Protocol for technical patient safety solutions for prevention of ventilator-associated pneumonia in adults

Selective Decontamination of the Digestive tract

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Aim
The aim of this systematic review is to consider the clinical and cost effectiveness evidence of Selective Decontamination of the Digestive tract (SDD) for the prevention of ventilator-associated pneumonia (VAP).

Background
Ventilator-associated pneumonia (VAP) is usually defined as a nosocomial pneumonia occurring more than 48 hours after the introduction of mechanical ventilatory support (by endotracheal tube or tracheostomy). It is a condition that results from infection which causes flooding of the small, air-filled sacs (alveoli) in the lung responsible for absorbing oxygen from the atmosphere.

The diagnosis of VAP is difficult and there are no universally accepted criteria upon which diagnosis is made. Most accurate diagnosis appears to comprise of various components that are used to determine the presence of VAP. These include both clinical, radiological and microbiological signs suggestive of the disease.1

Prospective studies found between 17.5-38% of ventilated patients developed VAP.2;3 In patients with VAP there is a 24-50% mortality rate which increases to 76% if infection is caused by multi-drug resistant pathogens.3 There is also an associated increase in length of stay in ITU.4 The high incidence of VAP and its significant impact on mortality and morbidity have made it a focus for prevention strategies. There are also sub-groups of patients who may be at greater risk of developing VAP. Where possible, these sub-groups will be analysed, however due to their susceptibility to VAP, these sub-groups are often excluded from trials examining interventions for the prevention of VAP.

VAP is distinguished from other kinds of infectious pneumonia because of the different types of microorganisms responsible, antibiotics used to treat, methods of diagnosis, ultimate prognosis, and effective preventive measures.

VAP is a primary problem in intensive care units, and causes complications in 8-28% of patients receiving mechanical ventilation.3 For critically ill and postoperative patients receiving mechanical ventilation, VAP is a significant cause of morbidity and mortality.5;6

As VAP is linked with higher morbidity, mortality and costs; preventing ventilated patients from developing VAP is an important patient safety objective. VAP is thought to be a common complication of the acute respiratory distress syndrome, and the significant burden of VAP justifies the implementation of specific preventive strategies.

The prevention of VAP may include a range of different interventions, however, this review is going to focus specifically on SDD as one aspect of VAP prevention. Current practice suggests that there are considerable variations in the use of SDD within the UK and uncertainty over the most effective treatments.7 The uncertainty about effective treatment is also compounded by concerns regarding the promotion of antimicrobial resistance.8
The Intervention
Anecdotal evidence suggests that in the UK there is substantial variation in VAP prevention strategies. The British Society for Antimicrobial Chemotherapy is developing guidelines on the diagnosis, prevention and treatment of hospital acquired pneumonia (including VAP). This includes a guideline on antibiotic treatment and prevention.

One strategy used to prevent VAP is selective decontamination of the digestive tract (SDD). There is no standard definition of SDD but it is centred around the use of antimicrobials to eradicate potentially pathogenic micro-organisms from the digestive tract. SDD is based on the premise that most infections that occur in hospitals are caused by a limited number of pathogens. In the case of VAP these are predominantly gram-negative aerobic bacteria which the patient may already be colonised with prior to admission to the ICU. SDD aims to eradicate these potentially pathogenic micro-organisms from the oropharynx, stomach and gut, without altering the micro-organisms that are usually present and that have a protective effect.

A number of different SDD regimens can be used, all of which are based on non-absorbable antibiotics. A paste (oropaste) containing the antibiotics is applied to the oral cavity (oropharynx). Solutions of the antibiotics are also administered through a naso-gastric tube into the digestive tract. Some SDD regimens also include non-absorbable antifungals. Prophylactic systemic antibiotic(s) may also be given intravenously for a few days. It is also essential that the appropriate measures to prevent cross-contamination (for example, hand hygiene) and surveillance cultures are performed to monitor for colonisation and resistance.

The most common SDD regimen that has been investigated in randomised controlled trials (RCTs) is polymixin, tobramycin and amphotericin (applied to the oral cavity and through a nasogastric tube) and cefotaxime given systemically. It is however unclear which regimens are currently being used within the NHS (if any). Anecdotal evidence suggests there is widespread variation in practice, including which patients receive SDD.

There are concerns about the use of antibiotics for SDD promoting colonisation with resistant organisms, in particular meticillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococcus. Studies have shown both an increase and decrease in antimicrobial resistance. SDD has also been associated with other complications, for example, Enterococcus faecalis pneumonia and endocarditis.

SDD encompasses different types of interventions with the purpose of decontaminating the digestive tract. This review will consider non-absorbable antibiotics given either alone or conjunction with non-absorbable antifungals and/or systemic antibiotics. A list of possible components of SDD is given in appendix I, but this is not a fully comprehensive list.

**Comparator intervention**
SDD will be compared to either no antimicrobial or a systemic antibiotic only. SDD will not be directly compared to other non-antimicrobial strategies for the prevention of VAP.

**Outcomes**
The primary outcome to be considered will be incidence and reduced risk of VAP, secondary outcomes will be mortality, average duration of mechanical ventilation and average length of stay in intensive care. Of interest is the prevalence of antimicrobial/antibiotic resistance and adverse events associated with SDD.
PICO
A PICO table is displayed below as a summary of the proposed review.

