ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1995, p. 941–947 Vol. 39, No. 4
0066-4804/95/$04.00+0

Prophylaxis with Enteral Antibiotics in Ventilated Patients: Selective Decontamination or Selective Cross-Infection?

JAMES C. HURLEY[1,2]*

Division of Infectious Diseases, Children's Hospital and Medical Center, Seattle, Washington 98105-0371,[1] *and Intensive Care Unit, Wimmera Base Hospital, Horsham, Victoria, 3400, Australia*[2]

Received 31 October 1994/Returned for modification 22 December 1994/Accepted 7 February 1995

Selective decontamination of the digestive tract (SDD) has been evaluated as a method to prevent colonization and infection in ventilated patients in 40 trials. On the basis of an assumption that cross-infection would be reduced as a consequence of SDD and that this would distort the results of SDD studies that used concurrent controls, 14 studies used historic controls. To test this assumption, three observations from the two types of studies were compared. (i) The differences between observed and expected event rates for each study were used to perform a meta-analysis. This revealed that the summary odds ratios for bacteremia and respiratory infection were marked by significant heterogeneity ($P > 0.95$) and inconsistencies between those derived from studies with concurrent versus studies with historic controls. (ii) Where the data were available, the rates of acquisition of colonization in control groups were higher in studies with concurrent controls than in studies with historic controls. (iii) At least four studies with concurrent controls have shown a pattern of pathogenic isolates consistent with cross-infection between groups. These results are contrary to the initial assumption and suggest the possibility that SDD represents a major cross-infection hazard.

Colonization and infection with gram-negative bacteria occur commonly in patients requiring prolonged intubation in intensive care units (ICUs) (12, 20, 62). Moreover, pneumonia is the most common fatal nosocomial infection, with mortality rates of 20 to 50% (12). In most instances, colonization of the gastrointestinal and respiratory tracts with pathogenic gram-negative bacteria precedes the development of infection in these patients. As an approach to prevent this progression from colonization through infection, the use of topical nonabsorbable antibiotics to selectively decontaminate the digestive tract (SDD) has been evaluated in 14 studies with historic controls (7, 18, 21, 23, 31, 33, 36, 37, 50, 52–54, 63) and 26 studies with concurrent controls (1, 3, 4, 7, 9, 10, 15, 19, 22, 25, 27, 29, 32, 38, 42, 44–46, 49, 54–56, 58, 63, 65).

A meta-analysis based on 22 randomized studies (4,142 patients) reported convincing evidence of a favorable effect of SDD on the incidence of respiratory infection (RI) with a reduction of approximately 63% (51). There may also be a difference in mortality as great as 20%, but this was shown to be statistically significant only when three studies (25, 46, 54) which had failed specific inclusion criteria for this meta-analysis were subsequently included. A criticism of this meta-analysis is that it failed to address the striking variability in RI rates in the control groups. In general, these rates were high (>40%) in studies in which a beneficial effect had been shown in contrast to studies that had not shown a beneficial effect (5).

The interpretation of these studies is controversial (30, 34, 57, 59, 61). Issues of patient mix, study size, and design have been considered. In these studies, observer blinding is inherently difficult to achieve as treated patients can readily be identified from the culture results. This raises two broader issues; whether RI is a sufficiently objective end point and whether studies using historical controls should be considered.

An assumption stated in the original study was that a trial format with concurrent controls seemed not to be appropriate because "in the first place it was considered likely that having heavily contaminated controls next to decontaminated patients might adversely affect the potential beneficial results. Secondly, a reduction in the number of contagious patients by applying SDD in half of them, might reduce the acquisition, colonization and infection incidence in the not SDD treated control group" (52).

The purpose here is to attempt to test this assumption through a comparison of studies with different types of control patients by the technique of meta-analysis, including rates of bacteremia, a more objective end point than RI. In addition, the rates of colonization in the control groups and the pattern of pathogenic RI isolates were also examined.

