Study protocol

Pediatric Intensive Care Ulcer Prevention (PIC-UP):
A multicentre pilot trial
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2. Trial Synopsis

Background: This pilot trial is part of a program of research leading to a large trial to determine if a strategy of withholding stress ulcer prophylaxis in critically ill children is not inferior to a strategy of routine stress ulcer prophylaxis with pantoprazole. We hypothesize that withholding stress ulcer prophylaxis will not result in an unacceptable increase in upper GI bleeding. An important secondary hypothesis is that there will be fewer nosocomial infections (ventilator-associated pneumonia [VAP] and C. difficile-associated diarrhea [CDAD]) in the group who do not receive prophylaxis.

Research question for this pilot trial: In critically ill children, is it feasible to conduct a large multicentre RCT of stress ulcer prophylaxis with pantoprazole to prevent upper GI bleeding vs. placebo?
Design: A multi-centre blinded pilot RCT of 120 children in 6 Canadian PICUs.

Methods: Children expected to require mechanical ventilation for more than 48 hours will be randomized to intravenous pantoprazole 1 mg/kg or matching placebo once daily until they no longer need mechanical ventilation.

Pilot Trial Outcomes: We have 4 feasibility outcomes and will consider the trial successful if we achieve:

1. Effective screening: We approach >80% of eligible patients for consent.
2. Satisfactory enrolment: We enroll an average of >2 patients/centre/month
3. Timely protocol implementation: We administer the first dose of study drug within 1 day of becoming eligible in >80% of participants,
4. Protocol adherence: We administer >90% of doses according to the protocol.

Significance: There are many uncertainties about the risks and benefits of stress ulcer prophylaxis. A carefully designed and implemented pilot trial is essential before embarking on a large, rigorous RCT designed to optimize the care of critically ill children. The results of the large RCT will help clinicians to reduce the burden of morbidity by balancing the risks and benefits of stress ulcer prophylaxis, and will provide the high-quality evidence needed to develop practice guidelines that are relevant for all critically ill children worldwide.

3. Background

No child should receive unnecessary medication. Despite sparse pediatric data on the effectiveness of stress ulcer prophylaxis to prevent gastrointestinal (GI) bleeding, 60% of critically ill children receive these medications. This may have unintended consequences – increasing the risk of nosocomial infections – which may be more serious and common than bleeding these drugs are prescribed to prevent. A large randomized trial (RCT) is needed to assess the balance of these risks and benefits, to determine if a strategy of withholding stress ulcer prophylaxis in critically ill children is not inferior to a strategy of routine stress ulcer prophylaxis. RCTs in pediatric critical care are exceptionally challenging to complete; thus, a rigorous pilot RCT is crucial. There are many uncertainties about the risks and benefits of stress ulcer prophylaxis. In an era of widespread use, where clinicians prescribe prophylaxis to the more severely ill, an observational study will not answer these questions. The best approach is a large RCT.

Such an RCT will be challenging. Only 320 RCTs have been published in pediatric critical care. They are typically small (median 50 children) and 30% were stopped early: 86% for futility or recruitment. Conducting a pilot trial first is thus a scientifically and ethically responsible approach. Within the Canadian Critical Care Trials Group, this approach has led to large, rigorous and practice-changing trials. Simply conducting a pilot will not guarantee the successful completion of a large trial; only 13% of pilot trials in pediatric critical care led to larger trials. This pilot trial is innovative in because:
1. It is part of a new multi-method program of research, building on a systematic review, survey and observational study (Fig 1).
2. It evaluates the important threats to the feasibility of a large RCT: screening, accrual, enrollment, and protocol adherence - with specific criteria for considering if a trial is feasible.
3. We have clear criteria – scientific and practical- about how the results will inform the design of the large trial.
4. It includes enough PICUs (more centres than 93% of published pilot trials) to ensure the results are generalizable beyond a few highly-motivated centres.

The pilot may prevent pursuit of a trial that is ultimately not feasible - which is ethically and financially responsible. It is more likely that this carefully designed pilot trial will ensure that the larger trial we undertake is successful.

