A pilot cluster randomisation clinical trial of the use of selective gut decontamination in critically ill children (Paediatric Intensive Care and Infection Control)

Chief Investigator: Dr Nazima Pathan

Refresher Session
PICnIC is a feasibility study designed to determine whether it is possible to conduct a cRCT of SDD in critically ill children who are likely to be ventilated for ≥48 hours.

Also, to explore the acceptability of key components of the study to healthcare professional and families of patients.
Objectives

Pilot cRCT

- Ability to randomise PICUs
- Willingness & ability of healthcare professionals to screen and recruit
- Recruitment rate
- Adherence to SDD protocol
- Assess procedures for clinical ecological outcomes
Objectives

Perspectives of PICU practitioner

- SDD intervention, recruitment, consent procedures
- Clinical and ecological data collection
- Interest in definitive trial in the wider PICU community

Perspectives of parents/guardians

- Definitive trial that includes SDD intervention
- Recruitment and consent procedures, including information materials
- Patient-centred primary and secondary outcomes for definitive trial
**Trial Design**

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Weeks</th>
<th>Recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecology Surveillance</td>
<td>1, 10, 20</td>
<td>All patients admitted to PICU during designated weeks</td>
</tr>
<tr>
<td>Period One (Usual Care)</td>
<td>2 - 9</td>
<td>144 patients - Usual Care</td>
</tr>
<tr>
<td>Period Two (Intervention and Usual Care)</td>
<td>11 - 19</td>
<td>90 patients - Intervention 90 patients - Usual Care</td>
</tr>
</tbody>
</table>

*Week 11 shall be treated as a transition period*
Period Two: Intervention

- Six PICU sites

<table>
<thead>
<tr>
<th>Week</th>
<th>Date</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>20 September</td>
<td>Ecology Surveillance</td>
</tr>
<tr>
<td>Week 2</td>
<td>27 September</td>
<td>Start of Period One</td>
</tr>
<tr>
<td>Week 10</td>
<td>22 November</td>
<td>Ecology Surveillance&lt;br&gt;First SDD delivery to randomised sites</td>
</tr>
<tr>
<td>Week 11</td>
<td>29 November</td>
<td>Start of Period Two (transition week)</td>
</tr>
<tr>
<td>Week 20</td>
<td>31 January</td>
<td>Ecology Surveillance</td>
</tr>
</tbody>
</table>

- Embedded questionnaires & interviews with parents / guardians

- Focus groups with PICU practitioners
Ecology Surveillance (weeks 1, 10, 20)

Screening and Enrolment

All patients admitted during the Ecology Surveillance Periods and have samples taken are enrolled and assigned an Ecology Surveillance Number.

Do not assign a number if samples have not been taken.

Please attempt to get consent for additional samples if routine/admission samples are missed.

Patients who have been previously enrolled into PICnIC should not be enrolled again.
Eligibility

Inclusion Criteria: All patients admitted to PICU regardless of ventilation status

Exclusion Criteria: None

Sampling for Ecology weeks

Taken on admission and then following consent, taken once more (e.g. on a Friday, if not taken in the previous 48 hours)

See SOP 012 - PICnIC Samples for further details on Laboratory Analysis
Screening and Enrolment

A patient is screened and deemed eligible based on the inclusion/exclusion criteria.

On the log please include:
- Patients who fulfil all inclusion and no exclusion criteria
- Patients who fulfil all inclusion but meet one or more exclusion criteria
- Patients who fulfill all inclusion criteria and no exclusion criteria but are not enrolled (give reason).

See SOP 003 - Patient Screening and enrolment for further details
Following eligibility confirmation, patients are enrolled into PICnIC and assigned a Study Number.

Please attempt to get consent for additional samples if routine/admission samples are missed.

