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PRACTICE

UNCERTAINTIES PAGE

Should selective digestive decontamination be used in critically ill patients?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic for this series, please email us at uncertainties@bmj.com.

Healthcare associated infection represents a major burden for critically ill patients; a recent point prevalence survey by the Health Protection Agency observed that 23.4% of patients in intensive care units had evidence of a healthcare associated infection.[1] Ventilator associated pneumonia remains the leading cause of nosocomial infection in this population, and, although recent estimates of attributable mortality (5-10%) are lower than previously thought, length of stay and treatment costs are substantially increased.[2 3] Colonisation of the oropharynx with enteric bacteria is considered a key step in the development of ventilator associated pneumonia and offers a potential site for intervention with oropharyngeal decontamination.

Selective digestive decontamination involves the administration of topical, non-absorbable antibiotics to the oropharynx and stomach via a nasogastric tube in combination with parenteral antimicrobials to reduce the burden of potentially pathogenic bacteria in the aerodigestive tract. Some studies have focused on decontamination strategies limited to the oropharynx alone (selective oral decontamination), avoiding enteral and intravenous antibiotics. Selective digestive decontamination was first used for immunocompromised haematology patients, but this intervention has been extensively studied in intensive care units over the past three decades. However, many clinicians remain sceptical as to whether this evidence is applicable to different healthcare systems, which vary according to environment and antibiotic resistance rates, and their own clinical practice.

What is the evidence of uncertainty?

A search of PubMed, the *Cochrane Library*, and Embase identified nine published meta-analyses on the topic of selective digestive decontamination in intensive care patients. The most recent was an updated Cochrane review in 2009, which identified 36 randomised clinical trials involving 6914 patients.[4] However the largest study of selective digestive decontamination[5] was not included on the basis that the cluster design prevented individual patient randomisation.[4] The odds ratio for death was 0.75 (95% confidence interval 0.65 to 0.87) with a number needed to treat of 18, although none of the individual studies was adequately powered to detect a reduction in mortality. Results for reducing ventilator associated pneumonia were more impressive, with an odds ratio of 0.28 (0.2 to 0.38) and a number needed to treat of only four.[4] With around 140 000 admissions to UK intensive care units each year, this implies there is the potential to save upwards of 7700 lives annually with this intervention, in addition to cost savings as a consequence of reduced length of stay from lower rates of ventilator associated pneumonia.

Despite this evidence, uptake of selective digestive decontamination has been poor in the UK and elsewhere. In a survey of 193 UK intensive care units, only 10 units used any form of selective digestive decontamination and just three used it in all mechanically ventilated patients.[6] Major reasons cited for avoiding this therapy were a lack of evidence (51%), fear of antibiotic resistance (47%), and failure of approval by therapeutic boards or pharmacy departments (22%). In 12% of respondents there was also a belief that microbiologists within hospitals would not support it.

Until recently no study had been adequately powered to show a mortality benefit. In a cluster randomised crossover study in 13 intensive care units in the Netherlands (excluded from the recent Cochrane review[4]) a comparison was made between

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selective digestive decontamination (including four days of intravenous cefotaxime), selective oral decontamination, and standard care, with a primary outcome measure of 28 day mortality in 5939 patients.[5] All patients with an expectation of mechanical ventilation for more than 48 hours or an intensive care unit stay more than 72 hours were included. All the units used each of the three treatment regimens for six month periods, with the order of interventions being randomised. Mortality associated with standard care was 27.5% and was reduced significantly by 3.5% with selective digestive decontamination (relative reduction 13%) and by 2.9% with selective oral decontamination (relative reduction 11%). During the periods of selective digestive decontamination and selective oral decontamination, defined daily doses of systemic antibiotics were not higher than they were with standard care, and acquisition rates for antibiotic resistant, Gram negative bacteria were significantly lower, even for bacteria resistant to the antibiotics used in selective digestive decontamination.[7] No increase in the detection of *Clostridium difficile* toxin was observed.

