Medical and psychosocial effects of early discharge after surgery for breast cancer: randomised trial

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Abstract

Objective: To assess the medical and psychosocial effects of early hospital discharge after surgery for breast cancer on complication rate, patient satisfaction, and psychosocial outcomes.
Design: Randomised trial comparing discharge from hospital 4 days after surgery (with drain in situ) with discharge after drain removal (mean 9 days in hospital). Psychosocial measurements performed before surgery and 1 and 4 months after.
Setting: General hospital and cancer clinic in Rotterdam with a socioeconomically diverse population.
Subjects: 125 women with operable breast cancer.
Main outcome measures: Incidence of complications after surgery for breast cancer, patient satisfaction with treatment, and psychosocial effects of short stay or long stay in hospital.
Results: Patient satisfaction with the short stay in hospital was high; only 4% (2/56 at 1 month after surgery and 2/52 at 4 months after surgery) of patients indicated that they would have preferred a longer stay. There were no significant differences in duration of drainage from the axilla between the short stay and long stay groups (median 8 *v* 9 days respectively, P = 0.45) or the incidence of wound complications (10 patients *v* 9 patients). The median number of seroma aspirations per patient was higher for the long stay group (1 *v* 3.5, P = 0.04). Leakage along the drain occurred more frequently in short stay patients (21 *v* 10 patients, P = 0.04). The two groups did not differ in scores for psychosocial problems (uncertainty, anxiety, loneliness, disturbed sleep, loss of control, threat to self esteem), physical or psychological complaints, or in the coping strategies used. Before surgery, short stay patients scored higher on scales of depression (P = 0.03) and after surgery they were more likely to discuss their disease with their families (at 1 month P = 0.004, at 4 months P = 0.04).
Conclusions: Early discharge from hospital after surgery for breast cancer is safe and is well received by patients. Early discharge seems to enhance the opportunity for social support within the family.

Introduction

The length of time patients spend in hospital after surgical procedures has been decreasing.[1,2] Patients having surgery for breast cancer are considered especially suitable for shorter stays in hospital because recovery after surgery is usually rapid. These patients usually remain in hospital for 9 to 12 days, until the serous fluid produced by the axilla is minimal and the closed suction drain is removed.[3] Shorter hospital stays are possible if patients are discharged with their drains in situ[4] or if drains are removed early.[5] Several studies have claimed that these procedures are safe.[4–8] However, these studies have been retrospective,[6] have given little information about the selection of controls,[4,5] or have used self selected patients.[8] These factors make the results difficult to interpret.

Patient satisfaction with early discharge is reported to be high.[4,7–9] Recovery in the patient's own environment may result in better psychosocial adjustment as a result of enhanced patient comfort, control, independence, and better interaction with family members.[10] In the only study of the psychological effects of early discharge, no adverse effects were found, but patients in this study decided for themselves that they would leave hospital early.[8]

We conducted a randomised trial to compare short and long postoperative stays in hospital after surgery for breast cancer to determine the effect of early discharge on complication rate, patient satisfaction, and psychosocial outcome. We hypothesised that there would be no differences between the two interventions.

Subjects and methods

Patients

Patients were eligible for inclusion in the study if they had stage I or II breast cancer, had been referred to the Daniel den Hoed Cancer Center and Zuider hospital, and had been selected for treatment by either modified radical mastectomy or lumpectomy with axillary dissection. Patients were excluded if they had received preoperative radiotherapy or chemotherapy, were at high risk of complications (category III or higher of the American Society of Anesthesiologists classification), or were mentally incompetent; patients who had difficulties with the Dutch language or an inappropriate home situation were also excluded.

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BMJ 1998;316:1267–71

Further data are available on the internet

Between October 1993 and April 1995, 139 out of 173 (80%) women with operable breast cancer were enrolled in the study: 69 were assigned to short stay treatment and 70 to long stay treatment. Women randomised to short stay treatment were discharged on the morning of the fourth day after surgery with the axillary drain in situ. Women randomised to long stay treatment were discharged after their drain had been removed.

Of the 34 women who were not entered into the study, 22 declined to participate, 10 had an unsatisfactory home situation, and two were not asked to participate. Fourteen more women were excluded after randomisation: two long stay patients received preoperative chemotherapy, one long stay patient was treated in another hospital, one short stay patient had no malignancy, and 10 patients withdrew from the study. Reasons given for short stay patients withdrawing from the study were: questionnaires too difficult (2), refusing home care (2), dissatisfaction with randomisation outcome (1), and unknown reason (1). Reasons for long stay patients withdrawing from the study were: dissatisfaction with randomisation outcome (1), unwillingness to fill out forms (2), and unknown reason (1). Thus, the final group consisted of 125 patients: 62 short stay and 63 long stay.

Randomisation and study design

Approval from the ethics committees of both hospitals was obtained before the start of the study. Written informed consent was obtained from all patients.

A randomisation list was prepared by the statistician (PIMS) using a program for the generation of random numbers and assignment into two groups with a prespecified size of blocks. The size of the blocks (8 patients) was not known by the investigators, and no stratification was applied. The randomisation list was accessible only to the data managers of the central trial office at the Daniel den Hoed Cancer Center. The patient was informed of her diagnosis, treatment plan, and the design of the study by her surgeon. The patient's home situation was subsequently assessed by a breast cancer nurse. Surgeons telephoned the trial office to discover each eligible patient's randomisation before admission.

An early discharge protocol was developed to guarantee continuity of care. It included structured patient education provided by the breast cancer nurse and also available in written form, referral to a community health nurse, provision of an emergency telephone number, the scheduling of follow up visits, and an information letter being sent to the general practitioner. The development and implementation of this protocol have been described.[11] For women assigned to short stay treatment, drain removal was performed at home or in the outpatient clinic. For both groups drains were removed when the production of serous fluid was less than 30 ml per day or after 14 days. Nursing care of the wound and drain, and the provision of arm exercises, protheses, and psychosocial guidance were standardised for both groups.

Patients were followed up for 4 months. At admission, patients were given a daily diary, to be used for one month, and a weekly diary, to be used for the following 3 months. The length of stay in hospital was recorded in the diaries. Clinical study end points were recorded in the diaries and patients' files by the doctors and nurses.

Three questionnaires were used to assess psychosocial variables and record demographic characteristics. The first was distributed at admission and completed the same day; the second questionnaire was distributed 1 month after surgery, and the third 3 months later, during outpatient visits.

Study end points

Complications

Complications recorded included infection, necrosis, haematoma, and dehiscence. Wound infection was defined according to the standards of the Centers for Disease Control and Prevention.[12] Necrosis was defined as any visible necrosis along the edge of the wound. Blood that had collected under the skin, and that was removed by puncture or opening of the wound, was considered to be a haematoma. Drain complications were also recorded. After the drain was removed, fluid collection in the axilla that was clinically apparent was defined as seroma and removed by percutaneous aspiration.

Patient satisfaction

Patient satisfaction with the length of stay was assessed with questions about preferences for a shorter or longer stay. Patients were also asked if they would recommend short stay treatment to other patients. Satisfaction with the care provided by the community health nurse was also assessed.

Psychosocial variables

The psychosocial functioning of patients was evaluated using validated scales based on a theoretical model of coping with cancer developed by van den Borne and Pruyn.[13 14] Some specific items concerning breast cancer were added. Scale structures were made by factor analyses and were similar to those found in previous research.[14] The reliability indices of the scales, assessed for each of the three questionnaires, were evaluated using Cronbach's α.[15] Scores varied between 0.62 and 0.95 with most >0.70. Three out of 57 scores were excluded from analysis because the reliability of the scale was too low ($\alpha < 0.60$).

The following variables were measured: uncertainty,[14 16–18] state and trait anxiety,[19] object anxiety,[14 16–18] loneliness,[14 16–18] depression,[14 16–18] sleep disturbances,[14 18] feelings of loss of control,[14 16 18] self esteem,[14 16 18] and the cancer locus of control.[20] Locus of control refers to whether patients attribute the cause of their cancer to personal or situational factors. The Rotterdam symptom checklist was used to assess physical and psychosocial complaints.[21]

Coping strategies were assessed with scales constructed previously.[14] Communication about the disease in the home was evaluated with a scale that assesses the openness of discussion within the family, with the patient's partner, and with the patient's children.[17]

Statistical considerations

A primary objective in this trial was to calculate a degree of patient satisfaction in the short stay group that would be about equal to the satisfaction found in

long stay patients. We hypothesised that at 1 month after surgery, 5% of long stay patients at most would have preferred a longer stay in hospital. We also supposed that if the percentage of patients satisfied with their stay in hospital was equal the upper 95% confidence limit for the difference in satisfaction should not exceed 10% with a probability of 80% ($\alpha = 5\%$ one tailed, $\beta = 20\%$[22]). For these specifications $2 \times 57 = 114$ patients were necessary. To allow for withdrawals we decided to randomly allocate interventions to 140-150 patients.

For the 125 patients who were studied the power for comparing several outcomes can be calculated (all comparisons with $\alpha = 0.05$). The statistical power was 99% (SD 400 ml within groups) for detecting a difference of 300 ml in total volume of axillary drainage between the groups. A difference between groups in the duration of axillary drainage of 1.5 days was detectable with a power of 80% (SD 3 days within groups). The sample size was inadequate to detect small but clinically significant wound complications (5%, power about 50%).

Data analysis

Psychosocial variables were analysed with the SPSS package. All other analyses were performed using STATA release 5.0 (StatCorp, College Station, TX). The χ^2 test was used to compare data between categories without correction for continuity. Fisher's test of exact probability was applied in 2×2 tables with small expected numbers. Student's *t* test was used to analyse continuous variables in the psychosocial part of the study. The Mann-Whitney U test was used to compare data on drainage between the two groups. Significance was defined as $P < 0.05$.

Results

The two groups were comparable in tumour stage, type of treatment, age, marital status, family income, and educational level (data available on the internet at www.bmj.com). Women in the short stay group were in hospital a median of 4 days (mean 4.1 including day of discharge, range 3-5); women in the long stay group had a median length of stay of 9 days (mean 9.0 including day of discharge, range 4-14).

Complications

There were no significant differences between short stay and long stay patients in drainage volume or duration of drainage, but the mean number of aspirations required per patient was higher in the long stay group ($P = 0.04$) (table 1). Clinically significant wound infection occurred in eight patients in the short stay group and in seven patients in the long stay group; all were treated with antibiotics. One short stay and two long stay patients also required abscess drainage. Two short stay patients were readmitted for removal of a persistent haematoma. Leakage of drainage fluid alongside the drain occurred more often in the short stay group (in 21 *v* 10 patients, $P = 0.04$). One short stay patient died of unsuspected distant metastases during the study.

Patient satisfaction

Table 2 shows patients' satisfaction with their length of stay. Most of the women in the short stay group indicated that they would recommend early discharge to other patients, as did 37% of the long stay patients at 1 month and 42% of long stay patients at 4 months, despite the fact that they had no experience of early discharge (table 2).

Evaluation of the nursing care provided at home showed that 42 out of 45 (93%) short stay patients were satisfied that they had received enough attention and that 30 out of 42 (71%) felt as secure at home as in hospital.

