REVIEW ARTICLE

Evidence-based first aid and prevention guidelines for laypeople in India

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Abstract

Background: Training first medical responders is considered an extremely cost-effective intervention for frequently occurring diseases and injuries in low and middle-income countries. **Aims & Objectives:** The Belgian Red Cross-Flanders together with the Indian Red Cross Society, aimed to develop evidence-based guidelines to train lay people on how to manage and prevent emergency situations in India. **Methods:** Evidence-based guidelines were developed adhering to the principles of AGREE II. The reporting of the systematic literature reviews was done according to the PRISMA statements. We identified evidence on the effectiveness of various first aid and preventive procedures from Indian studies and on alternative interventions that have been used by Indian laypeople. The quality of the scientific evidence was determined using the GRADE methodology. Values and preferences from the target group were collected and inputs from a multidisciplinary panel of 12 Indian experts were taken. **Result:** After developing 77 specific search strategies in PubMed, 10055 references were screened and 90 relevant studies were included as a basis for the recommendations in the guidelines. Examples of effective interventions include rice water for diarrhoea, and gargling to prevent respiratory infections. **Conclusion:** Evidence-based first aid and prevention guidelines for Indian laypeople were developed. These guidelines will increase the capacity of the Indian Red Cross Society in providing appropriate first aid training and first aid information to the public, and in delivering first aid assistance in case of disasters, disease outbreaks, emergencies, and road accidents in India.

Key Words

First aid; guideline; laypeople; prevention; Evidence-Based Practice; India

Introduction

First aid training is a major element in augmenting public resilience to disasters and emergency situations. Moreover, first aid training is known to be a very cost-effective way of improving the health and welfare of the local population in low and middle-income countries, at a cost of 8 $ per averted Disability-Adjusted Life Year. (1) We define first aid as “appropriate and beneficial help by a layperson, using minimal or no equipment, to a suddenly ill or injured person until that person has recovered or medical care is available”. (2)

Since 2005, Belgian Red Cross-Flanders has played a pioneering role in the development of evidence-based first aid guidelines and manuals in accordance with international standards on Evidence-Based Medicine and evidence-based guideline development. (3) The overall aim is to introduce harmonized first aid education to the public, since

first aid techniques being taught in first aid courses were not uniform even within Europe. To achieve this, collecting the best available evidence together with expert opinion and preferences/values of the target group are used in order to create evidence-based guidelines that recommend effective first aid techniques.

This approach resulted in the publication of the European First Aid Manual (EFAM) in 2007 and the African First Aid Manual and Materials (AFAM) in 2011.(4,5) AFAM aims to provide easy and practical tools so that local African organizations can introduce standardized high quality first aid training to the community.

The Indian Red Cross Society expressed its interest in evidence-based first aid materials adapted to the Indian context. India is very diverse politically, socially, economically and religiously. There are states which have very poor social indicators, while others have made tremendous progress on health, but still might remain behind in other social areas. (6) Access to the healthcare system and to emergency healthcare differs highly from region to region and the ambulance system is not uniformly distributed over the whole country. Despite several initiatives, including the installation of ambulance call systems and the use of specialized vehicles and teams, there is no guarantee that these trained healthcare providers and resources would reach an accident scene within an acceptable timeframe. In most cases transport to hospitals and health centres is being arranged via own means, taxis or police cars. (7,8) Moreover, a survey in the southern district of Tumkur among lay first responders (police, ambulance personnel, drivers and teachers) found that 81.4% of respondents reported that they did not have adequate skills to handle an emergency. (9) In addition, traditional healthcare methods with herbalists and priests are still commonly used. Based on a survey in a malaria endemic area of north-east India, it was shown that the choice of seeking help and treatment was significantly associated with area of residence, occupation, ethnicity, household income, as well as the distance to the nearest health centre. (10) All these elements call for first aid guidelines and community-based first aid training programs specific for the Indian context, in order to increase knowledge and skills in managing emergencies and to improve outcomes for victims of injuries and diseases. As we knew of no single evidence-based reference that comprehensively addressed how laypeople should be trained to manage emergency situations in an Indian context, we started a project building on the EFAM and AFAM experiences to develop evidence-based first aid guidelines specifically directed to the Indian and South Asian context. According to a survey of the Indian Red Cross Society, it is estimated that about five per cent of the population in India (i.e. 65 million of people) has acquired some first aid knowledge by attending first aid training. The Indian Red Cross Society, consisting of 35 state branches and 700 district branches, together with its sister organization St. John Ambulance India, trains more than 600000 laypeople yearly in basic first aid in India. (11)

The ultimate purpose of this project is to help decrease the burden of disease and injuries in India. Our initial objective was to develop guidelines for lay people which take into account the different socio-economic environments in the country. Because of the major importance of prevention in health care and because first aid recommendations are often linked to prevention advice, we also complemented the guideline with prevention recommendations. The guidelines are intended to provide guidance and support to those responsible for first aid programs.

Methods

Evidence-based guidelines were developed according to our methodological charter, adhering to the principles of AGREE II. (3,12) The reporting of the systematic literature reviews was done according to the PRISMA statements. (13) No protocol for the systematic literature searches was published beforehand.

Selection of guideline content: The selection of topics was based on published injury and disease statistics for South Asia (14,15): drowning, choking, fainting, fits, stroke, epilepsy, heart attack, external and internal bleeding, nosebleeds, cuts and grazes, animal bites and stings, burns, poisoning, injuries of the head, neck and back, eye injuries, injuries to muscles and joints, broken and dislocated limbs, fever, malaria, pneumonia, rash and measles, diarrhea, and emergency child birth.