This multicentre cluster randomised crossover study[5] seems to address the two major concerns among UK intensive care physicians—those of efficacy and emergence of antibiotic resistance. Nevertheless, several important caveats would support the uncertainty expressed by physicians. Although mortality was reduced, this was not measured beyond 28 days, and it is unknown if this benefit persists or is even reversed over a longer time. A prospective randomised clinical trial of selective digestive decontamination undertaken between two intensive care units at a single institution in the Netherlands reported a relative risk of 0.65 for death in the unit using selective digestive decontamination compared with the one using standard care (95% confidence interval 0.49 to 0.85, P=0.002). However, in this study follow-up extended beyond 28 days to hospital discharge, and this reduction in relative risk narrowed to 0.78 (0.63 to 0.96, P=0.02) for hospital mortality.

In this respect it is notable that in a prospective observational study (a substudy of the Dutch multicentre crossover study[5]) patients receiving selective digestive decontamination or selective oral decontamination had a tendency towards more healthcare associated infection after discharge from intensive care compared with standard care.[8] This observation may be related to changes in colonisation with antibiotic resistant Gram negative bacteria, which increases after cessation of selective oral decontamination and selective digestive decontamination.[9]

The effects of selective digestive decontamination on antibiotic resistance may also vary according to ecological levels of resistance within an intensive care unit population. Intensive care units in the Netherlands, where many of the studies on selective digestive decontamination have taken place, have low rates of antibiotic resistance, and it is unknown whether similar effects will be observed in healthcare systems with higher levels of antibiotic resistance. Indeed, some data suggest that selective digestive decontamination can increase colonisation rates with resistant bacteria in some intensive care units, including resistant Gram positive organisms such as meticillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococci.[10 11] Finally, as there was no significant difference in mortality between selective oral decontamination and selective digestive decontamination in Dutch patients,[5] systemic and enteral antibiotic administration might be unnecessary. Indeed a meta-analysis of oral decontamination that included 11 randomised clinical trials enrolling 4242 patients concluded that oral antiseptics such as chlorhexidine were effective at reducing ventilator associated pneumonia.[12]

Is ongoing research likely to provide an answer?

By searching www.controlled-trials.com and PubMed (for published trial protocols) and contacting trialists, we identified two studies likely to address the areas of uncertainty. The SuDDICU project is using case studies, questionnaires, and a Delphi survey to identify the barriers to implementation of selective digestive decontamination in the UK, Canada, Australia, and New Zealand.[13] Its results will help to guide implementation measures or the design of a controlled trial. The R-GNOSIS group (resistance in Gram negative organisms: studying intervention strategies) is planning a cluster randomised clinical trial across Europe in countries with higher (though not endemic) levels of microbiological drug resistance.[14] This study will compare standard care, selective digestive decontamination (without systemic antibiotics), selective oral decontamination, and oral decontamination with chlorhexidine in all intensive care unit patients for six month periods, with specific emphasis on the applicability of the intervention in a wider range of healthcare systems and longer term ecological effects on antibiotic resistance.

What should we do in light of the uncertainty?

Selective digestive decontamination seems to be a beneficial strategy for reducing healthcare associated infection in critically ill patients where low levels of antibiotic resistant bacteria exist within an intensive care unit population.[4 5] In healthcare systems with higher rates of antibiotic resistance clinicians should be cautious about embracing this intervention outside of well designed cluster randomised clinical trials, as there is uncertainty over the longer term benefits and ecological effects on drug resistant bacteria.

Decontamination of the oropharynx with antiseptics such as chlorhexidine seems to offer a safe and effective alternative across a variety of healthcare systems, although this intervention has never been directly compared with selective digestive decontamination or selective oral decontamination.[15]

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Recommendations for further research

Population: Adult critical care patients in environments with moderate levels of antibiotic resistance

Intervention: Unit-wide application of selective digestive decontamination

Comparitor: Unit-wide application of oral decontamination, unit-wide application of standard care

Outcomes: Hospital and sixth month survival, cost benefit analysis, colonisation with antibiotic resistant bacteria after discharge from intensive care

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