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

Susan J M Hahné, André Charlett, Bernadette Purcell, Susanne Samuelsson, Ivonne Camaroni, Ingrid Ehrhard, Sigrid Heuberger, Maria Santamaria and James M Stuart

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Research

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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

Invasive meningococcal disease is one of the most destructive acute infections in humans and remains an important cause of death in children in developed countries. Reducing such mortality depends on successful prevention and treatment. In most European countries, prevention of meningococcal disease is based on chemoprophylaxis and immunisation in contacts of patients with meningococcal disease. The United Kingdom, Ireland, Spain, Luxembourg, Belgium, and the Netherlands have started childhood immunisation programmes with a conjugate vaccine against *Neisseria meningitidis* serogroup C meningococcal disease. Attempts to reduce case fatality further remain necessary as in Europe most invasive meningococcal disease is caused by group B organisms,[1] for which a vaccine providing broad protection is not yet available.[2]

Mortality in patients with invasive meningococcal disease depends on variables including the age of the patient, the clinical manifestation (septicaemia/meningitis), characteristics of the organism (clonal complex), and case management.[3] Of these, only case management can be influenced by therapeutic intervention. Before serum therapy and effective antibiotic therapy were available, about 70% of patients with invasive meningococcal disease died.[4] After the introduction of treatment with antibiotics such as benzyl penicillin and cephalosporins, case fatality fell to around 10%. A tertiary care referral centre recently reported further reductions in case fatality that they attributed to improved clinical management.[5]

As meningococcal disease often progresses rapidly, it is not surprising that delays in starting antibiotic treatment in hospital have an adverse effect on outcome.[6] Whether giving antibiotics in primary care (that is, before admission) improves outcome of meningococcal disease, however, remains uncertain because studies of effectiveness show inconsistent results.[7 8] This absence of consensus is reflected in differing policies across Europe. Several countries, including the UK,[9] Ireland, and France, advise all doctors in primary care to consider giving parenteral antibiotics to all patients with suspected meningococcal disease before transfer to hospital. Many other countries do not give specific advice regarding such treatment.

A 1999 survey among members of the European Monitoring Group on Meningococci (EMGM) identified antibiotics before admission as one of the interventions for which public health policy differed most within Europe (J Stuart, personal communication). Chemoprophylaxis to prevent secondary cases of meningococcal disease is another, though a systematic review has shown it to be effective.[10] 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 seen initially 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). The textword terms and MESH headings used were: “meningococcal infections”,

Table 1 Cases of meningococcal disease and outcome stratified by oral antibiotic treatment before admission, excluding patients treated with parenteral antibiotics before admission

Study	Primary care*	No of deaths/No treated	No of deaths/No not treated	Total (% treated)	Case fatality (%)	Risk ratio for death† (95% CI)
Norgard[19]	Yes	0/27	26/375	402 (7)	6.5	0.25 (0.02 to 4.05)
Morant[17]	No	1/35	7/104	139 (25)	5.8	0.42 (0.05 to 3.33)
Barquet[18]	No	2/241	38/361	602 (40)	6.6	0.08 (0.02 to 0.32)
Strang[26]	Yes	0/5	6/23	28 (18)	21.4	0.31 (0.02 to 4.74)
Garcia[24]	No	0/16	7/58	74 (22)	9.5	0.23 (0.01 to 3.85)
Total	—	3/324	84/921	1245 (26)	7.0	0.17 (0.07 to 0.44)

*Study restricted to patients seen in primary care.
†In studies in which there were no deaths in patients treated with antibiotics, we added 0.5 to each of the four cells in the 2×2 table before the analysis.

"Neisseria meningitis", "chemoprevention", "prophylaxis", "chemoprophylaxis", "antibiotics", "drug therapy", "primary health care", "patient care management", "community health services", "communicable disease control", "disease outbreaks", "disease transmission", "cluster", "outbreak", "carrier state", "cases", "household". In addition, we checked bibliographies of existing reviews for potentially relevant papers. We contacted the Cochrane Acute Respiratory Infections group, WHO, 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 papers if we expected them to contain primary data on antibiotic treatment of meningococcal disease before admission and vital outcome. 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 whether these papers met criteria for inclusion in the review. If we identified two or more papers including the same data, we included only the one with the most data. We extracted data on numbers of deaths stratified by treatment before admission to calculate unadjusted risk ratios. In studies presenting data on both oral and parenteral antibiotic treatment, patients treated with oral antibiotics were classified as "untreated" when we analysed effect of parenteral antibiotics.

