relief in travellers' diarrhoea compared to the antibiotic alone, also in mild dysentery (15,17,18,38,41)
		– Contra-indicated in severe dysentery (gross blood in stools, high fever), active ulcerative and pseudomembranous colitis (situations at risk of toxic megacolon)
		– To be flexibly dosed in function of stools
		– Below 2 years : contra-indicated because of risk of ileus and central depression (mainly reported following overdosage ; liver and blood-brain barrier are immature) (33) ;
		– In children 2-6 years : cautious use, under medical supervision, in function of body weight and liquid stools
		– Use in young children not recommended by WHO, ESPGHAN and AAP (2,5,6)
		– In adults : overall well tolerated ; occasionally constipation, skin allergy and GI symptoms.

Self-medication discouraged for children

Self-medication is generally not recommended for children : it is always advisable to consult a physician, particularly in the young child up to 6 years. There is no consensus by this panel on the age limit for self-medication or mandatory referral. Whatever approach, care should be taken that the child drinks enough and that rehydration with ORS is started straightaway. An exception where self-medication of acute diarrhoea in children is justified, is when travelling and local medical care is difficult to reach. In that case, the same recommendations with regard to fluid intake should be observed. ORS sachets should thus best be taken along when travelling. Automedication with loperamide is not allowed below 6 years of age. An antibiotic should not be routinely given : it must only be used in children in the case of dysentery (high temperature > 38.5°C and bloody stools). The antibiotic itself can cause side effects and the pathogen can be resistant. It is only be justified in the travel kit, for use in the case of severe invasive, complicated cases of diarrhoea, in view of the frequent bacterial origin of travellers' diarrhoea (41,42,43). Whereas this is likely to be an effective approach, when *Shigella*, *Salmonella* or *Campylobacter* is suspected, restricted attitude and caution should be exerted in general. With severe diarrhoea in children, it always remains advisable to seek medical help on the spot.

Trimethoprim/sulfamethoxazole is an option that can be used in infectious diarrhoea in children, if the pathogen is "susceptible" (34) : its usefulness in travel medicine though is questionable due to the high bacterial resistance. The antibiotics currently proposed for children with traveller's diarrhoea are azithromycin (customary doses for 3 to 5 days), and in older children (per label above 15 years), also a short course of a fluoroquinolone (1-3 days) can be used (42,43). In younger patients, controversy remains about the use of fluoroquinolones in view of their potential interaction with cartilage formation. Empirical use in young children, deviating from the label, should thus be restricted to short courses for desperate cases of infectious diarrhoea – only a) under medical supervision (see "general recommendations"), or b) if no access to medical care in remote areas with high resistance to trimetoprim/-sulfamethoxazole (41). Antibiotics, if prescribed, thus require prior explanation of their use and risks by the doctor (see also section 'General recommendations for the physicians and parents').

To avoid aggravation of dehydration, it is also useful to point out to parents to keep their children out of the sun and for sure, not for long in a car.

II. Guidelines for the treatment of adults with acute diarrhoea

As diarrhoea is commonly treated by adult patient without prior medical advice, the following recommendations take account of self-medication. Consequently they are brief and targeted to simple, recognisable symptoms and situations. Although the pharmacist cannot make a diagnosis, he/she plays an important role in advising and educating the patient.

Medical advice mandatory in the following cases :

Because of potentially serious complications, it is always advisable to consult a physician in the following situations :

– elderly patients (> 60 to 65 years) ;
– patients with :
  – severe vomiting
  – signs of dehydration (dry mucosa, drowsiness, diminished consciousness or awareness) (see also Table 1)
  – general weakness ('toxic', pale and ill-looking patient)
  – persistent or recurrent diarrhoea

- high temperature and/or bloody stools (also called dysentery)
- patients with diminished mental ability (as a result of which they may not increase the fluid intake sufficiently).

