Meta-analysis of randomised controlled trials of selective decontamination of the digestive tract

Selective Decontamination of the Digestive Tract Trialists' Collaborative Group

Abstract

***Objective*—To determine the clinical benefits of selective decontamination of the digestive tract in patients treated in intensive care units.**

***Design*—Meta-analysis of 22 randomised trials that compared different combinations of oral non-absorbable antibiotics, with or without a systemic component, with no treatment in controls.**

***Subjects*—4142 patients seen in general and specialised intensive care units around the world. 2047 received some form of antibiotic treatment, the remainder no prophylaxis.**

***Data analysis*—Each trial was reviewed through direct contact with study investigators. Data collected were: the randomisation procedure, number of patients, number excluded from the analysis, and numbers of respiratory tract infections and deaths. Data were combined according to an intention to treat analysis with the Mantel-Haenszel-Peto method.**

***Main outcome measures*—Respiratory tract infections and total mortality.**

***Results*—Selective decontamination of the digestive tract significantly reduced respiratory tract infections (odds ratio 0·37; 95% confidence interval 0·31 to 0·43). The value of the common odds ratio for total mortality (0·90; 0·79 to 1·04) suggested at best a moderate treatment effect, reaching statistical significance only when the subgroup of trials of topical and systemic treatment combined was considered separately (odds ratio 0·80; 0·67 to 0·97). No firm conclusions could be drawn owing to large variations in patient mix and severity within and between trials.**

***Conclusions*—The findings strongly indicate that selective decontamination significantly reduces infection related morbidity in patients receiving intensive care. They also highlight why definite conclusions about the effect of prophylaxis on mortality cannot be drawn despite the large number of trials available. Based on the most favourable results obtained by pooling data from trials in which combined topical and systemic treatment was used it may be estimated that 6 (range 5-9) and 23 (13-139) patients would need to be treated to prevent one respiratory tract infection and one death respectively.**

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Introduction

Infections acquired in intensive care units are an important cause of morbidity and mortality, and considerable efforts have been made to test strategies aimed at preventing them. One such strategy entails selectively decontaminating the digestive tract. This is designed to prevent infection by eradicating and preventing carriage of aerobic potentially pathogenic micro-organisms from the oropharynx, stomach, and gut. Selective decontamination with combined oral non-absorbable and systemic antibiotics was first reported in 1984 by Stoutenbeek *et al* in a group of multiple trauma patients.[1] The incidence of nosocomial infection was reduced from 81% to 16% in a non-randomised comparison with a historical control group.[1] Other studies have tested the efficacy of selective decontamination in intensive care unit patients, using infection related morbidity as the main end point. Results suggest that selective decontamination may reduce infection, but it is not clear whether there is a corresponding effect on mortality. These conclusions have recently been supported by a meta-analysis[2] based on six randomised and six non-randomised trials which confirmed that selective decontamination is effective in preventing infections.[2] That study, however, had insufficient power to detect the extent of the reduction in relative mortality (10-20%) that is now seen as appropriate when the treatment is applied to heterogeneous populations of intensive care unit patients.

In preparation for the first European consensus conference on selective decontamination of the digestive trace, held in Paris in December 1991, a preliminary meta-analysis based on international collaboration among trialists was started. The findings presented at the conference[3] showed an effect of selective decontamination on infection but not on mortality.[4] This collaboration has continued and new trials have been traced. We report the results of this extended meta-analysis and discuss the implications in terms of end points and sample size requirements for design of future confirmatory studies.

Methods

STUDIES SEARCH AND SELECTION

We planned to analyse all randomised controlled trials of selective decontamination for the prevention of respiratory tract infections and death in intensive care unit patients. Only randomised trials were considered because otherwise control of selection bias cannot be guaranteed. Studies reported from January 1984 till June 1992 were identified by literature search Medline (mesh keywords "intensive care units"; "critical care"; "antibiotics combined therapeutic use"; "antibiotics combined administration and dosage"; "respiratory tract infections prevention and control"). This detected randomised controlled trials which compared selective decontamination of the digestive tract with placebo or no treatment. The organiser of the first European consensus conference on intensive care medicine also provided a list of all investigators who had ever published on the topic. At the time of the conference 17 trials were available.[5] An international secretariat was then established to trace other completed but unpublished trials. This further search examined proceedings of meetings held on selective decon-

tamination until June 1992 and made personal contact with workers in the field. All collaborating trialists were asked to indicate ongoing trials of which they were aware. No formal search was made through pharmaceutical companies. By this process eight additional trials were traced. Material used to trace studies, including proceedings of meetings at which data were presented, is available from the coordinating centre.

To test the validity of data all participants were asked to provide in standardised written form specific information independent of the publication status of their work. The following data were requested separately for each treatment arm: (*a*) number of patients and method of randomisation; (*b*) percentages of medical, surgical, and trauma patients; (*c*) number of patients with respiratory tract infections; (*d*) number of deaths recorded so far; (*e*) number of patients, if any, excluded from the final analysis in order to allow an "intention to treat analysis" and (*f*) number of patients, if any, with respiratory tract infections and number of deaths among those originally excluded from the analysis.