Statistical analysis

We combined results of individual studies using the metan command in Stata[11] assuming random effects. Pooled estimates of the risk ratio for death were obtained with the method of DerSimonian and Laird. In those studies in which there were no deaths in patients treated with antibiotics, we added 0.5 to each of the four cells in the 2×2 table before analysis. We tested heterogeneity using the appropriately weighted sum of the estimated log risk ratios from individual studies minus the Mantel-Haenszel pooled estimate. Heterogeneity 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.[12] In the resulting forest plots, the size of the circles presenting point estimates of the risk ratio for death is proportional to the weight of the study in the meta-analysis. We investigated heterogeneity between studies by stratifying by severity and by applying meta-regression (the metareg command in Stata). We carried out meta-regression by using two random effect regression models, separately including two study level covariates: the proportion of cases treated with parenteral antibiotics before admission and the proportion of cases classified as severe. The natural logarithm of the risk ratio and its standard error as estimated in the random effects meta-analysis have been used as the dependent variable and the within study standard error, respectively. We estimated the variance between studies with an iterative maximum likelihood approach.[13]

Results

The search yielded a total of 2620 references. After we examined all titles and available abstracts, we retained 66 papers. We identified five more potentially useful papers by searching reference lists of included papers and one more through contact with experts. Both reviewers agreed that 14 papers met the criteria for inclusion in the study (fig 1).[8 14–26] All 14 papers were observational cohort studies; no case-control study or randomised controlled trial met the inclusion criteria. The overall case fatality ratio was 6.0%, ranging from 3.3%[14] to 14.6%.[26] Twelve studies included both microbiologically confirmed and clinically diagnosed cases of meningococcal disease.[8 14–16 18–23 25 26] Two studies included only microbiologically confirmed cases.[17 24] Some studies included data from earlier publications by the same research group.[18 19] We did not include these earlier studies[7 27 28] in our analysis.

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; table 1 and fig 2). In one study this effect was significant ($P<0.05$).[18] The test for 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 (table 2). One beneficial effect was significant.[14] Seven studies presented data on

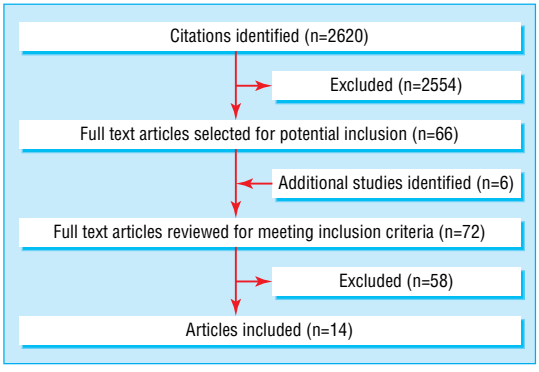

Fig 1 Eligibility of studies for inclusion in systematic review

Table 2 Cases of meningococcal disease and outcome stratified by parenteral treatment before admission, not excluding patients treated with oral antibiotics before admission

