OUT-PATIENT ANTIBIOTHERAPY AND MORTALITY CAUSED BY INVASIVE MENINGOCOCCAL DISEASE, ADJUSTING FOR INDICATION BIAS.

Running Title: Antibiotics and mortality for Neisseria meningitidis.

Word length: 2726.

ABSTRACT

Background: Mortality for invasive meningococcal disease (IMD) has remained stable in the last thirty years. It is unclear if out of hospital antibiotherapy truly decreases mortality. Objective: to investigate if out of hospital oral antibiotherapy reduces mortality for IMD, adjusting by indication bias. Design: retrospective analysis of clinical reports with main diagnosis of IMD since 1995 to 2000 in Andalucía and Canary Islands (Spain), exploring the relationship between use of out of hospital oral antibiotherapy and mortality. The indication bias was controlled using propensity score technique: a multivariate analysis was performed to assign each patients the probability to receive or not antibiotics in order to the symptoms previous at admission. Patients: all the patients discharged or death at hospital with main diagnosis in the clinical report of IMD. Measurements: death during admission at hospital, use of antibiotics, demographic variables. Results: 848 patients were collected, 49 (5.72%) of whom died. 226 had received oral antibiotics previously at admission at hospital, overall betalactámicos in the previous 48 hours. After adjusting relationship between use of antibiotics and death by age and the time between beginning of symptoms and in-hospital antibiotherapy treatment, out of hospital oral antibiotherapy remained as a protection factor (Odds ratio for death 0.37, CI 95%: 0.15-0.93). Conclusions: Out of hospital oral antibiotherapy is a beneficial intervention to reduce mortality for IMD.

Word length: 235.
INTRODUCTION

Invasive Meningococcal Disease (IMD) still remains an important cause of morbidity and mortality worldwide (1). Though the statistics have improved for in-hospital antibiotics use and intensive care support, mortality in relationship with IMD has remained stable in the last thirty years (2). Out of hospital antibiotic therapy has been recommended to lower the incidence of IMD-associated mortality (3,4), but an important controversy still remains: a recent systematic literature review showed that indication bias was present in all the studies published, and no definitive advice could therefore be given concerning this medication (5). The indication bias was present in outpatients receiving parenteral antibiotics and in those receiving oral antibiotic therapy. In the first, probably the worse prognosis patients are those that receive out of hospital parenteral antibiotics (6,7), and the benefit of the intervention is difficult to show. In the second group (patients receiving out of hospital oral antibiotics), probably the better a priori prognosis patients are those that receive the oral antibiotics, probably they have less explosive clinical course, or they have less alarm symptoms, we are indicating the antibiotics at those with less sever forms of IMD (indication bias), and therefore the actual effect of the intervention cannot be postulated.
To elucidate the repercussion of oral antibiotics use, a randomised, clinical trial within the context of IMD is difficult to design, as the disease generally requires a very high index of clinical suspicion for its diagnosis in the beginning of the process.

In this study we attempted to analyse the effect of out-patient oral antibiotics controlling for indication bias through the statistical technique called *propensity score*. Propensity score was proposed in 1983 as a technique to control the *a priori* probability of receiving one or another treatment (8), attempting to equate with randomisation in circumstances where this is not possible. In this study, we used the propensity score to assign each patient the possibility of out-patient oral antibiotherapy in accordance with symptoms registered before hospital admission, thereby attempting to match the likelihood of receiving or not receiving a treatment (extra-hospital antibiotic therapy) depending on the symptoms recorded in the clinical history, as these are not affected by the posterior use of antibiotics, rather they are the reason for the antibiotherapy. Recording the objective data found on examination in all the patients from the onset of symptoms is not possible. However, it is easy to collect the symptoms from a history and seek any possible association of any symptom or symptoms with a better or worse prognosis of the IMD.

**METHODS**

**Design**

We conducted a retrospective follow-up study from week 40th in 1995 to week 41st in 2000 in thirty-one hospitals from Andalucía and Canary Islands, in Spain.
Patients

All the cases of IMD were coded on patient discharge reports, from diagnostic registries at each hospital and were collected during the study period. Eligible patients were all those with a diagnosis of IMD who were older than one year. The diagnosis was interpreted as definite if there was a microbiologic culture of *Neisseria meningitidis* from a sterile sample, probable if this condition was not fulfilled but there was a gram stain compatible with *Neisseria meningitidis*, and possible if neither of these two were fulfilled but the diagnosis was based on clinical suspicion.

Variables and Measurements

The following variables were recorded: demographic data (sex, age); number of contacts with Health Services at which the patient presented similar symptoms to those leading to hospital admission; symptoms prior to admission; physical signs at admission to the emergency department, including axilar temperature, heart rate and systolic blood pressure; use of oral antibiotics during the two weeks before admission; time from onset of symptoms to administration of parenteral betalactams; and status at discharge. Microbiological data collected included the results of blood cultures and/or cerebrospinal fluid (CSF) and a Gram stain.

