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The Association of Paediatric Anaesthetists of Great Britain & Ireland

Guidelines on the Prevention of Post-operative Vomiting in Children

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Key to Evidence Statements and Grades and Strength of Recommendation:

Levels of Evidence

Levels of Evidence:	
1++	High quality Ms, SRs of RCTs, or RCTs with a very low risk of bias
1+	Well conducted Ms, SRs of RCTs, or RCTs with a low risk of bias
1 -	Ms, SRs of RCTs, or RCTs with a high risk of bias
2++	High quality SRs of CC or CSs High quality CC or CSs with very low risk of confounding, bias, or chance and high probability that relationship is causal
2+	Well conducted CC or CSs with low risk of confounding, bias, or chance and moderate probability that relationship is causal
2 -	CC or CSs with a high risk of confounding, bias, or chance and significant risk that relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

RCT= Randomised Controlled Trial
M= Metaanalyses
SR= Systematic Reviews
CC= Case Control Studies
CS= Cohort Studies

The guidelines have been prepared using SIGN Methodology[1] drawing together available evidence and recommending best practice based on the available evidence and on the clinical experience of the guidelines development group. Since the previous Guideline in 2009, SIGN have implemented the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology. In accordance with this, the recommendations for key areas influencing practice are now classified as unconditional or conditional. This Strength of Recommendation based on the quality of the evidence replaces the previous 'ABCD' system that was related to types of study. For reference the original guideline remains available on the APAGBI website.

Strength of Recommendation

Unconditional (UC)	Strong evidence, no important drawbacks
Conditional (C)	Weaker evidence, serious potential drawbacks

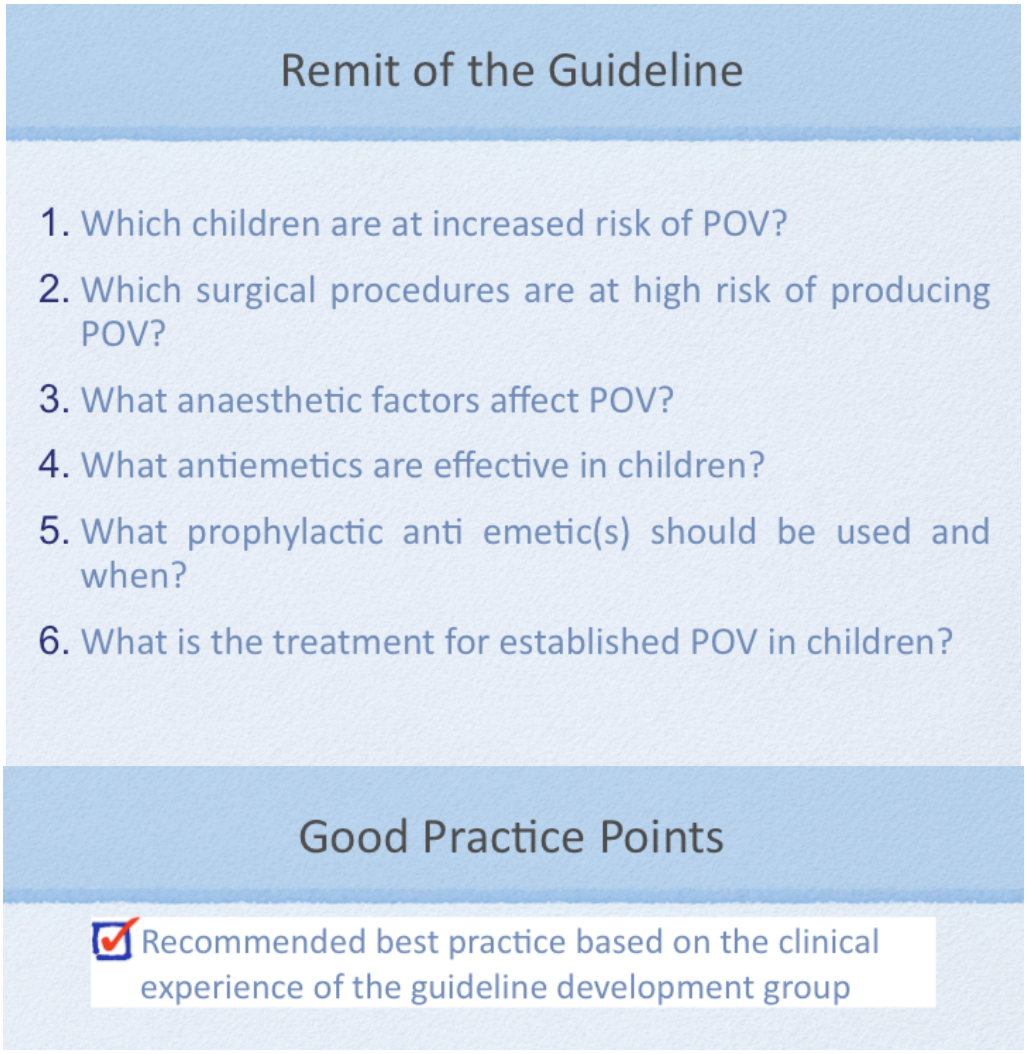
Introduction

Postoperative Vomiting (POV) is an important cause of morbidity in children. This report for the Association of Paediatric Anaesthetists of Great Britain & Ireland investigates the causes of post-operative vomiting in children and summarises the efficacy of treatments used to prevent and treat postoperative vomiting in children. The original guidance was published in 2009.

These updated guidelines were presented at the Association of Paediatric Anaesthetists of Great Britain & Ireland (APAGBI) Annual Scientific Meeting in May 2015. They have been written in good faith and will be revised as new information becomes available. Should the reader find any useful additional content please contact the Chair of the POV Guidelines group by email to inform a future revision.

