Acute and Persistent Diarrhea

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GLOBAL DIARRHEAL DISEASE BURDEN

Infectious diarrhea remains one of the leading causes of childhood morbidity and mortality worldwide. It results from infection of the intestinal tract by a wide range of enteric pathogens that can disrupt intestinal function. The resulting symptom complex of diarrhea is characterized by an increased number of loose or watery (≥ 3 in 24 hours) stools. The term dysentery is used when blood, mucus, and white blood cells are present in the stool. The annual global burden of infectious diarrhea is enormous, involving 3 to 5 billion cases and nearly 2 million deaths, with the latter accounting for almost 20% of all deaths in children younger than 5 years.1 Of these diarrhea-related deaths, acute watery diarrhea is responsible for 35%; dysentery, for 20%; and persistent or chronic diarrhea, 45%.2 Most deaths are in young children from rural regions of developing countries where there is limited access to safe drinking water, sewage disposal, and health care, and reduced opportunities for personal sanitation, hygiene, and safe food preparation. In this setting, repeated episodes of enteric...
infection can contribute to malnutrition by interfering with nutrient absorption. As these episodes usually occur during the first few years of life, a period critical for physical growth and brain development, they can be followed by impaired linear growth, intellectual function, and school performance.³

In industrialized countries, where medical access is more readily available and modern standards of water quality, personal hygiene, sanitation, and food safety exist, deaths from diarrheal illness have decreased dramatically.⁴ However, sporadic diarrheal illness remains an important cause of morbidity, second only to respiratory infections as the most common cause of childhood infectious disease resulting in health-care attendance.⁵⁻⁸ Most episodes are caused by enteric viruses and are self-limited in nature, rarely resulting in persistent diarrhea, malnutrition, or death in a previously healthy child. Nevertheless, socially disadvantaged Indigenous children living in western industrialized countries experience high rates of severe diarrheal disease and, in some communities, the pattern of morbidity resembles that seen in developing countries.

### BURDEN IN INDIGENOUS CHILDREN IN INDUSTRIALIZED SOCIETIES

In the United States, high rates of acute diarrheal disease are observed in American Indian (AI) and Alaskan Native (AN) infants residing in reservations or remote locations lacking adequate sanitation. Table 1 summarizes 2 separate studies spanning 25 years conducted by the Centers for Disease Control and Prevention.⁹,¹⁰ During the early 1980s, the annual incidence of diarrhea-associated hospitalization for AI/AN infants younger than 12 months living in or near reservations was 1148 per 10,000 infants, which was more than 3 times that of other infants residing in the United States.⁹ However, by the 1990s, the annual incidence in AI/AN infants had fallen to 275 cases per 10,000 infants. Rates of hospitalization for diarrhea in older AI/AN children were also similar to that of the general US population. At the same time, the

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<tr>
<td>&lt;1y</td>
<td>1148</td>
<td>348</td>
<td>230</td>
<td>275</td>
<td>192</td>
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<td>1–4y</td>
<td>81</td>
<td>78</td>
<td>4</td>
<td>36</td>
<td>64</td>
<td>-44</td>
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<tr>
<td>Total</td>
<td>236</td>
<td>136</td>
<td>74</td>
<td>71</td>
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Age-specific incidence rates are per 10,000 children.

* Indian Health Service hospital discharge data; rate estimates were calculated from the 1996 IHS user population.⁹

* Rate estimates were calculated from the National Hospital Discharge Survey and the 1981 and 1994 national census data, respectively.⁸

* National rate estimates for the US population were calculated from the 2003 Kids Inpatient Database and the 2003 national census data.⁹

median time spent in hospital for AI/AN children decreased significantly from 4 days in 1980 to 1982 to just 2 days in 1993 to 1995. Possible causes for this substantial decline in hospitalization rates include improved provision of safe drinking water, construction of sanitation facilities, increased coverage of measles vaccination, and introduction of oral glucose-electrolyte rehydration therapy into the routine management of acute infectious diarrhea.

