Use of selective gut decontamination in critically ill children: PICnIC a pilot RCT and mixed-methods study

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research, or similar, and contains language which may offend some readers.

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Scientific summary

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Scientific summary

Background

In critically ill children, healthcare-associated infections (HCAIs) are a major cause of morbidity and mortality, with a reported incidence of 7–14%. In this vulnerable population, contributing factors include the impact of critical illness on innate and adaptive immune responses, as well as the presence of invasive devices such as endotracheal tubes, urinary catheters and vascular lines.

Evidence from adult intensive care studies suggests that using selective decontamination of the digestive tract (SDD) alongside standard infection control measures reduces mortality and ventilator-associated pneumonia (VAP). A recent meta-analysis of 32 randomised controlled trials (RCTs) including 24,389 participants suggests that use of SDD compared with standard care or placebo was associated with reduced hospital mortality, VAP and intensive care unit (ICU)-acquired bacteraemia.

Selective decontamination of the digestive tract has not been compared directly with modern infection control protocols in the paediatric intensive care unit (PICU) population.

Infection Control in Paediatric Intensive Care (PICnIC) was a feasibility study designed to determine whether it is possible to conduct a cluster RCT (cRCT) of SDD in critically ill children expected to require mechanical ventilation for over 48 hours, and to explore and test the acceptability of key components of the study to healthcare professionals and caregivers. The study involved a pilot cRCT with an integrated mixed-methods study.

Infection Control in Paediatric Intensive Care pilot cluster-randomised controlled trial

Objectives

1. To test the ability to randomise PICUs to either control or intervention.
2. To test the willingness and ability of healthcare professionals to screen and recruit eligible children.
3. To estimate the recruitment rate of eligible children.
4. To test adherence to the SDD protocol.
5. To test the procedures for assessing and collecting selected clinical and ecological outcomes and for adverse event (AE) reporting.
6. To assess the generalisability of the study results to all PICUs using the Paediatric Intensive Care Audit Network (PICANet).
7. To explore parent and healthcare professional views on the acceptability of the proposed trial, including recruitment and consent procedures and patient-centred outcomes.

Methods

Study design
Multicentre pilot cRCT.

Sites
Six PICUs in the UK.

Recruitment
A research without prior consent (RWPC) model was used, and retrospective consent sought for additional samples. There were no inclusion/exclusion criteria during ecology weeks.

During Periods One and Two, the eligibility criteria were the following:

Inclusion criteria

- > 37 weeks corrected gestational age to 16 years.
- Receiving mechanical ventilation.
- Expected to remain on mechanical ventilation for ≥ 48 hours (from time of screening).

Exclusion criteria

- Known allergy, sensitivity or interaction to polymyxin E (colistin), tobramycin or nystatin.
- Known to be pregnant.
- Death perceived as imminent.

Randomisation

Participating PICUs were randomised by the trial statistician using computer-based randomisation to either the control or intervention arm for Period Two of the study.

Data collection

A secure, dedicated electronic case report form (eCRF) was set up and collection was nested within PICANet.

Sample size

A sample size of 324 children in 18 weeks was anticipated. A power calculation was deemed not appropriate given the feasibility nature of the study. The sample size was therefore determined on expected eligible caseload based on available data from PICANet.

Data analysis

The analyses were conducted using Stata/MP™ version 16.1 (StataCorp LP, College Station, TX, USA).

Results

1. As planned, six sites participated in the PICnIC pilot cRCT and were randomised in week 6.
2. We confirmed the willingness and ability of healthcare professionals to screen and recruit eligible children. Sites recruited a total of 368 children (85% of all those who were eligible) across six sites: in Period One, 207 children were recruited (93% of those who were eligible), and in Period Two, 161 children were recruited (76% of those who were eligible). All intervention sites delivered SDD during week 12 onwards.
3. We defined the recruitment rate of eligible children. Overall, 3.6 children/site/week were recruited (the recruitment rate for Period One was 4.3 children/site/week; for Period Two, this was 3.0 children/site/week), similar to the average pre-trial estimate of 3 children/site/week. The potential recruitment rate for a future definitive cRCT trial is 2.98 children/site/week, based on a potentially eligible population of 1730 children (national UK PICU data from PICANet) and the overall proportion of eligible children recruited (85%).
4. We confirmed the ability of healthcare professionals to adhere to the SDD protocol. The majority of children eligible for inclusion were recruited in the intervention sites (55/57, 98%) and most (68%) received at least one dose of SDD treatment within the first 6 hours of enrolment. The median number of SDD doses administered per patient was 14 [interquartile range (IQR) 9–32] for the Oral Paste and 14 (IQR 9–32) for Gastric Suspension. The number of missed doses was low: 9.2% for the oral paste and 9.1% for the gastric suspension. Reasons included children being nil by mouth (29.5% and 31.1% for oral paste and gastric suspensions, respectively) and dose missed by clinicians (26.2% and 24.6%).
5. We confirmed that procedures for assessing and collecting selected clinical and ecological outcomes and for AE reporting were adequate. Completeness of the ecology outcome measures