Psychosocial variables

There was no difference between the two groups in scores on scales measuring uncertainty, anxiety, loneliness, disturbed sleep, loss of control, or threats to self esteem. Before surgery short stay patients scored higher than long stay patients on scales measuring depression (score 10.3 *v* 8.9, $P = 0.03$; minimum score 6, maximum score 24).[14 18] This difference disappeared after surgery. There were no differences in physical or

Table 1 Complications among patients after surgery for breast cancer according to length of stay in hospital

	Short stay (n=61)*	Long stay (n=59)†	P value
Drainage			
Median (range) total volume (ml):			
From axillary drain	515 (400-3000)	685 (30-2130)	0.19
From drain in breast wound	175 (5-885)	80 (10-1070)	0.51
Duration (days):			
From axillary drain	8 (1-15)	9 (2-14)	0.45
From drain in breast wound	3 (1-12)	2 (1-9)	0.27
Aspiration			
No (%) of patients who had aspiration	10 (16)	8 (14)	0.80
Median No (range) aspirations per patient	1 (1-3)	3.5 (1-7)	0.04
Median (range) total volume aspirated (ml)	105 (5-650)	400 (150-880)	0.01
Wound complications			
No (%) of patients with:			
Haematoma	2 (3)	1 (2)	1.00
Necrosis	0	1 (2)	0.49
Infection	8 (13)	7 (12)	1.00
Dehiscence	1 (2)	1 (2)	1.00
Any type of wound complication	10 (16)	9 (15)	1.00
Drainage complications			
No (%) of patients with:			
Obstruction	20 (33)	15 (25)	0.42
Loss of vacuum	24 (39)	16 (27)	0.18
Leakage	21 (34)	10 (17)	0.04
Loss of drain	5 (8)	2 (3)	0.44
Any type of drain complication	38 (62)	27 (46)	0.10

*Discharged 4 days after surgery.
†Discharged after drain removal (median 9 days after surgery).

Table 2 Patient satisfaction with short stay or long stay in hospital after surgery for breast cancer. Values are numbers (percentages) of patients

	Short stay (n=62)*	Long stay (n=63)†	Mean difference (%) (95% CI)	P value
Patient would have preferred longer hospital stay:				
1 month after surgery	2/56 (4)	7/52 (14)	–10 (–20 to 0.6)	0.08
4 months after surgery	2/52 (4)	4/44 (9)	–5 (–15 to 5)	0.41
Patient would have preferred shorter hospital stay:				
1 month after surgery	8/55 (15)	16/53 (30)	–16 (–31 to –0.2)	0.05
4 months after surgery	7/51 (14)	15/46 (33)	–19 (–35 to –2)	0.03
Patient would recommend short stay to other patients:				
1 month after surgery	51/55 (93)	17/46 (37)	67 (40 to 71)	<0.001
4 months after surgery	50/52 (96)	19/45 (42)	54 (39 to 69)	<0.001

*Discharged 4 days after surgery.
†Discharged after drain removal (median 9 days after surgery).

psychological complaints, as measured by the Rotterdam symptom checklist, or in coping strategies used.

A shorter stay in hospital seemed to influence the extent to which the disease could be discussed within the patient's family. Before surgery there were no differences between the two groups, but at 1 and 4 months after surgery short stay patients were more likely to discuss their disease with their family (score 1 month after surgery 23.2 *v* 21.5, P = 0.004; score 4 months after surgery 23.5 *v* 21.9, P = 0.04; minimum score 7, maximum score 28).[17]

Discussion

This paper presents the results of a randomised trial evaluating the medical and psychosocial effects of short and long hospital stays after surgery for breast cancer. Comparison between the two groups found no significant differences in wound complications, duration of drainage, patient satisfaction, or psychosocial outcomes. In fact there seemed to be an increase in social support within the family among patients in the short stay group.

The high scores for treatment satisfaction among the short stay patients are in accordance with the results of other studies.[4 7–9] Short stay patients were highly satisfied with their community based nursing care. Support from a specialist nurse considerably reduces psychological morbidity.[23] In the home, community nurses take on the role of breast cancer nurses. We considered it important to continue this care after a short stay in hospital.

There were no adverse effects of a shorter stay in hospital on the rate of complications or the incidence of seroma formation. However, the number of patients in this study was too small to detect a difference of 5% in rates of wound complication; a sample size of more than 800 patients would have been necessary to do this. This is not feasible in this type of research. We decided to discharge patients with drains in situ and to remove drains when production of serous fluid was minimal. This practice leads to a low incidence of seroma aspiration[24 25] and fewer outpatient visits. The alternatives are to remove the drain after a fixed number of days regardless of fluid production[5 26 27] or not to place a drain in the axilla.[27 28] Seromas have been reported in as few as 10% of patients after early drain removal,[5] but others have reported seromas in as many as 40%[3] and 73%[27] of patients, though these did not affect the risk of infection. The length of time the drain was in situ was equal for both groups and is consistent with previous findings from our own clinic.[29]

Before surgery the patients randomly allocated to a short hospital stay scored higher on scales measuring depression than did those randomly allocated to a long stay. The uncertainty about the experimental treatment after surgery may have contributed to these feelings. A shorter stay in hospital seems to make it easier for a patient to discuss the disease with her family; however, the data should be interpreted carefully as this was the only significant difference in psychosocial variables found between the two groups after surgery. The positive effects of social support in psychosocial adjustment for patients with breast cancer have been discussed.[30 31] The ability to express emotions within the family is associated with less mood disturbance.[32] In our study there was no decrease in mood disturbance in the short stay group; our follow up was 4 months, but the positive effects may have become evident later.

Key messages

- Early discharge from hospital after breast cancer surgery does not lead to an increase in the incidence of wound infection or seroma formation
- A short stay in hospital, with support from community nurses on the patient's return home, is acceptable to patients
- Psychosocial rehabilitation is not influenced by early discharge
- Recovery in the family environment may facilitate discussion of the illness
- Patients recovering from surgery for breast cancer need not spend more than three days in hospital provided that they are in good physical condition and there is adequate nursing support available in the community

In the United States patients having surgery for breast cancer often stay in hospital only one or two days[4 10] or are treated as outpatients.[6] These changes were initially financially motivated but have gradually become accepted by surgeons.[10] In most European hospitals, however, these types of early discharge policies are not the normal practice. Our randomised study has proved that shortening the length of time a patient spends in hospital after surgery for breast cancer has no adverse effects. It would be interesting to evaluate the American practice in a European setting, paying special attention to the psychosocial effects of this policy, especially since no data have been available on these aspects until now.

We thank all participants who enrolled in the trial and those who contributed and are not mentioned here. We thank P Stringer and A M M Eggermont for reading the manuscript.

Contributors: JB contributed to the design of the protocol, performed the literature search, participated in the execution of the study, collected and analysed the data, wrote the paper, and is guarantor for the study. AMEAvW coordinated the study in both hospitals, discussed core ideas, studied the literature, participated in data collection and analysis, and contributed to writing the paper. JFAP initiated and coordinated the formulation of the study hypothesis, designed the protocol, contributed to the interpretation of findings, and edited the paper. PIMS contributed to the design of the protocol, coordinated randomisation procedures, and performed the statistical analysis of the data. MAP contributed to data collection and editing the paper. TW had the original idea for the study, initiated the research, participated in the execution of the study, and edited the paper.

Funding: Ministry of Welfare, Health, and Sports, the Netherlands.

Conflict of interest: None.

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(Accepted 22 October 1997)

Resolution of peanut allergy: case-control study

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Abstract

Objectives: To determine whether there are any differences between children who remain mildly or moderately allergic to peanut and children with similar histories but a negative reaction on challenge with peanut.
Design: Case-controls matched for age and sex.
Setting: Children's day wards in two teaching hospitals.
Intervention: Open food challenge with peanut.
Subjects: 15 children with resolved peanut allergy (resolvers) and 15 with persistent allergy (persisters).
Main outcome measure: Reaction on challenge with peanut, serum total and peanut specific IgE concentrations.
Results: The groups had a similar median age at first reaction to peanut (11 months, range 5-38) and similar symptoms. Allergy to other foods was less common in resolvers (2/15) than persisters (9/15) ($P = 0.02$). On skin prick testing with peanut all 13 resolvers tested but only 3/14 persisters had a weal of < 6 mm ($P < 0.0001$). Total and peanut specific IgE concentrations did not differ much between the groups.
Conclusion: Appropriately trained clinicians must be prepared to challenge preschool children with peanut as some will be tolerant despite a history of reactions to peanut and a positive skin prick test with peanut. Preschool children whose apparent peanut allergy is refuted by food challenge show allergy to other foods less often than those in whom peanut allergy persists. The size of weal on skin prick testing to peanut predicts reactivity but not severity on peanut challenge.

Introduction

The diagnosis of peanut allergy has important consequences for patients and their families. They are told that allergic reactions occur after frequent exposure, that reactions are often severe, and that the allergy persists indefinitely.[1]

The dietary habits of the British population have changed, with vegetarianism becoming more popular and the use of peanut butter apparently increasing as a snack food for children. These changes may be linked to a recently observed decrease in the age of onset of peanut allergy.[2 3]

In longitudinal studies allergies to cows' milk and egg usually resolve early in life; 85% of children with cows' milk allergy in the first two years of life are tolerant of milk by 3 years of age[4] and up to 80% of infants with egg allergy are tolerant of egg by 5 years of age.[5 6] There are no similar longitudinal studies of infants with peanut allergy, and the advice that peanut allergy persists is based on a study of older children.[1] The age differences between children with cows' milk or egg allergy and those with peanut allergy may account for the different rates of resolution. Follow up of a population based group of Danish children with cows' milk

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BMJ 1998;316:1271–5

allergy suggests resolution of the allergy is unusual if it has not occurred by 5 years of age.[7]

In our clinical practice we have observed apparent resolution of peanut allergy in several children affected by peanut allergy at a young age. We report the clinical features of these children and of those of age and sex matched controls who have remained allergic to peanut.

Subjects and methods

We studied children who were referred to the regional paediatric acute allergy and anaphylaxis clinic in Southampton (155 children) or to the paediatric allergy clinic in South Manchester (75 children) for evaluation of suspected peanut allergy between April 1995 and December 1996.

Identification of cases and controls

A child was considered to have been allergic to peanuts if the constellation of typical symptoms had been observed after an unequivocal exposure to peanuts in the 3 years before presentation. Children who had undergone peanut challenge were identified by the relevant author in each hospital. Patients were selected for challenges according to the clinical needs of the patient in each case. Some children were challenged because they had had negative results on skin prick testing with peanut despite a convincing history or because their dietary history suggested that an exposure to peanut had been uneventful. Children with life threatening reactions to peanut were not considered for challenge irrespective of the time since the last exposure. Controls and cases with positive results on skin prick testing were challenged either because the last reaction had been a long time before or because of parental request. Parents often wanted to know whether their child was allergic to peanuts before school entry—anecdotally, a time of great anxiety for parents of children allergic to certain foods. The challenges were all open food ones[8] using peanut butter or peanuts according to the age of the subject. Every challenge was performed in hospital.[9]

A child was considered to be no longer allergic to peanuts if two criteria were met: (a), they had a clear history of a reaction to peanut and (b), a formal challenge with peanuts or peanut butter gave negative results. We called these children resolvers.