Table 1 also shows that since the 1990s, there has been little improvement in hospitalization rates for AI/AN infants with diarrhea, which remain almost twice that of other US infants.10 Furthermore, diarrhea-associated outpatient visits for AI/AN infants are also more than twice that of the general infant population (2956 and 1312 per 10,000, respectively). The higher rates of infectious diarrhea-related morbidity amongst AI/AN infants are attributed to continuing limited access to safe water supply and inadequate sanitation in some communities and to more severe rotavirus-related diarrhea.10,11 Despite the high rate of health care utilization by AI/AN infants, diarrheal episodes are short, persistent diarrhea is uncommon, and malnutrition is rarely encountered.11

Diarrheal disease is also common among children in Australian Aboriginal communities, reflecting overcrowding and difficulties with sanitation and hygiene.12 The most robust data for Aboriginal children are collected at the state level,4,13,14 and these demonstrate sustained and disproportionately high rates of hospitalization for acute diarrheal illnesses.15 First recognized as a major health problem in the 1950s, episodes of infectious diarrhea in Aboriginal children were severe, with high rates of dehydration, hypokalemia, lactose intolerance, and prolonged hospital admission because of accompanying malnutrition, heavy intestinal parasitic infestation, and malabsorption.16 Even by the 1970s, hospital case fatality rates in Western Australia were approximately 5%, although these declined steeply during the next decade.16,17 Nevertheless, hospitalization rates for acute diarrhea were 16 to 20 times higher for infants and 12 to 15 times higher for children aged 1 to 5 years than for non-Aboriginal children of the same ages.18 Moreover, bed usage rates were 40 to 50 times greater in Aboriginal infants and 30 to 40 times greater in those aged 1 to 5 years than in similarly aged non-Aboriginal children.

During the last 2 decades there have been several initiatives to improve Aboriginal child health, including better housing, sanitation, and water supply, improved access to health care, enhanced surveillance, and concerted health and hygiene promotion campaigns. Deaths are now rare and during the 1990s, hospital admission rates in Western Australia for aboriginal infants and children with infectious diarrhea declined 20% to 30% (Fig. 1). Nevertheless, hospitalization rates for acute diarrhea in Aboriginal children remain 7 to 8 times higher than their non-Aboriginal peers.4,14 The disparity in hospitalization rates is greatest for Aboriginal infants where, for example, annual admission rates in the late 1990s in the Northern Territory of Australia exceeded 3330 cases per 10,000 infants, which is 16 times greater than that encountered for the non-Aboriginal infant population from that region.19 Furthermore, 38% of Aboriginal children hospitalized for acute diarrhea are subsequently readmitted with another diarrheal episode, a rate that is almost 3 times higher than for other children.20,21

Aboriginal children hospitalized for infectious diarrhea still have high rates of malnutrition (12%–50%), lactose intolerance (8%–27%), severe iron deficiency anemia (5%–8%), and other coinfections (25%–50%), such as lower respiratory tract infections, otitis media, urinary tract infections, or scabies.13,19–23 Diarrhea severity, comorbid conditions, and difficulties with arranging transport, often to remote settlements, contribute to the length of time in hospital, which on average is about twice that of non-Aboriginal children (4.8 vs 2.2 and 8.9 vs 3.9 days in Western Australia and the Northern Territory, respectively).13,19 The highest rates of hospital admission and other
comorbid conditions are found in Aboriginal infants and children from remote rural regions of Northern Australia, where disparities in housing quality, environmental and personal hygiene, sanitation, household crowding, and access to high quality food and to health care are most evident.

Other Indigenous populations living in western industrialized countries also have high rates of childhood diarrhea from an early age. For example, First Nations and Inuit infants from remote settlements in northern Canada had 3 times the rate of rotavirus infection during the first 6 months of life compared with infants from urban Winnipeg.24 High rates of diarrheal disease are reported amongst New Zealand’s Maori children, although more recently the incidence of diarrheal illness has been greatest amongst immigrant Polynesian infants living in the most socioeconomically deprived suburbs of New Zealand’s largest cities.25,26