4. Rationale

**Critically ill children are at risk of upper GI bleeding.** In observational studies the incidence of important bleeding ranged from 0.4 to 5%. Clinically important upper GI bleeding – but not minor bleeding – is associated with more red blood cell transfusions, increased duration of ventilation, longer PICU stay and costs.

**Prophylaxis is common.** In a US study of 42 hospitals, 60% of children admitted to a PICU received acid suppression. In a prospective observational study of 398 children from 5 PICUs in Brazil, 78% of children received prophylaxis. Proton-Pump Inhibitors (PPIs) and Histamine-2 Receptor antagonists (H2RAs) were most commonly used.

**Previous RCTs are not sufficient to assess the benefits of prophylaxis.** Any estimate of effect is very uncertain. In our systematic review we found 4 trials randomizing 465 children. Using the GRADE approach the quality of the evidence for the outcomes of clinically important bleeding, any overt bleeding, and VAP was all very low. No trial evaluated the risk CDAD. The 3 trials (340 children) that reported macroscopic or important bleeding did not find a difference between prophylaxis and no prophylaxis (RR 0.71; 95% CI 0.42 to 1.19, p=0.19). The confidence interval is wide and the strength of inference is low as there were only 21 bleeding events. Half of the trials are at high risk of bias and half were published over 20 years ago. The incidence of bleeding is likely lower with modern PICU care – increasing the number needed to treat to prevent a bleeding event. As the risk of adverse effects remains constant, the risk/benefit ratio changes.

**Accumulating data in other populations confirms the increased risks of infection.** Suppressing gastric acid secretion reduces a key host defense against pathogenic bacteria. Of particular concern in critically ill children are ventilator-associated pneumonia (VAP) and *C. difficile* associated disease (CDAD). These may also be linked, as increased exposure to antibiotics is associated with an increased risk of CDAD. These serious side effects have not been assessed
in critically ill children. The trial reporting VAP was very small and could not exclude an important effect (RR =1.14 ; 95% CI 0.74 to 1.77, p=0.54).\textsuperscript{18} No trial of stress ulcer prophylaxis has measured CDAD.

**There is important uncertainty: a large RCT is the best way to resolve this.** We do not know precisely the incidence of, and the risk factors for, GI bleeding in children. We do not know the magnitude of beneficial effects and the risk of adverse effects in the context of modern pediatric critical care. In an era when stress ulcer prophylaxis is administered to the majority of patients,\textsuperscript{13,21} and clinicians prescribe prophylaxis to more severely ill children,\textsuperscript{13,22} an observational study will not answer these questions. The best approach is a large RCT. The results of the large trial will be relevant for all critically ill children worldwide because of the prophylactic nature of the intervention and its widespread use. This pilot trial is a critical step towards the large trial needed to provide the high-quality evidence required to develop guidelines for stress ulcer prophylaxis. If withholding this conventional treatment does not result in an unacceptable increase in bleeding, clinical practice is likely to change. If the increase is small, it may be balanced by avoiding the adverse events and costs associated with universal prophylaxis. If withholding stress ulcer prophylaxis is inferior, then this good rationale to continue current practice. Finally, both the pilot trial and the large trial will serve as exemplars of the rigorous trials that are urgently needed in pediatric critical care.\textsuperscript{1,23}

5. **Study Objectives**

The objectives of this pilot trial are to assess the feasibility of a large trial and to evaluate and refine inclusion and exclusion criteria, test study procedures, streamline data collection, and to assess parental and physician acceptability.

6. **Design**

A multi-centre double-blinded pilot RCT.

7. **Setting**

We will conduct the pilot trial at 6 Canadian tertiary centres – enough so we can assess feasibility in many of the centres that will participate in the large trial, making the results more generalizable beyond a few highly-motivated centres. We will recruit centres from the Canadian Critical Care Trials Group (CCCTG) using the results of the national survey to target centres with high numbers of eligible patients and clinician interest. Appendix A shows the participating centres to date.
8. Study population

We aim to enroll children who will be in the PICU long enough to be at substantial risk of bleeding and who will be exposed to the intervention for long enough accrue any potential benefit or experience any potential harms.