Systematic literature search: *Search strategy:* The scientific basis for the Indian First Aid Guidelines is compiled by collecting evidence from the existing evidence-based EFAM and AFAM (search date March 2009 for first aid and September 2011 for prevention; databases: Guidelines International

Network database, the WHO Library Database, Best BETs, Medline, Embase, Cochrane Library, Safety lit), (4,5) and from additional India-specific searches for evidence, as detailed below.

For the new searches we searched Medline (PubMed interface) from the date of inception until December 2013, for evidence on the effectiveness of various first aid and preventive procedures (i) from Indian studies (making use of an in-house developed "India filter"), and (ii) from evidence supporting alternative interventions that are being used by Indian laypeople (without using a specific geographic search filter). For the new searches, study selection was performed by two reviewers (EDB, HVR). Titles and abstracts of the studies identified by the search were scanned. When a relevant article was found, full texts were retrieved. Studies that did not meet the in- and exclusion criteria were excluded. The citation and reference lists of included studies were searched, and the first 20 related items in PubMed were scanned for other potentially relevant studies. Any discrepancies among the reviewers were resolved by consensus. Qualitative research was selected based on the same search strategy in Medline as described above, however only studies from 2010 to December 2013 were searched for.

Selection criteria: We used the following in- and exclusion criteria for selection of articles (new searches):

Population: We included studies performed in India on sick or injured persons or healthy volunteers. Studies with hospitalized participants were also included if the intervention was relevant in a first aid context.

Intervention/Risk factor: We included studies on help provided by basic first responders, lay caregivers, community health workers, or healthcare professionals, where interventions were feasible for extrapolation to basic first responders. We also included studies on primary prevention of injuries and diseases at household or community levels that describe interventions with a potential immediate effect, as well as studies on preventive programs or campaigns that consist of training or provision of an information leaflet, booklet, or sticker. In addition, we included studies that described modifiable proximal risk factors with a potential immediate implication for practice that could result in primary prevention at the household or community level. We included risk factors that were independent, direct and related to healthy persons. We excluded interventions that require special equipment or competences or interventions that do not take place during the acute phase of an emergency and which can be considered as aftercare. Related to the prevention advice we excluded studies describing secondary (e.g. providing modified work for injured workers) or tertiary prevention (e.g. cardiac rehabilitation programs), interventions at policy level, interventions based on drugs or vaccines, or one of the following types of programs : 1-to-1 programs, home safety checks, free provision of materials, peer tutoring, or information by medical doctors. We also excluded interventions and risk factors that are based on common sense (e.g. leaving food unattended on a stove to prevent burn wounds).

Outcome: We included studies describing health outcome measures, adverse effects, incidence of accidents, and studies that measured the risk of injuries or diseases. We excluded studies that measured knowledge or attitudes. *Study design:* We included guidelines, systematic reviews, intervention studies, case-control studies and cohort studies, and excluded cross-sectional studies, case reports, case series, letters, comments, opinion pieces, and narrative reviews.

Language: We included studies in English, French, Dutch, or German.

In addition, in order to have a view on the preferences and values of our target group, qualitative studies were collected, including surveys, interviews and focus group discussions, performed in India. These studies provided more information on perceived causes/mechanisms of interventions, treatment-seeking behavior, information on beliefs/traditions, socio-cultural factors, knowledge, attitude, and behavior. We did not use this information as a basis for the recommendations, but as separate context-dependent information, that could be important when final didactic materials will be developed.

Data extraction: Data concerning study design, study population, outcome measures (expressed as risk ratio, odds ratio or incidence rate ratio for discontinuous variables and as mean differences for continuous variables), and study quality were extracted by two reviewers (EDB, HVR). Meta-analysis was not possible, since there was too much heterogeneity among the studies. Review Manager 5 was used to calculate effect measures, if not reported in the study and raw data were available.

The GRADE approach was used to assess the overall quality of evidence (going from high to very low) included in these guidelines. Limitations in study design were analyzed at the study level using the items listed by GRADE. (16)

Formulation of evidence-based recommendations: Based on the evidence identified and taking into account practice considerations, draft recommendations were formulated by the project coordinator (HG), who has first aid knowledge, practice experience and knowledge in the Indian context. The evidence summaries and draft recommendations were circulated electronically and in printed format to a multidisciplinary expert panel of 12 Indian experts, including specialists and representatives of the Indian Red Cross Society and the St. John's Ambulance Association of India (see Supplemental file 1 for more details). Specialists had expertise in Evidence-Based Medicine, primary care or emergency medicine focused on the Indian context. Representatives of the Indian Red Cross Society included managers and first aid trainers. We held a two-day consensus expert panel meeting twice (January 2014 and May 2014) in New Delhi to present the draft recommendations. (17) During the first meeting the evidence-based methods and consensus procedures were clarified. During the expert panel consensus meetings, the panel discussed each first aid or preventive recommendation until they reached agreement, using informal consensus methods. The experts decided to recommend or not to recommend certain interventions, taking into account the quality of the evidence, the benefits and harms of the intervention, the preferences of the Indian population (availability, feasibility), and costs. In addition, they were responsible for the final formulation of the recommendations, assignment of the strength of recommendations (weak or strong), and formulation of Good Practice Points when appropriate ("Good Practice Points are intended to assist guideline users by providing short pieces of advice which may not have an evidence base, but which are seen as essential to good clinical practice", according to the definition of the Scottish Intercollegiate Guidelines Network). (16;18) After each meeting the experts received an updated version of the guidelines for off-site review and commentary. Each updated guideline version was sent out for final review by all experts. We invited peer reviewers consisting of medical specialists in cardiology, gynecology, pediatrics and ophthalmology, to give feedback on the first aid and prevention guideline statements during a face-to-face meeting (see Supplemental file 1 for more details). The chair of the guideline development panel (SPA) then considered the responses. The final version of the guidelines was circulated electronically and approved by the panel members.