MATERIALS AND METHODS

Study selection. The studies considered were those listed in the two previous meta-analyses (51, 57). The literature search strategy as described for the first (57) was used to reveal two additional studies. An additional criterion used in selecting studies for inclusion was that the majority (>50%) of patients were mechanically ventilated for more than 48 h. Studies available only in abstract (38, 49) or dissertation (58) form were included when sufficient details were available from either the abstract or two review articles (51, 59). There were three excluded studies. Three were excluded (16, 35, 48) because either the mean duration of ventilation was less than 48 h or the proportion ventilated was less than 50%. Duplications of studies published more than once were also excluded.

The studies were classified into those with a control group composed of patients treated concurrently in the same unit (concurrent) and those with a control group composed of patients managed in another unit or in the same unit at a different time (historic). Neither the method of patient randomization nor observer blinding was considered in this classification.

There are 40 studies from 35 publications. Three studies (7, 54, 63) had control groups of both types, and hence, the treated groups are included in both categories with the appropriate control group. One study (23) was a two-unit study with a crossover design, and the results for the two units were reported separately. The two treatment groups of one study were separately compared with the single control group (58). The results for the two control groups of one study (1) were combined.

Quantitative analysis. Study-specific odds ratios were calculated as previously described (26, 57) for rates of RI, mortality, and bacteremia in each study. Each odds ratio is the ratio of the number with the event versus the number without the event for each of the two groups in the comparison. To generate summary odds ratios, the meta-analysis procedure of Yusuf et al. (64) was used. For each group pair, the expected number of events in the subject group was calculated

* Mailing address: Microbiology and Infectious Diseases Department, Alfred Hospital, Commercial Road, Prahran, Victoria, 3181, Australia. Phone: 61-3-2763009. Fax: 61-3-2762431.