Study	Primary care*	No of deaths/No treated	No of deaths/No not treated	Total (% treated)	Case fatality (%)	Risk ratio for death† (95% CI)	Antibiotic treatment
Barquet[18]	No	1/41	40/602	643 (6)	6.4	0.37 (0.05 to 2.60)	Parenteral
Cartwright[8]	Yes	5/93	22/246	339 (27)	8.0	0.60 (0.23 to 1.54)	Parenteral
Gunnell[25]	Yes	3/27	2/19	46 (59)	10.9	1.06 (0.19 to 5.72)	Benzyl penicillin
Halstensen[22]	No	2/11	16/200	211 (5)	8.5	2.27 (0.60 to 8.67)	Parenteral
Jefferies[16]	Yes	1/24	2/41	65 (37)	4.6	0.85 (0.08 to 8.93)	Parenteral
Jolly[20]	No	2/72	16/186	258 (28)	7.0	0.32 (0.08 to 1.37)	Benzyl penicillin
Martin[14]	Yes	7/442	29/650	1092 (40)	3.3	0.35 (0.16 to 0.80)	Parenteral
Norgard[19]	Yes	9/77	26/402	479 (16)	7.3	1.81 (0.88 to 3.70)	Parenteral
Palmer[23]	Yes	1/11	6/64	75 (15)	9.3	0.97 (0.13 to 7.30)	Penicillin
Strang[26]	Yes	0/13	6/28	41 (32)	14.6	0.16 (0.01 to 2.63)	Penicillin
Wood[21]	No	1/7	2/33	40 (18)	7.5	2.36 (0.25 to 22.54)	Benzyl penicillin
Woodward[15]	No	0/13	3/55	68 (19)	4.4	0.57 (0.03 to 10.43)	Parenteral
Total	—	32/831	170/2526	3357 (25)	6.0	—	—

*Study restricted to patients seen in primary care.
†In studies in which there were no deaths in those treated with antibiotics, we added 0.5 to each of the four cells in the 2×2 table before analysis.

patients seen in primary care (fig 3). 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%[23] to 59% (P < 0.001).[25] The results were similar when we included all 12 studies in the analysis (χ^2 for heterogeneity 16.94, P = 0.11).

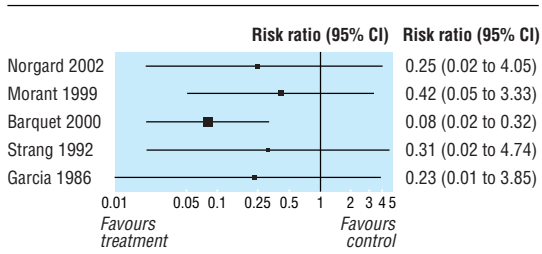

Fig 2 Estimated risk ratio for death in studies of oral antibiotic treatment before admission (square size is proportionate to study size)

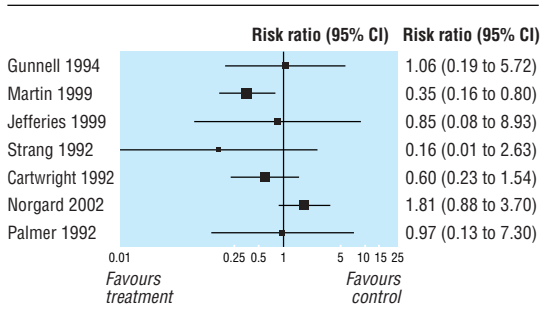

Fig 3 Estimated risk ratio for death in those studies of parenteral antibiotic treatment before admission in which all reported patients were seen in primary care (square size is proportionate to study size)

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%[19] to 76%[26] (P < 0.001). Severe disease was defined as skin bleeding (ecchymoses not petechiae) on admission to hospital,[19] rash noted by referring general practitioner,[8] septicaemia with hypotension (systolic blood pressure ≤ 70 mm Hg in those aged ≤ 12 years; ≤ 100 mm Hg in those aged > 12 years) or ecchymoses, or both, but no signs of meningitis,[22] diagnosis suspected by referring doctor,[26] and haemorrhagic rash on hospital admission.[15] 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,[8 26] whereas in one[19] it was associated with an adverse effect (table 3). 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 4). The proportion of cases classified as severe did not explain the heterogeneity between studies.

