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**Department of Health**



**San Lazaro Hospital**



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**Philippine Society for  
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of Family Physicians**

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**Department of Health**

**San Lazaro Hospital**

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# Contents

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Part 1 Introduction	8
I. Background	10
II. The Philippine Profile	11
a. Morbidity and mortality rates of specific FWBDs	12
b. Outbreaks due to FWBDs	13
III. Development of Clinical Practice Guideline	16

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Part 2 Clinical Practice Guidelines	19
I. Diagnosis	21
a. When is the diagnosis of acute infectious diarrhea suspected?	21
b. What pre-treatment clinical evaluations are recommended for immunocompetent patients presenting with acute infectious diarrhea?	22
c. What is the clinical use of diagnostic tests in children and adults with acute infectious diarrhea?	25
d. What are the clinical parameters that would indicate presence of dehydration in children with acute infectious diarrhea?	29
e. What are the clinical and laboratory parameters indicative of dehydration in adults with acute infectious diarrhea?	
f. What laboratory test should be done to assess for the presence of complications of acute infectious diarrhea?	
g. What is the role of colonoscopy in the evaluation of acute infectious diarrhea in adult and pediatric patients?	
II. Treatment (Children)	42
a. What are the criteria for admission among children presenting with acute infectious diarrhea?	
b. How should dehydration among children with acute infectious diarrhea be managed?	
c. What are the indications for empiric antibiotic treatment in children with acute infectious diarrhea?	
d. What are the recommended antimicrobials for the following etiologies of acute infectious diarrhea?	
e. Should zinc and racecadotril be given in children with acute infectious diarrhea?	
f. What is the role of anti-emetics in the management of vomiting in children with acute infectious diarrhea?	
g. What is the role of probiotics in the management of acute infectious diarrhea in children?	
h. What is the recommended diet for children with acute infectious diarrhea?	
i. What is the recommended management for complications of acute infectious diarrhea in children?	
III. Treatment (Adult)	76
a. Who should be admitted among adults presenting with acute infectious diarrhea?	
b. How should dehydration in adults be managed?	
c. What are the indications for empiric antimicrobial treatment in adults with acute infectious diarrhea?	
d. What are the recommended antimicrobials for the following etiologies of acute	

Infectious diarrhea in adults?

- e. Should loperamide and racecadotril be given in adults with acute infectious diarrhea?
- f. What is the role of probiotics in the treatment of acute infectious diarrhea among adults?
- g. What is the recommended management for complications of acute infectious diarrhea in adults?

#### IV. Prevention

92

- a. What interventions are effective in preventing acute infectious diarrhea?
- b. When is potential for outbreak suspected?
- c. How is outbreak managed?







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# Acronyms

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ABD	Acute bloody diarrhea
AWD	Acute watery diarrhea
ARMM	Autonomous Region of Muslim Mindanao
CPG	Clinical Practice Guidelines
DOH	Department of Health
DALY	Disability Adjusted Life Years
EB	Epidemiology Bureau
ESR	Event-Based Surveillance and Response
FHSIS	Field Health Service Information System
FWBD	Food and Water-Borne Disease
FWBD-PCP	Food & Water-borne Disease Prevention & Control Program
IMCI	Integrated Management of Childhood Illnesses
LGU	Local Government Unit
NDHS	National Demographic Health Survey
NCDs	Non-Communicable Diseases
ORT	Oral Rehydration Therapy
PSP	Paralytic Shellfish Poisoning
PHA	Philippine Health Agenda
PIDSR	Philippine Integrated Disease Surveillance and Response
RDT	Rapid Diagnostic Test
RHU	Rural Health Unit
TWG	Technical Working Group
WASH	Water, Sanitation and Hygiene
WHO	World Health Organization

# **INTRODUCTION**

## **Food and Water-Borne Diseases (FWBD) Burden of Disease**



## Rationale

An estimated 1.8 million people worldwide die annually from diarrheal diseases, with majority of cases attributed to contaminated food or water. Food and water-borne diseases (FWBDs) is still a significant health issue in developed and developing countries. Morbidity and mortality from FWBDs threaten public health security and the socio-economic development of any country. These diseases perpetuate a vicious cycle of diarrhea and malnutrition and causes strain in health care systems. FWBDs severely affect the vulnerable population in society, such as infants, young children, elderly, and the sick. In developing countries, about 80% of all illnesses are caused by FWBDs, with diarrhea being the leading cause of childhood death. In the Philippines, diarrhea remains to be 1 of the 10 leading causes of morbidity and mortality, and is most commonly due to FWBDs.

Although the exact burden and cost of FWBDs is still unknown, it is surmised to be substantial. According to the World Health Organization (WHO), the burden of diarrheal diseases is estimated to be 3.6% of the total Disability Adjusted Life Years (DALY) worldwide. Based on the latest Department of Health (DOH) report, acute watery diarrhea (AWD) ranked seventh among the top leading causes of morbidity, affecting 76.3 per 100,000 population. AWD is also the seventh leading cause of mortality among infants, with a rate of 0.5 per 1,000 live births.

Provision of clean drinking water and safe disposal of feces can greatly reduce the prevalence of FWBDs. These interventions must be supported by continuous health education and information dissemination, particularly in the promotion of recommended practices on water, sanitation and hygiene (WASH). However, about 1.1 billion people worldwide still lack access to clean drinking water, and about 2.4 billion lack access to adequate sanitation. In the Philippines, the proportion of households with access to safe water is 90%, which was the target of the 2015 Millennium Development Goals (MDG). However, the proportion of households with sanitary toilet did not reach the MDG target.

In recognition of the debilitating effects of FWBDs, DOH established the Food and Waterborne Diseases Prevention and Control Program (FWBD-PCP) in 1997 through Administrative Order (AO) No. 29-A. The goal of the program is to reduce morbidity and mortality due to FWBDs. The program has 6 major components:

- Information dissemination on personal hygiene, safe food preparation, storage and handling, and environmental sanitation practices
- Establishment of an FWBD Surveillance System composed of community-based and laboratory-based surveillance
- Proper case management of FWBD with emphasis on ORESOL (oral rehydration solution) therapy and rationale use of diagnostic tests
- Training on local program implementation
- Research/special studies
- Monitoring and evaluation

## **FWBD Definition, Inclusion and Exclusion**

FWBDs refer to a group of illnesses that manifest with diarrhea, nausea, vomiting, abdominal pain, headache, and body malaise, with or without fever. These are caused by ingestion of food or water contaminated by disease-causing microorganisms such as virus, parasites, and bacteria or its toxins.

### **A. Diseases Included As FWBDs**

The following are specific diseases that are considered FWBDs: typhoid and paratyphoid fever, cholera, rotavirus infection, amoebiasis, food poisoning, and shigellosis.

### **B. Diseases Excluded From FWBDs**

The FWBD-PCP does not cover diseases caused by chemicals. However, DOH needs to accord equal attention to these diseases by assigning their management to a specific unit under the Disease Prevention and Control Bureau (DPCB).

## **I. Background**

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Food and Water-Borne Diseases (FWBDs) constitute a large and growing global public health problem. FWBDs are usually caused by infectious organisms such as viruses, bacteria and parasites. They are transmitted from person-to-person through soiled hands and through consumption of food and water contaminated by human waste. The incidence of FWBDs peaks during the rainy season, and is usually high in areas with poor sanitation and hygienic practices, as well as in poverty-stricken areas.

FWBDs usually manifest as diarrhea. Based on the 2015 Global Health Observatory data, diarrhea accounts for 9% of the total deaths among children below 5 years old. In the Philippines, a total of 11,876 cases of acute bloody diarrhea (ABD) were reported from sentinel sites nationwide in 2015. In addition, 830 cases of hepatitis A and 74 cases of paralytic shellfish poisoning were reported. Based on the Philippine Health Statistics data, diarrhea was the 5<sup>th</sup> leading cause of morbidity in the general population in 2010, which was an improvement from the 1990s when diarrhea was the top or 2<sup>nd</sup> leading cause of morbidity. The morbidity rate due to diarrhea decreased from 1,520/100,000 population in 1990 to 347.3/100,000 population in 2010. Despite this decline however, several outbreaks continue to occur. It is believed that since the occurrence of FWBDs is essentially related to economic and socio-cultural factors, these outbreaks will continue to persist until underlying social ills are corrected.

In 1997, the Department of Health (DOH), issued Administrative Order (AO) No. 29-A to create the Food and Waterborne Diseases Prevention and Control Program (FWBD-PCP). The AO stipulated specific goals and objectives to be achieved by the program, and the operationalization and implementation of the components of the program. Since its inception, the FWBD-PCP has implemented several interventions in response to the increasing incidence

of FWBDs. These notable interventions include: (i) institutionalization of Oral Rehydration Therapy (ORT) corners in hospitals and outpatient public health facilities for the immediate management and treatment of diarrhea cases, (ii) integration of the identification and management of diarrhea among children in the Integrated Management of Childhood Illnesses (IMCI) protocol, (iii) design, installation and operationalization of an FWBD surveillance and response system to detect impending outbreaks and to provide immediate investigation and response, (iv) provision of medicines and supplies to augment the resources of identified local government units (LGUs) with high incidence of FWBDs, and (v) current development of clinic practice guidelines on the diagnosis, management and treatment of several FWBDs.

## II. The Philippine Profile

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The Philippines is an archipelago located in Southeast Asia and comprised of 7,107 islands clustered into Luzon, Visayas and Mindanao. It is divided into 16 administrative regions, with the Autonomous Region of Muslim Mindanao (ARMM) as the 17<sup>th</sup> region. There are 81 provinces, 167 component cities, 16 chartered cities, 1,495 municipalities and 42,008 barangays. The Philippines is considered the 12<sup>th</sup> most populous country in the world, with an estimated population of 100.98 million as of 2016. The population is comprised of multiple ethnic groups, with several groups residing in remote, hard-to-reach mountainous areas.

The Philippines is considered one of the most vulnerable countries in the world to extreme weather events, being first in vulnerability to tropical cyclones, third most vulnerable for the number of people exposed to these seasonal events, and fourth most vulnerable to natural disasters. It experiences an average of 20 typhoons per year and faces increasing disaster risks.<sup>1</sup> The country also faces intermittent political instability and episodic armed conflict in the southern areas and some localized areas in Luzon. These conditions limit the delivery of social services, causing population displacement that facilitate disease introduction or transmission.

In spite of the challenging global economic environment, the country's economic growth rate has increased in the last five years, with the economy growing by 6.8% in 2016 compared to 5.9% in 2015. The incidence of poverty among Filipinos decreased from 25.1% in 2012 to 21.6% in 2015. In 2013, the total health expenditures as a percentage of Gross Domestic Product was at 4.4%. Although the 2015 Human Development Report noted that the value of the Philippines' human development index increased by 20% from 1980 to 2014, the Philippines only ranked 115 out of 188 countries.

The Education for All 2015 National Review showed that basic literacy rates among Filipino adults improved from 93.4% in 2003 to 95.6% in 2008, while functional literacy increased from 84.1% to 86.4% over the same time period.

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<sup>1</sup> World Disaster Report in 2015

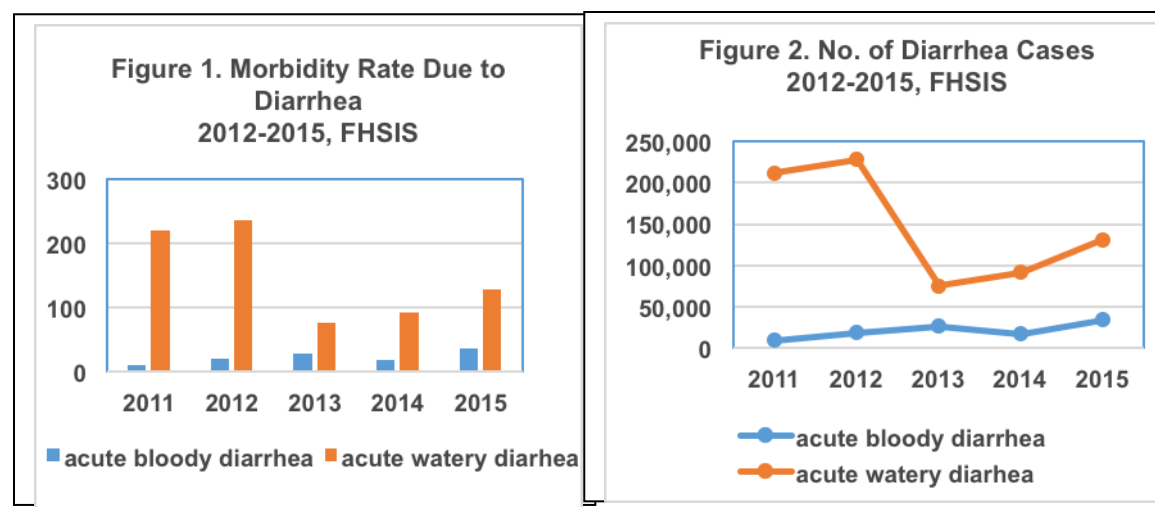
Life expectancy at birth is 65.3 years for males and 72.0 years for females.<sup>2</sup> The national burden of disease is increasingly dominated by non-communicable diseases (NCDs). The country continues to experience rising numbers of HIV and dengue cases. Neglected Tropical Diseases also continue to be a public health burden, although the Philippines is now nearing the elimination of malaria.

Around 2,000 mothers die each year from pregnancy-related conditions. The under-5 mortality rate is at 27/1,000 live births, while the infant mortality rate is at 21/1,000 live birth based on the 2015 National Demographic Health Survey (NDHS). Immunization coverage is quite low at 70.0% based on the 2015 Field Health Service Information System (FHSIS). More than 30% of children below 5 years old are stunted.

## A. Morbidity and Mortality Rates of Specific Food and Water-Borne Diseases

### Diarrhea

**Morbidity** due to diarrhea (both acute bloody diarrhea and acute watery diarrhea) has decreased by almost two thirds, affecting 288.7/100,000 population in 2010 and only 166.8/100,000 population in 2015. The number of acute bloody diarrhea and acute watery diarrhea cases was lowest in the year 2013, but it increased in 2014 and 2015. The fluctuating values reflect the difficulty in sustaining good control and prevention of diarrhea in the past 6 years.

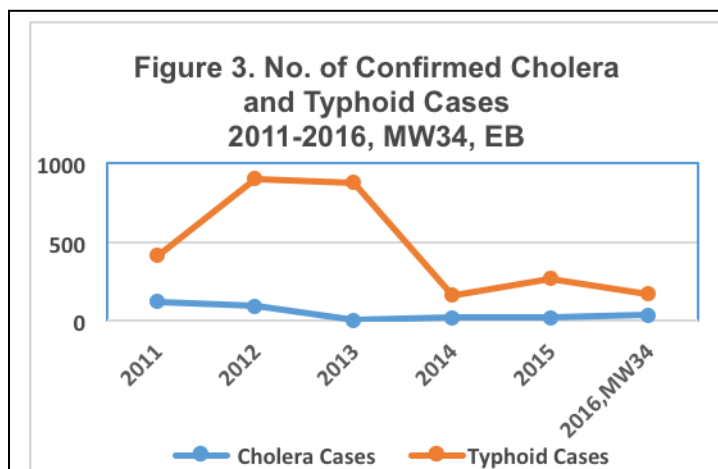


**Mortality.** The desired zero deaths due to diarrhea was not realized. Surveillance data in 2015 showed 18 deaths due to diarrhea, which increased to 44 deaths in 2016.

<sup>2</sup> WHO (2016) *World Health Statistics*

## Cholera and Typhoid

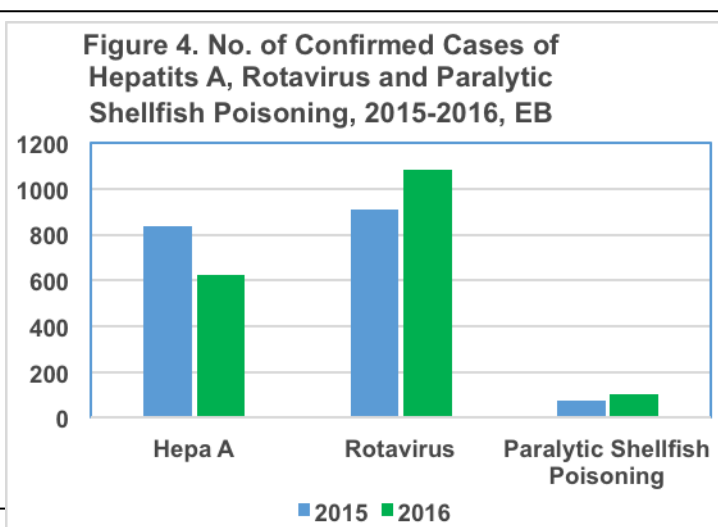
**Morbidity.** Although the number of confirmed typhoid and cholera cases decreased in the past 6 years, a substantial number of cases continues to be reported. The number of cholera cases increased slightly from 2013 to 2016. The number of typhoid cases decreased from 2013 to 2014; however, this number increased again in 2015.



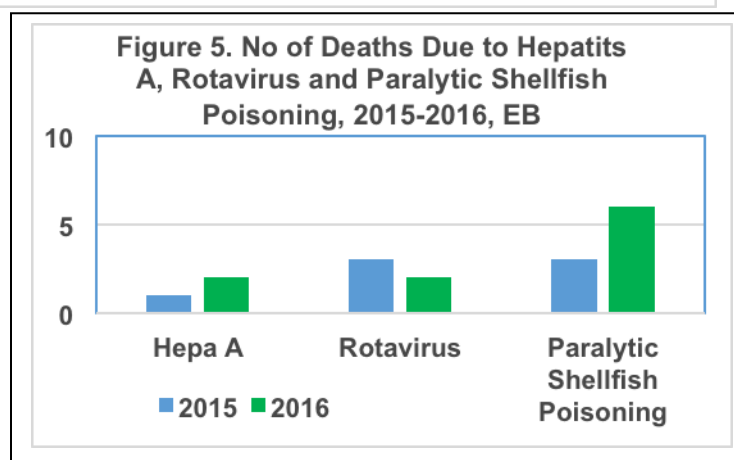
**Mortality.** There have been no reported deaths due to cholera from 2015 to 2016. No deaths from typhoid were reported in 2015, but 2 deaths were reported in the National Capital Region (NCR) in 2016.

## Other Food and Water-Borne Diseases

**Morbidity.** Surveillance data from the Epidemiology Bureau (EB) showed the incidence of hepatitis A, rotavirus and paralytic shellfish poisoning (PSP) in 2015 and 2016. The number of hepatitis A cases decreased, but rotavirus and PSP cases increased from 2015 to 2016. The increase in cases may be due to improved reporting of the sentinel sites during this period.

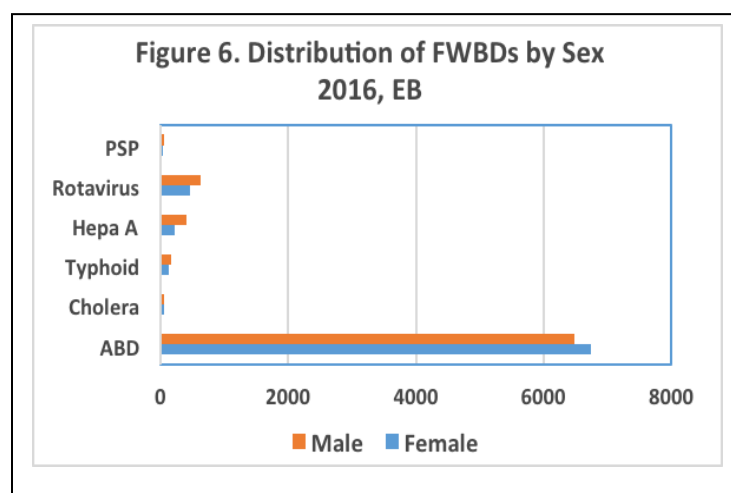


**Mortality.** The number of deaths due to PSP and hepatitis A doubled from 2015 to 2016. There were 3 deaths from PSP and 1 death from hepatitis A in 2015. In 2016, there were 6 deaths from PSP and 2 deaths from hepatitis A. There were only 5 reported deaths from rotavirus in this time period.



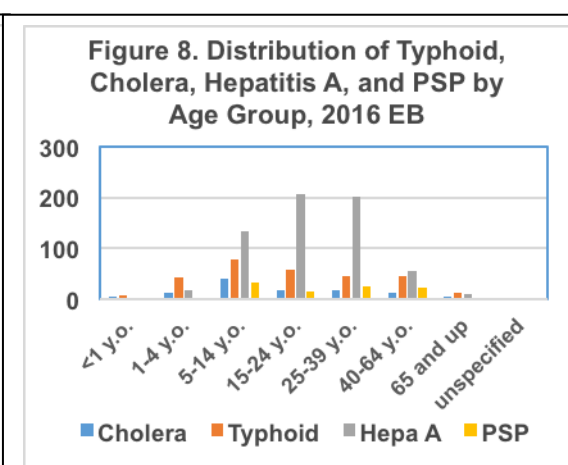
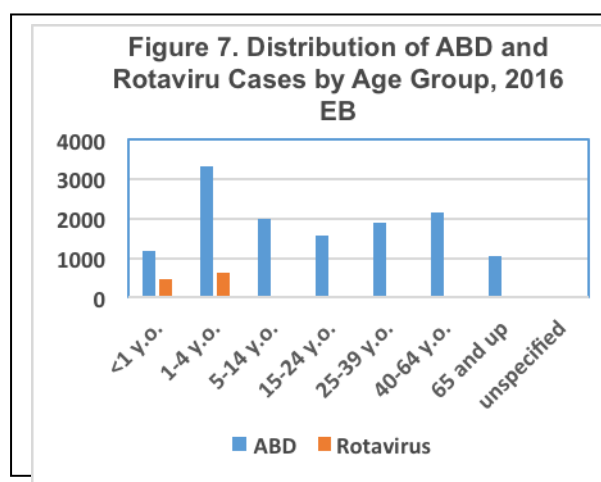
## FWBDs by Sex

Based on the 2016 Epidemiology Bureau (EB) data, there were slightly more males who experienced cholera, typhoid, hepatitis A, rotavirus and PSP than females. However, more females experienced acute bloody diarrhea.



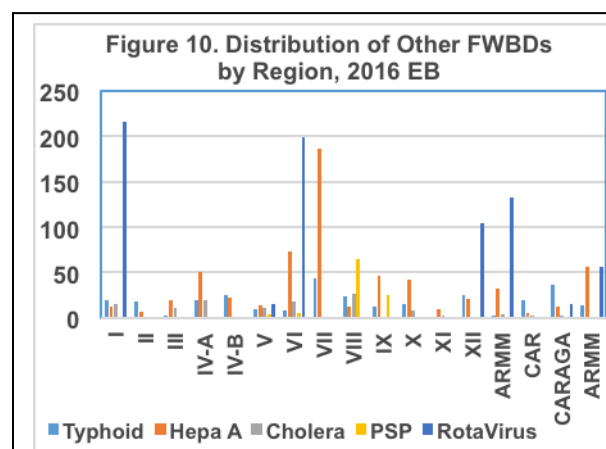
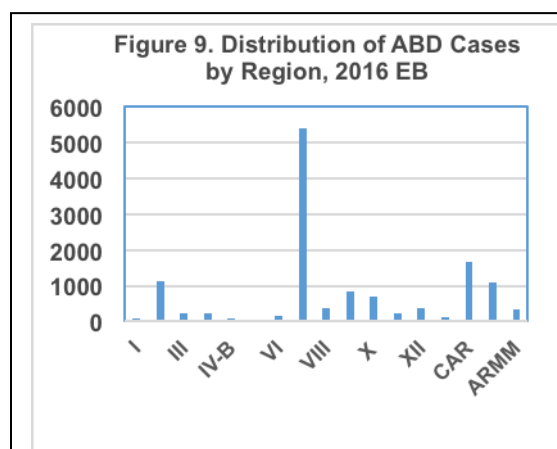
## FWBDs by Age Group

Majority of the reported cases of acute bloody diarrhea in 2016 occurred in the 1 – 4 year-old age group. Rotavirus occurred mainly in the 1 – 4 year-old and below 1 year-old age group. Hepatitis A most frequently affected the 15 – 39 year-old and 5 – 14 year-old age group. For typhoid, cholera and PSP, the highest number of cases reported was among the 5 – 14 year-old age group.



## FWBDs by Geographical Areas

The Visayas Region, particularly Regions VII and VIII, had the highest incidence of FWBDs in the country in the year 2016. Region VII had the highest incidence of ABD, hepatitis A and typhoid, while Region VIII had the highest incidence of cholera and PSP. Region I had the highest incidence of rotavirus in 2016.



## B. Outbreaks Due to FWBDs

The FWBD-PCP objective to eliminate FWBD outbreaks was not realized, with several reported FWBD-related events experienced in various parts of the country from 2012 to 2016. A total of 115 FWBD health events were verified by the Event-Based Surveillance and Response (ESR) Unit from 2012 – 2016. A total of 17,246 cases and 143 deaths were reported from these health events. Table 1 shows the summary of the FWBD health events from 2012 to 2016

**Table 1. Summary of FWBD Health Events from 2012 to 2016**

FWBD	2012			2013			2014			2015			2016		
	E	C	D	E	C	D	E	C	D	E	C	D	E	C	D
Acute bloody diarrhea	0	0	0	0	0	0	0	0	0	1	20	0	1	29	0
Shigella	2	194	1	4	2,368	9	2	662	3	0	0	0	1	30	2
Salmonella	2	1,036	4	4	317	5	2	41	0	3	29	2	1	4	0
Amoebiasis	6	385	5	4	83	0	10	389	3	12	284	5	20	2,268	12
Rotavirus	0	0	0	2	300	0	1	710	1	0	0	0	2	1,290	14
Hepatitis A	3	98	0	0	0	0	9	505	1	12	255	3	4	119	0
Paralytic Shellfish Poisoning	2	14	2	3	29	2	2	32	2	10	57	2	4	55	4
Capillariasis	0	0	0	0	0	0	4	4	0	0	0	0	3	3	1
Paragonimiasis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Others	0	0	0	2	12	0	1	1,447	10	2	221	0	2	3,956	22
<b>Total</b>	<b>15</b>	<b>1,727</b>	<b>12</b>	<b>19</b>	<b>3,109</b>	<b>16</b>	<b>31</b>	<b>3,790</b>	<b>20</b>	<b>40</b>	<b>866</b>	<b>12</b>	<b>38</b>	<b>7,754</b>	<b>55</b>
Most common FWBD health events	Amoebiasis health events (6/15 or 40%)			Diarrhea and Typhoid Fever health events (5/19 or 26%)			Amoebiasis health events (10/31 or 32%)			Amoebiasis and Hepatitis A health events (12/40 or 30% each)			Amoebiasis health events (20/38 or 53%)		
Most affected region (defined as most number of FWBD health events reported)	Region 6 (17, 26%)			Region 1 (23, 26%)			Region 1 (19, 19%)			Region 12 (32, 17%)					

\*E – events, C – cases, D – deaths

### III. Development of the Clinical Practice Guideline

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The purpose of this clinical practice guideline is to standardize the approach on diagnosis, management and prevention of acute infectious diarrhea to reduce the burden of morbidity and mortality among immunocompetent pediatric (0-18 years old) and adult (above 18 years old) patients. It is intended for clinicians and allied health professionals involved in the care of patients with acute infectious diarrhea in all types of healthcare setting. This document tThis will also further strengthen inter-agency collaboration among public and government institutions and societies.

#### **Committee Selection**

The Steering Committee headed by the Department of Health, San Lazaro Hospital and Philippines Society for Microbiology and Infectious Diseases (PSMID) provided organizational and logistic support. The committee also provided guidance on the scope, target audience, activities and timelines of the CPG development. A multidisciplinary technical working group (TWG) composed of adult and pediatric clinicians, academicians, epidemiologists, public health practitioners, and program implementers was convened. Designated representatives of the stakeholder medical societies were assigned into their respective committees based on their field of expertise. The voting panel consisted of experts from the government and private sectors. The participants of the TWG and Expert Panel included representatives from PSMID, PIDSP, PSPGHAN, PSG, PNSP, PSN, and PAFP. A Clinical Practice Guideline Development Workshop was conducted by the TWG Chair and Co-Chair for the TWG members and Expert Panel in 2016.

#### **Evidence Synthesis**

The Expert Panel and TWG members generated an initial list of relevant clinical questions on diagnosis, treatment and prevention of acute infectious diarrhea. The group identified and prioritized the outcomes of interest according to importance based on its impact on decision-making. Each member was assigned to least one question and was tasked to search the literature, review and appraise the articles, generate the evidence tables, draft the summary of evidence and the recommendations. Systematic search of electronic databases including MEDLINE, Cochrane Library and local databases was conducted. Studies that met the pre-specified inclusion criteria for each clinical question were retrieved and appraised to evaluate the risk of bias. Monthly group discussions and presentations were held from the years 2016 to 2017.

The TWG used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to systematically rate the quality of evidence and determine the strength of recommendation (Table 1).



**Table 2. Quality of evidence using the GRADE framework.<sup>1</sup>**

Quality of Evidence		Study Design	Lower if:	Higher if:
High	Further research is very unlikely to change confidence in the estimate of effect	Randomized controlled trials (RCTs)	Study quality: Poor quality of implementation of RCT	Stronger association: Large magnitude of effect, no plausible confounders
Moderate	Further research is likely to have an impact on the confidence in the estimate of effect	Downgraded RCTs or upgraded observational studies	Inconsistency of results	Very large magnitude of effect, no major threats to validity
Low	Further research is very likely to have an important impact on the confidence in the estimate of effect	Observational studies	Indirectness: Different population, intervention, outcomes	Dose-response gradient
Very Low	Any estimate of effect is very uncertain	Case series or expert opinion	Imprecise results: High probability of reporting bias	

<sup>1</sup>Reference: Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.

The TWG drafted the recommendations including the strength of recommendations. These recommendations were then presented to the Expert Panel for consensus. Factors that influenced the strength of recommendations included the balance between benefits and harms, values and preferences, baseline risks and resource implications (Table 2). The public's views and preferences were sought through information gathered from patient encounters.

**Table 3. Implications of strength of recommendations to patients, clinicians and policy makers using the GRADE approach.<sup>2</sup>**

Strength of Recommendation		Implications of the recommendations		
		Patients	Clinicians	Policy Makers
Strong	The benefits outweigh the harm. There are no costs or access issues for the general population	Most people in the situation would want the recommended course of action and only very few would not; request for discussion if the	Most patients should receive the recommended course of action. The recommendation can be used as a quality or	The recommendation can be adopted as a policy in most situations

		intervention is not offered	performance indicator	
Weak	<p>Best available evidence is very low to low quality</p> <p>The magnitude of benefits and risks is uncertain or closely balanced for the general population and applicable to a specific group, population or setting</p> <p>Benefits may not warrant the cost or resource requirements in all settings</p>	Most people in the situation would want the recommended course of action, but many would not	Different choices are appropriate for different patients, and clinicians must help patients arrive at a management decision consistent with the patients' values and preferences	Policy making will require substantial debate and involvement of stakeholders

<sup>2</sup> Reference: Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, and Schünemann HJ. Going from evidence to recommendations. *BMJ*. 2008;336(7652):1049-1051.

There are several Good Practice Statements (GPSs) found in this document. GPS is used when benefit and harm is equivocal, and the evidence cannot be assessed using the GRADE methodology. Table 3 outlines the criteria used by the TWG and Expert Panel in issuing GPSs.

**Table 4. Criteria for issuing Good Practice Statements.<sup>3</sup>**

1. Is the statement clear and actionable?
2. Is the message necessary in regard to actual health care practice?\*
3. After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences?\*
4. Is the evidence difficult to collect and summarize?\*
5. Is there a well-documented clear and explicit rationale connecting the indirect evidence?\*

\*Answer to this question should be yes in order to proceed.