TABLE 1. Results of selective decontamination studies

Study (reference no.)	Characteristics of control groups				Study treatment[a] (topical agents-systemic agent)	Event rate[b]					
	Mean age (yr)	% Oropharyngeal colonization[c]				Respiratory infection		Mortality		Bacteremia	
		Days 0–3	Days 7–14	Acquisition		SDD	Control	SDD	Control	SDD	Control
Studies with historic controls											
Sydow 1990 (53)	42	NS[d]	NS		PTA-C	3/45	36/48	NS/NS	NS/NS	3/45	4/48
Stoutenbeek 1984 (52)	37	38	70	32	PTA-C	5/63	35/59	0/63	5/59	2/63	25/59
Hartenauer-1 1990 (23)	55	40	45	5	PTA-C[e]	5/50	28/61	19/50	29/61	3/50	4/61
Schardey 1989 (50)	58	NS	NS		PTANeB	4/41	26/55	10/41	29/55	NS/NS	NS/NS
Hartenauer-2 1990 (23)	54	40	45	5	PTA-C[e]	5/49	18/40	15/49	17/40	8/49	3/40
Konrad 1989 (31)	52	41	43	2	PTA-C	5/82	22/83	25/82	18/83	NS/NS	NS/NS
Tetteroo-H 1990 (54)[f]	60	NS	NS		PTA-C	1/56	16/75	3/56	5/75	1/56	5/75
Ledingham 1988 (33)	52	10	40	30	PTA-C	3/163	18/161	39/163	39/161	8/163	11/161
Godard 1990 (21)	51	NS	NS		PT	2/97	13/84	12/97	15/84	10/97	10/84
McClelland 1990 (37)	54	25	40[g]	15	PTA-C	1/15	6/12	9/15	7/12	3/15	3/12
Winter-H 1992 (63)	57	30	35	5	PTA-C	3/91	11/84	33/91	34/84	NS/NS	NS/NS
McClelland 1992 (36)	56	NS	NS		PTA-C	0/9	3/6	6/9	4/6	1/9	3/6
Brun-Buisson-H 1989 (7)	57	NS	15[g]		PNeNA	3/36	19/124	8/36	25/124	7/36	22/124
Fox 1991 (18)	58	NS	40		PTA-C	8/12	6/12	2/12	8/12	1/12	1/12
Studies with concurrent controls											
Kerver 1988 (29)	56	30	55	25	PTA-C	6/49	40/47	14/49	15/47	15/49	27/47
Pugin 1991 (42)	46	35	80	45	PNeV	4/25	21/27	7/25	7/27	NS/NS	NS/NS
Aerdts 1991 (1)	48	NS	87		PNoA-C	1/17	27/39	2/17	6/39	1/17	16/39
Blair 1991 (4)	47	NS	50		PTA-C	12/124	45/131	17/124	22/131	5/124	16/131
Ulrich 1989 (55)	60	35	78	43	PNoA-Tr	7/48	26/52	15/48	28/52	10/48	12/52
Rocha 1992 (44)	44	20	90	70	PTA-C	7/47	25/54	10/47	24/54	3/47	10/54
Winter-C 1992 (63)	60	20	40	20	PTA-C	3/91	17/92	33/91	40/92	NS/NS	NS/NS
Palomar 1992 (38)	46	NS	NS		PTA-C	10/48	26/49	14/48	14/49	NS/NS	NS/NS
Unertl 1987 (56)	46	25	85	60	PGA	1/19	9/20	5/19	6/20	NS/NS	NS/NS
Rodriguez-Roldan 1990 (45)	49	53	93	40	PTA	3/13	11/15	4/13	5/15	NS/NS	NS/NS
Sanchez 1992 (49)	55	NS	NS		PGA-C	31/131	60/140	51/131	65/140	NS/NS	NS/NS
Verhaegen-2 1992 (58)	56	NS	NS		OA-O	22/193	40/185	47/220	40/220	NS/NS	NS/NS
Hünefeld 1989 (25)	48	NS	39		PTA	38/102	55/102	51/102	60/102	19/102	35/102
Tetteroo-C 1990 (54)	61	NS	81[g]		PTA-C[e]	1/56	8/58	3/56	2/58	1/56	1/58
Korinek 1993 (32)	47	50	70	20	PTAV	15/63	25/60	3/63	7/60	2/63	6/60
Cockerill 1992 (10)	65	NS	56[g]		PGNy-C	4/75	12/75	11/75	16/75	4/75	11/75
Verhaegen-1 1992 (58)	56	NS	NS		PTA-C	31/200	40/185	45/220	40/220	NS/NS	NS/NS
Bion 1994 (3)	52	NS	NS		PTA-C	0/21	8/31	0/21	5/31	2/21	1/31
Zobel 1991 (65)	2	10	52	42	PGA-C	1/25	6/25	3/25	2/25	1/25	4/25
Cerra 1992 (9)	64	NS	NS		NoNy	12/25[h]	15/21[h]	13/25	10/21	5/25[i]	12/21[i]
Gastinne 1992 (19)	54	NS	NS		PTA	26/220	33/225	88/220	82/225	NS/NS	NS/NS
Rolando 1993 (46)	35	NS	NS		PTA-C	8/28	11/31	9/28	17/31	1/28	1/31
Jacobs 1992 (27)	55	16	47[g]	31	PTA-C	0/36	4/43	14/36	23/43	5/36	7/43
Brun-Buisson-C 1989 (7)	60	NS	10[g]		PNeNa	3/36	6/50	8/36	12/50	7/36	5/50
Ferrer 1992 (15)	62	NS	78		PTA-C[e]	7/39	10/41	12/39	11/41	NS/NS	NS/NS
Hammond 1992 (22)	44	32	45	13	PTA-C[e]	8/114	8/125	21/114	21/125	8/114	9/125