Results

Identification of the best available evidence: 175 references identified in previous evidence-based first aid guidelines were included in the evidence base. (4,5) In addition, we performed 77 different India-specific searches, and retrieved 10055 references in total. Figure 1 shows a flowchart with an overview of the study selection.

Evaluation of titles and abstracts resulted in 231 references; 9824 studies did not answer our PICO questions and were therefore ineligible. We also included 25 related citations from PubMed. After full text evaluation, 166 studies were excluded because they did not meet the inclusion criteria (see Figure 1 for details) and 90 studies were finally selected as a basis for the recommendations in the guideline. For several interventions, there was no evidence of effect because of a large variability of the results or because the study population was too small. Examples of effective interventions, relevant for India, are: drinking rice water or intake of several alternative oral rehydration solutions (ORS) for diarrhoea, (19-29) gargling to prevent respiratory infections, (30-32) burning neem oil in a kerosene lamp to prevent malaria, (33) handwashing with mud (versus no handwashing) to prevent respiratory infections and diarrhoea, (34) and yoga to promote a safe pregnancy and delivery. (35,36) The evidence found for "alternative oral rehydration solutions for diarrhoea" and "gargling as a prevention for respiratory infections" is described below in two detailed examples.

Example 1: Alternative oral rehydration solutions as first aid treatment for diarrhoea

The PICO question was formulated as follows: In adults and children with diarrhoea (Population), are alternative ORS solutions (Intervention) effective compared to standard ORS solutions (Comparison) to recover from diarrhoea (Outcome)? To identify alternative ORS solutions relevant in the Indian context, we limited this search to Indian studies. We retrieved 233 references from PubMed (for search

strategy see Supplemental file 2) and included 12 additional related citations. We finally included 14 Indian studies, describing 7 alternative ORS solutions: diluted ORS, (20) rice ORS, (19,21-24,27,29) rice water, (23) lentil ORS, (19) HAMS (High Amylose Maize Starch) ORS, (25-27) glycine-based ORS, (21,37-39) and alanine-based ORS. (28) Only 2 of the 14 studies included adults in the study population; all other studies were performed in children. The characteristics of the included studies and synthesis of findings can be found in Table 1 and Table 2. The conclusions are narratively described below.

We found limited evidence in 1 experimental Indian study about drinking diluted ORS. In this study a statistically significant decreased stool output after drinking diluted ORS compared to standard WHO-ORS, could not be demonstrated. (20)

There is limited evidence from 7 Indian experimental studies in favor of rice ORS, where rice substitutes for glucose in standard ORS. (19,21-24,26,29) More in detail, it was shown that rice ORS resulted in a statistically significant decrease in stool output until recovery, duration of diarrhoea, duration of purging, a high stool frequency (6-7 times per day) on day 3, and a large stool volume on day 3, compared to glucose ORS. (21,23,26,29) In 3 studies the effect of rice ORS could not be shown, (19,22,24) and in 1 of the 7 studies a significant effect for some of the outcomes could not be demonstrated. (23)

In addition to rice ORS, we identified 1 experimental Indian study looking at the effect of rice water, showing limited evidence in favor of rice water, which is the supernatant obtained when rice is boiled for the preparation of rice congee: it was shown that rice water resulted in a statistically significant decrease in the stool frequency (6-7 times per day) on day 3 and in large stool volume on day 2 and 3 compared to using standard ORS. However, no statistical significant difference in stool frequency (6-7 times per day) or large stool volume was observed on day 1 and day 4. (23)

We found 1 Indian study on lentil-based ORS, with lentils instead of rice as compared to rice ORS. In this study a statistically significant difference in stool outputs and percentage of patients recovering, when compared to standard ORS, could not be demonstrated. (19)

Another alternative for ORS is ORS in which amylase resistant high amylose maize starch substitutes for glucose (HAMS ORS). We found evidence from 3 Indian experimental studies in favour of HAMS ORS: it was shown that HAMS ORS resulted in a statistically significant decreased time to first stool and fecal weight in the second 12 hours, compared to glucose ORS. (25-27)

A last type of alternative ORS solutions, is ORS with additional amino acids, such as glycine or alanine, which are capable of enhancing salt and water absorption. We found limited evidence from 4 experimental studies in favour of drinking glycine-based ORS: it was shown that drinking glycine-based ORS resulted in a statistically significant decreased stool output during the first 24 hours and duration of purging, compared to standard ORS. (21,39) In two other studies, the effect of glycine-based ORS could not be shown. (37,38) For alanine-based ORS we identified one experimental study in which a statistically significant decrease in diarrhoea using alanine-based ORS, compared to standard ORS, could not be demonstrated. (28)

In summary, we found (limited) evidence from Indian studies in favour of rice ORS, rice water, HAMS ORS and glycine-based ORS as an alternative to standard ORS. The results of all the studies are imprecise due to a limited sample size (n<400). In addition, there are limitations in study design for some studies: lack of allocation concealment (23) or unclear allocation concealment, (20,22,24,26,29,39) lack of blinding (22-242729) or lack of information about blinding. (20,21,25,26,37,39) As a consequence, the level of evidence is moderate for lentil-based ORS, HAMS ORS, glycine-based ORS and alanine-based ORS, and low for diluted ORS, rice ORS and rice water.

In addition to the evidence described above, we also identified information from Indian qualitative research about the use of ORS for treatment of diarrhoea. In a cross-sectional survey, conducted in an urban slum of Trans-Yamuna area in Delhi covering 1307 under-5 children, the use of ORS packets was reported in only 38.6% of the children, the use of home available fluids was 42% and continued feeding was 50% during the acute diarrhoeal diseases episode. (40) This additional information is important when developing didactic materials based on these guidelines: this intervention should be emphasized as much as possible, supported with drawings and sufficient explanation, in order to increase both the use of standard ORS and other effective ORS solutions.