Besides the general eligibility rule adopted in this meta-analysis—that is, randomised treatment allocation—the special features of four studies required ad hoc decisions. One study,[6] though not randomised formally, was included as it used a strictly double blind scheme. Three randomised trials were excluded for the following reasons. Direct inquiry with the principal investigator in a trial containing 204 patients (102 treated and 102 controls, with 92 respiratory tract infections and 158 deaths)[7] showed that a consecutive non-randomised treatment allocation was used despite the study being indexed as randomised. Two other trials (containing 114 patients[8] (56 treated and 58 controls, with nine respiratory tract infections and five deaths) and 104 patients[9] (52 treated and 52 controls, with 18 respiratory tract infections and 48 deaths)) were excluded because they were concerned with having oesophageal resection[8] or with acute fulminant hepatic failure.[9]

The results presented here are thus based on 22 independent randomised controlled trials. In the tables and figures, however, 23 studies are shown because the three arm trial[10] was split into two parts and contrasted the effects of two different treatments, but with the same control group. Only 22 trials contributed data on the effect of selective decontamination of the digestive tract on respiratory tract infections because one study[11] considered only septicaemia; mortality data were available from all 23 studies. Table I shows the general characteristics of the trials.

STATISTICAL METHODS

Crude proportions of respiratory tract infections and total mortality were assessed as treatment end points. Intention to treat analysis was carried out on the study populations, randomly assigned to control or selective decontamination. Odds ratios of each outcome in each trial were computed with the Mantel-Haenszel-Peto method.[12] Odds ratios and pooled odds ratios together with their 95% confidence intervals are reported separately for respiratory tract infections and deaths.

TABLE I—*General characteristics of randomised clinical trials included in meta-analysis*

Reference	Inclusion criteria	Mean age (years)	Mean severity score	% Trauma patients	% Survical patients	% Medical patients	Whether blinded	Type of treatment
Rocha *et al*[20]	Patients with >3 days of mechanical ventilation and >5 days of stay	43·5	15·5†	79	0	21	Yes	Topical: polymyxin-tobramycin-amphotericin B. systemic: cefotaxime
Pugin *et al*[26]	Patients at risk of ventilator associated pneumonia	45·5	15·3†	52	12	36	Yes	Topical: polymyxin-neomycin-vancomycin
Korinek *et al*[9]	Patients intubated from less than 24 hours and having at least 5 days of stay	45·0	10·9‡	50	50	0	Yes	Topical: polymyxin-tobramycin-amphotericin B.
Rodriguez-Roldan *et al*[24]	Patients mechanically ventillated for ≥72 hours	51·3	17·0†	48	16	36	Yes	Topical: polymyxin-tobramycin-amphotericin B
Palomar *et al*[25]	Non-infected, non-treated patients ventilated for >4 days	45·5	16·6†	45	17	38	No	Topical: polymyxin-tobramycin-amphotericin B. systemic: cefotaxime
Godard *et al*[8]	All patients	49·0	13·9‡	41	28	31	Yes	Topical: polymyxin-tobramycin
Blair *et al*[22]	Patients in intensive care unit for >48 hours	47·9	14·0†	40	45	15	No	Topical: polymyxin-tobramycin-amphotericin B. systemic: cefotaxime
Aerdts *et al*[21]	Patients expected to be ventilated for ≥5 days	46·7	22·3†	34	25	41	No	Topical: polymyxin-norfloxacin-amphotericin B. systemic: cefotaxime
Unertl *et al*[28]	Patients intubated within 24 hours after acute event and expected to be ventilated for >6 days	49·4	12·5‡	33	15	52	No	Topical: polymyxin-gentamicin-amphotericin B
Kerver *et al*[33]	Patients requiring intensive care for >5 days	55·6	14·8†	28	60	12	No	Topical: polymyxin-tobramycin-amphotericin B. systemic: cefotaxime
Hammond *et al*[32]	Patients expected to require intubation for >48 hours and to remain in intensive care for ≥5 days	43·3	14·7†	27	14	59	Yes	Topical: polymyxin-tobramycin-amphotericin B. systemic: cefotaxime. (Both arms)
Verhaegen 1[10]	Patients expected to be ventilated for >48 hours	55·8	18·3†	24	66	10	No	Topical: polymyxin-tobramycin-amphotericin B. systemic: cefotaxime
Ferrer *et al*[35]	Ventilated patients	61·0	12·4‡	23	13	64	Yes	Topical: polymyxin-tobramycin-amphotericin B. systemic: cefotaxime. (Both arms)
Verhaegen 2[10]	Patients expected to be ventilated for >48 hours	56·3	17·9†	22	68	10	No	Topical: ofloxacin-amphotericin B. systemic: ofloxacin
Jacobs *et al*[34]	Patients expected to remain in intensive care for >3 days	51·5	17·6†	18	57	25	No	Topical: polymyxin-tobramycin-amphotericin B. systemic: cefotaxime
Sanchez-Garcia[30]	Patients intubated for >48 hours	54·5	26·0†	17	12	71	Yes	Topical: polymyxin-gentamicin-amphotericin B. systemic: ceftriaxone
Cockerill *et al*[37]*	Patients expected to remain in intensive care for ≥3 days	65·0	18·4†	15	48	17	No	Topical: polymyxin-gentamicin-nystatin. systemic: cefotaxime
Gastinne *et al*[38]	Patients ventilated with intubation performed <48 hours before randomisation	55·0	13·5‡	15	13	72	Yes	Topical: polymyxin-tobramycin-amphotericin B
Ulrich *et al*[27]	Patients expected to remain in intensive care for >5 days	62·0	12·0‡	14	56	30	No	Topical: polymyxin-norfloxacin-amphotericin B. systemic: trimethoprim
Winter *et al*[29]	Patients expected to remain in intensive care for >48 hours	59·2	14·0†	12	39	49	No	Topical: polymyxin-tobramycin-amphotericin B. systemic: ceftazidime
Cerra *et al*[23]	Patients within 48 hours of acute event and expected to remain in intensive care for >5 days	63·5	Not done	4	96	0	Yes	Topical: norfloxacin-nystatin
Brun-Buisson *et al*[31]	Patients with unit stay of >2 days and severity score of >2	59·0	11·4‡	2	19	79	No	Topical: polymyxin-neomycin-nalidixic acid
Gaussorgues *et al*[11]	Patients mechanically ventilated	57·0	17·5‡	0	16	84	No	Topical: polymyxin-gentamicin-amphotericin B. vancomycin

