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A. Liberati
R. D'Amico
S. Pifferi
E. Telaro

Antibiotic prophylaxis in intensive care units: meta-analyses versus clinical practice

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A. Liberati (✉) · R. D'Amico · S. Pifferi · E. Telaro
Italian Cochrane Centre,
Mario Negri Institute, Via Eritrea 62,
I-20157 Milan, Italy
e-mail: Cochrane@irfmn.mnegri.it
Tel.: + 39-2-39014327
Fax: + 39-2-33200231

Abstract *Objective*: At least 7 meta-analyses (MA) have been published since 1991 on the effectiveness of antibiotic prophylaxis in Intensive care units (ICU) patients, but controversy still remains about the overall effectiveness and risk-benefits profile of the treatment. This paper aims to summarise available data on effectiveness and discuss reasons why the controversy is still open and possible directions for future research.
Design: Review of available published MA on the effectiveness of various regimens of antibiotic prophylaxis with particular emphasis on the results of the individual patient data analysis published in 1998.
Setting: MA or randomised control trials (RCTs), published and unpublished, conducted anywhere in the world.
Patients and participants: Unselected adult ICU populations included in studies, published and unpublished, comparing different forms of antibiotic prophylaxis.
Main outcome measure: Respiratory tract infections (RTIs) – however defined in individual studies – and total mortality.
Data sources: General information from the 7 MAs published between 1991 and 1999 and detailed information from the MA published in the *British Medical Journal* in 1998 that reported data on 5727 patients enrolled in 33 RCTs; access to individual patients data could be obtained from 25 of 33 RCTs and allowed a confirmatory individual patient MA on 4343 patients.
Results: Pooled estimates from 16 RCTs (including 3361 patients) testing the effect of the topical and systemic antibiotic combination indicates a significant reduction of both RTIs (OR = 0.35, 95% CI = 0.29–0.41) and total mortality (OR = 0.80, 95% CI = 0.69–0.93). Five and 23 patients need to be treated to prevent one infection and one death, respectively, using this treatment. Pooled data from the 17 RCTs (including 2366 patients) testing the effect of a regimen based on topical antimicrobials indicated a statistically significant reduction in RTIs (OR = 0.57, 95% CI = 0.46–0.69) but not in total mortality (OR = 1.01; 95% CI = 0.84–1.22). Individual patient data analyses confirmed these results.
Conclusions: After over 30 RCTs and seven MAs, there is strong evidence that antibiotic prophylaxis can reduce both RTIs and total mortality in ICUs patients in a statistically and clinically significant way. Concerns about the possible occurrence of antimicrobial resistance are not supported by available data but cannot, at the same time, be ruled out due to methodologic inadequacies of the studies carried out so far. Whether new trials are needed,

and how they should be designed to answer the question of the potential for antibiotic resistance following widespread use of the treatment, are now the main issues to be settled. Convening an international panel of clinical experts and methodologists could be appropriate, in order to explore the best way to resolve the controversy that seems to be preventing the widespread use of a treatment that the best analysis of available data now indicates is effective.

Key words Intensive care units · Critical care · Antibiotic combined therapeutic use · SDD · Systematic review

Introduction

Nosocomial infections, especially pneumonia, are an important cause of morbidity and mortality in intensive care units (ICUs). The incidence of pneumonia has been reported to vary from 7% to more than 40% in ICU patients. The crude mortality rate for patients with ventilator-associated pneumonia (VAP) may exceed 50%. Although not all deaths in patients with VAP are directly attributable to infection, VAP has been shown to contribute to ICU mortality independently of other factors that are also strongly associated with deaths of these patients [1]. In a case-control study an increase in mortality of 27.1% attributable to VAP was evidenced in ventilated patients [2]. Considerable efforts have been made to evaluate methods for reducing respiratory infection. One strategy involves the use of selective decontamination of the digestive tract (SDD). Different SDD protocols have been used in different trials, and investigators often disagree on the most appropriate definition of SDD. Traditionally SDD indicates a method designed to prevent infection by eradicating and preventing carriage of aerobic, potentially pathogenic micro-organisms from the oropharynx, stomach and gut. It consists of antimicrobials applied topically to the oropharynx and through a nasogastric tube. In some trials systemic antibiotic therapy has been added in the first days after patients' admission to prevent 'early' infections. An SDD protocol based on oral non-absorbable antibiotics was first used in 1984 by Stoutenbeek in a group of multiple trauma patients. The incidence of nosocomial infection was reduced from 81% to 16% in a non-randomised comparison with a historical control group [3]. Further studies tested the efficacy of SDD in ICU patients, with infection-related morbidity as the main point. The results showed that SDD reduced infection but it was not clear whether there was a reduction in mortality. Between 1991 and 1999, seven different meta-analyses (MAs) [4, 5, 6, 7, 8, 9, 10] on the effect of SDD on respiratory tract infections (RTIs) and mortality were published. Their results are summarised in Table 1.