Patients with an important medical history, or using medication such as immuno-suppressive agents, insulin, oral hypoglycaemic agents and diuretics, are also urged to seek advice from their physician, because of the increased risk for severe complications. Since some drugs can cause diarrhoea, it is important that the patient informs the physician of recent use of medication, as well as of past use of antibiotics to exclude them as cause.

Recommendations for treatment

- It is important to drink sufficient fluid, such as slightly sweetened beverages, broth and soups. ORS are essential in the event of severe dehydration. They can also be recommended for the travel kit. Yet, in most cases, it will be sufficient to drink a lot and eat light meals, which provide the necessary electrolytes and carbohydrates (44).
- Fasting or fat-free food is not required. It is recommended to resume, as soon as possible, normal nutrition, also with solid food, as guided by appetite, in order to allow optimal recovery of the bowel.
- For adults with uncomplicated diarrhoea who ask for a medication, there is no reason to withhold medication The discomfort and social dysfunction that the patient experiences motivates the use of an efficient, fast-acting medication. Loperamide, dosed flexibly in function of loose bowel movements, can be recommended (Table 6). It shortens the duration of the diarrhoea, reduces the number of stools and relieves cramping (15-19,45). Evidence from controlled studies shows that loperamide has no undesired effects in infectious non-dysenteric traveller's diarrhoea (without high fever of blood in stools) or mild dysentery, given either alone or in combination with antibiotics (15-19,45). It will however not be used in the case of high fever and bloody stools (see "dysentery") or following detection of *Clostridium difficile*. Other drugs, such as adsorbents and probiotics, are less suitable for treatment of acute diarrhoea because careful analysis of clinical trials show that evidence of adequate efficacy in acute diarrhoea in adults is lacking (Table 4,5) (41,46-50). Consistent benefits with probiotics in adults only pertain to "prophylaxis" of antibiotic-induced diarrhoea, which is beyond the scope of these recommendations (for prophylaxis of traveller's diarrhoea : see "special precautions") (47). Likewise, intestinal antiseptics, such as nifuroxazide, are likewise no longer recommended, mainly due to lack of recent confirmation of activity and because of resistance (38,39).
- Antibiotics are prescription drugs (Table 7). Although effective in acute diarrhoea (51), they are not recommended for the routine treatment of residential diarrhoea (contracted in one's own country), in view of the frequent viral origin of adult acute diarrhoea (52), and the possibility of inducing bacterial resistance and side-effects such as diarrhoea itself (53,54). Antibiotics are indicated in dysentery (diarrhoea with bloody stools and high temperature), as well as in severe diarrhoea in which the pathogen has been identified. Self-medication with antibiotics is, however, permitted when travelling (after prior consultation with the doctor). It is important that the physician informs the patient when and for how long the antibiotic may be used. In adults, the fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, pefloxacin) are currently recommended first-line, while trimetoprim/sulfamethoxazole – owing to the high bacterial resistance – second line (41). In mild traveller's diarrhoea, however, treatment with loperamide will usually suffice. Nevertheless, for persons travelling in difficult conditions, immediate treatment can be recommended, consisting of a daily dose (1 to 3 days) of fluoroquinolone combined with loperamide (15, 17,18). The antibiotic is to be taken only as long as the diarrhoea persists : often a single intake suffices. Azythromycin (3 to 5 days) can be used in areas where fluoroquinolone resistence of *Campylobacter* strains is common (55).
- In severe watery diarrhoea, and certainly in dysentery (diarrhoea with fever and severe cramping, and/or blood and mucus in stools), a short course of fluoroquinolone treatment is recommended : the duration of intake depends on the course of the disease (maximum 3-5 days). With such severe or persistent symptoms, loperamide will not be taken and it is best to consult a physician, if symptoms do not immediately ameliorate.
- It is important that the patient seeks medical advice, not only if the diarrhoea or condition deteriorates, but also if the diarrhoea lasts longer than 5-7 days (even if improved during the use of antibiotics for the condition). Uncomplicated diarrhoea normally resolves within two to five days. Upon persisting symptoms, loperamide will also be discontinued.
- Taking a culture is only indicated in severe, persistent or debilitating diarrhoea, in order to identify the pathogen, to establish its antibiotic spectrum and then, if necessary, to adjust the drug treatment in time. A microscopic examination of the stools (detection of white blood cells) or a culture is likewise recommended in cases of traveller's diarrhoea persisting after the patient returns home, even if the doctor has started antibiotic therapy straightaway because of the severity of the symptoms. In the case of diarrhoea caused by the use of antibiotics (*Clostridium difficile)* or in the event that *Shigella, Salmonella, Campylobacter, Yersinia, Giardia lamblia* or *Entamoeba histolytica* is detected, the decision regarding therapy should be taken in relation to the pathogen, the

