Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis

Richard Price intensivist¹, Graeme MacLennan senior statistician², John Glen intensivist³, on behalf of the SuDDICU collaboration

¹ Intensive Care Unit, Royal Alexandra Hospital, Paisley PA2 9PN, UK; ² Health Services Research Unit, Health Sciences Building, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK; ³ Intensive Care Unit, Glan Clwyd Hospital, Bodelwyddan LL18 5UJ, UK

Abstract

Objectives To determine the effect on mortality of selective digestive decontamination, selective oropharyngeal decontamination, and topical oropharyngeal chlorhexidine in adult patients in general intensive care units and to compare these interventions with each other in a network meta-analysis.

Design Systematic review, conventional meta-analysis, and network meta-analysis. Medline, Embase, and CENTRAL were searched to December 2012. Previous meta-analyses, conference abstracts, and key journals were also searched. We used pairwise meta-analyses to estimate direct evidence from intervention-control trials and a network meta-analysis within a Bayesian framework to combine direct and indirect evidence.

Inclusion criteria Prospective randomised controlled trials that recruited adult patients in general intensive care units and studied selective digestive decontamination, selective oropharyngeal decontamination, or oropharyngeal chlorhexidine compared with standard care or placebo.

Results Selective digestive decontamination had a favourable effect on mortality, with a direct evidence odds ratio of 0.73 (95% confidence interval 0.64 to 0.84). The direct evidence odds ratio for selective oropharyngeal decontamination was 0.85 (0.74 to 0.97). Chlorhexidine was associated with increased mortality (odds ratio 1.25, 1.05 to 1.50). When each intervention was compared with the other, both selective digestive decontamination and selective oropharyngeal decontamination were superior to chlorhexidine. The difference between selective digestive decontamination and selective oropharyngeal decontamination was uncertain.

Conclusion Selective digestive decontamination has a favourable effect on mortality in adult patients in general intensive care units. In these patients, the effect of selective oropharyngeal decontamination is less certain. Both selective digestive decontamination and selective oropharyngeal decontamination are superior to chlorhexidine, and there is a possibility that chlorhexidine is associated with increased mortality.

Introduction

The bacterial ecology of the oropharynx of patients in intensive care units undergoes substantial alteration.¹ ² This can lead to ventilator associated pneumonia, other infections, and death. In an attempt to reduce the incidence of these complications, approaches to decontamination include various forms of antibiotic prophylaxis or the use of topical oropharyngeal antiseptic agents (mostly chlorhexidine). Antibiotic prophylaxis can include any combination of oropharyngeal, intragastric, and intravenous antibiotics. There are, however, two main approaches: selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD).

Selective digestive decontamination consists of oropharyngeal and gastric application of non-absorbable antibiotics—often polymyxin, tobramycin, and amphoterin—in along with a short course of an intravenous antibiotic, often cefotaxime. Oropharyngeal antibiotics are applied as a paste, usually four times a day, during routine mouth care; gastric antibiotics are administered as a suspension through a nasogastric tube. Surveillance bacteriology, often twice a week, can be used to assess efficacy of decontamination. The choice of therapeutic antibiotics aims to minimise interference with the native anaerobic flora by avoiding agents such as broad spectrum penicillins. Selective oropharyngeal decontamination is the application of the topical antibiotic paste to the oropharynx only.
without enteral or empirical intravenous antibiotics. Chlorhexidine is applied as part of routine mouth care in gel or liquid form up to four times a day. There has been considerable debate about the role of antibiotic prophylaxis, and antibiotic prophylaxis is seldom used in the United Kingdom. Topical oropharyngeal antiseptic agents (usually chlorhexidine) have, by contrast, gained more widespread acceptance and appear as a key recommendation in UK, European, and US guidelines. Nevertheless, interest in this topic remains current.