[a] Abbreviations: P, polymyxin; T, tobramycin; A, amphotericin; Ne, neomycin; No, norfloxacin; G, gentamicin; B, bacitracin; Na, nalidixic acid; Ny, nystatin; V, vancomycin; O, ofloxacin (topical agents); C, broad-spectrum cephalosporin; Tr, trimethoprim; O, ofloxacin (systemic agents).
[b] Except where indicated, data are ratio of number of patients with event to total number of patients.
[c] Oropharyngeal colonization with gram-negative bacteria.
[d] NS, not stated.
[e] Systemic component of treatment routinely given to control patients.
[f] Tetteroo-H 1990 (54): data for historic controls are summarized in the Materials and Methods section.
[g] Colonization with gram-negative bacteria, including at sites other than oropharyngeal sites.
[h] Ratio of number of patients with a nosocomial infection to total number of patients.
[i] Ratio of number of bacteremic episodes to total number of patients.

relative to the comparison group. The summary odds ratio is the antilogarithm of the log odds ratios, which is the sum of the differences between the observed and expected numbers of events for each comparison divided by the sum of their individual variances. To assess the appropriateness of pooling, a chi-square test of heterogeneity in the effect size was calculated (64). The comparisons of rates of colonization in the different types of control groups were done with a Wilcoxon rank sum test.

RESULTS

Description of the trials. This meta-analysis was based on 14 historic and 26 concurrent controlled studies. Table 1 shows the heterogeneity of these trials with respect to trial therapies and rates of colonization in control groups and rates of RI, mortality, and bacteremia in treated and control groups.

Meta-analysis. The corresponding study-specific and summary odds ratios are presented in Fig. 1. Studies with outcomes favoring SDD recipients with respect to either mortality or bacteremia were less common than was the case for RI.

Table 2 contains the summary estimates for the three events. The test for heterogeneity was significant ($P > 0.95$) or borderline so ($P = 0.93$) for five of these summary estimates. As