Matching for age and sex was undertaken to control for effects that would be evident when comparing preschool children with peanut allergy and comparatively few other allergies (either to foods or inhalant allergens) with older children sensitised to a wider range of allergens.[2] For each case one control (persister) was identified from children who had a positive skin prick test and a positive challenge with peanut.

Skin prick testing

Skin prick testing was carried out at the initial hospital visit using a 1:20 (wt/vol) solution (Soluprick, ALK, Uppsala, Sweden). A reaction was considered positive if a weal was >3 mm in diameter in the presence of a reaction to 1% histamine of at least 3 mm in diameter.

Measurement of IgE concentration

The concentration of total IgE was measured in serum using an enzyme linked immunosorbent assay system developed by each hospital. The lower limit of detection was 5 KU/ml in each hospital. The concentration of peanut specific IgE was measured using either a commercially available enzyme linked immunosorbent assay kit (Alstat, Wales) in Southampton or the Pharmacia-CAP system (Pharmacia, Uppsala, Sweden) in Manchester. The lower limit of detection of both assays was 0.35 KU/ml.

Data handling

Data were collected from hospital notes by the responsible clinician using a standard data collection form for both the cases and controls. Details of the age of onset, number of exposures, clinical features of reactions, and length of time since last exposure or reaction were noted. The presence of coexisting asthma, eczema, rhinitis, and food allergies was also determined.

Data were entered blind to patient identity using SPSS software (Windows 6.1, Chicago). Categorical data were compared using Fisher's exact χ^2 test with Yates's correction. Continuous variables were compared using either Student's t test or the Mann-Whitney U test. A P value of <0.05 was considered significant.

Results

Overall, 230 children were referred to the regional paediatric acute allergy and anaphylaxis clinic in Southampton (155 children) or to the paediatric allergy clinic in South Manchester (75 children) for evaluation of suspected peanut allergy. A total of 120 (48%, equal numbers in each unit) were challenged with peanut.[8]

Twenty two cases of resolved peanut allergy were identified but suitable controls with positive results on peanut challenge were available for only 15 (eight in Southampton and seven in Manchester). The remaining seven resolvers were excluded from further analysis. Ten of the 15 resolvers were boys. The median age of the resolvers at the time of challenge was 5 years (range 2-9 years).

Historical features—Table 1 shows the historical features of resolvers and persisters. Allergy to food other than peanuts was less common in resolvers (one child

Table 1 Children whose peanut allergy resolved and children whose allergy persisted. Values are numbers (percentages) of children unless stated otherwise

Variables	Resolvers (n=15)	Persisters (n=15)
Sex ratio (male:female)	10:5	10:5
Median age (years) at challenge (range)	5 (2-9)	5 (2-10)
Asthma, eczema, or rhinitis	8/15 (53)	13/15 (86)
At time of challenge		
Asthma	5/15 (33)	7/15 (46)
Eczema	4/15 (26)	8/15 (53)
Rhinitis	1/15 (7)	3/15 (20)
Allergy to any other food*	2/15 (13)	9/15 (60)
Cows' milk	1/15 (7)	1/15 (7)
Egg†	0	5/15 (33)
Tree nut	1/15 (7)	2/15 (13)
Soy	0	0
Median peanut specific IgE (KU/ml) (range)	0 (0-280)	6.8 (0-30)
Median total IgE (KU/ml) (range)	54 (5-4-500)	375 (49-830)

*P=0.02. †P=0.04.

was allergic to milk, fish, and tomato and another to hazelnut) than persisters (nine children) ($\chi^2 = 7.03$, $P = 0.02$).

Features of reactions to peanut are shown in table 2. The age at first reaction to peanut was similar in each group (median 11 months, range 5-38). The severity of reactions did not differ between the groups and the number of reactions was similar in each group. The time between last reaction and challenge was longer, but not significantly so, in resolvers (median 40 months, range 15-72) than persisters, as proved by challenge (12 months, range 3-72, $P = 0.10$).

Skin prick testing

The results of skin prick tests were available for 13/15 resolvers and 14/15 persisters (figure). The two resolvers who did not have skin prick tests had raised serum concentrations of peanut specific IgE of 34 and 280 IU/ml. Eight resolvers had a negative skin prick test with peanut. No persister had a negative skin prick test. None of the five resolvers with positive skin prick tests had a weal of >5 mm compared with 17/21 persisters ($\chi^2 = 20.05$, $P < 0.0001$). If a cut off value of a 6 mm weal in response to a skin prick test was chosen, the skin prick test had a positive predictive value of 100% but a negative predictive value of 80% (3/14 children with proved allergy had weals of <6 mm) of reactivity on peanut challenge.

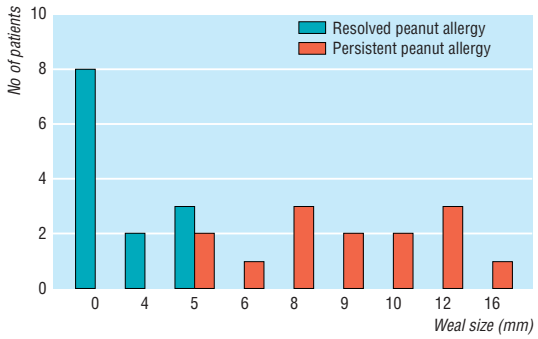
Total and peanut specific IgE concentrations

Total IgE and peanut specific IgE concentrations did not differ between the groups.

Peanut challenge

No subject with a positive challenge (persisters) needed adrenaline treatment for the reaction induced by the challenge test.

Follow up—Telephone follow up of 14 resolvers (one was lost to follow up) up to 2 years after challenge showed that only two had not eaten peanuts since the challenge. Five of the remaining 12 had eaten peanuts but not liked them. Six ate peanuts without problems but one child, who had negative results on skin prick testing, vomited after eating peanuts but did not have symptoms more typical of an allergic response; apparently, this child enjoys eating peanuts despite the vomiting. Two persisters were challenged a second time, which evoked reactions similar to the first challenge.



Results of skin prick testing for peanut in 13 children whose allergy resolved and 14 whose allergy persisted as shown by open challenge with peanut

Table 2 Features of reactions to peanut in children whose peanut allergy resolved and children whose allergy persisted. Values are numbers of children unless stated otherwise

Feature	Resolvers (n=15)	Persisters (n=15)
Median age (months) at first reaction (range)	11 (5-38)	12 (4-120)
Worst feature of severest reaction:		
Rash	3	2
Facial swelling	7	12
Tightness of throat or stridor	3	0
Wheeze	2	1
Collapse or faint	0	0
No of reactions:		
1	6	6
2	7	5
3	2	3
Uncertain	0	1
Median time (months) from last reaction to challenge (range)†	40 (15-72)	12(3-72)
Weal on skin prick testing <6 mm‡	13/13*	3/14

*Both of the resolvers who did not have skin prick tests had raised peanut specific IgE concentrations. †P=0.10. ‡P<0.0001.

Discussion

So far as we know, this case-control study is the first report of resolution of apparent peanut allergy, and it offers some reassurance to patients given a diagnosis early in life and to their families. The mechanism of resolution remains unknown.

Food challenges—Our study confirms the pivotal role of a food challenge in the diagnosis of food allergy. Many units are reluctant to undertake peanut challenges because of the risk of severe reactions. Certainly, all challenges need to be undertaken in appropriately staffed and equipped units,[8 9] and there must be compelling extra reasons to consider challenging people who have had severe reactions. In contrast, a child with positive results on skin prick testing but a doubtful history (such as reacting only to a large dose or having atypical symptoms) or a child with negative results on skin prick testing should always be offered an open challenge. Subjects who report a recent typical reaction need not be challenged. A minimum interval of 1 or 2 years after the most recent reaction is prudent.

Young children with peanut allergy—Our results suggest that preschool children with a history of mild or moderate allergic reactions to peanut who are challenged with peanut have a chance (22/120 challenges, 18%) that the challenge will be negative. The chance of negative results on challenge despite a clear reaction in the past are increased in subjects who do not have allergies to other foods at the time of challenge. Children whose peanut allergy had resolved reported a long time interval since the last reaction and had a negative or minimally positive reaction to peanut on skin prick testing. The benefits to affected children and their families are obvious if the fear of peanut allergy can be dispelled. During follow up of 14 resolvers we found that, to date, further exposures to peanuts had not resulted in allergic reactions, although aversion and continuing avoidance were common.

Limitations of study

The small sample size does not allow us to comment on the usefulness of measurement of serum total or peanut specific IgE concentrations as a predictor of reactivity in our group, but evidence suggests that

threshold concentrations of allergen specific IgE may predict reactivity on challenge.[10]

Some of the resolvers may never have had peanut allergy. Asymptomatic people may be found to be positive to peanut on skin prick testing during screening for other reasons such as in asthma clinics or population based studies.[11] Children with small reactions on skin prick testing to peanuts, tree nuts, or sesame seeds and negative results on challenge have been reported, but some of the children were identified while having skin prick tests for other reasons.[12] Clinical experience of both persisting and resolving peanut allergy suggests that the first reactions to peanut early in life are due usually to deliberate exposure in the form of a peanut butter snack. The link with peanut is usually made quickly by the parent or doctor. Until recently, referral to centres with expertise in paediatric allergy was not possible, and many children were seen in hospital clinics only several years later.

The resolvers all reported at least one reaction to peanut—that is, none was referred from other clinics because of a positive skin prick test to peanut and no history of exposure or reaction. The number of reactions reported did not distinguish resolvers from persisters. Only a challenge or uneventful definite exposure (to an adequate dose) in the community is evidence of resolution. Negative results from challenges in the community must be supported by negative results from a formal challenge in hospital before dietary restrictions and rescue drugs can be withdrawn.

A British population based study of preschool children (4 years old) found that 13 out of 981 (1.3%) had a positive skin prick test to peanut.[11] Only six (0.6%) of them had had an allergic reaction to peanut; the remaining seven (0.7%) had positive results on skin prick testing but were symptom free. The size of the weal on skin prick testing with peanut was not reported, and we suggest on the basis of our results that a proportion of both the allergic children (reporting reactions) and the symptomless children would be tolerant of peanut if tested by peanut challenge.[11]

Atopic features—Our clinical impression was that the children who were ultimately shown on challenge to have outgrown peanut allergy had fewer other signs of atopy at presentation. The prevalence of asthma, eczema, hay fever, and rhinitis was similar in resolvers and persisters. This may be because of the sample size. The relative scarcity of allergy to tree nuts in resolvers (1/15, 6.6%) and controls (7/30, 23%) compared with that in all children with peanut allergy (approximately 50%) is probably related to age, with preschool children not being exposed to tree nuts as frequently as they are to peanuts.[2 3]

Peanut avoidance—Resolvers tended to report successful avoidance of peanuts for longer than persisters, and we wonder whether people who are allergic to peanuts can really avoid them. Peanut allergy in some preschool children who had no reported symptoms for a long time may have actually resolved over time, with the children not reacting to the unavoidable exposures that are so characteristic of peanut allergy.[1 13]

Key messages

- Peanut allergy rarely resolves in older children and adults
- Skin prick testing with peanut has a high negative predictive value, but some people with positive skin tests do not react to peanut challenge
- Some preschool children with a convincing history of reaction to peanut may become tolerant of peanut. Such children have fewer other manifestations of atopy than children whose peanut allergy persists
- Paediatricians must be prepared to undertake peanut challenges or refer children to units that will undertake such challenges

Conclusion

The commonest food allergies of infancy are to egg or cows' milk. These allergies usually resolve in time.[4–6] Children in whom milk allergy persists often develop other allergies.[7] Severe allergy to peanut is more common in adults than children[13] and rarely resolves in older children or adults.[1] Our work suggests that allergy in a small proportion of young children who become sensitised to peanut early in life resolves in a similar way to allergies to egg or cows' milk in infants and preschool children.

