## Appendix: Summary of the 17 studies included in the literature review

| Author(s), design, sample size, country | Study population and inclusion criteria | Data collection |
|---|---|---|
| Cheng (2011)<br>Literature review of three RCTs, including one double-blind RCT<br>466 participants, Canada | » Children aged 6 months to 12 years who had vomited at least five times in the previous 24 hours<br>» Children aged 6 months to 10 years with mild-to-moderate dehydration who had had at least one episode of non-bilious, non-bloody vomiting in the previous four hours<br>» Children aged 1 to 10 years with a clinical diagnosis of gastroenteritis and mild-to-moderate dehydration in whom ORT had failed | Review of studies conducted in 2002, 2006 and 2008 comparing oral ondansetron with placebo and ORT |
| Danewa et al (2016)<br>Single, tertiary centre double-blind RCT<br>170 participants, India | » Children aged 3 months to 5 years<br>» Criteria of 'some' dehydration as defined by the WHO*<br>» At least two episodes of non-bilious, non-bloody vomiting within the previous six hours<br>» Children with a diagnosis of acute diarrhoea (duration less than 14 days) | » Observation<br>» Primary outcome measure was amount of ORS intake in four hours<br>» Secondary outcome measures were duration of dehydration correction, number of vomiting episodes in four hours, adverse effects (rash, headache, diarrhoea) and healthcare professional satisfaction<br>» No follow-up |
| Freedman et al (2011a)<br>Prospective multicentre cohort study<br>647 participants, Canada | Children aged 3 to 48 months who presented to 11 EDs with acute gastroenteritis (defined as >3 watery stools in 24 hours during the 72 hours preceding the visit to the ED) | Surveys, medical record reviews and phone follow-up evaluations two weeks later |
| Freedman et al (2011b)<br>Cross-sectional, internet-based survey<br>235 participants, US, Canada | » Survey sent to members of Paediatric Emergency Research Canada and the Paediatric Emergency Medicine Collaborative Research Committee who provide care to patients<br>» Children under 18 years of age<br>» ED settings | » 41-question survey delivered through online survey tool with reminder email<br>» Consent implied by survey completion<br>» Data entered into spreadsheet and comparison conducted using chi-square test |
| Freedman et al (2013)<br>Overview of systematic reviews<br>12,478 participants, Canada | » Four systematic reviews that encompassed 95 RCTs between themselves<br>» Inclusion of acute gastroenteritis and dehydration<br>» Children up to the age of 18 years | » Literature review<br>» Jadad scale used to evaluate methodological quality of RCTs |
| Freedman et al (2014)<br>Retrospective observational analysis<br>804,000 participants, Canada | Children younger than 18 years treated in 18 participating EDs with a diagnosis of gastroenteritis or dehydration based on discharge diagnostic code | Data collected from the Paediatric Health Information system |
| Freedman et al (2015)<br>Systematic review and meta-analysis<br>4,444 participants, Global (developed countries) | Children up to the age of 18 years with gastroenteritis | » Literature review<br>» A medical librarian developed the search strategy. MEDLINE, Cochrane Database of Systematic Reviews and EMBASE were accessed between 2000 and 2015. Grey literature explored<br>» Search originally conducted for the period 2000-12 and re-run in 2014 to identify more recently published articles |
| Freedman et al (2019a)<br>Double-centre, double-blind RCT<br>626 participants , Pakistan | » Children aged 6 months to 5 years without dehydration who had diarrhoea and at least one episode of vomiting within four hours of arrival<br>» Illness of less than seven days duration | » Observation<br>» Medical officers documented volumes of oral and IV fluids administered and frequency and volume of vomiting, diarrhoea and urination<br>» Dehydration parameters (as defined by the WHO*) and vital signs documented at four-hour assessment<br>» Discharged patients were reassessed after 24 hours and followed up at 48 and 72 hours by phone |
| Freedman et al (2019b)<br>Double centre, double-blind RCT<br>918 participants, Pakistan | » Dehydrated children aged 6 months to 5 years weighing greater than 8kg with at least one episode of diarrhoea and one episode of vomiting within the previous four hours<br>» Children with 'some' dehydration (as defined by the WHO*)<br>» Exclusion criteria included bilious vomiting and illness lasting longer than seven days | » Observation<br>» Medical officers documented volume of oral and IV fluids administered and frequency and volume of vomiting, diarrhoea and urination<br>» Dehydration parameters and vital signs were documented at four-hour assessment<br>» Discharged patients were reassessed after 24 hours and followed up at 48 and 72 hours by phone |
| Golshekan et al (2013)<br>Single-centre, double-blinded RCT<br>176 participants, Iran | Children aged 1 to 10 years with a simple clinical diagnosis of gastroenteritis, dehydration, onset within 24 hours, at least one episode of vomiting in the previous six hours and no fever | » Blinded investigations through observation<br>» Assessment four hours after administration of intervention and commencement of ORT<br>» After 48 hours, investigator called the child's family for follow-up |
| Marzuillo et al (2016)<br>Single centre experience<br>119 participants, Italy | Children aged 1 to 14 years with uncontrolled vomiting | » Observation (length of observation and who conducted the observations were not recorded)<br>» No follow-up |