<sup>3</sup>Reference: Guyatt GH, Alonso-Coello P, Schünemann HJ, Djulbegovic B, Nothacker M, Lange S, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. *Journal of Clinical Epidemiology*. 2016;80:3-7.

Each statement was presented to the Expert Panel for discussion and consensus using the nominal group technique. Results were tabulated and summarized. Two rounds of group

discussion were conducted on October 14, 2017 at Manila Grand Opera Hotel and on November 17, 2017 at Ramada Hotel to finalize the wording and strength of the recommendations.

Voting was done as follows: A=accept completely; B=accept with some reservations; C=accept with major reservations; D= reject with some reservations; and E= reject completely. Statements reached consensus if 80% voted A or B; rejected if less than 80% was reached or at least one (1) member voted D or E.

Statements that reached consensus were presented at the Annual Convention of the Philippine Society for Microbiology and Infectious Diseases last November 28-30, 2017 for external review prior to publication. Statements that did not reach consensus on the initial voting were deliberated and sent back to the TWG for revision or further review of literature. The succeeding drafts were circulated via electronic communication to the members of the panel for comments and approval. The penultimate draft was elevated to the Steering Committee for final review and approval.

### **Dissemination Plans**

To facilitate the implementation of this CPG, a Training of Trainers Workshop will be conducted among members of the participating society using standard slide decks summarizing the CPG recommendations. A manual of procedure shall also be developed to train frontline healthcare workers such as barangay health workers and midwives. The pocket guide and full text of the CPG will also be available in the websites of the participating societies and agencies. The funds needed to implement this CPG will be provided by DOH. The cost of implementing this CPG is expected to be far outweighed by the savings from reducing the burden of disease of acute infectious diarrhea. The impact of this CPG will be measured by monitoring the morbidity and mortality data of acute infectious diarrhea. A detailed description of the background, methods and evidence summaries that support each of the recommendations can be found in the full text of the guidelines.

### **Future Revision Dates**

The need to update this guideline will be determined annually by the Steering Committee by reviewing the current literature. If deemed necessary to be updated, the CPG Task Force will be reconvened.

### **Editorial Independence**

This CPG was developed with funding from DOH, San Lazaro Hospital, and the Philippine Society for Microbiology and Infectious Diseases. The views of the funding bodies have not influenced the content of this CPG. Competing interests of guideline development group members were recorded and addressed accordingly.

# **CLINICAL PRACTICE GUIDELINES**

## I. DIAGNOSIS

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### Question 1: When is the diagnosis of acute infectious diarrhea suspected?

Acute infectious diarrhea is suspected if a patient presents with the passage of 3 or more loose, watery or bloody stools within 24 hours that may be accompanied by any of the following symptoms:

- Nausea
- Vomiting
- Abdominal pain
- Fever

[Strong recommendation, low to moderate quality of evidence]

**Acute diarrhea** is the passage of three or more loose, watery or bloody stools from an immunocompetent person's normal baseline in a 24-hour period, with a duration of less than 14 days. The patient should not have received antibiotics within the last three months and should not have been hospitalized, and the diarrhea should not have occurred after more than 48 hours of hospital admission.<sup>1-4</sup> The change in stool consistency is more important to consider than the change in stool frequency in assessing if a patient has diarrhea.

**Acute infectious diarrhea** is acute diarrhea that is usually accompanied by symptoms such as nausea, vomiting, abdominal pain and fever, and is caused by infectious agents such as bacteria, viruses, fungi or protozoa. (Operational definition)

According to the World Health Organization (WHO), a young infant has diarrhea if the stools have changed from the usual pattern. The normally frequent or semi-solid stools of a breastfed baby is not considered diarrhea.<sup>2</sup>

### SUMMARY OF EVIDENCE

Low to moderate quality evidence from observational studies (cross-sectional, case control and cohort studies) examined the sensitivity and specificity of clinical manifestations for common etiologic agents of acute infectious diarrhea in adults and children. The data is summarized in Table 1. The presence of fever, vomiting and abdominal pain in patients with diarrhea is sensitive for diarrhea caused by *Salmonella*, *Shigella*, *E. coli*, *Campylobacter* and rotavirus. Bloody diarrhea is a specific sign for *Shigella*, *Campylobacter*, rotavirus and norovirus. Hence, the presence of these symptoms in patients with diarrhea warrants further work-up and management for acute infectious diarrhea.

Table 1. Sensitivities and specificities of clinical manifestations for common causes of infectious diarrhea.<sup>5-20</sup>

Etiologic agent		Clinical Manifestations			
		Bloody Diarrhea	Fever	Vomiting	Abdominal pain
<b>Bacterial Etiology</b>	Sn	4	59	59	-
	Sp	-	-	-	-
Invasive Enteropathogens	Sn	5-17	14-58	7-24	7-88
	Sp	96-98	69-94	90-94	14-96
<i>Salmonella</i>	Sn	0-2	75	70	-
	Sp	0-85	-	-	-
<i>Campylobacter</i>	Sn	20-33	64-67	27-100	89
	Sp	97	72	90	16
<i>Shigella</i>	Sn	14-29	40-93	21-73	73
	Sp	93-100	58-72	32-73	22
<i>Escherichia coli</i>	Sn	2	81	49	-
	Sp	-	-	-	-
<b>Viral Etiology</b>	Sn	0	68.5	60.3	-
	Sp	-	-	-	-
Rotavirus	Sn	0	3-84	2-79	53
	Sp	91.7-93	20-74	27-94	44
Adenovirus	Sn	0	50	50	-
	Sp	-	-	-	-
Norovirus	Sn	3	-	92	56
	Sp	92	-	25	38

Sn – sensitivity, Sp – specificity; All values are expressed in percentages

**Question 2: What pre-treatment clinical evaluations are recommended for immunocompetent patients presenting with acute infectious diarrhea?**

1. Extensive clinical history that includes questions on consumption of raw, ill-prepared, or rotten food, intake of contaminated food or water, and history of travel should be obtained since this could provide clues to the possible etiology.  
[Strong recommendation, low to moderate quality evidence]
2. Complete physical examination should be done to assess disease severity, degree of dehydration, presence of complications, and presence of comorbid conditions. (See question 4 for discussion)  
[Strong recommendation, low to moderate quality evidence]

The initial evaluation of patients with diarrhea should include a careful history to determine the duration of diarrhea, frequency of bowel movement, characteristics of the stool, and associated symptoms. Eliciting information regarding the patients' occupation, travel history, place of residence, history of food intake, and exposure to pets may provide further diagnostic clues.

The frequency of bowel movement and stool characteristics can suggest the likely anatomic location of the diarrhea. Diarrhea originating in the small intestine is typically watery, voluminous, and associated with abdominal pain, cramps and gas. Diarrhea originating in the large intestine is smaller in volume, more frequent, and may be bloody or mucoid.

## SUMMARY OF EVIDENCE

No single symptom is pathognomonic for an etiologic agent of acute infectious diarrhea.<sup>4</sup> However, certain symptoms and stool characteristics can suggest a specific etiologic agent. Watery stool is common in diarrhea caused by rotavirus and *Vibrio cholerae*, while bloody stool is common in diarrhea caused by *Shigella* and *Salmonella*. Table 2 shows the sensitivity and specificity of the different stool characteristics for common etiologic agents of acute infectious diarrhea.

Table 2. Sensitivity and specificity of stool characteristics to specific etiologic agents

Etiologic agent	Stool Quality		
	Bloody	Mucoid	Watery
Salmonella	Sensitivity: 2.2% <sup>9</sup> Specificity: 84.7% <sup>9</sup>		Sensitivity: 100% <sup>5</sup> Sp: not stated <sup>5</sup>
Campylobacter	Sensitivity: 20% <sup>16</sup> Specificity: 97% <sup>16</sup>		Sensitivity: 45% <sup>18</sup> Specificity: 72% <sup>18</sup>
			Sensitivity: 66.7% <sup>5</sup> Specificity: - <sup>5</sup>
Rotavirus	Sensitivity: 0% <sup>6</sup> Specificity: 91.7% <sup>6</sup>	Sensitivity: 53% <sup>6</sup> Specificity: 51% <sup>6</sup>	Sensitivity: 43% <sup>6</sup> Specificity: 77% <sup>6</sup>
	Sensitivity: 0% <sup>14</sup> Specificity: 93% <sup>14</sup>	Sensitivity: 7% <sup>14</sup> Specificity: 96% <sup>14</sup>	Sensitivity: 90% <sup>14</sup> Specificity: 16% <sup>14</sup>
			----- Sensitivity: 12% <sup>20</sup> Specificity: 67% <sup>20</sup>
	Sensitivity: 0 <sup>5</sup> Specificity: - <sup>5</sup>		Sensitivity: 100% <sup>5</sup> Specificity: - <sup>5</sup>
			Sensitivity: 64.6% <sup>10</sup> Specificity: 62.1% <sup>10</sup>
Adenovirus			Sensitivity: 100% <sup>5</sup> Specificity: - <sup>5</sup>
Shigella	Sensitivity: 29.2% <sup>12</sup> Specificity: 100% <sup>12</sup>	Sensitivity: 54% <sup>19</sup> Specificity: 70% <sup>19</sup>	Sensitivity: 65% <sup>19</sup> Specificity: 36% <sup>19</sup>
	Sensitivity: 27% <sup>19</sup> Specificity: 93% <sup>19</sup>		Sensitivity: 92.9% <sup>10</sup> Specificity: not stated <sup>10</sup>
Cholera			Sensitivity: 97% <sup>15</sup> Specificity: 30% <sup>15</sup>
Norovirus	Sensitivity : 3% <sup>16</sup>		

	Specificity: 92% <sup>16</sup>		
Invasive Enteropathogens	Sensitivity :17 % <sup>18</sup> Specificity: 96% <sup>18</sup> ----- Sensitivity: 5% <sup>13</sup> Specificity: 98% <sup>13</sup>		Sensitivity: 42% <sup>18</sup> Specificity: 87% <sup>18</sup> ----- Sensitivity: 25% <sup>13</sup> Specificity: 69% <sup>13</sup>
<i>E. coli</i>			Sensitivity: 97.6% <sup>10</sup> Sp: - <sup>10</sup>
Virus (Not specified)			Sensitivity: 100% <sup>10</sup> Specificity: - <sup>10</sup>
Bacterial Etiology (Not Specified)		Sensitivity: 72% <sup>13</sup> Specificity: 32% <sup>13</sup>	Sensitivity: 96.2% <sup>10</sup> Specificity: - <sup>10</sup>

<sup>9</sup> (Chan, Lyon, Ng , Cheung, Cheng, & Rainer, 2003), <sup>6</sup> (Borade, Bais, Bapat, & Dhongade, 2010), <sup>12</sup> (Ozmert, Orun, Sengelen, Yalcin, Yurdadok, & Gur, 2010), <sup>15</sup>(Seas, et al., 2000), <sup>18</sup> (Tribble, et al., 2008), <sup>14</sup> (Ribas, et al., 2015), <sup>19</sup> (von Seidlein, et al., 2006), <sup>20</sup>Ibrahim(2015), <sup>13</sup>Qu(2016), <sup>16</sup> (Sidler, et al., 2014)<sup>10</sup> Gurwith (1981) <sup>5</sup> (Bonkougou, et al., 2013)>

Most of the studies that predicted the likelihood of a bacterial cause for acute diarrhea based on the combination of symptoms and diagnostic test results were conducted among pediatric patients. An observational prospective study involving 200 children reported that those with bowel movement of >4 times a day and absence of associated vomiting have high probability of bacterial diarrhea, with a sensitivity of 86% and specificity of 60%.<sup>24</sup> Another study scored 337 children based on the presence of fever, vomiting, and mucoid and bloody stool. The patients were then categorized based on the prevalence of bacterial diarrhea in their region. Based on clinical features alone, this method had a sensitivity of 90% and specificity of 42%. The addition of high fecal WBC to the classification increased the specificity to 86%.<sup>25</sup>

One study determined predictors of bacterial diarrhea using logistic regression. Four factors were found to be predictive—unclean dietary history which was based on consumption of raw, ill-prepared food or rotten food; intake of unclean water; body temperature; and presence of abdominal pain and fecal leukocyte.<sup>26</sup>



### Question 3: What is the clinical use of diagnostic tests in children and adults with acute infectious diarrhea?

1. Diagnostic tests should be requested based on the patient's clinical status.  
[Strong recommendation, low quality of evidence]
2. Routine stool examination is not indicated in acute watery diarrhea, except in cases where parasitism is suspected or in the presence of bloody diarrhea.  
[Strong recommendation, low quality of evidence]
3. Stool cultures are indicated only for severe cases (significant dehydration, high fever, persistent vomiting, severe abdominal pain, dysenteric stool); high risk of transmission of enteric pathogens (food handlers); high risk of complications; and for epidemiologic purposes (when there is suspicion of an outbreak that is enteric in origin). Stool culture should be requested within 3 days of symptom onset and before administration of antibiotics to ensure that its yield is highest.  
[Strong recommendation, low quality of evidence]
4. There is insufficient evidence to support the use of biomarkers (CRP, calprotectin, ESR, procalcitonin, total serum WBC) in distinguishing the cause of acute infectious diarrhea.  
[Strong recommendation, low quality of evidence]
5. Rapid diagnostic tests may be used during suspected outbreaks of cholera and shigella, but confirmation with stool culture is still recommended.  
[Strong recommendation, low quality of evidence]
6. Clinical correlation is necessary in interpreting tests done using molecular diagnostics. Although these tests have high sensitivity, they are unable to distinguish between viable and non-viable organisms.  
[Strong recommendation, low quality of evidence]

### Summary of Evidence

#### Fecal Leukocytes

A meta-analysis of 15 studies with a total of 7,161 patients evaluated the utility of fecal leukocytes in distinguishing between bacterial and non-bacterial diarrhea. In resource-poor countries, the fecal leukocyte test, when used with a threshold of >5 cells/hpg, had a sensitivity of 50%, specificity of 83%, positive likelihood ratio (LR) of 2.94, and negative LR of 0.60. Since these values are low, the fecal

leukocyte test may not be able to distinguish the etiologic cause of diarrhea especially in ambiguous cases.<sup>27</sup>

A more recent case-control study conducted in Taiwan showed that the presence of fecal leukocytes was significantly associated with bacterial gastroenteritis (adjusted OR=2.08; 95% CI 1.42, 3.05). However, the presence of fecal leukocytes cannot predict the likelihood of bacterial diarrhea at any threshold level (positive LR=1.67).<sup>28</sup>

## **Stool Culture**

Because most cases of watery diarrhea are self-limited, testing is usually not indicated.<sup>29</sup> Routine stool cultures have low pathogen yield of 2% to <60%.<sup>30-37</sup> The results of routine stool cultures will usually not change management. In fact, most patients would have already recovered by the time results are available.

Stool diagnostic studies that identify etiologic agents are beneficial for patient with severe diarrhea, signs of dehydration, dysentery, persistent diarrhea, immunosuppressed conditions, suspected nosocomial infection, or involved in outbreaks.<sup>38</sup> Identification of the diarrheal pathogen enables tailoring of antibiotic therapy and avoidance of unnecessary use of antibiotics.

A cohort study involving 233 patients in Pakistan showed that patients with positive stool cultures were more likely to have younger age (adjusted OR=0.96; 95% CI 0.94, 0.98], greater number of unformed stools per day (adjusted OR=1.05; 95% CI 1.004, 1.09) and low bicarbonate levels (adjusted OR=0.87; 95% CI 0.80, 0.95).<sup>39</sup> In contrast, a study of adult patients in Hong Kong showed that factors associated with positive stool cultures include highest body temperature 37.5°C to 38.4°C (OR=3.49; 95% CI 1.44, 8.48), duration of abdominal pain >3 days (OR=0.27; 95% CI 0.12, 0.64), requirement of IV fluids (OR=2.35; 95% CI 1.13, 4.92), and presentation from May to October (OR=3.90; 1.93, 7.86).<sup>40</sup>

Stool cultures should be obtained within 3 days of hospitalization and prior to antibiotic administration. Cultures obtained after the 4<sup>th</sup> hospitalization day have lower yield compared to samples taken in the first 3 days. The first stool specimen usually detects 87% of pathogens in adults and 98% of pathogens in children.<sup>34,41,42</sup>

In the Philippines, routine stool culture only identifies *Shigella*, *Salmonella*, *Aeromonas*, and *Yersinia* species. If *Vibrio*, enterohemorrhagic *E. coli* or other shiga-toxin producing bacteria are clinically suspected, this should be indicated in the stool culture request since these pathogens require special media.

## **Routine Laboratory Tests**

Routine laboratory tests such as complete blood counts, electrolyte levels and renal function tests are not useful in patients with acute diarrhea. Serum WBC is not a useful indicator to distinguish between bacterial and viral causes of diarrhea given the variability of its values. However, these tests may be useful to detect complications of acute infectious diarrhea (see diagnostic question 5).

## Non-culture detection methods

Several culture-independent techniques to identify diarrheal pathogens have been developed in the past years. Enzyme immunoassays identify *Campylobacter* from stool specimens by detecting surface *Campylobacter*-specific antigens. However, it cannot differentiate between *C. jejuni* and *C. coli*. Results are rapidly available, but up to 50% of the results cannot be confirmed using other detection methods.

Multiplex molecular testing permits identification of a broader range of pathogens. It also has a fast turn-around time, with results available within a few hours. Unfortunately, these tests require a predefined set of microbes to be sought, do not discriminate between viable and non-viable organisms, and detects an increased number of mixed infections of unknown clinical significance. A recent systematic review of multiplex testing among patients with suspected infectious diarrhea demonstrated no robust evidence that the molecular panels are informative for the consequent clinical management of patients.<sup>43</sup> There was likewise uncertainty regarding the cost-effectiveness of these diagnostics in patient management.

## Biomarkers

### *Lactoferrin*

Lactoferrin is an iron-binding glycoprotein expressed by leukocytes. It is found in human milk, synovial fluid, and tears. It is stable in storage for >48 hours at room temperature.

A small study showed that lactoferrin latex agglutination assay had a sensitivity of 93%, specificity of 83%, and positive likelihood ratio of 5.57 in detecting *Shigella*, *Salmonella* or *Campylobacter* at a titer threshold of  $\geq 1:50$ .<sup>44</sup> Another study showed that lactoferrin determination, at a cut-off of 97 ug/g, has a sensitivity of 64% and a specificity of 81% for detecting bacterial pathogens. At a lower cut-off of 67 ug/g, sensitivity increases to 77% but specificity decreases to 65%. At any positive test value, the pooled sensitivity is 60% and the pooled specificity is 94.7%.<sup>45</sup>

### *CRP*

In a prospective cohort study among adults, CRP showed the best diagnostic performance in distinguishing between bacterial and viral gastroenteritis with a sensitivity of 85% and specificity of 73% at a cut-off at 40 mg/L.<sup>45</sup> Two studies involving children had similar results but used a different cut-off of >2mg/dl. One study reported a sensitivity of 83.3% and specificity of 76%,<sup>46</sup> while the other study reported a sensitivity of 92% and specificity of 59%.<sup>47</sup> Another study used the cut-off of  $\geq 2$ mg/L but involved mixed populations, with a larger percentage of participants having systemic involvement. Results showed that CRP did not perform well, with a sensitivity of 93% and specificity of 6%.<sup>48</sup>

### *Cytokines*

Interleukin-6 (IL-6) levels were higher in bacterial diarrhea compared to viral or nonspecific diarrhea, but results were not statistically significant. Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels were also not significantly different among patients with bacterial, viral or nonspecific diarrhea; hence, it cannot adequately discriminate between bacterial and viral gastroenteritis. Interferon- $\gamma$  (IFN- $\gamma$ ) levels were found to be significantly increased in patients with viral diarrhea compared to those with bacterial or nonspecific diarrhea.<sup>45</sup>

## Calprotectin

Calprotectin is a protein found in large amounts in neutrophils. It is released by the degranulation of neutrophils during bowel inflammation. It is a stable protein and may be found unaltered in the stool for more than 7 days. Calprotectin levels were significantly higher in patients with bacterial diarrhea compared to viral or nonspecific diarrhea. Thus, calprotectin may be a useful test to differentiate between bacterial and viral diarrhea.<sup>45</sup>

Table 3 summarizes the measures of diagnostic test accuracy of biomarkers in differentiating between bacterial and viral diarrhea.

Table 3. Measures of diagnostic test accuracy of biomarkers

Biomarkers	Cut off	Sn(%)	Sp(%)	PPV (%)	NPV (%)	LR+	LR-
<b>CRP</b>							
Weh et al. 2013	40 mg/L	85	73	-	-	3.14	0.2
Lin et al. 2006	>2 mg/dl	83.3	76.2	75	84.2	3.5	.22
Hsu et al. 2005	>2 mg/dl	92	58.8	68.4	84.6	2.1	.14
Thia et al. 2008	0.5 mg/L	100	5	-	-	1.1	.7
	2 mg/L	93	6	-	-	1	0
	10 mg/L	87	24	-	-	1.1	1
<b>Calprotectin</b>							
Weh et al. 2013	200 mg/kg	87	65	-	-	2.5	0.2
	274 mg/kg	70	83	-	-	4.1	0.36
<b>Lactoferrin</b>							
Weh et al. 2013	97 ug/g	64	81	-	-	3.4	0.44
	67 ug/g	77	65	-	-	2.2	0.35
Choi 1996 (latex agglutination)	>1:50	93	83	-	-	5.47	0.08
	>1:400	61	100	100	61	-	.39
<b>IL, TNF, INF</b>							
Lin et al. 2006	IL-6 >10 pg/ml	77.8	85.7	82.4	81.8	5.44	0.26
	IL-8 >70 pg/ml	50	66.7	56.3	60.9	1.5	0.75
	IL-6 and/or CRP	94.4	71.4	73.9	93.8	3.8	0.1
	IL-8 and/or CRP	88.9	52.4	61.6	84.7	1.87	0.21
Hsu et al. 2005	IL-10 >10 pg/ml	78.5	29.4	47.8	62.5	1.1	0.73
	TNF- $\alpha$ $\geq$ 7 pg/ml	78.6	88.2	88.6	83.3	6.5	0.24
<b>ESR</b>							
Thia et al. 2008	$\geq$ 10	60	44	-	-	1.1	0.6
	$\geq$ 15	47	55	-	-	1.1	0.9
	$\geq$ 20	47	67	-	-	1	1
<b>Procalcitonin</b>							
Thia et al. 2008	$\geq$ 0.1	93	50	-	-	1.9	0.13
	$\geq$ 0.5	40	92	-	-	5.3	0.7
	$\geq$ 2.0	27	100	-	-	Infinite	0.7
<b>Total WBC</b>							
Thia et al. 2008	$\geq$ 11	53	67	-	-	1.6	0.7
	$\geq$ 15	20	91	-	-	2.2	0.9
	$\geq$ 20	7	99	-	-	4.4	1

IFN- $\gamma$ (Determining viral cause of diarrhea)							
Weh et al. 2013	1.08 pg/ml	67	63	-	-	1.8	0.32
	3.42 pg/ml	85	40	-	-	1.4	0.38

## Rapid Diagnostic Tests for Cholera

Cholera is usually diagnosed clinically. Confirmation of diagnosis through culture studies is done only in reference laboratories. However, poor sampling and delays in shipment can affect the growth of cholera. Polymerase chain reaction (PCR) is more sensitive than culture, but is not always available especially in developing countries.

Currently, at least 20 different cholera rapid diagnostic tests (RDTs) are available in the market. These RDTs are based on the detection of O1 and O139 antigens using monoclonal antibodies. The RDTs have sensitivity values ranging from 58 – 100%, and specificity values ranging from 60 – 100%. The values are dependent on the test and setting where it is used.<sup>49</sup>

A review was conducted in 2012 to evaluate the developments in cholera RDTs. The review included 18 studies, majority of which were conducted in India. The most commonly evaluated RDTs were the coagglutination test (COAT), Institute Pasteur (IP) cholera dipstick, Sensitive Membrane Antigen Rapid Test (SMART), IP dipstick and Medicos. Overall, the studies were limited by the lack of standardized assessment criteria, making comparisons of diagnostic tests difficult. Most of the studies also used stool culture as a gold standard. The use of a low specificity gold standard may underestimate the specificity of the RDTs.<sup>49</sup>

## Polymerase Chain Reaction

PCR is advantageous over conventional techniques since it allows for rapid antigen detection and viral culture. It also detects viruses which cannot be cultured, such as norovirus, sapovirus and astrovirus. Because of its high sensitivity however, it can detect virus, even multiple viruses, from asymptomatic patients.

In a study involving 127 patients with acute gastroenteritis, 18 were culture positive for *Campylobacter* while 58 were PCR positive.<sup>50</sup> An investigation of real-time PCR detection of microsporidia demonstrated a lower limit of detection of  $10^2$  spores/ml stool compared to  $10^6$  spores/ml for microscopy.<sup>51</sup> Another study employed PCR to re-examine the stool samples of a case-control study on intestinal infectious disease in England which used microbiological examination to identify the etiologic agent of diarrhea. PCR increased the enteropathogen detection rate from 53% to 75% among the cases, and 19% to 42% among the controls. The detection rate increased for both viral and bacterial enteropathogens. PCR also increased the detection of multiple pathogens in the samples. Therefore, while the potential for increased diagnostic yield is substantial, the clinical significance of isolated PCR findings is also less clear.<sup>52</sup>

**Question 4A. What are the clinical parameters that would indicate presence of dehydration in children with acute infectious diarrhea?**

Physical examination findings indicative of dehydration in children which should be ascertained during the examination should include the following:

- Abnormal vital signs (tachycardia, tachypnea)
- Depressed level of consciousness
- Depressed fontanel
- Sunken eyes
- Decreased or absent tears
- Poor skin turgor
- Prolonged capillary refill time
- Abnormal respiratory pattern
- Decreased urine output

[Strong recommendation, moderate quality of evidence]

The most common complication of diarrhea is dehydration. Left untreated, it can lead to more serious complications such as hypovolemic shock and death. An accurate assessment of the degree of dehydration in infants and children is important for proper decision-making and treatment.<sup>53</sup>

The best measure of dehydration is the percentage loss of body weight.<sup>54</sup> Although this is the most accurate method of assessing dehydration, most infants and children presenting at the emergency department do not have a record of their recent weight. Because of this, several criteria using combinations of signs and symptoms were developed to assess the severity of dehydration. The panel has decided to adopt a modified set of criteria to assess the severity of dehydration based from the WHO scale, Gorelick scale, Clinical Dehydration Scale, and DHAKA scale, as shown in Table 4.

Table 4. Clinical manifestation of dehydration in children according to severity.<sup>53-60</sup>

Parameters		No signs of dehydration	Mild to Moderate dehydration	Severe dehydration
Fluid Deficit (% body weight)	Infant	<5%	5-10%	>10%
	Child	3%	6%	9%
Condition <sup>a</sup>		Well, alert	Restless, irritable	Lethargic, unconscious
Thirst		Drinks normally, not thirsty	Thirsty, drinks eagerly	Drinks poorly, not able to drink
Fontanel/Eyes <sup>a</sup>		Normal	Slightly depressed/ slightly sunken	Sunken
Tears		Present	Present or decreased	No tears
Cutaneous Perfusion/ Capillary Refill Time <sup>b</sup>		<2 seconds	Around 2 seconds	>3 seconds
Respiration		Normal	Deep, may be rapid	Deep and rapid 2mo-12mo: ≥50 breaths/min >12mo-5yrs: ≥40 breaths/min
Skin Pinch <sup>a</sup>		Goes back quickly	Goes back slowly	Goes back very slowly

<b>History of Urine Output</b>	Normal	Decreased (<0.5 ml/kg/hr in 8 hours)	Minimal (<0.3ml/kg/hr in 16 hours) or none (no urine output in 12 hours)
<b>Interpretation</b>		<b>If the patient has two or more of the above signs, there is MILD to MODERATE DEHYDRATION</b>	<b>If the patient has two or more of the above signs, there is SEVERE DEHYDRATION</b>

<sup>a</sup>These parameters are unreliable for patients with severe malnutrition. Use other parameters to distinguish malnutrition from dehydration.

<sup>b</sup>Capillary refill time is the time required for return of color after application of blanching pressure to a distal capillary bed.<sup>59</sup>

## SUMMARY OF EVIDENCE:

### Dehydration

Classification according to severity of dehydration is an essential basis for appropriate treatment. Data support the use of validated clinical dehydration scales for rapid and objective assessment of dehydration to facilitate stratification of patients into treatment categories, especially for patients whose pre-illness weights are unavailable.<sup>62-63</sup>

Evidence from a systematic review support that certain signs and symptoms are associated with dehydration. In this review, dehydration was measured using the gold standard of change in pre-hydration and post-hydration weight. The 3 best signs for assessment of dehydration are prolonged capillary refill time, abnormal skin turgor, and abnormal respiratory pattern. These signs were all included in the modified scale. The summary test characteristics for clinical findings to detect 5% dehydration is shown in Table 5.<sup>64</sup>

Table 5. Summary test characteristics for clinical findings to detect 5% dehydration.<sup>64</sup>

Finding	Total No. of Participants	Likelihood Ratio		Sensitivity	Specificity
		Value (95% CI) or Range		Value (95% CI) or Range	Value (95% CI) or Range
		Present	Absent		
Prolonged capillary refill	478	4.1 (1.7,9.8)	0.57 (0.39,0.82)	0.60 (0.29,0.91)	0.85 (0.72,0.98)
Abnormal skin turgor	602	2.5 (1.5,4.2)	0.66 (0.57,0.75)	0.58 (0.40,0.75)	0.76 (0.59,0.93)
Abnormal respiratory pattern	581	2.0 (1.5,2.7)	0.76 (0.62,0.88)	0.43 (0.31,0.55)	0.79 (0.72,0.86)
Sunken eyes	533	1.7 (1.1,2.5)	0.49 (0.38,0.63)	0.75 (0.62,0.88)	0.52 (0.22,0.81)
Dry mucous membranes	533	1.7 (1.1,2.6)	0.41 (0.21,0.79)	0.86 (0.80,0.92)	0.44 (0.13,0.74)
Cool extremity	206	1.5-18.8	0.89-0.97	0.10-0.11	0.93-1.00
Weak pulse	360	3.1-7.2	0.66-0.96	0.04-0.25	0.86-1.00
Absent tears	398	2.3 (0.9,5.8)	0.54 (0.26,1.13)	0.63 (0.42,0.84)	0.68 (0.43,0.94)
Increased heart rate	462	1.3 (0.8,2.0)	0.82 (0.64,1.05)	0.52	0.58

Sunken fontanelle	308	0.9 (0.6,1.3)	1.12 (0.82,1.54)	(0.44,0.60) 0.49 (0.37,0.60)	(0.33,0.82) 0.54 (0.22,0.87)
Poor overall appearance	398	1.9 (0.97,3.8)	0.46 (0.34,0.61)	0.80 (0.57,1.04)	0.45 (- 0.1,1.02)

CI-Confidence Interval

Blood pressure was not incorporated as part of the parameters for assessing dehydration because it was not included in the examination signs evaluated in the systematic review. In the review, signs were included if they were evaluated in 2 or more studies. Furthermore, a low blood pressure would indicate volume depletion which implies a deficit in extracellular fluid volume. In contrast, dehydration refers to a loss of total body water.<sup>65</sup>

#### 4B. What are the clinical and laboratory parameters indicative of dehydration in adults with acute infectious diarrhea?