Table 7. — **Antimicrobials (15,17,18,34,36,38,41,44,51,53-56)**

Properties	Clinical efficacy	Safety / Comments
– Bactericidal on bacterial pathogens, but also on bacteria of the natural gut flora – Some local acting gut antiseptic drugs : bacteriostatic acting only	Fluoroquinolones : – proven effective in acute infectious and traveller's diarrhoea (51) – combined with loperamide : faster symptom relief (17,18) – short treatments suffice (intake only as long as diarrhoea lasts) Trimetoprim/ sulfametoxazole : proven effective, but increasing resistance (15,41,53) Azithromycin : – also effective in fluoroquinolone-resistant diarrhoea (55) – in children (dysentery) (41) Other antimicrobial, such as nitrofuranes (including nifuroxazide) : – no recent confirmation of efficacy (38) – microbial resistance (38,41)	– Prescription-only drugs – Not routinely recommended for diarrhoea occurring at home (frequent viral cause, increasing microbial resistance) – Recommended in severe infectious diarrhoea (pathogen identified) ; in acute traveller's diarrhoea in the case of adults travelling in difficult conditions ; very restricted use in children (severe invasive diarrhoea) (11,34,36,43) – First-line : fluoroquinolones ; second-line ; trimetoprim/ sulfametoxazole (in infantile dysentery : azythromycin, eventually a short course of fluoroquinolones) (34,36,37) – Adverse events : secondary diarrhoea, rarely colitis and megacolon (62)

clinical symptoms, the risks of co-morbidity and the patient's age. Infections caused by *Giardia lamblia* and *Entamoeba histolytica* should be treated with imidazoles. A whole range of other single-cell intestinal parasites are non-pathogenic and require no treatment (such as *Entamoeba coli, Entamoeba dispar, Entamoeba hartmanni, Endolimax nana* and *Iodamoeba bütschlii*).

Special precautions

– As with all drugs, pregnant or breast-feeding women should preferably be given no medication. When there are clinical symptoms that require treatment, as in the case of dysentery, treatment should only be given after medical advice.
– Women who are taking oral contraceptives ('the pill') should be aware of the risk of interim vaginal bleeding and pregnancy, because of the decreased absorption of hormones. It is advisable to take additional precautions (condom) until the start of the next menstrual cycle (56).
– It is advisable for patients who are on medication to consult their physician and they should take into account the reduced absorption of other compounds, such as antiepileptics, digoxin or lithium. On the other hand, diuretics should be stopped for the time being since they promote diuresis and increase the risk of dehydration.
– Medication for prophylaxis for traveller's diarrhoea is not recommended (41). Nevertheless, antibiotic prophylaxis (fluoroquinolones) can exceptionally be considered, depending on the travel destination and only on doctor's advice, in the case of overriding interests, or patients at increased risk of intestinal complications or dehydration : namely, persons with active inflammatory bowel disease, AIDS, type-1 diabetes, renal failure, reduced acid production and taking diuretics. Prophylaxis with probiotics provides insufficient protection (41).