Example 2: Gargling as preventive advice for respiratory infections

We formulated the PICO question as follows: Is gargling (Intervention) compared to no gargling (Comparison) effective to prevent respiratory infectious diseases (Outcome) in adults and children (Population)?

To answer this question we did not limit our search to Indian studies. We retrieved 653 references from Medline (search strategy see Supplemental file 3) and included no additional related citations. We finally included 3 Japanese studies, describing water gargling, tea gargling and povidone-iodine gargling. (30-32) The characteristics of the included studies and synthesis of findings can be found in Table 3 and Table 4, and the conclusions are described in the next paragraphs.

There is limited evidence from 1 experimental (31) and 1 observational study (30) in favour of gargling with water or functional water (alkali ion water or ozone water). It was shown that gargling water consecutively three times a day, resulted in a statistically significant decreased incidence of upper respiratory tract infection compared to previous gargling habits. (31) In addition, it was shown in an observational study that gargling with tap water or functional water resulted in a statistically significant decreased fever onset compared to no gargling. (30) In the same study gargling saline water was also observed. In this study a statistically significant decrease in fever onset, compared to not gargling saline water, could not be demonstrated. (30)

We identified two studies looking at the effect of gargling tea, both reporting limited evidence in favour of tea gargling: it was shown that green tea gargling resulted in a statistically significant decrease in fever onset, compared to no gargling, (30) and that gargling a tea catechin extract solution resulted in a statistically significant decreased incidence of influenza infection compared to gargling without a tea catechin extract solution. (32)

There is limited evidence from 1 experimental study concerning povidone-iodine gargling (compared to previous gargling habits), in which a statistically significant decrease in incidence of upper respiratory tract infections could not be demonstrated. (31)

In summary, we found limited evidence in favour of (functional) water gargling or green tea gargling. The study of Noda *et al*. is an observational study and therefore the evidence based on this study has an initial low level of evidence. In addition, there are some limitations in design, such as inappropriate eligibility criteria, (30) lack of randomization and lack of blinding, (32) and there is a limited sample size in two studies, (31,32) and a large variability of results for some outcomes in two studies, (30,31) which is a reason to downgrade the level of evidence for imprecision. As a result, the level of evidence is moderate for regular water gargling and povidone-iodine gargling versus previous gargling habits, low for gargling tap water or functional water versus no gargling, gargling with green tea versus no gargling and gargling a tea catechin extract solution versus no tea catechin extract solution, and very low for saline water versus no gargling.

From evidence to recommendations

Based on the identified evidence, draft recommendations were formulated and discussed by the expert panel.

Example 1: Alternative oral rehydration solutions as first aid treatment for diarrhoea

The expert panel provided information about the diarrhoea-ORS programme ("Oral Rehydration Therapy Programme") that is being promoted by the Indian Government. In this programme, ORS use is being promoted through mass media and educational activities, and ORS is freely available in government hospitals and primary health care facilities. As a consequence, the panel suggested to focus on the use of standard ORS packages, supported by the current governmental approach (the evidence for standard ORS is not presented in this paper). Recommendations concerning alternative ORS solutions were also formulated so that these could be included in specific didactic materials if supported by the local context (e.g. first aid manuals for the rural context where it may be sometimes more difficult to obtain ORS provided by the Government). The recommendations were formulated as follows: "Let the sick person drink ORS (package bought at chemist), if available. Prepare ORS and use it as instructed on the package (strong). Do not dilute prepared or bought ORS drinks; avoid drinking diluted ORS drinks (weak). If no standard ORS packages are available: let the sick person preferably drink rice-based ORS, rice water, HAMS ORS or glycine-based ORS (package bought at chemist); as an alternative you might use lentil-based or alanine-based ORS (package bought at chemist) (weak)." In addition to the recommendations, recipes were provided on how to prepare rice- and lentil-based and HAMS ORS at home.

Example 2: Gargling as preventive advice for respiratory infections

The expert panel provided information about gargling with warm saline solutions, which is a common practice in India, while iodine solutions are not widespread. The panel decided to include a recommendation about iodine solutions in the guideline so that these could be included in specific didactic materials if supported by the local context. The recommendation was formulated as follows: "You can gargle with tap water, functional water, or tea to decrease throat infections (strong), if possible three times a day and a couple of times consecutively (strong). If available, gargling with warm saline water or iodine solution might reduce the spread of respiratory viruses."

Discussion

Evidence-based first aid guidelines adapted to the Indian context were developed based on the collection of scientific evidence, the preferences of the target group and the expertise of Indian experts. We identified 90 studies, specifically relevant for India, as a basis for the recommendations in the guideline, in addition to the 175 references we used from existing evidence-based first aid guidelines. (4,5)

We acknowledge that there are some limitations to this guideline project. First of all, all new searches (Indian studies and searches for alternative Indian interventions) were performed only in Medline, due to time constraints. However, two third of the final included references (from existing evidence-based guidelines) are retrieved from Medline, Embase, The Cochrane Library and additional databases. An Indian-specific database IndMED, covering about 100 Indian medical journals, was not used since almost 70% of the journals in this database are also indexed in Medline, the aim of the journals in this database is mainly to inform medical professionals, and possibilities of the search engine are limited. Secondly, the searches that formed the basis for the recommendations of our previous first aid guidelines projects (searches performed between March 2009 and September 2011) were not updated in the context of this project. However, every search was run again in the presence of an India-specific geographic search filter (without time constraints). A third limitation is that we only developed guidelines, and no didactic materials. This choice was made by the expert panel, because it is not possible to develop a generic manual for the whole of India. A disadvantage of this approach is that the didactic materials are not approved yet by the expert panel.