All confirmed a statistically significant reduction in RTIs, though the magnitude of the treatment effect varied from one review to another. The estimated impact on overall mortality was less evident, however, and clearly emerged as both statistically and clinically significant only in the two most recent MAs [9,10] where studies using a combination of systemic and topical antibiotics were analysed separately from those using topical antimicrobials only.

In this paper the results of the most comprehensive MA will be briefly summarised and their results discussed in light of the fact that opinion amongst intensivists is polarised as to whether the treatment should or should not be routinely used in clinical practice.

Patients and methods

Details about description of the search strategy, eligibility criteria, data extraction, methodologic quality assessment, operational definition of the outcomes assessed are all available in the original publication [9].

Briefly, the search for RCTs covered the time span from January 1984 to December 1997. Studies were identified by MEDLINE literature search, and examining the reference list of previous MAs. Additional search focused on proceedings of scientific meetings held on the subject and personal contacts were established with other known investigators in the field. All RCTs, published and unpublished, without language restriction and testing the effect of antibiotic prophylaxis for the prevention of RTIs and deaths in adult ICU patients were considered. Only RCTs were accepted because otherwise control of selection bias could not be guaranteed; studies found – upon closer scrutiny – not to be randomised were not included.

Studies based on specific pre-selected types of patients (i.e. patients undergoing elective oesophageal resection, cardiac or gastric surgery, liver transplant or suffering from acute liver failure) were not included in this MA. Studies in which the majority of patients did not undergo mechanical ventilation for more than 48 h were also excluded. Available RCTs have been grouped into two categories defined according to the type of antibiotic prophylaxis: (a) studies where a combination of a systemic and a topical antibiotic was tested against no prophylactic treatment (hereafter referred to as 'topical plus systemic vs no prophylaxis'); (b) studies where the experimental treatment was a topical preparation (hereafter referred to as 'topical vs control'). In this latter category two subgroups of RCTs have been gathered, i.e. those where a topical antibiotic was tested against an untreated control group, and those in which the combination of a topical plus a systemic drug was compared with a protocol based on a systemic antimicrobial only. Any topical or systemic antimicrobial combination (i.e. type of drugs) was accepted.

In order to perform individual patients meta-analysis the following information was sought: treatment arm, date of birth, sex, date of admission to ICU, date of randomisation, type of patient (medical, surgical, trauma), severity score (SAPS, APACHE and, if applicable, ISS trauma score for trauma patients), injury severity

Table 1 Results of the 7 available meta-analyses on antibiotic prophylaxis

Authors			
End-points	OR (95% CI)	RR (95% CI)	RD (95% CI)
Vandenbroucke-Grauls 6 RCTs, 491 pts			
Mortality	0.70 (0.45–1.09)		
RTIs	0.12 (0.08–0.19)		
SDD Trialists' Group 22 RCTs, 4142 pts			
Mortality	0.90 (0.79–1.04)	0.80 (0.67–0.97)	
RTIs	0.37 (0.31–0.43)	0.37 (0.31–0.43)	0.37 (0.31–0.43)
Heyland 24 RCTs, 3312 pts			
Mortality	0.87 (0.79–0.97)	RTIs 0.46 (0.39–0.56)	
Kollef 16 RCTs, 2270 pts			
Mortality	0.019 (–0.016 to 0.054)	RTIs 0.145 (0.116 to 0.174)	
Tracheobronchitis	0.052 (0.017 to 0.087)		
Hurley 26 RCTs, 3768 pts			
Mortality	0.86 (0.74–0.99)	RTIs 0.35 (0.30–0.42)	
D'Amico et al 33 RCTs 5727 pts			
Mortality			
– Syst + topical	0.80 (0.69–0.93)		
– Topical only	1.01 (0.84–1.22)		
RTIs			
– Syst + topical	0.35 (0.29–0.41)		
– Topical only	0.56 (0.46–0.68)		
Nathens et al 21 RCTs			
# of pts not clearly reported			
Mortality			
Surgical pts	0.70 (0.52–0.93)		
Medical pts	0.91 (0.71–1.18)		
Pneumonia			
– Surgical pts	0.19 (0.15–0.26)		
– Medical pts	0.45 (0.33–0.62)		

score, systemic treatment, respiratory infections, vital status at ICU discharge, vital status at last follow-up, inclusion/exclusion, reason(s) for exclusion.

