

Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review

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Abstract

Objective To review the evidence for effectiveness of treatment with antibiotics before admission in reducing case fatality from meningococcal disease.

Design Systematic review.

Data sources Cochrane register of trials and systematic reviews, database of abstracts of reviews of effectiveness, health technology assessment, and national research register in England and Wales, Medline, Embase, and CAB Health.

Included studies Studies describing vital outcome of at least 10 cases of meningococcal disease classified by whether or not antibiotics were given before admission to hospital.

Results 14 observational studies met the review criteria. Oral antibiotic treatment given before admission was associated with reduced mortality among cases (combined risk ratio 0.17, 95% confidence interval 0.07 to 0.44). In seven studies in which all included patients were seen in primary care, the association between parenteral antibiotics before admission and outcome was inconsistent (χ^2 for heterogeneity 11.02, $P=0.09$). After adjustment for the proportion given parenteral antibiotics before admission, there was no residual heterogeneity. A higher proportion of patients given parenteral antibiotics before admission was associated with reduced mortality after such treatment and vice versa ($P=0.04$).

Conclusion Confounding by severity is the most likely explanation both for the beneficial effect of oral antibiotics and the harmful effect observed in some studies of parenteral antibiotics. We cannot conclude whether or not antibiotics given before admission have an effect on case fatality. The data are consistent with benefit when a substantial proportion of cases are treated.

Introduction

Meningococcal disease often progresses rapidly, and delays in starting antibiotic treatment in hospital have an adverse effect on outcome.¹ Whether giving antibiotics before admission improves outcome of meningococcal disease, however, remains uncertain because studies of effectiveness show inconsistent results.^{2 3} This absence of consensus is reflected in differing policies across Europe. We reviewed the evidence for effectiveness of antibiotic treatment before admission on survival of patients with meningococcal disease to inform treatment policies in countries where these patients are likely to be initially seen in primary care.

Methods

We searched the Cochrane register of trials and systematic reviews, the database of abstracts of reviews

of effectiveness, the health technology assessment and the national research register in England and Wales, Medline (1 January 1966 to 31 January 2005), Embase (1 January 1983 to 31 January 2005), and CAB Health (1 January 1973 to 31 January 2005). See bmj.com for search terms. We also checked bibliographies of existing reviews. We contacted the Cochrane Acute Respiratory Infections group, World Health Organization, the European Monitoring Group on Meningococci, the Communicable Disease Surveillance Centre in the UK, and the Centers for Disease Control and Prevention in the United States for data that might be eligible for inclusion. We did not restrict on language.

We examined all titles, and abstracts when available, and retrieved full text of relevant papers; studies met inclusion criteria if they contained information on vital outcome of meningococcal disease and whether patients were treated with parenteral (intravenous or intramuscular) or oral antibiotics before admission and if they included at least 10 patients. Two reviewers independently assessed the papers. We extracted data on numbers of deaths stratified by treatment before admission to calculate unadjusted risk ratios.

Statistical analysis

We combined results of individual studies assuming random effects. Pooled estimates of the risk ratio for death were obtained with the method of DerSimonian and Laird. We tested for heterogeneity that was quantified by χ^2 and I^2 , which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than to chance. We investigated heterogeneity between studies by stratifying by severity and by applying meta-regression (see bmj.com).

Results

The search yielded a total of 2620 references. Fourteen papers met the criteria for inclusion in the study (see bmj.com). All 14 papers were observational cohort studies. The overall case fatality ratio was 6.0%, ranging from 3.3% to 14.6%. Twelve studies included both microbiologically confirmed and clinically diagnosed cases of meningococcal disease. Two studies included only microbiologically confirmed cases.

Oral antibiotics given before admission

In all five studies that included data on oral antibiotics given before admission this treatment was associated with reduced mortality (combined risk ratio 0.17, 95% confidence interval 0.07 to 0.44; fig 1). In one study this effect was significant ($P<0.05$). The test for



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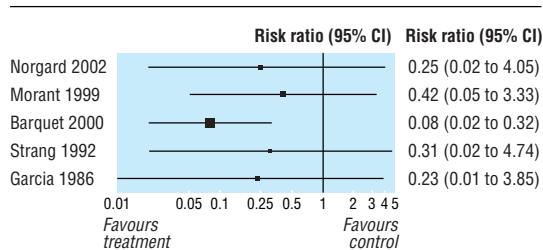