Conclusions

Acute diarrhoea episodes are usually self-limiting, but can be disabling. Self-medication is advisable in otherwise healthy adults, provided they suffer from uncomplicated symptoms (diarrhoea without high fever and without gross blood in stools). Symptomatic treatment with a medication such as loperamide can be considered. In case of travel, a short course of a broad-spectrum antibiotic (fluoroquinolone), possibly combined with loperamide, can be recommended : it is then to be taken only as long as the diarrhoea lasts. In the case of severe dysentery, antibiotics (no loperamide) are recommended. Self-medication should not last beyond 5 days and should certainly not be started once back in the country. The patient needs to consult a physician if the symptoms do not readily improve, worsen during self-medication, or persist for several days despite treatment.

Medical intervention is recommended in infants, frail and elderly adults, and persons with serious concurrent disease. In infants, ORS constitutes the primary and essential treatment to guarantee sufficient hydration and benefits of medication, if any, are limited, so that they are not routinely recommended. Whatever the patient's age and whatever the approach (self-medication or consultation), it is always important to stimulate fluid intake and early resumption of normal feeding.

Acknowledgements

The interuniversity assessment addressed the same problem statements as the consensus panel Wingate *et al*, recently published in *Al. Pharm. Ther.* 15 : 773-782, 2001. The evaluation was performed independently, taking into account de Belgian situation and differences in recommendations between infantile and adult diarrhoea. The outcome of the interuniversity assessment has been published in more detail in Louvain Médical, 2001 ; 120 : 354-361. The logistics of the meeting were sponsored by Janssen-Cilag, which did not participate in the discussion or writing of the guidelines.