Numerous meta-analyses of antibiotic and antiseptic prophylaxis have been published over the years. A 2009 Cochrane review suggested that mortality was significantly reduced by selective digestive decontamination. Another review and meta-analysis from 2007 concluded that mortality was unaffected by oropharyngeal antibiotic or antiseptic decontamination. More recent meta-analyses of oropharyngeal antiseptics (mostly chlorhexidine) have focused on the incidence of ventilator associated pneumonia, although some meta-analyses of oropharyngeal chlorhexidine have reported a trend towards increased mortality.

Despite the favourable results seen in meta-analyses of selective digestive decontamination, interpretation should be tempered by the use of standard care as a control group in the contributory trials. Given the likely widespread use of chlorhexidine, any putative mortality advantage of selective digestive decontamination or selective oropharyngeal decontamination needs to be re-defined. As we are not aware of any clinical trials directly comparing selective digestive decontamination or selective oropharyngeal decontamination with topical chlorhexidine, we aimed to use a network meta-analysis to compare the effect of these interventions on mortality. This required us to undertake an updated systematic review looking for randomised controlled trials reporting the effect of selective digestive decontamination, selective oropharyngeal decontamination, and topical chlorhexidine on mortality in adult patients in general intensive care units. We also wanted to update conventional intervention-control meta-analyses of the three interventions in light of any recent studies. We elected not to study the outcome of ventilator associated pneumonia as we consider mortality to be the most robust outcome, and this was the focus of recent large trials of selective digestive decontamination.

Method
Sources of data
We searched Medline, Embase, and the Cochrane Register of Clinical Trials from 1984 until December 2012. We constructed a search strategy around patients in intensive care, intervention with antibiotic or antiseptic prophylaxis, and the outcome of death. The Medline search strategy is shown in the appendix and similar strategies were applied to the Embase and CENTRAL databases. There were no language restrictions. We screened results of the database searches by title and abstract. Given the extent of previous systematic reviews, we reviewed recent meta-analyses (published from 2005 to 2012) for included studies that were missed in database searches. Congress abstracts were searched from 2005 to 2012 for the European Society for Intensive Care Medicine, Society for Critical Care Medicine, Symposium of Intensive Care and Emergency Medicine, and Chest. The contents pages of the journals Intensive Care Medicine, Critical Care Medicine, Chest, Critical Care, American Journal of Respiratory and Critical Care Medicine, Journal of Hospital Infection, and Infection Control and Hospital Epidemiology were reviewed from January 2005 to December 2012. The website controlled-trials.com was used to search registers of clinical trials. We did not search for unpublished studies or contact experts in the field. We wrote to authors if indicated.

Inclusion criteria
We sought prospective randomised controlled clinical trials in adult patients in general intensive care units. We did not stipulate placebo control or blinding. We defined “selective digestive decontamination” as the application of a combination of poorly absorbable antibiotics to the oropharynx and the stomach combined with empirical intravenous antibiotics. “Selective oropharyngeal decontamination” was defined as the application of a combination of poorly absorbable antibiotics only to the oropharynx. “Chlorhexidine” was defined as the application of any concentration of chlorhexidine in any formulation to the oropharynx. The control group must have received only standard care or placebo.

Exclusion criteria
We excluded trials that recruited only children, populations not in intensive care, and specialised populations (such as cardiac surgery and liver transplantation). We excluded trials in which both groups received active topical drugs or in which the control group received empirical intravenous antibiotics. Finally we excluded studies combining oropharyngeal and gastric application of antibiotics or gastric or subglottic application alone from the selective oropharyngeal decontamination meta-analysis.

Quality assessment
We summarised potential biases with the Cochrane risk of bias tool. There are six domains: sequence generation; allocation concealment; blinding; if the outcomes reported were prespecified; completeness of outcome data; and other potential sources of bias. We have also presented information on each study to show potential issues of clinical heterogeneity.

Data extraction
Results were extracted from the included studies, from our own communication with authors, or from previous meta-analyses if intention to treat data had been verified with the original study authors.

Consensus
Two authors (RP, JG) independently performed study inclusion, data extraction, and quality assessment. Disagreement at the stage of abstract screening was resolved by inclusion of the full paper for review. Disagreement at later stages was resolved by discussion. Our approaches to studies with a three arm design are presented in the appendix.