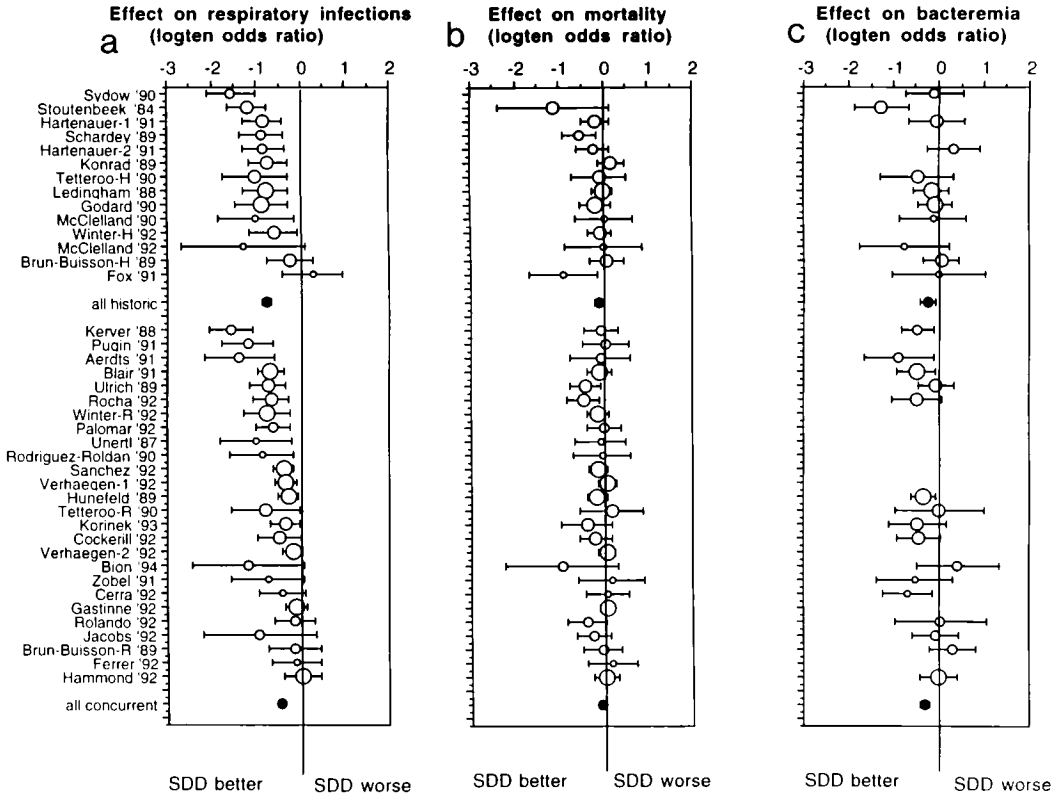

FIG. 1. Risk of RI (a), mortality (b), and bacteremia (c) for patients receiving selective decontamination versus comparison patients in studies with concurrent controls and studies with historic controls, shown as study-specific (open symbols) and group summary (closed symbols) odds ratios and 95% confidence intervals. Study size is indicated by symbol size: ◦, <50 patients; ○, 51 to 100 patients; ○, 101 to 175 patients; ◯, >175 patients.

with the previous published meta-analyses (51, 57), these summary estimates were sensitive to the inclusion or exclusion of specific studies. The summary odds ratio for bacteremia derived from the historic controlled studies changed considerably when the Stoutenbeek study (52) was excluded to reveal a striking inconsistency between the two types of studies. For RI, the summary odds ratio showed a greater benefit in the case of the historic controlled studies, whereas with bacteremia, the reverse was noted. Recalculation of the odds ratio for mortality after the exclusion of three concurrent controlled studies (25, 46, 54) which had failed specific inclusion criteria of a previous analysis (51) yielded a result (0.88; 0.75 to 1.03) that was no longer significant.

TABLE 2. Odds ratios

Event	Odds ratio (95% confidence interval)	Heterogeneity		
		Chi-square	*df*	*P*
Studies with historic controls				
Respiratory infection	0.18 (0.14–0.23)	23.8	13	0.97
Mortality	0.77 (0.61–0.97)	19.9	12	0.93
Bacteremia	0.57 (0.39–0.83)	25.1	10	0.99
Studies with historic controls (excluding Stoutenbeek study)				
Respiratory infection	0.19 (0.14–0.25)	21.3	12	0.95
Mortality	0.79 (0.62–1.01)	15.6	11	0.84
Bacteremia	0.84 (0.56–1.28)	6.2	9	0.28
Studies with concurrent controls				
Respiratory infection	0.35 (0.30–0.42)	72.0	25	1.00
Mortality	0.86 (0.74–0.99)	26.4	25	0.45
Bacteremia	0.48 (0.37–0.64)	19.8	15	0.77

Control group colonization and infection rates. The rates of RI in the historic control groups ranged from 11 to 75% and for the concurrent control groups ranged from 6 to 85%. The baseline rates of colonization of the oropharynx of control patients with gram-negative bacteria were comparable for the 11 concurrent control groups (range, 10 to 53%; median, 30%) versus the 7 historic control groups (range, 10 to 41%; median, 38%; $P = 0.47$) where these data were available. The rate of colonization at the second week was significantly higher for 18 concurrent control groups (range, 10 to 93%; median, 58%) in comparison with 9 historic control groups (range, 15 to 70%; median, 40%; $P = 0.009$). There were 18 studies with data on the rate of colonization at both time points, and in these, the rate of acquisition of colonization was significantly higher for the 11 concurrent control groups (range, 13 to 70%; median, 37%) than the 7 historic control groups (range, 2 to 32%; median, 5%; $P < 0.01$, rank sum test).

Bacteriology. Figure 2 indicates the pattern of four categories of key respiratory pathogens from the SDD recipients of 10 studies and the patients of 12 concurrent control groups and seven historic control groups and the same data for three literature studies (14, 39, 41) and National Nosocomial Infections Surveillance nosocomial pneumonia data (8, 24). For the remaining 21 SDD studies, these data were not available. The most frequent pathogens and their relative rankings vary from study to study. In the historic control groups and the literature control groups presented here and four additional studies of ventilator-associated pneumonia reviewed by George (20), no single pathogen accounted for more than 40% of isolates and