was excellent in intervention sites (range between 97.6% and 100%) and very good in the usual care sites (range between 93.1% and 100%). Patient-centred potential outcomes measures had an excellent completion rate and were similar between groups with a range between 96.3% and 100%. Ecological outcomes had high completion rates and were similar between groups. Consent for the collection of additional samples for study-specific ecology monitoring were obtained in 162 patients (44% of those recruited). Over 30% of the recruited patients were deemed unable to approach for consent.

6. We confirmed the generalisability of the study results to all PICUs using the PICANet. Children who were recruited to the PICnIC study were representative of similar potentially eligible patients in the study PICUs and all UK PICUs but were more likely to be male (62% vs. 56%) and with a primary diagnosis of infection (12.8% vs. 7%) when compared with all UK PICUs.

Infection Control in Paediatric Intensive Care mixed-methods study

Objectives

To assess with input from PICU healthcare professionals:

1. the acceptability of implementation of the SDD intervention, recruitment and consent procedures
2. the acceptability of collecting data to assess the selected clinical and ecological data
3. the acceptability of the SDD intervention and confirm interest in participation in a definitive trial in the wider PICU community.

To review, explore and test with input from parents/guardians of recruited patients:

1. the acceptability of a definitive trial that includes the SDD intervention
2. the acceptability of the recruitment and consent procedures for the definitive trial, including all proposed information materials
3. the selection of important, relevant, patient-centred primary and secondary outcomes for a definitive trial.

Methods

Study design

This was a mixed-methods study, which employed questionnaires and interviews with parents/legal representatives of children involved in the pilot cRCT and focus groups, as well as an online survey with PICU practitioners (involved in the pilot cRCT and wider UK PICU).

Recruitment

Parent/legal representatives were recruited via the same process and information materials used in the pilot cRCT. During the recruitment discussion, practitioners invited parents to complete the questionnaire and/or provide contact details if they wished to take part in an interview.

Pilot cRCT practitioners were recruited to focus groups via an e-mail invitation, while wider PICU staff were recruited via a Twitter [now X (X Corp., San Francisco, CA, USA); www.twitter.com] advert and presentation (with QR Code link to survey) at the Paediatric Intensive Care Society Study Group biannual meeting.

Data collection

Informed consent was sought before interviews and focus groups. All methods were online [via Zoom (Zoom Video Communications, San Jose, CA, USA)] or telephone due to the COVID-19 pandemic. Screening and interviews stopped when information power was reached. Parent questionnaires were placed in an envelope and posted to the University of Liverpool team.

Sample size

It was anticipated that 15–25 parent/legal representatives would be recruited to an interview, that is, until information power and a balance parents of children in each trial arm were reached. Based on previous studies and the pilot cRCT sample size, we aimed to receive approximately 100 parent questionnaires. For practitioners, we aimed to include approximately 8–10 practitioners in each of the focus groups and up to 10 interviews (for those who could not attend a focus group), as well as an online survey using snowball sampling to involve wider PICU staff not involved in the pilot cRCT.

Data analysis

Qualitative thematic analysis was interpretative and iterative and informed by the constant comparative approach. NVivo 10 software (QSR International, Warrington, UK) was used to assist the coding of data. Survey data were analysed using SPSS version 27 (IBM SPSS Statistics, Armonk, NY, USA) for descriptive statistics. Qualitative and quantitative data were analysed separately and then synthesised through constant comparative analysis.