PATHOGENS

The most frequently detected enteric pathogens in Indigenous communities are displayed in Table 2. These organisms are similar to those causing diarrhea in children from developing countries. Multiple pathogens are often isolated from individual patients, reflecting the effects of overcrowding, inadequate sanitation, and poor personal hygiene. The predominant enteric pathogens can vary by region, by season, and with time. Older studies may therefore no longer reliably predict the major causes of infectious diarrhea in some Indigenous communities. Where improvements in drinking water and personal and environmental hygiene have taken place, there should be decreased illness from bacterial and parasitic agents.9 Similarly, rotavirus vaccines are likely to further reduce episodes of severe diarrhea in infants and young children, where for example, in Australia, rural Aboriginal children have had the greatest disease burden.27,28 Indeed, shortly after their introduction, rotavirus vaccines protected immunized Aboriginal infants from a rotavirus outbreak simultaneously affecting several remote settlements in Central Australia.29 Finally, modern molecular
diagnostic techniques have shown that previously difficult-to-detect gastrointestinal pathogens, such as noroviruses, play an important etiologic role in acute diarrhea amongst disadvantaged populations.30 In tropical Northern Australia, the pattern of diarrheal disease is similar to many developing countries, with peak prevalence of bacterial and parasitic infections during the warm, wet season and rotavirus outbreaks during the cooler, dry months of the year. Dysentery is uncommon and most affected children present with acute watery diarrhea. The most frequently isolated enteric pathogens from hospitalized Aboriginal children are rotavirus (27%), enteroaggregative *Escherichia coli* (EAEC; 29%), enteropathogenic *E coli* (EPEC; 17%), nontyphoidal *Salmonella* spp (11%), enterotoxigenic *E coli* (ETEC; 11%), *Cryptosporidium parvum* (7%), and *Strongyloides stercoralis* (7%).16,31,32 At the community level, the predominant pathogens associated with diarrhea are rotavirus (12%), nontyphoidal *Salmonella* (13%), *Shigella* spp (5%), ETEC (15%), and *C parvum* (8%), and *S stercoralis* (1%).16,33,34 In Australia’s Northern Territory, the burden from rotavirus disease is particularly high, with notifications for Aboriginal children younger than 5 years almost 3 times that of non-Aboriginal children from the same region (2.75 vs 0.98 per year), and hospitalization duration is also about 3 times that recorded for non-Aboriginal children.28,35 In addition, rotavirus notifications begin at a younger age for Aboriginal children, where 56% are younger than 1 year and 24%, younger than 6 months. Comparable figures for non-Aboriginal children are 31% and 7%, respectively. As observed previously, in AI/AN children, unpredictable and explosive outbreaks of rotavirus diarrhea can happen simultaneously in several remote settlements, resulting in severe illness in susceptible individuals.36,37 Noroviruses are an important cause of diarrhea in urban Australian children38 and, given their global importance, they are also likely to play an important role in diarrheal disease in Aboriginal children living in tropical Australia.7

Multiple enteric pathogens are frequently isolated from Aboriginal children.16,32–34 Nontyphoidal *Salmonella* spp, *Giardia* spp., diarrheagenic *E coli* and *Campylobacter* spp are found in 12% to 45% of asymptomatic children living in remote, rural Aboriginal settlements.32–34 These organisms are transmitted from person-to-person or in food and water contaminated by human or animal feces. Detection of these pathogens reflects the overcrowding, inadequate water supply and personal hygiene, and poor sanitation that persist in these communities.19

### PERSISTENT DIARRHEA AND ENTEROPATHY

Persistent diarrhea is defined as diarrhea that begins acutely, but persists for more than 14 days. Cases of persistent diarrhea occur predominantly in children younger

<table>
<thead>
<tr>
<th>Viral</th>
<th>Bacterial</th>
<th>Parasitic</th>
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<tbody>
<tr>
<td>Rotavirus</td>
<td>Nontyphoidal Salmonella</td>
<td><em>Giardia</em></td>
</tr>
<tr>
<td>Norovirus</td>
<td>Campylobacter</td>
<td><em>Cryptosporidium</em></td>
</tr>
<tr>
<td>Enteric adenovirus</td>
<td><em>Shigella</em></td>
<td><em>Strongyloides</em></td>
</tr>
</tbody>
</table>

*a* Predominantly (1) enteroaggregative or EAEC; (2) enteropathogenic or EPEC; and (3) enterotoxigenic or ETEC pathotypes.
than 3 years. Poor nutrition is a risk factor and an outcome of persistent diarrhea. Consequently, there is a vicious cycle of infection, malabsorption, and malnutrition leading to stunted growth and cognitive impairment in some children. Although noninfectious causes, such as celiac disease, food protein-related enteropathies, and rare congenital causes of intractable diarrhea need to be considered, most cases in the developing world and amongst disadvantaged Indigenous children living in industrialized countries are likely to result from repeated enteric infections. Although still not fully understood, multiple consecutive infections can lead to small-bowel mucosal injury with blunting of the villi, cellular infiltration of the lamina propria, and loss of epithelial barrier and absorptive functions, which can persist into adulthood. Undernutrition delays epithelial cell repair, and secondary carbohydrate malabsorption from reduced production of disaccharidase enzymes prolongs the diarrheal symptoms and has an adverse effect on growth. Pathogens that are frequently isolated in persistent diarrhea include EAEC, EPEC, and Cryptosporidium spp, although Giardia, Cyclospora, and Strongyloides spp may also be important, especially in malnourished or immunocompromised children.