References

1. WINGATE D., PHILIPS S.F., LEWIS S.J., MALAGELADA J.-J., SPEELMAN P. *et al.* Guidelines for adults on self-medication for the treatment of acute diarrhoea. *Aliment Pharmacol. Ther.*, 2001, **15** : 773-782.
2. WHO Diarrhoeal Disease Control Programme. Drugs in the management of acute diarrhoea in infants and young children. Report WHO/CDD/CMT/86.1. 1986.
3. BOOTH I., CUNHA FERREIRA R., DESJEUX J.-F., FARTHING M., GUANDALINI S. *et al.* Report of an ESPGAN working group. Recommendations for composition of oral rehydratation solutions for the children of Europe. *J. Pediatr. Gastroenterol. Nutr.*, 1992, **14** (1) : 113-115.
4. CLAESON M., MERSON M.H. Global progress in the control of diarrheal diseases. *Pediatr. Infect. Dis. J.*, 1990, **9** : 345-355.
5. American Academy of Pediatrics, Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. Practice parameter : The management of acute gastroenteritis in young children. *Pediatrics*, 1996, **97** : 424-433.
6. HOEKSTRA J.H. for the ESPGHAN Working Group on diarrhoea. Acute gastroenteritis in industrialized countries : compliance with guidelines for treatment. *J. Pediatr. Gastroenterol. Nutr.*, 2001, **33** (Suppl 2) : S31-5.
7. WALKER-SMITH J.A., SANDHU B.K., ISOLAURI E. *et al.* Medical position paper. Guidelines prepared by the ESPGAN working group on acute diarrhoea. Recommendations for feeding in childhood gastroenteritis. *J. Pediatr. Gastroenterol. Nutr.*, 1997, **2** : 619-20.
8. SWANSON V., MCINTOSH I.B., HOWELL K. A study of GP attitudes to acute diarrhoea management. Scottish Medicine Volume, 1999, **18** : 6-7.
9. NHG standaard Acute Diarree. *Huisarts en Wetenschap*, 1993, **36** (9) : 294-299.
10. CHAK A., BANWELL J.G. : Traveller's diarrhoea. *Gastroenterology Clinics of North America*, 1993, **22** (3) : 549-561.
11. GUERRERO G. : Acute invasive diarrhoea in the paediatric patient. *Scand. J. Gastroenterol.*, 1989, **24** (S169) : 24-27.
12. DU PONT H.L., HORNICK A.B. : Adverse effect of Lomotil therapy in Shigellosis. *JAMA*, 1973, **226** : 1525-8.
13. FINE K.D. : Diarrhoea. *In* : FELDMAN M., SCHARSCHMIDT B.F., SLEISENGER M.H. (eds). Sleisenger and Fortran's gastro-intestinal and liver disease. Saunders Company, 1998, chapter 10.
14. HAMER D.K., GORBACH S.L. Infectious diarrhoea and bacterial food poisoning. *In* : FELDMAN M., SCHARSCHMIDT B.F., SLEISENGER M.H. (eds). Sleisenger and Fortran's gastro-intestinal and liver disease. Saunders Company,, 1998, pp 1594-1632.
15. ERICSSON C.D., DUPONT H.L., MATHEWSON J.J., WEST S., JOHNSON P.C., BITSURA J.A. Treatment of traveller's diarrhoea with sulfamethoxazole and trimethoprim and loperamide. *JAMA*, 1990, **263** : 257-261.
16. JOHNSON P.C., ERICSSON C.D., DU PONT H.L., MORGAN D.R., BITSURA J.A.M., WOOD L.V. Comparison of loperamide with bismuth subsalicylate for the treatment of acute travelers' diarrhoea. *JAMA*, 1986, **255** : 757-760.
17. MURPHY G.S., BODHIDATTA L., ECHEVERRIA P. *et al.* Ciprofloxacin and loperamide in the treatment of bacillary dysentery. *Annals of Internal Medecine*, 1993, **118** : 582-586.
18. TAYLOR D.N., SANCHEZ J.L., CANDLER W., THORNTON S., MCQUEEN C., ECHEVERRIA P. Treatment of traveller's diarrhoea : ciprofloxacin plus loperamide compared with ciprofloxacin alone. A placebo-controlled randomized trial. *Ann Intern Med*, 1991, **114** : 731-734.
19. VAN LOON F.P., BENNISH M.L., SPEELMAN P., BUTLER C. Double blind trial of loperamide for treating acute watery diarrhoea in expatriates in Bangladesh. *Gut*, 1989, **30** : 492-495.
20. IMS Pharmatrend, Mat Oktober, 2000.
21. ISLAM A., MOLLA AM, AHMED M.A. *et al.* Is rice based oral rehydration therapy effective in young infants ? *Arch. Dis. Child*, 1994, **71** : 19-23.
22. GORE S.M., FONTAINE O., PIERCE N.F. Impact of rice-based oral rehydration solution on stool output and duration of diarrhoea : meta-analysis of 13 clinical trials. *BMJ*, 1992, **304** : 287-291.
23. LIFSCHITZ C.H. Treatment of acute diarrhoea in children. *Curr. Opin. Pediatr.*, 1997, **5** : 498-501.
24. GRACEY M. Nutritional effects and management of diarrhoea in infancy. *Acta Paediatr.*, 1999, **Suppl. 430** : 110-26.
25. MURPHY M.S. Guidelines for managing acute gastroenteritis based on a systematic review of published research. *Arch. Dis. Child*, 1998, **79** : 279-84.
26. ARMON K., STEPHENSON T., MACFAUL R., ECCLESTON P., WERNECKE U. An evidence and consensus based guideline for acute diarrhoea management. *Arch. Dis. Child*, 2001, **85** : 132-142.
27. CHAPOY P. Traitement des diarrhées aiguës infantiles : essai contrôlé de *Saccharomyces boulardii*. *Ann. Pédiatr.*, 1985, **32** : 561-563.