In the near future, several specific manuals and didactic materials, in English and in Hindi, will be developed based on the guidelines we presented in this paper, taking into account the preferences and specificities of the target groups. These will include illustrations and pictures, didactic movies, and materials for specific target groups such as youth, young parents, elderly, and victims of road accidents. Materials for the latter target groups are very relevant, since road safety is a major issue in India, and in the future a higher percentage of elderly will be living alone without direct family assistance. (41,42) The didactic materials will contain simple instructions enabling the public to recognize emergency and dangerous situations easily, practical instructions on how to respond to these situations, concurring to the technical capabilities of lay people and the locally available materials to provide the first care, advice on when and how to search further medical assistance, and a set of practical prevention tips to prevent future injuries and illness.

The didactic materials will be tested in a pilot implementation phase in different states of India in 2015. In this pilot study, it will be tested if the first aid instructions and illustrations are clear and understandable, if there are local didactic needs, if the material is adapted to the target group etc. The lessons learnt from this pilot test will be incorporated in an implementation guide, a document with guidance to implement the contextualized first aid trainings to the local needs.

In the long run, these guidelines and materials will be implemented throughout India. This will be a challenge because the target group is extremely heterogeneous. Distinct cultural differences, language barriers, the existence of different social-economic levels and classes, a large variety in educational background, existing gender issues and dissimilarities in the application of local customs are only a snapshot of the challenges to overcome. (6) The Indian Red Cross Society provides the potential to reach more than twelve million Red Cross volunteers, well spread over the Indian peninsula and offers the potential of reaching the communities of the 1.2 billion Indian citizens. Their existing training programs whereby a top down Training-of-Trainers methodology is being used, allows to spread the first aid knowledge from the National

Headquarters via its state branches and district branches into the local communities. (11)

Since first aid education is one of the Red Cross core activities and competencies, we are continuously reviewing the scientific literature with relevance to first aid. As a consequence, these guidelines will be updated when new evidence or new evidence-based guidelines become available, at the latest five years from now.

Authors Contribution

All authors have contributed significantly to this work. PV and SPA proposed the guideline concept. and HG and AVV coordinated the project. EDB and HVR performed the literature review and analysed the data. HG, AVV, MS, PV and SPA attended the expert panel meetings. EDB drafted the manuscript, and all other authors critically revised and approved the final manuscript.

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Tables

TABLE 1 CHARACTERISTICS OF INCLUDED STUDIES FOR EVIDENCE REVIEW CONCERNING ALTERNATIVE ORS SOLUTIONS

Author, year, Country	Study design	Population	Comparison	Remarks
Antony, 1989, India[37]	Experimental: randomised controlled trial	50 male infants aged 3 months to 3 years, hospitalized with dehydration secondary to acute watery non-choleric diarrhoea (< 5 days)	Intervention: glycine-fortified ORS (111 mmol/L glycine) Control: standard WHO-ORS The solutions were administered in a supervised *ad libitum* manner.	Patients who were severely dehydrated and/or in shock at admission were administered 20 ml/kg/h Ringer lactate. Once hydration was complete, based on clinical assessment, the patients received breast feeds or half strength milk.
Bhan, 1987, India[19]	Experimental: randomised controlled trial	93 children in the hospital (New Delhi) with following characteristics: males, passage of more than four loose or watery stools in the preceding 24 h, age between 3 months and 5 years, duration of diarrhoea ≤ 5 days, obvious clinical signs of dehydration but without shock, weight for height > 70 percent of 50th percentile of reference value	Intervention 1: ORS, in which glucose was substituted with pop rice Intervention 2: ORS, in which glucose was substituted with mung bean (lentil) powder Control: standard ORS (WHO)	
Bhargava, 1986, India[20]	Experimental: randomised controlled trial	50 male infants aged 0-3 months, hospitalised with the diagnosis of dehydration secondary to acute non-cholera diarrhoea	Intervention: rehydration with a 2:1 regimen (two parts, i.e. 60 ml, WHO-ORS followed by one part, i.e. 30 ml, plain water in an alternating regime) Control: diluted WHO-ORS (1.5 L water instead of 1 L)	
Bhattacharya, 1989, India[38]	Experimental: randomised controlled trial	75 male children aged 4 months to 5 years, hospitalised in the Infectious Diseases Hospital in Calcutta, with uncomplicated acute watery diarrhoea with elicitable signs of dehydration (such as sunken eyes, dry mouth) but not in shock.	Intervention: citrate ORS of WHO formula fortified with 8.4 g/l of glycine Control: citrate ORS of WHO formula During the first 6 to 8 hours of therapy, solutions were given *ad libitum*. Thereafter, each solution was given by matching with stool volume until diarrhoea stopped.	Cessation of diarrhoea was defined as the passage of last stool or no stool for the past 12 h. Water, milk formula, bread and banana were offered after correction of initial dehydration.
Fakhir, 1990, India[21]	Experimental: randomised controlled trial	75 infants and children aged 6 months to 4 years admitted to paediatric services of J.N. Medical College, Aligarh, with acute watery diarrhoea with or without vomiting and associated with varying degree of dehydration	Intervention 1: super ORS (standard ORS + 111 mmol/L of glycine) Intervention 2: rice water electrolyte solution (30 g rice + standard WHO electrolytes) Control: standard ORS (WHO); commercially prepared ORS packets (Prolyte-Cipla)	Strict four hourly intake and output records were maintained.
Faruque, 1997, India[22]	Experimental: randomised controlled trial	472 children aged 3-35 months, presenting with a history of watery diarrhoea for 72 h or less, who attended the triage area of the Clinical Research and Service Centre at the International Centre for Diarrhoeal Disease Research, Bangladesh	Intervention: ready-to-mix rice ORS Control: standard glucose ORS The electrolyte content of both solutions was identical and was as recommended by the WHO (sodium 90 $mmol^{-1}$, chloride 80 $mmol^{-1}$, potassium 20 $mmol^{-1}$ and citrate 10 $mmol^{-1}$). In the case of rice ORS, glucose (20 g) was replaced by 50 g Galactina instant rice.	The amount of ORS consumed at home was estimated by measuring the number of mug quarters (approximately 125 ml) of ORS used. ORS was given by the mothers under the supervision of female health workers. Mothers were encouraged to breastfeed during the study. In addition, children were offered a milk-cereal mixture containing rice powder (1 $kcal \cdot ml^{-1}$) four times a day, but the food intake was not measured. They also received plain water in small amounts from time to time during treatment.
Mehta, 1986, India[23]		150 infants aged under 6 months	Intervention 1: rice ORS, prepared by boiling 30 g of rice in 1 litre of water to make rice congee; when it	Estimated weight loss of 5% was classed as mild dehydration, of 5-10% as moderate dehydration, and