Statistical Analysis

We estimated that at least 1,103 patients would be needed to achieve 80% power to detect an odds ratio (OR) of 2, assuming a 30% prevalence of outpatient antibiotic use, a mortality rate of 5% in persons not using antibiotics and a two-sided α of 5%. The primary end point was mortality during hospital stay. The mean and 95% confidence interval (CI) were calculated for the quantitative
variables, and the percentages for the qualitative variables. A univariate analysis was performed for the result variable “death”, estimating the OR and its corresponding 95% CI.

*Propensity score* was defined as the probability of receiving out-patient oral antibiotics in accordance with the symptoms present prior to admission. We chose the symptoms according to the natural progression of IMD and so, decided to prescribe antibiotics. To estimate this probability, we performed a logistic regression analysis with all the symptoms as independent variables and the use of antibiotherapy (yes/no) as the dependent one, using as inclusion criteria for independent variables a p<0.05. Secondly, we performed a further logistic regression with *propensity score*, out-patient oral antibiotics, time from onset of symptoms to parenteral antibiotics and age as independent variables and mortality as the dependent variable. The extra-hospital use of antibiotherapy and the variable *propensity score* were forced to enter the model, with the other variables included in the model if they fulfilled the statistical criteria (p<0.05). We repeated this analysis excluding clinical suspicions.

**RESULTS**

**Description of the cohort and univariate association with death.**

A total of 848 patients were studied, 49 (5.72%) of whom died. The mean age of the cohort, 449 (52.9%) of whom were male, was 10.36 years (95% CI, 9.44-11.27). The older the patient, the greater the mortality, with 4.9% deaths in patients under 11 years of age vs. 25% deaths in those older than 65.

The number of health service contacts prior to admission was zero in 502 patients (59.2%) and one in 269 (31.7%). No difference in mortality was
observed depending on the number of health service contacts. No deaths occurred among those who had three or more contacts prior to admission.

Table 1 shows the symptoms recorded in the clinical history, with the corresponding OR exploring the association with mortality. The most frequent symptom was fever, while convulsions were the first symptom to appear on admission. More specific symptoms of IMD, such as petechiae, occurred in just over half the patients, and had a mean duration of eight hours before admission. The presence of convulsions and cold-like symptoms was significantly associated with a greater proportion of deaths, whereas the presence of nausea/vomiting was a protective factor. The physical signs and symptoms on admission to hospital are shown in Table 2. Again, the most frequent symptom was fever, followed by petechiae.

The mean axillary temperature, measured in the emergency room in 678 patients (80%), was 38.23°C (95% CI, 38.15-38.33). The average heart rate, measured in 519 patients (61.2%), was 127.99 beats per minute (95% CI, 125.13-130.85) and the mean systolic blood pressure, measured in 572 patients (67.5%), was 102.66 mmHg (95% CI, 100.78-104.54). An axillary temperature \( \geq 40^\circ C \), a heart rate \( \leq 60 \) bpm or a systolic blood pressure \( \leq 80 \) mmHg were associated with a greater proportion of deaths (OR for each: 3.97, 95% CI, 1.14-14.29; 20.69, 95% CI, 4.43-96.54, and 2.71, 95% CI, 1.31-5.6, respectively).

Of the entire cohort, 226 patients (26.7%) received out-patient oral antibiotics. The mortality in patients taking antibiotics was 2.7% vs. 6.9% in patients who were not (OR: 0.37, 95% CI: 0.15-0.88). The main group of antibiotics used was betalactams (181 patients), followed by macrolides (36 patients). The vast majority of patients (92.16%) had begun antibiotics in the 48
hours prior to admission. The main point of indication for antibiotic therapy was the primary care physician (48.2%), followed by hospital doctors (26.8%). Ten point five percent of the patients who took antibiotics had self-medicated. The mean time from the first symptoms to the first dose of parenteral antibiotic in the hospital was 29h 45 min. No difference was seen in survival between those who had taken antibiotics prior to arrival at the hospital and those who had not.

A total of 323 patients (38.1%) had sepsis, 336 (39.6%) meningitis and the rest a mixed clinical form, with mortality rates of 10.7%, 2.1% and 4.2%, respectively (p<0.001). Sepsis vs. the other clinical forms had an OR for death of 4.08 (2.18-7.62).

**Logistic regression analysis**

The prior regression model to estimate the predicted probability of the indication for pre-hospital antibiotics use included all of the symptoms in Table 1. Logistic regression analysis was made to control the association between out-patient antibiotherapy and in-hospital mortality, adjusting for propensity score, time from first symptoms to first dose of parenteral antibiotic in hospital and age. Clinical forms was excluded because it presented colinearity with symptoms. In this analysis, only age and use of antibiotics were significantly associated with death. The OR for age was 1.03 (95% CI, 1.01-1.04) and for the use of antibiotics 0.37 (95% CI, 0.15-0.93). No other variable had a significant association. Thus, the OR for death in patients who did not take antibiotics was 2.7 (95% CI, 1.07-6.66) and the number needed to treat (NNT) to avoid a death was 23.48 (95% CI, 13.98-73.22).
When the logistic regression analysis was performed with the cohort excluding the clinical suspicions, age continued showing a significant association with death (OR 1.03; 95% CI, 1.01-1.05) but not the use of antibiotics (OR 0.4; 95% CI, 0.11-1.4).