Persistent diarrhea is not commonly reported in Aboriginal children. This has been attributed to prolonged breastfeeding and prompt treatment of diarrhea with low-osmolarity lactose-free milk formula. Nevertheless, in Northern and Central Australia more than one-third of Aboriginal children without gastrointestinal symptoms have abnormal intestinal permeability, with evidence of impaired barrier function and decreased absorptive function as markers of underlying partial villous atrophy and intestinal inflammation. Others have observed that the stools of young Aboriginal children from remote communities are frequently loose and unformed, suggesting the acceptance of persistent loose stools as normal in children from isolated Indigenous communities. A recent health survey from Western Australia found that 6% of Aboriginal children had recurring episodes of diarrhea, with prevalence doubling amongst those living in remote rural settlements. Although cow’s milk protein intolerance does not appear to be an important cause of enteropathy in Aboriginal children, pathogens associated with small-bowel enteropathy, such as Cryptosporidium and Strongyloides may cause severe acute diarrheal episodes and contribute to malnutrition and reduced “catch-up” growth between episodes of diarrhea. Although Brachyspira spp have been identified in Aboriginal children with persistent diarrhea and poor growth, whether they play a genuine pathogenic role is still uncertain. Coinfections with rotavirus and diarrheagenic E coli strains can also result in more severe disease. Acute enteric infections, superimposed on underlying enteropathy, are thought to lead to further reductions in brush-border disaccharidase levels so that breast or cow’s milk results in osmotic diarrhea, dehydration, acidosis, and hypokalemia. Thus, repeated and frequent subclinical enteric infections associated with poor environmental hygiene can lead to an underlying enteropathy with impaired growth and, on occasions, episodes of severe gastroenteritis in young children.

**MANAGEMENT**

**Assessment**

Children presenting with acute diarrhea should be assessed quickly to determine whether they have infectious diarrhea. Next, the nature (watery or bloody dysenteric stools) and duration of the diarrhea, the presence and degree of dehydration, and the existence of associated conditions, such as pneumonia or malnutrition, must be established. Bile-stained vomiting, severe abdominal pain, tenderness, distension,
or masses suggest a surgical cause, whereas high fever, pallor, drowsiness, signs of circulatory impairment or respiratory distress inconsistent with the history of vomiting or diarrhea should raise the possibility of sepsis, pneumonia, urine infection or other serious illness. Malnourished Aboriginal children with diarrhea are at greater risk of dehydration, acidosis, and hypokalemia and are more likely to harbor multiple enteric pathogens or have other comorbidities than well-nourished non-Aboriginal children with gastroenteritis.16,19,23,47

A systematic review of 13 studies (1246 participants) found that prolonged capillary refill time greater than 2 seconds, skin turgor greater than 2 seconds, and abnormal respiratory pattern, alone or together, were the best individual signs for predicting 5% dehydration in children.48 Signs appear at about 3% dehydration, and children can be categorized as having mild-to-moderate dehydration if they are about 5% dehydrated (range; 3%–8%) and having severe dehydration if they are dehydrated by 9% or more. There is no direct evidence of when serum electrolytes should be measured in a child with diarrhea. Nevertheless, if feasible, children requiring intravenous rehydration should have their serum electrolytes measured.49 Furthermore, because rates of hypokalemia can exceed 60% in Aboriginal children hospitalized with diarrhea, these children should also have their serum electrolytes and glucose measured, especially if they are malnourished, have impaired conscious state or seizures, are younger than 3 months, or are dehydrated or suffering from persistent diarrhea.50 Similarly, when dysentery is present, stools should be examined for enteric pathogens and, if diarrhea is persistent, the stools should be tested for reducing sugars.51

Treatment

Treatment recommendations and evidence are summarized in Table 3. The pillars of clinical management of acute diarrhea are (1) correction of any dehydration and electrolyte and acid-base disturbance, (2) maintenance of nutrition, (3) treatment of associated conditions, and (4) prudent use of antimicrobial agents. Much of the evidence for managing and preventing infectious diarrhea in Tables 3 and 4 comes from studies conducted at large tertiary pediatric hospitals or community-based trials in developing regions of the world. In contrast, there are relatively few studies involving Indigenous children from industrialized countries.