		admitted primarily or secondarily with acute gastroenteritis to the paediatric wards (Mobay)	cooled electrolytes as in the standard WHO formula were added and the water was made up to 1 litre Intervention 2: rice water, which was the supernatant obtained when rice was boiled for the preparation of rice congee and contained starch and bits of rice Control: glucose ORS (WHO)	of more than 10% as severe dehydration. Stool volume is described as large, moderate or small stool volume, however it is not defined how these categories differ.
Mohan, 1986, India[24]	Experimental: randomised controlled trial	50 children in the hospital (Delhi) aged 3 to 36 months, with acute watery diarrhoea, presence of dehydration	Intervention: rice ORS Control: glucose oral rehydration solution (ORS) (osmolarity ≥ 310 mOsm/L)	
Patra, 1989, India[39]	Experimental: randomised controlled trial	51 infants and young children aged 3 months to 5 years, with a history of watery diarrhoea and with clinical signs of moderate to severe dehydration	Intervention: WHO recommended ORS with 111 mmol/L of glycine added Control: WHO recommended ORS	Breast feeding was continued. The infants and younger children received dilute milk with added cooked rice cereal and the older children received a hospital diet (e.g. rice, lentil, fish etc.) as soon as the initial dehydration was corrected.
Raghupathy, 2006, India[25]	Experimental: randomised controlled trial	183 children aged 6 months to 3 years, presenting to the outpatient clinics or the paediatric emergency services of the Department of Child Health, Christian Medical College and Hospital, Vellore	Intervention: standard ORS with additional amylase-resistant starch 50 g/L (HAMS-ORS) Control: standard ORS (WHO) The contents of the packets dissolved in 200 mL of water	The composition of standard ORS reflected the WHO recommendations at the time the study was initiated in 2001 (Na, 90 mEq/L; K, 20 mEq/L; Cl, 80 mEq/L; citrate, 10 mmol/L; glucose, 111 mmol/L; osmolarity, 311 mOsm/kg). Diarrhoea was defined as more than 3 watery stools in the past 24 hours with clinically detectable dehydration.
Ramakrishna, 2000, India[26]	Experimental: randomised controlled trial	48 participants aged 14 to 58 years old, with acute watery diarrhoea < 72 hours, positive for *Vibrio Cholerae*, hospitalised in Vellore	Intervention 1: rice ORS Intervention 2: amylase-resistant starch ORS Control: glucose oral rehydration solution (ORS) (osmolarity ≥ 310 mOsm/L)	
Ramakrishna, 2008, India[27]	Experimental: randomised controlled trial	50 males, aged 12-65 years, with severe watery diarrhoea of less than three days duration and moderate to severe dehydration, recruited at a tertiary referral hospital in southern India	Intervention: hypo-osmolar ORS (HO-ORS) in which amylase-resistant high amylose maize starch 50 g/L substituted for glucose (HAMS-ORS) Control: HO-ORS (glucose) ORS was administered in a dose of 200 ml per hour and 200 ml after each loose stool.	Intake of water and other fluids was allowed and a standard Indian diet was immediately allowed. Patients were evaluated after four hours by the study doctor and subsequently every four hours if diarrhoea continued or if urine output was not satisfactorily established.
Sharma, 1998, India[29]	Experimental: randomised controlled trial	100 children in the hospital (Rohtak) aged 7 to 36 months, with acute diarrhoea, some dehydration, non-cholera; weight >80% of reference standard	Intervention: rice ORS Control: glucose oral rehydration solution (ORS) (osmolarity ≥ 310 mOsm/L)	Sharma, 1998, India [29]
Sazawal, 1991, India[28]	Experimental: randomised controlled trial	129 male children, aged 3-48 months, with acute diarrhoea	Intervention: alanine-ORS (90 mmol/L of glucose and 90 mmol/L of alanine) Control: WHO-ORS (111 mmol/L of glucose) 120 ml/kg ORS was offered during the initial 6 h; if dehydration persisted after 6 h, a second dose was given in the next 6 h.	

TABLE 2 SYNTHESIS OF FINDINGS FOR EVIDENCE REVIEW CONCERNING ALTERNATIVE ORS SOLUTIONS.