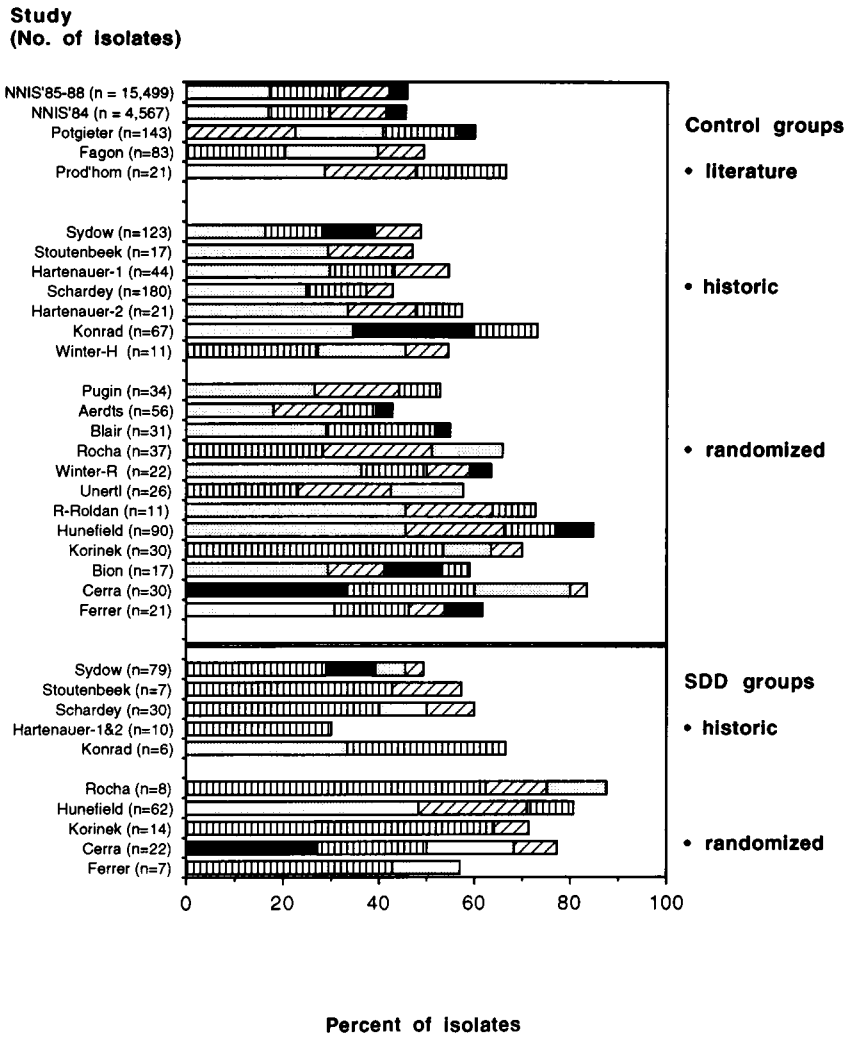

FIG. 2. Ranking of four categories of respiratory tract isolates from patients with nosocomial pneumonia: *P. aeruginosa* (stippled bar), and, for each study respectively, the most common gram-negative bacterium other than *P. aeruginosa* (diagonally striped bar), the most common gram-positive coccus (vertically striped bar), and the most common fungal isolate (solid bar). For any category of any given study, the isolate is the same for the treated and control groups of that study. Data are from SDD studies for which the data are available; three studies (Potgieter [39], Prod'hom [41], and Fagon [14]) broadly representative of the literature experience; and National Nosocomial Infections Surveillance data (8, 24). The pattern of isolates in the SDD groups of either study type reflects the emergence of gram-positive and yeast infections with this type of therapy. By contrast, the pattern of isolates in the control groups varies for historic in comparison with concurrent controlled studies. SDD groups with fewer than six isolates (six studies) are not shown. The number and type of isolates from these studies were as follows: Winter (63), three *P. aeruginosa* isolates; Aerdts (1), one *Serratia* isolate; Unertl (56), one *S. aureus* isolate; Rodriguez-Roldan (45), zero isolates; Bion (3), three *Candida* isolates; and Blair (4), four isolates. For Blair (4), identifications of control or SDD group gram-positive cocci were not separately listed and the whole gram-positive cocci category is indicated. For Pugin (42), the four SDD group isolates were not separately listed from the 30 control group isolates and the combined listing has been used.