Clinical and laboratory parameters indicative of dehydration in adults, which should be ascertained, may include the following:

- Fatigue
- Thirst
- Sunken eyes
- Orthostatic hypotension
- Increased respiratory rate
- Increased heart rate
- Cold, clammy skin
- Lethargy
- Dry oral mucosa
- Muscle weakness
- Decreased skin turgor (>2 seconds)
- Increased capillary refill time (>2 seconds)
- Decreased urine output (<0.5 ml/kg/hr)
- Reduction or increase after rehydration of 3-5% of body weight within seven days
- Increased urine specific gravity ( $\geq 1.010$ )
- Increased urine osmolality ( $>800$  mosm/kg)
- Increased serum osmolality ( $\geq 295$  mosm/kg)
- Increased BUN/creatinine ratio ( $>20$ )
- Metabolic Acidosis ( $\text{pH} < 7.35$ ,  $\text{HCO}_3^- < 22$  mmol/L)

[Strong recommendation, low quality evidence]



## SUMMARY OF EVIDENCE:

Published data regarding objective assessment of dehydration in adults are limited. The lack of literature may be due to the difficulty in performing studies on dehydration since there are no exact measurements or criteria for assessing the degree of dehydration to date.<sup>66</sup>

Evaluation of the presence and severity of dehydration is often based on “subjective” clinical parameters. Since the 1960s, only a few studies have tried to verify the accuracy of the clinical signs of dehydration. These signs include sunken eyes, loss of tongue moisture, longitudinal tongue furrows, oral mucosal dryness, upper body weakness, confusion, and speech difficulty. Some studies report that tachycardia is the most useful vital sign in detecting dehydration rather than orthostatic hypotension.<sup>60,67,68</sup>

Several studies have highlighted the use of change in body weight over a short time period to assess fluid status. These studies concluded that a reduction of  $\geq 3\%$  of body weight within seven days may be considered to be a clear indication of dehydration, as would an increase of  $\geq 3\%$  of body weight on rehydration within seven days. However, this parameter relies on obtaining more than one measurement, and the measurements need to be truly accurate with considerations made for possible associated conditions such as edema or third-spacing.<sup>69,70</sup>

Dehydration must be differentiated from malnutrition, since one of the symptoms of malnutrition is also unintentional weight loss. Malnutrition is defined as “a state of nutrition in which a deficiency, or excess, of energy, protein and micronutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome.”<sup>71</sup> It is possible for a person who has normal or above normal weight to be malnourished.

The best available reference standard in assessing hydration status, against which other parameters are compared, is directly measured serum or plasma osmolality. Serum osmolality values of  $\geq 295$  mOsm/kg suggests dehydration.<sup>72,73</sup>

A 2015 systematic review found that fatigue, urine osmolality and axillary moisture showed *some potential* in diagnosing dehydration.<sup>73</sup> At present however, there is no strong evidence for the use of any single symptom, sign, or test to diagnose dehydration in older people.

The parameters that may be used to diagnose and classify dehydration in adults are summarized in Tables 6 and 7.

Table 6. Clinical manifestations of dehydration in adults according to severity.<sup>73-76</sup>

Parameters	Mild dehydration	Moderate dehydration	Severe dehydration
Fatigue	+/-	+	+
Thirst	+/-	+	+
Sunken eyes	-	+	+
Blood pressure	Normal	Orthostatic hypotension	Shock
Respiratory rate (breaths per minute)	Normal	21 - 25	$\geq 25$
Pulse rate (beats per minute) <sup>a</sup>	$\geq 80$	$\geq 100$	Faint or thready pulses
Peripheral circulation	Warm extremities	Cold, clammy skin	
Level of	Alert	Lethargic	Coma or stupor

<b>consciousness</b>			
<b>Oral mucosa</b>	Moist	Dry	
<b>Muscle weakness</b>	None	Mild to moderate	Severe
<b>Skin turgor<sup>b</sup></b>	≤2 seconds	>2 seconds	
<b>Capillary refill time<sup>c</sup></b>	≤2 seconds	>2 seconds	
<b>Urine output (ml/kg/hr)</b>	≥0.5	<0.5	

<sup>a</sup>These values are appropriate for assessing severity of dehydration if the patient has no fever

<sup>b</sup>Skin turgor is best assessed at the anterior forearm, anterior thigh, anterior chest, subclavicular area, or sternum

<sup>c</sup>Capillary refill time should be assessed with the examiner's middle finger at the same level as the patient's heart

Table 7. Other parameters used in assessing dehydration in adults.<sup>73,75-77</sup>

Table 7: Other parameters used in assessing dehydration in adults.			
Parameters	Mild dehydration	Moderate dehydration	Severe dehydration
Body Weight Change	Reduction of 3-5% of body weight in ≤7 days or Increase of 3-5% of body weight in ≤7 days as an indication that a person was dehydrated before rehydration	Change of >5% of body weight	
Urine Specific Gravity	≥1.010	≥1.020	
Urine Osmolality (mosm/kg)	>800		
Serum Osmolality (mosm/kg)	295-300	>300	
BUN/Creatinine Ratio		>20	
Metabolic acidosis (pH <7.35, HCO3 <22 mmol/L)	-	-	+

**Question 5. What laboratory test should be done to assess for the presence of complications of acute infectious diarrhea?**

Complications such as acute kidney injury and electrolyte imbalances can occur in pediatric and adult patients with acute infectious diarrhea. The following laboratory tests may be requested for patients suspected to have complications of acute infectious diarrhea:

- Complete blood count
- Urinalysis
- Serum electrolytes (Na, K, Cl)
- BUN and creatinine
- Serum bicarbonate or total CO<sub>2</sub> (if available) or ABG (optional)

[Strong recommendation, low quality of evidence]

## SUMMARY OF EVIDENCE

### Acute Kidney Injury (AKI)

Acute diarrhea is an important cause of preventable AKI. Delayed restoration of gastrointestinal losses may result in AKI due to decreased blood supply to the kidneys. This condition is usually marked by a rise in serum creatinine or blood urea nitrogen (BUN). Immediately after kidney injury however, creatinine and BUN levels may be normal, and the only sign of AKI may be decreased urine output. With volume repletion, the kidney dysfunction can usually be reversed.

The Kidney Disease Improving Global Outcomes (KDIGO) 2012 clinical practice guidelines define AKI as any of the following:<sup>78</sup>

- Increase in serum creatinine by  $\geq 0.3$  mg/dL within 48 hours
- Increase in serum creatinine to  $\geq 1.5$  times from baseline within the last 7 days
- Urine output  $< 0.5$  ml/kg/hr for 6 hours

The stages of AKI based on the KDIGO guidelines are shown in Table 8.

Table 8. Stages of acute kidney injury in adults.<sup>78</sup>

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline or $\geq 0.3$ mg/dL increase	$< 0.5$ ml/kg/hr for 6 hours
2	2-2.9 times baseline	$< 0.5$ ml/kg/hr for 12 hours
3	3 times baseline or Increase in serum creatinine to $\geq 4$ mg/dL or Initiation of renal replacement therapy	$< 0.3$ ml/kg/hr for 24 hours or No urine output for $\geq 12$ hours

Several studies evaluating the outcome of patients with AKI in relation to the timing of referrals to nephrologists have been conducted. These studies show that patients with AKI who were not referred or were referred late have increased risk for morbidity and mortality. In one study involving 366 AKI patients, delayed nephrology consult (defined as consult done 2 days after the onset of AKI) was associated with higher mortality rate (OR=4.04; 95% CI 1.60, 10.17) and increased dialysis dependence on hospital discharge (OR=3.00; 95% CI 1.43, 6.29).<sup>79</sup> Since AKI is a serious and potentially life-threatening complication, immediate referral to a kidney specialist at the first sign of AKI is recommended.

### Electrolyte Imbalances

Electrolyte problems that may complicate acute diarrhea include hyponatremia, hypernatremia and hypokalemia. Symptoms often correspond to the degree of electrolyte imbalance.

#### Hyponatremia

Hyponatremia is often caused by inappropriate use of oral fluids that are low in sodium, such as water, juice and soda. Table 9 shows the symptoms of hyponatremia according to severity.

Table 9. Symptoms associated with hyponatremia.<sup>80</sup>

<b>Stratification</b>	<b>Serum Level</b>	<b>Symptoms</b>
<b>Mild</b>	130 – 135 meq/L	Usually non-specific:  Headache, nausea, vomiting, fatigue, gait disturbances, confusion, restlessness, irritability
<b>Moderate</b>	120 – 129 meq/L	
<b>Severe</b>	< 120 meq/L	Seizure, obtundation, coma, respiratory arrest

Hospital treatment and close monitoring is recommended for patients with severe hyponatremia and for symptomatic patients regardless of the degree of hyponatremia. Oral rehydration salts (ORS) solution is safe and effective therapy for nearly all children with mild to moderate hyponatremia.<sup>81</sup>

### **Hypernatremia**

Gastrointestinal losses may result in hypernatremia when water intake is insufficient. Osmotic diarrhea may also result in hypernatremia since the gastrointestinal losses that are mostly water, with lower sodium concentration compared to plasma. Table 10 shows the symptoms of hypernatremia according to severity.

Table 10. Symptoms associated with hypernatremia.

<b>Stratification</b>	<b>Serum Level</b>	<b>Symptoms</b>
<b>Mild</b>	145 – 150 meq/L	Usually asymptomatic
<b>Moderate</b>	151 – 158 meq/L	Lethargy, weakness, irritability
<b>Severe</b>	>158 meq/L	Twitching, hyperreflexia, seizure, coma

Clinical findings of hypernatremia in children include a “doughy” feeling rather than tenting when testing for skin turgor, increased muscle tone, irritability, and a high-pitched cry.<sup>82</sup> Patients with hypernatremia usually have underlying conditions that impair their ability to respond to thirst. These patients usually require hospitalization to correct their hypernatremia.

### **Hypokalemia**

Severe diarrhea is the most common extra-renal cause of hypokalemia. Although the absorption of potassium is not disturbed by diarrhea, there is increased fecal loss of potassium.<sup>83</sup>

Mild hypokalemia usually does not cause symptoms. Patients become symptomatic when their serum potassium levels are critically low. Table 11 shows the symptoms of hypokalemia according to severity.

Table 11. Symptoms associated with hypokalemia.

<b>Stratification</b>	<b>Serum Level</b>	<b>Symptoms</b>
<b>Mild</b>	3-3.5 meq/L	Usually asymptomatic

<b>Moderate</b>	2.6-2.9 meq/L	Muscle weakness, muscle cramps, fatigue
<b>Severe</b>	<2.6 meq/L	Rhabdomyolysis, bradycardia, arrhythmia, respiratory failure

Overcorrection of potassium may also lead to fatal consequences; hence, potassium replacement should be done in the hospital with the supervision of a medical doctor. It is recommended that patients be referred immediately to a tertiary hospital and a specialist for prompt management and close monitoring.

### **Acid – Base Disturbances**

Metabolic acidosis is a dreaded complication of acute infectious diarrhea. It is usually diagnosed when the serum pH is <7.35 and the serum bicarbonate concentration is low (often defined as  $\text{HCO}_3^-$  <22 meq/L).

Large volume losses from diarrhea can lead to a significant decrease in extracellular fluid volume, and consequently, a reduction in glomerular filtration rate. Lactic acidosis may occur as a result of tissue hypoperfusion.<sup>84</sup>

Acute diarrhea may also cause hyperchloremic metabolic acidosis or normal anion gap metabolic acidosis. This is a typical finding in patients with cholera due to the excessive loss of bicarbonate in the diarrheal fluid.<sup>85</sup> It may also be a result of giving large quantities of chloride-containing solutions during hypovolemia and shock.<sup>86</sup>

Treatment should be directed at reversing the underlying pathology. Most clinicians initiate treatment when the bicarbonate level is very low ( $\text{HCO}_3^-$  <10 meq/L) and the pH is <7.10, since symptoms such as myocardial depression, decreased catecholamine efficacy, and arrhythmias are usually noted at these levels.

Other clinical manifestations of metabolic acidosis include headache, lethargy, mental confusion, anorexia, nausea, vomiting, and deep and rapid respirations (Kussmaul respirations).

### **Hemolytic – Uremic Syndrome (HUS)**

Another possible complication of diarrhea is HUS, which is best explained by microvascular injury caused by Shiga-toxin-producing organisms such as *Shigella dysenteriae* and Shiga-toxin-producing *E. coli* (STEC serotype O157:H7).<sup>87-88</sup> HUS manifests as non-immune hemolytic anemia, low platelet count, and renal impairment following gastroenteritis caused by the above-mentioned organisms.<sup>89</sup> Diagnosis is established by the following laboratory tests: complete blood count, peripheral blood smear and renal function tests (creatinine or BUN).

Although most patients with diarrhea-associated HUS recover from the acute episode, there is potential for long-term renal impairment and extra-renal complications (e.g. seizures, colitis, etc.). Early recognition and prompt supportive therapy with fluid restriction, renal replacement therapy and transfusion of blood products are important.<sup>90-91</sup> Patients suspected to have HUS warrant immediate referral to a specialist for further evaluation and management.

## Question 6. What is the role of colonoscopy in the evaluation of acute infectious gastroenteritis in adult and pediatric patients?

Colonoscopy is not warranted in the initial evaluation of acute infectious diarrhea.

[Strong recommendation, moderate quality of evidence]

### SUMMARY OF EVIDENCE

The value of colonoscopy in the diagnosis of acute infectious colitis was evaluated in a 1994 study which prospectively compared cultures from colonoscopy-obtained biopsies with stool cultures among 20 patients with acute diarrhea. The study reported that the sensitivity of biopsy culture is 50%, while the sensitivity of stool culture is 20%.<sup>92</sup> Another study showed that the sensitivity of stool culture is 58%.<sup>93</sup> More recent studies with similar objectives were not found. The high cost of colonoscopy, as well as the possible complications of the procedure, limits its usefulness in the initial evaluation of acute infectious diarrhea. The use of colonoscopy to obtain samples for culture in the evaluation of infectious diarrhea is therefore not recommended.

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## II. TREATMENT (CHILDREN)

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**Question 1A. What are the criteria for admission among children presenting with acute infectious diarrhea?**

1. Children with acute infectious diarrhea who have any of the following signs and symptoms should be admitted:
  - *Based on clinical history*: unable to tolerate fluids, suspected electrolyte abnormalities, or conditions for safe follow-up and home management are not met\*
  - *Based on physical findings*: altered consciousness, abdominal distention, respiratory distress, or hypothermia (temperature <36°C)[Strong recommendation, very low to low quality of evidence]
  
2. Children with acute infectious diarrhea who have any of the following co-existing medical conditions should be admitted:
  - Co-existing infections such as pneumonia, meningitis/encephalitis, or sepsis
  - Moderate to severe malnutrition
  - Suspected surgical condition\*[Strong recommendation, very low to low quality of evidence]

\*No studies were found regarding suspected surgical condition and unmet conditions for safe follow-up and home management, so these are considered as best practice statements.

### Summary of Evidence

No studies that investigate factors warranting admission among pediatric patients with acute infectious diarrhea were found. Based on consensus and expert opinion, various international and foreign guidelines listed admission criteria for pediatric patients with acute gastroenteritis. These criteria are shown in Table 1.

Table 1. Recommendations for admission criteria for children with diarrhea.<sup>1-4</sup>

ESPGHAN/ESPID 2014	WGO 2012	WHO 2005	AAP/CDC 2003
<ul style="list-style-type: none"> <li>• Shock</li> <li>• Severe dehydration (&gt;9% of body weight)</li> <li>• Neurological abnormalities (lethargy, seizures, etc.)</li> <li>• Intractable or bilious vomiting</li> <li>• Failure of oral rehydration</li> <li>• Suspected surgical condition</li> <li>• Conditions for a safe follow-up and home management are not met</li> </ul>	<ul style="list-style-type: none"> <li>• Caregiver's report of signs consistent with dehydration</li> <li>• Changing mental status</li> <li>• History of premature birth, chronic medical conditions, or concurrent illness</li> <li>• Young age (&lt;6 months or &lt;8 kg weight)</li> <li>• Fever <math>\geq 38^{\circ}\text{C}</math> for infants &lt;3 months old or <math>\geq 39^{\circ}\text{C}</math> for children aged 3–36 months</li> <li>• Visible blood in stool</li> <li>• High-output diarrhea, including frequent and substantial volumes</li> <li>• Persistent vomiting, severe dehydration, persistent fever</li> <li>• Suboptimal response to oral rehydration therapy (ORT) or inability of caregiver to administer ORT</li> <li>• No improvement within 48 hours—symptoms exacerbate and overall condition gets worse</li> <li>• No urine in the previous 12 hours</li> </ul>	<ul style="list-style-type: none"> <li>• Children with a serious systemic infection, such as pneumonia or sepsis</li> <li>• Children with signs of dehydration</li> <li>• Infants below 4 months of age</li> </ul>	<ul style="list-style-type: none"> <li>• Caregivers cannot provide adequate care at home</li> <li>• Substantial difficulties exist in administering ORT, including intractable vomiting, ORS refusal, or inadequate ORS intake</li> <li>• Concern exists for other possible illnesses complicating the clinical course</li> <li>• ORS treatment fails, including worsening diarrhea or dehydration despite adequate volumes</li> <li>• Severe dehydration (&gt;9% of body weight) exists;</li> <li>• Social or logistical concerns exist that might prevent return evaluation, if necessary</li> <li>• Factors such as young age, unusual irritability or drowsiness, progressive course of symptoms, or uncertainty of diagnosis exists that might indicate a need for close observation.</li> <li>• In addition, studies of mortality caused by acute diarrhea in the United States have identified prematurity, young maternal age, black race, and rural residence as risk factors for suboptimal outcome; thus, these factors should also be considered when deciding if hospital care is required</li> </ul>

Factors that increase the risk of mortality among patients with acute infectious diarrhea were used as admission criteria since these patients would need immediate and close medical attention. Seventeen observational studies that evaluated various clinical and laboratory parameters as risk factors for mortality in admitted children with acute diarrhea were found. Most of these studies were case control and cohort studies conducted in developing countries. However, no local studies were found. The studies are shown in Table 2.

Table 2. Summary of studies on risk factors for mortality in pediatric patients with acute diarrhea.<sup>5-21</sup>

Study	Study Design	Patients	No. of participants	Study Period	Location
Abhulimhen-Iyoha 2013	Cross-sectional study	Admitted children 29 days–59 months old	135	July 2010-January 2012	Benin
Bennish 1990	Case control	Adult and children admitted with <i>Shigella</i> on stool culture (mostly children)	201	1974-1988	Dhaka, Bangladesh
Bhattacharya 1995	Case control	Admitted children $\leq 2$ years old with acute watery diarrhea	379	October 1991-June 1993	Calcutta, India
Bhutta 1996	Case control	Admitted children with primary diagnosis of diarrhea	126	1989-1993	Karachi, Pakistan
Chisti 2011	Prospective cohort	Admitted children aged 0-59 months with diarrhea	258	September-December 2007	Dhaka, Bangladesh
Creek 2010	Cross-sectional study	Admitted children <5 years old with diarrhea	153	February 20 - March 10, 2006 (conducted during an outbreak)	Botswana
Griffin 1988	Case control	Children <24 months old admitted for non-bloody diarrhea	99	1983-1984	Lesotho
Islam 1986	Case control	Admitted children with diarrhea	692	July 1980-June 1981	Dhaka, Bangladesh

Kilgore 1995	Retrospective cohort	Deaths among children 1 month—4 years old compiled by the National Center for Health Statistics, CDC	14,137	1968-1991	USA
Lindtjørn 1991	Case control	Children <5 years old admitted for non-bloody diarrhea	105	September 1985-August 1987	Ethiopia
Nathoo 1998	Retrospective cohort	Children aged 1 month—12 years old admitted for bloody diarrhea	312	January 1993-June 1994	Zimbabwe
O'Reilly 2012	Retrospective cohort	Children <5 years old admitted for diarrhea	1,146	May 2005-May 2007	Western Kenya
Sachdev 1991	Prospective cohort	Children <5 years old admitted for diarrhea	382	June 1988- Aug 1988	New Delhi, India
Santhanakrishnan 1987	Prospective cohort	Admitted infants and children up to 3 years old with acute watery diarrhea or dysentery lasting $\geq 5$ days	575	Not stated in the article	Madras, India
Teka 1996	Case control	Admitted patients with diarrhea <5 years old	184	1990-1994	Dhaka, Bangladesh
Uysal 2000	Retrospective cohort	Children 1 month – 5 years old admitted for diarrhea	400	January 1995-December 1997	Turkey
Van den Broek 2005	Case control	Admitted severely-malnourished children with diarrhea and positive stool culture for <i>Shigella</i> , age <4 years old.	200	December 1993-January 1999	Dhaka, Bangladesh

These studies evaluated the following clinical and laboratory findings to determine their effect on the risk of mortality among children with acute diarrhea.

### ***Poor oral intake***

Poor oral intake was evaluated by three studies through direct and indirect parameters. One study showed that anorexia was a significant risk factor for mortality among children admitted for diarrhea (OR=3.90; 95% CI 1.40, 10.87).<sup>8</sup> A study in US showed that among children 1—11 months old with diarrhea, nausea/vomiting was associated with increased mortality (RR=2.5; 95% CI 1.9, 3.2).<sup>13</sup> The third study showed increased risk of mortality among patients with diarrhea who vomited >2 times/day (OR=2.4; 95% CI 1.4, 4.0), patients not given ORS (OR=2.1; 95% CI 1.2, 3.6), and patients in whom breastfeeding was withdrawn during diarrhea (OR=6.8; 95% CI 3.8, 12.2).<sup>7</sup>

### ***Moderate/ severe dehydration***

Three studies have shown that moderate or severe dehydration significantly increases the risk of mortality in children. Nathoo, et. al reported that severe dehydration is a significant risk factor for mortality (OR=1.70; 95% CI 1.15, 2.53).<sup>15</sup> Two studies showed that moderate or severe dehydration is a significant risk factor (OR=4.10; 95% CI 1.62, 16.93 by Abhulimhen-Iyoha, et. al and OR=8.17; 95% CI 1.53, 43.67 by Uysal, et. al).<sup>5,20</sup>

Other studies that evaluated findings related to dehydration were also found. Chisti, et. al showed that absent peripheral pulses even after complete rehydration increased the risk of mortality by 10 times (OR=10.9; 95% CI 2.1, 56.8).<sup>9</sup> Another study reported that dehydration that failed to improve after 12 hours in the hospital increased the risk of mortality by 16 times (RR=16.0; 95% CI 2.4, 170.1).<sup>11</sup> Bhattacharya, et. al showed that passage of stools >8 times/day increased the risk of mortality by four times (OR=4.1; 95% CI 2.4, 7.0).<sup>7</sup> Abhulimhen-Iyoha, et.al also reported increased risk of mortality among patients with diarrhea episodes >6 times/day (OR=23.63; 95% CI 6.50, 55.84) and diarrhea lasting >3 days (OR=3.63; 95% CI 1.07, 12.33).<sup>5</sup>

### ***Altered consciousness***

Altered consciousness in patients with acute diarrhea was associated with increased mortality in two studies. Bhutta, et. al reported drowsiness as a significant risk factor (OR=4.41; 95% CI 1.27, 15.35)<sup>8</sup> while another study showed that lethargic or comatose patients have higher risk of death (OR=4.80; 95% CI 1.64, 14.04).<sup>6</sup>

### ***Respiratory distress***

One study (Bhutta, 1996) showed that patients with respiratory distress have significantly increased risk of mortality (OR=7.03; 95% CI 1.35, 36.63).<sup>8</sup>

### ***Hypothermia***

Two studies<sup>15,21</sup> showed that hypothermia, defined as temperature <36°C, is a significant risk factor for mortality. Fever was also evaluated in 2 studies as a risk factor; however, the evidence was mixed. A case control study of 21 cases with 85 controls (Lindtjörn, 1991)<sup>14</sup> demonstrated that fever

(temperature >38°C) was a significant risk factor for mortality (adjusted OR 4.9, p-value <0.05). In contrast, a cohort study involving 1,146 children showed that undocumented fever is not associated with mortality (OR=0.8; 95% CI 0.5, 1.2).<sup>16</sup>

### ***Abdominal distention***

Abdominal distention was associated with increased risk of mortality (OR=1.67; 95% CI 1.16, 2.41 (Nathoo, et. al)<sup>15</sup> and OR=4.31; 95% CI 1.20, 16.19 (Bhutta, et. al)<sup>8</sup> in 2 studies.

### ***Electrolyte imbalance***

Four studies showed increased risk of death among patients with electrolyte imbalance. Low serum sodium (Na <120 to 130mmol/L), high serum sodium (Na >150), low serum bicarbonate (bicarbonate <20mmol/L), and high serum potassium (K >5.5mmol/L) increased the risk of mortality in pediatric patients with diarrhea.<sup>9,12,13,15</sup>

Kilgore et. al reported that electrolyte imbalance was one of the most common complications of diarrhea and a significant risk factor for mortality (RR 2.7, 95% CI 2.4-2.9) among children 1-11 months old.<sup>13</sup>

### ***Co-existing illnesses***

Acute diarrhea in children may be complicated by co-existing illness or may be the presenting symptom of an infection (e.g. sepsis). Various studies evaluated the presence of co-existing illnesses as a risk factor for mortality in children with diarrhea.

Two studies showed that dual diagnosis with other infectious diseases increased the risk of mortality in children with diarrhea. Sachdev et. al reported that co-occurrence of a major infection such as pneumonia, septicemia, or meningitis was a significant risk factor for mortality (OR=4.7; 95% CI 3.9, 5.6).<sup>17</sup> Griffin et. al similarly showed that co-existing pneumonia, measles, sepsis, or meningitis was a significant risk factor (RR=7.7; 95% CI 2.5, 24.2).<sup>11</sup>

Four studies evaluated the co-occurrence of pneumonia in children with diarrhea. Two studies conducted in Bangladesh showed increased risk of mortality with co-occurrence of pneumonia.<sup>9,21</sup> A study done in Benin reported that co-occurrence of pneumonia increased the risk of mortality by almost 20 times (OR=16.38; 95% CI 3.36, 97.54).<sup>5</sup> A study done in the US (Kilgore 1995) similarly showed increased risk of mortality by 5 times among children 1 month – 11 months old (RR=4.8; 95% CI 3.9, 5.9) and by 3 times among children 12 month—59 months old (RR=3.1; 95% CI 2.2,4.4).<sup>13</sup>

A case-control study conducted in Bangladesh determined the association of pneumonia and one other co-morbid illness with diarrhea mortality. The presence of pneumonia and protein energy malnutrition increased the risk of mortality 2 times (OR=2.17; 95% CI 1.02, 4.60), while the presence of pneumonia and sepsis increased the risk of mortality by >20 times (OR=21.16; 95% CI 5.09, 87.92).<sup>12</sup>

Co-occurrence of sepsis with acute diarrhea also increases the risk of mortality. Islam and Khanshowed that co-occurrence of sepsis increased the risk of mortality by >2 times (OR=2.42; 95% CI 1.12, 5.24).<sup>12</sup> Another study conducted in Turkey similarly showed that sepsis increased mortality risk by almost 40 times (OR=37.26; 95% CI 6.94, 200.06).<sup>20</sup> A study done in Pakistan showed that positive blood culture (majority of which were *Enterobacteriaceae*) increased the mortality risk by >8 times (OR=8.71; 95% CI 2.47, 30.65).<sup>8</sup>

Malnutrition among children with acute diarrhea has been associated with significant risk of mortality, with OR ranging from 1.9-84.2 based on several observational studies done in India,<sup>7,17,18</sup> Bangladesh<sup>9,19</sup>, Benin<sup>5</sup>, Kenya<sup>16</sup>, and Botswana<sup>10</sup>.

### Conditions for a safe follow-up and home management, suspected surgical condition

Although no studies were found on their effect on mortality, unmet conditions for a safe follow-up and home management and presence of suspected surgical condition were included in the criteria by the guideline panel. These factors were deemed by the panel as important considerations to prevent possible morbidity and mortality.

Table 3 summarizes the significant risk factors for mortality among children with diarrhea. All the evidence were graded as VERY LOW due to indirectness - the studies do not directly answer the question whether the clinical symptoms, laboratory findings, and other factors warrant admission, but rather, whether these factors lead to patient mortality. There could also be bias in the included studies since the recruited participants were already admitted; thus, results may be overestimated. Lastly, some results are imprecise due to the wide confidence intervals.

Table 3. Risk factors for mortality in pediatric patients presenting with acute diarrhea

Parameter	OR/RR (95% CI)	Study
Anorexia	OR 3.90 (1.40, 10.87)	Bhutta 1996
Nausea and vomiting	RR 2.5 (1.9, 3.2)	Kilgore 1995
Frequency of vomiting (>2 times/day)	OR 2.4 (1.4, 4.0)	Bhattacharya 1995
Non-usage of ORS	OR 2.1 (1.2, 3.6)	Bhattacharya 1995
	OR 16.52 (3.81, 41.58)	Abhulimhen-lyoha 2013
Severe dehydration	OR 1.70 (1.15, 2.53)	Nathoo 1998
Moderate/severe dehydration	OR 4.10 (1.62, 16.93)	Abhulimhen-lyoha 2013
	OR 8.17 (1.53, 43.67)	Uysal 2000



Absent peripheral pulses after rehydration	OR 10.9 (2.1, 56.8)	Chisti 2011
Dehydration not improving after 12 hours	RR 16.0 (2.4 to 170.1)	Griffin et.al 1998
Diarrhea >8 times/day	OR 4.1 (2.4, 7.0)	Bhattacharya 1995
Diarrhea >6 times/day	OR 23.63 (6.5, 55.84)	Abhulimhen-lyoha 2013
Diarrhea >3 days	OR 3.63 (1.07, 12.33)	Abhulimhen-lyoha 2013
Altered consciousness (drowsiness)	OR 4.41 (1.27, 15.35)	Bhutta 1996
Altered consciousness (lethargy or coma)	OR 4.80 (1.64, 14.04)	Bennish 1990
Respiratory distress	OR 7.03 (1.35, 36.63)	Bhutta 1996
Hypothermia	OR 5.7 (1.5, 22.1)	van den Broek 2005
	OR 2.12 (1.33, 3.39)	Nathoo 1998
Abdominal distention	OR 1.67 (1.16, 2.41)	Nathoo 1998
	OR 4.31 (1.20, 16.19)	Bhutta 1996
Sodium <120 mmol/L	OR 1.57 (1.17, 2.11)	Nathoo 1998
Sodium <130 mmol/L	OR 1.97 (1.31, 2.99)	Islam 1986
Hypernatremia >150 mmol/L	OR 15.8 (3.00, 81.80)	Chisti 2011
Bicarbonate <20 mmol/L	OR 1.90 (1.28, 2.57)	Islam 1986
Anion gap >14.9	OR 1.76 (1.21, 2.57)	Islam 1986
Hyperkalemia >5.5 mmol/L	OR 1.74 (1.01, 1.97)	Nathoo 1998
Electrolyte disorder	RR 2.7 (2.4, 2.9)	Kilgore 1995
Major infection (pneumonia, sepsis, meningitis)	OR 4.7 (3.9, 5.6)	Sachdev 1991
Major infection (pneumonia, measles, sepsis, meningitis)	RR 7.7 (2.5, 24.2)	Griffin 1998
Pneumonia	OR 2.5 (1.1, 5.5)	van den Broek 2005
	OR 17.8 (3.7, 84.5)	Chisti 2011
	OR 16.38 (3.36, 97.54)	Abhulimhen-lyoha 2013

Pneumonia among 1—11 months old	RR 4.8 (3.9, 5.9)	Kilgore 1995
Pneumonia among 12—59 months old	RR 3.1 (2.2, 4.4)	Kilgore 1995
Pneumonia and protein energy malnutrition	OR 2.17 (1.02, 4.60)	Islam 1986
Pneumonia and sepsis	OR 21.16 (5.09, 87.92)	Islam 1986
Sepsis	OR 2.42 (1.12, 5.24)	Islam 1986
	OR 37.26 (6.94, 200.06)	Uysal 2000
Positive blood culture	OR 8.71 (2.47, 30.65)	Bhutta 1996
Kwashiorkor	RR 2.0 (1.1 to 3.7)	Creek 2010
Protein <50 g/L	OR 4.5 (2.01, 10.47)	Islam 1986
Severe malnutrition	OR 3.1 (1.6, 5.9)	Bhattacharya 1995
	OR 84.2 (9.1, 775.9)	Teka 1996
	OR 7.9 (1.8, 34.8)	Chisti 2011
Severe wasting ( $\leq 50\%$ weight for age)	OR 3.3 (2.7, 4.0)	Sachdev 1991
Severe stunting ( $\leq 85\%$ height for age)	OR 1.9 (1.6, 2.3)	Sachdev 1991
Malnutrition	OR 4.2 (2.1, 8.7)	O'Reilly 2012
	OR 3.06 (1.79, 11.89)	Abhulimhen-Iyoha 2013
Birth weight <2 kg	OR 13.6 (5.0, 34.3) <sup>a</sup>	Santhanakrishnan 1987

<sup>a</sup>OR of neonatal deaths.