*Thirty patients (20%) were classified by Cockerill *et al* as trauma and surgical patients and did not fit our mutually exclusive categories.
†Acute physiological and chronic health evaluation score.
‡Simplified acute physiological score.

TABLE II—*Details of randomised clinical trials included in meta-analysis assessed with respect or respiratory tract infection*

Reference	Whether protected catheter	Incidence of infection among controls (%)	Patients given active treatment		Controls		Odds ratio (95% confidence interval)
			No in group	No with infection	No in group	No with infection	
Rocha *et al*[20]	Yes	46	47	7	54	25	0·24 (0·1 to 0·55)
Pugin *et al*[26]	Yes	59	38	4	41	24	0·13 (0·05 to 0·32)
Korinek *et al*[19]	Yes	39	96	20	95	37	0·42 (0·23 to 0·78)
Rodriguez-Roldan[34]	Yes	65	14	1	17	11	0·01 (0·02 to 0·40)
Palomar *et al*[25]	Yes	53	48	10	49	26	0·25 (0·11 to 0·58)
Godard *et al*[6]	Yes	15	101	2	84	13	0·17 (0·06 to 0·48)
Blair *et al*[22]	No	22	161	12	170	38	0·31 (0·17 to 0·57)
Aerdts *et al*[21]	No	48	28	1	60	29	0·14 (0·05 to 0·36)
Unertl *et al*[28]	No	45	19	1	20	9	0·13 (0·03 to 0·54)
Kerver *et al*[33]	No	94	49	22	47	44	0·11 (0·04 to 0·25)
Hammond *et al*[32]	No	19	162	25	160	30	0·79 (0·44 to 0·41)
Verhaegen 1[10]	No	22	200	31	185	40	0·67 (0·40 to 1·12)
Ferrer *et al*[35]	Yes	24	39	9	41	10	0·93 (0·33 to 2·59)
Verhaegen 2[10]	No	22	193	22	185	40	0·48 (0·28 to 0·82)
Jacobs *et al*[24]	No	9	45	0	46	4	0·13 (0·02 to 0·95)
Sanchez-Garcia[30]	No	43	131	31	140	60	0·42 (0·26 to 0·70)
Cockerill *et al*[17]	No	16	75	4	75	12	0·33 (0·12 to 0·92)
Gastrinne *et al*[18]	Yes	19	220	31	225	42	0·72 (0·43 to 1·18)
Ulrich *et al*[27]	No	46	55	7	57	26	0·21 (0·09 to 0·47)
Winter *et al*[29]	No	18	91	3	92	17	0·21 (0·08 to 0·54)
Cerra *et al*[23]	No	100	25	14	23	23	0·09 (0·02 to 0·33)
Brun-Buisson *et al*[31]	Yes	9	65	3	68	6	0·52 (0·13 to 1·99)

We also used the random effect model as proposed by DerSimonian and Laird,[13] where the variable of interest in each study is the difference in event rates between the treated and control groups. As the two methods gave similar p values for the difference between treated and control groups only the results of analysis by the Mantel-Haenszel-Peto method are given.

Heterogeneity between trials was tested by χ^2 test. However, such a test of heterogeneity among many different trials has limited value for reasons specific to this meta-analysis and for more general reasons. Firstly, in this series a substantial quantitative variation in treatment effect, possibly due to differences in patient mix and severity of disease, was evident. Furthermore, whatever results are obtained this test provides limited reassurance, given that it has low power and is dominated by the unstable contributions from the smaller studies that might obscure any real heterogeneity among the larger studies.

In order to make our results more intelligible and illustrate the clinical relevance of the treatment we computed the number of intensive care unit patients who would need to be treated in order to prevent one respiratory tract infection and one death according to the method proposed by Laupacis *et al*.[14] The calculation was based on the median rates of respiratory tract infection and death in untreated controls (29% in both instances) and the common odds ratio for all trials. The ranges of these estimates were computed with reference to the values of the upper and lower 95% confidence intervals. Sensitivity analyses of these estimates were also carried out to see how the number of patients needed to be treated varied at different levels of baseline risk of infection and mortality while the estimated odds of infection and mortality reduction were being held constant.

A series of pre-specified subgroup analyses was also carried out. To analyse the effect of selective decontamination on respiratory tract infections trials were grouped according to (*a*) type of diagnostic procedures (use of quantitative microbiology on distal protected specimen *v* other sampling techniques); (*b*) blinding of patients and doctors to allocated treatment (yes or no); (*c*) type of selective decontamination used (topical regimen *v* topical plus systemic); (*d*) quality of randomisation procedures (that is, efforts to blind doctors to the treatment in the next case—for example, by using telephone randomisation or sealed envelopes *v* other mechanisms, such as an open randomisation list, date of birth, and odd and even numbers).