A Cochrane review of 17 randomized controlled trials (RCTs; 1811 participants with acute gastroenteritis) found that there were no clinically important differences between oral glucose-electrolyte solutions and intravenous (IV) fluid therapy for managing children with mild-to-moderate dehydration from different countries or in different states of nutrition.52 For every 25 children receiving oral rehydration therapy, one will fail and require IV fluid replacement. A systematic review and meta-analysis reached similar conclusions.53,54 Best results were achieved with low osmolarity (eg, sodium [Na] 60, potassium [K] 20, chloride [Cl] 50, citrate 10, glucose 86 mmol/L; osmolarity 226 mOsm/L) oral rehydration solutions. Cereal-based oral rehydration solutions offer theoretical advantages, but these benefits may be negated by early feeding, and further studies are required to define their role in the management of non-cholera gastroenteritis.55 Although, nasogastric tubes allow continuous administration of oral rehydration fluids for children with persistent vomiting, they may not be acceptable in some cultures.56 Rehydration can usually be achieved within 4 to 6 hours. Overall, oral rehydration therapy for acute diarrhea in young children is safer and associated with lower costs, fewer hospital admissions, and less time spent in health care facilities.57 Contraindications to oral rehydration include severe dehydration, impaired conscious state, paralytic ileus, severe hypokalemia, alternative diagnoses, such as
<table>
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<tr>
<th>Intervention</th>
<th>Recommendation</th>
<th>Grading of Recommendation</th>
<th>Quality of Supporting Evidence</th>
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<tbody>
<tr>
<td>Oral glucose-electrolyte fluid</td>
<td>Use low-osmolarity oral rehydration solution over 4–6h to correct mild-to-moderate dehydration</td>
<td>Strong</td>
<td>High</td>
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<tr>
<td>Intravenous isotonic fluids</td>
<td>Use to correct severe dehydration over 3–4h or when oral rehydration therapy is contraindicated</td>
<td>Strong</td>
<td>High</td>
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<tr>
<td>Antiemetics</td>
<td>Not recommended</td>
<td>Weak</td>
<td>Low</td>
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<tr>
<td>Antidiarrheal agents</td>
<td>Not recommended</td>
<td>Strong</td>
<td>High</td>
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<tr>
<td>Early feeding, including breastfeeding</td>
<td>Recommended</td>
<td>Strong</td>
<td>Moderate</td>
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<tr>
<td>Lactose-free formula</td>
<td>Recommended for those with malnutrition, severe or persistent diarrhea, and if high rates of enteropathy exist</td>
<td>Strong</td>
<td>High</td>
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<td>Micronutrients:</td>
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<tr>
<td>Zinc</td>
<td>Recommended for those with malnutrition, severe or persistent diarrhea, and if high rates of enteropathy exist</td>
<td>Weak</td>
<td>Low</td>
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<tr>
<td>Vitamin A</td>
<td>Not recommended</td>
<td>Strong</td>
<td>Low</td>
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<tr>
<td>Probiotics</td>
<td>Not recommended</td>
<td>Strong</td>
<td>Moderate</td>
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<td>Antimicrobials</td>
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<tr>
<td>Acute watery diarrhea (noncholera)</td>
<td>Recommended only for giardiasis</td>
<td>Strong</td>
<td>High</td>
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<tr>
<td>Dysentery</td>
<td>Recommended only for select pathogens</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Persistent diarrhea</td>
<td>Recommended only for select pathogens</td>
<td>Strong</td>
<td>Moderate</td>
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surgical abdomen or sepsis, and some preexisting medical conditions, such as short gut syndrome, cyanotic heart disease, or renal impairment.\textsuperscript{50,51}

Children who have severe dehydration, other contraindications to oral rehydration solutions, or failed oral glucose-electrolyte solution treatment require IV fluid resuscitation with isotonic fluids, preferably Ringer’s lactate solution (Na 130, K 4, Cl 109, lactate 28 mmol/L).\textsuperscript{40,58} Evidence is limited to cohort studies, but IV rehydration can be safely accomplished within 4 hours and this includes Aboriginal children with acidosis and hypokalemia complicating their diarrheal illness.\textsuperscript{50,59} Although IV normal saline can be used to rapidly restore the circulation of severely dehydrated children, it is important to start oral rehydration fluids as soon as the children are able to drink, so as to replenish their depleted electrolytes, especially potassium. Risks associated with rapid IV fluid administration include electrolyte disturbance and fluid overload from hypotonic IV fluids and overestimating the degree of dehydration. Cardiac failure and hypoglycemia may result if there is severe malnutrition and phlebitis can follow IV cannulation.\textsuperscript{60} These risks are minimized by careful clinical assessment and monitoring and avoiding hypotonic IV fluids. If the child is severely malnourished or presenting with hypernatremic dehydration, IV fluid replacement rates are decreased, followed by early introduction of oral rehydration solutions with regular checking of serum glucose and electrolytes.