**Question 2. How should dehydration among children with acute infectious diarrhea be managed?**

**1. The following is the recommended management for each level of dehydration**

**No Signs of Dehydration**

- Reduced osmolarity oral rehydration solution (ORS) is recommended to replace ongoing losses. [Strong recommendation, moderate quality of evidence]
- If commercial ORS is not available, homemade ORS may be given. (4-5 teaspoons of sugar and 1 teaspoon of salt in 1 liter of clean drinking water)

**Mild to Moderate Dehydration**

- Reduced osmolarity oral rehydration solution (ORS) is recommended to replace ongoing losses. [Strong recommendation, moderate quality of evidence]
- If oral rehydration is not feasible, administration of OR via nasogastric tube is preferred over IV hydration. [Strong recommendation, low quality of evidence]

**Severe Dehydration**

- Rapid intravenous rehydration is recommended with plain Lactated Ringer's (LR) Solution or 0.9% Sodium Chloride. [Strong recommendation, low quality of evidence]

**2. Monitoring**

- Check the child from time to time during rehydration to ensure that ORS is being taken satisfactorily and that signs of dehydration are not worsening. Evaluate the child's hydration status at least hourly.

**3. For breastfed infants, breastfeeding should be continued in addition to hydration therapy.**

[Strong recommendation, moderate quality of evidence]

**4. Carbonated, sweetened, caffeinated and sports beverages are not recommended for fluid replacement.**

[Good practice statement]

**SUMMARY OF EVIDENCE**

**Reduced osmolarity oral rehydration solution**

Multiple studies have been published on the effectiveness of ORS for the treatment of mild to moderate dehydration secondary to diarrhea. ORS use has been associated with lesser adverse

events and reduced length of hospital stay.<sup>22,23</sup> (Atherly, 2002) It is important to note that oral rehydration is also the recommended treatment for severely malnourished patients.<sup>24</sup>

Based on a systematic review of 13 trials involving 1,551 participants with acute gastroenteritis, treatment failure was lower in the intravenous therapy group compared to the oral rehydration group [risk difference (RD)=0.04; 95% CI 0.01, 0.07]. A subgroup analysis of 5 trials conducted among outpatients with mostly mild to moderate dehydration showed no difference in the risk of treatment failure between oral and intravenous rehydration. The risk of phlebitis was higher in the IV group, while the risk of paralytic ileus was higher in the oral rehydration group.<sup>25</sup> (Hartling L, 2006) Although intravenous rehydration was found to be more effective than oral rehydration, the difference is minimal. Since oral rehydration is non-invasive, there is less risk for complications compared to intravenous hydration. Thus, oral rehydration is still recommended for children with acute infectious diarrhea presenting with mild to moderate dehydration.

Reduced osmolarity ORS is the recommended first-line treatment for all children with no and some signs of dehydration.<sup>1,3,25</sup> A meta-analysis of 11 randomized controlled trials (RCTs) involving 1,996 children with acute diarrhea showed lower risk for the need of IV therapy among those given reduced osmolarity ORS compared to standard ORS (OR=0.59; 95% CI 0.45, 0.79). Use of reduced osmolarity ORS was also associated with less stool output and less vomiting compared to standard ORS.<sup>26</sup>

Reduced osmolarity ORS has a lower treatment failure rate that is not significantly different from the failure rate of intravenous hydration. Subgroup analysis of a systematic review that compared oral and IV hydration showed that reduced osmolarity ORS had the same risk for treatment failure with intravenous rehydration, based on 6 trials of 729 children with diarrhea (RD=0.01; 95% CI -0.01, 0.02).<sup>25</sup>

The use of polymer-based ORS, which is prepared using rice or wheat, has also been introduced as an alternative to glucose-based ORS packets because of its supposed slower release of glucose. A Cochrane review of 8 trials involving 752 participants showed that polymer-based ORS may lower the stool output by 24ml/kg and the duration of diarrhea by 8 hours compared to reduced osmolarity glucose-based ORS. However, this finding is underpowered so there was insufficient evidence to conclude that one is better than the other.<sup>27</sup>

### **Rapid infusion in severe dehydration**

An RCT involving 150 children showed that rapid intravenous hydration is as effective as standard rehydration (given over 24 hours) in the treatment of dehydration in children with diarrhea.<sup>1,28</sup> Hence, rapid IV infusion is recommended for severe dehydration.

### **TREATMENT PROTOCOL**

The technical working group and expert panel have agreed to adapt and modify the recommendations of the WHO and ESPGHAN for the treatment of diarrhea.<sup>1,3</sup> Figures 1 and 2 show the algorithm for fluid resuscitation of children according to level of dehydration.

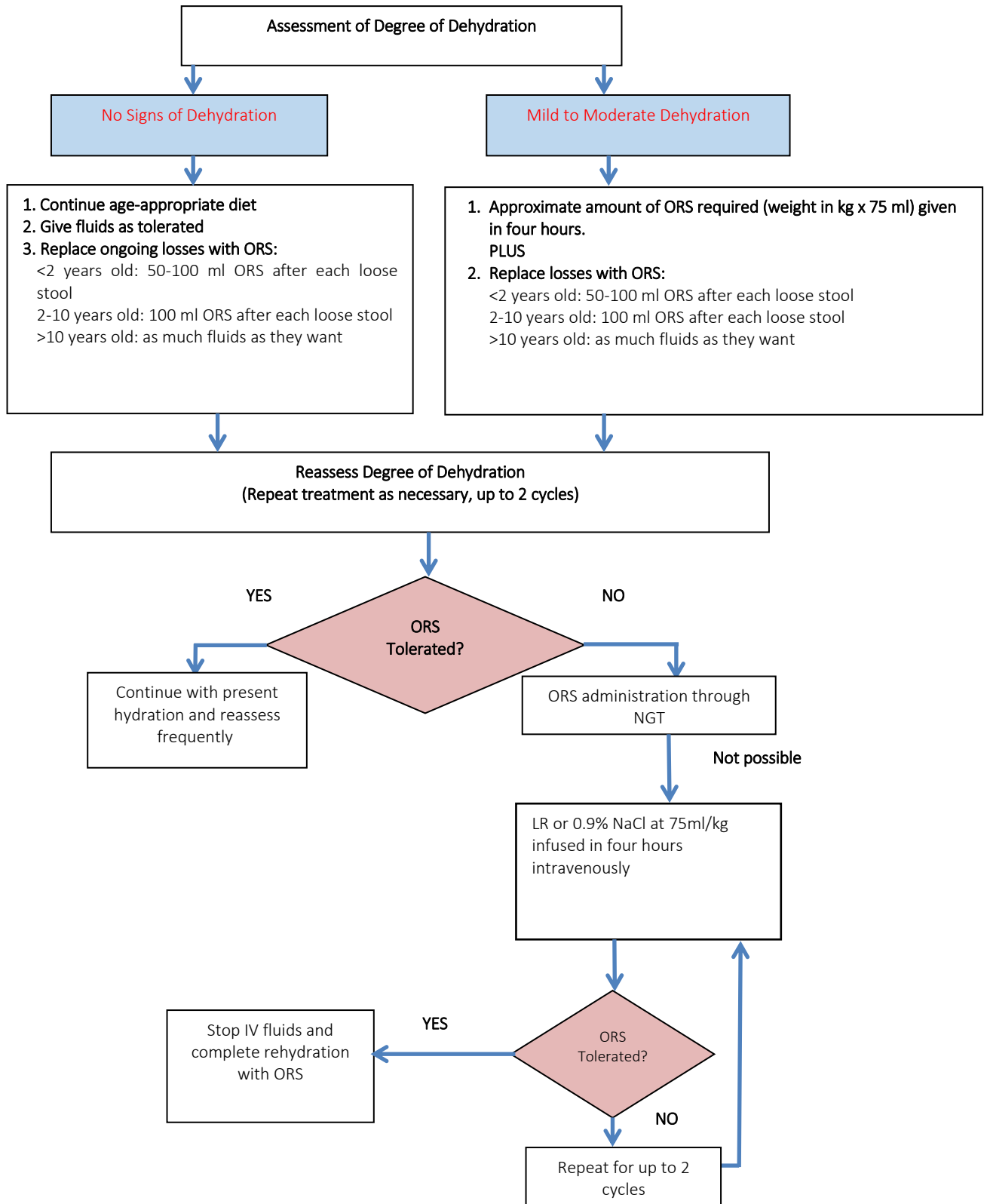


Figure 1. Protocol for no signs of dehydration and mild to moderate dehydration. (Adapted with modifications<sup>1,24</sup>)

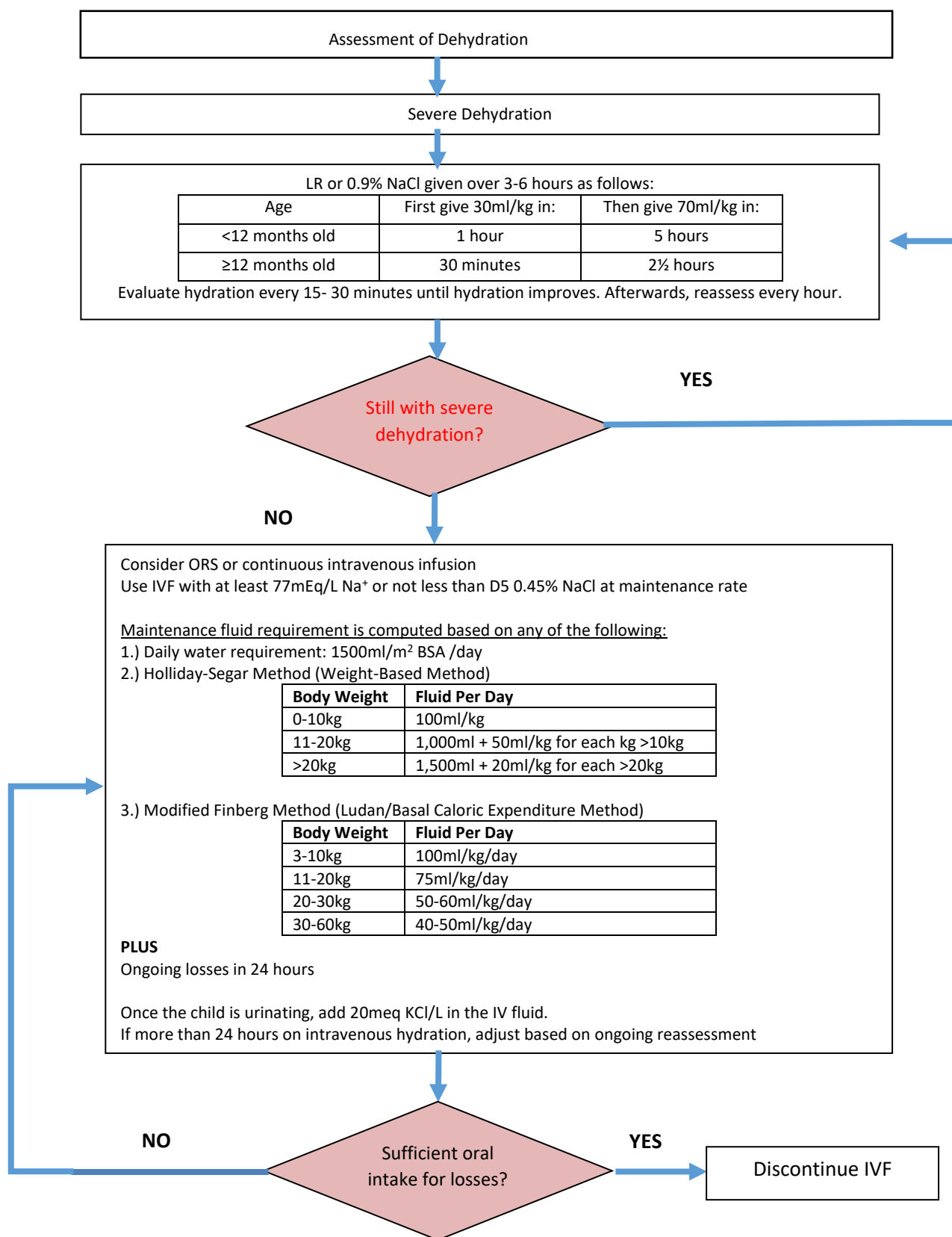


Figure 2. Protocol for severe dehydration. (Adapted with modifications <sup>1,24</sup>)

## No Signs of Dehydration

Age-appropriate food should be continued for children with no signs of dehydration. Fluids should be provided as tolerated. Reduced ORS should be provided after each episode of loose stool. The amount of ORS to be given is summarized in Table 4.

Table 4. Amount of ORS to be given according to age

Age (years)	Amount of ORS to give (ml)
Less than 2	50 to 100 ml
2 to 10	100 ml
More than 10	As much fluids as they want

### *Reduced Osmolarity Oral Rehydration Solution*

The composition of commercially available reduced osmolarity ORS is shown in Table 5. In areas where commercial ORS is not available, homemade ORS containing table salt and sugar can be made as follows:<sup>3</sup>

- 1 liter of clean water
- 3 grams of table salt (one teaspoon of table salt)
- 18 grams of common sugar/sucrose (4-5 teaspoons of table sugar)

Table 5. Components of reduced osmolarity oral rehydration solution

Components	Concentration	
Glucose	75 mmol/L	13.5 g/L
Sodium	75 mmol/L	2.6 g/L (as chloride)
Potassium	20 mmol/L	1.5 g/L (as chloride)
Chloride	65 mmol/L	-
Citrate	10 mmol/L	2.9 g/L

### How to give ORS

The solution should be given to infants and young children using a clean spoon or cup. For babies, a dropper or syringe (without the needle) can be used to put small amounts of solution into the mouth. Children under 2 years of age should be offered a teaspoonful every 1-2 minutes; older children may take frequent sips directly from the bottle or cup.<sup>6</sup>

### *Monitoring the progress of oral rehydration therapy*

The child should be checked frequently during rehydration to ensure that the ORS is being taken appropriately and that signs of dehydration are not worsening. The child should be reassessed fully before making decisions on the succeeding treatment. A child with signs and symptoms of mild to moderate dehydration should be treated accordingly based on the treatment algorithm (see Figure 1).

However, if at any time the child develops signs of severe dehydration, intravenous hydration must be started (see Figure 2).<sup>3</sup>

### **Mild to Moderate Dehydration**

Children with mild to moderate dehydration should be given the appropriate amount of ORS in 4 hours (amount in ml computed by multiplying weight in kg by 75). If the weight is unknown, Table 6 can be used to guide the amount of ORS to be given based on age. However, it is recommended to use the child's weight to compute the amount of ORS as much as possible. More than the required amount of ORS may be given if tolerated by the patient.

Table 6. Amount of ORS to be given according to age for children with mild to moderate dehydration

<b>Age</b>	<b>Required amount in 4 hours (ml)</b>
Less than 4 months	200 to 400
4 to 11 months	400 to 600
12 to 23 months	600 to 800
2 to 4 years	800 to 1200
5 to 14 years	1200 to 2200
15 years and older	2200 to 4000

### *Nasogastric Rehydration*

When oral rehydration is not feasible, enteral rehydration by nasogastric route is preferred over IV hydration.<sup>1,3</sup> However, if the child fails to respond to ORS, hydration may be done intravenously at 75ml/kg in four hours with frequent reassessment. During intravenous fluid therapy, attempts to reintroduce oral rehydration therapy must be continued. If oral rehydration is tolerated, intravenous fluids should be discontinued and rehydration should be completed with oral rehydration therapy.<sup>24,29</sup>

### *Indications for IV hydration*

The following are indications for IV hydration: shock, dehydration with altered level of consciousness or severe acidosis, worsening of dehydration or lack of improvement despite oral or nasogastric rehydration therapy, persistent vomiting despite appropriate oral or nasogastric fluid administration, severe abdominal distention, paralytic ileus, and glucose malabsorption as indicated by increased stool output when ORS is given.<sup>1,24,25</sup>

### *Choice of IV fluid*

Up to 79% children with diarrhea have some form of electrolyte abnormality. The most common abnormalities include hyponatremia, hypokalemia and metabolic acidosis.<sup>30,31</sup> In reference to the expected electrolyte imbalances among children with diarrhea, the composition of the different intravenous fluids are shown in Table 7.



Table 7. Composition of stool losses with diarrhea and different intravenous fluids used in hydration.<sup>24,32</sup>

Fluid	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	HC03 (mmol/L)
Diarrhea	10-90	10-80	10-110	15-50
Normal saline (NSS or 0.9% NaCl)	154	0	154	0
Lactated Ringer's	130	4	109	28 (as Lactate)
Half normal saline (0.45% NaCl)	77	0	77	0
0.3% NaCl	51	0	51	0
Half strength Darrow's Solution	61	17	51	27 (as lactate)

Based on the expected electrolyte abnormalities, an isotonic fluid (NSS or LR) is recommended as the initial intravenous fluid to be used for hydration.<sup>1,24</sup> The advantage of LR over NSS is that aside from having adequate sodium concentration, there is lactate that may aid in the correction of metabolic acidosis. There is also a low concentration of potassium to supplement the potassium losses incurred with diarrhea.<sup>24</sup>

The use of hypotonic solutions have been introduced; however, due to the stipulated antidiuretic hormone release in patients with diarrhea, the use of such fluids put patients at risk for hyponatremia.<sup>33,34</sup> The use of 0.45% saline was associated with a significant decrease in the plasma sodium concentration of patients with normal plasma sodium compared to those given 0.9% saline. A prospective randomized study involving 102 children found that hypotonic saline solutions exacerbate the tendency to develop dilutional hyponatremia in children with gastroenteritis, while isotonic saline solutions are protective.<sup>35</sup>

## Severe Dehydration

Rapid intravenous rehydration is reserved for children with severe dehydration and those initially managed with oral rehydration therapy but developed signs of severe dehydration.<sup>1,24,29</sup> Children who fail ORS therapy are those who continue to rapidly pass stool (>15-20ml/kg/hour) and those who are unable to tolerate ORS due to severe fatigue, altered consciousness and frequent, severe vomiting.<sup>24,29</sup>

Patients with severe dehydration need rapid intravenous rehydration. A randomized controlled trial of 150 children showed that rapid intravenous hydration is as effective as standard rehydration regimen (over 24 hours) in the treatment of dehydration and vomiting children.<sup>28</sup> IV fluids are started immediately, with hydration of 100ml/kg fluids given over 3-6 hours. The fluid of choice is an isotonic solution using LR or NSS. There is no available evidence comparing the effectiveness of these two isotonic fluids. Reassessments should be done to determine the need for intravenous or oral

hydration depending on the degree of dehydration. Rapid intravenous therapy may be repeated if patients still have severe dehydration.<sup>1,28</sup>

Children with shock secondary to gastrointestinal losses should receive rapid IV hydration of 20ml/kg bolus of isotonic crystalloid solution. Boluses may be repeated up to two times if necessary. Evaluation of other causes of shock should also be considered.<sup>1</sup>

#### *Maintenance fluids once child is rehydrated*

Once hydration status improves, ORS may be started or intravenous infusion may be continued. Whether IV fluid therapy is given for fluid resuscitation or for maintenance fluid requirements, frequent monitoring for complications of intravenous hydration such as hypervolemia, congestion and heart failure must be done. These complications may manifest as difficulty in breathing, edema, and signs of fluid accumulation in the lungs (crackles, decreased breath sounds signifying pleural effusion). Reassessments must be frequently done and shifting to oral rehydration for stool losses must be started as early as possible in order to discontinue intravenous therapy.<sup>3,29</sup>

#### **Breastfeeding**

In a small randomized controlled trial done in Burma among children 6-24 months, children with acute infectious diarrhea who were breastfed and given ORS had significantly fewer passage of stools compared to children given ORS alone. The mean number of stools passed by the breastfed children was 12.1, while children given ORS alone had a mean of 17.4 (p-value <0.05). Breastfed children also required lesser amount of ORS for rehydration (1570.4ml/patient) compared to those given ORS alone (2119.2 ml/patient), with a p-value of 0.02.<sup>44</sup>

#### **Carbonated, sweetened and caffeinated drinks**

Sweetened beverages such as fruit juice and sweetened tea may cause osmotic diarrhea and hypernatremia. Caffeinated drinks have stimulating, diuretic and purgative effect that may worsen diarrhea. These drinks should be avoided in children with diarrhea.<sup>3</sup>

### Question 3. What are the indications for empiric antibiotic treatment in children with acute infectious diarrhea?

1. Primary management of acute infectious diarrhea in children is still rehydration therapy. Routine empiric antibiotic therapy is NOT recommended.  
[Strong recommendation, very low quality of evidence]
2. Antimicrobials may be recommended for the following conditions:
  - Suspected cholera.
  - Bloody diarrhea.
  - Diarrhea associated with other acute infections (e.g. pneumonia, meningitis, etc.)

[Strong recommendation, very low quality of evidence]

### SUMMARY OF EVIDENCE

No studies evaluating the use of empiric antibiotics for acute infectious diarrhea in children were found. Most studies involved bloody diarrhea or traveller's diarrhea in older populations.

Local studies done in the 1980s showed that rotavirus is the most common cause of acute diarrhea, accounting for 7-34% of cases, followed by *Escherichia coli*, *Salmonella* and *Shigella* (Table 8).<sup>37-39</sup> Since the most common cause of acute diarrhea in children is self-limiting, the primary management is rehydration therapy. Routine empiric antibiotic therapy is not recommended. This recommendation is based from the consensus of the technical working group and expert panel, and is also in accordance with various international guidelines. The recommendations of the international guidelines are summarized in Table 9.

Table 8. Common etiology of acute diarrhea in children in the Philippines.<sup>76-39</sup>

Organisms	Lucero (n=620) 1984	Saniel 1986 (n=453)	San Pedro 1991 (n=186)
Rotavirus	17%	7.1%	33.9 %
Escherichia coli (ETEC)	15%	9.4%	9.1%
Salmonella	15%	10.1%	5.4%
Shigella	3%	4.1%	4.8%

The technical working group and expert panel recommend giving empiric antimicrobial therapy in suspected cases of cholera, bloody diarrhea and those associated with other acute infections. A local study conducted in a tertiary hospital showed that *Entamoeba histolytica*, *Salmonella* and *Shigella* were the most common causes of bloody diarrhea; hence, the use of antibiotics in bloody diarrhea is warranted.<sup>40</sup> These are in accordance with the WHO guidelines in the treatment of gastroenteritis. (Table 9)

Table 9. Summary of recommendations for empiric antibiotic therapy for diarrhea in children.<sup>1,3,41</sup>

ESPGHAN 2014	WHO 2005	AAP/CDC 2003
<p>“In children with watery diarrhea, antibiotic therapy is not recommended unless the patient has recently traveled or may have been exposed to cholera (strong recommendation, moderate-quality evidence).”</p>	<p>“Antimicrobial therapy should not be given routinely to children with diarrhoea. Such treatment is ineffective and may be dangerous.</p> <p>The diseases for which antimicrobials should be given are listed below:</p> <ul style="list-style-type: none"> <li>• Cases of bloody diarrhoea (dysentery)</li> <li>• Suspected cases of cholera with severe dehydration.</li> <li>• Laboratory proven, symptomatic infection with <i>Giardia duodenalis</i>... Children with acute diarrhoea should not be treated for giardiasis.</li> <li>• When diarrhoea is associated with another acute infection (e.g. pneumonia, urinary tract infection), that infection also requires specific antimicrobial therapy.”</li> </ul>	<p>“Because viruses (e.g., rotavirus, astrovirus, enteric adenovirus, norovirus, and sapovirus) are the predominant cause of acute diarrhea in developed countries, the routine use of antimicrobial agents for treating diarrhea wastes resources and might lead to increased antimicrobial resistance. Even when a bacterial cause is suspected in an outpatient setting, antimicrobial therapy is not usually indicated among children because the majority of cases of acute diarrhea are self-limited and not shortened by antimicrobial agents. Exceptions to these rules involve special needs of individual children (e.g., immune-compromised hosts, premature infants, or children with underlying disorders).”</p>

**Question 4. What are the recommended antimicrobials for the following etiologies of acute infectious diarrhea in children?**

**1. Cholera**

Antibiotic therapy should be given to children with suspected or confirmed cholera. The following antibiotics are recommended:

- Azithromycin 10 mg/kg/dose once a day for 3 days, or 20mg/kg single dose (max dose: 500 mg/24 hours)
  - Doxycycline (use only for >8 years old): 2mg/kg single dose (max dose: 100 mg/dose)
- Alternatives (when susceptible) include:

- Co-trimoxazole 8–12 mg/kg/day PO (based on trimethoprim component) divided into 2 doses for 3-5 days (max dose: 160 mg/dose)
- Chloramphenicol 50-100 mg/kg/day PO every 6 hours for 3 days (max dose: 750 mg/dose)
- Erythromycin 12.5 mg/kg/dose PO every 6 hours for 3 days (max dose: 4g/24 hours)

[Strong recommendation, low to moderate quality of evidence]

**2. Shigella**

Antibiotic therapy should be given to children with suspected or culture-proven *Shigella* gastroenteritis. The following antibiotics are recommended:

- Ceftriaxone IV 75-100 mg/kg/day every 12-24 hours (max dose 2g/24 hours) for 2-5 days
- Ciprofloxacin 30 mg/kg/day PO divided into 2 doses x 3 days (max dose: IV 800 mg/24hours).
- Azithromycin 10 mg PO once a day for 3 days (max dose: 500mg/dose)

[Strong recommendation, moderate quality of evidence]

**3. Non-typhoidal *Salmonella* (NTS)**

Antibiotic treatment is NOT recommended for children with non-typhoidal *Salmonella* EXCEPT in high-risk children to prevent secondary bacteremia, such as:

- Neonates or young infants <3 months old
- Immunodeficient patients
- Anatomical or functional asplenia, corticosteroid or immunosuppressive therapy, inflammatory bowel disease, or achlorhydria

[Strong recommendation, low quality of evidence]

**4. Amoebiasis**

Metronidazole 10 mg/kg/dose IV/PO 3 times a day (max dose: 750 mg/dose) for 10-14 days is recommended for confirmed cases of amoebiasis to avoid relapse.

[Strong recommendation, very low quality of evidence]

## SUMMARY OF EVIDENCE

### Cholera

Cholera causes acute watery diarrhea that may lead to mortality if untreated. Most infected people are asymptomatic, but shed bacteria in their feces for 1-10 days after infection. Among symptomatic patients, most will develop mild or moderate symptoms, while a minority will develop acute watery diarrhea with severe dehydration.<sup>42</sup> The WHO guidelines state that cholera should be suspected in the following conditions:

- Any patient >5 years old who develops severe dehydration from acute watery diarrhea, usually with vomiting, OR
- Any patient >2 years old with acute watery diarrhea in an area where there is an outbreak of cholera.<sup>43</sup>

A systematic review and meta-analysis of 39 RCTs involving 4,623 adults and children evaluated the use of antibiotics in cholera. Nine trials included only children, while 7 trials included both adults and children. The case definition in most trials was a history of acute watery diarrhea, lasting 24 hours or less. All trials included only patients with bacteriologically proven cholera in their final analysis.<sup>44</sup>

Over-all, compared to placebo or no treatment, antimicrobial therapy resulted in: 1) shortened mean duration of diarrhea by about a day and a half [mean difference (MD)= -36.77 hours; 95% CI -43.51, -30.3], 2) reduced total stool volume by 50% [ratio of means (ROM)=0.5; 95% CI 0.45, 0.56], 3) reduced amount of required rehydration fluids by 40% (ROM=0.60; 95% CI 0.53, 0.68), and 4) reduced mean duration of fecal excretion of *Vibrio* by almost 3 days (MD= -2.74 days; 95% CI -3.07, -2.40). There were no reported deaths in the studies included in the review.<sup>44</sup>

The Technical Working Group conducted a subgroup analysis of studies with children as participants (children only and children with adults) for this guideline. The use of antibiotics (tetracycline, erythromycin, co-trimoxazole, and chloramphenicol) significantly decreased clinical failure and diarrhea duration compared to no treatment or placebo, although clinical failure was variably defined among the studies. The results of the subgroup analysis are shown in Table 10.

Table 10. Effects of specific antibiotic therapy compared to no treatment or placebo

Outcome	Antibiotic	Results
		Relative Risk (95% CI)
Clinical Failure	Tetracycline	0.09 (0.04, 0.21)
	Erythromycin	0.47 (0.20, 1.10)
	Co-trimoxazole	0.05 (0.02, 0.14)
	Chloramphenicol	0.22 (0.09, 0.56)
		Mean Difference (95% CI)
Diarrhea duration	Tetracycline	-47.25 (-57.08, -37.41)
	Doxycycline	-36.00 (-53.76, -18.24)
	Erythromycin	-33.73 (-56.53, -10.92)
	Co-trimoxazole	-31.40 (-51.52, -11.29)
	Chloramphenicol	-23.20 (-41.73, -4.67)

Comparisons of individual antibiotics for the outcomes of clinical failure and diarrhea duration were also done for studies involving children. Comparisons of azithromycin versus erythromycin and co-trimoxazole versus erythromycin showed no difference in terms of clinical failure, although this outcome was variably defined among the studies. Comparison of tetracycline and co-trimoxazole from 2 pooled studies showed reduced risk of clinical failure with tetracycline (RR=0.56; 95% CI 0.34, 0.92). Comparison of tetracycline and chloramphenicol in 1 study showed reduced risk of clinical failure in tetracycline (RR=0.18; 95% CI 0.04, 0.91). Azithromycin showed a significantly decreased risk of clinical failure compared to ciprofloxacin in 1 study (RR=0.19; 95% CI 0.08, 0.47).

Comparison of tetracycline versus doxycycline, tetracycline versus norfloxacin, tetracycline versus co-trimoxazole, and co-trimoxazole versus erythromycin showed no significant difference in diarrhea duration. Pooled results from 4 studies showed a 2-day decrease in duration of diarrhea among those given tetracycline compared to placebo (MD= -47.25 hours; 95% CI -57.08, -37.41). Tetracycline also showed significant decrease in diarrhea duration compared to chloramphenicol (MD= -27.20 hours; 95% CI -39.64, -14.76). Azithromycin showed significant decrease in diarrhea duration compared to ciprofloxacin (MD= -16.90 hours; 95% CI -24.14, -9.66) and erythromycin (MD= -18.00 hours; 95% CI -27.59, -8.41). There was no study which compared azithromycin with tetracycline.

