



Critically Appraised Article

There are no studies of sufficient quality to determine the effectiveness of antibiotic treatment administered before admission to the hospital in reducing the mortality of invasive meningococcal disease

José Cristóbal Buñuel Álvarez. ABS Girona-4 (Institut Català de la Salut). Girona (Spain).
e mail: p416ucua@pgirona.scs.es

English key words: meningitis, meningococcal: drug therapy; meningitis, meningococcal: mortality; sepsis: drug therapy; sepsis: mortality

Spanish key words: meningitis meningocócica: tratamiento farmacológico; meningitis meningocócica: mortalidad; sepsis: tratamiento farmacológico; sepsis: mortalidad

Received: 12 July 2006
Accepted: 19 July 2006

Publisher: 1 December 2006

Evid Pediatr. 2006; 2: 68 doi: vol2/2006_numero_4/2006_vol2_numero4.4e.htm

How to cite this article

Buñuel Álvarez JC. There are no studies of sufficient quality to determine the effectiveness of antibiotic treatment administered before admission to the hospital in reducing the mortality of invasive meningococcal disease. Evid Pediatr. 2006; 2: 68

To receive Evidences in Paediatrics in his e-mail you must be discharged in our bulletin by ETOC
<http://www.aepap.org/EvidPediatr/etoc.htm>

Este artículo está disponible en: http://www.aepap.org/EvidPediatr/numeros/vol2/2006_numero_4/2006_vol2_numero4.4e.htm
EVIDENCIAS EN PEDIATRÍA es la revista oficial del Grupo de Pediatría Basada en la Evidencia de la Asociación Española de Pediatría de Atención Primaria. © 2005-06. Todos los derechos reservados

There are no studies of sufficient quality to determine the effectiveness of antibiotic treatment administered before admission to the hospital in reducing the mortality of invasive meningococcal disease

José Cristóbal Buñuel Álvarez. ABS Girona-4 (Institut Català de la Salut). Girona (Spain).
e mail: p416ucua@pgirona.scs.es

Bibliographic reference: Hahné SJM, Charlett A, Purcell B, Samuelsson S, Camaroni I, Ehrhard I, et al. Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. *BMJ*. 2006; 332: 1299-303

Structured abstract:

Objective: to determine if the administration of antibiotic (ATB) treatment before admission to hospital reduces mortality by invasive meningococcal disease (IMD).

Data sources: the authors 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", "Neisseria meningitidis", "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, they checked bibliographies of existing reviews for potentially relevant papers. They also contacted the Cochrane Acute Respiratory Infections group, WHO, the European Monitoring Group on Meningococci, the Communicable Disease Surveillance Centre in the UK, and the Centres for Disease Control and Prevention in the United States for data that might be eligible for inclusion. They did not restrict on language.

Selection of studies: selection criteria: 1) studies that included information on the final result of the participants; 2) they should have information on the use or not of oral or parenteral (intramuscular or intravenous) antibiotic treatment before admission; 3) sample size of at least 10 persons. There is no reference in the study to the method used to evaluate the validity of the selected studies. The search recovered 2.629 references. Fourteen met the inclusion criteria. All studies were cohort studies. No clinical essay was recovered.

Data extraction: two reviewers evaluated independently the fulfilment of the selection criteria and extracted data for deaths and ATB treatment before admission to hospital. Analysis of heterogeneity was applied. The results were combined, when indicated, by meta-analysis (MA) based on a model of aleatorial effects.

Main results: 1.-Oral ATB treatment before admission (five studies): reduced mortality was detected (relative risk: 0.17; confidence interval 95% (CI 95%): 0.07 to 0.44; test for heterogeneity: I^2 : 0%; CI 95%: 0 to 79%.

2.-Parenteral antibiotic treatment before admission (12 studies): The results were not combined due to the variability between the studies, especially in the percentage of cases that received treatment (15-59%). Eleven studies showed no significant association between treatment and survival, and one did show a protective effect. A considerable percentage of variability can be due to the heterogeneity between the studies (I^2 : 46%; CI 95%: 0 to 77 %).

3.-Parenteral antibiotic treatment before admission in patients with severe IMD (five studies): the percentage of cases considered serious varied widely between studies -11% to 76%-, with significant heterogeneity (I^2 : 75%; CI 95%: 17-92%). The studies were not combined. Two studies showed a non significant tendency towards a beneficial effect for the reduction of mortality and one showed a harmful effect. Association existed between the number of cases that received parenteral ATB and a reduction in mortality: the more cases treated, the lower the mortality ($p = 0,04$).