Recent reports suggest that the presence of IgE to linear epitopes of ovomucoid predicts persistence of egg allergy into later childhood, whereas IgE to conformational epitopes is associated with resolution in the usual time scale in infancy and the preschool years.[14] More detailed identification of peanut proteins and their epitopes[15] may allow such a study of peanut allergy, previously regarded as a persistent food allergy. Our report of preschool children in whom clinical peanut allergy apparently has resolved has important implications for both research and clinical paediatric practice.

We thank all the children who underwent the peanut challenges; nurses Nikki Barker, Melanie Seabrook, Dorothy Denton, and Sandra Croft, who supervised the challenges; and Mrs Lesley Ann Gudgeon and Ms Linda Butler for their secretarial help.

Contributors: JH supervised the challenges in Southampton, initiated and co-ordinated data collations, and drafted the first paper; he will act as guarantor for the paper. SAR supervised the challenges in Manchester, contributed to the design and execution of the study, and helped write the paper. JOW was the consultant responsible for the Southampton children; he also provided input into the design and interpretation of the data, and reviewed and contributed to drafts of the paper.

Funding: None.

Conflict of interest: None.

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(Accepted 21 January 1998)

Science commentary: Why do some children grow out of peanut allergy?

Editorial
Berger and Smith

One hypothesis which may explain why some children grow out of their peanut allergy lies in the physical structure of the peanut proteins. If the protein is visualised as a string of amino acid beads scrunched up into a 3-dimensional ball there are two ways an antibody can bind to that structure. Firstly, an antibody can bind to a specific antigen by attaching itself to sequential amino acid beads in the protein. These sections of the protein are known as linear epitopes. Alternatively, an antibody binds to a section which is effectively folded up so that it not only binds to a number of amino acid beads in one part of the protein string but also to beads in other sections of the string. These antigenic binding sites are known as conformational epitopes.

Research in other food allergies suggests that children who develop tolerance to peanuts may have peanut specific IgE which binds much more to conformational peanut epitopes (which are generally more labile and easily destroyed by heat) and that children who remain reactive to peanuts have IgE which binds mostly to linear epitopes (which are very stable). As the gut matures with age more linear epitopes than conformational epitopes pass through the gut wall. So if the hypothesis is found to be true this could explain why some people continue to react to peanuts and others seemingly outgrow their allergy.

Such differences in IgE binding have already been observed in children with egg or cows' milk allergy. An interesting question is why up to 50% of children with egg or cows' milk allergy outgrow the allergy while only about 10% seem to develop tolerance to peanuts.

Abi Berger, *science editor, BMJ*

Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials

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Abstract

Objective: To determine whether antibiotic prophylaxis reduces respiratory tract infections and overall mortality in unselected critically ill adult patients.

Design: Meta-analysis of randomised controlled trials from 1984 and 1996 that compared different forms of antibiotic prophylaxis used to reduce respiratory tract infections and mortality with aggregate data and, in a subset of trials, data from individual patients.

Subjects: Unselected critically ill adult patients; 5727 patients for aggregate data meta-analysis, 4343 for confirmatory meta-analysis with data from individual patients.

Main outcome measures: Respiratory tract infections and total mortality.

Results: Two categories of eligible trials were defined: topical plus systemic antibiotics versus no treatment and topical preparation with or without a systemic antibiotic versus a systemic agent or placebo. Estimates from aggregate data meta-analysis of 16 trials (3361 patients) that tested combined treatment indicated a strong significant reduction in infection (odds ratio 0.35; 95% confidence interval 0.29 to 0.41) and total mortality (0.80; 0.69 to 0.93). With this treatment five and 23 patients would need to be treated to prevent one infection and one death, respectively. Similar analysis of 17 trials (2366 patients) that tested only topical antibiotics indicated a clear reduction in infection (0.56; 0.46 to 0.68) without a significant effect on total mortality (1.01; 0.84 to 1.22). Analysis of data from individual patients yielded similar results. No significant differences in treatment effect by major subgroups of patients emerged from the analyses.

Conclusions: This meta-analysis of 15 years of clinical research suggests that antibiotic prophylaxis with a combination of topical and systemic drugs can reduce respiratory tract infections and overall mortality in critically ill patients. This effect is significant and worth while, and it should be considered when practice guidelines are defined.

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BMJ 1998;316:1275–85

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Introduction

Nosocomial infections, especially pneumonia, are an important cause of morbidity and mortality in critically ill patients. The incidence of pneumonia in such patients ranges between 7% and 40%, and the crude mortality from ventilator associated pneumonia (VAP) may exceed 50%. Although not all deaths in patients with this form of pneumonia are directly attributable to infection, it has been shown to contribute to mortality in intensive care units independently of other factors that are also strongly associated with such deaths.[1] In a case-control study of ventilated patients an increase in mortality of 27% was attributable to ventilator associated pneumonia.[2] Considerable efforts have been made to develop and evaluate methods for reducing respiratory infections. One strategy involves the use of selective decontamination of the digestive tract (SDD). Different decontamination protocols have been used in different trials, and investigators often disagree on its most appropriate definition. Traditionally, selective decontamination of the digestive tract indicates a method designed to prevent infection by eradicating and preventing carriage of potentially pathogenic aerobic microorganisms from the oropharynx, stomach, and gut. It consists of antibiotics applied topically to the oropharynx and through a nasogastric tube. In many trials treatment with systemic antibiotics has been added in the first days after patients are admitted to prevent "early" infections.

A decontamination regimen based on oral non-absorbable antibiotics was first used in 1984 by Stoutenbeek et al in a group of patients with multiple trauma.[3] The incidence of nosocomial infections was reduced from 81% to 16% in a non-randomised comparison with a historical control group. Further studies tested the efficacy of decontamination in patients in intensive care with morbidity related to infection as the main end point. The results showed that decontamination reduced infection, but it was not clear whether there was a reduction in mortality.

Between 1991 and 1995 five different meta-analyses on the effect of antibiotic prophylaxis on infections and mortality were published.[4–8] Their results are summarised in table 1. All confirmed a significant reduction in infections, though the magnitude of the effect varied from one review to another. The estimated impact on overall mortality was less evident and generated considerable controversy on the cost effectiveness of the treatment. Only one among the five available reviews, however, suggested that a weak association between respiratory tract infections and mortality and lack of sufficient statistical power may have accounted for the limited effect on mortality.[5] The authors suggested that, given the baseline risk of death in the populations typically enrolled in existing trials, between 2000 and 3000 patients were probably needed to detect reliably a relative reduction in mortality in the 10%-20% range.[5]

We report here on an updated and refined meta-analysis made possible by the enthusiastic collaboration of most investigators in the topic. Besides updating the results by using data from randomised controlled trials published since the 1993 paper,[5] there are two main differences between this and previously published meta-analyses. The first is the way trials have been grouped to test the effectiveness of the treatment. Contrary to previous practice we have separately analysed trials that tested combinations of topical and systemic antibiotics from trials that tested the effect of topical drugs alone. The second is that information for individual patients was sought from all trials. Results from this more refined type of meta-analysis, which proved feasible in 4343/5727 (76%) patients, are reported and compared with findings from the corresponding aggregate datasets.

Table 1 Results of five published meta-analyses of randomised controlled trials on antibiotic prophylaxis for mortality and respiratory tract infection in patients in intensive care

	Point estimates (95% CI)		
End points	**All trials**	**Topical plus systemic antibiotics**	**Topical antibiotics alone**
Vandenbroucke-Grauls et al[4] (6 trials, 491 patients)			
Mortality	0.70* (0.45 to 1.09)	NA	NA
Infection	0.12* (0.08 to 0.19)	NA	NA
SDD Trialists' Group[5] (22 trials, 4142 patients)			
Mortality	0.90* (0.79 to 1.04)	0.80 (0.67 to 0.97)	1.07 (0.86 to 1.32)
Infection	0.37* (0.31 to 0.43)	0.33 (0.27 to 0.40)	0.43 (0.33 to 0.56)
Heyland et al[6] (24 trials, 3312 patients)			
Mortality	0.87† (0.79 to 0.97)	0.81 (0.71 to 0.95)	1.00 (0.83 to 1.19)
Pneumonia	0.46† (0.39 to 0.56)	0.48 (0.39 to 0.60)	0.43 (0.32 to 0.59)
Kollef et al[8] (16 trials, 2270 patients)			
Mortality	0.02‡ (–0.02 to 0.05)	NA	NA
Pneumonia	0.14‡ (0.12 to 0.17)	NA	NA
Tracheobronchitis	0.05‡ (0.02 to 0.09)	NA	NA
Hurley et al[7] (26 trials, 3768 patients)			
Mortality	0.86* (0.74 to 0.99)	NA	NA
Infection	0.35* (0.30 to 0.42)	NA	NA

NA=data not in published articles. *Odds ratio. †Relative risk. ‡Risk difference.

Patients and methods

Search strategy

We searched for randomised controlled trials published from January 1984 to December 1996. Studies were identified through Medline (MeSH keywords: "Intensive care units," "Critical care," "Antibiotic combined therapeutic use," "Antibiotics combined administration and dosage," "Respiratory tract infections prevention and control" with the keyword "SDD"). Other studies were evaluated because they were listed in previous meta-analyses. The organiser of the first European Consensus Conference on Intensive Care Medicine (held in December 1991) also provided a list of all investigators who had ever published on the topic. An additional search focused on proceedings of scientific meetings held on the subject and personal contacts were established with other known investigators. No formal inquiry was made through pharmaceutical companies.

Eligibility criteria for studies

All trials, published and unpublished, which tested the effect of antibiotic prophylaxis for the prevention of respiratory tract infections and deaths in unselected critically ill adult patients were considered. No language restriction was applied. Only randomised trials were accepted to guarantee control of selection bias. Studies that were determined on closer scrutiny not to be properly randomised (see definition below) were not included.