Statistical methods
Intervention-control pairwise meta-analyses
We summarised data from each study with log odds ratios and 95% confidence intervals. This approach was used to allow the inclusion of the study by de Smet and colleagues, which used a cluster randomised crossover design analysed by the authors using multilevel logistic regression. We used the log odds ratios and standard errors that de Smet and colleagues reported and calculated the log odds ratios and standard errors for the remaining studies based on the reported events and sample sizes.
Forest plots are included as a visual aid to interpret the direct evidence. Pairwise meta-analyses were done in Review Manager (RevMan), version 5.0 (Cochrane Collaboration, 2008).

Network meta-analysis
We used a generalised linear modelling framework as outlined in Dias and colleagues to do a network meta-analysis. A “trial level” approach was used, in which the data modelled were the summary log odds ratios and standard errors for each trial as outlined above. All model parameters were estimated within a Bayesian framework with WinBUGS software. We present estimates of treatment effects as odds ratios and 95% central credible intervals (CrI). The credible interval shows the degree of uncertainty around estimated treatment effects.

We also calculated individual estimates of the probability of death for each intervention. These estimates were derived from the model by using a baseline distribution for the probability of death in the control group, in combination with the odds ratio between each intervention and control. We present distributions were used on the necessary parameters: the log odds ratios of intervention procedures versus control and the standard deviation between studies. A run-in period of 50 000 iterations was adequate to achieve convergence, and a further 100 000 samples were taken.

Results
Systematic review
We identified 29 studies as suitable for inclusion (figure 1). Tables 1-3 show the components of the Cochrane risk of bias tool for each intervention. Tables 4-6 show areas of potential clinical heterogeneity between the studies and our data source. Raw outcome data are presented in table A in the appendix.

Intervention-control pairwise meta-analyses
The random effects estimate for selective digestive decontamination compared with control on mortality gave an odds ratio of 0.73 (95% confidence interval 0.64 to 0.84), favouring selective digestive decontamination (fig 2). For selective oropharyngeal decontamination and chlorhexidine the odds ratios were 0.85 (0.74 to 0.97) and 1.25 (1.05 to 1.50), respectively (figs 3 and 4). The only direct evidence for selective digestive decontamination was from a single trial, which gave an odds ratio of 0.97 (0.79 to 1.18). Results are summarised in table 7.

Results of network meta-analyses
The odds ratios (95% credible interval) for mortality for active treatment compared with control were 0.74 (0.63 to 0.86) for selective digestive decontamination, 0.82 (0.62 to 1.02) for selective oropharyngeal decontamination, and 1.23 (0.99 to 1.49) for chlorhexidine (table 7). For the comparison between treatments, the odds ratios were 0.61 (0.47 to 0.78) for selective digestive decontamination compared with chlorhexidine and 0.67 (0.48 to 0.91) for selective oropharyngeal decontamination compared with chlorhexidine. There was uncertainty around the difference between selective digestive decontamination and selective oropharyngeal decontamination. Table 8 shows probabilistic ranking of interventions.

Discussion
Using a network meta-analysis to compare each intervention indirectly, we conclude that both selective digestive decontamination and selective oropharyngeal decontamination are superior to chlorhexidine in preventing death in adults in intensive care. This suggests that the mortality advantage of both these options remains relevant even if chlorhexidine is widely used. Any difference between these treatments is inconclusive, with considerable uncertainty.

Our finding that selective digestive decontamination is associated with a survival benefit in adults in general intensive care units agrees with the conclusions of earlier meta-analyses, but we have now integrated the results of a large cluster randomised crossover trial. Results were similar with both conventional and Bayesian analysis. Selective oropharyngeal decontamination was associated with a reduction in death in the meta-analysis of direct evidence. Contrary to our expectations, use of oropharyngeal chlorhexidine was associated with an increase in mortality in adults in general intensive care units.

Limitations of our study
Despite our inclusion criteria, our results are limited by the inevitable heterogeneity among the included studies (tables 4-6), with some common themes.