Fig 1 Estimated risk ratio for death in studies of oral antibiotic treatment before admission (square size is proportionate to study size)

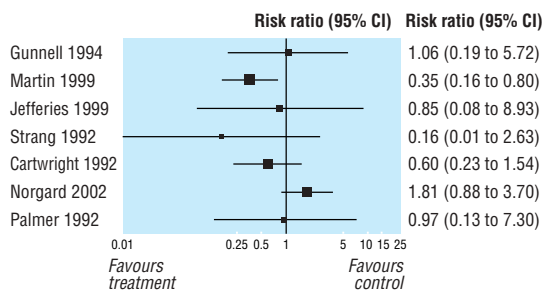


Fig 2 Estimated risk ratio for death in those studies of parenteral antibiotic treatment before admission in which all reported patients were seen in primary care (square size is proportionate to study size)

heterogeneity resulted in a χ^2 of 2.29 ($P = 0.68$), $I^2 = 0\%$ (95% uncertainty interval 0% to 79%).

Parenteral antibiotics given before admission

Twelve papers contained information on parenteral antibiotics given before admission and outcome. Eight papers showed a beneficial effect and four an adverse effect. One beneficial effect was significant. Seven studies presented data on patients seen in primary care (fig 2). The χ^2 for heterogeneity was 11.02 ($P = 0.09$), $I^2 = 46\%$ (95% uncertainty interval 0% to 77%). The proportion of cases treated differed among these studies, ranging from 15% to 59% ($P < 0.001$). The results were similar when we included all 12 studies in the analysis (χ^2 for heterogeneity 16.94, $P = 0.11$).

Parenteral antibiotics before admission in patients with “severe” disease

Five papers included data stratified by severity of disease. The proportion of all cases classified as severe differed between studies, ranging from 11% to 76% ($P < 0.001$). Severe disease was defined as skin bleeding (ecchymoses not petechiae) on admission to hospital, rash noted by referring general practitioner, septicaemia with hypotension or ecchymoses, or both, but no signs of meningitis, diagnosis suspected by referring doctor, and haemorrhagic rash on hospital admission. Three of these five studies presented data on patients seen in primary care. The χ^2 for heterogeneity was 7.97 ($P = 0.02$), $I^2 = 75\%$ (95% uncertainty interval 17% to 92%). In two studies parenteral treatment was associated with a beneficial effect on mortality among severe cases, whereas in one it was associated with an adverse effect. None of these effects was significant.

Explaining the heterogeneity

The estimated variance between studies in the log risk ratio from the meta-regression with the proportion of

cases treated as a covariate was 0.000 v 0.2263 from the “null” model. Thus, the proportion of cases treated explains 100% of the variance between studies. We found a log linear relation such that a higher proportion of patients given parenteral antibiotics before admission was associated with reduced mortality after such treatment and vice versa ($P = 0.04$, fig 3). The proportion of cases classified as severe did not explain the heterogeneity between studies.

Discussion

We must be cautious in drawing conclusions from this systematic review of the effects of antibiotic treatment before admission on survival from meningococcal disease. As all of the studies included were observational, they are prone to bias and confounding. In studies in which associations between treatment and outcome are investigated, prognostic factors may systematically differ between compared treatment groups as a doctor’s perception of severity is likely to determine the choice of treatment. This leads to confounding by severity.⁴

Studies in our review with data on oral antibiotics given before admission showed consistently improved survival among patients with meningococcal disease who received such treatment compared with those who did not. This is hardly surprising as doctors are likely to prescribe oral antibiotics only when they do not consider the diagnosis to be meningococcal disease. The latter is more probable in milder or slower progressing disease. Therefore we consider that the observed beneficial effect of oral antibiotics on survival is strongly confounded by severity, and we cannot conclude that the positive effect is genuine.

The effect of parenteral antibiotics was inconsistent in the papers included in our review. This inconsistency precluded estimation of a combined effect through meta-analysis. After we adjusted for the proportion of cases treated, the heterogeneity was removed. A higher proportion of patients given parenteral antibiotics before admission was associated with reduced mortality after such treatment and vice versa. This observation could be explained either through confounding by severity or by effect modification.