Studies based on specific preselected types of patients (that is, patients undergoing elective oesophageal resection, cardiac or gastric surgery, and liver transplantation or suffering from acute liver failure) were excluded from this meta-analysis. Similarly, we excluded studies in which over half the patients did not undergo mechanical ventilation for more than 48 hours. Details on the reasons for exclusion are reported in the appendix.[9–18]

We grouped eligible trials into two categories according to the type of antibiotic prophylaxis. The first group comprised studies in which a combination of systemic and topical antibiotics was compared with no prophylactic treatment.[19–34] The second comprised studies in which topical antibiotics alone were tested. In this second category two types of trials were considered together—those in which topical antibiotics were tested against an untreated group (S Jacobs, M Zuleika, personal communication)[35–44] and those in which the combination of topical plus a systemic drug was compared with a protocol based on a systemic antibiotic agent only.[45–50] Any combination of topical or systemic antibiotic (that is, type of drugs) was accepted.

Data extraction and relevant information sought

The results of the meta-analysis of aggregate data presented in table 2 are based on 33 trials; in the other tables, however, more studies and patients are shown because the two trials with three arms were split into two parts in which two different treatments were compared with the same control group.[33 49]

In a qualitative review of published studies it was recently documented that in many trials some patients had been excluded from the final analysis.[51] We therefore tried to contact all investigators to analyse the whole original population enrolled into the trials. In 25/33 trials information on all randomised patients was retrieved according to the treatment arm to which they were originally allocated, allowing an "intention to treat" analysis. This, however, proved impossible in the trials of Finch et al,[24] Rocha et al,[29] and Verwaest et al[33] for respiratory tract infections and those of Lenhart et al,[27] Georges et al,[38] Wiener et al,[44] and Laggner et al[48] for infections and mortality.

Data on key variables relevant for this review were available from published reports. For 30 studies published figures were integrated with the following

Table 2 General characteristics of randomised clinical trials included in meta-analysis. Data were aggregate or for individual patients or both. End points were respiratory tract infection or mortality or both

Study name	Type of treatment: Topical	Type of treatment: Systemic	Mean age (years)	Trauma patients (%)	Surgical patients (%)	Medical patients (%)	Type of data	End points
Abele-Horn et al[19]	Polymyxin, tobramycin, amphotericin	Cefotaxime	41.5	84	16	0	Aggregate	Both
Aerdts et al[20]	Polymyxin, norfloxacin, amphotericin	Ceftriaxone	46.7	34	26	40	Both	Both
Blair et al[21]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	47.6	40	46	14	Both	Both
Boland et al[22]	Polymyxin, tobramycin, nystatin	Ceftriaxone	33.9	100	0	0	Both	Both
Brun-Buisson et al[35]	Polymyxin, neomycin, nalidixic acid	None	59.0	2	23	75	Both	Both
Cerra et al[36]	Norfloxacin, nystatin	None	63.5	4	96	0	Aggregate	Mortality
Cockerill et al[23]	Nystatin, polymyxin, gentamicin	Ceftriaxone	65.0	34	48	18	Both	Both
Ferrer et al[45]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	61.0	20	14	66	Both	Both
Finch et al[24]	Polymyxin, gentamicin, amphotericin	Ceftriaxone	59.2	4	37	59	Both	Both
Gastinne et al[37]	Tobramycin, amphotericin, polymyxin		55.0	15	13	72	Both	Both
Gaussorgues et al[46]	Polymyxin, gentamicin, vancomycin, amphotericin	Not specified	57.0	17	0	83	Aggregate	Mortality
Georges et al[38]	Polymyxin, netilmicin, amphotericin	None	32.3	100	0	0	Both	Both
Hammond et al[47]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	43.3	31	14	55	Both	Both
Jacobs et al[25]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	51.5	18	57	25	Aggregate	Both
Jacobs and Zuleika*	Polymyxin, gentamicin, amphotericin	None	49.4	21	21	58	Both	Both
Kerver et al[26]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	55.6	28	60	12	Aggregate	Both
Korinek et al[39]	Polymyxin, tobramycin, amphotericin, vancomycin	None	45.0	50	50	0	Both	Both
Laggner et al[48]	Gentamicin, amphotericin	Not specified	53.8	2	10	88	Both	Both
Lenhart et al[27]	Polymyxin, gentamicin	Ciprofloxacin	Information not available				Aggregate	Mortality
Lingnau et al[49]	1: Polymyxin, tobramycin, amphotericin 2: Polymyxin, ciprofloxacin, amphotericin	Ciprofloxacin	38.0	100	0	0	Both	Both
Palomar et al[28]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	45.5	50	10	40	Both	Both
Pugin et al[40]	Polymyxin, vancomycin, neomicin	None	45.5	56	33	11	Both	Both
Quinio et al[41]	Polymyxin, gentamicin, amphotericin	None	34.6	98	0	2	Both	Both
Rocha et al[29]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	43.5	68	4	28	Both	Both
Rodriguez-Roldan et al[42]	Polymyxin, tobramycin/netilmicin, amphotericin	None	51.3	42	19	39	Both	Both
Sanchez-Garcia et al[30]	Polymyxin, gentamicin, amphotericin	Ceftriaxone	54.4	18	12	70	Both	Both
Stoutenbeek et al[3]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	40.4	100	0	0	Both	Both
Stoutenbeek et al[31]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	39.8	100	0	0	Both	Both
Ulrich et al[32]	Polymyxin, norfloxacin, amphotericin	Trimethoprim	62.0	16	50	34	Both	Both
Unertl et al[43]	Polymyxin, gentamicin, amphotericin		49.4	33	15	52	Aggregate	Both
Verwaest et al[33]	1: Ofloxacin, amphotericin 2: Polymyxin, tobramycin, amphotericin	1: Ofloxacin 2: Ceftriaxone	55.8	23	67	10	Both	Both
Wiener et al[44]	Polymyxin, gentamicin, nystatin	None	Information not available				Aggregate	Both
Winter et al[34]	Polymyxin, tobramycin, amphotericin	Ceftazidime	59.2	13	47	40	Both	Both

*Personal communication.

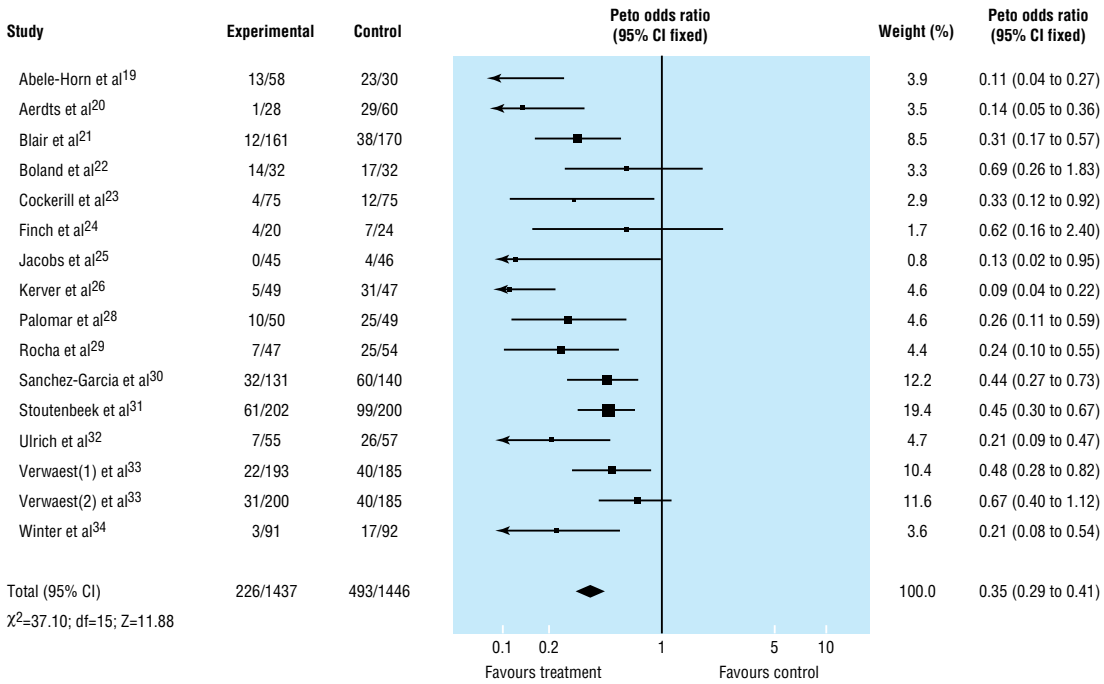

Fig 1 Meta-analysis of aggregate data. Effect of combination of topical and systemic antibiotics as prophylaxis for respiratory tract infections in patients in intensive care units

information that we obtained, in a standardised format, directly through personal contacts with study investigators: number of patients and their treatment allocation; method of randomisation and use of blinding techniques; type of comparison (type and dose of antibiotic); number of patients with at least one respiratory infection by treatment arm; number of deaths by treatment arm; and number of excluded patients, and number of respiratory infections and deaths among them.

To perform a meta-analysis on data from individual patients we sought the following information for each randomised subject: treatment arm; date of birth; sex; date of admission to intensive care unit; date of randomisation; type of diagnostic category (medical, surgical, trauma); severity score (simplified acute physiology score (SAPS)), acute physiological and chronic health evaluation (APACHE), and injury severity score (ISS) for trauma patients; systemic antibiotic treatment in the first 3 days; respiratory infections; vital status at discharge from intensive care; vital status at last follow up; and inclusion or exclusion and reason(s) for exclusion.

To explore whether the trials for which we obtained data on individual patients differed from all the trials we compared the results of pooled estimates of treatment effects on respiratory infections and mortality in the two datasets.

Quality assessment of studies

Study quality was assessed by looking at methods of randomisation (blind versus open) and use of blinding techniques (double blind versus unblind studies). The randomisation procedure was classified as blind when it was done by telephone through a pharmacy or a central office or by using sealed envelopes. It was classified as open when it was done with a computer generated list directly managed by study investigators or when patients were allocated by odd-even number or other types of open lists.

The assignment of a study to a double blind or unblind category was according to what was reported by the authors. No attempt was made to measure the extent to which studies that were defined double blind kept their masked nature during the study.

Outcome measures and statistical analysis

Two main outcome measures were considered: respiratory tract infections and overall mortality. No restriction was made on type of infection considered and on diagnostic criteria for infection chosen by the trialists. Both tracheobronchitis and pneumonia were acceptable. Both primary (diagnosed within 48 hours after admission) and acquired (diagnosed after 48 hours after admission) infections were considered, even if we used data on acquired infections when information on both was available. Mortality was evaluated at hospital discharge, if this information was available, otherwise mortality in the intensive care unit was considered.

All patient records, for both aggregated and individual data, were converted to an agreed format and the following checks (performed by CL and SP) run on each dataset: simple checks of missing values; no duplicate patient records; treatment group assigned and survival status; range of prognostic variables; and checks for random allocation. For trials for which data on individual patients were available we constructed a plot of cumulative proportion of patients per arm versus time of randomisation for each study to check for major unbalances in the sequence of randomisation.

In the analysis of data on individual patients we classified patients into three diagnostic categories: medical, surgical, and trauma. For classification of severity we relied on the APACHE II score in most cases; in seven trials for which the SAPS score was reported,[24 32 35 37 39 41 45] we transformed it into APACHE II using the following algorithm: APACHE II = – 1.24 + 1.484*(SAPS).[52] Patients were grouped into three mutually exclusive classes within groups defined by the main diagnostic categories (medical, surgical, trauma) according to severity of disease. APACHE II cut off points were chosen to define low or medium or high severity with reference to the "expected mortality rate" (< 10%, 10-60%, > 60%).[53]

In addition to odds ratios of each outcome in each trial, computed with the fixed effects model (Peto method),[54] we estimated the number of patients in intensive care who would need to be treated to prevent one infection and one death. The calculation was based on the median rates of infections and deaths in untreated controls and the common odds ratio for all trials.