Study quality was assessed on two criteria: (a) methods of randomisation ('blind' vs 'open'); (b) use of blinding techniques ('double-blind' vs 'unblind' studies).

Two main outcome measures were considered: RTIs and overall mortality. No restriction was made on type of RTIs considered or on RTIs diagnostic criteria chosen by the trialists. Both tracheobronchitis and pneumonia were acceptable. Both primary (diagnosed within 48 h from admission) and acquired (diagnosed after 48 h from admission) infections were considered, even if we used data on acquired infections when both information was available.

Mortality was evaluated at hospital discharge if this information was provided; otherwise mortality in ICU was considered.

In addition to odds ratios of each outcome in each trial, computed with the Fixed Effects model, we computed the number of ICU patients who needed to be treated in order to prevent one infection and one death. The calculation was based on the median rates of RTIs and deaths in untreated controls and the common odds ratio for all trials. Two pre-specified subgroup analyses based on quality criteria were carried out within the above mentioned two main groups of RCTs: quality of randomisation procedures (blind vs open); blinding of patients and doctors to allocated treatment (yes vs no). Results of the individual patients MA have been calculated using fixed effect modelling and are presented as odds ratios stratified by prognostic factors.

Results

As already mentioned in the introduction to this paper we will report here in details the results of the MA which has the largest data set available for aggregate patient data and which is also based on the results of individual patients' data analysis for a subset of the total number of studies.

Respiratory tract infection

RTIs analysis based on aggregate data analysis

Overall, results from 30 RCTs including 4898 patients were available for the analysis of the effects of different types of antibiotic prophylaxis on RTIs; 1184 patients developed one or more infection(s). The frequency of RTIs was 16% among treated patients and 36% among controls in RCTs using a combination of topical plus systemic antibiotic, and 18% and 28% respectively in RCTs testing the effectiveness of topical SDD. Overall, the odds ratio was lower than unity in all but two trials

Table 2 Effect of antibiotic prophylaxis based the combination of a topical and systemic antimicrobial on RTIs derived from an individual patient data analysis

APACHE II	nº of studies	Treated	Control	Odds Ratio 95%	Confidence Intervals
Medical					
0–14	10	10/67	23/76	0.37	0.16–0.87
15–29	10	14/155	3/180	0.28	0.16–0.48
> 30	10	7/54	12/52	0.57	0.20–1.69
Total		31/276	88/308	0.33	0.21–0.51
Surgical					
0–14	9	15/166	24/142	0.47	0.23–0.94
15–29	9	36/299	70/309	0.51	0.33–0.78
> 30	9	4/22	6/26	0.87	0.21–3.64
Total		55/487	100/477	0.51	0.36–0.73
Trauma					
0–14	11	54/269	116/294	0.40	0.28–0.58
15–29	12	59/258	108/249	0.37	0.25–0.54
> 30	12	5/13	4/10	0.07	0.01–1.63
Total		118/540	228/553	0.38	0.38–0.50
Overall		204/1303	476/1338	0.40	0.33–0.49

and reached conventional statistical significance ($P < 0.05$) in 21 of 32 comparisons.

Results indicate a strong protective effect on RCTs where the combination of topical and systemic treatment (OR = 0.35, 95% CI = 0.29–0.41) was studied. A marked – though less extreme – protection also emerged (OR = 0.56, 95% CI = 0.46–0.68) when treatment effect was explored in RCTs using a topical antimicrobial.

These results suggest that 5 (95% CI = 4–5) or 9 (95% CI = 7–13) patients need to be treated to prevent one infection depending on whether a combination of topical and systemic treatment or a topical antimicrobial only is used (assuming, as baseline risk, the median values 0.44% and 0.32%, respectively, among control patients).

The effect of the quality of randomisation could meaningfully be explored only among RCTs testing the relative effectiveness of topical antimicrobials (given that all but one of the topical plus systemic group had blind randomisation); RCTs with "blind" randomisation showed a greater effect (OR = 0.51, 95% CI = 0.40–0.66) compared to those where the procedure was "open" (OR = 0.66, 95% CI = 0.48–0.91). Results from "double-blind" trials did not differ from those obtained in "unblinded" studies.

RTIs results based on individual patient data analysis

Results are reported in Tables 2 and 3. Odds ratios, with their relative confidence intervals, are presented within specific categories of diagnostic category and severity score.