Vomiting is a common and distressing symptom of acute diarrhea. If severe, it may hinder successful oral rehydration therapy.\textsuperscript{27} Adverse effects, including drowsiness and extrapyramidal reactions, have meant that antiemetic agents are not recommended for young children with acute gastroenteritis.\textsuperscript{49,51} Ondansetron, a 5-hydroxytryptamine antagonist, is a new class of antiemetic, which is well tolerated by patients with cancer following chemotherapy, including young infants. A recent Cochrane review of 4 RCTs (501 subjects) and a systematic review that included a meta-analysis of 6 RCTs (745 participants) found that ondansetron decreased vomiting in mildly dehydrated children and reduced the risk of receiving IV fluids or admission to hospital by about 50%.\textsuperscript{61,62} To prevent one hospitalization, the number needed to treat was 14 (95% confidence interval 9, 44).\textsuperscript{62} Ondansetron resulted in increased diarrhea, but this was not deemed clinically important for the study population, which consisted mainly of children presenting to emergency departments at large tertiary pediatric hospitals. Although promising, ondansetron remains expensive, and additional studies demonstrating safety and efficacy in severely dehydrated Indigenous or malnourished children are required before a general recommendation in its favor.
can be made. Similarly, antidiarrheal agents are not recommended in children because of concerns over safety.\textsuperscript{40,51} Loperamide is widely prescribed for adults, but a recent systematic review of 13 RCTs, involving 1788 subjects, found that for a 1 day reduction of diarrhea in mildly dehydrated children, about 2\% of those younger than 3 years experienced severe adverse effects, including paralytic ileus, abdominal distension, lethargy, and even death.\textsuperscript{63} The main goals for the initial treatment of acute diarrhea should therefore remain the correction of fluid and electrolyte deficits and any acid-base disturbance present.

For 2 decades, early refeeding, including continuation of breastfeeding, has been recommended for children with diarrhea, because it may decrease stool output, shorten the duration of illness, and improve nutrition.\textsuperscript{64,65} Surprisingly, there are only limited clinical data supporting this recommendation.\textsuperscript{66} The development of lactose intolerance has been of concern,\textsuperscript{67} but a meta-analysis of 29 RCTs (2215 subjects) found that when oral rehydration, early refeeding, and reintroduction of milk were an integral part of management, only young children with severe dehydration, malnutrition, or persistent diarrhea benefited from lactose-free formulae.\textsuperscript{68} However, lactose intolerance is still an important clinical problem for Indigenous children, especially when an acute infection is superimposed on an underlying enteropathy.\textsuperscript{19} In such circumstances, low-osmolarity, lactose-free formula hastens clinical recovery in Aboriginal and AI children\textsuperscript{69,70} and should be used when there is severe dehydration, malnutrition, or high rates of enteropathy present.\textsuperscript{71}

Zinc has pleiotropic functions, including positive effects on immune and mucosal barrier functions. Although its mechanisms of action are unknown, it reduces the severity and duration of acute and persistent diarrhea in children living in developing countries, where zinc deficiency is common. A Cochrane review of 18 RCTs (6165 participants) and a recent systematic review and meta-analysis of 22 studies (18,199 participants) concluded that zinc administration of 10 to 20 mg/d to infants and children older than 6 months presenting to hospital with acute or persistent diarrhea resulted in almost a 20\% reduction in diarrheal frequency and duration.\textsuperscript{72,73} In contrast, vitamin A supplementation is not recommended for managing infectious diarrhea. Results from studies of vitamin A supplementation are contradictory. A meta-analysis of 9 RCTs (45,468 subjects) failed to detect any overall benefit.\textsuperscript{74} Recent studies from Mexico show that vitamin A and zinc have distinct effects on different enteric pathogens; for example vitamin A seems protective for some E\textit{coli} pathotypes and norovirus infections, possibly from its regulatory effects upon types 1 and 2 helper cell function.\textsuperscript{75,76} Although zinc continues to be prescribed for malnourished Aboriginal children with diarrhea,\textsuperscript{77} an RCT from Central Australia found that neither zinc nor vitamin A, alone or in combination, provided short-term benefits for Aboriginal children hospitalized because of diarrhea.\textsuperscript{78} However, none of these children were severely dehydrated and only a small proportion had signs of stunting. The roles for both micronutrients in the treatment of acute and persistent diarrhea caused by specific pathogens require further evaluation. Finally, probiotics in acute, childhood, infectious diarrhea appear to have moderate beneficial effects that are strain- and dose-dependent, limited to watery diarrhea, and best seen if administered early in the course of the illness.\textsuperscript{79} Further questions over dose, duration, and safety must be addressed before probiotics can be recommended.