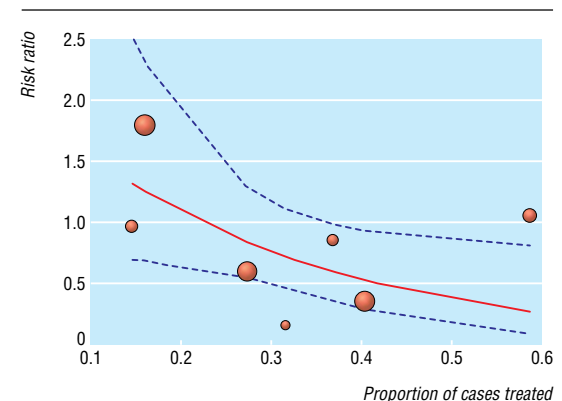


Fig 3 Relation between estimated risk ratio and proportion of treated cases in those studies of parenteral antibiotic treatment before admission in which all reported patients were seen in primary care (circle size is proportionate to study size; the solid line indicates the best fit regression model; the dotted line indicates the 95% confidence interval for this)

Confounding could account for an adverse effect if studies in which a lower proportion is treated are biased towards treating those with a higher a priori chance of dying. Effect modification, where the strength and direction of the association between parenteral antibiotics before admission and mortality depends on the proportion of cases treated, could also explain the observations in our review. This would imply a harmful effect of treatment when a low proportion of cases is treated, presumably in those with more severe disease.² The main concern with parenteral antibiotic treatment before admission is that treatment facilities in primary care may be inadequate to deal with haemodynamic instability that might result from massive release of meningococcal endotoxins during initial phases of the therapy.² However, this argument is not supported by experimental evidence.^{5,6} A case-control study published since we completed this review found an adverse effect of antibiotics before admission on outcome but no evidence of clinical deterioration in the interval between administration of penicillin and admission to hospital.⁷

Fear of anaphylactic reactions to benzyl penicillin could prevent general practitioners from treating patients when meningococcal disease is suspected, but genuine anaphylaxis is rare (about 1 in 7000-25 000 cases). Other concerns that have been raised argue that antibiotic treatment before admission may lower the proportion of patients who can subsequently be diagnosed by microbiological tests and delay the start of appropriate treatment in hospital.^{8,9} Clearly, this argument against giving antibiotics before admission is valid only if any adverse effect on outcome is greater than any positive effect of treatment before admission. Also, there are diagnostic alternatives available, such as polymerase chain reaction in blood or cerebrospinal fluid, which is much less affected by previous benzyl penicillin treatment.¹⁰

Confounding by severity is the most likely explanation both for the beneficial effect of oral antibiotics and the harmful effect observed in some studies of parenteral antibiotics. It is unlikely that studies of sufficient quality to give evidence of the effectiveness of antibiotic treatment before admission on survival in meningococcal disease will become available in view of the anticipated logistical and ethical difficulties. We cannot conclude from this review whether or not antibiotics given before admission have an effect on case fatality. The data are consistent with benefit when a substantial proportion of cases are treated.

What is already known on this topic

Delay in starting antibiotic treatment of meningococcal disease in hospital has an adverse effect on outcome

National guidelines in several European countries advise doctors in primary care to give parenteral antibiotics to patients with suspected meningococcal disease before transfer to hospital, though evidence of benefit is conflicting

What this study adds

Robust evidence of benefit (or harm) may never be obtained

Lower mortality after parenteral antibiotics before admission is associated with a higher proportion treated and vice versa

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Ethical approval: Not required.

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Parent power

It was never easy organising an examination in paediatrics. Inevitably, the most obvious patients to choose were those with chronic disease who had attended the hospital many times. During such visits, the family would have encountered any number of doctors and had to recite their child's history many times. Nevertheless, most recognised the importance of training and examinations, and so they were prepared to help. Of course, not only did they know a great deal about their child's condition, something the junior staff needed to recognise, but they often had shrewd opinion of the staff.

One exam candidate did quite unexpectedly badly in the long case. The child he had examined had a rare disorder and a

complex history, but the mother was a good historian and very capable. I discreetly inquired of the mother about the candidate's performance, and she implied she did not like his manner and approach—"So I did not help him."

I have no doubt that this mother had an excellent understanding of her child's condition and, from long experience, was a sound judge of the candidate's qualities. Should experienced parents be more involved in the training and assessment of aspiring paediatricians?

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