Though the effect of the treatment on RTIs emerges for both types of treatment protocols – i.e. topical plus systemic (OR = 0.40, 95% CI = 0.33–0.49) and topical only (OR = 0.61, 95% CI = 0.49–0.75) – when considered in the aggregate, results appear more consistent in trials where the combination was used. In RCTs testing the combined protocol, in fact, treatment effect reaches – with only one exception – statistical significance in all subgroups defined by disease category and severity (see Table 2).

Interestingly, the widespread belief that the treatment is more effective in patients with more severe disease and less effective among "medical" patients is not supported by our results (see Tables 2 and 3) for either type of treatment protocol.

Mortality

Mortality based on aggregate data analysis

Overall, 33 RCTs including 5727 patients were available for the mortality analysis: a total of 1515 deaths occurred. The mortality was 24% among treated patients and 30% among controls on RCTs using a combination of topical plus systemic antibiotic, while it was 26% in both groups on RCTs testing the effectiveness of topical SDD. The odds ratio was lower than unity in 23 of 35 comparisons but reached conventional statistical significance in only two RCTs; no trial showed a significant harmful effect of antibiotic prophylaxis. Results indicate a statistically significant reduction in mortality attributable to the use of a combination of topical and systemic treatment (OR = 0.80, 95% CI = 0.69–0.93).

This suggests that 23 patients (95% CI = 14–68) (assuming a baseline risk of 0.29 median of among control patients) need to be treated to prevent one death. On the other hand, no effect emerged when RCTs using a

Table 3 Effect of antibiotic prophylaxis based on topical antimicrobials on RTIs derived from an individual patient data analysis

APACHE II	n° of studies	Treated	Control	Odds Ratio 95%	Confidence Intervals
IPDM					
Medical					
0–14	8	11/108	17/117	0.75	0.34–1.67
15–29	8	17/205	43/232	0.44	0.25–0.77
> 30	9	1/29	4/23	1.03	0.06–16.69
Total		29/34	264/372	0.54	0.34–0.84
Surgical					
0–14	8	8/48	13/57	0.52	0.17–1.53
15–29	9	15/64	17/63	0.84	0.35–1.99
> 30	9	3/6	0/4	12.18	0.55–270.15
Total		26/118	30/124	0.79	0.41–1.53
Trauma					
0–14	12	52/238	103/303	0.59	0.40–0.88
15–29	11	77/231	148/312	0.59	0.41–0.85
> 30	12	4/8	6/12	5.29	0.31–89.62
Total		133/476	257/627	0.60	0.46–0.79
Overall		188/937	351/1123	0.61	0.49–0.75

topical antimicrobial only were analysed (OR = 1.01, 95% CI = 0.84–1.22). While analyses by quality of randomisation did not materially affect the results, mortality reduction among RCTs using a combination of topical and systemic antimicrobials was greater in trials using a "double-blind" design (OR = 0.63, 95% CI = 0.48–0.83) than in "unblind" studies (OR = 0.90, 95% CI = 0.74–1.08).

Mortality based on individual patient data analysis

Results are reported in Tables 5 and 6. Odds ratios, with their relative confidence intervals, are presented within specific categories of diagnostic category and severity score. Similarly to what emerged from the corresponding analyses – based on the larger data set available for the aggregate data analysis – a statistically significant reduction in overall mortality emerged from RCTs using a combination of topical and systemic antimicrobials (OR = 0.79, 95% CI = .65–0.97) but not from studies where the treatment protocol included only a topical drug (OR = 1.02, 95% CI = 0.81–1.30). Overall, the treatment effect did not seem to vary substantially by main diagnostic category or disease severity and, again, no clear trend by disease severity emerged.

Discussion

Ever since its introduction as an infection prevention method in critically ill patients, antibiotic prophylaxis based on SDD has remained controversial (Stoutenbeek et al. 1984). Lack of standard protocols and insufficient numbers of patients have made it difficult to derive meaningful conclusions from individual clinical trials. After initial enthusiasm following results from early uncontrolled studies and initial RCTs, antibiotic prophylaxis does not seem to be widely used as routine treatment in ICUs. The concern about the risk of long-term emergence of antimicrobial resistance and increased costs dominates in the most important documents on prevention of infections, such as the 'Guidelines for Prevention of Nosocomial Pneumonia' recently published by the Centre of Disease Control and Prevention and the Consensus Statement of the American Thoracic Society on 'Hospital-Acquired Pneumonia in Adults'. A conservative attitude in introducing a new treatment into practice is understandable as long as doubts regarding its efficacy and effectiveness exist. In fact, studies on prevention of ventilator-associated pneumonia in ICU patients are very complex because patients are heterogeneous, diagnosis of pneumonia is controversial, and outcome depends on so many factors. Despite the fact that the ability of antibiotic prophylaxis to reduce RTIs had emerged with remarkable consistency across individual trials, the effect on mortality was statistically significant in only one individual trial. Now that several MAs are available, however, the full potential of the treatment can be appreciated and it has become clear that the main reason why most trials failed to reach statistical significance was because they were substantially undersized in relation to the realistic magnitude of the treatment effect.