Inclusion criteria

a. less than 18 years of age
b. >12 months of age
c. requires respiratory support in the form of invasive mechanical ventilation, non-invasive mechanical ventilation, or high-flow oxygen
d. the attending physician expects the child to require respiratory support for at least 2 more days

Exclusion criteria

a. H2RA or PPI use for >1 week in the past month
b. active GI bleeding
   Blood in the NG tube or coffee-ground emesis suspected by the attending physician to be from the oropharynx is not an exclusion criterion.
c. documented severe reflux, active H. pylori infection, severe esophagitis, Zollinger Ellison syndrome, Barrett’s esophagus, peptic ulcer bleeding within 8 weeks
d. are receiving methylprednisolone 15 mg/kg/day or more (or equivalent)
   Equivalent doses: methylprednisolone, prednisone or prednisolone 15 mg/kg/day; dexamethasone 3 mg/kg/day; hydrocortisone 60 mg/kg/day
e. are receiving mycophenolate (enteral), methotrexate, nelfinavir, atazanavir, saquinavir, posiconazole
f. chronic ventilation on usual pressure settings and rate
g. nocturnal or intermittent non-invasive ventilation only
h. are eating, nursing, or if chronically fed via feeding tube, receiving usual feeds
i. received more than 1 daily-dose equivalent of acid suppressive medication in the PICU
j. were previously enrolled in this trial
k. are currently enrolled in a potentially confounding trial
l. are known to be pregnant or breastfeeding
m. are known to be allergic to pantoprazole or any other ingredient in the product
n. are not expected to survive this PICU admission because of palliative care or limited life support

9. Screening and recruitment

Children may be enrolled in this trial at any point in their PICU stay once they fulfill the eligibility criteria and have none of the exclusion criteria for the first time. Research Coordinators will screen all children daily and will maintain screening logs including the reasons for exclusion and
the reasons why those who were eligible were not approached for consent. Parents may not be approached for consent if there is no substitute decision maker available to obtain consent or the attending physician declines enrollment and for administrative reasons such as vacation, illness or conference leave of the research staff.

10. Consent

Research staff will approach the parents or guardians for consent for their child to participate in this trial. As all children will be sedated and critically ill, they will be unable to provide assent. Participants may withdraw from the trial at their request or the request of their parent or guardian. We will include all data collected prior to the withdrawal of consent.

The median consent rate in published pediatric critical care RCTs is 90%. We anticipate that more than 80% of parents will provide consent given the nature of the intervention and the focus on preventing adverse effects from medications.

11. Randomization

Participants will be randomized to pantoprazole or placebo in a 1:1 ratio in randomly varying, undisclosed blocks by the hospital pharmacy research staff using a computer generated, centrally prepared allocation schedule.

12. Trial Interventions

**Study drug**: Participants will be randomized to intravenous pantoprazole or matching placebo once daily. The intervention will continue until the participants no longer need mechanical ventilation – to a maximum of 30 days or until PICU discharge. The study medication will be stopped if the attending physicians believe it is imperative to start open-label acid suppressive medication for GI bleeding or if IV access is lost. When the study intervention is discontinued (for any reason) the treating team can follow their usual practice with respect to acid suppression.

In the absence of pediatric-specific data, we have chosen a PPI because this class may be more effective in preventing clinically important bleeding in adults than H2RAs (RR 0.36; 95% CI 0.19–0.68; p=0.002).24 Pantoprazole is the only intravenous PPI marketed in Canada. Intravenous administration is necessary because oral or enteral administration will not always be feasible and the extent of absorption is uncertain in many critically ill children. Based on data from McMaster Children’s Hospital we anticipate that participants would receive the study intervention for a median of 5 to 6 days.

Pantoprazole for injection is available in Canada as the brand-name product and 4 generic products (Table 1) Each site may use any of these products.