Within the chlorhexidine studies, the concentration of chlorhexidine used varied from 0.12% to 2% and the number of daily applications varied from one to four. In addition, the duration of the course of treatment varied and in one study was limited to seven days.

Within the selective digestive decontamination studies, most were not blinded and were not placebo controlled. Of those that were blinded, only one explicitly reported concealment of microbial culture results. We consider that this lack of blinding would have had the least influence on the robust outcome of mortality. We could not find any suggestion of differential treatment of patients in the active treatment group over control patients, although we cannot entirely exclude it. Infected patients were excluded in three studies. There was some variability in the exact antimicrobial regimen used; the influence of different regimens has previously been discussed and has been shown to influence at least infective outcomes.

Two studies differed slightly in their protocols by locally decontaminating blind bowel loops and tracheal stomas and by treating persistent tracheal colonisation with aerosolised polymyxin or amphotericin.

For each included selective digestive decontamination study, the total proportion of patients in the intensive care unit that were included in the trial was generally unclear. The only included study to use a whole unit approach showed a mortality benefit that was greater than that seen in meta-analyses (although problems with this study have been highlighted). Thus the generalisability of these studies to a unit where selective digestive decontamination or selective oropharyngeal decontamination is applied to every patient needs to be considered as selective digestive decontamination can alter the ecology of the unit.

When we considered all studies, there was variability in the minimum predicted ventilator time or stay in the intensive care unit. The proportion of ventilated patients varied from 36% in one study to 100%.

A network meta-analysis rests on the comparability of a common control group. Given the temporal variation (year of publication ranging from 1989 to 2011) and wide geographic representation...
(tables 4-6), there is probably variation among the control groups of the included studies. Control group treatments were generally poorly detailed, although we have identified some variation—for example, the use of topical bicarbonate or potassium permanganate. When other control group treatments were described, they were generally limited to the use of gastric ulcer protection or non-pharmacological mouth care strategies.

When we considered the effect of chlorhexidine on mortality, mortality was not the primary outcome of any of the included studies and a significant increase in mortality was seen in only one of the 11 studies. Additionally, we are aware of one further study of the use of oropharyngeal chlorhexidine that could have fulfilled our inclusion criteria, but we were unable to include it as we could not obtain mortality data.

### Implications of this study

In adult patients in general intensive care units, and within the limits of a network meta-analysis, we propose that both selective digestive decontamination and selective oropharyngeal decontamination are superior to chlorhexidine. In keeping with results of earlier studies, we have shown that selective digestive decontamination is associated with reduced mortality. We raise the possibility that oropharyngeal chlorhexidine might be associated with an increase in mortality, and we therefore question whether oropharyngeal chlorhexidine is “safe and effective.” Certainly our findings are at odds with the apparently favourable effects of chlorhexidine on the incidence of ventilator associated pneumonia. Although the attributable mortality of this might be small. We consider that the role of oropharyngeal chlorhexidine in these patients needs to be explored further. We agree that it would be appropriate to undertake additional prospective studies comparing selective digestive decontamination, selective oropharyngeal decontamination, and chlorhexidine as barriers to implementation or any further trials have been explored.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coiDisclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: No additional data available.

Transparency: The lead author (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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What is already known on this topic
Numerous studies and meta-analyses have shown a mortality benefit with use of selective digestive decontamination in patients in intensive care.

What this paper adds
This network meta-analysis showed that both selective digestive decontamination and selective oropharyngeal decontamination confer a mortality benefit when compared with chlorhexidine in adults in general intensive care units.

In these patients, selective digestive decontamination was associated with reduced mortality, as in earlier meta-analyses, but the current analysis integrated a large recent cluster crossover study.

It is possible that use of chlorhexidine is associated with an increase in mortality.