no single gram-positive or fungal isolate accounted for more than 30% of isolates. This was not the case for the SDD-treated groups from the studies with either concurrent or historic controls. Moreover, this was not the case for the control groups of 5 (9, 25, 32, 44, 45) of the 12 studies with concurrent controls for which data were available. Interestingly, the patterns of the pathogens in both the treated and the control groups of four of five of these concurrent controlled SDD studies (9, 25, 32, 44) were unusual because of the high degree of identity, with at least 50% of isolates of the two groups being the same for each of these four studies. For example, at least 50% of respiratory pathogens in both the SDD and the control groups in one study (32) were *Staphylococcus aureus* or, in another study (9), were either *Candida* spp. or *Staphylococcus epidermidis*, three organisms commonly isolated from patients receiving SDD.

DISCUSSION

The rationale for SDD is based on the concept that the pathogenesis of ventilator-associated RI is a two-step process: colonization of the oropharynx and gastrointestinal and respiratory tracts followed by aspiration and pneumonia. Johanson et al. (28) demonstrated an incidence of 22% colonization on the day of admission to an ICU, which rose to 45% by day 12 after admission. Pneumonia occurred in 23% of those who were colonized compared with 3% of those in whom colonization was never shown.

There is some flux in the colonizing flora of patients during their transit through an ICU which increases in relation to length of stay and exposure to antimicrobial agents (14). Patients requiring prolonged ventilatory support in an ICU, the patient group to which SDD is targeted, were found in one

study to be an important source of cross-infection within an ICU (17). However, based on the findings of prospective studies (17, 40), it is generally believed that cross-infection accounts for only a minority of infections acquired in the ICU in comparison with the proportion that emerges from the colonizing flora present on admission.

As with the two previous meta-analyses of SDD, the summary estimates calculated in this analysis suggest a difference in rates or morbidity favoring the treated patients. However, the validity of the meta-analysis technique to attempt to aggregate the results across SDD studies with disparate results is questionable. The degree of heterogeneity in the RI odds ratios is greater than that usually considered to be acceptable. As in the previous two analyses, the odds ratios are not robust and are subject to change with the exclusion of specific studies, and in the current analysis, this reveals inconsistencies between the results of the historic controlled studies and the results of concurrent controlled studies.

In general, in the investigation of a new therapy, a trial that has used historic controls is much more likely to report a benefit than is a randomized trial. This difference is often attributable to inequalities in the prognostic factors resulting in a worse outcome for historic control groups in comparison with randomized control groups (47). While there were inconsistencies between the results for the occurrence of infections in the SDD studies that used historic controls in comparison with studies that used concurrent controls, they did not fit this pattern. With bacteremia, there is evidence for an effect of SDD favoring the treated patients which was apparent only for the concurrent controlled studies and not for the historic controlled studies with an outlier study excluded.

With RI, by contrast, the summary odds ratio indicates a more favorable benefit for treated patients in historic than in concurrent controlled studies, and yet there is no evidence for a worse outcome for the control patients in historic control groups with respect to either the rates of RI or the rates of acquisition of oropharyngeal colonization with gram-negative bacteria, a key risk factor for pneumonia. The control group rates of ventilator-associated RI were highly variable in comparison with other studies in the literature. Among 31 studies which have reported the incidence of ventilator-associated pneumonia (reference 14 and other studies listed in reference 20), including 9 studies of stress ulcer prophylaxis in this patient group (reference 41, and other studies listed in reference 11), the highest incidence of pneumonia was 52% in a group of 60 antacid-treated patients (13). By contrast, acquisition of RI occurred at high rates (>50%) in the control groups in 9 of the 40 SDD studies, including 7 (1, 9, 25, 29, 38, 42, 45) of the concurrent controlled studies. Indeed, the rates of acquisition of oropharyngeal colonization with gram-negative bacteria in concurrent control groups were significantly higher than in the historic control groups, an inequality that is the reverse of the usual pattern of a risk factor for historic and concurrent control groups.