Remit of the Guideline

The guideline seeks to answer the following questions:



Glossary

NNT: Number needed to treat	The number of patients who need to be treated to reduce the expected number of cases of a defined endpoint by one.
Meta-analysis	A statistical method that combines the results of independent trials to give a precise estimate of treatment effect.
Case control study	A study that compares patients with an identified outcome against patients without that outcome, and reviewing them to see if they had an exposure of interest.
Cohort study	A study in which subjects who have a certain condition and/or receive a particular treatment are followed over time and are compared with another group who are not affected by that condition.
Systematic review	A review of relevant literature focused on a specific question that tries to identify, evaluate and synthesize all high quality research evidence relevant to that question.
Randomised control study	A study whereby different treatments are randomly allocated to study participants. This attempts to ensures that both known and unknown confounding factors are evenly distributed between treatment groups, thereby reducing error and bias.
Sensitivity	Probability of a positive test among patients with a disease
Specificity	Probability of a negative test among patients without a disease
Positive (negative) predictive value	The ratio of the true positives (negatives) divided by the sum of the true positives (negatives) and false positives (negatives).
Odds ratio	The ratio of the odds of an event occurring in one group to the odds of it occurring in another group. An odds ratio of 1 indicates that the condition or event under study is equally likely in both groups. It provides an estimate (with confidence interval) for the relationship between two binary ("yes or no") variables.
Confidence interval	An indication of the reliability of an estimate. The confidence level will define how likely the interval is to contain the parameter.
Relative risk	The ratio of the probability of an event occurring in a treatment group versus the control group.

1. Identifying Children at High Risk of Postoperative Vomiting

Background

Postoperative Vomiting (POV) is approximately twice as frequent amongst children as adults with an incidence of 13-42% in all paediatric patients [2,3.] Severe POV can result in a range of complications including wound dehiscence, dehydration and electrolyte imbalance and pulmonary aspiration [4]. It is one of the leading causes of parental dissatisfaction after surgery and is the leading cause of unanticipated hospital admission following ambulatory surgery with resulting increased health care costs [5,6]. Importantly, no research has focused on the **children's** perspective of POV, and whether they perceive this symptom with the same distress and loathing as adults [7].

Identifying children at high risk of POV is beneficial as prophylactic antiemetic therapy can then be targeted at this group. Indiscriminate prophylaxis is probably unnecessary as it is financially costly and may result in excessive adverse drug reactions [8]. Research into this important area is hampered by the difficulty in diagnosing nausea in younger children. Hence, vomiting and retching are used as the end-points in most of the paediatric literature on this subject [3].

The main risk factors for POV in children may be considered in the following categories:

- Patient-related issues
- Surgical factors
- Anaesthetic (technique & drugs used in peri-operative period)

A. Patient Factors

Age

Paediatric patients have a higher incidence of POV compared to adults with children over 5 years of age having around a 34-50% overall risk of vomiting after surgery. The lowest incidence occurs in infancy (5% incidence of emesis) while the preschool child has a 20% risk of vomiting [9]. In a cohort study of 1401 children < 14 years old, a sharp increase in POV risk occurs around age 3 with a 0.2-0.8% per year increase in risk continuing into adolescence [10]. This increase in risk around 3 years of age agrees with the findings of an earlier study which found an 8% incidence of POV in children <3 years old, increasing to 29% in children > 12 years old [11].

2++, 2+

UC Risk of POV increases markedly above three years old and continues to rise throughout early childhood into adolescence.

☑ Troublesome POV is rare in children under three years old and patients in this age-group rarely require prophylactic antiemetic medication.

History of POV

This has proved to be an important risk factor in the majority of studies in the adult and paediatric POV literature and is included in all of the risk scoring systems to aid prediction of POV that have been published to date [12]. A specific paediatric cohort study identified "previous POV" and "POV in a parent or sibling" as important independent risk factors [10].
A combined adult and paediatric study (with < 10% of the study group children) found a previous history of POV to be the second strongest predictor of postoperative nausea and vomiting [13].

2++, 2-

UC A previous history of POV is an independent risk factor of subsequent POV in children.

☑ Children with a past history of POV should be considered for prophylactic antiemetic medication.

Motion Sickness

Several studies that have looked at risk factors for POV in children mention a history of motion sickness (MS) as a potential problem.

In a large adult study, history of MS was identified as a strong predictor of POV [14] however caution is required when extrapolating from adult data.

One study in children looked specifically at MS as a predictor of POV.[15] Seventy consecutive children were studied undergoing surgery not high risk for POV.

2+

The overall incidence of POV was 29%. Fourteen children (20%) had a history of MS; MS-positive children were more likely to vomit than those who were MS-negative (P < 0.01). There were no other significant variables between groups. The sensitivity of MS as a predictor of POV was 45% and the specificity 90%, giving a positive predictive value of 64.3% and a negative predictive value of 80.4%. It was concluded that MS was associated with POV but its positive predictive value was fairly low.

C A previous history of motion sickness is likely to be an independent risk factor of subsequent POV in children.

☑ Children with a past history of motion sickness should be considered for prophylactic antiemetic medication.

Gender

Female gender is a strong risk factor from puberty onwards in all adult POV studies. Adolescent and adult females have a two to four-fold increased POV risk whilst prepubescent girls lack increased likelihood of POV compared to males [10,11,12,16,17]. The marked increase in POV risk at the menarche suggests that sex hormones are implicated. Reports suggesting that POV was more common during the first week of the menstrual cycle have been challenged in a systematic review[18].

2+ adults, 2- children

C Post-pubertal girls have an increased incidence of POV which may be sex hormone related although phase of the menstrual cycle does not appear to affect the incidence.

Post-pubertal girls should be considered for prophylactic antiemetic medication.

Preoperative anxiety

Although preoperative anxiety has been shown to be a weak risk factor for POV in adults, this was not confirmed in a previous small, but well conducted study in school-age children [19,20]. | 2-

Obesity

Early studies from the 1950s and 1960s suggested an association between obesity and POV in adults. However, a systematic review with adjustment for multiple confounding factors failed to confirm these earlier findings [21]. There is no comparable evidence regarding a relationship between obesity and POV in children. | 1+ adults

Smoking

Adult smokers are less susceptible to POV from convincing data in several studies [14,22,23]. No data on this topic are published in children. A recent review posed the intriguing question if children of smokers had decreased POV due to passive smoking [4]. | 2+ adults

B. Surgical Factors

Duration of surgery

The incidence of POV increases with longer duration of surgery and anaesthesia in both adult and paediatric studies [10,23]. Surgery under general anaesthesia of > 30 minutes duration was identified as an independent risk factor in a large paediatric study with an odds ratio of 3.25 [10]. Half of the published risk scoring systems for POV in adults and children include duration of surgery as an important risk factor[17.] | 2+ +

C POV increases significantly if operative procedures under GA last more than 30 minutes.

Type of surgery

The status of type of surgery as a risk factor for POV is controversial. Although numerous studies have identified a variety of procedures as being associated with increased risk of POV, there is often conflicting evidence between studies for the same procedure. This area of POV research suffers from the problem of separating 'true' from 'surrogate' risk factors[3]. For example, certain types of surgery associated with high postoperative opioid requirements might be the surrogate for increased POV risk rather than the procedure

itself. This has resulted in most of the established risk scores for POV not including any type of surgery in their risk model [10].