For the analysis of overall mortality trials were grouped according to (*a*) blinding of patients and doctors to allocated treatment (yes or no); (*b*) type of selective decontamination used (topical regimen *v* topical plus systemic); (*c*) quality of randomisation procedures (as above). In the relevant subgroup analysis trials in which a systemic antibiotic was delivered to all patients (that is, to treated patients and controls) were included in the topical group only.

An estimate of the magnitude of the relation between respiratory tract infections and mortality was attempted by means of a weighted multiple regression analysis. The weights were constructed in such a way that study arms with more information contributed more to the regression.[15] The slope of the weighted linear regression coefficient fit to these data is the regression coefficient β relating ln odds of respiratory tract infections to ln odds of death. This analysis did not compare treatment arms of different trials, and thus estimates based on comparisons within the same clinical trials only.

In all tables and figures trials are presented in decreasing order of proportions of trauma patients enrolled: there is widespread belief that this group is likely to benefit most from selective decontamination.[16]

Results

STUDY POPULATION

Studies reported between January 1984 and June 1992 included 4142 patients. By June 1993, 18 studies had been published, one was accepted for publication, and three were unpublished. Methods of randomisation were as follows: 15 studies used blind randomisation (four by telephone,[17-20] 11 with sealed envelopes[10 21-30]); six used methods such as odd and even numbers[11 31-35]; and one used a double blind allocation method.[6] Ten used a double blind design (table I), and nine used a protected catheter to distinguish pneumonia from respiratory tract infections (table II).

PATIENT MIX AND TREATMENTS

All trials included unselected general patients with an expected stay in intensive care of five days or more or a projected need for mechanical ventilation for 48 hours or more (table I). Trial populations differed in age (mean range 43-65 years), size (range 31-445 members), severity scores, and proportions of medical (range 0-84%), surgical (0-96%), and trauma (0-79%) patients. Timing of mortality assessment was also variable, most trials referring to intensive care unit mortality.

Nineteen trials had two arms, the control being a placebo or non-treatment arm. Three studies had three arms. One study[21] had one treated and two control groups with different policies for treating infection, and two studies[10 25] had one control and two different treatment groups. Only two arms (selective decontamination and untreated control in the study of Palomar *et al*[25]) were considered and the sucralfate treated arm was excluded. The study by Verhaegen[10] was split into two parts, a different selective decontamination regimen being tested in each but the same control group being used. In all tables and figures the total number of trials is 23, this last trial being listed as Verhaegen 1[10] (comparing polymyxin, tobramycin, and amphotericin B plus systemic cefotaxime *v* no treatment) and Verhaegen 2[10] (comparing ofloxacin plus amphotericin B *v* no treatment) (table I). There was great variability among the antibiotic protocols used in different studies. Only three regimens were tested in more than one trial, one regimen (polymyxin, tobramycin, amphotericin B, and systemic cefotaxime) being tested in six of the 23 studies.

EFFECTS ON RESPIRATORY TRACT INFECTIONS

The protective effect of selective decontamination on respiratory tract infections was by far the most common end point. The odds ratio was lower than 1·0 in all trials and reached conventional statistical significance ($p<0·05$) in 17 of 22. Analysis of the effect of selective decontamination on respiratory tract infections was based on 3836 patients and 826 events (in 260 treated patients and 566 controls) and suggested a significant 64% reduction in the relative odds of developing an infection (odds ratio 0·37; 95% confidence interval 0·31 to 0·43) when patients treated by selective decontamination were compared with untreated controls (fig 1). This effect was consistent across all subgroups (fig 2). The number of patients who would need to be treated to prevent one respiratory tract infection was six (range five to nine), and these estimates seemed to be fairly stable for baseline values of respiratory tract infections ranging from 20% to 60% (table III). As expected, owing to the large variation in treatment across trials the value of the heterogeneity test for the overall comparison was significant ($\chi^2=61·5$, df=21; $p<0·001$).

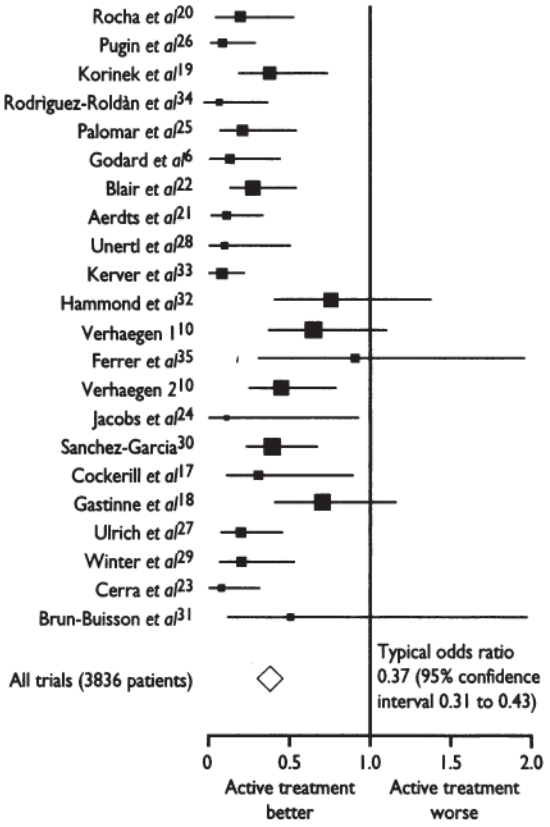

FIG 1—*Overall effect of selective decontamination of the digestive tract on respiratory tract infections*

