Antibiotic prophylaxis to prevent nosocomial infections in patients in intensive care units: evidence that struggle to convince practising clinicians

Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev 2006, in press.

Background. Pneumonia is an important cause of mortality in intensive care units. The incidence of pneumonia in such patients ranges between 7 and 40%, and the crude mortality from ventilator associated pneumonia may exceed 50%. Although not all deaths in patients with this form of pneumonia are directly attributable to pneumonia, it has been shown to contribute to mortality in intensive care units independently of other factors that are also strongly associated with such deaths.

Objectives. The objective of this review was to assess the effects of antibiotics for preventing respiratory tract infections and overall mortality in adults receiving intensive care.

Search strategy. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (issue 3, 2003), which contains the Acute Respiratory Infections (ARI) Group specialised trials register; MEDLINE (January 1966 to September 2003); EMBASE (January 1990 to September 2003); proceedings of scientific meetings and reference lists of articles from January 1984 to December 2002. We also contacted investigators in the field.

Selection criteria. Randomised trials of antibiotic prophylaxis for respiratory tract infections and deaths among adult intensive care unit patients.

Data collection and analysis. At least two reviewers independently extracted data and assessed trial quality.

Results. Overall 36 trials involving 6922 people were included. There was variation in the antibiotics used, patient characteristics and risk of respiratory tract infections and mortality in the control groups. In 17 trials (involving 4295 patients) that tested a combination of topical and systemic antibiotic, the average rates of respiratory tract infections and deaths in the control group were 36% and 29% respectively. There was a significant reduction of both respiratory tract infections (odds ratio 0.35, 95% confidence interval [CI] 0.29-0.41) and total mortality (odds ratio 0.78, 95% CI 0.68-0.89) in the treated group. On average 5 patients needed to be treated to prevent one infection and 21 patients to prevent one death. In 17 trials (involving 2664 patients) that tested topical antimicrobials alone (or comparing topical plus systemic versus systemic alone) the rates of respiratory tract infections and deaths in the control groups were 30 and 26% respectively. There was a significant reduction of respiratory tract infections (odds ratio 0.52, 95% CI 0.43-0.63), but not in total mortality (odds ratio 0.97, 95% CI 0.81-1.16) in the treated group.

Conclusions. A combination of topical and systemic prophylactic antibiotics reduces respiratory tract infections and overall mortality in adult patients receiving intensive care. A treatment based on the use of topical prophylaxis alone reduces respiratory infections, but not mortality. The risk of occurrence of resistance as a negative consequence of antibiotic use was appropriately explored only in the most recent trial by de Jonge, which did not show any such effect.

The methodologist's point of view

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Antibiotic prophylaxis in intensive care units: a simple interventions with multiple implications

People who need ventilation in intensive care units (ICUs) can develop respiratory tract infections or pneumonia. Some people die because of these infections and therefore attempts should be made to minimise the risks. 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 infections VAP has been shown to contribute to ICUs mortality independently on other factors, which are strongly associated with deaths oh these patients. Different antibiotic prophylaxis protocols have been used in different trials. The most common such protocol has been targeted to prevent infections by eradicating and preventing carriage of aerobic, potentially pathogenic micro-organisms from the oropharynx, stomach and the 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 day after patients admission to prevent "early" infections. Initial studies looked at infection morbidity as the main end-point and indicated that the treatment can reduce them, but it remained unclear whether there was a reduction in total mortality. Subsequent studies conducted between 1995 and 2000 tested different treatment regimes which did or did not included a systemic antibiotic in addition to the topical treatment and reported variable results which not always included a full account on the effect on mortality[1].

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An area where several systematic reviews exists, but not with a consistent message

Between 1991 and 1999 seven different systematic reviews (SRs) have been reported[1]. All confirmed a statistically significant reduction of respiratory tract infections, though the magnitudes of this effect varied as they were conducted at different time-points, included a different number of studies and used different quality threshold as study inclusion criteria. The effect on mortality emerged as both clinically relevant and statistically significant only in the two more recent SRs preceding the one that is now available in the Cochrane Library, where studies using a combined topical and systemic treatment were analysed separately from those using topical antimicrobials only.