28. CETINA-SAURI G., SIERRA BASTO G. Evaluation thérapeutique de *Saccharomyces boulardii* chez des enfants souffrant de diarrhée aiguë. *Ann. Pédiatr.*, 1994, **41** : 397-400.
29. GUANDALINI S., PENSABENE L., ZIKRI M.A. *et al. Lactibacillus GG* administered in oral rehydration solution to children in acute diarrhoea : a multicenter European trial. *J. Paed. Gasteroenterol. Nutr.*, 2000, **30** : 54-60.
30. SIMAKACHORN N., PICHAIPAT V., RITHIPORNPAISARN P., KONAEW C., TONGPRADIT P., VARAVITH Y.A. Clinical evaluation of the addition of lyophilized, heat-kiled *Lactobacillus acidophilus* LB to oral rehydration therapy in the treatment of acute diarrhoea in children. *J. Paediatr. Gasteroenterol. Nutr.*, 2000, **30** : 68-72.
31. MADKOUR A.A., MADINA E.M., EL-AZOUNI O.E., AMER M.A., EL-WALILI T.M., ABBASS T. Smectite in acute doiarrhoea in children : a double-blind placebo-controlled trial. *J. Paeditr. Gastroenterol. Nutr.*, 1993, **17** : 176-81.
32. KAPLAN M.A., PRIOR M.J., MCKONLY K., DUPONT H.L., TEMPLE A.R., NELSON E.B. A multicentre randomised controlled trial of a liquid loperamide product versus placebo in the treatment of acute diarrhoea in children. *Clin. Paediatrics*, 1999, **38** : 579-91.
33. LITOVITZ T., CLANCY C., KORBERLY B., TEMPLE A.R., MANN K.V. Surveillance of loperamide ingestions : an analysis of 216 poison center reports. *Clin. Toxicol.*, 1997, **35** : 11-19.
34. GUERRANT R.L., VAN GILDER T., STEINER T.S. *et al.* Practice guidelines for management of infectious diarrhoea. *Clinical Infectious Diseases*, 2001, **32** : 331-50.
35. CHIU C.H., LIN T.Y., QU J.T. A clinical trial comparing oral azithromycin, cefixime and no antibiotics in the treatment of acute uncomplicated Salmonella enteritis in children. *J. Paediatr. Child Health*, 1999, **35** : 372-4.
36. OLDFIELD E.C., WALLACE M.R. The role of antibiotics in the treatment of infectious diarrhea. *Gastroenterol. Clin. North Am.*, 2001, **30** : 817-36.
37. WONG C.S., JELACIC S., HABEEB R.L., WATKINS S.L., TARR P.I. The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Esccherichia coli* O157 : H7 infections. *N. Engl. J. Med.*, 2000 , **342** : 1930-1936.
38. MEURIS B. Observational study of travelers' diarrhoea. *J. Travel Med.*, 1995, **2** (1) : 11-15.
39. CAVALLO J.D., NIEL L., RAMARIN A., DUBROUS P. Antibiotic sensitivity to epidemic strains of *Vibrio cholera* and *Shigella dysenteriae* 1 in Rwandan refugee camps in Zaire. *Med. Trop.*, 1995, **55** : 351-353.
40. SZAJEWSKA H., HOEKSTRA J.H., SANDHU B**.** Management of acute gastroenteritis in Europe and the impact of the new recommendations : a multicenter study. The Working Group on acute Diarrhoea of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. *J. Pediatr. Gastroenterol. Nutr.*, 2000 May **30** : 522-7.
41. DE LAS CASAS C., ADACHI J., DU PONT H. Review article : travellers' diarrhoea. *Aliment Phamacol. Ther.*, 1999, **13** : 1373-8.
42. OSTROSKY-ZEICHNER L., ERICSSON C.D. Travelers' diarrhea. *In* : ZUCKERMAN J. (ed). Principles and practice of travel medicine. John Wiley & Sons ltd., 2001, Chapter 10, pp. 153-163.
43. FISHER P.R. Traveling with children. *In* : ZUCKERMAN J. (ed). Principles and practice of travel medicine. John Wiley & Sons ltd., 2001, Chapter 10, pp. 153-163.
44. CAEIRO J.P., DUPONT H.L., ALBRECHT H., ERICSSON C.E. Oral rehydration therapy plus loperamide versus loperamide alone in the treatment of traveller's diarrhea. *Clin. Infect. Dis.*, 1999, **28** : 1286-1289.
45. STEFFEN R., HEUSSER R., TSCHOPP A., DUPONT H.L. Efficacy and side-effects of six agents in the self-treatment of travellers' diarrhoea. *Trav. Med. Intern.*, 1988, **6** : 153-157.
46. ISOLAURI E. Probiotics and gut inflammation. *Curr. Opin. Gastroenterol.*, 1999, **15** : 534-537.
47. LEWIS S.J., FREEDMAN A.R. Review article : the use of biotherapeutic agents in the prevention and treatment of gastrointestinal disease. *Aliment Pharmacol. Ther.*, 1998, **12** : 807-822.
48. SCHILLER L.R. Review article : anti-diarrhoeal pharmacology and therapeutics. *Aliment Pharmacol. Ther.*, 1995, **9** : 87-106.
49. VANDENPLAS Y. Bacteria and yeast in the treatment of acute and chronic infections. Part I. Bacteria. *Clin. Microbiol. Inf.*, 1999, **5** : 299-307.
50. VANDENPLAS Y. Bacteria and yeast in the treatment of acute and chronic infections. Part II. Yeast. *Clin. Microbiol. Inf.*, 1999, **5** : 389-395.
51. Cochrane review, De Bruyne *et al.* May 2000. www.update-software.com/abstracts/ab002242.htm.
52. ALLEMEND H., AMOURETTI M., COLOMBEL J.F. *et al.* A French survey on epidemiology and management of acute diarrhoea. *Gut*, 1996, **39** (Suppl 3) : A173.
53. SACK R.B., RAHMAN M., YUNUS M., KHAN E.H. Antimicrobial resistance in organisms causing diarrhoeal disease. *Clin. Infect. Dis.*, 1997, **24** (Supp1), S102-S105.