With these considerations in mind, the following procedures in children have been associated with increased POV risk:

a. Strabismus surgery — 1++

This is perhaps the paediatric surgical procedure that has the strongest evidence of POV risk with a high frequency of emetic episodes reported in a systematic review (mean incidence late vomiting 59%, but as high as 87% in one of the included studies) [24]. It is the only surgical procedure included in the established paediatric POV risk score with an odds ratio of 4.33, the highest risk factor of the four independent factors identified in this study[10].

UC Children undergoing strabismus surgery are at high risk of POV.

☑ Minimising POV following strabismus surgery requires a multimodal approach utilising antiemetics, dexamethasone and avoiding early mobilisation in the recovery period.

b. Adenotonsillectomy — 1+

Without antiemetic prophylaxis, a high proportion of children undergoing adenotonsillectomy will experience at least one episode of postoperative vomiting (89% without prophylaxis in one series) [11, 25,26]. However, many of these studies suffer from the drawback of the compounding effect of perioperative opioid administration that may be acting as a surrogate risk factor, as in the absence of opioids in one study only 11% of children vomited[27].

UC Children undergoing adenotonsillectomy are at increased risk of POV.

☑ Minimising POV is essential for a successful day-case tonsillectomy programme. Scrupulous surgical technique to decrease swallowed blood, avoidance of long-acting opioid analgesia and prophylactic antiemetics and dexamethasone are key factors in achieving this goal.

c. Otoplasty — 2-

Otoplasty in children is recognised for its emetic potential with an incidence of vomiting in the absence of antiemetic prophylaxis of 60% [28]. However, surgical dressings, in particular packing of the external ear canal, may influence the incidence of POV in these patients [29].

d. Other procedures — 2-

Groin surgery (herniotomy and orchidopexy) and penile surgery have a modest increased incidence of POV, but the evidence is from older studies with numerous compounding variables such as opioid administration [11,16].

☑ The evidence that procedures other than strabismus surgery and adenotonsillectomy are associated with a high incidence of POV is less compelling. However, when the consequences of POV may significantly affect clinical outcomes e.g. result in admission after day-case surgery, consideration should be given to using prophylactic anti-emetics.

C. Anaesthetic factors

A variety of anaesthetic-related factors have been implicated in producing increased POV in children. However, few of these factors are included in any of the POV risk scoring systems in the published literature for paediatric patients [4].

Nitrous oxide

A mixed adult and paediatric systematic review concluded that omission of nitrous oxide reduced the incidence of postoperative vomiting but not nausea in high-risk patients with a NNT of 5. The reduction in emesis, by avoiding nitrous oxide, was achieved at the cost of an increased risk of intraoperative awareness [30].

In children, avoiding nitrous oxide has conflicting effects on POV; it produces a small reduction in early POV following dental surgery but not after grommet insertion without any difference in late POV rates with either procedure [31,32]. In a small RCT, there was no difference in POV rates in paediatric T&As patients who received nitrous oxide compared to those who did not receive the agent.[33]

1+, 2-

C The use of nitrous oxide does not appear to be associated with a high risk of POV in children

☑ Nitrous oxide may be used for anaesthesia in children without increasing the incidence of POV.

Volatile agents

Although modern volatile agents are less emetogenic than older agents (e.g. ether), there is evidence that volatile agents may significantly contribute to early POV particularly in high- risk patients. There is also a strong dose-response relationship between POV and duration of exposure to volatile agents[34]. Volatile agents are far more emetogenic when used for maintenance of anaesthesia when compared to propofol maintenance in a large meta-analysis[35]. There is little evidence that any of the modern agents is less or more emetogenic than the others [34,35].

1++, 1+

UC Use of volatile anaesthetic agents is associated with increased risk of emesis particularly in children who have other risk factors for POV.

☑ It is recommended that total intravenous anaesthesia should be considered when children who are at high risk of POV undergo surgery that has a high risk of producing POV.

Peri-operative opioids

Despite the widely held belief that peri-operative opioid administration is strongly implicated in increased POV, the evidence from the literature is less categorical. 1+, 1-

Intraoperative opioid use in children in two large studies was associated with **reduced** or only slight increased incidence of POV [10,34], whereas postoperative administration in both these studies was associated with increased POV risk with odds ratios of 1.64 and 2.3 respectively.

Conversely, the use of perioperative morphine in children is associated with increased POV risk for a range of procedures including adenotonsillectomy, strabismus surgery and dental surgery [27,36,37,38]

Although administration of perioperative opioids is included in half of the published adult POV risk scores, opioid use was not regarded as an independent, statistically significant predictor of POV in the most widely quoted paediatric POV risk scoring system.[11]

C Use of opioids may be associated with increased risk of POV particularly if longer-acting agents are used in the postoperative period

☑ The anaesthetist should try to achieve satisfactory postoperative analgesia without the use of opioids whenever possible if POV is to be minimised, particularly in high risk patients.

Use of regional and local anaesthesia techniques are recommended where appropriate to reduce the need for opioids.

Use of anticholinesterase drugs

Antagonism of neuromuscular blockade has been associated with increased risk of POV. In a systematic review of this subject in a mixed adult and paediatric population (25% children), higher dose neostigmine (> 2.5 mgs in adults) was associated with a significantly increased risk of POV, although the study did not analyse the paediatric and adult patients separately [39]. 2-

C Use of anticholinesterase drugs may increase POV in children.

☑ In situations where a child is at high risk of POV, anaesthesia without muscle relaxants should be considered to avoid the risk of requiring reversal of neuromuscular blockade.