Table 1. Acceptable brands of pantoprazole
<table>
<thead>
<tr>
<th>Drug Identification Number</th>
<th>Manufacturer</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>02239616</td>
<td>TAKEDA CANADA</td>
<td>PANTO IV</td>
</tr>
<tr>
<td>02336308</td>
<td>TEVA CANADA</td>
<td>PANTOPRAZOLE FOR INJECTION</td>
</tr>
<tr>
<td>02352214</td>
<td>FRESENIUS KABI CANADA</td>
<td>PANTOPRAZOLE FOR INJECTION</td>
</tr>
<tr>
<td>02306727</td>
<td>Sandoz Canada</td>
<td>PANTOPRAZOLE SODIUM FOR INJECTION</td>
</tr>
<tr>
<td>02291665</td>
<td>PHARMASCIENCE</td>
<td>PMS-PANTOPRAZOLE</td>
</tr>
</tbody>
</table>

**Dosing:** Participants will receive 1 mg/kg (maximum 40 mg) of pantoprazole or placebo once daily. Doses will be calculated on the patient’s admission weight and rounded to the nearest mg. Doses will not be adjusted to account for weight changes in the PICU. The placebo will be an equivalent volume of 0.9% saline.

**Study drug preparation:** The research pharmacist at each site will supply individualized unit-dose syringes of pantoprazole 4 mg/mL (in 0.9% saline) or placebo (an equivalent volume 0.9% saline) daily for each participant.

Individual sites may also elect to prepare numbered kits, containing the first dose of the study intervention, which will be stored in the PICU and opened in sequence once each participant is enrolled. This will permit enrollment at any time of day and reduce the time gap between consent and study drug administration. Each syringe will contain pantoprazole 40 mg or placebo. The volume will be adjusted by the PICU nursing staff to give the ordered dose. Subsequent doses will be individualized by the research pharmacist and supplied daily.

**Stability:** Both pantoprazole and placebo syringes will use the same stability. Pantoprazole 4 mg/mL in polypropylene syringes is stable for 28 days when stored at 2-8°C and protected from light.

**Storage:** Prepared syringes should be refrigerated and protected from light.

**Study drug administration:** The PICU nursing staff will administer the pantoprazole or placebo intravenously over 1 hour or less using their hospital’s usual practice. The first dose will be given as soon as possible after randomization. Subsequent doses will be given once daily at a time of day consistent with the hospital’s usual practice.

13. **Blinding**

Pantoprazole solution is clear and colourless. All clinicians, research staff, and parents and guardians will be unaware of the treatment allocation. Only the Research Pharmacist at each site will be aware of the treatment allocation. The group assignment will not be revealed upon request.
of the treating team as the treatment for adverse events and accidental overdoses is symptomatic
and knowledge of the group assignment will not be clinically useful.

### 14. Outcomes

The pilot trial will focus on 4 feasibility outcomes. We will consider it to be successful if we
achieve:

1. **Effective screening**: If >80% of eligible patients are approached for consent. Children
   may be eligible, but not enrolled if the attending physician declines or if research staff
   are unavailable or are unable to coordinate meeting with the parents or guardians
   while the child remains eligible.
2. **Timely enrollment**: if >80% of participants receive their first dose of the assigned
   study drug within 1 day of becoming eligible.
3. **Participant accrual**: If the average monthly enrolment is 2 or more participants per
   centre.
4. **Protocol adherence**: if >90% of doses are administered according to the protocol.
   We expect that protocol adherence to be high as the intervention is a single IV
   infusion once daily of a commonly used and well-tolerated medication.

In each PICU, the Research Coordinator will record the time required for screening, enrollment
and data collection. At the Methods Centre, we will document the time required for data
validation and trial coordination. Although not the focus of the pilot trial, we will collect the
following clinical outcomes to test and refine the data collection process for the main trial:

1. **Clinically important bleeding**: Overt bleeding from the GI tract (can be hematemesis,
   nasogastric blood, melena, hematochezia) associated with one of the following within
   24 hours: a decrease in hemoglobin of >20 g/L, hypotension (a decrease in systolic
   blood pressure of >10 mmHg or the need for new or increased doses of vasoactive
   medications), tachycardia (an increase in heart rate of >20 beats per minute) or a red
   blood cell transfusion. All bleeding events will be assessed by 2 blinded adjudicators to
determine if they meet these criteria. The definition has been validated, shows
excellent inter-rater agreement (kappa=0.76), and has been used in adult RCTs. 26,27
2. **VAP**: As assessed by 2 blinded adjudicators using the Centers for Disease Control
   Criteria
3. **CDAD**: Diarrhea with a positive test (using each hospital’s usual laboratory methods)
   for C. difficile.
4. **Other clinical outcomes**: Death in the PICU, endoscopy or surgery for bleeding,
   transfusions, minor GI bleeding, treatments used for VAP, CDAD and GI bleeding,
   PICU and hospital length of stay, and duration of mechanical ventilation.
15. Duration of follow-up