The 2016 Antimicrobial Resistance Surveillance Program report states that *V. cholerae* isolates remain susceptible to co-trimoxazole, chloramphenicol and tetracycline, with no reported resistant isolate for 2016. In addition, resistant rates have remained stable over the past 10 years, with reported rates at ≤5% since 2007 for each of the 3 antibiotics.<sup>45</sup>

## ***Shigella***

According to WHO, clinical presentations suggestive of *Shigella* dysentery include simple watery diarrhea or bloody diarrhea; abdominal pain, tenesmus, fever, and anorexia; and mild or moderate dehydration. Routine microscopy of fresh stool is a diagnostic test for *Shigella*, wherein presence of numerous polymorphonucleocytes suggests bacterial etiology. Isolation of *Shigella* in stool culture provides definite diagnosis.<sup>3,46</sup>

A meta-analysis of 16 trials with 1,748 participants evaluated antibiotic use in *Shigella* dysentery. Ten trials involved only children, 5 trials involved adults, and 1 included both adult and pediatric participants. Studies which compared antibiotics of the same class were not included in the review.<sup>47</sup>

The 2 primary outcomes of the review were diarrhea on follow-up and relapse. Two studies compared antibiotic usage and no treatment, and found that the use of antibiotics reduced incidence of diarrhea on follow-up, time to resolution of diarrhea, fever, and bloody stools. The effect estimates are shown in Table 11. None of the trials reported any deaths. There was also no significant difference in adverse events.<sup>47</sup>

The review authors noted that the included trials had methodological limitations, including inadequate reporting of allocation sequence generation, inadequate allocation concealment, lack of blinding, and attrition bias. Thus, most trials were graded as low or very low quality, and the authors stated that further research may change the efficacy estimates and confidence in the data estimates.<sup>47</sup>

Table 11. Effects of specific antibiotics compared to no treatment or placebo

<b>Diarrhea on follow up</b>	<b>Risk Ratio (95% CI)</b>
Furazolidone versus no drug	0.21 (0.09, 0.48)
Co-trimoxazole versus no drug	0.30 (0.15, 0.59)
<b>Time to cessation of fever (in days)</b>	<b>Mean Difference (95% CI)</b>
Ceftriaxone versus placebo	-1.20 (-2.20, -0.20)
Ampicillin versus placebo	-1.50 (-2.41, -0.59)
<b>Time to cessation of diarrhea (in days)</b>	<b>Mean Difference (95% CI)</b>
Ceftriaxone versus placebo	-0.30 (-1.41, 0.81)
Ampicillin versus placebo	-0.30 (-1.37, 0.77)
<b>Time to cessation of blood in stools (in days)</b>	<b>Mean Difference (95% CI)</b>
Ceftriaxone versus placebo	-0.30 (-1.43, 0.83)
Ampicillin versus placebo	-0.30 (-1.41, 0.81)
<b>Other adverse events</b>	RR=1.43 (95% CI 0.06, 34.13)

Studies in children comparing fluoroquinolones and beta-lactams showed no significant difference in the incidence of diarrhea on follow-up, fever on follow-up, relapse, bacteriologic failure, development of severe complications, and serious adverse events (see Table 12).

Table 12. Comparison of fluoroquinolones and beta-lactams

<b>Outcome</b>	<b>Risk Ratio (95% CI)</b>
<i>Subgroup analysis (involving only children)</i>	
Diarrhea on follow up, children (subgroup)	1.46 (0.64, 3.34)
Fever at follow up	0.87 (0.25, 3.06)
Relapse	0.91 (0.11, 7.55)
Bacteriological failure, children (subgroup)	0.95 (0.43, 2.09)
Development of severe complications	0.89 (0.28, 2.85)
Serious adverse events	10.90 (0.61, 194.82)
<i>Over-all analysis (involving adults and children)</i>	
Adverse events leading to discontinuation of treatment	1.02 (0.27 to 3.89)
Other adverse events	1.03 (0.77 to 1.39)

Subgroup analysis involving 2 trials where  $\geq 90\%$  of included patients were confirmed to have *Shigella* showed that beta-lactams were more effective than fluoroquinolones in reducing diarrhea on follow-up (RR=4.68; 95% CI 1.74, 12.59).

Analysis of studies comparing fluoroquinolones and macrolides showed a trend favoring quinolones, but there was no significant difference in terms of diarrhea on follow-up, fever on follow-up, time to cessation of bloody stools, bacteriologic failure, development of severe complications, and adverse events (see Table 13).



Table 13. Comparison of fluoroquinolones and macrolides

Outcome	Treatment Effect (95% CI)
Diarrhea on follow up	RR=0.6 (0.24, 1.49)
Fever at follow up	RR=0.33 (0.08, 1.35)
Time to cessation of blood in stools	MD= -0.20 (-0.68, 0.28)
Bacteriological failure	RR=0.33 (0.07, 1.55)
Other adverse events	RR=1.33 (0.32, 5.56)

One RCT published after the above-mentioned meta-analysis compared gatifloxacin and ciprofloxacin. There was no significant difference in treatment failure and time to cessation of individual symptoms between the two quinolones.<sup>48</sup>

WHO recommends the use of ciprofloxacin for treating shigellosis, and pivmecillinam, ceftriaxone, or azithromycin as second-line treatment. A consideration on the most recent antibiotic resistance pattern in the community is important in deciding empiric treatment for suspected shigellosis. The 2016 report of the ARSP showed 13.7% resistance to ciprofloxacin.<sup>45</sup> There were high resistance rates to ampicillin and co-trimoxazole, but there were no cited susceptibility patterns for azithromycin; thus, these antibiotics are recommended to be given only in susceptible isolates. Pivmecillinam is not available in the Philippines.

### Non-typhoidal *Salmonella*

A Cochrane review which included 12 studies with 767 adult and pediatric participants found no significant difference between antibiotics and placebo on the following outcomes: diarrhea duration (RR=0.00; 95% CI -0.54, 0.54 ), presence of diarrhea at 5-7 days (RR=0.83; 95% CI 0.62, 1.12), clinical failure (RR=0.82; 95% CI 0.57, 1.18), duration of fever (RR=0.27; 95% CI -0.11, 0.65), and duration of illness (RR=0.00; 95% CI -0.68, 0.68).<sup>49</sup>

The ESPGHAN/ESPID 2014 guidelines recommend antibiotic therapy for neonates, young infants <3 months old, and children with underlying conditions (immunodeficiency, anatomical or functional asplenia, corticosteroid or immunosuppressive therapy, inflammatory bowel disease, and achlorhydria) since they have higher occurrence of secondary *Salmonella* bacteremia and extra-intestinal focal infections. Thus, antibiotic therapy is suggested among these children to reduce the risk of bacteremia.<sup>1</sup> This recommendation was adopted by the expert panel.

Ceftriaxone (50–100 mg/kg/day) is the drug of choice in the ESPGHAN/ESPID guidelines. Alternative drugs include azithromycin (10 mg/kg/day), ciprofloxacin (20–30 mg/kg/day), and for known susceptible strains, co-trimoxazole (8 mg/kg/day of trimethoprim component).

### Amoebiasis

A systematic review and meta-analysis of 37 trials with 4,487 participants evaluated antimicrobial use for amoebic colitis. The review included studies on both adults and children. However, the included studies were not of high quality. Only 1 trial used adequate methods for randomization and allocation concealment, was blinded, and analyzed all randomized participants.<sup>50</sup>

Pooled results from 8 trials showed that tinidazole significantly reduced clinical failure compared to metronidazole (RR=0.28; 95% CI 0.15, 0.51) and was associated with fewer adverse events. Based on 3 trials, combination therapy was found to result in fewer parasitological failures compared to metronidazole (RR=0.36; 95% CI 0.15, 0.86;).<sup>50</sup>

Among studies which enrolled children only and children and adults, treatment with an anti-amoebic drug showed benefit compared to no treatment. The administration of any anti-amoebic drug for amoebic colitis or intestinal amoebiasis showed significant decrease in parasitological failure compared to placebo (RR=0.33; 95% CI 0.17, 0.62).<sup>50</sup>

Analysis of studies which enrolled only children or children and adults was done, with focus on studies comparing metronidazole to other anti-amoebic drugs. Compared to metronidazole, tinidazole showed no significant difference in clinical failure, parasitological failure, and relapse. There were less adverse events with tinidazole (RR=0.35; 95% CI 0.20, 0.63). Comparison of ornidazole and metronidazole showed no significant difference in clinical failure, parasitological failure, relapse events, and adverse events.

#### **Question 5. Should zinc and racecadotril be given in children with acute infectious diarrhea?**

1. Zinc supplementation (not in combination with vitamins and minerals) at 20mg/day for 10-14 days should be given routinely as adjunctive therapy for acute infectious diarrhea in children >6 months old to shorten the duration of diarrhea and reduce frequency of stools.  
[Strong recommendation, low to moderate quality of evidence]
2. Zinc supplementation is NOT routinely given as adjunctive therapy for acute infectious diarrhea in children <6 months old as it may cause diarrhea to persist.  
[Strong recommendation, low to moderate quality of evidence]
3. Racecadotril (1.5 mg/kg/dose) 3 times a day during the first 3 days of watery diarrhea may be given to infants and children as adjunctive therapy to shorten duration of diarrhea.  
[Weak recommendation, low quality of evidence]
4. Loperamide is NOT recommended for children with acute infectious gastroenteritis due to serious adverse events.  
[Strong recommendation, moderate quality of evidence]

## SUMMARY OF EVIDENCE

### Zinc

WHO and the United Nations Children's Fund (UNICEF) recommend 10-20 mg of zinc per day for children with diarrhea. Zinc supplementation could help reduce the duration and severity of diarrhea, and therefore have benefit in addition to ORS in reducing children mortality.<sup>24</sup>

A systematic review analyzed 33 trials involving 10,841 children with diarrhea to determine the effect of zinc supplementation in children with acute gastroenteritis.<sup>51</sup> Nine trials on 2,581 children aged >6 months demonstrated that zinc supplementation shortened the duration of diarrhea by 12 hours (MD= -11.46 hours; 95% CI -19.72, -3.19) and reduced the risk of diarrhea persisting up to the 7<sup>th</sup> day (RR=0.73; 95% CI 0.61, 0.88). Four trials in 1,233 children aged ≥6 months showed that zinc supplementation led to less frequent stooling per day compared to those on placebo (MD= -0.32; 95% CI -0.58, -0.06).

However, among children <six months old, meta-analysis of 2 trials consisting of 1,334 children revealed that zinc supplementation may have no effect on the duration of diarrhea (MD=5.23; 95% CI -4.00, 14.45) and stool frequency (MD=0.0; 95% CI -0.17, 0.17), and may in fact increase the risk of diarrhea persisting until the 7<sup>th</sup> day (RR=1.24; 95% CI 0.99, 1.54).<sup>5</sup>

In the same review, there were no serious adverse events reported; however, zinc supplementation significantly increased the risk of vomiting compared to placebo.<sup>51</sup>

### Racecadotril

Racecadotril is an anti-secretory agent that inhibits enkephalinase, an enzyme that degrades pro-absorptive and anti-secretory neuropeptides known as enkephalins. Racecadotril ultimately reduces hypersecretion of water and electrolytes without affecting intestinal motility.<sup>52</sup> It can be used as adjunct to ORS therapy in acute diarrhea in children.

Racecadotril treatment should be started following 3 episodes of watery diarrhea in a 24-hour period, until 2 normal stools have been produced. The product should be used for a maximum of 7 days.<sup>53</sup>

A systematic review and meta-analysis of 7 RCTs was conducted to determine the efficacy of racecadotril in children with acute diarrhea. Three studies in 642 children showed that racecadotril decreased the duration of diarrhea by 53 hours compared to placebo or no intervention (MD= -53.48; 95% CI -65.64, -41.33). Two studies in 405 hospitalized children showed significantly less stool output in the first 48 hours of treatment with racecadotril compared to placebo or no intervention (MD= -150 g/kg, 95% CI -291, -8.9).<sup>53</sup>

Based on 9 studies on 949 children, there was no significant difference in adverse events between racecadotril and placebo (OR=0.99, 95% CI 0.73, 1.34). No serious adverse events were reported in any of the studies.<sup>53</sup>

### Loperamide

Loperamide is an opiate agonist that acts on  $\mu$  receptors, leading to inhibition of peristalsis and increased intestinal transit time. This results in decreased stool output and prevents fluid loss.<sup>54</sup>

A systematic review and meta-analysis analyzed the effect of loperamide in children with acute diarrhea.<sup>55</sup> The review included 13 trials in 1,788 children <12 years old. In 4 trials, the risk of persistence of diarrhea at 24 hours (RR=0.66; 95% CI 0.57, 0.78) and 48 hours (RR=0.59; 95% CI 0.45, 0.78) were decreased in the loperamide group compared to the placebo group. In 6 trials, loperamide was found to significantly reduce the duration of diarrhea (MD= -0.55; 95% CI -0.95, -0.16), but there was no significant difference in the number of stools within 24 hours (RR=0.8; 95% CI 0.62, 1.04).

Serious adverse effects such as ileus, lethargy or death were reported in 8 out of 927 children in the loperamide group, while there were none in the placebo group. (RD=0.8%; 95% CI -0.1, 1.8). All serious side effects occurred in children <3 years of age.<sup>55</sup>

**Question 6. What is the role of anti-emetics in the management of vomiting in children with acute infectious diarrhea?**

Anti-emetics are NOT recommended in children with acute infectious diarrhea due to potential adverse effects.

[Strong recommendation, low quality of evidence]

**SUMMARY OF EVIDENCE**

A systematic review of 10 trials in 1,479 children with acute gastroenteritis investigated the effectiveness of 5 anti-emetics (dexamethasone, dimenhydrinate, granisetron, metoclopramide, and ondansetron).<sup>56</sup> Data from 4 trials in 574 children showed that only orally administered ondansetron was found to be effective in cessation of vomiting (RR=1.44; 95% CI 1.29, 1.61), reduction of immediate hospital admission rate (RR=0.40; 95% CI 0.19, 0.83) and the need for intravenous rehydration therapy (RR=0.41; 95% CI 0.29, 0.59). However, 3 studies reported a significant increase in the incidence of diarrhea in the ondansetron group. No serious adverse events were reported, although the studies were not powered to detect such rare events.

ESPHGAN 2014 guidelines state that although ondansetron is effective in stopping vomiting in children with diarrhea, clinicians should be aware of potential adverse effects such as prolongation of QT interval.<sup>1</sup>

Ondansetron is not recommended because of its possible adverse effects, including the potential to increase the episodes of diarrhea. There are no or limited evidence in the use of other antiemetics.

**Question 7. What is the role of probiotics in the management of acute infectious diarrhea in children?**

1. Probiotics are recommended as an adjunct therapy throughout the duration of the diarrhea in children. Probiotics have been shown to reduce symptom severity and duration of diarrhea.  
[Strong recommendation, moderate quality of evidence]
2. Probiotics may be extended for 7 more days after completion of antibiotics.  
[Strong recommendation, moderate quality of evidence]
3. The following probiotics may be used:
  - a. *Saccharomyces boulardii* 250-750mg/day for 5-7 days  
[Strong recommendation, moderate quality of evidence]
  - b. *Lactobacillus rhamnosus* GG  $\geq 10^{10}$  CFU/day for 5-7 days  
[Strong recommendation, moderate quality of evidence]
  - c. *Lactobacillus reuteri* DSM 17938  $10^8$  to  $4 \times 10^8$  CFU/day for 5-7 days  
[Weak recommendation, very low quality of evidence]
  - d. There is insufficient evidence to recommend *Bacillus clausii*.

**SUMMARY OF EVIDENCE**

Probiotics are “live microorganisms, which when administered in adequate amounts, confer a health benefit on the host”.<sup>57</sup> Administration of probiotics in infectious diarrhea may act against enteric pathogens by competing for available nutrients and binding sites, acidifying gut contents, producing a variety of chemicals, and increasing specific and non-specific immune responses.<sup>58-60</sup> Because of these mechanisms, the use of probiotics in treating and preventing diarrheal diseases have been studied.

Various systematic reviews and meta-analyses have evaluated the effects of probiotics on the treatment of acute diarrhea. One of the recent systematic reviews is a Cochrane review of 63 RCTs involving 8,014 participants, where majority were infants and children. Probiotics, as a group, reduced the duration of diarrhea by approximately 1 day in 35 RCTs (MD= -25 hours; 95% CI 16, 34) and reduced the risk of diarrhea lasting  $\geq 4$  days in 29 RCTs (RR=0.41; 95% CI 0.32, 0.53).<sup>61</sup>

Probiotic effects are strain-specific, which means the safety and clinical effects of 1 probiotic microorganism cannot be generalized to other probiotic microorganisms. Three strains of probiotics were shown to be effective in diarrhea, namely *Lactobacillus rhamnosus* GG (LGG), *Saccharomyces boulardii* and *Lactobacillus reuteri*.

***Lactobacillus rhamnosus* GG**

A Cochrane review found that in both adults and children, LGG reduced the duration of diarrhea by almost a day based on 11 RCTs (MD= -27 hours; 95% CI -41, -13), the mean stool frequency on day 2 based on 6 RCTs (MD= -0.8; 95% CI -1.3, -0.2), and the risk of diarrhea lasting  $\geq 4$  days based on 4 RCTs (RR=0.6; 95% CI 0.4, 0.9).<sup>61</sup>

A more recent systematic review of 15 RCTs involving 2,963 participants focused on the efficacy of LGG in acute gastroenteritis in children. Pooled data from 11 RCTs in 2,444 children showed that LGG significantly reduced the duration of diarrhea compared to placebo or no treatment (MD= -1.05 days; 95% CI -1.7, -0.4). LGG was more effective when used at a daily dose of  $\geq 10^{10}$  colony-forming units (CFU) than at a daily dose of  $\leq 10^{10}$  CFU. Based on 2 RCTs, LGG was found to have no significant effect on the total stool volume compared to control (MD=8.97 mL/g; 95% CI -86.26, 104.2). Limited evidence from trials in which the etiology of diarrhea was assessed suggests that LGG is more effective in treating diarrhea caused by rotavirus.<sup>62</sup>

### ***Saccharomyces boulardii***

A Cochrane review found that the use of *S. boulardii* reduced the risk of diarrhea lasting  $\geq 4$  days, based on pooled data from 6 RCTs with 606 participants (RR=0.37; 95% CI 0.2, -0.65).<sup>63</sup> A meta-analysis of 9 RCTs in 1,117 children with gastroenteritis concluded that in otherwise healthy infants and children, the use of *S. boulardii* reduces the duration of diarrhea by approximately 1 day (MD= -1.08; 95%CI -1.64, -0.53).<sup>63</sup>

The most recent systematic review analyzed 13 RCTs that used daily doses of *S. boulardii* ranging from 250 to 750 mg. Compared with placebo or no intervention groups, *S. boulardii* significantly reduced the duration of diarrhea based on 11 RCTs (MD= -0.99 days; 95% CI -1.4, -0.6) and the risk of diarrhea on day 3 based on 9 RCTs (RR=0.52; 95% CI 0.42, 0.65). For both outcomes, significant heterogeneity was observed ( $I^2$  of 83% and 63% respectively). The use of *S. boulardii* reduced the duration of hospitalization among admitted children (MD= -0.8 days; 95% CI -1.1, -.5). None of the studies evaluated the effect of *S. boulardii* on stool volume.<sup>64</sup>

### ***Lactobacillus reuteri***

A recent systematic review on the effectiveness of *Lactobacillus reuteri* DSM 17938 on diarrheal diseases in children analyzed 3 RCTs with 256 participants.<sup>65</sup> Meta-analysis showed that administration of *Lactobacillus reuteri* significantly decreased the duration of diarrhea by 1 day compared to placebo or no intervention [weighted mean difference (WMD)= -24.82 hours; 95% CI -38.8, -10.8). Two RCTs showed non-significant reduction in the duration of hospitalization (MD= -1.15 days; 95% CI -1.7, 0.6). Adverse events of *L. reuteri* administration were not significant. Study conclusions were however limited because of high heterogeneity of studies and because all studies were conducted in Europe.

## 8. What is the recommended diet for children with acute infectious diarrhea?

1. Breastfeeding should be continued in breastfed infants.  
[Strong recommendation, moderate quality of evidence]
2. In general, feeding should be continued. However, if feeding is not tolerated, early refeeding may be started as soon as the child is able.  
[Strong recommendation, low to moderate quality of evidence]
3. If diarrhea persists for >7 days or if patients are hospitalized due to severe diarrhea, lactose-free diet may be given to children who are predominantly bottle-fed to reduce treatment failure and decrease the duration of diarrhea.  
[Strong recommendation, very low to low quality of evidence]
4. No change from age-appropriate diet is recommended.  
[Strong recommendation, low quality of evidence]
5. Diluted lactose milk is not recommended.  
[Strong recommendation, low quality of evidence]
6. Restrictive diet such as BRAT (banana, rice, apple, tea) diet is not recommended because of the risk of malnutrition from its inadequate nutritional value.  
[Strong recommendation, low quality of evidence]

## SUMMARY OF EVIDENCE

International guidelines are in agreement that age-appropriate feeding should be continued during and after rehydration, and that modified or diluted milk are not recommended. These recommendations are also adopted here.<sup>1,2,24</sup>

### Early Refeeding

In a meta-analysis of 12 trials involving 1,283 children <5 years old, early refeeding had no significant difference compared to late refeeding in the duration of diarrhea (MD= -6.90 hours; 95% CI -18.70, 4.91), need for intravenous therapy (RR=0.87; 95% CI 0.48, 1.59), vomiting episodes (RR=1.16; 95% CI 0.72, 1.86) and development of persistent diarrhea (RR=0.57; 95% CI 0.18, 1.85).<sup>66</sup> If feeding is not tolerated, early refeeding may be started as soon as the child is able.

## Lactose-free products

In a systematic review of 16 trials from middle to high-income countries, there was earlier resolution of diarrhea among children <12 months old who received lactose-free products compared to those who received lactose-containing milk, milk products or foodstuffs (MD= -17.77 hours; 95% CI -25.32, -10.21). There were also fewer episodes of treatment failure among those given lactose-free products (RR=0.52; 95% CI 0.39, 0.68). There was no significant difference in the need for hospitalization. Applicability of these findings to community settings is uncertain since most participants in the included trials were inpatients. The review also noted that based on 9 RCTs, diluted lactose-containing milk reduced the risk of treatment failure (RR=0.65; 95% CI 0.45, 0.94) compared to undiluted lactose-containing milk, but it has no significant benefit in reducing the duration of diarrhea.<sup>67</sup>

## BRAT diet

The selection of a single type of restrictive diet (e.g. the BRAT diet) during diarrhea can impair nutritional recovery and lead to severe malnutrition. Dietary management during any acute illness should be balanced, providing all 3 major macronutrients and meeting the dietary reference intakes for micronutrients. Prompt feeding during an acute episode of diarrhea and avoiding unnecessarily restrictive diets are recommended during acute diarrhea. Nursing should be continued for breastfed infants, while standard full strength formula should be given to formula-fed infants. Age-appropriate foods from varied sources are recommended to optimize health outcomes. Future studies should evaluate whether certain dietary patterns are associated with more rapid recovery from acute diarrhea, but until these data are available, overly restricted diets should not be recommended.

## Question 9. What is the recommended management for complications of acute infectious diarrhea in children?

1. Acute kidney injury (AKI) is a serious and potentially life-threatening complication. It is best to refer the patient immediately to a specialist at the first sign of AKI.  
[Good practice statement]
2. ORS is safe and effective therapy for nearly all children with hyponatremia.  
[Good practice statement]
3. Hospital treatment and close monitoring are recommended for patients suspected to have hyponatremia. Referral to a specialist is advised.  
[Good practice statement]



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### III. TREATMENT (ADULT)

#### Question 1. Who should be admitted among adults presenting with acute infectious diarrhea?

Presence of any of the following clinical history and physical findings warrant admission:

- Poor tolerance to oral rehydration
- Moderate to severe dehydration
- Acute kidney injury
- Electrolyte abnormalities
- Unstable comorbid conditions (e.g. uncontrolled diabetes, congestive heart failure, unstable coronary artery disease, chronic kidney disease, chronic liver disease, immunocompromised conditions)
- Frail or elderly ( $\geq 60$  years old) patients
- Poor nutritional status
- Patients with unique social circumstances (living alone, residence far from a hospital)

[Strong recommendation, low to moderate quality of evidence]

#### SUMMARY OF EVIDENCE

After careful assessment of the history and physical examination, clinicians should determine the patients' level of hydration, hemodynamic status, need for hospital admission, and need for referral to specialists.

Among the 28,583 diarrheal deaths in the United States from 1979 to 1987, 51% occurred among the elderly (defined as  $>74$  years old) and 27% occurred among those  $>55$  years old.<sup>1</sup>

A case control study reviewed 1,353 deaths due to gastroenteritis of unknown etiology in the United States. Deaths occurred more commonly among patients  $>65$  years old. Septicemia, volume depletion, protein-calorie malnutrition, electrolyte and fluid disorders, and comorbid conditions were among those identified to be associated with these deaths.<sup>2</sup> Patients with the above conditions require close monitoring and immediate intervention, and hence should be admitted. Table 1 shows the proportionate mortality ratio of various conditions.

Table 1. Summary of co-existing conditions and their proportionate mortality ratio.<sup>2</sup>

Co-existing Condition	Proportionate mortality ratio (95% CI)
Volume depletion (dehydration)	9.63 (9.48, 9.7)
Electrolyte and fluid disorder	10.03 (8.88, 11.29)
Acute renal failure	3.32 (3.03, 3.64)
Unspecified septicemia	4.45 (4.04, 4.9)
Shock	3.47 (2.97, 4.02)
HIV / AIDS	4.07 (3.78, 4.37)

## Question 2. How should dehydration in adults be managed?

### Mild dehydration

- Oral rehydration solution is recommended at 1.5 - 2 times the estimated amount of volume deficits plus concurrent gastrointestinal losses. Sports drinks and soda are not recommended.

[Strong recommendation, low quality of evidence]

### Moderate dehydration

- 500 to 1,000 ml of plain Lactated Ringer's solution (PLRS) in the first 2 hours is recommended.
- Once hemodynamically stable, give 2 - 3 ml/kg/hour PLRS for patients with actual or estimated body weight of <50 kg, and 1.5 - 2 ml/kg/hour PLRS for patients with actual or estimated body weight of >50 kg. Use ideal body weight for overweight or obese patients.
- Replace ongoing losses volume per volume with PLRS boluses or ORS (if tolerated).

[Strong recommendation, low quality of evidence]

### Severe dehydration

1,000 to 2,000 ml of PLRS within the first hour is recommended.

Once hemodynamically stable, give 2 – 3 ml/kg/hour PLRS for patients with actual or estimated body weight of <50 kg and 1.5 – 2 ml/kg/hour PLRS for patients with actual or estimated body weight of >50 kg. Use ideal body weight for overweight or obese patients.

Replace ongoing losses volume per volume with PLRS boluses. ORS is not recommended since patients with severe dehydration may have compromised mental status and therefore have high risk for aspiration.

[Strong recommendation, low quality of evidence]

For calculations of maintenance fluid rate, it is suggested to use the actual or estimated body weight. However, the ideal body weight should be used for overweight or obese patients. [Weak recommendation, low quality of evidence]

### Population at risk

Elderly patients and those at risk of fluid overload (patients with heart failure or kidney disease) should be referred to a specialist for individualized fluid management.

[Strong recommendation, low quality of evidence]

### Type of Fluid

PLRS, a chloride-restrictive intravenous (IV) fluid, is the fluid of choice for hydration and fluid resuscitation of patients with diarrhea. If PLRS is not available, plain normal saline solution (PNSS) may still be used.

[Strong recommendation, low quality of evidence]

During initial resuscitation, hourly monitoring of vital signs, mental status, peripheral perfusion, and urine output must be done. The subsequent frequency of monitoring should be based on the clinician's judgment.

[Strong recommendation, very low quality of evidence]

The routine use of albumin, hydroxyethyl starch (HES), dextran, or gelatin for fluid resuscitation of dehydrated patients is not recommended.

[Strong recommendation, moderate quality of evidence]

## SUMMARY OF EVIDENCE

### Actual versus ideal body weight

According to the consensus guidelines of the Dietitian/Nutritionists from the Nutrition Education Materials Online "NEMO" team; the weights to be used for calculating energy, protein and fluid requirements are the following:<sup>3</sup>

Table 2. Weight for calculation of energy, protein and fluid requirements<sup>3</sup>

Classification	Weight used for calculation
Healthy weight (BMI 18.5-22 kg/m <sup>2</sup> )	Actual body weight*
Underweight	Actual body weight*
Overweight or obese	May consider using adjusted body weight: IBW + [(actual weight – IBW) x 25%]  *IBW (ideal body weight)= weight at BMI 25 kg/m <sup>2</sup>

\*Actual body weight should be taken once the patient is hydrated.

WHO also recommends the use of IBW in calculating energy and fluid requirements in obese patients. The IBW for overweight or obese adults can be estimated using the following formula:

Female: 45.5 kg + 0.91 (height in cm – 152.4)

Male: 50.0 kg + 0.91 (height in cm – 152.4)

## **Mild Dehydration**

Patients with mild dehydration who have no significant comorbid conditions and can tolerate oral rehydration may be sent home. Treatment of these patients should focus on replacement of fluids and electrolytes. Oral rehydration therapy using ORS should be adequate in these cases.<sup>4-6</sup> The amount of ORS to be taken should be approximately 1.5 - 2 times the estimated amount of volume deficit plus concurrent gastrointestinal losses.<sup>7,8</sup>

Patients and their caregivers should be given clear and concise instructions on home care. They should also be informed about warning signs that would necessitate bringing the patient back to the hospital.

### *Sports Drinks*

The use of sports drinks as an alternative to ORS is not recommended in the fluid therapy of acute diarrhea. Compared to ORS, sports drinks in general contain lower concentrations of sodium and potassium, but have higher osmolality because of higher sugar content. Use of sports drinks may aggravate electrolyte abnormalities and may induce further osmotic diarrhea.<sup>9</sup>

## **Moderate-Severe Dehydration**

### *Type of Fluid*

In general, crystalloids such as saline or PLRS are preferred over colloid-containing solutions for the management of patients with severe volume depletion.<sup>7,10-14</sup> Crystalloids, in particular saline solutions, are equally effective as colloids in expanding the plasma volume and are much less expensive.<sup>13-16</sup> Hyperoncotic HES solutions should be avoided since they increase the risk of acute kidney injury, need for renal replacement therapy, and mortality.<sup>15,16</sup>

In common practice, the usual IV fluid for hydration and resuscitation are saline-based fluids. Saline-based fluids may cause homeostatic imbalances, most importantly metabolic acidosis, due to the following: 1) significantly higher chloride levels compared to plasma (154 mmol/L versus 98-102 mmol/L); 2) lack of electrolytes normally present in the serum, including potassium, calcium, glucose, and magnesium; and 3) lack of bicarbonate or bicarbonate precursor buffers necessary to maintain normal plasma pH levels. The excessively high, non-physiologic concentrations of chloride have been demonstrated to cause various adverse effects. High chloride delivery to the macula densa activates the tubuloglomerular feedback, which causes afferent arteriolar vasoconstriction and mesangial contraction leading to reductions in GFR.