Conclusion: due to the variability between the studies and the presence confounding effect of severity on survival, it is not possible to determine whether ATB administered before admission reduce mortality by IMD.

Competing interests: none declared.

Financial source: two meetings of the group that developed the review were financed by Wyeth-Lederle. SMJ. Hahmé y I. Camarón received a scholarship from the European Programme for Intervention Epidemiology Training (EPIET).

Commentary:

Justification: IMD is the infectious disease that causes greatest morbi-mortality in the developed countries. Some health services recommend the antibiotic administration before admission in those cases that are visited by the primary care doctor in the first case^{1,2}. The efficacy of this measure is, however, object of controversy.

Validity: this is a correctly designed systematic review (SR), of cohort studies.

Limitations are: the lack of a validity analysis of each individual study and the lack of an a priori definition of the degree of severity of the disease, basing the classification of severity of disease on each individual study (principal cause of heterogeneity). The severity in the moment of

diagnostic suspicion may have acted as a confusion factor due to the fact it was related to a greater probability of antibiotic treatment and with mortality.

Clinical relevance: one case control study³ of 448 children with IMD found that parenteral ATB before hospital admission was associated with a greater mortality (odds ratio [OR]: 7.4; CI 95%: 1.5 to 37.7). This type of studies are very prone to bias because they depend on the existence of exhaustive medical records and on the capacity of the general doctor of recalling with precision information on cases treated long ago. In this case both biases can be present. The OR was calculated only in a subgroup of 156 children that were seen by the general practitioner and were eligible for antibiotic treatment, selecting in this way the more severe cases. The percentage of deaths in this group of children was 19.7% versus 36.2% -77 of 213- of the children that, were either seen by the general doctor and were not diagnosed of IMD or else went directly to the emergency. The authors recognize the possible existence in their study of this paradox of Simpson^{4**}.

The consideration of the severity of the disease in the outpatient clinics, in the SR and also in the case-control study mentioned previously, can have acted as a confusion factor: 1) suggesting that oral antibiotics are effective in reducing the mortality (SR), due to the fact that the doctor probably diagnosed another type of mild infectious disease when it was really a low grade IMD in the moment of consultation, and 2) suggesting that parenteral ATBs increase mortality by the disease, when what probably occurs is that the more severe cases are those that do not pose a diagnostic doubt to the practitioner, but have a worse prognosis and a greater mortality.

New Zealand² has a national register for the follow up of cases that in the periods 2001-2005 found a reduced mortality in the children treated with ATB before admission (1.8% versus 2.7%, also included in the SR).

Applicability in clinical practice: it is not possible in the present situation to determine whether ATB (oral or parenteral) given in the pre-hospital settings are effective in reducing the mortality from IMD. The only possibility is the making of a clinical trial. However it seems reasonable that in the pre hospital setting, especially if the referral hospital is far away to administer parenteral antibiotics as well as other measures of vital support (iv. fluids) if the state of the patient requires it, and the existence of a pre established emergency system that assures an adequate stabilization of the child during its transfer to the hospital.

Methodological note:

* I²: Quantifies the percentage of variability of effect estimated attributable to heterogeneity more than to chance. Values greater than 50% are considered substantial.

** Simpson's paradox: exceptional mathematic effect by which the presence of a confounding factor can invert the direction of association. In this case, the severity

(confounding factor) could have been the cause of this inverse finding (from potentially protective to very harmful).

Bibliography:

- 1.- Public health laboratory service. Pre-admission benzyl penicillin for suspected meningococcal disease: other antibiotics not handed in the GP bag [en línea] [fecha de consulta: 11-IV-2006]. Disponible en: <http://www.hpa.org.uk/cdr/archives/2001/cdr0701.pdf>
- 2.- Martin D, Lopez L, McDowell R. The Epidemiology of Meningococcal Disease in New Zealand in 2005. Report prepared for the Ministry of Health by the Institute of Environmental Science and Research Limited (ESR). Wellington: Ministry of Health; 2006.
- 3.- Harnden A, Ninis N, Thompsom M, Perera R, Levin M, Mant D, et al. Parenteral penicillin for children with meningococcal disease before hospital admission: case-control study. *BMJ*. 2006; 332: 1295-8..
- 4.- Perera R. Statistics and death from meningococcal disease in children. *BMJ*. 2006; 332: 1297-8.