Peri-operative Fluids

For minor surgical procedures, giving large volumes of IV crystalloid intraoperatively reduced POV in children after strabismus surgery in the first 24 hours after surgery.[40] One hundred children were randomly assigned to receive 30 ml·kg^{-1}·h^{-1} ("superhydration group") or 10 ml· kg^{-1}·h^{-1} (control group) of Ringer's solution intra-operatively. Nausea and vomiting occurred in 11 (22%) of patients in the superhydration group and 27 patients (54%) of the control group (P= 0.001). A similar study randomised 100 children undergoing elective tonsillectomy to either 10 ml· kg^{-1} or 30 ml·kg^{-1} of intraoperative Ringer's solution. [41] The incidence of post- 1+,

operative vomiting at 24 hours was 82% in the 10ml· kg^{-1} and 62% in the 30ml· kg^{-1} group (P=0.026). No intra-operative antiemetic prophylaxis was given to these patients, which accounts for the high incidence of post-operative vomiting and limits this work's external validity. In a study of children admitted for day case surgery, 989 children (aged 1 month- 18years) were randomised to two groups: mandatory drinkers and elective drinkers.[42] The 464 mandatory drinkers had to demonstrate ability to drink clear liquids without vomiting prior to discharge whereas 525 elective drinkers chose whether they wished to drink or not before discharge. All patients received adequate IV fluids to supply a calculated 8-h fluid deficit prior to discharge. The incidence of vomiting did not differ between groups in the operating room, the post-anesthesia care unit or after discharge from hospital. In the day surgery unit, only 14% elective drinkers vomited compared to 23% mandatory drinkers (P < 0.001). The mandatory drinkers stayed longer than elective drinkers in the day care unit (P < 0.001). No children were admitted to hospital with persistent vomiting.

2+

1+

C Intra-operative IV fluids may reduce POV in children after day case surgery.

POV in children may be increased if tolerance of oral fluids is mandatory before discharge from day case surgery.

☑ Intra-operative fluids may reduce POV in children after day case surgery.

Oral fluids should be offered to children wishing to drink before discharge after day case surgery but should not be mandatory.

2. Pharmacological Treatment of Post-operative Vomiting in Children

In this section, the evidence for the efficacy of commonly used anti-emetics in reducing post-operative vomiting in children is reported and recommendation made for preventing POV. In addition, recommendations are made on treating established POV in children.

A. Anti-emetics for Prevention & Reduction of Post-operative Vomiting in Children

$5HT_3$ Antagonists

$5HT_3$ antagonists are effective anti-emetics in children. There are a large number of studies available examining the increasing number of these agents available as well as some of the other issues related to administration of $5HT_3$ antagonists. Ramosetron is a recent addition with new evidence to support its use in children.

Ondansetron

Ondansetron is licensed for use in the UK in children and young people (aged 2-18 years) for reducing post-operative vomiting and is commonly used. The product licence is for ondansetron 0.1mg.kg^{-1} up to a maximum of 4mg.

What is the optimal dose of ondansetron for reducing POV in children?

The efficacy of ondansetron was studied in dose ranges 0.05 to 0.3 mg.kg^{-1} and a dose related response was demonstrated [43-45]. The overall odds ratio for POV was 0.36 [43]. The summary odds ratio per 0.1 mg.kg^{-1} increase in dose was 0.43. 1++

Subgroup analysis of the paediatric data (1688 children) showed that in the prevention of early vomiting, doses of 0.10 and 0.15mg.kg^{-1} were clinically effective with NNT of 4.68 and 2.82 respectively [45]. In the prevention of late vomiting, 0.10 and 0.15 mg.kg^{-1} gave NNT of 5.35 and 3.67 respectively.

A lower dose of 0.05 mg.kg^{-1} had an odds ratio with confidence intervals 0.49 to 11.39 and was considered not effective [46].

In children < 24 months given a dose of 0.1 mg.kg^{-1} the odds ratio for reduction in emetic events was 0.36. [47] If required in patients < 6 months a dose of 0.1 mg.kg^{-1} should be used. This dose produces similar Ondansetron levels to the 0.15 mg.kg^{-1} dose used in older children. [48] The incidence of POV in infants < 6 months is relatively low however.

UC Ondansetron is a clinically effective antiemetic in children undergoing procedures associated with a high risk of POV. There is a dose related response with the optimal dose being 0.15 mg.kg^{-1}.

☑ Children at increased risk of POV should be given ondansetron 0.15 mg.kg^{-1}. Ondansetron can be used as a single agent to prevent early and late POV.

What routes of administration are effective for ondansetron?

In a meta-analysis of children undergoing tonsillectomy, studies using both oral and intravenous ondansetron were included. There was no evidence that IV was more effective than the oral preparation in children undergoing tonsillectomy[42]. 1+

One RCT of 140 children found oral ondansetron 0.15 mg.kg^{-1} reduced POV significantly whereas an oral dose of 0.075 mg.kg^{-1} was no more effective than placebo [49]. An oral dispersible preparation of ondansetron 4mg was well tolerated by children and efficacious [50].

UC The oral route is as effective as the intravenous route for the administration of ondansetron in preventing POV in children.

☑ The oral route may be considered an alternative route for ondansetron administration in situations where intravenous access is not available.

When is the best time to administer ondansetron to reduce POV?

In a RCT of 120 children, administering ondansetron 0.10 mg.kg^{-1} at the beginning or end of surgery made no difference to rates of early, late or total POV [49]. 1+, 1++

A recent Cochrane review of all adult and paediatric POV studies also found no evidence that the risk of POV differed in groups given ondansetron before induction, at induction, intra-operatively or post-operatively [51].

UC There is no evidence demonstrating a benefit of timing ondansetron administration in children with respect to the time of surgery.

☑ Ondansetron may be given before induction, at induction, intra-operatively or post-operatively.

How does the efficacy of ondansetron compare to other anti-emetics for reducing POV in children?

Ondansetron has high efficacy when compared with other anti-emetics.

In a meta-analysis examining studies comparing ondansetron with metoclopramide (6 studies) or droperidol (9 studies) in children undergoing different types of surgery, the pooled odds ratio showed ondansetron to be more effective than droperidol, OR 0.49, and metoclopramide, OR 0.33 [45]. 1+

In a single RCT of 130 children (45 per group) ondansetron and dexamethasone (1mg.kg $^{-1}$) were compared to placebo. Both ondansetron and dexamethasone significantly reduced total POV and early POV effectively. However, in late vomiting, ondansetron did not reduce POV compared to placebo whereas dexamethasone was clinically effective compared to both placebo and to ondansetron [51].

In a Bayesian analysis of different antiemetic regimens, a sensitivity analysis to correct for possible publication bias was conducted[53]. Ondansetron had a greater relative risk reduction (0.55) than the other antagonists, Dolasetron (0.84), Granisetron (0.78) and Tropisetron (0.73). This was for single agent compared with placebo. This analysis excluded the redacted publications by Fujii et al. Ondansetron was the only $5HT_3$ antagonist with a similar relative risk reduction in the initial analysis (0.54 vs 0.55). This gives further confidence in the accuracy of the published data on Ondansetron.

What effect does Ondansetron have on the QT interval?