Yunos et al. studied the association of chloride-liberal fluids (including PNSS with 150 mmol chloride/L) and chloride-restrictive fluids (including PLRS with 109 mmol chloride/L) with the development of acute kidney injury in critically ill adult patients. Results showed that the use of chloride-restrictive fluids was associated with a significantly lower increase in serum creatinine compared to chloride-liberal fluids (14.8 umol/L versus 22.6 umol/L respectively). Even after adjusting for confounding factors, the chloride-restrictive fluids group had significantly lower incidence of kidney injury and failure based on the RIFLE criteria (OR=0.52; 95% CI 0.37, 0.75), and significantly lower use of renal replacement therapy (OR=0.52; 95% CI 0.33, 0.81).<sup>17</sup> Additional advantages of using PLRS over PNSS include shorter time to micturition, greater urine output, and better renal cortical perfusion.<sup>18</sup>

### *Rate of Fluid Resuscitation*

Patients with moderate to severe dehydration need urgent assessment and resuscitation. There are limited controlled studies on the adequate rate of fluid resuscitation for moderate to severe dehydration in adults. IV fluid rates ranging from 2-3 mL/kg/hr have been used in studies.

Patients with moderate dehydration should be given 500-1,000 mL of IV fluids within 1-2 hours. For patients with severe dehydration, 1-2 liters of IV fluids should be given within 1 hour. Once hemodynamic stability has been restored, fluids to replace ongoing losses in addition to maintenance IV fluid of at least 25-30 mL/kg/day should be given.<sup>19,20</sup>

DOH and WHO adopted the 4-2-1 rule for computing maintenance fluid requirements in adults.<sup>21,22</sup>

Treatment protocol for maintenance IV fluids:

- 4 mL/kg/hour for the first 10 kg body weight
- + 2 mL/kg/hour for the next 10 kg body weight
- + 1 mL/kg/hour for every subsequent kg body weight

For quick calculation of hourly maintenance fluid rate for adults, the following formula may also be used:<sup>19,20,22</sup>

BW <50 kg	2 – 3 mL/kg/hour
BW >50 kg	1.5 – 2 mL/kg/hour

If the patient remains hemodynamically unstable despite initial fluid resuscitation and needs inotropic support, referral to a specialist should be done.<sup>18</sup> Vasopressors should only be started after the patient has been properly hydrated. In patients with septic shock, at least 2 liters of IV fluid should have already been given prior to initiation of vasopressors in order for vasopressors to be maximally effective.

Elderly patients and those at risk of fluid overload (patients with heart failure, kidney disease) should also be referred to a specialist for individualized fluid management. Some experts suggest 20-25 mL/kg as a starting point for IV fluid administration among these patients.<sup>18</sup>

The volume of ongoing losses is estimated based on frequency of vomiting or diarrhea. The estimated fluid loss is added to the maintenance fluid requirement to approximate the required fluid intake as closely as possible.



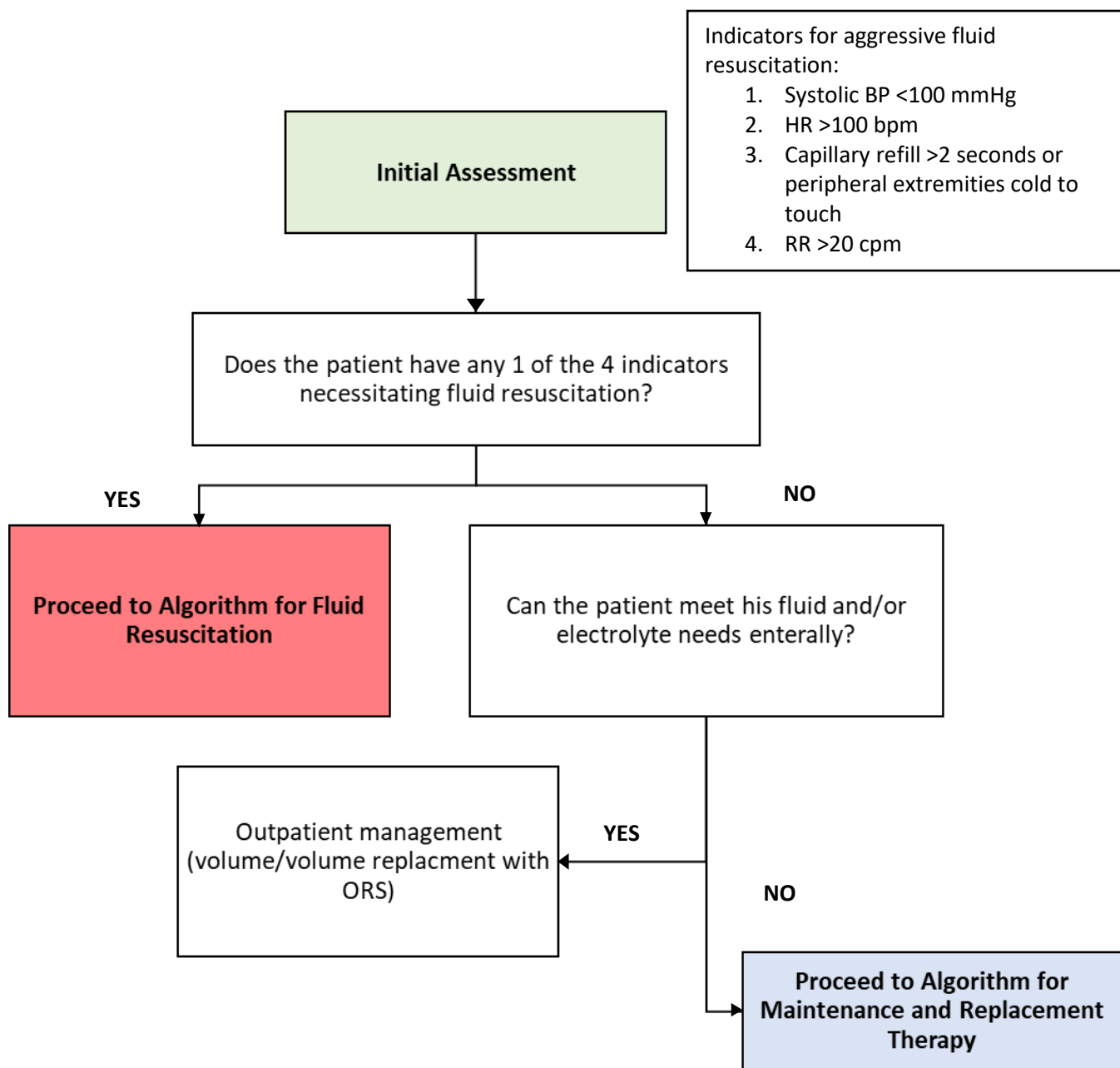


Figure 1. Algorithm for initial assessment of dehydration in adult patients.

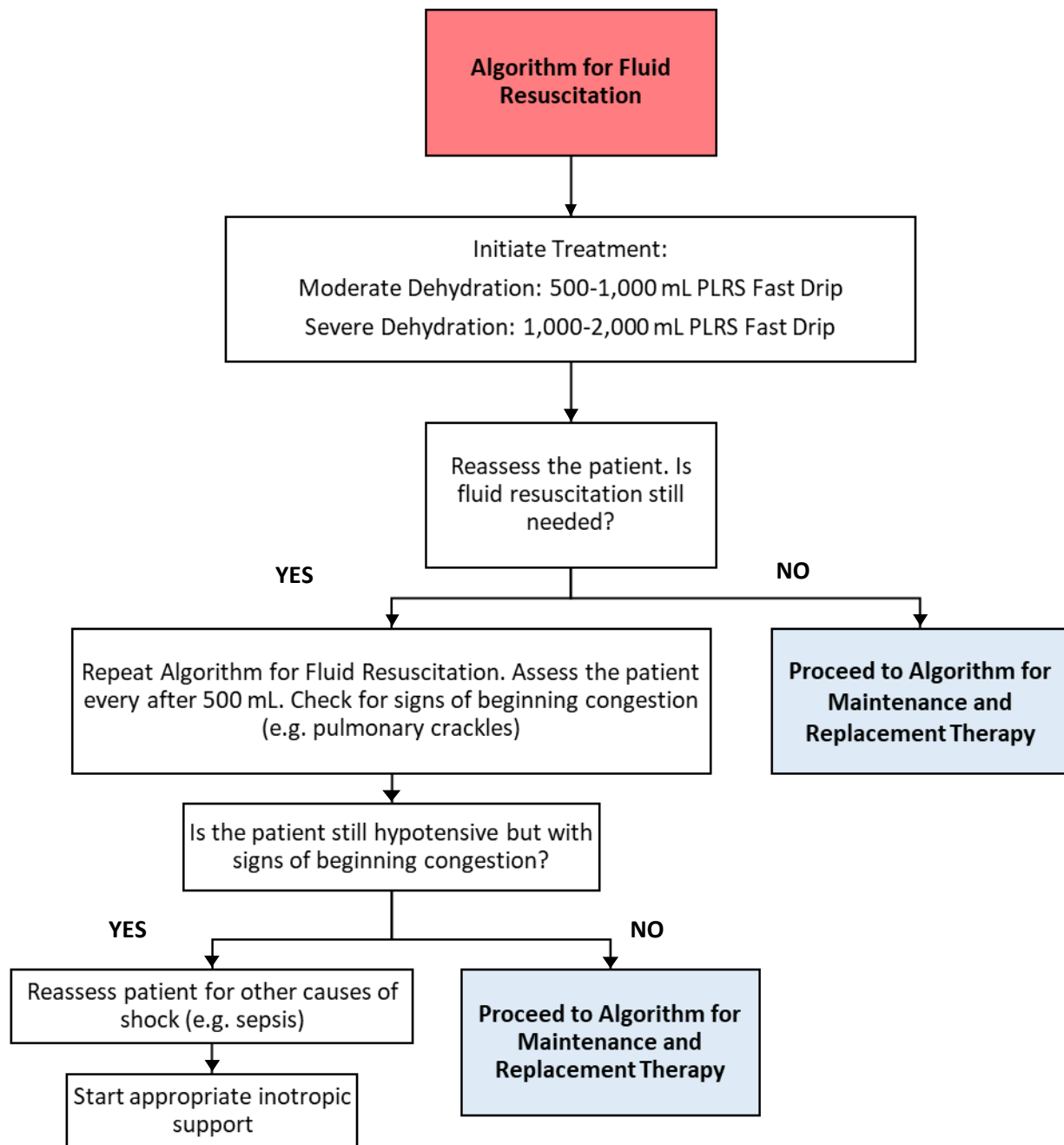


Figure 2. Algorithm for fluid resuscitation of adult patients.

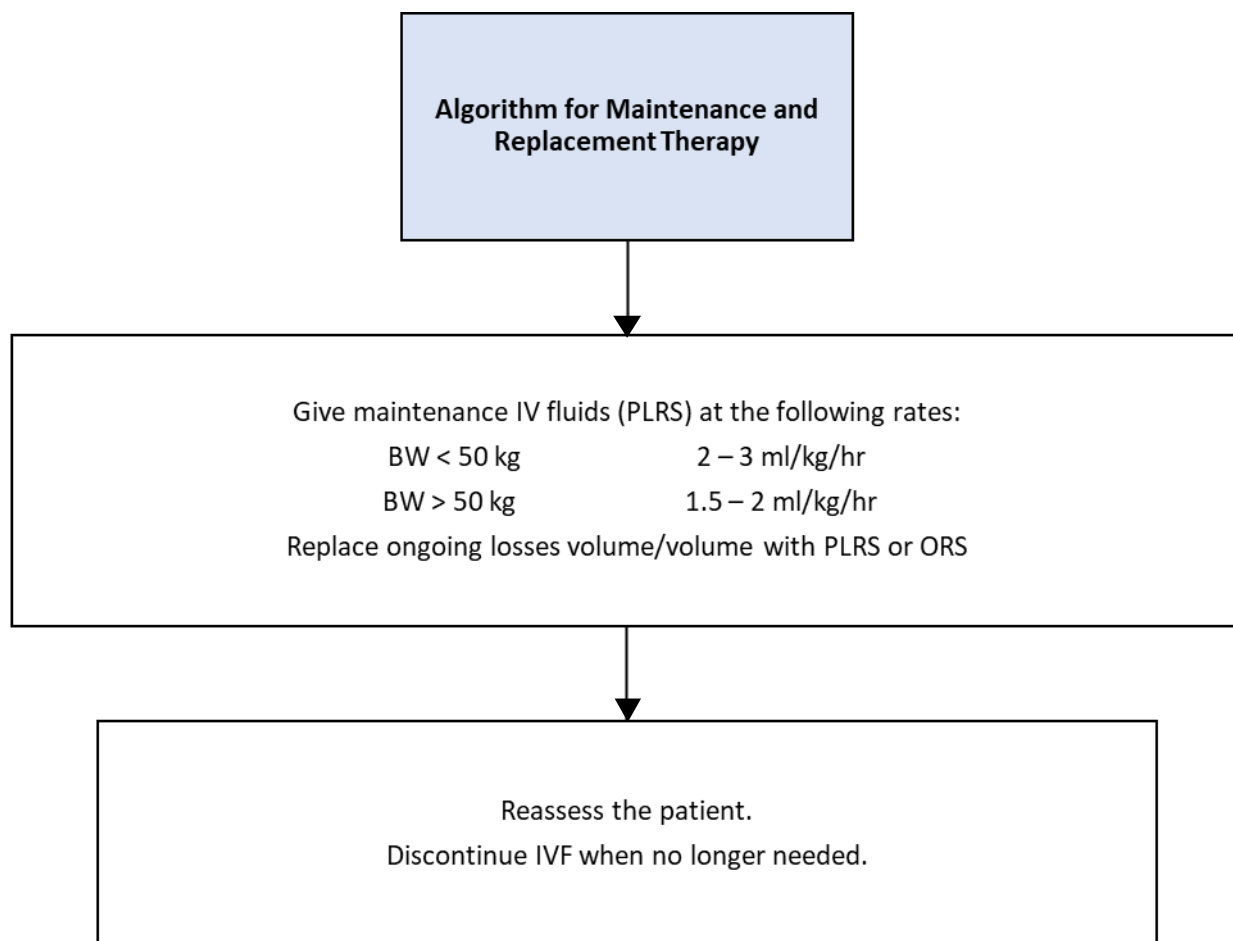


Figure 3. Algorithm for maintenance and replacement therapy.

### 3B. What are the indications for empiric antimicrobial treatment in adults with acute infectious diarrhea?

1. Empiric antimicrobial treatment is **NOT recommended** for adults with acute diarrhea and the following clinical features:
  - Mild to moderate dehydration
  - Non-bloody stools
  - Symptoms <3 days

[Strong recommendation, low quality of evidence]

2. Empiric antimicrobial treatment is recommended for patients with acute diarrhea with moderate to severe dehydration plus any of the following clinical features:
  - Fever alone
  - Fever and bloody stools
  - Symptoms persisting >3 days

[Strong recommendation, low quality of evidence]

3. The following antimicrobials are recommended for empiric treatment of acute infectious diarrhea:

- Azithromycin 1g single dose OR
- Ciprofloxacin 500 mg twice daily for 3-5 days

[Strong recommendation, low quality of evidence]

Once the suspected organism is confirmed, antimicrobial therapy may be modified accordingly.

### SUMMARY OF EVIDENCE:

A systematic review by Gottlieb and Heather of 2 RCTs compared antibiotics and placebo as empiric treatment for diarrhea. One RCT reported that among patients with mild acute infectious diarrhea, there was no significant difference in the mean number of unformed stools passed during the 3-day study (4.2 for co-trimoxazole group, 4.2 for clloquinol group, and 5.3 for placebo group; p-value not reported). The other RCT reported no significant difference in the proportion of people who were well by 72 hours (49% for enoxacin group, 49% for co-trimoxazole group, and 33% for placebo group;  $p>0.05$ ).<sup>23</sup>

Based on a review by Zollner-Schwetz and Krause, empiric antimicrobial therapy is recommended for patients with any of the following:  $\geq 6$  stools per day, fever, fever and bloody diarrhea, symptoms persisting >1 week, or immunocompromised status.<sup>24</sup> Another review by DuPont recommended empiric antibiotic therapy for sporadic cases of febrile dysentery especially if the patients are toxic since this suggests the possibility of systemic infection, and for severe cases of travelers' diarrhea, hospital-associated diarrhea, or antibiotic-associated diarrhea.<sup>25</sup> However, the systematic review by Gottlieb and Heather found no RCTs evaluating the effect of empiric antibiotic therapy in treating severe diarrhea among adults living in resource-poor countries.<sup>23</sup>

In the review by Zollner-Schwetz and Krause, azithromycin, ciprofloxacin and co-trimoxazole may be given as empiric antibiotic therapy for severe diarrhea.<sup>24</sup> However, the 2016 Antimicrobial Resistance Surveillance Program (ARSP) report showed that *Shigella* had resistance rates of 55.3% to co-trimoxazole.<sup>26</sup> An RCT by Goodman et al. showed that Ciprofloxacin 500 mg twice daily for 5 days significantly shortened the duration of diarrhea (2.4 days for ciprofloxacin group and 3.4 days for placebo group;  $p < 0.0005$ ), while co-trimoxazole 160/800 mg twice daily did not have a significant effect (4.2 days for co-trimoxazole and 4.0 days for placebo).<sup>27</sup> Another RCT by Dryden et al. showed significant reduction in symptom duration by 2 days for the ciprofloxacin group compared to placebo (2.2 days for ciprofloxacin group and 4.6 days for placebo group;  $p < 0.0001$ ).<sup>28</sup>

#### **4B. What are the recommended antimicrobials for the following etiologies of acute infectious diarrhea in adults?**

##### **1. Cholera**

The following drugs are recommended for adults with suspected or confirmed cholera:

- Azithromycin 1 g PO single dose [Strong recommendation, high quality of evidence]
- Ciprofloxacin 1-2 g PO single dose or 500 mg twice a day for 3 days [Strong recommendation, low to moderate quality of evidence]
- Alternative: Doxycycline 100 mg PO twice a day for 3 days [Strong recommendation, low to moderate quality evidence]

##### **2. *Shigella***

The following drugs are recommended for adults with suspected or confirmed *Shigella* dysentery:

- Ceftriaxone 1 g IV once a day for 5 days OR
  - Ciprofloxacin 500 mg PO twice a day for 5 days OR
  - Azithromycin 1 g PO single dose
- [Strong recommendation, moderate to high quality of evidence]

Once culture results are available, antimicrobial therapy can be modified accordingly.

##### **3. Non-typhoidal *Salmonella***

The following drugs are recommended for adults with suspected or confirmed non-typhoidal *Salmonella* dysentery:

- Ciprofloxacin 500 mg PO twice a day for 5 days [Strong recommendation, low to high quality of evidence]
- Ceftriaxone 1 g IV once a day for 5 days

Once culture results are available, antimicrobial therapy can be modified accordingly.

##### **4. Ameobiasis**

For adults with confirmed amoebiasis, the recommended treatment is metronidazole 500-750 mg tablet three times a day for 10 days. [Strong recommendation, high quality of evidence]

The following are alternative antimicrobials that may be used:

- Tinidazole 2 g once a day for 3 days
  - Secnidazole 2 g single dose
- [Strong recommendation, high quality of evidence]

Diloxanide furoate 500 mg three times a day may be added to metronidazole, if available.

## SUMMARY OF EVIDENCE

### ***Cholera***

Based on a systematic review, patients suspected of cholera who received antibiotics had decreased duration of diarrhea compared to placebo (SMD= -43.37, 95% CI -57.48, -29.97 in ciprofloxacin group; SMD= -13.36, 95% CI -21.29, -9.43 in tetracycline group; and SMD= -25.44, 95% CI -38.9, -11.9 in doxycycline group). Patients given doxycycline had significantly less bacteriologic failure compared to placebo (RR=0.11; 95% CI 0.04, 0.30). There was no significant difference in mortality between patients given tetracycline and placebo (RR=0.0; 95% CI -0.08, 0.08).<sup>29</sup> An RCT showed no significant difference in mortality between adults patients given doxycycline and placebo (RR=0.0; 95% CI -0.13, 0.13).<sup>30</sup>

Among all the antibiotics, azithromycin is most beneficial for treating cholera. One RCT reported that patients given azithromycin had significantly shorter duration of diarrhea (MD= -48.00; 95% CI -55.64, -40.36), less clinical failure (RR=0.36; 95% CI 0.26, 0.52), and less bacteriologic failure (RR=0.24; 95% CI 0.16, 0.35) compared to ciprofloxacin.<sup>31</sup> Another study reported no significant difference between tetracycline and quinolones in the duration of diarrhea (MD=-3.2, 95% CI -8.45, 2.05), clinical failure (RR=0.67; 95% CI 0.33, 1.38) and bacteriological failure (RR=0.99; 95% CI 0.14, 6.82).<sup>32</sup> An RCT involving patients  $\geq 15$  years old showed no significant difference in bacteriologic failure rates (RR=0.24; 95% CI 0.05, 10.09) and duration of diarrhea (MD= 0.0; 95% CI -5.32, 5.32) among patients given tetracycline and doxycycline.<sup>33</sup> Pooled results from 4 studies showed that patients given doxycycline had more bacteriologic failure compared to those given fluoroquinolone (RR=5.84; 95% CI 2.70, 12.65), but there was no significant difference in diarrhea duration (MD=4.64; 95% CI -2.14, 11.42) and mortality (RR=0.0; 95% CI -0.07, 0.07). Based on pooled data from 3 studies, there was no significant difference in duration of diarrhea among patients given tetracycline and chloramphenicol (MD= -11.49; 95% CI -25.93, 2.96). One RCT showed no significant difference in clinical failure among patients given tetracycline compared to chloramphenicol (RR=0.71; 95% CI 0.16, 3.08).<sup>29</sup>

According to ARSP 2016 data, cholera isolates are still susceptible to co-trimoxazole, chloramphenicol, and tetracycline.<sup>26</sup>

### ***Shigella***

Adult patients given ceftriaxone or ampicillin experienced significantly earlier resolution of fever compared to placebo (MD= -1.20, 95% CI -2.20, -0.20 for ceftriaxone; MD= -1.50, 95% CI -2.41, -0.59 for ampicillin). However, ceftriaxone and ampicillin had no significant effect on the time to resolution of diarrhea and blood in the stool compared to placebo.<sup>34</sup> A systematic review on the treatment of *Shigella* showed that patients who received ciprofloxacin had earlier cessation of fever and blood in stools, as well as fewer bacteriologic failure, compared to those given azithromycin.<sup>35</sup> Another study found that ciprofloxacin was associated with less bacteriologic failure (RR=0.28; 95% CI 0.08, 0.95) and fewer episodes of diarrhea on follow-up (RR=0.14; 95% CI 0.04, 0.44) compared to ampicillin.<sup>36</sup>

ARSP data showed that *Shigella* strains had 58% resistant rate for ampicillin, 13.7% for ciprofloxacin, and 11.1% for ceftriaxone.<sup>26</sup> Thus, ceftriaxone and ciprofloxacin are recommended as treatment options for *Shigella* dysentery.

## Non-typhoidal *Salmonella*

A systematic review of 3 trials compared ciprofloxacin given for 5 days and co-trimoxazole given for 5 days with placebo. There was significantly less microbiologic failure in the antibiotic treatment groups (RR=0.38; 95% CI 0.21, 0.69).<sup>37</sup> An RCT involving 65 patients who were culture positive for non-typhoidal *Salmonella* showed no significant difference in the resolution of symptoms among patients given ciprofloxacin and placebo (MD=0.2 days; 95% CI -0.5, 0.9) and among patients given co-trimoxazole and placebo (MD=0.2 days; 95% CI -1.0, 0.6).<sup>38</sup> However, based on the latest resistance rates from ARSP 2016, co-trimoxazole is not recommended for non-typhoidal *Salmonella* except if it is culture sensitive.<sup>26</sup>

## Amoebiasis

A Cochrane systematic review studied the efficacy of different anti-amoebic drugs. Comparison of metronidazole with diiodohydroxyquinoline versus metronidazole alone among adult patients with amoebiasis showed less clinical failure (RR=0.17; 95% CI 0.13, 0.21) and less parasitological failure (RR=0.23; 95% CI 0.11, 0.45) in 1-14 days for patients given combination therapy. However, the said combination is not available in the Philippines. There was no significant difference between tinidazole and metronidazole in parasitological failure in 1-14 days (RR=0.17; 95% CI 0.02, 1.30) and 15-60 days (RR=0.64; 95% CI 0.25, 1.64). There was also no significant difference between secnidazole and metronidazole in parasitological failure (RR=0.13; 95% CI 0.01, 7.12). No RCTs were found studying the combination of metronidazole and diloxanide furoate.<sup>39</sup>

## 5B. Should loperamide and racecadotril be given in adults with acute infectious diarrhea?

Loperamide is NOT recommended in adults with acute infectious diarrhea.

[Weak recommendation, low quality of evidence]

Racecadotril may be given to decrease the frequency and duration of diarrhea. The dose is 100 mg capsule 3 times a day

[Weak recommendation, low quality of evidence]

## SUMMARY OF EVIDENCE

Loperamide is an anti-motility drug used in acute diarrhea to allow individuals to resume their usual activities. This synthetic opiate exerts its action by producing segmental contractions in the intestines, resulting in greater gut absorption and delayed fluid passage through the intestines.<sup>40</sup> Mucosal secretion is also attenuated by this medication through its inhibition of calmodulin.<sup>41</sup> This drug is

generally tolerated well, with side effects such as constipation, cramps, headaches, and dizziness occurring in less than 1% of patients.<sup>42</sup> Constipation has been shown to be dose-dependent.<sup>43</sup>

Several studies comparing loperamide with other opioid-receptor agonists have shown that loperamide significantly reduces stool frequency and diarrhea duration.<sup>43</sup> Two double-blind RCTs showed that loperamide significantly reduced the number of loose stools compared to placebo; however, these studies were small and indirect since patients with mucoid, bloody diarrhea and fever were excluded. Furthermore, the trials did not mention any safety outcomes.<sup>44,45</sup>

A meta-analysis involving 7 studies with a total of 1,644 individuals with acute diarrhea compared racecadotril and loperamide. Racecadotril was not significantly different in terms of proportion of patients who recovered from diarrhea [hazard ratio (HR)=1.08; 95% CI 0.95, 1.22], and this finding was homogeneous among studies ( $I^2=0$ , Q test=5.48,  $p=0.55$ ). However, post-treatment constipation was significantly lower among patients who took racecadotril (RR=0.34; 95% CI 0.22, 0.51), with no significant heterogeneity in the studies ( $I^2=10\%$  and  $30\%$  respectively,  $p>0.5$ ).<sup>46</sup>

#### **Question 6. What is the role of probiotics in the treatment of acute diarrhea among adults?**

There is insufficient evidence to recommend the use of probiotics in adults with acute diarrhea.

[Weak recommendation, very low to low quality of evidence]

### **SUMMARY OF EVIDENCE**

The number of RCTs on the use of probiotics for acute gastroenteritis in adults is limited. A Cochrane systematic review on the efficacy of probiotics in infectious diarrhea found only 6 trials on adult patients.<sup>47</sup>

Because of limited trials and varied end points, the review was not able to include studies on adults in the primary analysis of mean duration of diarrhea. The review concluded that there was insufficient evidence regarding the usefulness of probiotics in adults.<sup>47</sup>

There are no subsequent published RCTs on the use of probiotics in adults with acute gastroenteritis other than those included in the systematic review. Most studies on probiotics in adults investigate the potential of probiotics in preventing antibiotic-associated diarrhea and *Clostridium difficile* infection.



**Question 7. What is the recommended management for complications of acute infectious diarrhea in adults?**

Acute kidney injury is a serious and potentially life-threatening complication. It is best to refer the patient immediately to a specialist at the first sign of AKI.

[Good practice statement]

Hospital treatment and close monitoring is recommended for patients with severe hyponatremia, severe hypernatremia, or symptomatic patients regardless of the degree of sodium imbalance. The approach to therapy depends on the patients' risk stratification. Referral to a specialist is advised.

[Good practice statement]

Hospital treatment and close monitoring is recommended for patients with severe hypokalemia, severe hyperkalemia, or symptomatic patients regardless of the degree of potassium imbalance. Referral to a specialist is advised.

[Good practice statement]

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## IV. PREVENTION

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### 1. What interventions are effective in the prevention of acute infectious diarrhea?

Transmission of pathogens that cause acute infectious diarrhea can be prevented by hand hygiene promotion, access to clean and safe water, proper food handling, proper excreta disposal, vaccination, supplements, and breastfeeding.

#### A. Hand Hygiene and Hand Hygiene Promotion

The promotion of hand hygiene in all settings and on all occasions is recommended to reduce transmission of microbes that cause acute infectious diarrhea.

[Strong recommendation, moderate quality of evidence]

All efforts should be made to provide access to clean water, soap and hand drying materials.

[Strong recommendation, moderate quality of evidence]

#### SUMMARY OF EVIDENCE

Hand hygiene is an important strategy to prevent acute infectious diarrhea since this is the most convenient way to eliminate microbes from the skin.<sup>1</sup> This strategy may require behavioral changes and infrastructural resources.

##### Hand hygiene

Washing hands with soap and water is the best way to reduce the number of microbes in most situations. WHO recommends that hands should be washed with soap and water when visibly dirty, visibly soiled, and after using the toilet.<sup>2</sup> Hands should be dried thoroughly with paper towels (as these are considered hygienic) since moist hands more readily transfer microorganisms compared to dry hands.<sup>1</sup>

If soap and water are not available, alcohol-based hand sanitizers that contain at least 60% alcohol can be used.<sup>2</sup> Alcohol-based hand sanitizers can quickly reduce the number of microbes on hands in some situations, but sanitizers do not eliminate all types of germs. A meta-analysis showed that no significant reduction in the number of gastrointestinal illnesses with the use of alcohol-based sanitizers and educational intervention (RR=0.77; 95% CI 0.52, 1.13) or the use of benzalkonium chloride-based hand sanitizers (RR=0.58; 95% CI 0.30, 1.12) compared to control.<sup>3</sup> Another study reported that giving alcohol-based hand disinfectants to office workers can reduce absences due to diarrhea compared to no intervention (OR=0.11; 95% CI 0.01, 0.93).<sup>4</sup> However, food handlers must do handwashing with soap and water instead of sanitizers.

# How to Handrub?

**RUB HANDS FOR HAND HYGIENE! WASH HANDS WHEN VISIBLY SOILED**


 **Duration of the entire procedure: 20-30 seconds**

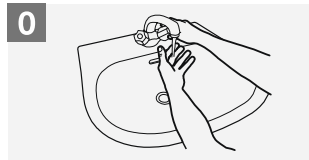


Figure 1. Proper handwashing technique using alcohol-based hand rub<sup>5</sup>  
(Reference: World Health Organization. How to Hand Rub. [www.who.int/gpsc/5may/How\\_To\\_HandRub\\_Poster.pdf](http://www.who.int/gpsc/5may/How_To_HandRub_Poster.pdf). Revised 2009. Accessed August 10, 2018.)

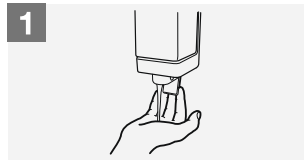
# How to Handwash?