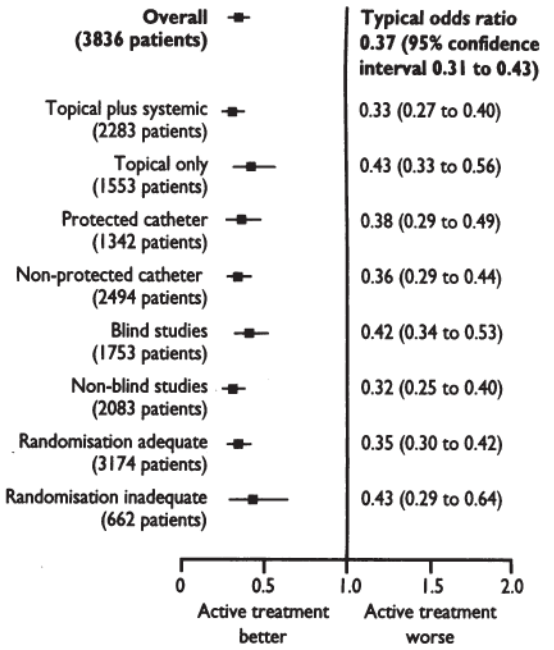

FIG 2—*Results of subgroup analyses of effects on respiratory tract infection*

TABLE III—*Numbers of patients needed to be treated to prevent one respiratory tract infection and one death expressed as a function of different baseline risks*

Baseline risk (%)	Patients needed to be treated to prevent: One respiratory tract infection (No (range))	One death (No (range))
10	16 (15-17)	52 (32-395)
20	8 (7-9)	30 (18-222)
30	6 (5-7)	23 (13-161)
40	5 (4-6)	19 (11-140)
50	4 (3-5)	18 (10-131)
60	4 (3-5)	18 (10-136)

EFFECT ON OVERALL MORTALITY

Pooled analysis of available trials yielded less clear cut results (table IV). The odds ratio was lower than 1·0 in 14 trials and reached borderline significance ($p=0·006$) in three.[20 24 27] No trial showed a significant or borderline harmful effect of selective decontamination. The overall mortality analysis, based on 4142 patients and 1160 deaths (553 among treated patients, 607 among controls), showed no significant difference in the relative odds of death when patients treated by selective decontamination were compared with untreated controls (odds ratio 0·90; 95% confidence interval 0·79 to 1·04) (fig 3). Results of subgroup analysis (fig 4) of 2450 patients suggested that for mortality the most promising results came from trials in which the combined topical and systemic treatment was used. In this subgroup a significant reduction of 20% in the odds of death occurred (odds ratio 0·80; 0·67 to 0·97), corresponding to 23 patients needing treatment to prevent one death (range 13-139). These estimates were fairly stable for baseline values of mortality ranging from 30% to 60% (table III).

No differences emerged with the design of the study (that is, double blind or not) or the quality of the randomisation process. The test for heterogeneity between odds ratios for the overall mortality analysis yielded a non-significant result ($\chi^2=17·9$, df=22; $p=0·7$).

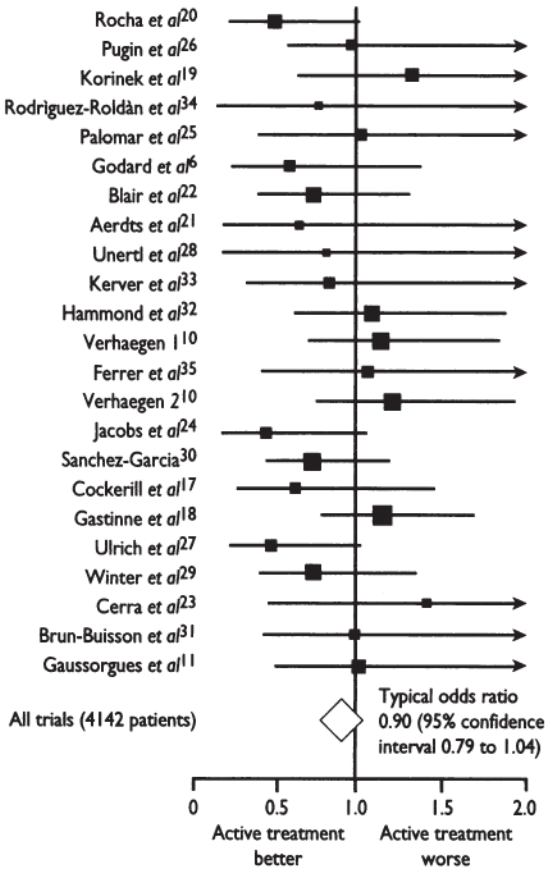

FIG 3—*Overall effect of selective decontamination of the digestive tract on mortality*

SENSITIVITY ANALYSIS

Publication bias is unlikely to have affected the validity of our conclusions for at least three reasons: (*a*) our search detected most if not all published trials and also some unpublished studies; (*b*) most trial results were not statistically significant on their own, so making systematic result dependent publication extremely unlikely; (*c*) even if one or more negative studies remained undetected we estimate that they would need to have contained at least 20 000 and 2000 patients to change our conclusions on respiratory tract infections and morality respectively.[36] Different decisions about eligibility would not have changed our results: had we included the three trials[7-9] excluded by design from this meta-analysis there would have been no major effect on the results. The overall odds ratio for respiratory tract infections would have been 0·37 (95% confidence interval 0·32 to 0·43) and for overall mortality 0·84 (0·74 to 0·97). Similarly, results for overall and subgroup analyses obtained with the DerSimonian-Laird method[13] gave similar p values for the difference between treated and control groups in terms of both infections and mortality (results available on request).