As acute watery diarrhea in Indigenous children from industrialized countries is usually self-limiting or caused by viruses, antibiotics do not have an important role in management. An exception is metronidazole for giardiasis. In contrast, for some patients presenting with dysentery or persistent diarrhea, there is evidence that antibiotics may shorten symptom duration and decrease disease transmission when
caused by certain pathogens. Nonetheless, indiscriminate antibiotic usage increases the likelihood of persistent diarrhea, is associated with increased rates of antibiotic resistance, and can result in adverse outcomes, such as the hemolytic uremic syndrome in enterohemorrhagic *E coli* infections or prolonging carriage of *Salmonella* spp. Decisions to prescribe antibiotics are further complicated by limited access to laboratory facilities, unavailability of specialized tests (eg, molecular probes for diarrheagenic *E coli*), antibiotic resistance, and difficulties obtaining some recommended agents, such as nitazoxanide, for treating persistent cryptosporidiosis or giardiasis. Moreover, enteric pathogens are often found in asymptomatic children living in remote communities, so their presence in diarrheal stools does not always mean that they have a causative role. In general, children with dysentery require treatment if *Shigella* spp or *Entamoeba histolytica* are isolated from their stools. The choice is determined by local antibiotic susceptibility patterns, but trimethoprim-sulfamethoxazole, quinolones, (eg, nalidixic acid), or azithromycin for shigellosis and metronidazole for amoebic dysentery are the usual choices. Antibiotics are unnecessary for self-limited infections caused by nontyphoidal *Salmonella* or *Campylobacter* spp., unless the diarrhea becomes persistent or, for *Salmonella*, if the patient is younger than 3 months, immunocompromised, or shows signs of invasive disease. In addition to oral rehydration therapy, dietary management, and zinc supplementation, Indigenous children with persistent diarrhea may benefit from treating *Giardia*, *Cyclospora*, *Strongyloides* and EAEC with agents such as metronidazole, trimethoprim-sulfamethoxazole, ivermectin, or albendazole and azithromycin, respectively. Although antibiotic treatment of comorbid extraintestinal infections is appropriate, there is little evidence to support empiric antimicrobial therapy for children with persistent diarrhea from no known cause. Earlier enthusiasm for treatment of potential bacterial overgrowth using broad-spectrum nonabsorbable antibiotics has not been sustained following an RCT from India, which failed to demonstrate either symptom reduction or accelerated recovery.

**Prevention**

Recommendations and evidence for the prevention of acute and persistent diarrhea in Indigenous children are summarized in Table 4. Provision of safe water for drinking and food preparation, safe food handling, sufficient water to allow regular hand washing, and other hygienic practices, including adequate sanitation with secure disposal of human feces, are required to reduce recurrent diarrheal disease, enteropathy, and malnutrition amongst Indigenous populations. Recent Cochrane reviews provide a level of support for this approach. An analysis of 5 cluster RCTs involving whole communities (8055 participants) from the low- or middle-income countries of Africa and Asia reported a 32% reduction in diarrheal episodes following the introduction of hand washing education programs. Another review of 30 trials (53,000 participants) also found that interventions to improve the microbiologic quality of the water in countries where infectious diarrhea is endemic, successfully reduced diarrheal disease for all age groups by almost 30%, with interventions at the household proving to be most successful. However, significant heterogeneity, variable study quality, and limited follow-up means the effectiveness of these interventions may vary substantially between communities. Two systematic reviews examined the impact of measures to improve environmental hygiene on the incidence of diarrheal illness. Both commented on continuing limitations in study design. One included 46 studies and a meta-analysis, which found that attention to hand hygiene, sanitation, and water supply and quality reduced diarrhea by about 30%, although no additive effects were observed when single and multiple interventions were compared. The second
review selected 19 studies from developing countries and highlighted the complexity of implementing and measuring the effectiveness of hygiene interventions. The investigators concluded that for Aboriginal children living in remote settlements, education and hand washing with soap was likely to have the greatest impact and could lead to a 50% reduction in diarrheal episodes. Just over a decade ago, a survey of Aboriginal people from remote and rural settlements in Western Australia found that 70% lived in substandard housing and 33% of the communities had inadequate water supply and sanitation. Although more government resources for improving infrastructure have later become available, the health inequalities between Aboriginal and non-Aboriginal children remain. Care must be taken to ensure that improving the social determinants of health, such as education, employment, child care, and housing, should also play a central role in policies to decrease malnutrition and burden of disease.