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Total stool output during hospitalisation (ml/kg)	Diluted ORS versus ORS	Not statistically significant: 117.5±81.5 vs 142.8±97 MD: -25.30, 95% CI [-74.96;24.36]*	1, 25 vs 25	Bhargava, 1986[20]

Stool output	Rice ORS versus standard ORS	During first 24 h (g/kg): Not statistically significant: 105.8±58.5 vs 106.6±62.4 MD: -0.80, 95% CI [-11.72;10.12]*	1, 236 vs 235	Faruque,1997[22]
		During first 24 h (ml/kg/h): Not statistically significant: 3.19±2.3 vs 4.02±4.3 MD: -0.83, 95% CI [-2.82;1.16]*	1, 23 vs 23	Mohan, 1986[24]
		Until recovery (ml/kg/h): Not statistically significant: 2.49±1.5 vs 2.91±2.0 MD: -0.42, 95% CI [-1.28;0.44]*	1, 31 vs 33	Bhan, 1987[19]
		Until recovery (ml/kg): Statistically significant: 168.8±24.4 vs 310±24.6 MD:-141.20,95%CI [-155.88;-126.52]*	1, 20 vs 23	Fakhir,1990[21]
Number of stools during first 24 h		Not statistically significant: 12.6±8.3 vs 12.7±7.3 MD: -0.10, 95% CI [-1.51;1.31]*	1, 236 vs 235	Faruque,1997[22]
Duration of diarrhoea (h)		Statistically significant: 33.9±8.03 vs 38.8±7.6 MD: -4.90, 95% CI [-9.23;-0.57]*	1, 25 vs 25	Sharma, 1998[29]
		Statistically significant: 70.8±20.2 vs 90.9±29.8 MD: -20.10, 95% CI [-37.74;-2.46]*	1, 16 vs16	Ramakrishna, 2000[26]
Duration of purging in the hospital (h)		Statistically significant: 60.2±2.6 vs 78.6±4.6 MD: -18.40, 95% CI [-20.60;-16.20]*	1, 20 vs 23	Fakhir,1990[21]
Stool frequency between 6 and 7 per day		Day 1: Not statistically significant: 36/50 vs 39/50 RR: 0.92, 95% CI [0.74;1.16]* Day 2: Not statistically significant: 15/50 vs 23/50 RR: 0.65, 95% CI [0.39;1.10]* Day 3: Statistically significant: 2/50 vs 10/50 RR: 0.20, 95% CI [0.05;0.87]* Day 4: Not statistically significant: 1/50 vs 5/50 RR: 0.20, 95% CI [0.02;1.65]*	1, 50 vs 50	Mehta, 1986[23]
Small stool volume		Day 1: Not statistically significant: 43/50 vs 44/50 RR: 0.98, 95% CI [0.84;1.14]* Day 2: Statistically significant: 4/50 vs 12/50 RR: 0.33, 95% CI [0.12;0.96]* Day 3: Statistically significant: 1/50 vs 9/50 RR: 0.11, 95% CI [0.01;0.84]* Day 4: Not statistically significant: 2/50 vs 4/50 RR: 0.50, 95% CI [0.10;2.61]*		
Percentage of patients recovering within 72 h		Not statistically significant: 18±58.0 vs 16±48.4 MD: 2.00, 95% CI [-24.26;28.26]*	1, 31 vs 33	Bhan, 1987[19]
Stool frequency between 6 and 7 per day	Rice water versus standard ORS	Day 1: Not statistically significant: 35/50 vs 39/50 RR: 0.90, 95% CI [0.71;1.13]* Day 2: Not statistically significant: 14/50 vs 23/50 RR: 0.61, 95% CI [0.36;1.04]* Day 3: Statistically significant: 1/50 vs 10/50 RR: 0.10, 95% CI [0.01;0.75]* Day 4: Not statistically significant: 0/50 vs 5/50 RR: 0.09, 95% CI [0.01;1.60]*	1, 50 vs 50	Mehta, 1986[23]
Large stool volume		Day 1: Not statistically significant:		

		41/50 vs 44/50 RR: 0.93, 95% CI [0.79;1.10]* Day 2: Statistically significant: 3/50 vs 12/50 RR: 0.25, 95% CI [0.08;0.83]* Day 3: Statistically significant: 1/50 vs 9/50 RR: 0.11, 95% CI [0.01;0.84]* Day 4: Not statistically significant: 1/50 vs 4/50 RR: 0.25, 95% CI [0.03;2.16]*		
Stool output until recovery (ml/kg/h)	Lentil-based ORS versus standard ORS	Not statistically significant: 3.41±1.7 vs 2.91±2.0 MD: 0.50, 95% CI [-0.42;1.42]*	1, 29 vs 33	Bhan, 1987[19]
Percentage of patients recovering within 72 h		Not statistically significant: 13±44.8 vs 16±48.4 MD: -3.00, 95% CI [-26.21;20.21]*		
Time to first stool (h)	HAMS ORS versus standard ORS	Statistically significant: 19.0 (IQR 10-28) vs 42.0 (IQR 24-50)	1, 25 vs 25	Ramakrishna, 2008[27]
		Statistically significant: 18.25 (95% CI [13.09;23.41]) vs 21.50 (95%CI [17.26;25.74])	1, 87 vs 91	Raghupathy, 2006[25]
		Statistically significant: 56.7±18.6 vs 90.9±29.8 MD: -34.20, 95% CI [-51.41;-16.99]*	1, 16 vs 16	Ramakrishna, 2000[26]
Fecal weight (g)		During first 12 h: Not statistically significant: 1970 (IQR 1005-4565) vs 2160 (IQR 1285-4870)	1, 25 vs 25	Ramakrishna, 2008[27]
		In the second 12h: Statistically significant: 280 (IQR 0-965) vs 1360 (IQR 405-2985)		
Stool output	Glycine-based ORS versus standard ORS	During first 24 h (g/kg): Not statistically significant: 172.0±128.4 vs 120.7±91.9 MD: 51.30, 95%CI [-6.51;109.11]*	1, 29 vs 28	Bhattacharya, 1989[38]
		During first 24 h (ml/kg): Statistically significant: 96.3±99.8 vs 166.2±113.7 MD: -69.90, 95% CI [-131.00;-8.80]*	1, 23 vs 24	Patra, 1987[39]
		During first 48 h (ml/kg/h): Not statistically significant: 3.49±22.1 vs 3.01±2.0 MD: 0.48, 95%CI [-8.59;9.55]*	1, 23 vs 23	Antony, 1989[37]
Duration of diarrhoea (h)		Not statistically significant: 37.1±22.1 vs 34.6±16.8 MD: 2.50, 95% CI [-7.67;12.67]*	1, 29 vs 28	Bhattacharya, 1989[38]
Duration of purging in the hospital (h)		Statistically significant: 58.8±2.8 vs 78.6±4.6 MD: -19.80, 95%CI [-22.01;-17.59]*	1, 22 vs 23	Fakhir, 1990[21]
Stool output until recovery (g/kg)	Alanine-based ORS versus standard ORS	Not statistically significant: Median (quartile), range: 188 (69,465), 14-1191 vs 216 (104,404), 27-982 MD: 9.4, 95%CI [-99.4;118.2]	1, 66 vs 63	Sazawal, 1991[28]
Duration of diarrhoea (h)		Not statistically significant: Median (quartile), range: 56 (38,88), 20-211 vs 65 (46,93), 21-167 MD: 4.8, 95%CI [-11.1;20.7]		