We will collect daily data for a maximum of 30 days after randomization. After that point, we will only collect the duration of PICU and hospital stay, vital status and incidence of CDAD.

16. Data collection

Appendix B contains the data elements we will collect along with the associated definitions and timing. Research staff will enter the data directly into a secure web application (REDCap) hosted by the Department of Pediatrics at McMaster University. The database will include both range checks and logic checks and will alert users to any missing data. The database is stored on a secure, firewall protected server with regular backup in the Faculty of Health Sciences Computer Services Unit with only the https port available to the internet. Data can be entered by designated users or survey respondents from any computer with an internet connection. User accounts include electronic signatures comprised of a username and password and an audit trail is generated for all activity within each REDCap project.

17. Participant safety and reporting of adverse effects

Adverse effects with pantoprazole are generally mild and transient. In RCTs conducted outside of the ICU, 1-3% of participants reported GI disorders (constipation, diarrhea, nausea, vomiting, bloating and discomfort), headache, skin reactions, and injection site reactions. The most likely adverse effects associated with stress ulcer prophylaxis and withholding stress ulcer prophylaxis are bleeding and nosocomial infection, both of which are captured as outcomes and thus not reported as serious adverse events.

The design of this trial will seek to protect participants from harm by careful participant selection, choice of intervention and appropriate monitoring. Through the exclusion criteria we will seek to exclude those children at highest risk for adverse effects. The extensive routine monitoring in the PICU will allow the detection and treatment of any adverse effects that do occur.

Critically ill patients are at high risk of serious adverse events and the usual approach of reporting all serious adverse events to the REB would result in large numbers of reports of events not related to the trial intervention, but rather reflect the underlying disease process or expected complications of critical illness. The most likely adverse effects associated with stress ulcer prophylaxis and withholding stress ulcer prophylaxis are bleeding and nosocomial infection, both of which are captured as outcomes and thus not reported as serious adverse events. Only serious adverse events that might reasonably be a consequence of participation in the trial and are judged by the investigators not due to the underlying disease or expected complications of critical illness will be reported to the Health Canada, DSMB and REB.
18. Ethical and regulatory approval

This study will be reviewed by the Hamilton Integrated Research Ethics Board and the Research Ethics Board at each participating site. We will file an Clinical Trials Application with Health Canada and obtain a No Objection Letter.

19. Clinical management of participants

Additional investigations or monitoring will not be required as part of this study protocol. The clinical management of the study participants – including the diagnosis and management of bleeding, VAP, and CDAD – will be at the discretion of the PICU clinicians.

20. Sample size justification

We will randomize 120 children. Factors we considered in estimating the sample size were 3-fold:

1. Participants per centre: To ensure we are able to assess the feasibility and test study procedures and infrastructure at each site we will aim to enroll at least 15 participants per centre.
2. Number of centres: To ensure that the results are generalizable beyond a few highly-motivated centres and to reflect the centres that will enroll children in the large trial, 6 PICUs will recruit participants.
3. Precision of feasibility estimates: To ensure that we will estimate our feasibility measures with sufficient precision, we calculated the number of children required so that the lower bound of the 95% confidence interval was above the threshold of 80% (for both effective screening and timely enrolment, the most important feasibility outcomes). If 105 of 120 participants meet one of those criteria, the lower limit of the 95% confidence interval is 80%.