| McLaren et al (2016)<br>Retrospective comparative cohort study<br>11,785 participants, US | » Children aged 6 months to 18 years with a discharge diagnostic code 9 (gastroenteritis)<br>» Illness severity determined using the local institution's dehydration score | » Medical records of all children with gastroenteritis reviewed<br>» Clinical history, interventions, diagnostic studies and final diagnosis reviewed |
| Mullarkey et al (2013)<br>Retrospective study<br>234 participants, Ireland | Children up to 16 years weighing more than 5kg who presented to the ED with signs and symptoms of acute gastroenteritis (defined as acute diarrhoeal illness with or without vomiting) and suboptimal oral intake | » Data collected over six weeks in 2009<br>» All patients with discharge diagnosis of gastroenteritis on the 'Symphony ED electronic database' were included<br>» Data collected included age, sex, weight, length of ED stay and documentation of ORT<br>» Outcome measures looked at children requiring IV fluids, admission and representation rates |
| Pelc et al (2014)<br>Cross-sectional survey describing a scenario in which a young child has moderate dehydration caused by gastroenteritis<br>68 completed studies, Belgium, France, the Netherlands, Switzerland | » Across four countries, primarily in teaching hospitals<br>» Each centre asked to include at least three participants | » Electronic survey conducted between February and July 2012<br>» Survey emailed, followed by phone call plus reminder email<br>» Data analysed using the Kruskal-Wallis rank test |
| Schnadower et al (2015)<br>Overview of four studies<br>73 participants, US | » Four studies of children with gastroenteritis<br>» Study selection method not disclosed<br>» Gastroenteritis definition not discussed | Review of four studies |
| Tomasik et al (2016)<br>Systematic review and meta-analysis<br>1,215 participants, Poland | Review of 10 RCTs comparing ondansetron with placebo or no intervention for vomiting in children with acute gastroenteritis | » Systematic literature review<br>» Cochrane Central Register of Controlled Trials, MEDLINE and Embase searched for relevant studies published up to April 2016<br>» Searches undertaken independently by three reviewers |
| Zanon et al (2013)<br>Italy | Children younger than 18 years with vomiting related to acute gastroenteritis | » Review of databases across eight EDs in Italy between 2004 and 2007 of children with diagnosis of acute gastroenteritis<br>» Included patient data, sex, age and information about medicine used (indication, dose, frequency and route of administration) |

ECG = electrocardiogram; ED = emergency department; IM = intramuscular; IV = intravenous; ORS = oral rehydration solution; ORT = oral rehydration therapy; RCT = randomised controlled trial; WHO = World Health Organization

* World Health Organization (2005) The Treatment of Diarrhoea: A Manual for Physicians and Other Senior Health Workers. www.who.int/maternal_child_adolescent/documents/9241593180/en/ (Last accessed: 22 February 2021.)

| Interventions | Findings |
|---|---|
| » Ondansetron in tablet form compared with placebo followed by ORT 15 minutes later<br>» Oral ondansetron solution compared with placebo followed by ORT 30 minutes later<br>» Double-blind RCT of oral ondansetron or placebo followed by ORT 15 minutes later | » Children who received a single dose of ondansetron were less likely to vomit, had greater oral intake and were less likely to receive IV fluid therapy compared with those who received placebo<br>» Children who received oral ondansetron were less likely to be admitted to hospital<br>» Most common side effect of ondansetron was diarrhoea<br>» Number of diarrhoea episodes was similar in both groups |
| » Ondansetron in syrup form compared with placebo<br>» One dose given and only repeated if patients vomited within 30 minutes of dose administration<br>» Patients were then given ORT at the rate of 75ml/kg in the first four hours | » Proportion of children receiving IV fluid therapy was not statistically different between intervention and placebo groups<br>» Amount of ORS consumed in four hours significantly larger in children receiving ondansetron<br>» Median duration of dehydration correction significantly smaller in children receiving ondansetron<br>» Mean number of vomiting episodes during four hours of observed ORT significantly smaller in children receiving ondansetron<br>» Carer satisfaction in all fields was better in intervention group than placebo group |
| » No interventions<br>» Review of practice<br>» Main discussion was about the use of IV fluid therapy and ORT, but ondansetron also discussed | » Ondansetron was administered to 13% of children<br>» Ondansetron was administered more frequently by physicians who had completed a paediatric emergency medicine fellowship<br>» 42% of children were discharged with instructions for taking ondansetron at home<br>» Significant variations in the treatment of acute gastroenteritis in Canadian EDs<br>» Children who received IV fluid therapy were more likely to re-visit ED<br>» Use of ondansetron varied significantly |
| No interventions | » Ondansetron was the antiemetic administered most often<br>» Reasons for not giving ondansetron were lack of evidence of clinical benefit and concern about side effects<br>» Inconsistencies in management between Canada and the US |