At a dose of 0.15 $mg.kg^{-1}$, Ondansetron produces clinically insignificant QT interval prolongation in healthy children[54]. In children with congenital long QT interval, polymorphic ventricular tachycardia following 0.1 $mg.kg^{-1}$ of Ondansetron has been described[55]. The prevalence of congenital long QT is 1 in 2500[56]. Ondansetron and other 5HT3 antagonists should be avoided in children where prolonged QT interval is known or suspected.

What effect does Ondansetron have on the efficacy of Paracetamol?

Previously it was suggested that there may be a reduction of analgesic effects of paracetamol by $5HT_3$ antagonists. [57] Granisetron and Tropisetron have been shown to block the analgesic effect of Paracetamol in clinical trials of healthy adult volunteers. However, recent evidence has demonstrated a synergistic effect between Ondansetron and Paracetamol. Ondanestron does not appear to reduce the analgesic effects of paracetamol and recent evidence suggests a synergistic effect. [58]

UC	Ondansetron is more clinically effective than droperidol or metoclopramide in preventing POV in children. Ondansetron is equally effective to dexamethasone for early POV although the latter may be more effective in reducing late POV.
☑	Ondansetron should be considered as a first line treatment in children with a high risk of POV. Combination therapy with a second agent may improve its efficacy (as detailed below).

Tropisetron

Tropisetron is an effective anti-emetic for POV in children. It does not yet have a product license for use in children in the UK.

Two studies using tropisetron 0.1-0.2 $mg.kg^{-1}$ in children demonstrate an overall odds ratio of 0.15 for POV with no clear dose related response [43]. One study of 120 children found no difference in outcome with early or late administration of tropisetron[59]. Another study examined the addition of dexamethasone to tropisetron and found that overall vomiting was reduced from 53% (tropisetron 0.1 $mg.kg^{-1}$) to 26% (tropisetron 0.1 $mg.kg^{-1}$ + dexamethasone 0.5$mg.kg^{-1}$) [60]. However, this reduction was not detected until after 4 hours post-operatively.

1+

UC	Tropisetron is an effective anti-emetic in children at high risk of POV and this efficacy is increased by the addition of dexamethasone.
☑	Although tropisteron is effective in reducing POV in children, it is not licensed for use in children. Ondansetron should be used for reducing POV in children.

Granisetron

Three studies of the efficacy of granisetron in children undergoing tonsillectomy demonstrate an odds ratio for POV of 0.11 using a dose range of 10-80 mcg.kg^{-1}. There is no clear dose related response as seen with ondansetron.[43] Furthermore a Cochrane meta-analysis suggests that the effect of granisetron on reducing POV may be overestimated by these papers. [51]

1+

C	Granisetron may be an effective anti-emetic for POV in children.
☑	More evidence is required on the efficacy of granisetron in reducing POV in children.

Dolasetron

In a dose finding study in 204 children undergoing daycase surgery, dolasetron 350 mcg.kg^{-1} was as effective at preventing POV as ondansetron 100 mcg.kg^{-1}. [61] One study on 150 dexamethasone-pretreated children undergoing tonsillectomy showed an odds ratio of 0.25 for POV in children given dolasetron.[62]

Acute electrocardiographic changes in children and adolescents occur very commonly with dolasetron. (http://emc.medicines.org.uk) There is evidence to suggest that acute changes in QTc interval are greater in children than in adults. Individual cases of sustained supraventricular and ventricular arrhythmias, cardiac arrest and myocardial infarction have been reported in children and adolescents. The use of dolasetron in children and adolescents under 18 years old is contraindicated.

1+

UC	Dolasetron is contraindicated for use in children and adolescents under 18 years old.
☑	Dolasetron is contraindicated for prevention of POV in children.

Ramosetron

This recent addition to the 5-HT3 antagonists has a higher affinity and longer duration of action than Ondansetron. A meta-analysis conducted without the fabricated literature of Fujii et al. compared Ramosetron with Ondansetron or Placebo in adults.[63] The relative risk reduction in POV of 0.3mg of Ramosetron compared with Placebo was 0.48 (<6hr) and 0.5

(6-12 hr). Prophylactic Ramosetron (0.3mg) was superior to Ondansetron (4mg) in reducing the relative risk of both early, (RR 0.5)and late POV, (RR 0.53) in adults. There was no difference in the relative risk reduction of Post-operative nausea. A prospective RCT investigating the incidence of POV over children receiving a Fentanyl PCA following orthopaedic surgery compared a single post-op dose of Ondansetron (0.1mg/kg) with Ramosetron (6mcg/kg).[64] Vomiting was the primary outcome measure at 0-6hrs, 6-24hrs and 24-48hr post-operatively. Ramosetron appears to be more effective than ondansetron in the 6-24hr time period at reducing vomiting. However the number of PCAs stopped due to vomiting was higher in the Ramosetron group.

Ramosetron is not currently licensed for use in children. The pharmacokinetics need to be in evaluated in children and dose ranging studies carried out. Further evidence of Ramosetron's use in paediatric POV is required before it can be recommended in preference to Ondansetron.

Dexamethasone

Dexamethasone has increasingly become recognised as an effective anti-emetic in children on its own and in combination with $5HT_3$ antagonists.

What is the optimal dose of dexamethasone for reducing POV in children?

1+, 1++

A Cochrane database review in 2011 examining children undergoing tonsillectomy concluded that children given a single dose of IV dexamethasone 0.15 to 1.0 $mg.kg^{-1}$ (max 8-25mg) were half as likely to vomit in the first 24 hours after tonsillectomy (Relative Risk = 0.49, 95% CI 0.41-0.58) [65]. Routine use of dexamethasone in children was associated with a NNT of 5. The authors do not provide a dose recommendation due to the pitfalls of subgroups analysis within a meta-analysis.

A dose finding study of dexamethasone (0.25 to 1.0 $mg.kg^{-1}$) in 168 children undergoing strabismus surgery compared to placebo identified no additional benefit of using doses greater than 0.25 $mg.kg^{-1}$. For all groups studied, there was an NNT of 2.2- 2.7. In all groups receiving dexamethasone there was no evidence of side effects relating to increased blood sugars or increased wound infection rates.[66]

In another dose finding study 215 children undergoing tonsillectomy were given dexamethasone (0.05 to 0.5 $mg.kg^{-1}$) or placebo. The relative risk of POV (first 24hr) was reduced from 0.54 for 0.15 $mg.kg^{-1}$to 0.23 with 0.5 $mg.kg^{-1}$dexamethasone.[67]

Three studies have shown lower doses of dexamethasone provide similar clinically significant prevention of POV.[68-70]

One study in 140 children used dexamethasone 150 $mcg.kg^{-1}$ (max 8mg) and found an overall reduction in POV from 71% to 40%. [68]

Another study compared low dose dexamethasone (50 $mcg.kg^{-1}$ to 250 $mcg.kg^{-1}$) finding a significant reduction in POV even with doses as small as 50 $mcg.kg^{-1}$. [69] The NNT range for all groups was 2-2.9.