We carried out two prespecified subgroup analyses on the basis of quality criteria within the above mentioned two main groups of trials: quality of randomisation procedures (blind versus open) and blinding of patients and doctors to allocated treatment (double blind versus unblind). For analyses on data on individual patients odds ratios, stratified by prognostic factor, were calculated with the fixed effects model.

Results

Information from 33 trials that between 1984 and 1996 enrolled a total of 5727 patients was the base for the aggregate data meta-analysis (table 2). Data on individual patients were obtained from 25/33 trials including 4343/5727 (76%) patients.

Respiratory tract infections

Evaluation from meta-analysis of aggregate data

Overall, results from 30 trials including 4898 patients were available for the analysis of the effects of different types of antibiotic prophylaxis on respiratory tract infections: 1184 patients developed one or more infections (S Jacobs and M Zuleika, personal communication).[19–26 28–35 37–45 47–50]

The prevalence of respiratory infections was 16% among treated patients and 36% among controls in trials that used a combination of topical plus systemic antibiotics and 18% and 28%, respectively, in trials that tested the effectiveness of topical prophylaxis alone. Overall, the odds ratio was lower than unity in all but two comparisons[44 49] and reached conventional significance ($P < 0.05$) in 21/32 comparisons.

The results indicated a strong protective effect of the combination of topical and systemic treatment (odds ratio 0.35; 95% confidence interval 0.29 to 0.41) (fig 1). A clear though less extreme protection was also seen when treatment effect was explored in trials that tested topical antibiotics (0.56; 0.46 to 0.68)(fig 2).

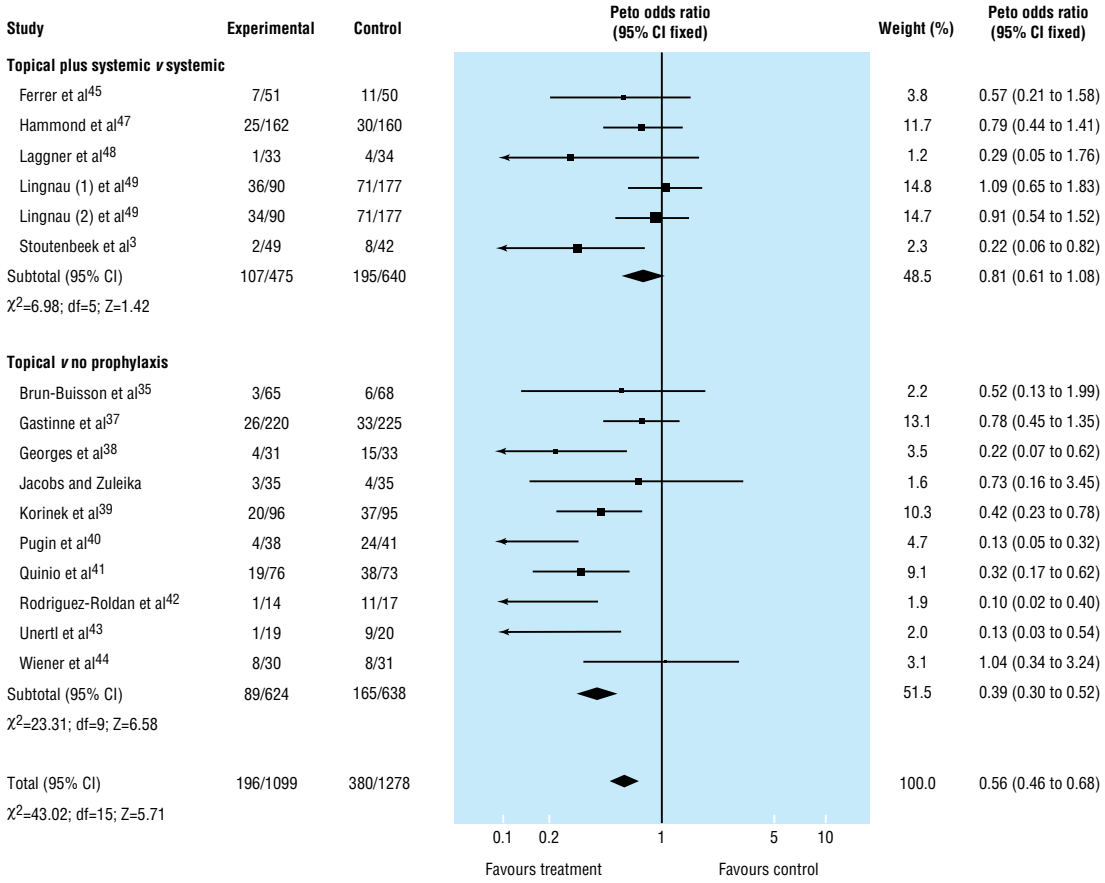

Fig 2 Meta-analysis of aggregate data. Effect of topical antibiotics as prophylaxis for respiratory tract infections in patients in intensive care units

Table 3 Meta-analysis of data from individual patients. Effect of combination of topical and systemic antibiotics as prophylaxis for respiratory tract infections in patients in intensive care

APACHE II scores	No of studies	No treated	No of controls	Odds ratio (95% CI)
Medical patients				
0-14	10	10/67	23/76	0.37 (0.16 to 0.87)
15-29	10	14/155	53/180	0.28 (0.16 to 0.48)
⩾30	10	7/54	12/52	0.57 (0.20 to 1.69)
Total		31/276	88/308	0.33 (0.22 to 0.51)
Surgical patients				
0-14	9	15/166	24/142	0.47 (0.23 to 0.94)
15-29	9	36/299	70/309	0.51 (0.33 to 0.78)
⩾30	9	4/22	6/26	0.87 (0.21 to 3.64)
Total		55/487	100/477	0.51 (0.36 to 0.73)
Trauma patients				
0-14	11	54/269	116/294	0.40 (0.28 to 0.58)
15-29	12	59/258	108/249	0.37 (0.25 to 0.54)
⩾30	12	5/13	4/10	0.07 (0.01 to 1.63)
Total		118/540	228/553	0.38 (0.29 to 0.50)
Overall		204/1303	476/1338	0.40 (0.33 to 0.49)

Table 4 Meta-analysis of data from individual patients. Effect of topical antibiotics as prophylaxis for respiratory tract infections in patients in intensive care

APACHE II scores	No of studies	No treated	No of controls	Odds ratio (95% CI)
Medical patients				
0-14	8	11/108	17/117	0.75 (0.34 to 1.67)
15-29	8	17/205	43/232	0.44 (0.25 to 0.77)
⩾30	9	1/29	4/23	1.03 (0.06 to 16.69)
Total		29/342	64/372	0.54 (0.34 to 0.84)
Surgical patients				
0-14	8	8/48	13/57	0.52 (0.17 to 1.53)
15-29	9	15/64	17/63	0.84 (0.35 to 1.99)
⩾30	9	3/6	0/4	12.18 (0.55 to 270.15)
Total		26/118	30/124	0.79 (0.41 to 1.53)
Trauma patients				
0-14	12	52/238	103/303	0.59 (0.40 to 0.88)
15-29	11	77/231	148/312	0.59 (0.41 to 0.85)
⩾30	12	4/8	6/12	5.29 (0.31 to 89.62)
Total		133/477	257/627	0.60 (0.46 to 0.79)
Overall		188/937	351/1123	0.61 (0.49 to 0.75)

Table 5 Comparison of results of randomised controlled trials according to availability of data from individual patients for prophylaxis with topical and systemic antibiotics and topical antibiotics only

	Topical plus systemic		Topical alone	
End points and dataset used	No of trials	Odds ratio (95% CI)	No of trials	Odds ratio (95% CI)
Mortality				
Aggregate and individual data	12	0.86 (0.72 to 1.02)	13	1.03 (0.84 to 1.26)
Aggregate data only	3	0.61 (0.44 to 0.86)	4	0.93 (0.57 to 1.52)
Respiratory tract infection				
Aggregate and individual data	12	0.39 (0.32 to 0.47)	13	0.57 (0.47 to 0.70)
Aggregate data only	2	0.10 (0.05 to 0.21)	2	0.47 (0.19 to 1.13)

These results suggest that 5 (4 to 5) and 9 (7 to 13) patients would need to be treated to prevent one infection, depending on whether a combination of topical and systemic drugs or a topical antibiotic only is tested. This assumes the median values of 44% and 32% for baseline risk, respectively, as seen among control patients.

The effect of the quality of randomisation could meaningfully be explored only among trials that tested the relative effectiveness of topical antibiotic agents (given that all but two trials of the topical plus systemic group had blind randomisation): trials with blind randomisation showed a greater effect (0.51; 0.40 to 0.66) compared with those in which the procedure was open (0.66; 0.48 to 0.91). Results from double blind trials did not differ from those obtained in unblind studies.

Evaluation from meta-analysis of data from individual patients

The results from the 25 studies for which data were provided by the trialist are reported in tables 3 and 4 (S Jacobs and M Zuleika, personal communication).[20–24 28–35 37–42 45 47–50] Odds ratios and relative confidence intervals are presented within specific groups of diagnostic category and severity score. The effect of the treatment on infections is shown for both types of treatment protocols—that is, topical plus systemic (0.40; 0.33 to 0.49) and topical alone (0.61; 0.49 to 0.75). The results seem more pronounced, however, in trials in which the combination was used.

The widespread belief that the treatment is more effective in patients with intermediate severity scores (that is, APACHE II score 15-29) and less effective among "medical" patients was not supported by the data from trials that tested the topical and systemic combination. The extent of the treatment effect was quite consistent across disease categories and severity groups. Data from trials that tested topical antibiotics are more difficult to interpret because of the small number of patients in the highest APACHE II category—that is, ⩾30.

Overall, these results did not differ substantially from those obtained by pooling data from trials for which data on individual patients were not available (table 5), suggesting that no bias was introduced by lack of data provided by study investigators.

Mortality

Evaluation from meta-analysis of aggregate data

A total of 1515 deaths occurred in the 33 trials with 5727 patients available for analysis (S Jacobs and M Zuleika, personal communication).[19–50] The mortality was 24% in treated patients and 30% in controls for trials that tested a combination of topical plus systemic antibiotics and 26% in control and treated patients for trials that tested the effectiveness of topical treatment. The odds ratio was lower than unity in 23/35 comparisons but reached significance in only two trials[27 31]; no trial suggested a significant harmful effect of antibiotic prophylaxis. Results indicate a significant reduction in mortality attributable to the use of a combination of topical and systemic treatment (0.80; 0.69 to 0.93) (fig 3). Twenty three patients (14 to 68) would need to be treated to prevent one death (if we assume a median baseline risk of 29% among control patients). No effect was seen when trials that tested topical antibiotics alone were analysed (1.01; 0.84 to 1.22) (fig 4).