Raw data are presented as mean ± SD (SD was calculated from SE if necessary), unless indicated otherwise.
**The effect size was calculated by the reviewer using the Review Manager Software.*

TABLE 3 CHARACTERISTICS OF INCLUDED STUDIES FOR THE EVIDENCE REVIEW CONCERNING GARGLING

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks

Noda, 2012, Japan[30]	Observational: cohort study	19 595 children aged 2-6 years from 145 mayor-authorised nursery schools in Fukuoka City who were observed for a period of 20 weekdays	Cases: gargling tap water, saline water, green tea or functional water (alkali ion or ozone water) (n=15859, age 4.48±1.16, 52% boys) Controls: no gargling (n=3736, age 2.42±0.71, 52% boys)	Gargling information was collected via a questionnaire and analysed on an intention-to-treat basis. A classroom teacher instructed children to gargle at all scheduled times and visually confirmed that they had gargled. Some classrooms in each school had a policy of letting children gargle, others did not.
Satomura, 2005, Japan[31]	Experimental: randomised controlled trial	387 healthy Japanese volunteers of both sexes, aged 18-65 years	Intervention 1: gargling with 20 mL of diluted 7% povidone-iodine for about 15 sec three times consecutively, repeated at least three times a day Intervention 2: gargling with 20 mL of water for about 15 sec three times consecutively, repeated at least three times a day Control: continue their previous gargling habits	Index cases were defined as all of the following conditions: (1) both nasal and pharyngeal symptoms, (2) severity of at least one symptom increased by two grades or more, and (3) worsening of a symptom of one increment or more for > 3 days.
Yamada, 2006, Japan[32]	Experimental: controlled clinical trial	124 elderly residents of at least 65 years of age, recruited from White Cross Nursing Home, Higashi-Murayama, Japan	Intervention: gargling tea catechin extract solution with sterilised tap water (200 μg/mL catechins, 60% of catechins comprised epigallocatechin gallate) three times daily for 3 months (n=67, age 83±8.2 years, 31% men) Control: gargling without tea extract solution three times daily for 3 months *(unclear which substance was used for gargling)* (n=48, age- and sex-matched, age 83±7.7 years, 33% men)	Prior to entering the study, all the residents in the nursing home were vaccinated with a single lot of influenza vaccine. The concentration of catechin extract solution was half that of commercially sold green tea beverages in Japan; therefore, the taste of the catechin extract solution was not very unpleasant for Japanese green tea drinkers.

TABLE 4 SYNTHESIS OF FINDINGS FOR EVIDENCE REVIEW CONCERNING GARGLING

Outcome	Comparison/risk factor	Effect Size	#studies, # participants	Reference
Water gargling				
Upper respiratory tract infection incidence	Water gargling (three times consecutively, three times a day) versus control (previous gargling habits)	After 60 days: Statistically significant: 0.17 episodes/30 person-days versus 0.26 episodes per 30 person-days Multivariate hazard ratio: 0.60, 95% CI [0.38;0.93]	1, 122 vs 130	Satomura, 2005[31]
Fever onset	Tap water gargling versus no gargling	After 20 weekdays: Statistically significant: No raw data available Multivariate odds ratio: 0.70, 95% CI [0.58;0.85]	1,14140 vs 3736	Noda, 2012[30]
	Saline water gargling versus no gargling	After 20 weekdays: Not statistically significant: No raw data available Multivariate odds ratio: 0.50, 95% CI [0.22;1.12]	1, 173 vs 3736	
	Functional water gargling versus no gargling	After 20 weekdays: Statistically significant: No raw data available Multivariate odds ratio: 0.46, 95% CI [0.24;0.86]	1, 306 vs 3736	
Tea gargling				
Incidence of influenza infection	Gargling tea catechin extract solution versus gargling without tea catechin extract solution	After 3 months: Statistically significant: 1/76 vs 5/48 Multivariate odds ratio: 15.711, 95% CI [1.883;399.658]	1, 76 vs 48	Yamada, 2006[32]
Fever onset	Green tea gargling versus no gargling	After 20 weekdays: Statistically significant: No raw data available Multivariate odds ratio: 0.32, 95% CI [0.17;0.61]	1, 407 vs 3736	Noda, 2012[30]
Povidone-iodine gargling				
Upper respiratory tract infection incidence	Povidone-iodine gargling versus control (previous gargling habits)	After 60 days: Not statistically significant:	1, 132 vs 130	Satomura, 2005[31]

		0.24 episodes/30 person-days versus 0.26 episodes per 30 person-days Multivariate hazard ratio: 0.88, 95% CI [0.58;1.34]		

Figures

FIGURE 1 PRISMA FLOWCHART OF IDENTIFICATION AND SELECTION OF STUDIES