In another study. 125 children undergoing adenotonsillectomy or tonsillectomy

were enrolled in a dose-escalating study of dexamethasone: 0.0625, 0.125, 0.25, 0.5, or 1 mg.kg^{-1}, maximum dose 24 mg.[70] There was no dose-escalation response to dexamethasone for preventing vomiting, reducing pain, shortening time to first liquid intake, or the incidence of voice change. The lowest dose of dexamethasone (0.0625 mg.kg^{-1}) was as effective as the highest dose (1.0 mg.kg^{-1}) for preventing POV or reducing the incidence of other secondary outcomes. The authors conclude there is no justification for the use of high-dose dexamethasone for the prevention of PONV in this cohort of children.

A dose of 0.5 mg.kg^{-1} was associated with a significantly higher relative risk of postoperative bleeding, 7.42 vs. 1.04 for 0.15 mg.kg^{-1}.[67] This is likely a type 1 error due to flaws in this trial's methodology. A retrospective cohort study to determine the associated risk of postoperative bleeding in 97000 paediatric tonsillectomy patients found a small increase in bleeding rates with dexamethasone of 3.1% vs 2.7%.[71] The authors conclude that the benefits of dexamethasone outweigh this small increase in absolute risk.

IV dexamethasone may cause perineal warmth and should be injected slowly in the conscious child. Dexamethasone may also cause insomnolence if given late in the evening. There is one case control study in adults evaluating the association between postoperative infection and single dose Dexamethasone (4-8mg).[72] The odds ratio for postoperative infection was 3. However, the editorial concludes the benefit of dexamethasone outweighs this. There is no long-term follow-up study evaluating effects of dexamethasone on the immune system in children.

Several reports of acute tumour lysis syndrome have been described after dexamethasone has been given to a susceptible patient in doses used in preventing POV[73-75]. Tumour Lysis Syndrome is a potentially lethal condition that occurs particularly in haematological malignancies after treatment with cytotoxic therapies. Dexamethasone has induced acute tumour lysis in patients with non-Hodgkin's lymphoma [73] and acute leukaemia [74-75]. Dexamethasone should not be used in patients at risk of tumour lysis syndrome.

UC Dexamethasone given alone reduces the risk of POV in children. It appears to be particularly effective in preventing late POV (>6 hr).

Metoclopramide

Metoclopramide in doses ranging from 0.15 mcg.kg^{-1} to 0.25 mcg.kg^{-1} has been shown to reduce POV in children in some studies only [76-78]. Overall, there is little support in the literature for the use of metoclopramide as an anti-emetic in children for the prophylaxis of post-operative vomiting in the doses tested (usually 0.25 mcg.kg^{-1}) [15, 44, 79-83].

1+, 1++

The extrapyramidal effects associated with metoclopramide are more common in

children and have occurred in doses used to treat post-operative vomiting[84]. The European Medicines Agency, in response to reports of neurological side effects has issued recommendations that metoclopramide[85]:

- Is contraindicated in children under one year of age
- Is only indicated as second-line therapy in patients aged between 1 year and 20 years
- Total daily dosage, especially for children and young adults should not normally exceed 0.5 mg/kg, with a maximum of 30 mg daily

UC Metoclopramide in doses of 0.25 mcg.kg^{-1} or less does not reliably reduce POV in children. Further dose-response studies of metoclopramide are required to see if improved efficacy for preventing POV in children can be achieved at higher doses.

☑ Metoclopramide is not a reliable anti-emetic in children and is not recommended for reducing POV in children. The role of metoclopramide in the treatment of established post-operative vomiting requires further investigation.

Prochlorperazine

The anti-emetic effect of prochlorperazine in children has not been determined. Side-effects have been reported when children have been given prochlorperazine [86]. These are predominantly neurological, independent of dose and disappeared spontaneously after discontinuation of the drug. Impaired consciousness, dyskinesia, pyramidal signs and hypertonus were the main neurological manifestations.

4

UC There is no evidence in the literature for the efficacy of prochlorperazine for reducing POV in children.

☑ Prochlorperazine is not recommended for prevention of POV in children.

Cyclizine

Cyclizine is a piperazine antihistamine available over-the-counter and by prescription in the UK, Canada, US and Australia. In Canada the use of cyclizine for patients under 6 years old is off-label. It has been reported as a drug with potential for abuse [87].

There are only 2 studies on the use of cyclizine for treating POV in children and neither had positive findings [88-89]. It has been concluded that there is no detectable anti-emetic effect with cyclizine and furthermore there was significant pain on injection [85]. 1+

UC There is currently no evidence to support the use of cyclizine for POV in children either for prophylaxis or for treatment.

☑ Cyclizine is not recommended for reducing POV in children.

Dimenhydrinate

Dimenhydrinate is the theoclate salt of diphenhydramine. Dimenhydrinate is available in Canada, the US and Australia both over-the counter and by prescription. It is not available in the UK. It can be given orally, intravenously and as a suppository. It was synthesized with the intention of antagonizing the moderately sedative effects of diphenhydramine with the mildly stimulant effects of theophylline. However sedation and dry mouth and other anti-muscarinic side effects do occur. Serious adverse reactions appear to be rare although it is a weakness of both published RCTs and meta-analyses that there is little documentation of side effects.

Two systematic reviews report on dimenhydrinate [43, 90]. In a systematic review and meta-analysis of anti-emetic prophylaxis for children undergoing tonsillectomy, dimenhydrinate was not effective in the doses studied [43]. In another systematic review, the effectiveness of dimenhydrinate for prophylaxis of postoperative nausea and vomiting was reported in both adults and children [90]. The paediatric studies were analysed as a subgroup and the NNT for children was reported as 4.76 for IV/ IM administration and 3.57 for rectal administration of a single equivalent dose of dimenhydrinate however the confidence intervals are wide (2.56-33.3 and 1.92-20). 1+, 1++

In a small RCT of 100 children undergoing reconstructive surgery for burns, dimenhydrinate 0.5 mg.kg^{-1} was found to be as clinically effective as ondansetron but much more cost effective [91]. Dimenhydrinate 0.5 mg.kg^{-1} has also been shown to be effective in strabismus surgery [92].