Table 3 Cases of meningococcal disease and outcome stratified by parenteral treatment before admission, not excluding patients treated with oral antibiotics before admission, in those cases classified as severe

Study	Primary care*	No of deaths/No treated	No of deaths/No not treated	Total (% treated)	Case fatality (%)	Risk ratio for death† (95% CI)
Cartwright[8]	Yes	4/75	12/102	177 (42)	9.0	0.45 (0.15 to 1.35)
Halstensen[22]	No	2/4	12/35	39 (10)	35.9	1.46 (0.49 to 4.30)
Norgard[19]	Yes	7/16	7/37	53 (30)	26.4	2.31 (0.97 to 5.51)
Strang[26]	Yes	0/13	4/18	31 (42)	12.9	0.15 (0.01 to 2.58)
Woodward[15]	No	0/12	3/35	47 (26)	6.4	0.40 (0.02 to 7.15)
Total	—	13/120	38/227	347 (35)	14.7	—

*Study restricted to patients seen in primary care.
†In studies in which there were no deaths in those treated with antibiotics, we added 0.5 to each of the four cells in the 2×2 table before analysis.

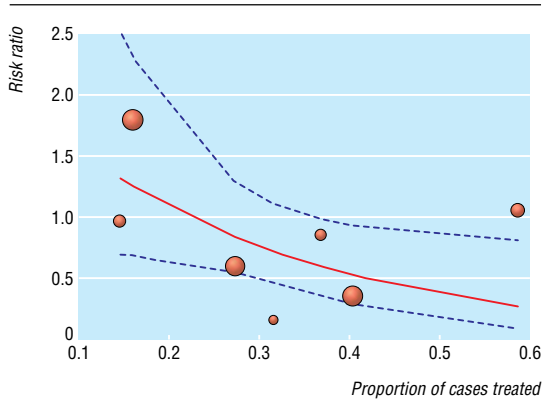

Fig 4 Relation between estimated risk ratio and proportion of treated cases in those studies of parenteral antibiotic treatment before admission in which all reported patients were seen in primary care (circle size is proportionate to study size; the solid line indicates the best fit regression model; the broken line indicates the 95% confidence interval for this)

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. Though all of the studies included were observational, they can provide useful information in instances where randomised controlled trials are unethical or impracticable. Such studies, however, are prone to bias and confounding. In studies in which associations between treatment and outcome are investigated, such as those included in our review, 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.[29]

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 case of 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.

Confounding

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. For example, in Denmark, at the time of the study of Norgard et al,[19] antibiotics before admission were recommended only in those cases of suspected meningococcal disease when petechiae or other signs of meningococcal sepsis were present or if the patient showed other signs of severe meningitis and the transport time to the nearest hospital was more than half an hour.

Effect modification

Effect modification, where the strength and direction of the association between parenteral antibiotics before admission and mortality depend 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.[7] 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.[7] However, this argument is not supported by experimental evidence. Prins et al found that free endotoxin and cytokine concentrations were significantly lower after exposure to antibiotics in vitro compared with in untreated samples.[30] Also, in vivo studies have consistently shown rapid decreasing concentrations of lipopolysaccharides (the main endotoxin) after bactericidal antibiotic treatment in meningococcal disease.[31] A case-control study published since we completed this review found an adverse effect on outcome of antibiotics before admission but no evidence of clinical deterioration in the interval between administration of penicillin and admission to hospital.[32]

Fear of anaphylactic reactions to benzyl penicillin could prevent general practitioners from treating patients when meningococcal disease is suspected, but genuine anaphylaxis is rare; it is estimated to occur in about 1 in 7000-25 000 cases.[33] 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.[34 35] 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, or isolation of meningococci from the posterior pharyngeal wall, which are much less affected by previous benzyl penicillin treatment.[36]

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. Studies with detailed data on severity of disease, disease evolution, and characteristics of subsequent hospital treatment could allow improved adjustment for confounding. As severity of disease and disease evolution are difficult to measure accurately, especially in retrospective studies, adequate adjustment for these factors is not likely to be achievable. Randomised controlled trials investigating the effect of antibiotic treatment before admission on outcome of meningococcal disease would be needed to examine this question. Such studies may never be done 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.

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Contributions: JMS initiated the working group, SJMH, BP, SS, IC, IE, SH, and MS were members of the working group sharing discussions on methods, findings, and interpretations. SJMH and JMS reviewed all included papers and are guarantors. SJMH extracted the data. AC did the statistical analyses. All authors contributed to writing the paper.

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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