Breastfeeding provides important protection against infectious diarrhea. A meta-analysis of 6 studies (18,162 infants) from developing countries that attempted to address difficulties associated with self-selection, reverse causation, and potential confounding reported that during the first 6 months of life, non–breastfed infants had a 6-fold greater chance of dying from diarrheal disease than infants receiving breast milk. However, protection decreased thereafter, presumably as potentially contaminated solid food and water are introduced into the diet. This is supported by the high diarrhea-related hospitalization and breastfeeding rates observed during the first 2 years of life for Aboriginal infants living in remote and rural communities. Similarly, although exclusive breastfeeding may reduce the risk of severe rotavirus diarrhea by as much as 90%, this protection disappears once it is discontinued or when mixed feeding is introduced. In contrast, neither routine vitamin A nor zinc supplementation is recommended for otherwise healthy Indigenous children. The aforementioned meta-analysis and a later-published systematic review for vitamin A supplementation found no evidence for a protective effect against diarrhea. Another meta-analysis of 17 RCTs of zinc supplementation in 7660 children younger than 5 years from 10 developing countries found a 15% reduction in diarrheal illness and 25% fewer episodes of persistent diarrhea. These reviews found evidence for publication bias, follow-up was fairly short, and adverse effects and adherence to treatment were not reported. The emergence of data from Mexico suggesting that vitamin A and zinc have different effects on enteric pathogens means further studies are needed in specific populations and communities, taking into account predominant pathogens, age, nutritional state, safety, adherence, and duration of effect.

Another major approach to diarrhea prevention is immunization. The World Health Organization (WHO) has given the highest priority to the development of new and improved vaccines against rotavirus, Shigella spp., ETEC, Vibrio cholerae O1 and Salmonella typhi. Of these, the most recent major advance is the development and licensure of 2 live-attenuated oral rotavirus vaccines. Their safety and efficacy have been confirmed in large field trials, each involving more than 60,000 infants from Europe, the United States and Latin America. One vaccine, RIX4414, (Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium), derived from a single human G1P8 strain relies on inducing homologous and broadly reactive heterotypic immunity for protection, whereas the other, RotaTeq (Merck & Co, Inc, Whitehouse Station, NJ, USA), is a multi-strain G1 to G4,P8 bovine-human reassortant vaccine, which elicits serotype-specific responses to the most common circulating human rotavirus strains. For both vaccines, protective efficacy for any form of rotavirus diarrhea was 67% to 79% and for severe rotavirus disease, 81% to 100%. The WHO is awaiting the results from field trials in Africa and Asia to be published before issuing a global
recommendation for rotavirus vaccines (WHO made a global recommendation of including rotavirus vaccines in national immunization programs in June 2009). Meanwhile, early postlicensure surveillance data from the United States and Australia show that the numbers of laboratory-confirmed cases of rotavirus diarrhea have declined by almost 70% and the onset of the rotavirus season has been delayed by 2 to 4 months. Data are limited for rotavirus vaccines in Indigenous infants. The previously licensed rhesus-human reassortant rotavirus vaccine, RRV-TV (RotaShield, Wyeth Lederle Vaccines, Philadelphia, PA, USA), provided a protective efficacy of just 69% against severe rotavirus diarrhea in AI infants living in Arizona tribal reservations. More than 500 AI infants received the multi-strain G1-G4,P[8] bovine-human reassortant vaccine, RotaTeq, in the pivotal phase III trial, although no specific safety and efficacy details were provided for AI vaccine recipients. Outbreaks provide another opportunity to determine vaccine effectiveness. In March 2007, the single human G1P[8] strain vaccine, Rotarix, reduced the risk of hospitalization from gastroenteritis in fully immunized Aboriginal infants by 78% during a G9P[8] rotavirus outbreak in Central Australia. However, 2 years later the vaccine appeared less effective for a G2P[4] outbreak, once again involving Aboriginal infants from the same region (Carl Kirkwood, PhD, Melbourne, Australia, personal communication, May 2009). It remains too early to judge whether this outbreak is part of a natural cycle of G2P[4] outbreaks in Central Australia or whether it results from reduced effectiveness of this vaccine. Concerns have been raised previously in Brazil over increased G2P[4] activity since the introduction of Rotarix into the national infant immunization schedule, emphasizing the importance of continuing surveillance to determine the effectiveness of rotavirus vaccine programs and their impact on rotavirus ecology and to inform immunization policies.

SUMMARY

Despite recent improvements, hospitalization rates for infectious diarrhea in disadvantaged Indigenous children remain higher than for other children living in western industrialized societies. This is particularly true for Australian Aboriginal children. The patterns of disease resemble those observed in developing countries, where poor environmental hygiene and overcrowding contribute to high rates of infection and intestinal mucosal injury, leading to malnutrition and, for some children, poor growth, and impaired intellectual function. Judicious use of oral rehydration solutions, early refeeding, dietary management, micronutrients, and selective prescribing of antimicrobial agents can assist recovery for individual episodes. However, it is by implementing equitable social and educational policies to enable self-determination and full community participation in decision making that will have the greatest impact. Only then will sustainable high standards in housing and environmental hygiene be achieved, which when accompanied by easily accessible health care and immunization programs “delivered on time”, will help lead to decreased health inequalities for many Indigenous communities.

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