TABLE IV—*Mortality results of randomised clinical trials included in meta-analysis*

Reference	% Mortality in controls	Patients given active treatment: No in group	Patients given active treatment: No of deaths	Controls: No in group	Controls: No of deaths	Odds ratio (95% confidence interval)
Rocha *et al*[20]	52	74	27	77	40	0·54 (0·28 to 1·02)
Pugin *et al*[26]	27	38	10	41	11	0·97 (0·36 to 2·63)
Korinek *et al*[19]	18	96	22	95	17	1·36 (0·67 to 2·74)
Rodriguez-Roldan[34]	41	14	5	17	7	0·80 (0·19 to 3·34)
Palomar *et al*[25]	29	48	14	49	14	1·03 (0·43 to 2·47)
Godard *et al*[6]	18	101	12	84	15	0·62 (0·27 to 1·41)
Blair *et al*[22]	19	161	24	170	32	0·76 (0·43 to 1·34)
Aerdts *et al*[21]	20	28	4	60	12	0·68 (0·22 to 2·17)
Unertl *et al*[28]	30	19	5	20	6	0·84 (0·21 to 3·32)
Kerver *et al*[33]	32	49	14	47	15	0·85 (0·36 to 2·03)
Hammond *et al*[32]	19	162	34	160	31	1·10 (0·64 to 1·90)
Verhaegen 1[10]	18	220	45	220	40	1·16 (0·72 to 1·86)
Ferrer *et al*[35]	28	51	15	50	14	1·07 (0·45 to 2·52)
Verhaegen 2[10]	18	220	47	220	40	1·22 (0·76 to 1·95)
Jacobs *et al*[24]	50	45	14	46	23	0·46 (0·20 to 1·06)
Sanchez-Garcia[30]	46	131	51	140	65	0·74 (0·46 to 1·19)
Cockerill *et al*[17]	21	75	11	75	16	0·64 (0·28 to 1·46)
Gastinne *et al*[18]	36	220	88	225	82	1·16 (0·79 to 1·70)
Ulrich *et al*[27]	58	55	22	57	33	0·49 (0·24 to 1·03)
Winter *et al*[29]	43	91	33	92	40	0·74 (0·41 to 1·34)
Cerra *et al*[23]	43	25	13	23	10	1·40 (0·46 to 4·29)
Brun-Buisson *et al*[31]	22	65	14	68	15	0·97 (0·43 to 2·20)
Gaussorgues *et al*[11]	49	59	29	59	29	1·00 (0·49 to 2·05)

Discussion

CONTRIBUTION OF THIS META-ANALYSIS

The concept of selective decontamination, first applied by Stoutenbeek *et al* to patients in intensive care units,[1] has received widespread attention. In some instances interest was created by the initial results of reduction of infection in trauma patients.[16] Others were concerned that this unusual use of antimicrobials might select resistant micro-organisms.[37] In fact, the original selective decontamination concept of preventive use of oral non-absorbable antimicrobials combined with systemic cefotaxime for at least four days represented a profound shift in traditional infection control policy based on restricted use of narrow spectrum antibiotics only if infection, not colonisation, occurred.[38]

Many studies have assessed the value of selective decontamination but most suffer from conceptual and methodological problems.[3,4] The ideal study should include (*a*) enrolment of a clinically homogeneous group of patients, (*b*) the use of a well defined treatment regimen, (*c*) stringent criteria for defining infections, and (*d*) compliance with accepted principles of study design (that is, double blind schemes of allocation and proper diagnostic measurements). As shown in tables I and II many of the studies we evaluated lacked one or more of these characteristics. Moreover, variations in patient mix both within and between studies prevented scrutiny of specific subgroups who may particularly benefit from treatment.

There is little doubt that selective decontamination as an overall treatment strategy reduces respiratory tract infections, by far the most common and serious infections in intensive care units. However, the variation in prescribed antibiotics and patient mix in individual studies was so large that it may be difficult for a clinician to decide what to do. Nevertheless, we cannot ignore the remarkable consistency in the direction of treatment effect, which held true regardless of the type of treatment, criteria for outcome ascertainment, and study design (fig 2).

The question now is whether selective decontamination affects mortality in a way that is both clinically

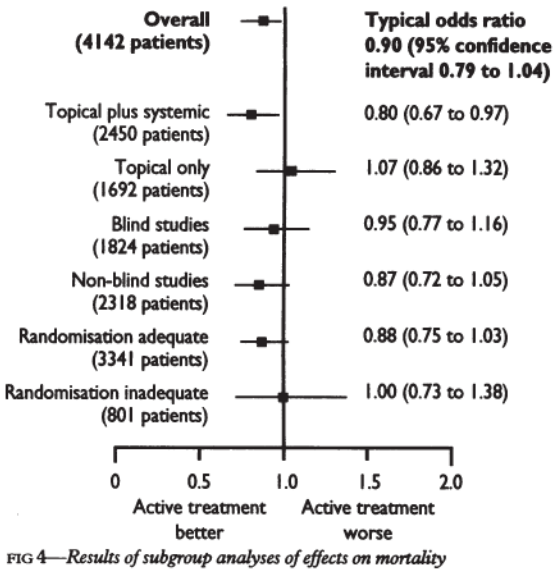

FIG 4—*Results of subgroup analyses of effects on mortality*

relevant for physicians and worth while for public health. Our meta-analysis provides new insights on the effect of selective decontamination on mortality and represents the reference point against which any claim of efficacy should be judged. Thus it allows us to set realistic expectations of the effect of selective decontamination on mortality when it is applied to heterogeneous patient populations such as those studied so far.