WASH HANDS WHEN VISIBLY SOILED! OTHERWISE, USE HANDRUB

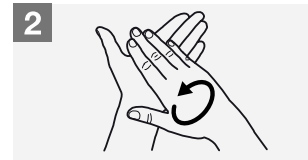
 **Duration of the entire procedure: 40-60 seconds**



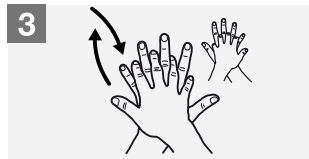
Wet hands with water;



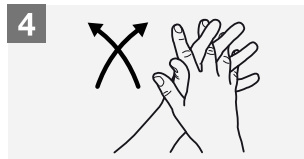
Apply enough soap to cover all hand surfaces;



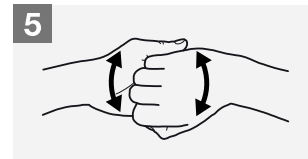
Rub hands palm to palm;



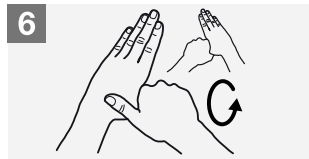
Right palm over left dorsum with interlaced fingers and vice versa;



Palm to palm with fingers interlaced;



Backs of fingers to opposing palms with fingers interlocked;



Rotational rubbing of left thumb clasped in right palm and vice versa;



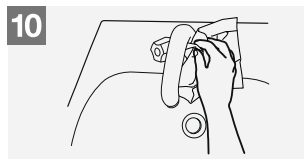
Rotational rubbing, backwards and forwards with clasped fingers of right hand in left palm and vice versa;



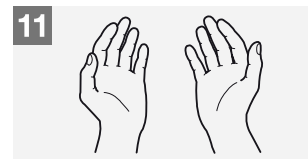
Rinse hands with water;



Dry hands thoroughly with a single use towel;



Use towel to turn off faucet;



Your hands are now safe.



**World Health Organization**

**Patient Safety**

A World Alliance for Safer Health Care

**SAVE LIVES**

Clean Your Hands

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May 2009

Figure 2. Proper handwashing technique with soap and water

(Reference: World Health Organization. How to Handwash? [http://www.who.int/gpsc/5may/How\\_To\\_HandWash\\_Poster.pdf](http://www.who.int/gpsc/5may/How_To_HandWash_Poster.pdf). Revised 2009. Accessed August 10, 2018.)

## Hand hygiene promotion

Hygiene promotion interventions are one of the strategies identified by WHO to control diarrhea. These interventions consist of activities that encourage individuals and communities to adopt safer practices in domestic and community settings to prevent hygiene-related diseases such as diarrhea.

Several systematic reviews report that diarrhea can be prevented with promotion of handwashing. A Cochrane review studied several interventions that promote handwashing, such as hygiene education (group trainings, reminders, peer trainers, booklets, newsletters, songs about hand hygiene) and provision of equipment. The evidence is summarized in Table 1.<sup>6</sup> Two experimental studies looked at the incidence of diarrhea in low to middle-income countries at child day care facilities and schools. These studies show that hand washing promotion could prevent 33% of diarrhea episodes (RR=0.66; 95% CI 0.43, 0.99). Although results favor the intervention, the authors were unsure if these benefits would be maintained if trials are replicated in less controlled situations or in other settings. Two trials that focused only on handwashing as the intervention showed no significant difference in the effect estimate compared to no intervention (RR=0.69; 95% CI 0.43, 1.09). Nine studies involving multiple hygiene interventions showed decreased incidence of diarrhea compared to no intervention (RR=0.69; 95% CI 0.57, 0.84). Handwashing promotion among communities in low to middle-income countries in Asia (6 studies), South America (1 study), and Africa (1 study) resulted in prevention of around one quarter of diarrhea episodes (RR=0.72; 95% CI 0.62, 0.83) with moderate quality evidence. In 6 trials, free soap was provided alongside handwashing education. The over-all effect size was larger in the 6 trials with soap provided (RR=0.66; 95% CI 0.56, 0.78) compared to the two trials which had handwashing education but did not provide soap (RR=0.84; 95% CI 0.67, 1.05). Almost all studies used soap and water for handwashing and did not report on proper technique.

Another systematic review reported that nonbacterial soap combined with hand hygiene education reduced episodes of diarrhea by 39% (RR=0.61; 95% CI 0.43, 0.88), with hand hygiene education showing the strongest protective effect (RR=0.69; 95% CI 0.43, 0.88), based on pooled data from 6 studies.<sup>3</sup>

Table 1. Summary of studies on hand hygiene promotion and the incidence of diarrhea.<sup>6</sup>

Number of RCTs	Total study population size	Intervention	Control	Outcome (incidence of diarrhea)
2	45,382	Handwashing promotion at childcare centers and schools	No intervention	Reduced incidence of diarrhea (RR=0.66; 95% CI 0.43, 0.99)
2	1,045 children	Focused only on handwashing at childcare centers and schools	No intervention	No difference (RR=0.69; 95% CI 0.43, 1.09)
9	48,999 children	Multiple hygiene interventions at childcare centers and schools	No intervention	Reduced incidence of diarrhea (RR=0.69; 95% CI 0.57, 0.84)
7	14,672	Handwashing in the community	No intervention	Reduced incidence of diarrhea (RR=0.72; 95% CI 0.62, 0.83)
6	11,422	Handwashing in the community with provision of soap	No intervention	Reduction of incidence of diarrhea (RR=0.66; 95% CI 0.56, 0.78)

2	3,304	Handwashing in the community without provision of soap	No intervention	No difference (RR=0.84; 95% CI 0.67, 1.08)
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RCT – randomized controlled trials, RR – relative risk

## B. Water Safety Interventions

1. Drinking water should be clean and safe. Recommended methods to ensure clean and safe water include boiling, chemical disinfection, and filtration with ultraviolet radiation.  
[Strong recommendation, low quality of evidence]
2. Drinking water should comply with the Philippine National Standards for Drinking Water (DENR Administrative Order No. 26-A. Series 1994).  
[Good practice statement]

## SUMMARY OF EVIDENCE

Boiling, chemical disinfection, ultraviolet (UV) radiation, and filtration are some of the interventions recommended to improve water quality. Point-of-use interventions are available to achieve safe supply of drinking water.

A systematic review evaluated the different point-of-use methods to improve water quality and their effects on prevention of diarrhea. Results showed that chlorination, flocculation, filtration, and solar disinfection (SODIS) were all beneficial in reducing the incidence of diarrhea. There were differences in the magnitude of effect among these techniques. Filtration had the highest reduction rate at 52%, while chlorination had the lowest reduction rate at 33%. The relative risks of each technique is shown in Table 2.<sup>7</sup>

Table 2. Effect of different water safety interventions in the reduction of incidence of diarrhea.<sup>7</sup>

Intervention	Comparison	RR (95% CI)	Interpretation
Chlorination	No intervention	0.77 (0.67, 0.91)	Reduced incidence of diarrhea
Flocculation/disinfection	No intervention	0.69 (0.58, 0.82)	Reduced incidence of diarrhea
Filtration	No intervention	0.48 (0.38, 0.59)	Reduced incidence of diarrhea
Solar disinfection	No intervention	0.62 (0.42, 0.94)	Reduced incidence of diarrhea

Application of heat to water, like boiling, is an effective way to kill all water-borne pathogens. Microorganisms such as enteric bacteria, protozoa and viruses are sufficiently inactivated in the process of heating water to a rolling boil for 1 minute, or for 3 minutes if done at altitudes greater than 6562 feet (2000 meters).<sup>8</sup> Clarification methods should be done prior to boiling. The boiled water must then be allowed to cool down without adding ice to prevent contamination.<sup>9</sup> Temperature and time can affect the effectiveness of boiling.



If boiling water is not possible, a combination of interventions is recommended. These interventions include chlorination, iodination, portable filtering devices, and SODIS. Chlorination and iodination are considered chemical disinfection methods. The household bleach (5% solution of sodium hypochlorite) may be used for chlorination. Four drops of the bleach should be added to clear water. For iodination, 5 drops of tincture of iodine (2% solution) or 8 drops of 10% iodine solution may be added to a liter of clear water. For both chlorination and iodination, the water to be used must have been settled or clarified at room temperature (25°C) and must have been left to stand for at least 30 minutes before use. If the water is cold, the time is doubled before use for every 10°C drop in temperature. The effectiveness of chemical disinfection methods are affected by contact time, disinfectant concentration, water temperature, water turbidity, water pH, and many other factors. Both chlorination and iodination are highly effective against bacteria and viruses but not against cryptosporidium.

Different filtration techniques were also studied, but the effectiveness depends on the pore size of the filter, amount and particle size of the contaminant, and charge of the contaminant particle. Recommendations of the specific manufacturer of the filters must be followed. Smaller filter pore sizes can prevent more contaminants.

The SODIS method uses the combined effects of UV light-induced DNA damage, thermal inactivation and photo-oxidative destruction to inactivate disease-causing organisms. It is done by filling 0.3-2.0 liter plastic soda bottles with low turbidity water. The bottles are shaken to allow oxygenation, and then placed on a roof or rack for 6 hours (if sunny) or 2 days (if cloudy). Although UV light alone is effective, this technique requires pre-filtering of water because of its dependence on low water turbidity. There should also be appropriate UV power delivery and appropriate exposure time to achieve maximum pathogen reduction. The spectrum of activity of this method is unknown.

With strict adherence to the manufacturers' recommendations, the combination of chemical disinfection and filtration is the most effective alternative to boiling in killing all water-borne pathogens.<sup>8,9</sup> Filtration alone prevents protozoa but has no effect on viruses. Disinfection or chlorination is effective against viruses but not very effective against protozoa. The effects of the water safety interventions against various microorganisms are summarized in Table 3.

Table 3. Effects of water safety interventions against different targeted microorganisms.<sup>8</sup>

Contaminant	Boiling	Filtration	Disinfection		Combination of Filtration and Disinfection
			Iodine/Chlorine	Dioxide	
Protozoa: <i>Cryptosporidium</i>	++++	+++ (using absolute ≤1 micron filter)	-	+ to ++	++++ (using absolute ≤ 1 micron filter)
Protozoa: <i>Giardia intestinalis</i> (aka <i>Giardia lamblia</i> )	++++	+++ (using absolute ≤1 micron filter)	+ to ++	+++	++++ (using absolute ≤ 1 micron filter)
Bacteria: <i>Campylobacter</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>E. coli</i>	++++	++ (using absolute ≤0.3 micron filter)	+++	+++	++++ (using absolute ≤ 0.3 micron filter)
Viruses: Enterovirus, hepatitis A, norovirus, rotavirus	++++	-	+++	+++	+++

Interpretation: - not effective, + low effectiveness, ++ moderate effectiveness, +++ high effectiveness, ++++ very high effectiveness

The Philippine National Standards for Drinking Water<sup>10</sup> was designed to guide health and sanitation authorities and the general public regarding acceptable values of the determined parameters in measuring water quality. For bacteriologic quality of drinking water, no amount of bacteria is acceptable. Testing to determine water potability should be done routinely and adequate treatment will have to be instituted to deal with changes in the quality of the raw water. The aim is to produce a clean and safe water supply.

### C. Proper Food Handling

1. There is no standard recommended screening test for food handlers in the Philippines.
2. No person shall be employed in any food establishment without a health certificate issued by the city or municipal health officer in accordance with the Code on Sanitation of the Philippines (P.D.856). This certificate shall be issued only after compliance with the required medical examinations and immunizations.  
[Good practice statement]
3. The local health offices should provide training on food safety and hygiene before issuance of the health certificate to the recipient.  
[Good practice statement]
4. Food industry workers need to notify their employers if they have any of the following conditions, since these could temporarily disqualify them from handling food:
  - a. Hepatitis A
  - b. Diarrhea
  - c. Vomiting
  - d. Fever
  - e. Sore throat
  - f. Skin rash or other skin lesions (e.g. boils, cuts, etc.)
  - g. Discharge from the ears, eyes, or nose  
[Good practice statement]
5. Food handlers involved in the preparation of raw, unwrapped food or food served without further cooking should be screened for *Salmonella* after a bout of diarrhea. Two negative stool culture samples at least 24 hours apart are necessary before allowing them to resume work.  
[Good practice statement]

## **SUMMARY OF EVIDENCE**

Food hygiene refers to measures that ensure consumption of safe food. Food hygiene must be observed by any domestic or professional food handler. A food handler is any person who routinely comes into contact with packed or unpacked food.<sup>11</sup> Food handlers play a crucial role in the etiology of most foodborne illnesses.

Although there is limited evidence on effective and sustainable food hygiene interventions, WHO promotes the Five Keys to Safer Food Manual as a tool to promote the principles of safe food handling. The 5 keys shown in Figure 2.<sup>11</sup> According to the implementing rules and regulations of the Code on Sanitation of the Philippines, food handlers should obtain a health certificate from local health units prior to food handling. Health certificates are issued only after compliance with necessary requirements.<sup>12</sup>

# Five keys to safer food



## Keep clean

- ✓ Wash your hands before handling food and often during food preparation
- ✓ Wash your hands after going to the toilet
- ✓ Wash and sanitize all surfaces and equipment used for food preparation
- ✓ Protect kitchen areas and food from insects, pests and other animals

### Why?

While most microorganisms do not cause disease, dangerous microorganisms are widely found in soil, water, animals and people. These microorganisms are carried on hands, wiping cloths and utensils, especially cutting boards and the slightest contact can transfer them to food and cause foodborne diseases.



## Separate raw and cooked

- ✓ Separate raw meat, poultry and seafood from other foods
- ✓ Use separate equipment and utensils such as knives and cutting boards for handling raw foods
- ✓ Store food in containers to avoid contact between raw and prepared foods

### Why?

Raw food, especially meat, poultry and seafood, and their juices, can contain dangerous microorganisms which may be transferred onto other foods during food preparation and storage.

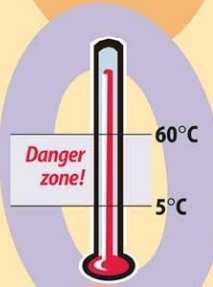


## Cook thoroughly

- ✓ Cook food thoroughly, especially meat, poultry, eggs and seafood
- ✓ Bring foods like soups and stews to boiling to make sure that they have reached 70°C. For meat and poultry, make sure that juices are clear, not pink. Ideally, use a thermometer
- ✓ Reheat cooked food thoroughly

### Why?

Proper cooking kills almost all dangerous microorganisms. Studies have shown that cooking food to a temperature of 70°C can help ensure it is safe for consumption. Foods that require special attention include minced meats, rolled roasts, large joints of meat and whole poultry.



## Keep food at safe temperatures

- ✓ Do not leave cooked food at room temperature for more than 2 hours
- ✓ Refrigerate promptly all cooked and perishable food (preferably below 5°C)
- ✓ Keep cooked food piping hot (more than 60°C) prior to serving
- ✓ Do not store food too long even in the refrigerator
- ✓ Do not thaw frozen food at room temperature

### Why?

Microorganisms can multiply very quickly if food is stored at room temperature. By holding at temperatures below 5°C or above 60°C, the growth of microorganisms is slowed down or stopped. Some dangerous microorganisms still grow below 5°C.



## Use safe water and raw materials

- ✓ Use safe water or treat it to make it safe
- ✓ Select fresh and wholesome foods
- ✓ Choose foods processed for safety, such as pasteurized milk
- ✓ Wash fruits and vegetables, especially if eaten raw
- ✓ Do not use food beyond its expiry date

### Why?

Raw materials, including water and ice, may be contaminated with dangerous microorganisms and chemicals. Toxic chemicals may be formed in damaged and mouldy foods. Care in selection of raw materials and simple measures such as washing and peeling may reduce the risk.

Figure 3. The 5 Keys to Safer Food. (Adapted from WHO Five keys to Safer food Manual)<sup>11</sup>

A systematic review evaluating the effectiveness of food handler training programs (FHTP) in preventing foodborne diseases showed that despite good food safety knowledge and practices in Malaysia and Ireland, food handlers are still the biggest contributor to foodborne diseases. These results highlight that FHTP may not be effective in preventing foodborne diseases.<sup>13</sup> Another systematic review of 79 studies from developed countries showed there was no significant benefit in giving food safety education to consumers to improve food hygiene practices. However, the studies included in the review were very heterogenous and indirect, and some studies did not provide data on study design.<sup>14</sup>

Employees should be encouraged to report illnesses to management, and managers should have a general knowledge on foodborne- and waterborne-related illnesses to make decisions on whom to excuse from work. Guidelines on the time period employees should be excused from work after certain illnesses are shown in Table 4. Although there was no evidence in literature about temporary disqualification from work because of certain illnesses, the technical working group who made the guidelines deemed this measure as practical to protect the public and the co-workers. This measure was voted to be given a strong recommendation.<sup>15</sup>

Table 4. Time frame of exclusion from work after an illness.<sup>15</sup>

Illness	Time frame
Hepatitis A	6 weeks from the onset of jaundice
Parasite condition	Until successfully treated
Staphylococcal and streptococcal infections	Until successfully treated
All other gastrointestinal illnesses	Until symptom-free

#### D. Proper Excreta Disposal

1. Safe stool disposal and hand hygiene are key behaviors to prevent infectious diarrhea.  
[Strong recommendation, low to moderate quality of evidence]
2. The following are approved excreta disposal facilities based on the Code on Sanitation of the Philippines:
  - a. Flush toilet connected to a community sewer, Imhoff tank, septic tank, digester tank, or chemical tank
  - b. Ventilated improved pit (VIP) latrine, sanitary pit in rural areas, pit type, or “antipolo” toilet
  - c. Any disposal device approved by the Secretary of health or his duly authorized representative

[Strong recommendation, low to moderate quality of evidence]

3. Open defecation threatens public health and safety and is unacceptable.

[Strong recommendation, low to moderate quality of evidence]

## SUMMARY OF EVIDENCE

The integrated promotion of safe water supply, sanitation and hygiene practices is beneficial in preventing infectious diarrhea. A systematic review included 13 quasi-randomized controlled trials (RCTs) conducted in 6 low to middle-income countries that evaluated the effect of improved disposal of human excreta on the incidence of diarrhea. Most of the studies showed that interventions to improve human excreta disposal were effective in reducing the incidence of diarrhea by 20% to 80%. The results of the studies are summarized in Table 5.<sup>16</sup>

Table 5. Effects of interventions to improve disposal of excreta on prevention of diarrhea.<sup>16</sup>

<b>Interventions</b>	<b>RR (95% CI)</b>	<b>Interpretation</b>
Double pit, water-sealed latrine, improved water supply, hygiene promotion	0.75	Intervention is beneficial
Cement sanitary platforms, VIP latrines, household water treatment with sodium hypochlorite, improved water storage vessel (clay pot with tap, narrow mouth and lid), improved water supplies (protection of shallow wells), hygiene promotion	0.71 (0.54, 0.92)	Intervention is beneficial
Biogas latrine connected to fermentation reactor	0.56	Intervention is beneficial
VIP latrines, improved water supply	1.03	Intervention has no effect
Replaced “surface” and other “unsatisfactory privies” with new privy, or rehabilitated old privy with 8-ft deep bored well, additional privies remodeled at schools, churches and commercial buildings	0.53	Intervention is beneficial
Double pit latrine, improved water supply, hygiene promotion, oral rehydration therapy	0.64	Intervention is beneficial
Toilets connected to sewer, piped-in water supplies	0.33	Intervention is beneficial
Improved school toilets, maintained and improved school sanitary environment, hygiene promotion, improved water supply, point-of-use drinking water treatment (boiling), improved handwashing facilities	0.20	Intervention is beneficial
Public latrines connected to septic tank	0.80	Intervention is beneficial
Toilet connected to septic tank or biogas reactor	0.94 (0.54, 1.64)	Intervention has no effect
Construction of double urn funnel toilet and feces disposal management	0.43	Intervention is beneficial
Double vault funnel toilet, improved water supply	0.37	Intervention is beneficial
Improved school-based latrines (various types), with maintenance programs including non-hazardous treatment of feces, improved hygiene facilities, point-of-use water treatment, health and hygiene promotion	0.40	Intervention is beneficial

RR – relative risk, CI – confidence interval

The interventions evaluated in the 13 studies include double pit latrines, sanitary platforms and VIP latrines, biogas latrine connected to fermentation reactor, bored hole privy, shared double pit latrine, water-sealed pour flush latrine, relocation of toilets away from water sources, toilets connected to septic tank, and double urn funnel toilet. The studies were assessed to have low quality due to heterogeneity of outcomes and methods used. Two of the studies showed no beneficial effect; the rest demonstrated beneficial effect of the interventions. Majority of the studies evaluated combined interventions, in which interventions to improve excreta disposal were combined with other interventions such as like health education on diarrhea prevention and management, improved water supply, hand hygiene, corralling of livestock, fly control, road developments, and drain improvements. Thus, it was impossible to assess the sole effect of improving fecal disposal in preventing diarrhea. Another systematic review included four quasi-RCTs from China that examined the effect of proper human excreta disposal alone. Pooled estimates were not calculated for the 4 studies. The relative risk of morbidity from diarrhea of these four studies ranged from 0.37 to 0.92.<sup>17</sup>

The Department of Health issued administrative order (AO) 2010-0021: Sustainable Sanitation as a National Policy and a National Priority Program to lay down clear policies and action programs to improve sanitation facilities. The AO called for community initiatives and behavioral modification, with cooperation from the local government units and other departments. According to the AO, the improved sanitation facilities should be accessible and safely managed through sanitation safety planning.

The Code on Sanitation of the Philippines listed approved excreta disposal facilities, and included detailed instructions on the construction of such facilities.<sup>18</sup> Type I facilities require no water to wash the excreta (e.g. ventilated improved pit latrine and sanitary pit privy), or a small amount of water to wash excreta into the receiving space or pit (e.g. pour flush toilets). Type II facilities are water carriage types, having a pour-flush or flush-type toilet leading to septic tanks. Type III facilities are water carriage types that lead to sewerage systems and treatment plants.<sup>19</sup>

In summary, proper disposal of feces can prevent diarrhea; however, this should always be in conjunction with other public health measures such as adequate water supply and hand hygiene education.

## E. Vaccines

1. Killed oral cholera vaccine may be given to children and adults living in endemic areas and during outbreaks to prevent acute infectious diarrhea caused by cholera.

[Strong recommendation, moderate to high quality of evidence]

2. Universal immunization of infants against rotavirus is recommended. Rotavirus vaccines are effective in preventing rotavirus diarrhea and rotavirus diarrhea-associated hospitalization.

[Strong recommendation, moderate quality of evidence]

## SUMMARY OF EVIDENCE

### Cholera Vaccine

A systematic review on cholera vaccine involved 4 large-scale efficacy trials (total of 249,935 participants) that evaluated 5 variations of the killed whole cell vaccine. The over-all vaccine efficacy in the first year after administration was 52% (95% CI 35%, 65%). In the second year, the over-all efficacy increased to 62% (95% CI 51%, 62%). Protective efficacy was lower in children aged less than 5 years (efficacy of 38%; 95% CI 20%, 53%) compared to older children and adults (efficacy of 66%; 95% CI 57%, 73%). There was no clinically significant increase in adverse events in the vaccine group compared to placebo.<sup>20</sup>

The oral killed whole cell vaccine that is currently available in the Philippines can prevent 50 – 60% of cholera episodes in the first two years after administration of the primary vaccination schedule. It can provide high levels of short-term protection against cholera in all age groups within 4-6 months following vaccination. Full protection is expected one week after the 2<sup>nd</sup> dose.

The impact and cost-effectiveness of adopting oral cholera vaccines into the routine vaccination schedule of endemic countries will depend on the prevalence of cholera, the frequency of epidemics, and access to basic services providing rapid rehydration therapy.<sup>20</sup> WHO recommends that oral cholera vaccines should be a major part of cholera control programs in endemic areas, and should also be considered as an integral part of control programs in areas with cholera outbreak.

Based on the Handbook on Adult Immunization for Filipinos, oral cholera vaccine is not routinely given. Indications for cholera vaccination include: a. travelers visiting endemic areas or areas with concurrent outbreaks; b. persons living in highly endemic areas with unsanitary conditions and without access to medical care; c. persons with compromised gastric defense mechanisms (such as achlorhydria, prior ulcer surgery, antacids intake) who are visiting areas with risk of cholera; and d. refugees from areas with known risk of cholera.<sup>21</sup>

The evidence profile for cholera vaccine is shown in Tables 6 to 8.

Table 6. Evidence profile for the effect of cholera vaccine in preventing disease during the first 2 years.

Oral killed whole cell vaccines for preventing cholera						Patient or population: Adults and children Settings: Endemic areas Intervention: Killed whole cell vaccines administered orally Comparison: Placebo			
Quality assessment									
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Vaccine efficacy	95% CI	Quality of evidence	Interpretation
<b>How many people are protected during the first 2 years after vaccination?</b>									
<b>Children aged less than 5 years</b>									
4	Randomized trials	Low risk	not serious	not serious	none	38%	20 to 53%	⊕⊕⊕⊕ HIGH	Oral cholera vaccine prevents a little over one third of cholera



									illnesses
<b>Older children and adults</b>									
<b>4</b>	Randomized trials	Low risk	not serious	not serious	none	66%	57 to 73%	⊕⊕⊕⊕ HIGH	Oral cholera vaccine prevents two thirds of cholera illnesses

Table 7. Evidence profile on the duration of protection of cholera vaccine.

<b>Oral killed whole cell vaccines for preventing cholera</b> <b>Quality assessment</b>						<b>Patient or population: Adults and children</b> <b>Settings: Endemic areas</b> <b>Intervention: Killed whole cell vaccines administered orally</b> <b>Comparison: Placebo</b>			
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Vaccine efficacy	95% CI	Quality of evidence	Interpretation
<b>How long does the protection last?</b>									
<b>1<sup>st</sup> YEAR</b>									
<b>1</b>	Randomized trials	Low risk	not serious	not serious	none	52%	35 to 65%	⊕⊕⊕⊕ MODERATE	
<b>2<sup>nd</sup> YEAR</b>									
<b>1</b>	Randomized trials	Low risk	not serious	not serious	none	62%	51 to 62%	⊕⊕⊕⊕ MODERATE	
<b>3<sup>rd</sup> YEAR</b>									
<b>1</b>	Randomized trials	Low risk	not serious	not serious	none	30%	2 to 50%	⊕⊕⊕⊕ MODERATE	Oral cholera vaccine is probably less effective in the third year
<b>4<sup>th</sup> YEAR</b>									
<b>1</b>	Randomized trials	Low risk	not serious	not serious	none	-5%	-84 to 40%	⊕⊕⊕⊕ MODERATE	Oral cholera vaccine is probably ineffective after 4 years

Table 8. Evidence profile on the effectiveness and efficacy of a 2-dose cholera vaccine.

Oral killed whole cell vaccines for preventing cholera Quality assessment						Patient or population: Adults and children Settings: Endemic areas Intervention: Killed whole cell vaccines administered orally Comparison: Placebo			
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Vaccine efficacy	95% CI	Quality of evidence	Interpretation
<b>What is the effectiveness of a two-dose killed whole cell oral cholera vaccine?</b>									
<b>5</b>	Randomized trials	Low risk	not serious	not serious	none	76%	62 to 85%	⊕⊕⊕⊕ HIGH	
<b>What is the efficacy of a two-dose killed whole cell oral cholera vaccine?</b>									
<b>4</b>	Cohort (1) Case Control (4) Case Cohort (1)	Low risk	not serious	not serious	none	66%	57 to 73%	⊕⊕⊕○ MODERATE	

## Rotavirus vaccine

Rotavirus is the most common cause of vaccine-preventable diarrhea in children under five years. It is associated with approximately 28% of diarrheal deaths. Low-income countries have the highest burden of severe disease and deaths due to rotavirus infections.<sup>22</sup> WHO recommends the inclusion of rotavirus vaccination in all national immunization programs.<sup>23</sup>

There are two rotavirus vaccines available in the Philippines, and both are live, oral, attenuated vaccines. The monovalent human rotavirus vaccine (RV1, HRV, Rotarix) and the pentavalent human-bovine reassortant rotavirus vaccine (RV5, PRV, RotaTeg) have similar efficacy and safety profiles; thus, neither vaccine is preferred over the other.<sup>1,3</sup> Comparisons between RV1 and RV5 are summarized in Table 9. The recommended schedule for RV1 is 2 and 4 months of age, while RV5 is administered at 2, 4, and 6 months of age. The vaccine series should be completed with the same product whenever possible, but vaccination should not be deferred if the product used for previous doses is unknown.<sup>24</sup>

Table 9. Comparison of Rotavirus vaccine.<sup>24</sup>

	Monovalent human rotavirus vaccine (RV1, HRV)	Pentavalent human-bovine reassortant rotavirus vaccine (RV5, PRV)
Trade Name	Rotarix	Rotateq
Manufacturing company	GlaxoSmithKline	Merck
Serotypes contained	G1P [8]	G1, G2, G3, G4, P1[8]
Dose	1 ml	2 ml
Route	Oral	Oral

Administration	Requires reconstitution	Ready-to-use
Number of doses in series	2	3
Recommended schedule	2, 4 months	2, 4, 6 months
Minimum age for first dose	6 weeks of age	6 weeks of age
Maximum age of first dose	14 weeks and 6 days of age	14 weeks and 6 days of age
Minimum interval between doses	4 weeks	4 weeks
Maximum age for last dose	8 months and 0 days of age	8 months and 0 days of age
Oral applicator	Contains latex (contraindicated in patients with severe allergy to latex)	Latex-free

The effectiveness of rotavirus vaccine varies among countries that have introduced rotavirus vaccine into the routine immunization schedule, as shown in Table 10. A 2012 systematic review that evaluated the effect of rotavirus vaccination among children reported that rotavirus vaccines (either RV1 or RV5) are effective in preventing severe rotavirus diarrhea and rotavirus diarrhea-related hospitalizations. There were 29 trials on RV1 and 12 trials on RV5 included in the review. There was no significant difference in the risk of serious adverse events and intussusception among children who received RV1 or RV5 compared to placebo.<sup>25</sup>

Table 10. Effectiveness of rotavirus vaccination among children younger than 5 years.

Location	Outcome	
	Severe rotavirus diarrhea RR (95% CI)	Diarrhea hospitalizations RR (95% CI)
Developed region	0.90 (82.3, 95.0%)	94.3% (72.8, 98.8%)
Eastern/Southeastern Asia	88.4% (67.1, 95.9%)	No studies
Latin America and the Caribbean	79.6%; (71.3, 85.5%)	76.7% (75.6, 77.7%)
Southern Asia	50.0% (34.4, 61.9%)	No studies
Sub Saharan Africa	46.1% (29.1, 59.1%)	57.5% (7.2, 80.8%)

Contraindications to rotavirus vaccination include: a. history of a severe allergic reaction after a previous dose of rotavirus vaccine or to a vaccine component (e.g. anaphylaxis to latex rubber found in RV1), b. severe combined immune deficiency, and c. history of intussusception. Gastroenteritis, including severe diarrhea and prolonged shedding of vaccine virus, have been reported in infants who were administered live rotavirus vaccines and later identified as having SCID.<sup>24</sup>

Precautions for administration of rotavirus vaccine include manifestations of altered immunocompetence other than SCID, moderate to severe illness including gastroenteritis, preexisting chronic intestinal tract disease, spina bifida, and bladder extrophy.<sup>24</sup>

## F. Supplements

1. The following probiotic strains may be given to children and adults to prevent acute infectious diarrhea or its recurrence:

- a. *Bifidobacterium lactis*
- b. *Lactobacillus rhamnosus* GG
- c. *Lactobacillus reuteri*

[Strong recommendation, low quality of evidence]

2. Zinc supplementation is recommended to prevent acute infectious diarrhea among children 6 months to 12 years old. It should NOT be given to children <6 months old.

[Strong recommendation, moderate quality of evidence]

3. Vitamin A supplementation may be given to children ≥6 months to reduce the incidence of acute infectious diarrhea. The recommended doses are:

- 100,000 IU every 4-6 months for infants 6-12 months
- 200,000 IU every 4-6 months for children >12 months

[Strong recommendation, low quality of evidence]

## SUMMARY OF EVIDENCE

### Probiotics

The Latin American Expert Group consensus recommends the use of the following probiotic strains for the prevention of acute infectious diarrhea: *Bifidobacterium lactis*, *Lactobacillus rhamnosus* GG (LGG), and *L. reuteri*.<sup>26</sup> Although majority of trials showed benefit of probiotic administration in preventing acute infectious diarrhea, the evidence to support routine use of probiotics to prevent infectious diarrhea was inconsistent.