While analyses by quality of randomisation did not affect the results, reduction in mortality among trials that tested a combination of topical and systemic antibiotics was greater in trials that used a double blind design (0.63; 0.48 to 0.83) compared with unblind studies (0.90; 0.74 to 1.08).

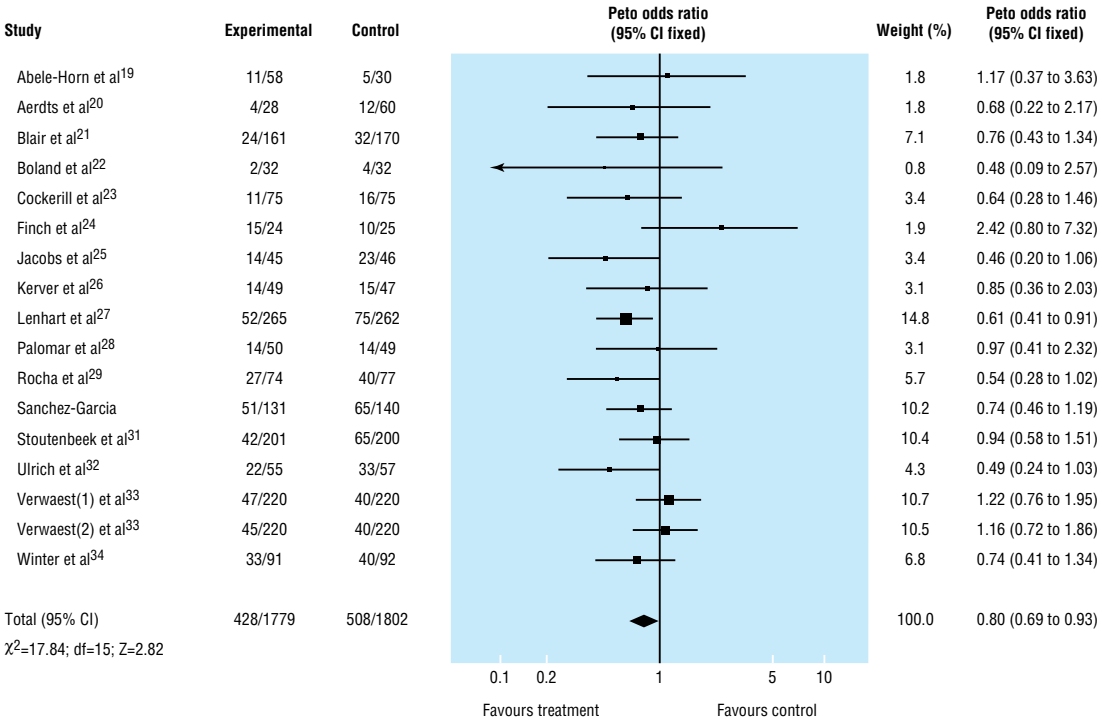

Fig 3 Meta-analysis of aggregate data. Effect of combination of topical and systemic antibiotics on mortality in patients in intensive care units

Evaluation from meta-analysis of data from individual patients

Results from 25 studies are reported in table 6 and 7 (S Jacobs and M Zuleika, personal communication).[20–24 28–35 37–42 45 47–50] Odds ratios with their relative confidence intervals are presented within specific groups of diagnostic categories and severity scores. Similarly to the results derived from the corresponding aggregate data analysis, a significant reduction in overall mortality was observed for trials that tested a combination of topical and systemic antibiotics (0.79; 0.65 to 0.97) but not from studies that tested topical drugs alone (1.02; 0.81 to 1.30). Treatment effect did not vary substantially by main diagnostic category.

Overall, these results did not differ substantially from those obtained by pooling data from trials for which individual patient data were available (table 5).

Discussion

Effectiveness of antibiotic prophylaxis

Since its introduction as a method designed to prevent infection in critically ill patients the effectiveness of antibiotic prophylaxis has remained controversial.[3] The lack of standard protocols and insufficient numbers of patients have made it difficult to derive meaningful conclusions from individual randomised controlled trials. Despite initial enthusiasm after results from early uncontrolled studies and initial trials, antibiotic prophylaxis—as tested in available trials—is not widely used in intensive care units. The concern about the risk of long term emergence of antibiotic resistance and of increasing costs dominates in recent American documents based on expert opinions on prevention of infections such as the *Guidelines for Prevention of Nosocomial Pneumonia* recently published by the Centers for Disease Control and Prevention[55] and the consensus statement of the American Thoracic Society on *Hospital-Acquired Pneumonia in Adults*.[56] A conservative attitude in introducing a new treatment into practice is understandable as long as doubts exist about its efficacy. In fact studies on prevention of ventilator associated pneumonia in patients in intensive care units are complex because patients are heterogeneous, diagnosis of pneumonia is controversial, and outcome depends on many factors. Although the ability of antibiotic prophylaxis to reduce respiratory tract infections emerged with remarkable consistency across individual trials, the effect on mortality was significant in only two. It was never fully realised that this was

Table 6 Meta-analysis of data from individual patients. Effect of combination of prophylactic topical and systemic antibiotics on mortality in patients in intensive care

APACHE II score	No of studies	No treated	No of controls	Odds ratio (95% CI)
Medical patients				
0-14	10	16/67	15/76	1.45 (0.63 to 3.36)
15-29	10	57/155	77/180	0.80 (0.50 to 1.29)
⩾30	10	26/54	26/52	0.72 (0.32 to 1.63)
Total		99/276	118/308	0.88 (0.61 to 1.27)
Surgical patients				
0-14	10	12/166	20/142	0.43 (0.21 to 0.92)
15-29	9	67/299	76/309	0.91 (0.61 to 1.34)
⩾30	9	12/22	21/26	0.26 (0.06 to 1.20)
Total		91/487	117/477	0.73 (0.52 to 1.03)
Trauma patients				
0-14	11	26/268	35/294	0.81 (0.48 to 1.39)
15-29	12	57/258	65/249	0.76 (0.49 to 1.16)
⩾30	12	8/13	5/10	0.95 (0.08 to 10.93)
Total		91/539	105/553	0.78 (0.56 to 1.09)
Overall		281/1302	340/1338	0.79 (0.65 to 0.97)

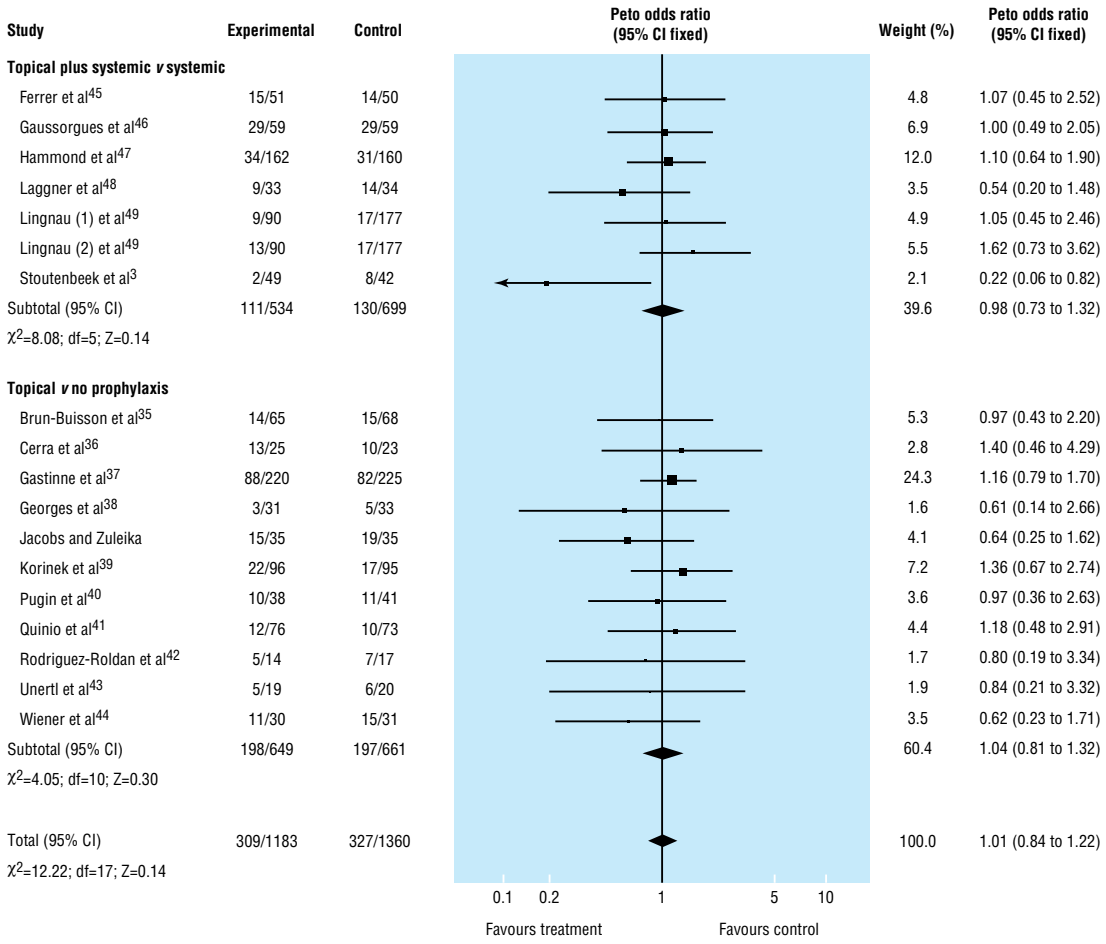

Fig 4 Meta-analysis of aggregate data. Effect of topical antibiotics on mortality in patients in intensive care units

probably because of the small sample sizes of individual studies and, possibly, the weak association between respiratory infections and mortality.

The meta-analysis reported here combines data across studies to estimate treatment effects with more precision than in a single study.[57] Moreover, for a large proportion of trials data on individual patients were available, thus allowing a more refined analysis.

Table 7 Meta-analysis of data from individual patients. Effect of prophylactic topical antibiotics on mortality in patients in intensive care

APACHE II score	No of studies	No treated	No of controls	Odds ratio (95% CI)
Medical patients				
0-14	8	18/108	19/117	0.99 (0.47 to 2.06)
15-29	6	77/205	77/232	1.08 (0.72 to 1.62)
⩾30	9	15/29	13/23	1.09 (0.32 to 3.68)
Total		104/342	109/372	1.06 (0.75 to 1.49)
Surgical patients				
0-14	8	10/48	11/57	1.25 (0.44 to 3.53)
15-29	9	18/64	15/63	1.18 (0.52 to 2.70)
⩾30	9	2/6	3/4	0.46 (0.04 to 5.27)
Total		30/118	29/124	1.13 (0.61 to 2.12)
Trauma patients				
0-14	12	17/238	19/303	1.20 (0.59 to 2.46)
15-29	11	36/231	54/312	0.84 (0.52 to 1.34)
⩾30	12	4/8	6/12	1.17 (0.10 to 13.26)
Total		57/477	79/627	0.94 (0.64 to 1.39)
Overall		191/937	217/1123	1.02 (0.81 to 1.30)

Compared with the five previously published meta-analyses we decided to analyse separately trials that tested a combination of topical and systemic antibiotics and those that tested topical antibiotics alone. Though there is no consensus on the best way to classify antibiotic prophylaxis regimens,[56] it seemed rational to analyse these two groups of trials separately without combining all trials together. Our results confirm that both of these methods of prophylaxis have a strong protective effect on infections—with a more pronounced effect when patients are treated with the combination of topical plus systemic antibiotics. This effect was consistent for all subgroups of patients regardless of study design (blind or open randomisation, double blind or unblind studies). Overall, these results seem convincing even though it is acknowledged that no diagnostic test or procedure is ideal for diagnosing respiratory infections in patients in intensive care units.