We now know that the mean frequency of respiratory tract infections in selective decontamination trials is around 30%, that selective decontamination can reduce respiratory tract infections by around 60%, and that baseline mortality among untreated patients in selective decontamination trials is between 30% and 35%. Given these figures, an estimate of likely benefit of selective decontamination might be around 10-20% and could reliably be detected (with conventional levels of type I and type II errors) only if at least 2000 patients were randomised between selective decontamination and no treatment or placebo groups. This is important because two reports of individual trials enrolling a few hundred patients[18 32] and the first meta-analysis[2] based on only 400 patients concluded with unjustified confidence that selective decontamination is unlikely to affect mortality. It is also of interest that with about 2450 patients in the topical plus systemic subgroup we found a reduction in mortality of this magnitude.

The infection-mortality relation is important. According to our multiple regression analysis there is a significant association between respiratory tract infection and mortality (overall estimate $\beta=0{\cdot}141$ (SE=0·041); p=0·003). However, the predicted absolute reduction in death rates given an overall relative reduction in odds of respiratory tract infection of 63% (that is, the value of the common reduction in odds of infections) ranges from 2% to 3% and the predicted relative reduction in odds of death ranges from 5% to 10% (table V). The weak association between reduction of infection and reduction in mortality will not surprise those who believe that selective decontamination is not worth while; in their view most intensive care unit patients die with but not of infection. This may be the case, especially for patients classified as "medical," and might explain the relative dissonance between the effect of selective decontamination on infection and mortality in some studies. However, those who believe that selective decontamination can be beneficial will assume that our effect detected from within a mix of heterogeneous studies will be greater when applied to appropriate patients, thus avoiding the dilution of treatment likely to have occurred in these studies.

Results of subgroup analyses, even if planned beforehand, should always be interpreted with caution. With the exception of the one comparing trials in which the combined topical and systemic treatment was used with that where only the topical regimen was administered other subgroup analyses did not provide any meaningful insight. On the contrary, they tended to make the interpretation more complicated. When we grouped trials on the basis of different proportions of medical, surgical, and trauma patients we found inconsistent and somewhat conflicting results which depended on the cut off points chosen. As our unit of analysis was the trials (not the patients) it was impossible to separate the relative contribution of treatment and patient mix to the overall effect of selective decontamination. Such a limitation can be overcome only by a meta-analysis based on individual patient data.[39] This might enable a group of patients who would benefit from selective decontamination to be identified. For example, in patients who were not infected when entered into the trials (that is, trauma patients) the parenteral antibiotic component might have prevented primary endogenous infections. If so, this together with the topical antimicrobials may have lowered the risk of secondary endogenous infections known to be responsible for substantial mortality.[16]

TABLE V—*Estimates of predicted for different baseline death rates, given 63% reduction in odds of respiratory tract infection attributable to selective decontamination of the digestive tract according to meta-analysis*

Baseline death rate (%)	Predicted death rate (%)	90% Confidence interval (%)
60	57	55 to 58
50	47	45 to 48
40	37	35 to 38
30	27	26 to 29
20	18	17 to 19
10	9	8 to 10

OPEN QUESTIONS

Given the methodology adopted in most trials, there are some important issues that we could not address properly. Mortality as the end point used in our analysis was unqualified; no information on cause specific or underlying related comorbidity was available. This together with the lack of stratification by patient mix prevents more meaningful conclusions. Subgroup analyses were not possible for all the open questions posed at the recent consensus conference,[4] including which patient subgroups will benefit most. Even the apparent superiority of combined systemic and topical selective decontamination over topical treatment alone should be interpreted cautiously, as we could not simultaneously control for the possible imbalances in patient mix between the two types of trials. The role of systemic antibiotic alone could not be evaluated: in only two trials[32 35] the same systemic antibiotic prophylaxis was given to all patients, and consequently we were unable to determine the relative contribution of the two components to the effect of the combination. Finally, the problem of safety in terms of resistance could not be examined, given that this information was lacking in most trials.

METHODOLOGICAL CONSIDERATIONS

Comment is needed on the statistical method used to combine data across trials and measure treatment benefits. The odds ratio is often used an an approximation of the relative risk in case referent studies. It is also a valid measure of treatment effect in clinical trials. The odds ratio has a distinct statistical advantage over the relative risk in terms of its sampling distribution and suitability for modelling and has become the preferred statistic for pooling data across different trials in the form of meta-analysis.[40]

The major limitation of the odds ratio is its relative insensitivity to the magnitude of risk without treatment. To overcome this problem the "number of patients needing treatment" has been proposed as a measure able to relate treatment burden to therapeutic yields in a clinically relevant manner.[14] This has the same advantage over the relative risk or the odds ratios of the absolute risk reduction in that it expresses efficacy in a manner that incorporates both the baseline risk without treatment and the risk reduction with treatment. If the event rate in the control group is high even a smaller relative risk reduction will produce a low number to be treated indicative of a favourable yields to burden ratio. Conversely, if the event rate in the control group is low the risk reduction must be large in order to produce a low number of patients needed to be treated. As mentioned above, we calculated these numbers with reference to the value of the common odds ratios. When we consider the heterogeneity of case mix and the above mentioned possibility of a dilution of treatment effect owing to the inclusion of

Clinical implications

- Around half of patients who need ventilation in intensive care develop respiratory tract infections
- Respiratory tract infections are thought to be responsible for some excess mortality in intensive care patients
- Selective decontamination of the digestive tract reduces the incidence of respiratory tract infections by 63%
- A full protocol including parenteral and topical antimicrobials may reduce mortality by around 20%, though present evidence does not permit firm conclusions
- The association between respiratory tract infection and mortality seems weak in the heterogeneous populations studied to date

patients with severe underlying diseases (likely to die even if infections are prevented) the lower limit of the range of estimates is probably more realistic than the upper.