54. SMITH K.E., BESSER J.M., HEDBERG C.W. *et al.* Quinolone resistant *Campylobacter jejuni* infections in Minnesota, 1992-1998. *NEMJ*, 1999, **340** : 1525-1529.
55. KUSCHNER R.A., TROFA A.F., THOMAS R.J. *et al.* Use of azithromycin for the treatment of *Campylobacter* enteritis in travelers to Thailand and areas where ciprofloxacin resistance is prevalent. *Clin. Inf. Dis.*, 1995, **21** : 536-41.
56. KOZARSKY P.E., VAN GOMPEL A. Pregnancy, nursing, contraception and travel. Chapter 37 in Textbook of Travel Medicine and Health. DuPont & Steffen (editors). Second edition B.C. Decker Inc Hamilton, London, 2001.
57. Package insert Perenterol (*Saccharomyces boulardii*) , Germany.
58. AWOUTERS F., MEGENS A., VERLINDEN M., SCHUURKES J., NIEMEGEERS C., JANSSEN P. Loperamide. Survey of studies on mechanism of its anti-diarrhoeal activity. *Dig. Dis. Sci.*, 1993, **38** : 977-979.
59. VAN WYK M., SOMMERS D.K., STEYN A.G. Evaluation of gastrointestinal motility using the hydrogen breath test. *Br. J. Clin. Pharmacol.*, 1985, **20** : 479-481.
60. STACHER G., STEINRINGER H., SCHNEIDER C. *et al.* Effects of the prodrug loperamide oxide, loperamide and placebo on jejunal motor activity. *Dig. Dis. Scie.*, 1992, **2** : 198-204.
61. CORBETT C.L., THOMAS S., READ N.W., HOBSON N., BERGMAN I., HOLDSWORTH C.D. Electrochemical detector for breath hydrogen determination : measurement of small bowel transit time in normal subjects and patients with the irritable bowel syndrome. *Gut*, 1981, **22** : 836-840.
62. MOSS P.J., READ R.C. For debate. Empiric antibiotic therapy for acute infective diarrhoea in the developed world. *J. Antimicrob. Chemother.*, 1995, **35** : 903-913.