C In summary, there is evidence to support the use of dimenhydrinate as prophylaxis in children at moderate or high risk of postoperative nausea and vomiting except for tonsillectomy

☑ Dimenhydrinate 0.5 mg.kg^{-1} may be used to reduce POV in children except for children undergoing tonsillectomy.

There are no studies examining the use of dimenhydrinate to treat postoperative vomiting but nonetheless it is cited as rescue therapy in one review article on peri-operative nausea and vomiting in children [93]. | 4

C Dimenhydrinate has been used for rescue therapy in established POV in children.

☑ Dimenhydrinate may be useful for rescue therapy in established POV in children.

Droperidol

This drug has been used as an antipsychotic and anti-emetic drug for several decades. It is a dopaminergic and GABA receptor antagonist. It has sedative effects, prolongs the Qt interval and is known to cause extra-pyramidal symptoms on occasion. These latter issues have meant that the drug has not been widely used, especially in the US, where the FDA issued a "black box warning" about arrhythmias in 2001. This was controversial, and is generally felt to be unfounded. A study in children showed that both droperidol and ondansetron, in clinically relevant doses (and in combination) showed transient increases in Qtc interval, but not statistically different from placebo.[54] It is also clear that Qtc is a poor predictor of the likelihood of toursades de pointes, even in some symptomatic patients. However arrhythmias have been reported in patients with long QT syndrome who have received ondansetron or droperidol. | 1+

Droperidol is an effective anti-emetic and relieves nausea singly and in combination. It can be used both as prophylaxis and as rescue therapy. A systematic review specifically including paediatric trials concluded that the NNT was 4.2 at a dose of 75 $mcg.kg^{-1}$, and that the NNH for extrapyramidal symptoms was 91 for children[94]. Droperidol was consistently more effective in controlling nausea than vomiting. The dosing recommendations generally favour lower doses than 75 $mcg.kg^{-1}$.

The use of droperidol is generally confined to rescue therapy, rather than prophylaxis because of the concerns around sedation, extrapyramidal side effects (although they are infrequent and dose related), and the FDA warnings. However it is an inexpensive, effective medication for both prophylaxis and treatment of both nausea and vomiting, and should certainly be considered in patients in whom dexamethasone is contra-indicated.

C Droperidol 25$mcg.kg^{-1}$ can be effective for both prophylaxis and treatment of POV.

☑ There is conditional evidence to support the use of droperidol for both prophylaxis and treatment of POV, as a second drug, particularly in situations where dexamethasone is contra-indicated. The use of droperidol is contra-indicated in patients with known Long QT syndrome

Combination Therapy:

Ondansetron and Dexamethasone

Three randomized control studies have examined the efficacy of ondansetron combined with dexamethasone for prevention of POV [95-97]. 1+

Two large studies demonstrated that ondansetron 50 mcg.kg^{-1} combined with dexamethasone 150 mcg.kg^{-1} was more effective at preventing POV in children undergoing strabismus surgery than ondansetron 150 mcg.kg^{-1} alone or dexamethasone 150 mcg.kg^{-1} alone [95, 96]. A study of 193 children undergoing strabismus surgery compared dexamethasone (150 mcg.kg^{-1}) alone to dexamethasone (150 mcg.kg^{-1}) plus ondansetron (50 mcg.kg^{-1}**)** [95]. The addition of ondansetron reduced overall vomiting from 23% to 5%. A study of 200 children undergoing strabismus surgery compared ondansetron (150 mcg.kg^{-1}, maximum dose 8mg) alone to dexamethasone (150 mcg.kg^{-1}) plus ondansetron (50 mcg.kg^{-1}**)** [96]. The incidence of POV was significantly less in the combination group (9%) than in the ondansetron only group (28%).

In another study no difference between treatments was detected between several combination treatment groups containing ondansetron and a range of dexamethasone doses and placebo [84]. This was attributed to the particularly low baseline incidence of vomiting in the placebo group.

UC Ondansetron combined with dexamethasone increases the effectiveness in preventing POV in children.

In children at high risk of POV, combination therapy of ondansetron and dexamethasone should be given. IV Ondansetron 150 mcg.kg^{-1} and IV dexamethasone 150 mcg.kg^{-1} should be given to children scheduled for adenotonsillectomy or strabismus surgery.

Ondansetron and Droperidol

The combination of droperidol plus ondansetron may be synergistic, as has been shown in adults, and in a study of children undergoing strabismus repair[98]. 1+

A meta-analysis examining anti-emetic combination therapy included 8 paediatric studies [99]. Although no separate data or analysis was presented, ondansetron combined with droperidol or dexamethasone was more effective in preventing POV than ondansetron alone. A Bayesian meta-analysis of risk reduction in the prophylaxis of paediatric PONV derived an 80% risk reduction in children at high risk when given ondansetron plus droperidol[53]. The findings were similar using a combination of ondansetron plus dexamethasone.

C In children at high risk of POV unable to receive dexamethasone consider prophylactically IV ondansetron 150 mcg.kg^{-1} and IV droperidol 25 mcg.kg^{-1}

☑ Combination anti-emetic therapy should be used for children at high risk of POV or where single agent therapy has failed previously. Ondansetron and dexamethasone is the most effective combination of anti-emetics for reducing POV in children and is recommended for situations at high risk of POV.

Tropisetron and Dexamethasone

In a study of 132 children, tropisetron 0.1 mg.kg^{-1} alone was compared to tropisetron 0.1 mg.kg^{-1} with dexamethasone 0.5 mg.kg^{-1} for prevention of POV after tonsillectomy [86]. Addition of dexamethasone reduced the overall incidence of POV from 53% to 26%. This reduction was not evident at less than 4 hours.

1+, 1++

UC Tropisetron plus dexamethasone is more effective than tropisetron alone for the prevention of postoperative nausea and vomiting in children undergoing tonsillectomy.

☑ Although IV tropisetron and IV dexamethasone is effective in reducing POV in children, tropisetron is not licensed for use in children. Ondansetron and dexamethasone should be used for reducing POV in children at high risk of POV.

B. Anti-emetics for Treating Established Post-operative Vomiting in Children

There are few trials of efficacy of anti-emetics in controlling established POV in the recovery room in adults and even fewer in children[101], compared to the multitude of trials on prophylaxis of POV.