Conclusions

This meta-analysis, although informative, should be seen as an intermediate step in the evolution of selective decontamination. The international collaboration, a very important byproduct, will now pursue a more refined meta-analysis based on individual patient data. For those who believe that the organisation of new trials is the necessary next step this meta-analysis indicates what the sample size (1500-2000 patients) should be of one or more studies properly designed with mortality as the main end point. Two possible strategies should be considered: a single large international study or, more realistically, a series of national, smaller scale prospectively coordinated trials.

What has been achieved should be seen as a direct outcome of the European consensus conference.[4] Without that organisational effort it would have been impossible to undertake such a large international collaboration. This is important from a research policy viewpoint, as there is often scepticism about the true value of consensus conferences. If anything, this study suggests that the idea of worldwide collaborative meta-analyses as an essential component of consensus conferences may broaden their impact on research policies well beyond the traditional production and diffusion of recommendations.[41]

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Termination of pregnancy with reduced doses of mifepristone

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Abstract

***Objectives*—To compare the abortifacient efficacy and side effects of three doses of the antiprogestin mifepristone plus prostaglandin for termination of early pregnancy.**

***Design*—Randomised, double blind multicentre trial.**

***Setting*—11 departments of obstetrics and gynaecology and of family planning, mostly in university hospitals, in seven countries.**

***Subjects*—1182 women with an early pregnancy (menstrual delay of 7-28 days) requesting abortion.**

***Interventions*—Single doses of 200 mg, 400 mg, or 600 mg mifepristone followed, 48 hours later, by vaginal pessary of 1 mg of the prostaglandin E_1 analogue gemeprost.**

***Main outcome measures*—Outcome of treatment; duration and subjective amount of menstrual bleeding; side effects and complications; and concentrations of haemoglobin.**

***Results*—Outcome was similar with the three doses of mifepristone. Of the 1151 women with known outcome, 95·5% had a complete abortion (364 (93·8%) of those given 200 mg mifepristone, 368 (94·1%) of those given 400 mg, and 367 (94·3%) of those given 600 mg), 3·7% had an incomplete abortion (14 (3·6%), 15 (3·8%), and 14 (3·6%)), 0·3% had a missed abortion (three (0·8%), one (0·3%), and none), and 0·4% had a continuing live pregnancy (two (0·5%), two (0·5%), and one (0·3%)). Of the 43 women who had incomplete abortion, 23 underwent emergency uterine curettage (usually for haemostatic purposes) and three of these women were given a blood transfusion. The numbers of reported complaints, bleeding patterns, and changes in blood pressure and haemoglobin concentrations were similar with the three treatments.**

***Conclusions*—For termination of early pregnancy a single dose of 200 mg mifepristone is as effective as the currently recommended dose of 600 mg when used in combination with a vaginal pessary of 1 mg gemeprost.**

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Introduction

The antiprogestin mifepristone (RU 486; 11β-[p-(dimethylamino)-phenyl]-17β-hydroxy-17-[1-propynyl]estra-4,9-dien-3-one) has been registered for termination of early pregnancy in France and China since September 1988, in Great Britain since July 1991, and in Sweden since September 1992. In France and China mifepristone can be used for inducing abortion in pregnancies of up to seven weeks of amenorrhoea, while in Britain and Sweden it can be used in pregnancies of up to nine weeks of amenorrhoea. In all four countries the recommended treatment is a single dose of 600 mg mifepristone (three tablets of 200 mg) followed 36-48 hours later by a suitable prostaglandin analogue with uterotonic activity (such as a vaginal suppository of gemeprost or oral tablets of misoprostol), and this combination gives complete abortion in 95-96% of cases.[1] In the largest series reported to date efficacy was 95·3% among 15 709 women treated in France with vaginal gemeprost or intramuscular sulprostone as the prostaglandin.[2] The failures consisted of persisting pregnancies (1·2%), incomplete expulsion (2·8%), and women requiring a haemostatic surgical procedure (0·7%).

Several studies conducted on the pharmacokinetics of orally administered mifepristone indicate that concentrations of the antiprogestin in the blood do not increase proportionally with increasing oral doses.[3] This is probably because in humans mifepristone is bound to α_1 acid glycoprotein, which acts as a low affinity carrier protein. The carrying capacity of α_1 acid glycoprotein is limited so that plasma levels of mifepristone correlate with the concentration of this protein rather than the administered dose.[4] From these studies it seemed likely that the percentage of successful abortions achieved by a single dose of 600 mg mifepristone could be obtained with smaller doses of the antiprogestin. Support for this assumption is provided by studies conducted under the auspices of the World Health Organisation,[5,6] including a recent randomised multicentre trial in which five 25 mg doses of mifepristone given at 12 hour intervals were shown to be as effective as the recommended single dose of 600 mg.[7] Rodger and Baird administered single doses of 600 mg, 500 mg, and 400 mg of mifepristone and reported rates of complete abortion of 100%, 97%, and 90% respectively.[8] The number of women in each group was too small, however, to assess if the apparent downward trend was statistically significant.

The purpose of the present randomised, double