21. Analysis and reporting

All analyses will be performed without knowledge of group assignment and using an intention-to-treat principle. There will be no interim analyses for this pilot trial. For the feasibility outcomes we will report the proportions of children meeting each success criterion and the associated 95% confidence intervals. If, after the completion of the pilot trial, the Steering Committee determines that there are no important changes to the inclusion and exclusion criteria, the results will not be unblinded for the clinical outcomes of the pilot trial. Instead, we will report the feasibility outcomes, present the clinical outcomes a single cohort, and consider the pilot trial to be an internal pilot, meaning that we will include the pilot trial patients in the larger RCT. If the Steering Committee determines a large trial is infeasible or if including the pilot trial patients in the larger RCT is inappropriate, the clinical outcomes will be reported by group so that the trial can be included in future meta-analyses. We will use the CONSORT guidelines for reporting.
22. Trial Management

Steering Committee

Mark Duffett is the Principal Investigator and will chair the Steering Committee for this trial. The Steering Committee will meet monthly and will be responsible for the design, conduct, analysis and reporting of the trial. It is composed of Lehana Thabane (the trial biostatistician), Dr Deborah Cook (adult intensivist), Dr Nikhil Pai (pediatric gastroenterologist), the Methods Centre Research Coordinator (to be recruited), and the Site Investigators – to date Drs Karen Choong (McMaster University), Jacques Lacroix (Université de Montréal), Jennifer Foster (Dalhousie University) and Elaine Gilfoyle (University of Calgary).

Data Safety Monitoring Committee

The Data Safety Monitoring Committee will be composed of three to five members with experience and expertise in methods, statistics and pediatric critical care collectively. None of the members will be on the steering committee or otherwise involved in the trial to maintain their independence. The primary purpose of the DSMC is to ensure the safety of the children enrolled in the trial. The DSMC will also ensure the credibility of the trial and the validity of its results.

The committee will meet and review the available data after 25% and 50% of the patients have been enrolled. Additional meetings may be held at the discretion of the Chair of the DSMC. The committee will receive SAE reports as they occur. All data will be presented to the DSMC tabulated by intervention group but the members will remain blinded to the actual group assignment. The committee will review serious adverse events and centre performance (enrollment, data quality and protocol adherence) and any pertinent external data such as newly published studies or other potentially relevant safety information. The DSMC will keep all trial data, committee deliberations and meeting minutes confidential until the end of the trial.

The committee will make recommendations to the Steering Committee on continuation of the trial and modifications to the trial protocol and procedures. They may recommend early termination of the trial if there are severe adverse events associated with the trial intervention, but no formal stopping rules will be used: this decision will be based on clinical judgment of the DSMC. Terms of reference agreeable to all parties will be drafted and refined when the trial start-up is nearing.

Methods Centre

The Methods Centre at McMaster University will oversee the daily trial operation, responsible for creating and maintaining a central database, data entry, data validation and analysis. The Methods Centre will also monitor the quality, timeliness and completeness of data collection and data entry, performing regular audit and feedback exercises and providing monthly reports to the participating centres on data completeness, any problems that arise, suggested solutions and overall trial progression.
23. The large multicentre trial

If the pilot trial leads to a conclusion that a larger trial is feasible, we will conduct a large multicentre trial focusing on clinical outcomes. We will use the same Methods Centre and Steering Committee. We propose using the same inclusion and exclusion criteria, and intervention, but these may be modified based on the results of the pilot trial. Although we will employ methods similar to the pilot trial, there will be some important differences:

Objectives: The objective of the large trial is to determine if a strategy of withholding stress ulcer prophylaxis in critically ill children is not inferior to a strategy of routine stress ulcer prophylaxis. We hypothesize that withholding stress ulcer prophylaxis will not result in an unacceptable increase in upper GI bleeding. An important secondary hypothesis is that there will be fewer nosocomial infections (VAP and CDAD) in the group who do not receive prophylaxis.

Design: We will use a non-inferiority design because stress ulcer prophylaxis is already commonly used and we wish to test if withholding this conventional treatment results in an important increase in bleeding events. If the increase is small, it may be balanced by avoiding the adverse events and costs associated with universal prophylaxis.

Outcomes: The primary outcome will be clinically important upper GI bleeding. Secondary outcomes include new VAP and CDAD. An economic analysis will be conducted as part of a separate grant application.

24. Budget

See Appendix C
25. References