The important new finding from this meta-analysis is that for prophylactic regimens that combine topical and systemic antibiotics there is also a relevant reduction of overall mortality.

Given the enthusiastic collaboration provided by most investigators and the efforts to include unpublished studies, it is unlikely that we have missed any important trials conducted so far. Moreover, as nearly all trials did not show significant reduction in mortality

on their own, there is no good reason to believe that publication bias represents a major problem in this literature.

The inability to obtain data on individual patients from all trials is unlikely to have biased results of the meta-analysis of such data. As table 5 shows, results of trials for which we could not obtain information on individual patients were not substantially different from those with such data available. Further details on patients mix and treatments can be found in the version of this review available in the Cochrane Library.[58]

Insights from meta-analysis on data from individual patients

A methodological strength of this review is the availability of data from individual patients for a large number of trials. Firstly, this allowed a comprehensive quality check of the data, which, by and large, confirmed the validity of the aggregate analysis. Secondly, the availability of data on individual patients permitted the identification of subgroups more likely to benefit from treatment. There is a widespread belief among clinicians that some patients may respond more favourably to the treatment. For example, patients categorised according to their underlying conditions as surgical or trauma patients and those with medium severity of illness scores are expected to respond more favourably to antibiotic prophylaxis than those labelled as medical patients or with low or high severity scores. Our subgroup analyses, however, do not support this view. The data in tables 3, 4, and 6 suggest that when the treatment works there is no difference in the size of treatment effect of the combined prophylaxis regimens among medical, surgical, and trauma patients within corresponding severity of disease.

Even though findings from subgroup analyses should always be treated with great caution these results could be important as they challenge a commonly held view among clinicians and provide useful information to orient the design of future trials. Indeed our failure to detect differences by diagnostic group could be because of lack of statistical power within subgroups. With the studies now available, however, claims suggesting that surgical and trauma patients[59] and patients with high APACHE scores[60 61] have better outcomes do not seem well founded and cannot be accepted.

Implications for practice

This systematic review indicates that a protocol that uses a combination of topical and systemic antibiotics reduces both the occurrence of respiratory tract infections and overall mortality. The effect of this intervention expressed in terms of patients needed to be treated to prevent one infection and one death is substantial—five and 23, respectively—and compares favourably with several interventions largely used in clinical practice. Though 8/16 trials used an identical regimen, including polymyxin, tobramycin, and amphotericin as the topical combination and cefotaxime as the systemic component,[19 21 24–26 28 29 50] this review does not allow a unique regimen to be recommended. The use of topical antibiotics alone, however, is not justified by available data.

Finally, it is important to bear in mind that given the lack of valid data no absolute conclusion can be drawn from this systematic review on the risk of antibiotic resistance. Future studies should look at this problem more carefully.

Implications for research

The number of trials examining antibiotic prophylaxis provides sufficient statistical power to detect a moderate but worthwhile effect of the treatment on mortality.[5] According to this systematic review a protocol of a combination of topical and systemic antibiotics should be the standard against which new treatments are tested.

This meta-analysis could be criticised for the way trials have been grouped. We in fact assumed that the different drug combinations categorised as either topical plus systemic or topical only were equivalent. Although this may be inaccurate—as it may obscure the fact that the effective digestive decontamination achieved by different regimens can vary[62–64]—we did not envision a viable alternative and preferred to be consistent with the other published meta-analyses. On the other hand, even if results of all available trials are combined—as has been done in other recent meta-analyses[6–8]—the reduction in mortality is still significant (odds ratio 0.88; 95% confidence interval 0.78 to 0.98).

A logical next step for future trials would thus be the comparison of this protocol against a regimen of a systemic antibiotic agent only to see whether the topical component can be dropped. We have already identified six such trials[31 45–49] but the total number of patients so far enrolled (1056) is too small for us to be confident that the two treatments are really equally effective. If the hypothesis is therefore considered worth testing more and larger randomised controlled trials are warranted.

Trials of this kind, however, would not resolve the relevant issue of treatment induced resistance. To produce a satisfactory answer to this, studies with a different design would be necessary. Though a detailed discussion goes beyond the scope of this paper, studies in which the intensive care unit rather than the individual patient is the unit of randomisation and in which the occurrence of antibiotic resistance is monitored over a long period of time should be undertaken. One or more coordinated trials of this sort should be able to enrol a few thousands patients and should be designed in a pragmatic fashion concentrating on outcomes such as mortality, resistance, and costs. On the basis of our results it is not clear whether enrollment in these trials should be limited to specific categories of patients or should be open to all patients in intensive care. Given the uncertainty on this issue that stems from our analysis, trials with less strict eligibility criteria would be preferable. The growing collaboration among intensivists in the European Union Biomed Programme could provide a framework for designing and carrying out efficient studies aimed at settling this important research question.

The steering committee comprised DJ Cook (McMaster University Faculty of Health Sciences, Ontario), J Carlet (Hopital Saint-Joseph, Paris), M Langer (Ospedale Maggiore Policlinico IRCCS, Milan), P Loirat (CMC FOCH Suresnes, Paris), and HFK Van Saene (University of Liverpool, Liverpool). The investiga-

Key messages

- Over 40% of patients who need ventilation in intensive care develop respiratory tract infections and about 30% may die in the units
- If the most effective antibiotic prophylaxis (that is, a protocol combining topical and systemic antibiotics) is used the incidence of respiratory tract infections can be reduced by 65% and total mortality by 20%
- A regimen of topical antibiotics alone reduces respiratory tract infections but does not influence survival
- The concern that widespread antibiotic use may lead to resistance cannot be confirmed or ruled out by this review. Trials with different design are probably warranted to handle this question
- This important effect of antibiotic prophylaxis with a combination of topical and systemic antibiotics on survival should be considered by intensivists when treatment policies are designed

tors who were coauthors of this paper and provided data for meta-analysis of data from individual patients were SJA Aerdts (Sophia Hospital, Zwolle, the Netherlands); P Blair, BJ Rowlands, H Webb, and K Lowry (Royal Victoria Hospital, Belfast); JP Bowland, D Sadler, A Stewart, and J Pollock (Health Science Center Charlestone, West Virginia University); FR Cockerill and RI Thomson (Mayo Clinic, Rochester, Minnesota); M Ferrer and A Torres (Servei de Pneumologia, Hospital Clinic, Barcelona); RG Finch, P Tomlinson, and G Rocker (Nottingham City Hospital, Nottingham); H Gastinne (on behalf of the French Study Group on Selective Decontamination of the Digestive Tract); B Georges (Hôpital de Rangueil, Toulouse); JMJ Hammond and PD Potgieter (Groote Schuur Hospital, Cape Town); S Jacobs and M Zuleika (Riyadh Armed Forces Hospital, Riyadh); AM Korinek (Hôpital Pitié-Salpêtrière, Paris); AN Laggner (Vienna General Hospital, Vienna); W Lingnau (Leopold-Franzens-Universitat Innsbruck, Innsbruck); A Martinez-Pellus and J Rodriguez-Roldan (General Hospital, Murcia); M Palomar (Hospital Vall d'Hebron, Barcelona); J Pugin and P Suter (University Hospital, Geneva); C Martin, B Quinio, and J Albanese (Hôpital Nord, Marseilles); LA Rocha (Hospital Juan Canalejo, La Coruna); M Sanchez-Garcia (Hospital PPE Asturias, Alcala de Henares); CP Stoutenbeek (Academisch Ziekenhuis, Universiteit van Amsterdam, Amsterdam); C Ulrich and JE Harinck-De Weerd (Westeinde Hospital, The Hague); J Verhaegen and C Verwaest (University Hospital, Louvain); R Winter (Queen's Medical Centre University Hospital, Nottingham).

Appendix

Studies excluded from this meta-analysis

Author	Reason for exclusion
Bion et al[9]	Included selected population of patients undergoing liver transplant
Flaherty et al[10]	Included selected population of cardiosurgical patients
Hunefeldt et al[11]	Not properly randomised (that is, enrollment of consecutive patients)
Lipman et al[12]	Not properly randomised (that is, enrollment of consecutive patients)
Luiten et al[13]	Included selected population of patients with pancreatitis characterised by low percentage of admissions to intensive care unit randomised (that is, enrollment of consecutive patients)
Martinez-Pellus et al[14]	Included selected population of cardiosurgical patients
Rolando et al[15]	Included selected population of patients with acute hepatic failure
Schardey et al[16]	Included selected population of patients undergoing gastric surgery and characterised by low percentage of admissions to intensive care unit
Smith et al[17]	Included selected population of paediatric liver transplanted patients
Tetteroo et al[18]	Included selected population of patients undergoing oesophageal resection and characterised by short length of stay in intensive care unit

We thank L Brazzi (Ospedale Maggiore IRCCS, Milan) for his help and contribution in the earlier phases of this project, C Brun-Buisson (Hôpital Henry Monor, Creteil, Paris) for his useful comments and criticisms on several earlier drafts of this manuscript, and D Baxby (University of Liverpool, Liverpool) for editing an earlier draft of this manuscript. An earlier version of this paper won the Thomas C Chalmers Award at the fourth Cochrane Colloquium in Adelaide in October 1996.

Contributors: RD'A discussed core ideas of the project, participated in the design of the protocol for the meta-analysis of data from individual patients, had the main responsibility for data analysis and interpretation, and participated in writing the paper. SP discussed core ideas of the project, participated in the design of the protocol for the meta-analysis of data from individual patients, organised data collection, maintained contacts with the trialists checking data validity and accuracy, contributed to the interpretation of results, and participated in writing the paper. CL participated in the design of the protocol for the meta-analysis of data from individual patients, organised data collection, maintained contacts with the trialists checking data validity and accuracy, and contributed to the interpretation of results. VT discussed core ideas of the project, participated in the design of the protocol for the meta-analysis of data from individual patients, contributed to data analysis, and provided useful suggestions to the various drafts of the paper. AT designed and prepared the software for data management and helped with data analysis. AL initiated and coordinated the earlier phases of this research, discussed core ideas of the project, participated in the design of the protocol for the meta-analysis of data from individual patients, contributed to data analysis and interpretation, and had the main responsibility for writing the paper.

Funding: The meta-analysis of data from individual patients was supported by a grant from Hoechst Marion Roussel, Italy.

Conflict of Interest: None.

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(Accepted 16 December 1997)

Endpiece

Alternative definitions

Ambition: An overmastering desire to be vilified by enemies while living and made ridiculous by friends when dead.

Ambrose Bierce, *The Cynic's Word Book* (1906), subsequently titled *The Devil's Dictionary*