Indeed, the main limitation of MAs is that the patient populations, the antibiotic regimen and the outcome definitions are not the same across studies. Nonetheless, we believe that this type of analysis provides the best global picture of the effectiveness of the intervention.

Table 4 Effect of antibiotic prophylaxis based on a combination of topical and systemic antimicrobials on mortality derived from an individual patient data analysis

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

Table 5 Effect of antibiotic prophylaxis based on topical antimicrobials on mortality derived from an individual patient data analysis

APACHE II	nº of studies	Treated	Control	Odds Ratio 95%	Confidence Intervals
Medical					
0–14	8	18/108	19/117	0.99	0.47–2.06
15–29	6	77/205	77/232	1.08	0.72–1.62
> 30	9	15/29	13/23	1.09	0.32–3.68
Total		104/342	109/372	1.06	0.75–1.49
Surgical					
0–14	8	10/48	11/57	1.25	0.44–3.53
15–29	9	18/64	15/63	1.18	0.52–2.70
> 30	9	2/6	3/4	0.46	0.04–5.27
Total		30/118	29/124	1.13	0.16–2.12
Trauma					
0–14	12	17/238	19/303	1.20	0.59–2.46
15–29	11	36/231	54/312	0.84	0.52–1.34
> 30	12	4/8	6/12	1.17	0.10–13.26
Total		57/477	79/627	0.94	0.64–1.39
Overall		191/937	217/1123	1.02	0.81–1.30

Though there is no consensus on the best way to classify antibiotic prophylaxis regimens it seems appropriate to critically appraise the yield of the treatment considering separately regimens depending on the presence or absence of the systemic component.

Overall, the results of the two most recent MAs [9, 10] confirmed that both types of prophylaxis have a strong protective effect on RTIs – with the effect being more marked when patients are treated with a protocol using a topical plus systemic antibiotic. More importantly, they indicate that an antibiotic prophylaxis regimen including a combination of topical and systemic antibiotic significantly reduces overall mortality.

The treatment effect suggested by this systematic review looks important from a clinical and public health point of view (in terms of the therapeutic implications for the care of ventilated patients in ICUs) and is also relevant from the scientific standpoint as it highlights the future directions that research should take.

Implications for practice

The most efficient use of available data through MAs now indicates that a protocol using a combination of topical and systemic antibiotics reduces the occurrence of RTIs and overall mortality. The yield of the treatment (5 and 23 patients need to be treated to prevent one infection and one death, respectively) compares very favourably used in clinical practice. Results of this review should now be carefully considered by those intensivists who have been so far been unconvinced of the effective-

ness of antibiotic prophylaxis. Lack of data on cost-effectiveness and insufficient data on antibiotic resistance should stimulate future research rather than prevent the adoption of a seemingly effective intervention. Cost-effectiveness analysis in this context is – on the other hand – likely to be problematic. The impact of antibiotic prophylaxis on costs has been evaluated only rarely and, more importantly, in an improper way (the analysis being essentially based on comparisons of lengths of stay and computation of charges due to antibiotic use). A proper economic analysis is likely to be difficult in a highly specialised setting, such as the ICU, where it is hard to quantify the relative contribution of single procedures.

Implications for research

The number of RCTs of antibiotic prophylaxis so far conducted is substantial and provides sufficient statistical power to detect a moderate but humanly worthwhile effect of the treatment on mortality [9]. The combination of topical and systemic antibiotic is now the standard against which new treatments should be tested. A logical next step for future trials would seem to be the comparison of this protocol against a regimen based on a systemic antimicrobial only. It is unlikely, however, that one or more even large conventional trials can satisfy the concerns of those afraid that antimicrobial resistance may occur as a consequence of widespread use of antibiotics. In order to produce a satisfactory answer to this dilemma, perhaps trials with a different design should be conceived where the ICU, rather than the individual patient, becomes the unit of randomisation and where the occurrence of antibiotic resistance is monitored over a long period of time. Trials of this sort should be able to enrol a few thousand patients and should be designed in a pragmatic fashion concentrating on outcomes such as mortality, resistance and costs.

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