The pattern of isolates from patients with ventilator-associated RI varies from unit to unit, presumably as a consequence of prevailing unit practices such as patterns of antimicrobial use and criteria for defining and techniques for diagnosing RI (20, 43). The higher proportion of gram-positive and fungal isolates found in SDD recipients represents an extreme example of this variation. In the control groups of four concurrent controlled studies, there is evidence of unusual patterns of four key RI isolates in comparison with that in historic controlled studies and other non-SDD studies reported in the literature. In each case, the similarity of the pattern found in the control group to that in the SDD recipients of the same study is consistent with the occurrence of cross-infection. That the isolates from control patients were of a type seen in SDD recipients suggests that they were acquired from the SDD recipients in these four studies. Of more concern, in the six studies (1, 4, 9, 25, 29, 52) in which a significant study-specific odds ratio favored the SDD recipients for bacteremias, in five (1, 9, 25, 29, 52) the bacteremia rate in the control group exceeded 30%; two (9, 25) of these five were studies in which there was evidence consistent with cross-infection for RI isolates; and for one of these concurrent controlled studies (9), the unusually high number of *Candida* isolates from tracheal aspirates was also reflected in a high frequency of candidemia in control patients (4 of 12 blood culture isolates).

Conclusive evidence of cross-infection in ICUs requires detailed phenotyping and genotyping of isolates. The limited data in the context of controlled SDD studies have revealed some subtle examples of cross-contamination and cross-infection (2, 6, 7, 60, 63). For example, some have reported the elimination of an endemic resistant *Klebsiella* isolate (7), while others have noted significant increases in frequency of resistant *Acinetobacter* isolates (63). In both of these studies, the effects were not limited to the SDD recipients. Molecular typing of the staphylococcal isolates of a third study indicated that cross-colonization between SDD and concurrent control cases (4) "readily occurred" (60). In this same study, a significant reduction in rates of infections and overall pharyngeal colonization with *Pseudomonas aeruginosa* was noted in SDD recipients, and yet despite this, persistent rectal colonization was noted in some. Antibiogram and pyocine typing of the *P. aeruginosa* isolates indicated that this colonization in SDD patients represented a significant reservoir of persistent strains within the unit that caused a disproportionate number of infections in control patients (2).

Differences in the rates and types of infection in the control groups of the SDD studies versus those reported in non-SDD studies of ventilator-associated pneumonia cannot readily be accounted for by the rationale of endogenous origin stated earlier. A range of potential explanations, including differences in study design, must be considered. It is possible that historical controls were not examined for acquisition of colonization as carefully as concurrent controls. Moreover, the discovery of either a cross-infection problem or a high rate of RI in a unit might have stimulated a decision to mount a trial of SDD with concurrent controls.

In answer to the starting assumption, the increase in colonization and infection rates in concurrent control groups and the similarities in pathogens are consistent with the possibility of cross-infection in at least some of the concurrent controlled trials, although the direction of the cross-infection, being to control patients, would be opposite to that initially assumed. It is important to consider this possibility as a basis to explain the variable results in the concurrent controlled studies and the disparity with the results of the historical controlled studies. This possibility of cross-infection needs to be closely examined by modern methods of epidemiological typing in any further trials using concurrent controls. The undertaking of a patient-based meta-analysis in an attempt to examine subgroups may obscure the possible contribution of cross-infection to the outcome, which is unit specific.

ACKNOWLEDGMENTS

The author is currently supported by the American Cystic Fibrosis Foundation and a travelling fellowship administered by the Royal Australasian College of Physicians.

I acknowledge the assistance of Fritz D. Schoenknecht, Department

of Laboratory Medicine, University of Washington Medical Center, in the translation of the German language references.

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