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### Tables

**Table 1** Methodological aspects of included trials on effect of selective digestive decontamination (SDD) for prevention of death in adults in intensive care

| Adequate sequence generation | Allocation concealment | Blinding | Outcome prespecified | Incomplete outcome data addressed | Other bias |
|------------------------------|------------------------|----------|----------------------|-----------------------------------|------------|
| Aerdtz                        | Yes                     | No       | Per protocol mortality reported in published paper | Intention to treat analysis possible from previous communication with authors*      | —         |
| Blair                        | Unclear                 | No       | Mortality reported   | Intention to treat analysis possible from data provided                        | —         |
| Boland                       | Yes*                    | Unclear  | Yes                  | Mortality not reported            | —         |
| Cockerill                    | Yes                     | Yes      | No                   | Study powered for mortality. Mortality reported                                  | Active and control ICUs, potential for other differences in care |
| De Jonge                     | Yes                     | Yes      | No                   | Study powered for mortality. Mortality reported                                  | —         |
| De Smet                      | Yes                     | Yes      | No                   | Study powered for mortality. Mortality reported                                  | Statistical correction of baseline differences discussed |
| Jacobs                       | Unclear                 | Yes      | No                   | Mortality reported                | Uncorrected relevant baseline imbalance |
| Kreuger                      | Yes                     | Yes      | Yes                  | Mortality reported                | —         |
| Palomar                      | Yes                     | Yes      | No                   | Per protocol mortality reported in published paper                             | —         |
| Rocha                        | Yes                     | Yes      | Yes                  | Per protocol mortality reported in published paper                             | —         |
| Sanchez-Garcia               | Yes                     | Yes      | Yes                  | Mortality defined secondary endpoint. Mortality reported                         | —         |
| Stoutenbeek                  | Yes                     | Yes      | No                   | Mortality primary endpoint. Mortality reported                                  | Minor baseline imbalances. |
| Ulrich                       | Unclear                 | Yes      | No                   | Mortality reported (incomplete)                                                | —         |
| Verwaest                     | Yes                     | No       | Mortality a defined endpoint. Mortality reported                              | —         |
| Winter                       | Yes                     | Yes      | No                   | Mortality reported                | —         |

*Information taken from Cochrane* or Chan after their correspondence with authors.
Table 2 | Methodological aspects of included trials on effect of selective oropharyngeal decontamination (SOD) for prevention of death in adults in intensive care

| Bergmans* | De Smet* | Pugin* | Rios* |
|-----------|----------|--------|-------|
| Adequate sequence generation | Allocation concealment | Blinding | Outcome prespecified | Incomplete outcome data addressed | Other bias |
| Unclear | Yes | Yes | Mortality defined secondary endpoint. Mortality reported | 226/245 patients analysed | — |
| Yes | Yes | No | Study powered for mortality. Mortality reported | Adjusted 28 day mortality used: 1979/1990 in standard care; 1886/1904 in SOD | Statistical correction of baseline differences discussed |
| Unclear | Yes* | Yes | Per protocol mortality reported in published paper | Intention to treat analysis possible from previous communication with authors* | — |
| Unclear | Unclear | Yes | Per protocol mortality reported in published paper | 96/116 patients analysed | Published only in abstract form |

*Information taken from Cochrane or Chan after their correspondence with authors.
**Table 3** Methodological aspects of included trials on effect of topical oropharyngeal chlorhexidine for prevention of death in adults in intensive care