A 2011 study on Finnish children from daycare centers reported that participants who consumed milk containing *L. rhamnosus* had 16% fewer days of absence from daycare because of diarrhea and gastrointestinal infections compared to controls.<sup>27</sup>

A 2005 multi-arm trial involving healthy term infants from childcare centers in Israel evaluated the effect of *B. lactis* and *L. reuteri*. Results showed significant reduction in episodes of diarrhea among the *L. reuteri* group (average of 0.02 episodes; 95% CI 0.01, 0.05) and the *B. lactis* group (average=0.13; 95% CI 0.05, 0.21) compared to controls (average=0.31; 95% CI 0.22, 0.40).<sup>28</sup>

A 2009 meta-analysis showed that selected *Lactobacillus* strains had a modest but significant effect in primary prevention of diarrhea.<sup>29</sup> Another meta-analysis conducted last 2006 analyzed 15 trials, with a total of 3,452 participants, to determine the efficacy of probiotics in the prevention of pediatric

diarrhea. The outcome measured was the frequency of subjects who developed new episodes of diarrhea by the end of the study. The characteristics of the included studies are shown in Table 11.<sup>30</sup>

Table 11. Prevention of pediatric diarrhea by various probiotics from randomized controlled trials.<sup>30</sup>

N	Subjects (age in months)	Probiotic	Dose per day	Duration (days)	Probiotic (developing diarrhea)		Control group		Quality	Reference	+ or -
					# failed	# cured	# failed	# cured			
81	1-36	<i>L. rhamnosus</i> GG	$1.2 \times 10^{10}$	varied	3 ( 6.7)	42	12 (33)	24	3	Szajewska 2001a	+
188	6-120	<i>L. rhamnosus</i> GG	$2 \times 10^{10}$	10	7 ( 7)	87	25 (26)	69	3	Vanderhoof 1999	+
204	6-24	<i>L. rhamnosus</i> GG	$3.7 \times 10^{10}$	450	5 ( 5.2)	94	6 ( 6)	99	3	Oberhelman 1999	+
220	1-18	<i>L. rhamnosus</i> GG	$1 \times 10^{10}$	varied	29 (25.4)	85	32 (30.2)	74	3	Mastretta 2002	-
59	5-132	<i>L. rhamnosus</i> GG	$8 \times 10^{10}$	7	6 (26)	17	8 (22)	28	2	Vaisanen 1998	-
239	12-36	<i>L. reuteri</i>	$1 \times 10^{8-10}$	98	29 (24)	90	43 (36)	77	2	Ruiz-Palacios 1999	+
928	6-24	<i>L. casei</i> DN114	$1 \times 10^8$	60	74 (15.9)	390	102 (22)	362	3	Pedone 2000	+
354	12-216	<i>L. acidophilus</i>	$2 \times 10^9$	varied	10 (4.6)	205	30 (21.6)	109	2	Pancheva-Dimitrova 2004	+
466	12-180	<i>S. boulardii</i>	$5 \times 10^9$	varied	14 (5.7)	230	42 (18.9)	180	2	Erdevi 2004	+
269	6-168	<i>S. boulardii</i>	$1 \times 10^{10}$	14	4 (3)	115	22 (17.3)	105	3	Kotowska 2005	+
110	1-180	<i>Cl. butyricum</i> miyairi	$1-4 \times 10^7$	6	6 (7)	77	16 (59)	11	2	Seki 2003	+
128	4-10	<i>L. reuteri</i> 55730	$1 \times 10^9$	84	2 ( 3)	66	18 (30)	42	3	Weizman 2005	+
133	4-10	<i>B. lactis</i> BB-12	$1 \times 10^9$	84	9 (12)	64	18 (30)	42	3	Weizman 2005	+
18	1-36	<i>L. acidophilus</i> + <i>Bifid. infantis</i>	$6 \times 10^9$	7	3 (37.5)	5	8 (80)	2	2	Jirapinyo 2002	-
55	5-24	<i>Bifido. bifidum</i> + <i>Strept thermophilus</i>	$2 \times 10^8$	varied	2 ( 7)	27	8 (31)	18	3	Saavedra 1994	+

Quality of evidence: 1= poor, 2= fair, 3= good

Probiotics were found to significantly reduce the frequency of pediatric diarrhea compared to controls (RR=0.39; 95% CI 0.27, 0.55). The forest plot is shown in Figure 3. However, significant heterogeneity was observed among the included trials. To investigate the source of heterogeneity, subgroup analysis based on the type of probiotic strain was conducted. The subgroup analysis involving 5 trials on LGG showed no significant effect of LGG in preventing pediatric diarrhea (RR=0.57; 95% CI 0.30, 1.09). The subgroup analysis involving the trials that used strains other than LGG showed did not result in a significantly different pooled estimate compared to the pooled estimate from the full analysis with 15 trials (RR=0.32; 95% CI 0.21, 0.50).

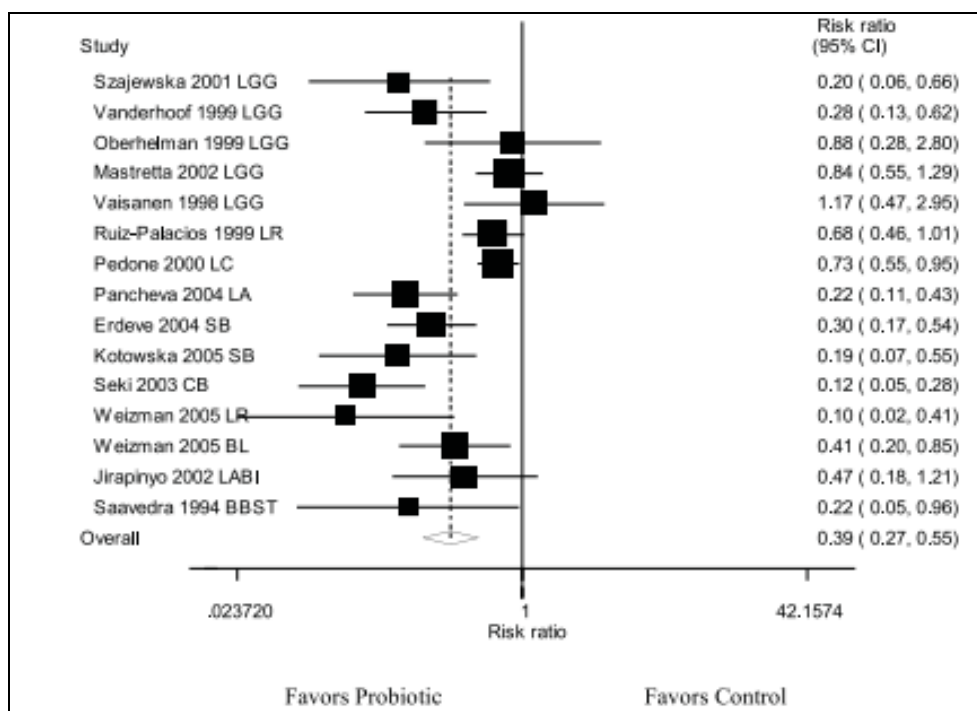


Figure 4. Forest plot of 15 RCTs on probiotics for the prevention of pediatric diarrhea with percent failure as the outcome.<sup>30</sup>

Analysis of the individual studies demonstrated varying frequency of positive efficacy findings per probiotic strain. *S. boulardii* had 100% positive efficacy findings in 8 trials, *C. butyricum* had 100% positive finding in 1 trial, *B. lactis* had 100% in 1 trial, LGG had 79% in 14 trials, other *Lactobacilli* strains had 88% in 8 trials, and probiotic mixtures had 44% in 9 trials.<sup>30</sup>

Another source of heterogeneity is the probiotic dose, which ranged from 0 (for killed preparations) up to  $2 \times 10^{11}$  cfu/day. Studies on adults with diarrhea reported a therapeutic threshold of  $>10^{10}$ /day.<sup>31-32</sup> Unlike adults, children may not require high doses of probiotics. There was no significant difference in the frequency of positive efficacy findings among children given low doses ( $1 \times 10^7 - 6 \times 10^9$ /day) which had 79% positive findings and high doses ( $1 \times 10^{10} - 2 \times 10^{11}$ /day) which had 75% positive findings.<sup>30</sup>

Several limitations were found in the trials, including differences in treatment duration, doses, potency, lack of reported safety data, and lack of cost-effectiveness data.

Currently, treatment of pediatric diarrhea is limited to supportive and symptomatic care. Antibiotic therapy is not useful in 85-95% of cases of diarrhea because the etiology is usually unknown or viral in nature. Probiotics may offer an attractive supportive therapy for acute pediatric diarrhea since they are particularly useful in diseases associated with disruption of the normally protective microflora. The normal flora possesses "colonization resistance", a complex phenomena that leads to protection against colonization of opportunistic pathogens that may invade the intestines after broad-spectrum antibiotic use, medications or surgery.<sup>33</sup> Disruption of normal flora makes the body susceptible to infection. Recovery of the normal flora may take up to eight weeks after discontinuation of antibiotics. Probiotics are uniquely suited for this window of susceptibility, as they may act as surrogate normal flora. Probiotics exert their beneficial effects through production of antimicrobial substances,

modification of toxins, interference with attachment of microorganisms, stimulation of the immune system, or a combination of these mechanisms.<sup>33-35</sup>

### Research Recommendations:

Future studies on the therapeutic potential of probiotics are necessary. To increase comparability, efforts should be made to standardize doses, treatment duration, and study populations. Direct comparisons of probiotics to placebo are indicated. Adverse reaction data and cost-effectiveness analyses would be helpful.

## Zinc

Regular intake of zinc in the diet is necessary because it is an essential micronutrient. The human body does not have adequate mechanisms for production, storage or release of zinc. Severe zinc deficiency can impair the proper functioning of the immune, gastrointestinal, skeletal, reproductive, and central nervous systems. Marginal zinc deficiency may negatively affect physical development and immune system functioning.<sup>36</sup>

Children are particularly susceptible to zinc deficiency because of increased requirements during periods of rapid growth. Zinc deficiency is prevalent among children of low to middle-income families in developing countries, including countries in South and Southeast Asia, sub-Saharan Africa, and parts of Latin America. Zinc deficiency in children is associated with growth stunting and mortality from diarrhea, pneumonia, and malaria.<sup>36</sup> Preventive zinc supplementation in healthy children could reduce mortality from these common illnesses.

A systematic review evaluating zinc supplementation among children showed that zinc supplementation led to significant reductions in the incidence and prevalence of diarrhea and persistent diarrhea. However, pooled estimates for diarrhea-associated mortality and hospitalization showed no statistical significance. The results are summarized in Table 12.<sup>36</sup>

Table 12. Effect of zinc supplementation in preventing acute infectious diarrhea

No. of studies	No. of participants	Quality of evidence	Outcome analyzed	Effect of estimate RR (95% CI)
4	132,321	Moderate	Mortality due to all-caused diarrhea	0.95 (0.69, 1.31)
26	15,042	Moderate	Incidence of all-cause diarrhea	0.87 (0.85, 0.89)
13	8,519	Moderate	Prevalence of all cause diarrhea	0.88 (0.86, 0.90)
4	74,039	Moderate	Hospitalization due to all-cause diarrhea	1.03 (0.87, 1.22)
7	6,216	Moderate	Incidence of persistent diarrhea	0.73 (0.62, 0.85)
1	665	Moderate	Prevalence of persistent diarrhea	0.70 (0.64, 0.76)

The recommended daily zinc intake for children ranges from 2—11 mg per day, depending on the child's age and diet.<sup>37-39</sup> For children 6—59 months old with diarrhea, WHO recommends supplemental doses of 20 mg per day for 10—14 days.<sup>40</sup> The International Zinc Nutrition Consultative Group recommends a daily dose of 5 mg or 10 mg per for preventive zinc supplementation among children under 14 years of age.<sup>38</sup>

### **Research Recommendations:**

Further studies looking at the optimal dose, duration, frequency and formulation of zinc supplementation may be undertaken to achieve clinically meaningful improvements in mortality and morbidity. In addition, the timing for initiation of preventive supplementation in children could be further investigated.

### **Vitamin A**

Vitamin A is an essential nutrient that affects vision, red blood cell production, immune system function, and reproduction. Vitamin A is not produced by the human body; thus, inadequate dietary intake leads to vitamin A deficiency. Deficiency occurs more commonly among developing countries such as the Philippines. In countries with high prevalence of Vitamin A deficiency, supplements reduce the number of deaths in children 6 months to 5 years of age. Vitamin A supplements can be given orally in capsule form or liquid form. The recommended dose by the WHO is 50,000 IU for infants under 6 months, 100,000 IU for infants 6—12 months, and 200,000 IU for children over 12 months, given every 4—6 months.<sup>41</sup>

A 2017 systematic review evaluated the effect of vitamin A supplementation in preventing morbidity and mortality in children aged 6 months – 5 years. A total of 43 studies were included in the review. All the studies used oral retinol palmitate. Except for 5 studies that gave small doses of vitamin A (3866 IU, 3 times a week), the rest of the studies gave high doses ranging from 50,000 IU to 200,000 IU every 4—6 months, depending on the age of participants.<sup>42</sup>

Pooled data from 9 trials show that supplementation led to a statistically significant decrease in death due to diarrhea, with a combined 12% reduction in mortality (RR=0.88; 95% CI 0.79, 0.98). There was no significant heterogeneity observed in the included studies. Vitamin A supplementation also led to a 15% decrease in diarrhea incidence (RR=0.85, 95% CI 0.82, 0.87), based on 15 studies. However, there was significant heterogeneity among these studies. One study evaluated the incidence of hospitalization from diarrhea. Results of this study showed inconclusive evidence for vitamin A supplementation (RR=0.25; 95% CI 0.01, 6.11). The pooled estimate from 4 trials showed significant increase in the risk of vomiting with vitamin A supplementation (RR=1.97; 95% CI 1.44, 2.69). Table 13 summarizes the results on vitamin A supplementation.<sup>42</sup>



Table 13. Summary of effects of vitamin A supplementation in children 6 months to 5 years.<sup>42</sup>

Outcome	Relative Effect RR (95% CI)	Number of Participants	Quality of Evidence
Mortality due to diarrhea (Follow up: 48-104 weeks)	0.88 (0.79, 0.98)	1,098,538 (9 studies)	High
Incidence of diarrhea (Follow up: 24-60 weeks)	0.85 (0.82, 0.87)	77, 946 (15 studies)	Low
Vomiting (Follow up 0.14-52 weeks)	1.97 (1.44, 2.69)	10,541 (4 studies)	Moderate

## G. Breastfeeding and Breastfeeding Promotion

Exclusive breastfeeding is recommended during the first 6 months of life to prevent diarrhea

[Strong recommendation, moderate quality of evidence]

All healthcare providers should promote breastfeeding.

[Strong recommendation, moderate quality of evidence]

## SUMMARY OF EVIDENCE

Breastmilk contains several antimicrobial and anti-inflammatory factors, hormones, digestive enzymes and growth modulation factors which protects against infections. Breastmilk also confers immunity against gastrointestinal infections by carrying antibodies (secretory IgA) produced by mothers who have been exposed to such pathogens.<sup>43</sup>

Early initiation of breastfeeding and exclusive breastfeeding are protective of diarrhea. A pooled analysis of 15 studies from Jamaica, Colombia, Peru, Iraq, Ethiopia, United Arab Emirates, Philippines, United States, Brazil, Iran, Ghana, India, Peru, Bangladesh, Zimbabwe and Hongkong published by the WHO showed significant reduction in morbidity from infectious diarrhea among children less than 5 years old (RR=0.69; 95% CI 0.58, 0.82). The highest reduction of incidence of diarrhea was observed among infants less than 6 months who were exclusively breastfed compared to those who were not breastfed (9 studies with pooled RR=0.20; 95% CI 0.13, 0.29), predominantly breastfed (10 studies with pooled RR=0.44; 95% CI 0.39, 0.50), and partially breastfed (4 studies with pooled RR=0.51; 95% CI 0.37, 0.70). Exclusively breastfed infants also had significantly reduced risk of hospitalization from diarrhea compared to infants who were not breastfed (2 studies with pooled RR=0.09; 95% CI 0.02, 0.44) and those who were partially breastfed (2 studies with pooled RR=0.20; 95% CI 0.10, 0.40). There was no significant difference in the reduction of hospitalization from diarrhea among exclusively breastfed compared to predominantly breastfed infants. Breastfeeding also reduced the incidence of diarrhea among children more than 6 months of age (11 studies with pooled RR=0.46; 95% CI 0.28, 0.78). Mortality was also reduced among breastfed children compared to those not breastfed (7 studies with pooled RR=0.23; 95% CI 0.13, 0.42). The systematic review also showed that promotion of breastfeeding led to decreased diarrhea morbidity (3 trials with pooled RR=0.69; 95% CI 0.49, 0.96).<sup>43</sup> Evidence are of moderate quality because most studies were case-controls, cohorts and cross-sectional studies, since randomized trials directly evaluating breastfeeding and no breastfeeding are unethical.

## 2A. When is potential for outbreak suspected?

Outbreak is suspected in the presence of cases of acute infectious diarrhea in excess of what would normally be expected in a defined community, geographical area or season, and lasting a few days, weeks, or several years”(World Health Organization)<sup>44</sup>

Surveillance systems are designed to detect epidemics. The goal of outbreak investigation is to identify the source and to institute measures to control and prevent the spread of disease. A potential outbreak is usually suspected by astute individuals such as healthcare workers and citizens who observe a clustering pattern of cases with similar symptoms emerge with respect to time and location. This observation is then reported to health authorities. A pattern can be any of the following:<sup>45</sup>

- A school with increasing number of absentees due to diarrhea
- Attendees of any gathering become ill with diarrhea with or without other similar signs and symptoms

A clear definition of outbreak is critical to the investigation. This standardizes the cases that is of interest to clinicians and public health authorities involved in the immediate event, and can also be used for future reference.

## 2B. How is outbreak managed?

1. Suspected cases of outbreaks should be reported immediately to disease reporting units or disease surveillance coordinators at the rural health units (RHU) and city health offices (CHO) for verification.
2. Collection of demographic data and specimens is mandatory. Stool samples (rectal swab or bulk stool) should be sent to designated laboratories for analysis and confirmation. Water and food samples may also be collected to determine the source of the outbreak.
3. Response to outbreaks should involve epidemiologic investigation and formation of hypotheses, treatment of cases, implementation of control and preventive measures, and risk communication.

In a setting where there are changes in the pattern of diarrhea, all healthcare workers or disease reporting advocates should immediately report to disease reporting units or disease surveillance coordinators.<sup>45</sup> Cases are reported simultaneously to the provincial health office (PHO)/Provincial Epidemiology and Surveillance Unit (PESU), Center for Health Development (CHD)/Regional Epidemiology and Surveillance Unit (RESU), and Epidemiology Bureau (EB) within 24 hours of detection through the fastest means of communication possible. Reports can be communicated verbally via the telephone or radiophone, or written via facsimile or email. Feedback to stakeholders should be provided within 24 hours. Coordinating efforts should be done at all levels to implement an integrated response to the outbreak. The flow of investigation, reporting, and response to a suspected or reported epidemic is shown in Figure 4.

**Figure 16: Flow of Investigation, Reporting and Response to a Suspect Epidemic or Reported Epidemic**

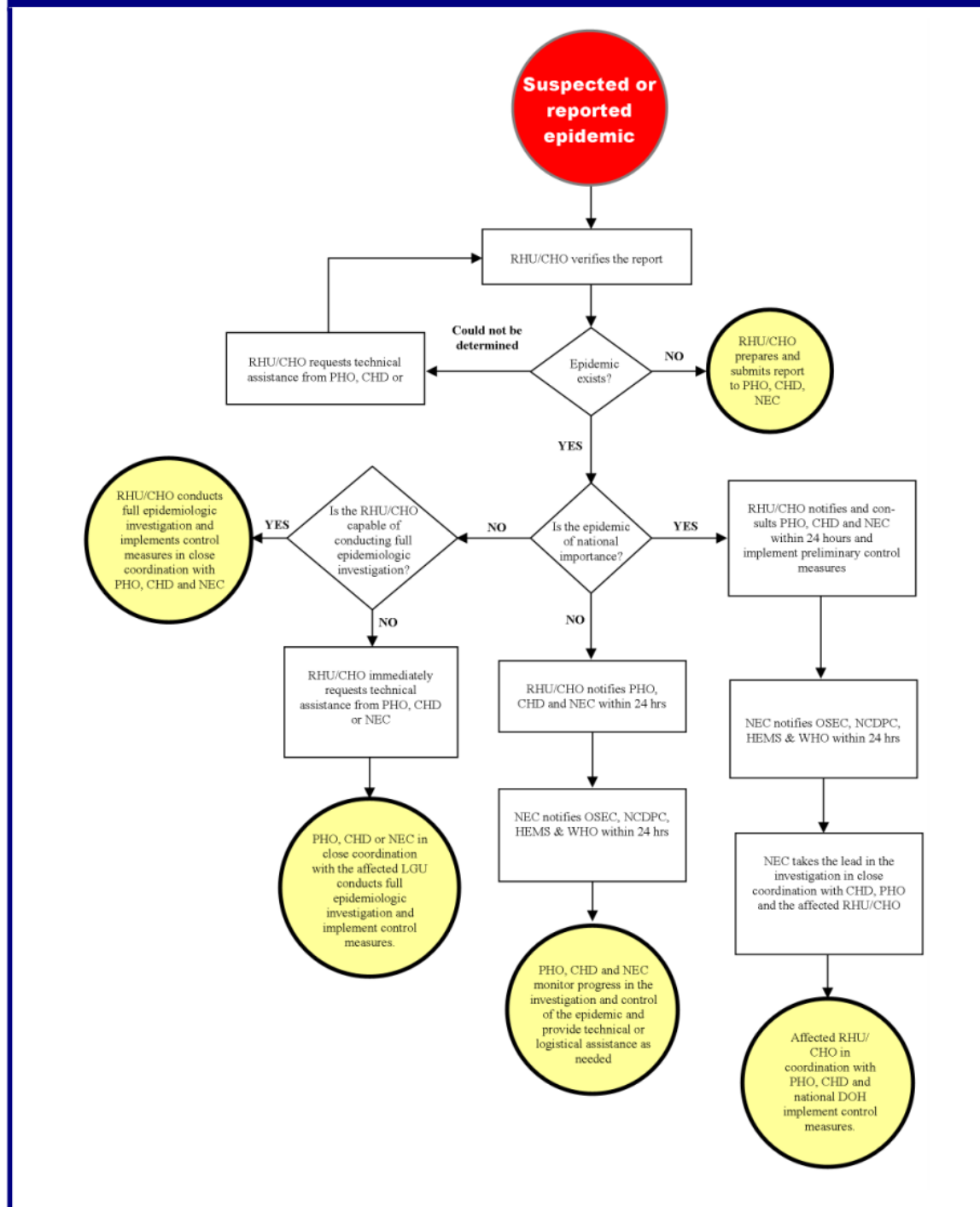


Figure 5. Flow of investigation, reporting and response to a suspected or reported epidemic.(Adapted from PIDSR)<sup>45</sup>

After establishing the case definition, all cases and contacts should be identified. In order to generate a hypothesis about the source of the outbreak, the following should be collected: personal information (including but not limited to name, address, sex, age, and occupation); signs and symptoms; and relevant exposures (recent travel, intake of water and food, living condition, and sanitation type). The number of cases who were hospitalized and who had complications should also be described.<sup>45</sup>

During an outbreak, submission of stool is mandatory to provide crucial information for the investigating team. The disease surveillance officers (DSOs) must ensure that specimens are brought to diagnostic laboratories. Rectal swab culture is recommended because it has higher sensitivity, specificity, and positive likelihood ratios compared to bulk stools (see table below); thus, collection kits must be readily available at the regional and provincial levels. For suspected waterborne outbreaks, water should be subjected to bacteriological tests in reference water laboratories located in the respective regional or local levels. Food samples may also be collected in separate containers and brought to a laboratory for specific analytic tests. Guidelines on the collection and transport of specimens are found in the Manual of Procedures for the Surveillance, Outbreak Investigation and Response to Microbial Agents of Food and Waterborne Diseases.<sup>46</sup> The proper method of collecting stool samples and rectal swabs are shown in Figures 5-7.

Cases should be treated accordingly. There should be adequate supplies for treatment such as ORS, intravenous fluids and antibiotics. Any request for logistical assistance should be immediately reported. Public health measures should also be identified and implemented. The result of the investigation and the plan of action to control the outbreak should be effectively communicated to all stakeholders.

Table 14. Comparison of accuracy of rectal swab culture and bulk stool using PCR.

Organism	STUDY	Sample (N)	Study event rates		PPV	NPV	Likelihood Ratio	
			Sensitivity	Specificity			LR+	LR-
Rectab swab VS bulk stool								
rotavirus	Arvelo, wences, et al 2013	100	0.92	0.90	0.90	0.92	9.03	0.09
Norovirus		100	0.50	0.93	0.57	0.91	7	0.54
Rectal swab vs bulk stool								
ETEC ( elt B)	Kabayiza et al 2013	326	0.29	0.58	0.55	0.55	0.69	1.22
ETEC (est A)			0.15	0.87	0.66	0.37	1.11	0.98
E coli ( bfp A)			0.17	0.91	0.76	0.39	1.83	0.92
E. coli ( eae)			0.22	0.75	0.60	0.35	0.86	1.05
Shigella			0.19	0.78	0.60	0.36	0.86	1.04
campylobacter			0.20	0.80	0.64	0.37	1.01	1.00
Cryptosporidium			0.09	0.93	0.70	0.37	1.37	0.97
Norovirus			0.08	0.97	0.81	0.38	2.44	0.95
Rotavirus			0.23	0.99	0.98	0.43	27.59	0.77
adenovirus			0.16	0.45	0.34	0.24	0.29	1.85



Figure 6. Method of collecting stool samples in adults.<sup>48</sup>

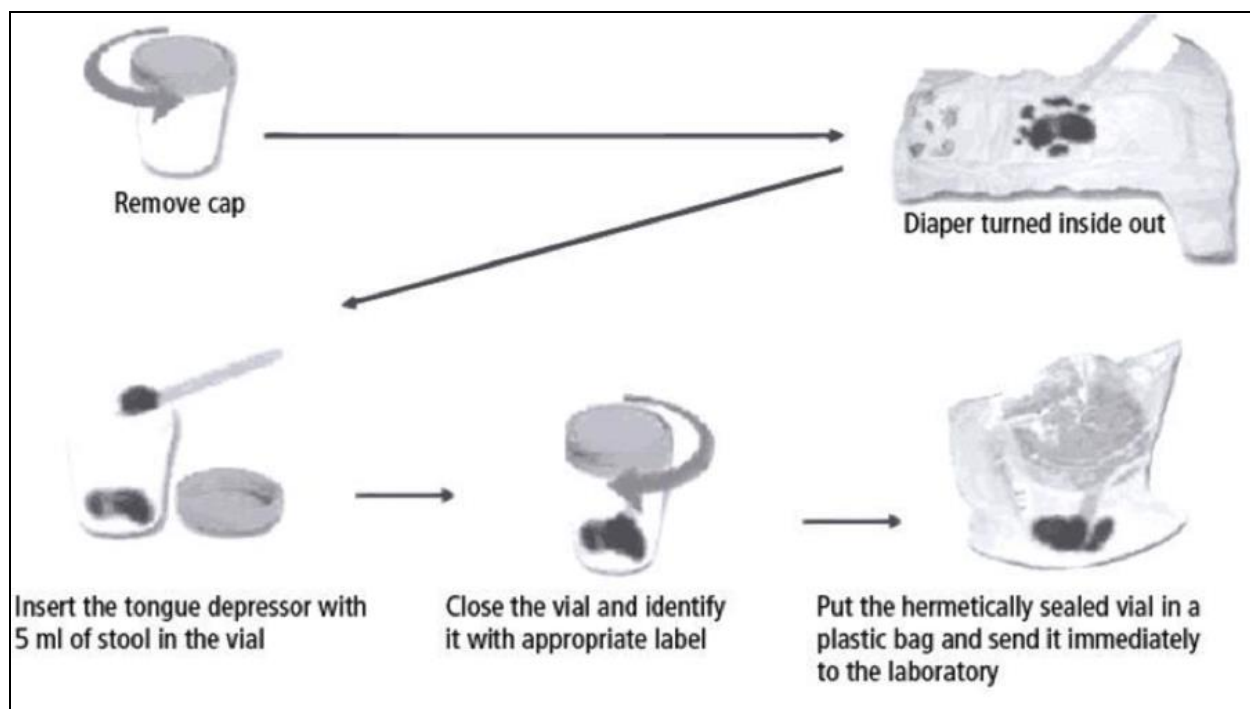


Figure 7. Method of collecting stool samples in children.<sup>47</sup>

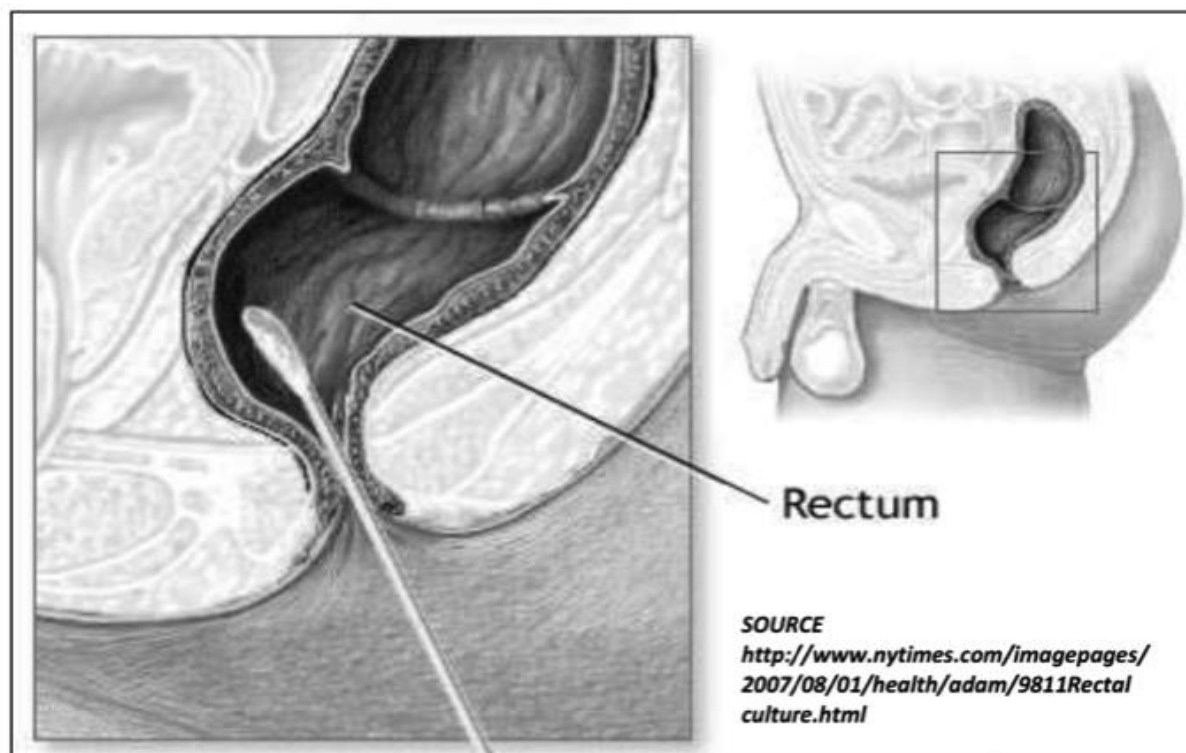


Figure 8. Method of collecting rectal swabs

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