Patients who have been previously enrolled into PICnIC should not be enrolled again.
Eligibility

Inclusion Criteria
- >37 weeks corrected gestational to ≤16
- Receiving mechanical ventilation, expected to last at least 48 hours
- Expected to remain on mechanical ventilation until the day after tomorrow (from the 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

Sampling
Taken on admission then twice-weekly until discharge. For stays <7 days, should be taken at discharge
Sampling

Samples taken as part of routine care (e.g. admission samples) will be used without consent. These include:

- A nasopharyngeal swab
- A stool/rectal swab

If clinically indicated (processed as per routine local protocol):

- Urine
- Sputum/secretions from the endotracheal tube
- Wound swabs, if present

Any additional samples should be taken following consent

See SOP 012 - PICnIC Samples for further details on Laboratory Analysis
Consent

Consent will be required for:

- additional study-specific samples, before they are taken (expect if using bereaved CF)
- identifiable data being collected and processed for the embedded study (contact details for interviews)
- Monitoring of medical records
Consent

Consent will not be required for:

• samples that are collected as part of routine care (e.g. at admission)

• anonymised data collection and processing from routine sources (to be captured on CRFs)

• administration of the SDD intervention
Consent on MACRO

- Ensure to enter study number
- Record each aspect that was consented ‘yes’ or ‘no’
- Add date of consent/refusal

- Selecting ‘unable to approach for consent’ will blank all consent options out. Please provide reason.
- If parent/guardian was approached but you’re unable to get a completed consent form, choose ‘no’ options, add date and add a comment explaining this.
- If withdrawal occurs following consent, add date & reason.
Mixed methods embedded study

- Questionnaire and interviews with parents following consent
- Two focus groups with site staff - including doctors, nurses, pharmacists and allied health professionals
- Up to 10 telephone/online interviews will be conducted with practitioners who cannot attend the focus groups
- Online survey of staff

The researcher will contact you to arrange focus groups and interviews and online survey of staff.
Questionnaire/interview enrolment

Sites provided with questionnaires and stamped self-addressed envelopes addressed to Kerry Woolfall’s team at the Institute of Population Health at the University of Liverpool.

Please give a copy of the questionnaire to each parent/legal representative to complete (if consented).

If both parents are present, both will be asked to consent and complete a questionnaire. Completed questionnaires will be placed in a stamped self-addressed envelope and returned the PICnIC team member (e.g. within 12 hours) via post to the University of Liverpool team.

UoL researcher will be conducting interviews of the parents/guardians. A research team member at site will be contacted prior to the telephone interview to check the status of the child.
SDD Intervention delivery

• Sites prepare to receive 25 boxes (each box approx size: 215mm x 175mm x 68mm)
  - week 10 (22 Nov)
  - Week 15 (27 Dec)

• Keep refrigerated at 2-8°C before use
• Once reconstituted and in use, keep at room temperature (up to 5 days)

5 day supply of SDD treatment:
- Gastric Suspension powder for reconstitution
- 20 x 1ml Oral Paste syringes

Enrolled patients should be allocated SDD kit & commence treatment within six hours. Do not share kits between patients.
Labels

Period Two - Intervention
Gastric Suspension

- Loosen powder in bottle
- Add 100ml sterile water & shake
- Add further 95ml to bring volume to graduation mark
- Add use by date = 5 days from date of reconstitution
- Keep upright
- Store in locked bedside cabinet

• Do not use two different SDD kits for a single patient at any given time
• SDD paste and gastric suspension must be from the same kit
• Do not share SDD kits between patients
Dose/Frequency SDD Gastric Suspension

- via gastric tube
- x4 daily to coincide with six-hourly care policies
- Stop gastric feed immediately prior to administration
- Flush gastric feeding tube with sterile water before and after administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>0 – 4 years</th>
<th>5 – 12 years</th>
<th>≥13 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymyxin E (Colistin)</td>
<td>25mg</td>
<td>50mg</td>
<td>100mg</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>20mg</td>
<td>40mg</td>
<td>80mg</td>
</tr>
<tr>
<td>Nystatin</td>
<td>0.5 x 10^6 IU</td>
<td>1 x 10^6 IU</td>
<td>2 x 10^6 IU</td>
</tr>
<tr>
<td>Volumes</td>
<td>2.5ml</td>
<td>5ml</td>
<td>10ml</td>
</tr>
</tbody>
</table>
Dose/Frequency SDD Oral Paste

- x4 daily to coincide with six-hourly care policies
- Perform oral hygiene and suction out any excess oral secretions, removing any visible paste from the previous SDD oral paste dose.
- Apply the contents of the syringe onto a mouth swab.
- Apply paste evenly throughout the oral cavity including teeth, gums, tongue and entire oral mucosa.
- If the patient is ventilated by tracheostomy, the paste will also be applied around the tracheostomy site.
- It is recommended not to perform oral hygiene within 2 hours after applying SDD oral paste unless clinically indicated.
Logs

- Kit inventory log
- Temp deviation log
- Patient accountability log
SDD FAQs answers

- If gastric tube is on free drainage and patient is able to receive SDD gastric suspension, administer and spigot gastric tube post administration as per hospital policy.