| » No interventions<br>» The four systematic reviews had reviewed probiotics, antiemetics, IV fluid therapy and ORT | » No difference in hospitalisation rate within 72 hours of discharge<br>» Some clinicians prescribed multiple doses of ondansetron, but this is not supported by evidence<br>» Administration of ondansetron increases the likelihood that children will stop vomiting |
| IV fluid therapy compared with ondansetron | » Dramatic increase in rate of ondansetron administration in children with gastroenteritis during 10-year review period<br>» During the 'high ondansetron use period', rates of IV fluid therapy were lower<br>» Children who presented to EDs in the 'high ondansetron use period' were less likely to return within three days |
| Among the 31 RCTs selected:<br>» Ten compared ORT to IV fluid therapy<br>» Six examined different probiotics<br>» Six compared the different rates or compositions of IV fluids<br>» Nine RCTs involving 1,691 patients evaluated three antiemetics (ondansetron, dimenhydrinate and granisetron) | » Ondansetron offers short-term benefits but makes no difference in terms of return visits to the ED<br>» Ondansetron increases the frequency of diarrhoea<br>» Despite previous concerns about the arrhythmogenic potential of ondansetron, more recent evidence has reduced such concerns with single dosing in healthy children |
| » Disintegrating tablet of ondansetron compared with placebo<br>» One dose repeated if patients vomited within 15 minutes<br>» Volume of ORS measured after four hours | » 19.6% of children in the ondansetron group vomited during the four-hour observation period compared with 24% in the placebo group<br>» Receiving ondansetron or placebo had no effect on the proportion of children hospitalised after 24 hours or on those who became dehydrated within 72 hours<br>» Number of diarrhoea-like stools during the 72-hour follow-up period similar between the two groups<br>» Oral ondansetron did not reduce IV fluid therapy requirements |
| » Disintegrating tablet of ondansetron versus placebo<br>» One dose repeated if the patients vomited within 15 minutes<br>» Volume of ORS measured after four hours | » 13.2% of children in the ondansetron group vomited during the four-hour observation period compared with 26.1% in the placebo group<br>» No difference between groups in volume of oral fluids consumed<br>» Number of children hospitalised within 72 hours did not differ between groups<br>» Children were less likely to have IV fluid therapy if they had received ondansetron |
| » Oral ondansetron compared with oral placebo<br>» Medicine dosed according to weight<br>» ORT initiated 30 minutes after medicine given | » Ondansetron decreased the failure of ORT<br>» There was a reduction, in the ondansetron group, of more than 50% in the proportion of children who vomited during ORT and in the proportion of children treated with IV fluids<br>» No significant reduction in hospital admissions<br>» No evidence of complications. Ondansetron is easy to administer, has few side effects and is safe and effective |
| » Single dose of IV ondansetron given if patient required IV fluid therapy<br>» Single dose of IM ondansetron if patient only required ORT<br>» All patients started ORT according to local guidelines 30 minutes after medicine administration | » Ondansetron is safe to use despite previous doubts<br>» Ondansetron is effective as a first approach to managing gastroenteritis |
| » No active interventions<br>» Review of management | » Children were discharged with a prescription for ondansetron<br>» Children given a prescription for ondansetron had an increased risk of return visit to the ED and of admission following revisit |
| » No interventions<br>» Retrospective study | » Single dose of oral ondansetron reduces the number of children requiring IV fluids<br>» Ondansetron administered in the ED is likely to be cost-effective<br>» Ondansetron given by triage nurse can mask a serious underlying condition<br>» Ondansetron is a useful adjunct in the treatment of children with dehydration secondary to acute gastroenteritis |
| » No active interventions<br>» Survey-based study | » Antiemetics rarely prescribed<br>» 90% of respondents reported using ORT as first-line rehydration therapy |
| » No active interventions<br>» Studies had looked at ondansetron and probiotics | » Administration of a single oral dose of ondansetron supports the prevention of nausea and vomiting<br>» Use of ondansetron is increasing<br>» Ondansetron does not require ECG monitoring of patients with no known risk factors |
| Review of literature, but only of RCTs that compared ondansetron with placebo or no interventions for vomiting in children with acute gastroenteritis | » Ondansetron has no effect on ED return visit rates<br>» Evidence of the effect of ondansetron on diarrhoea-type stools is inconclusive<br>» Arrhythmias unlikely to occur with a single dose of ondansetron<br>» Ondansetron reduces the risk of ORT failure<br>» Cost-effectiveness of ondansetron not explored but ondansetron is likely to be cost-effective |
| Different antiemetics used in the management of acute gastroenteritis:<br>» Domperidone<br>» Metoclopramide<br>» Ondansetron<br>» Granisetron<br>» Thiethylperazine<br>» Tropisetron<br>» Prochlorperazine | » 30% off-label prescription of antiemetics<br>» Metoclopramide and ondansetron administered off label to children of varying age and indication in all centres reviewed<br>» Domperidone is the only antiemetic used that is labelled for use in gastroenteritis in children |