| Method                        | Adequate sequence generation | Allocation concealment | Blinding | Outcome prespecified                        | Incomplete outcome data addressed | Other bias |
|-------------------------------|------------------------------|------------------------|----------|--------------------------------------------|-----------------------------------|------------|
| Bellissimo-Rodrigues et al.   | Unclear                      | Yes                    | Yes      | Mortality a defined secondary endpoint. Mortality reported | 194/200 patients analysed. Reasons for exclusions discussed | —          |
| Berry et al.                  | Yes                          | Yes                    | No       | Mortality not reported                     | Intention to treat data obtained from author | —          |
| Cabov et al.                  | Yes                          | Unclear                | Yes      | Mortality reported                         | Intention to treat analysis performed | —          |
| Fourrier 2000                  | Yes                          | Unclear                | Partial  | Mortality reported                         | Intention to treat analysis performed | —          |
| Fourrier 2005                  | Unclear                      | Yes                    | Yes      | Mortality a defined secondary endpoint. Mortality reported | Intention to treat analysis performed | Censored at 28 days |
| Koeman et al.                 | Yes                          | Unclear                | Yes      | Mortality defined secondary endpoint. Mortality reported as hazard ratio only | Intention to treat analysis possible from previous communication with authors<sup>11</sup> | —          |
| MacNaughton et al.            | Unclear                      | Unclear                | Yes      | Mortality not reported                     | Unclear                           | Published only in abstract form |
| Munro et al.                  | Yes                          | Unclear                | No       | Mortality reported (subgroup of total population) | Intention to treat data obtained from author | Stopped intervention at day 7 |
| Panchabhai et al.             | Unclear                      | Unclear                | No       | Mortality a defined secondary endpoint. Per protocol mortality reported | 471/512 patients analysed. Reasons for exclusions discussed | —          |
| Scannapieco et al.            | Yes                          | Yes                    | Yes      | Mortality a defined secondary endpoint. Mortality reported | Intention to treat data obtained from author | Censored at 21 days |
| Tantipong et al.              | Unclear                      | Unclear                | No       | Mortality reported                         | Intention to treat analysis performed | —          |