- Patients with a trans-anastomotic tube should NOT be given SDD suspension.

- Patients subsequently re-intubated (either during this PICU admission or readmission to PICU from another ward) during the treatment period will restart the intervention.

- SDD gastric suspension can be administered before or after other oral medications, however gastric tubing must be flushed between administrations.

- SDD treatment should start within 6 hours of becoming eligible and continue for a maximum of 30 days (treatment period).

  Or until removal of mechanical ventilation.

  Or Safety reason (serious adverse reaction of SDD)

  Or Administration (nasogastric feeding tube removed for clinical reasons
Case Report Forms

- Ecology Surveillance CRFs (for weeks 1, 10, 20)
  - surveillance & microbiology results

- PICnIC Intervention
  - admission
  - weekly surveillance
  - HACI, microbiology results
  - SDD administration & deviation
  - antibiotic use
  - discharge
  - Safety monitoring

- SAE reporting form

See SOP 007 - Guidance for completion of Case Report Forms for further details

Period Two - Intervention
SDD Administration & Deviation

- Details of 4 doses per day of paste & suspension
- Record time for each or if not given

If one or both SDD treatments not given AND mechanically ventilated, complete deviation form

- Ensure study date and time match the deviation
- Specify reason treatment not given or select NA if deviation was not for that route
SDD Administration & Deviation

On the first and last days, if 4 doses were not given please ensure that ‘not given’ is selected for the doses that are not relevant.

- E.g. date/time of confirming eligibility at 15:30 on 01-Nov-2021
SDD Administration & Deviation

- E.g. date/time of confirming eligibility at 23:45 on 01-Nov-2021, but first dose is given on day 2
SDD Administration & Deviation

Inform messages will fire if the patient was mechanically ventilated and one or both SDD treatments were not administered.

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose 1</th>
<th>Time dose given (24 hrs)</th>
<th>Mechanically Ventilated</th>
<th>Oral paste given (1 syringe)</th>
<th>Gastric suspension given (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td>00:30</td>
<td>Yes</td>
<td>Yes</td>
<td>0.0</td>
</tr>
<tr>
<td>02/11/2021</td>
<td>Dose 2</td>
<td>06:45</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SDD Administration & Deviation

Ensure the ‘study date’ and ‘time dose due’ matches the deviation on the SDD Administration part of the eForm

If one treatment was given, select N/A for the treatment that did not deviate.
Safety Monitoring CRF

Should be completed for all patients enrolled during Period Two until discharge

Only AEs deemed possibly, probably or definitely related to trial intervention should be reported

If event did not occur, severity should be ‘0’ = None

Any AE not listed as ‘expected’ and therefore an unexpected reaction to the study medication should be listed on the Safety Monitoring CRF under ‘other’.

If Severity = severe, life-threatening or fatal then SAE Reporting Form needs to be completed

* Severity: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life-threatening, 5 = Fatal.

If the adverse events specified did not occur, then record Severity as 0

# Related (to intervention treatment): 0 = None, 1 = Unlikely, 2 = Possibly, 3 = Probably, 4 = Definitely

See SOP 007 - Guidance for completion of Case Report Forms for further details
Safety Monitoring CRF

If specified adverse events were not reported, answer severity as ‘None’

Events can be reported multiple times. If severity is reported, ensure start date/time and relatedness have been recorded

See SOP 007 - Guidance for completion of Case Report Forms for further details
To be completed on paper CRF and uploaded and reported on MACRO with 24 hours of the event.

Please inform trial team it has been uploaded (do not send copy via email)

Ensure causal relationship to the event (possibly, probably, definitely) and expectedness is completed

Dose of SDD given should correspond to the single dose given before the event occurred.

See SOP 007 - Guidance for completion of Case Report Forms for further details
Q&A