Results

A total of 65 parents (44 mothers, 21 fathers) completed the survey across five PICU pilot sites. Of these, 15 (23%) were approached when the child was in the intervention group, 24 (36%) in the control group, and 24 (36%) during ecology week (missing $n = 2$).

Telephone interviews were conducted with 23 parents (7 of which also completed the survey), including 15 mothers (2 ecology week, 7 control and 6 intervention) and 8 fathers (1 ecology week, 4 control and 3 intervention) across five out of the six PICU pilot sites in the UK (3 intervention and 2 control sites). Parents were recruited via sites and 123 parents registered interest. Out of these, 39 were contacted to arrange an interview. Three were no longer interested, six said it was not a good time, and seven did not answer the phone or respond to e-mail.

A total of 44 PICU staff completed the survey representing 11 UK PICUs. Of these, 36 (81%) were involved in the PICnIC pilot and were from other PICUs representing six units. Six focus groups with 26 staff were conducted, which was an additional four than originally planned to ensure staff from all PICnIC pilot sites had an opportunity to participate.

Overall, the mixed-methods study showed that parents and practitioners found the proposed trial acceptable, but highlighted a number of areas that should be carefully considered when developing the trial protocol and staff site training.

Issues with eligible children being missed were due to difficulties in staff knowing whether children would be ventilated for 48 hours, as per the inclusion criteria. Some sites screened more than once up until the 48-hour window, which increased the number of eligible patients identified. Staffing issues due to the pandemic and not remembering to rescreen after the point of admission impacted upon recruitment. Multiple studies recruiting at the same time, as well as difficulties processing samples in overstretched labs, appeared to exacerbate the issues. Staff described how missing data for additional samples was due to concerns about child discomfort, not wishing to broach taking swabs with parents when a child was critically ill, or staff capacity issues. Parents were less concerned about the additional samples, but many stated that consent should be sought prospectively for sample collection. Parents who declined consent for additional samples mentioned their child having gone through a lot and they did not want to add further distress. Having the option to decline certain aspects of trial involvement appeared to make the pilot trial more acceptable for parents.

Most parents and staff supported the cRCT design and approach to consent, although any future information materials must make clear that a RWPC approach is being used. Although information leaflets were described as being clear, they were often not read by parents who prioritised discussions with staff. There appeared to be subtle differences in how staff described the nature of the intervention

at sites administering SDD, which may have led to parental misconceptions, such as believing that their child would have received the intervention as standard practice outside of the trial. Many parents did not understand that units rather than children had been randomised, as cluster randomisation had not been explained by practitioners. Our findings highlight the need to develop training for recruiters on how to explain the nature of the proposed trial to assist parental understanding, including how whole PICUs are randomised to control or intervention, and the nature of the intervention including information about gut microbiota to address potential parental concerns and to help ensure informed decision-making.

Parents' top prioritised outcomes for the proposed trial were survival and health complications/AEs.

Findings suggest that staff were in equipoise and the SDD intervention was acceptable to both parents and staff. Insight from site and wider PICU staff highlights challenges to consider in a definitive proposed trial including delivering the SDD due to the thickness of the paste, sufficient support and engagement of nurse research teams, and sufficient time for trial set-up to help improve trial acceptability and ultimately trial success.

Conclusions

Insight from parents and PICU staff suggests the proposed trial, SDD intervention and approach to consent was acceptable. Issues such as staff capacity, missed eligible patients and additional sample collection, and parental misunderstandings about the nature of the study were identified. Staff training on recruitment and consent processes is required in any future trial, as well as adaptations on ecology monitoring and dosing regimen of the paste, which should be incorporated into the study design. Patient outcomes for the proposed trial should include complications such as healthcare-acquired infections and antimicrobial use, as well as standard organ failure outcomes such as the need for mechanical ventilation and duration of PICU stay.

Recommendations for research

- A definitive clinical trial for the use of SDD-enhanced infection control using the current PICnIC protocol should not be conducted.
- A definitive clinical trial for the use of SDD-enhanced infection control using a modified protocol should be conducted.
- Further work is needed to agree the appropriate measures to monitor ecology in a definitive trial.

Trial registration

The PICnIC Pilot RCT is registered as Current Controlled Trials ISRCTN40310490.

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