The methodological challenges in interpreting trials on the effect of antibiotic prophylaxis

The interpretation of the totality of evidence on the effects of this intervention faces some common challenges inherent in the conduct of SRs as well as some specific ones.

Among the common challenges is worth reminding the difficulty of making sense and combine results from small individuals clinical trials of variable methodological quality (quality of randomisation, use of blinding techniques, etc.) and with often incomplete reporting on all the outcomes of interest. Among the specific ones worth mentioning here it has to be reminded that:

- different trials have been carried out in patients with highly variable spectrum of co-morbidities and therefore underlying risk of deaths;
- the risk of leading to an "epidemic of antibiotic resistance" should be seriously considered in situations where a large number of patients is exposed to antibiotic treatments in a close ecological environment such as the one of ICUs. Such risk, however, can hardly be assessed with the traditional short-term design of the typical clinical trials that are available for this review.

The main message of this review and its limited uptake in clinical practice

This review, which now includes studies published up to the end of 2005 and that is currently being updated, includes almost 7000 patients in 36 randomised control trials carried between 1984 and 2004. It suggests that the combined use of a topical and a systemic treatment can significantly reduce respiratory tract infections and overall mortality. The use of the topical combination alone seems to have a more modest effect on infections, which does not translate into an appreciable impact on mortality. The possible harm, due to the upsurge of antibiotic resistance as consequence of the widespread use of the treatment, has been formally assessed in only one recent trial where ICUs rather than patients have been the units of randomisation[2]. This is indeed the best design to assess whether antibiotic resistances emerge in an unbiased manner and further independent studies may be needed to rule out that this untoward effect may offset the positive effect of the prophylactic use of antibiotics. Although there are not reliable data on the current utilisation of antibiotic prophylaxis in patients seen in intensive care, most experts warns against its widespread use on the ground of the above-mentioned risk. It is therefore possible that many patients suffer avoidable morbidity and die because an effective treatment is not provided. Lacking this evidence of a negative effect intensivists should consider carefully the result of this Cochrane review when deciding whether a seemingly effective treatment, with a solid evidence of a favourable effect, should be withhold due to the possible harmful effect that has not been so far reliably measured. While it is true that lack of evidence of an effect is not demonstration of a lack of effect, this review indicates that even in the "evidence-based era" doctors should be ready to cope with uncertainty, but also weigh appropriately the consequence of positive and negative consequences of the application of incomplete information.

References

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The clinician's point of view

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Doctors operating in the era of evidence-based medicine every day face clinical problems requiring evidence, but fail to find consistent or complete evidence.

The problem of antibiotic prophylaxis to reduce

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respiratory tract infections and mortality in adults receiving intensive care finds useful information in this review.

However, the evidence indicating the efficacy of the combination of topical and systemic antibiotics is far from being definitive.

Normally, the translation into practice of this evidence is difficult and possibly confusing since:

- the methodological quality of the studies considered is not homogeneous;
- the antibiotics, their dosage and administration schedule are markedly different;
- the clinical conditions, the co-morbidities and related prognosis are very different;
- no clear indication is present, except in one study, on the possible occurrence of antibiotic resistance.

Therefore, in spite of the important meaning of this review, the intensivists going to treat his/her patient with the combination of treatments evaluated in this review will not apply a truly "evidence-based" treatment since the long-term possible untoward effect of antibiotic resistance, unrelevant for the actual patients, but potentially very harmful in the long-term for future patients, has only been addressed in one study.

At present and in the near future intensivists will have to decide whether or not to try to protect their patients although they are not provided with all the relevant evidence.

In the light of the favourable effect of the combined prophylaxis, information on the possible occurrence of antibiotic resistance under these conditions is urgently needed.