<sup>*Information taken from Cochrane<sup>10</sup> or Chan<sup>11</sup> after their correspondence with authors.</sup>
| Study | Topical drugs | Intravenous drugs | Control group | Accrual period | Population | Place study undertaken | Projected ventilator or ICU time | Timing of outcome |
|-------|---------------|------------------|---------------|---------------|------------|------------------------|-------------------------------|------------------|
| Aerds¹⁰ | Polymyxin, Norfloxacin, Ampicillin | Cefotaxime 500 mg TDS/5 days | No antibiotic prophylaxis | May 1986-Sep 1987 | Nijmegen, Netherlands | >5 days of mechanical ventilation | ICU discharge |
| Blair²⁰ | Polymyxin, Tobramycin, Amphotericin | Cefotaxime 50 mg/kg/day/4 days | Standard antibiotic therapy | Sep 1988-Jan 1990 | Belfast, UK | >48 hr in ICU | ICU discharge |
| Boland⁴⁰ | Polymyxin, Tobramycin, Nystatin | Cefotaxime 5 days | Placebo | Not specified | Multiple trauma, all ventilated | >5 days intubated | ICU discharge |
| Cockerill⁴⁰ | Polymyxin, Gentamicin, Nystatin | Cefotaxime 1 g TDS/3 days | No antibiotic prophylaxis | 1986-1989 | Rochester, MN, US | >3 days in ICU | ICU discharge |
| De Jonge⁴⁰ | Polymyxin, Tobramycin, Amphotericin | Cefotaxime 1 g QDS/4 days, or none. | No antibiotic prophylaxis | May 2004-Jul 2006 | Multiple sites (13), Netherlands | >48 hr of mechanical ventilation or 3 days in ICU | ICU discharge |
| De Smet⁴⁰ | Polymyxin, Tobramycin, Amphotericin | Cefotaxime 1 g QDS/4 days | No antibiotic prophylaxis | Sep 1999- Dec 2001 | Amsterdam, Netherlands | >48 hr of mechanical ventilation or 3 days in ICU | ICU discharge |
| Jacobs⁴⁰ | Polymyxin, Tobramycin, Amphotericin | Cefotaxime 50 mg/kg/day/4 days | Normal management, Low gastric pH encouraged. | July 1989-Aug 1990 | Cardiff, UK | >3 days in ICU | Unclear |
| Kreuger⁴⁰ | Polymyxin, Gentamicin (Vancomycin & Amphotericin) | Ciprofloxacin 400 mg BD/4 days | Placebo | 2.5 yr, dates not given (published 2002) | 2 sites, Tübingen, Germany | >48 hr in ICU | ICU discharge |
| Palomar⁴⁰ | Polymyxin, Tobramycin, Amphotericin | Cefotaxime 1 g TDS/4 days | No antibiotic prophylaxis | July 1989- July 1991 | Multiple sites (10), Catalonia, Spain | >4 days of mechanical ventilation | ICU discharge |
| Rocha⁴⁰ | Polymyxin, Tobramycin, Amphotericin | Cefotaxime 2 g TDS/4 days | Placebo | 14 months, dates not given (published 1992) | La Coruna, Spain | >3 days of mechanical ventilation and > 5 days ICU stay | ICU discharge |
| Sanchez-Garcia⁴⁰ | Polymyxin, Gentamicin, Amphotericin | Ceftriaxone 2 g OD/3 days | Placebo | Not stated (published 1998) | Multiple sites (5), Madrid, Spain | >48 hr of intubation | ICU discharge |
| Stoutenbeek⁴⁰ | Polymyxin, Tobramycin, Amphotericin | Cefotaxime 1 g QDS/4 days | Standard antibiotic therapy for each centre | Oct 1991-June 1994 | Blunt multi trauma, all ventilated | Not a criterion | ICU discharge or up to 2 weeks following ICU discharge |
| Ulrich⁴⁰ | Polymyxin, Norfloxacin, Ampicillin | Trimethoprim 500 mg OD/3 days | Appropriate perioperative prophylaxis | Oct 1986-Sep 1987 | Hague, Netherlands | >5 days in ICU | ICU discharge |
| Verwaest⁴⁰ | Ofloxacin, Amphotericin | Ofloxacin 200 mg OD/4 days | Conventional antibiotic policy | 19 months, dates not given (published 1997) | Leuven, Belgium | >48 hr of mechanical ventilation | ICU discharge |
| Winter⁴⁰ | Polymyxin, Tobramycin, Amphotericin | Cefazidime 50 mg/kg/day/3 days | Nothing specified | 22 months, dates not given (published 1992) | Bristol, UK | >48 hr in ICU | Hospital discharge |
| Study | Topical drugs | Control group | Accrual period | Population | Place study undertaken | Projected ventilator or ICU time | Timing of outcome |
|-------|---------------|---------------|----------------|------------|------------------------|-------------------------------|------------------|
| Bergmans<sup>44</sup> | Gentamicin, Polymyxin, Vancomycin / QDS | Placebo | Sep 1994-Dec 1996 | Mixed ICU, all ventilated | Multiple sites (3), Netherlands | >48 hr of mechanical ventilation | ICU discharge |
| Pugin<sup>45</sup> | Polymyxin, Neomycin, Vancomycin / 4 hourly | Placebo | Apr-Nov 1989 | Surgical ICU, all ventilated | Geneva, Switzerland | >48 hr of intubation | Hospital discharge |
| Rios<sup>46</sup> | Polymyxin, Gentamicin / TDS | Placebo | Uncertain | Uncertain | Buenos Aires, Argentina | >4 days of mechanical ventilation | Unclear |
| Study | Chlorhexidine | Control group | Accrual period | Population | Place study undertaken | Projected ventilator or ICU time | Timing of outcome |
|-------|---------------|---------------|----------------|------------|------------------------|---------------------------------|------------------|
| Bellissimo-Rodrigues⁵⁵ | 0.12% solution TDS | Placebo | Mar 2006-Feb 2008 | Mixed ICU, 69% ventilated | Sao Paulo, Brazil | >48 hr in ICU | ICU discharge |
| Berry²⁵ | 0.2% solution BD | Either water or bicarbonate mouth rinses | Uncertain, 15 month recruitment period | Mixed ICU, 100% ventilated | Sydney, Australia | Not specified | ICU discharge |
| Cabov⁵⁶ | 0.2% gel TDS | Placebo | Mar 2008-Dec 2008 | Surgical ICU, 100% ventilated | Zagreb, Croatia | >3 days in ICU and requiring mechanical ventilation | ICU discharge |
| Fourrier 2000⁵⁷ | 0.2% gel TDS | Bicarbonate mouth rinses | June 1997-July 1998 | Mixed ICU, 100% ventilated | Lille, France | >5 days in ICU and requiring mechanical ventilation | Unclear |
| Fourrier 2005⁵⁸ | 0.2% gel TDS | Placebo | Jan 2001-Sep 2002 | Mixed ICU, 100% ventilated | Lille, France | >5 days in ICU and requiring mechanical ventilation | 28 days |
| Koeman⁵⁹ | 2% gel QDS | Placebo | Feb 2001-Mar 2003 | Multiple sites (7), Netherlands | Multiple sites (6), France | >48 hr of mechanical ventilation | ICU discharge |
| MacNaughton⁶⁰ | 0.2% BD | Placebo | Uncertain | Mixed ICU, 100% ventilated | Plymouth, UK | >48 hr of mechanical ventilation | ICU discharge |
| Munro⁶¹ | 0.12% solution BD | Either usual care or toothbrushing groups | Uncertain | Mixed ICU, 100% ventilated | Richmond, VA, US | Not specified | Hospital discharge |
| Panchabhai⁶² | 0.12% solution BD | 0.01% potassium permanganate | Uncertain, 8 month recruitment period | Mediconeuro ICU, 171/471 ventilated | Mumbai, India | >48 hr in ICU | ICU discharge |
| Scannapieco⁶³ | 0.12% solution OD or BD | Placebo | Mar 2004-Nov 2007 | Trauma ICU, 100% ventilated | Buffalo, NY, US | Not specified | 21 days |
| Tantipong⁶⁴ | 2% solution QDS | Normal saline | Jan 2006-Mar 2007 | Surgical or medical ICU or general medical ward, 100% ventilated | Bangkok, Thailand | Not specified | Unclear |
Table 7 | Results of meta-analyses of effect of selective digestive decontamination (SDD), selective oropharyngeal decontamination (SOD), and topical oropharyngeal chlorhexidine for prevention of death in adults in intensive care