There is only one trial of a single dose of ondansetron (0.1 $mg.kg^{-1}$) versus placebo for managing established POV in children who have not received prophylactic therapy [102]: children experiencing two emetic episodes within 2 h of discontinuing anaesthesia were given IV ondansetron 0.1 $mg.kg^{-1}$ up to 4mg (n = 192) or placebo (n = 183). The proportion of children with no emetic episodes and no use of rescue medication was significantly greater (P < 0.001) in the ondansetron group compared with placebo for both 2- and 24-h periods after study drug administration (78% of the ondansetron group and 34% of the placebo group for 2 h; 53% of the ondansetron group and 17% of the placebo group for 24 h). Conclusions were a single dose of ondansetron (0.1 $mg.kg^{-1}$ up to 4 mg) is effective and well tolerated in the prevention of further episodes of postoperative emesis in children after outpatient surgery. 1+

Dose ranging studies of a single drug and comparative studies of different drugs are absent in this patient population in these circumstances.

An important study of 428 patients who developed POV despite prophylaxis with ondansetron 4mg IV demonstrated that giving a second dose of ondansetron was as effective as giving placebo [103]. If prophylaxis with one drug fails, a second drug from another class should be used for rescue. 1+

C IV Ondansetron may be effective for treating established POV in children who have not already received ondansetron.

Ondansetron is unlikely to be effective for established POV occurring after ondansetron has been administered.

☑ IV Ondansetron 0.15 $mg.kg^{-1}$ should be used to treat established POV in children who have not already received ondansetron.

For children who have already been given ondansetron prophylactically, it is recommended that a second antiemetic from another class should be given, such as IV dexamethasone 0.15 $mg.kg^{-1}$ or IV droperidol 25 $mcg.kg^{-1}$ injected slowly.

3. Non-Pharmacological Treatment of Post-operative Vomiting in Children

A variety of different non-pharmacological options have been described in order to prevent or treat PONV in children but the number of publications as well as patient numbers and study design are often insufficient to allow for a meta-analysis or structured review (i.e. type of bandaging following bat-ear surgery [104]). Thus, this section will only focus on the different types of stimulation of the P6 acupuncture point (acupuncture, acupressure, or electrical/laser stimulation) that has been reported in children.

Stimulation of the P6 Acupuncture Point

A meta-analysis in 1999 concluded various types of acustimulation in adults were equally effective compared to anti-emetic drugs in preventing vomiting after surgery and that such non-pharmacologic alternatives were more effective than placebo in preventing PONV in the early postoperative period [105]. No benefit was found within the paediatric population in this review.

1+, 1++

Since then two further reviews have been published that incorporate more recent publications within this field. In a large Cochrane report from 2004 (up-date of the 1999 meta-analysis above, 26 trials, n = 3,347) [106] acustimulation was again found to be of benefit in adults compared to control. In this Cochrane report, acustimulation was also found to be of benefit in children in reducing the incidence of nausea and also pointing to a borderline significant reduction in vomiting compared to sham treatment. When compared to anti-emetic drugs used for prevention of POV, acustimulation appeared to be equally effective.

A meta-analysis focusing on children included twelve RCTs, mainly performed in the context of high-risk surgery (e.g. adenotonsillectomy or strabismus surgery) [107]. The meta-analysis showed that all acustimulation modalities reduced vomiting (RR= 0.69, 95% CI: 0.59-0.80, $p < 0.0001$) and nausea (RR= 0.59, 95% CI: 0.46-0.76, $p < 0.0001$) compared to non-active control. In three trials where acustimulation had been compared to anti-emetic drugs there was no difference in reducing vomiting between groups (RR= 1.25, 95% CI: 0.54-2.3, $p = 0.60$). Comparing the different modalities, acupuncture was found more effective compared to acupressure and electrical stimulation.

UC Current evidence base supports acustimulation reducing POV compared to the non-active control situation. Acustimulation appears to be equally effective in preventing POV as anti-emetic drugs in children.

☑ The use of acustimulation can be considered as an alternative treatment to anti-emetic medications for surgery where there is a high-risk POV in children.

4. Summary of Findings & Recommendations

Strength of Recommendation	
Unconditional (UC)	Strong evidence, no important drawbacks
Conditional (C)	Weaker evidence, serious potential drawbacks

Patient Factors associated with a high risk of POV:

Children at High Risk of POV	
UC	Risk of POV increases > 3 years old and continues to rise throughout early childhood into adolescence.
UC	A previous history of POV is an independent risk factor of subsequent POV in children.
C	A previous history of motion sickness is likely to be an independent risk factor of subsequent POV in children.
C	Post-pubertal girls have an increased incidence of POV

Surgical procedures associated with a high risk of POV:

Surgical procedures associated with high risk of POV	
UC	Children undergoing strabismus surgery are at high risk of POV.
UC	Tonsillectomy +/- Adenoidectomy
C	Surgical procedures > 30 minutes duration

Anaesthetic factors affecting POV in children

UC	Use of volatile anaesthetic agents is associated with increased risk of emesis particularly in children who have other risk factors for POV.
C	The use of nitrous oxide does not appear to be associated with a high risk of POV in children
C	Use of opioids may be associated with increased risk of POV particularly if longer-acting agents are used in the postoperative period.
C	Use of anticholinesterase drugs may increase POV in children.
C	Intra-operative IV fluids may reduce POV in children after day case surgery.
	POV in children may be increased if tolerance of oral fluids is mandatory before discharge from day case surgery.

Summary of recommendations for prevention of POV in children:

Recommendations for Prevention of POV in children

UC	Children at **increased** risk of POV should be given IV ondansetron 0.15 mg.kg $^{-1}$ prophylactically
UC	Children at **high** risk of POV should be given prophylactically IV ondansetron 0.15 0.15 mg.kg $^{-1}$ and IV dexamethasone 0.15 mg.kg $^{-1}$
C	In children at high risk of POV unable to receive dexamethasone consider prophylactically IV ondansetron 0.15 mg.kg $^{-1}$ and IV droperidol 0.025 mg.kg^{-1}
C	Consider intravenous anaesthesia and alternatives to opioid analgesia in children at high risk of POV

Summary of recommendations for treatment of established POV in children:

Treatment of Established POV in children

UC	IV ondansetron 0.15 mg.kg $^{-1}$ should be given to children who have not already been given ondansetron for prophylaxis of POV
C	For children who have already been given ondansetron a second antiemetic from another class should be given, such as:
	IV dexamethasone 0.15 mg.kg^{-1} injected slowly or IV droperidol 0.025 mg.kg^{-1}

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