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Mixed group of adult (&gt;16 years) ICU patients, at risk of ventilator associated pneumonia (occurring 48 hours after endotracheal intubation and initiation of mechanical ventilation).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Regimens for selective decontamination of the digestive tract comprising: Non-absorbable antibiotics (applied to the oropharynx and through a nasogastric tube) given either alone or conjunction with non-absorbable antifungals and/or systemic antibiotics.</td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td>SDD will be compared to either no antimicrobial or a systemic antibiotic only. SDD will not be directly compared to other non-antimicrobial strategies for the prevention of VAP.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Relevant outcome measures include: incidence and reduced risk of VAP as a primary outcome and mortality; average duration of mechanical ventilation and average length of stay in intensive care as secondary outcomes; emergence of resistant micro-organisms (for example, multiresistant aerobic gram-negative bacilli (AGNB), meticillin-resistant <em>Staphylococcus aureus</em> (MRSA) and vancomycin-resistant enterococci (VRE)); adverse events associated with SDD, including <em>Clostridium difficile</em> associated diarrhoea.</td>
</tr>
<tr>
<td><strong>Economic analysis</strong></td>
<td>Cost effectiveness will be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation will be sufficient to ensure that the outcomes are taken into account. Costs will be considered from a NHS perspective.</td>
</tr>
</tbody>
</table>

**Literature Searching**
Extensive electronic searches will be conducted to identify reports of published, unpublished and ongoing studies. The search strategies will be designed to be sensitive and will include appropriate subject headings and text word terms. The databases searched are presented as an appendix II.

In addition we will hand search reference lists of included studies for additional papers and seek expert opinion.

**Inclusion and exclusion criteria**

**Types of studies**
We will include systematic reviews and Randomised Controlled Trials (RCTs) to assess the effectiveness of different SDD interventions used in the prevention of VAP.

Where the same data are reported in multiple publications, we will include only the most recent unless there are any new or additional data. Case studies and cohort studies will be examined for safety aspects. We will include conference abstracts and other grey literature sources if they are the only source on safety aspects.

We will not reject a study only on the grounds of sample size, but we will restrict the language to English only due to the short time scale of this review. If safety data or adverse
events associated with SDD are reported in the English language abstract, then we may include these.

Animal studies will be excluded from the review.

The population of interest will be adult patients receiving mechanical ventilation for 48 hours or more in an intensive care setting. Accurate data on the epidemiology of VAP are limited by the lack of standardised criteria for its diagnosis, therefore we will adopt the definition reported in the included studies.

**Analysis**
The quality of the studies will be assessed using standard quality assessment checklist. Two assessors will abstract the data using the agreed data abstraction forms and tabulate the data.

Summary tables will be presented for study results. Where sufficient data are available, meta-analysis will be carried out. Where it is not possible to carry out a meta-analysis, other statistical techniques will be applied where possible calculating confidence intervals. Where this is not possible qualitative analysis of the data will be presented.

**Scoping Searches**
The scoping searches have identified the following papers, which may be potentially relevant:

- One meta-analysis of SDD,
- Three reviews (not systematic) of SDD,
- 16 RCTs of SDD,
- Six cohort studies of SDD.

A list of papers identified so far as of possible relevance to the review is presented in appendix III.

**Conclusions**
We consider that due to the short time scale of this review, only systematic reviews and RCTs in the English language will be included in the main review for the effectiveness of SDD. Where appropriate, cohort studies and case studies will be included for the reporting of adverse events or safety issues.
Appendix I Potential SDD components

Antibiotics
Cefotaxime
Ceftazidime
Ceftriaxone
Ciprofloxacin
Clavulanic acid
Colistin,
Gentamicin,
Iseganan
Ofloxacin
Polymyxin E
Polymyxin B
Nalidixic acid
Neomycin
Netilmicin
Norfloxacin
Tobramycin
Trimethoprim
Vancomycin

Antiseptics
Chlorhexidine
Saline solution

Antifungal
Amphotericin
Amphotericin B
Nystatin
### Appendix II Databases searched

<table>
<thead>
<tr>
<th>Database</th>
<th>Host/system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoping search</td>
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<td>CENTRAL</td>
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<tr>
<td>Embase</td>
<td>Ovid</td>
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<td>1980 -</td>
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<tr>
<td>MEDLINE 1950-</td>
<td>Ovid</td>
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<td>Cochrane Library</td>
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<td>NHS HTA</td>
<td>Cochrane Library</td>
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<tr>
<td>Other Reviews</td>
<td>Cochrane Library</td>
</tr>
<tr>
<td>MEDLINE in Process</td>
<td>Ovid</td>
</tr>
</tbody>
</table>
Appendix III Papers of possible interest

Meta Analysis

Reviews


Randomised Controlled Trials


Cohort Studies


Of possible interest


Bonten MJ, Bonten MJM. Selective digestive tract decontamination--will it prevent infection with multidrug-resistant gram-negative pathogens but still be applicable in institutions where methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci are endemic?. [Review] [35 refs]. *Clinical Infectious Diseases* 2006;43 Suppl 2:S70-S74


Kollef MH. Selective digestive decontamination should not be routinely employed. *Chest* 2003;123: 5 Suppl.464S-468S.

Krueger WA, Unertl KE, Krueger WA, Unertl KE. Selective decontamination of the digestive tract. [Review] [70 refs]. *Current Opinion in Critical Care* 2002;8: 2.139-144.

Liberati A, D’Amico R, Pifferi, Torri V, Brazzi L. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. 2004;Issue 1:


study [Abstract]. *American Thoracic Society 2005 International Conference: May 20 25; San Diego, California 2005;C95*


References