| Comparison               | OR (95% CI/CrI)               | Direct evidence | Mixed (direct and indirect) evidence |
|--------------------------|-------------------------------|-----------------|-------------------------------------|
| Chlorhexidine v control  | 1.25 (1.05 to 1.50)           | 1.23 (0.99 to 1.49) |
| SDD v control            | 0.73 (0.64 to 0.84)           | 0.74 (0.63 to 0.86) |
| SOD v control            | 0.85 (0.74 to 0.97)           | 0.82 (0.62 to 1.02) |
| SDD v chlorhexidine      | —                             | 0.61 (0.47 to 0.78) |
| SOD v chlorhexidine      | —                             | 0.67 (0.48 to 0.91) |
| SDD v SOD                | 0.97 (0.79 to 1.18)           | 0.91 (0.70 to 1.19) |
Table 8  Probabilistic ranking of interventions and estimated probability of death in adults in intensive care treated with selective digestive decontamination (SDD), selective oropharyngeal decontamination (SOD), or topical oropharyngeal chlorhexidine

| Intervention | Rank | Estimated probability of death | Probability of intervention being best |
|--------------|------|--------------------------------|---------------------------------------|
| SDD          | 1    | 0.213                          | 0.740                                 |
| SOD          | 2    | 0.228                          | 0.260                                 |
| Control      | 3    | 0.266                          | <0.001                                |
| Chlorhexidine| 4    | 0.305                          | <0.001                                |
Figures

Fig 1 Inclusion of studies in analysis of effect of selective digestive decontamination (SDD), selective oropharyngeal decontamination (SOD), and topical oropharyngeal chlorhexidine for prevention of death in adults in intensive care

Fig 2 Forest plot of intervention-control pairwise meta-analysis of selective digestive decontamination v control in adult patients in intensive care
Fig 3 Forest plot of intervention-control pairwise meta-analysis of selective oropharyngeal decontamination v control in adult patients in intensive care

Fig 4 Forest plot of intervention-control pairwise meta-analysis of chlorhexidine v control in adult patients in intensive care