**Discussion**

The use of oral antibiotherapy prior to hospital admission showed a significant benefit in terms of mortality. This effect was controlled for indication bias. It is evident that the use of antibiotics diminishes the mass of *Neisseria meningitidis*, and that the production of cytokines and endotoxins could be lower in patients taking pre-hospital antibiotics(9). Previous studies have shown that the use of prehospital antibiotics is associated with less culture positivity (supporting the hypothesis of a greater reduction in bacterial mass) and a lower rate of clinical complications (10).

Our study was developed before the massive vaccination of children against *Neisseria meningitidis* but the effect of antibiotics later on is very probably the same now, because the protection was independent of serogroup. On the other hand, mortality during outbreaks is greater than during an endemic situation(11). The first was when Spain was suffering an outbreak and cases for this study were being collected. In order to our results, we cannot therefore affirm that the use of extra-hospital oral antibiotherapy is beneficial out of an outbreak. In fact, we did not collect data concerning whether prehospital antibiotherapy was oral or parenteral, but we assumed what we considered the worst possibility as antibiotic therapy had, in most cases, been prescribed by the primary care physician, with no suspicion of IMD.
An important group of patients not included in this study involves those who died before hospital admission with a diagnosis of IMD. This, obviously, is a special group and we cannot assess the efficacy of their treatment. Another source of confusion concerns the patients with suspected IMD, as symptoms could pertain to diseases other than IMD. However, the logistic regression results for the entire cohort and for the cohort excluding these patients were similar.

Only five cohort studies have so far been published exploring the relationship between the use of oral antibiotics and mortality for IMD (12-16). Except for the cohort published by Barquet et al, no other study controlled the relationship between use of antibiotics and death for any covariable. Although all the studies found a benefit in the use of oral antibiotics, some authors, such as Morant, advise not using them, because their use reduces the possibility of a microbiological diagnosis and the benefit in terms of survival is not significant. Indication bias can be observed in the work of García et al, in which all the patients who received oral antibiotherapy presented meningitis as a clinical form at admission to hospital. Only the study by Barquet et al found a significant association between oral antibiotics and mortality. This association was controlled for age, neurological focus and haemorrhagic diathesis. Of these groups studied two could be inferred by the use of antibiotics (neurological focus and haemorrhagic diathesis), in other words, pre-hospital antibiotics could, theoretically, influence in the appearance or not of these two symptoms; thus, the use of clinical items at admission to hospital is not a good way of controlling the previous use of antibiotherapy. As the use of antibiotics may well modify the progression and prognosis of IMD, it is preferable to control the
relationship between antibiotics and mortality through a variable that is less affected by treatment. Accordingly, we built our propensity score using symptoms studied in the anamnesis. This explains why antibiotics were prescribed and deaths were less affective than all the facts collected in the emergency room. The other three studies did not control for the effect of antibiotics on mortality due to IMD. The comments to the studies with oral antibiotics were uniform. We did not know if they were giving treatment to a group of patients who were healthier than those not taking antibiotics, as a recent systematic review of the literature noted (17).

Simulation studies show that the choice of variables used to construct the propensity score affects the bias (18). Variables not associated with exposure but associated with the result should be included in the design of the propensity score, as they reduce the variance in the effect of the exposure without affecting the bias. Inclusion of variables associated with exposure but not with effect, increases the variance of the effect of the exposure without reducing the bias. However, certain limitations exist for the adequate use of the propensity score. Simulation studies suggest that standard model-building tools designed to create good predictive models of the exposure will not always lead to optimal propensity score models, particularly in small studies, which is not our case. No evidence was found in our study for these problems related with the construction of the propensity score. On the contrary, the univariate analysis showed that the variables of prehospital symptoms were associated with mortality due to IMD and the choice of pre-hospital treatment with antibiotics was associated with the presence or not at the time of the first symptoms. So,
they conform the clinical form, which is associated with the likelihood of death, even with the limitations of the mixed forms.

It seems difficult to elucidate the actual value of pre-hospital antibiotics to reduce mortality in the context of IMD. One of the solutions for this would be to perform a randomised clinical trial. However, IMD is a very difficult disease to diagnose prior to hospital admission. Only a large cohort study including cases diagnosed at all levels of the Health Service could answer this dilemma. Control by statistical techniques through the propensity score and the indication bias due to the level of severity of IMD at admission could be modified with treatment.

At a time when patients who receive in-hospital antibiotics generally have a good response, support treatment has improved and population vaccinations have been extended, the extra-hospital use of antibiotics remains one of the few treatments that can be implemented to improve survival in patients with IMD, to avoid to say again that “no infection kills so quickly”(19).

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Reference List

(1) http://www.who.int/csr/don/archive/disease/meningococcal_disease/en/. World Health Organization. 3-12-2007. Ref Type: Electronic Citation


(4) Chief Medical Officer. Meningococcal infection. London: Department of Health. 1999;((PL/CMO/99/1)).


(16) Strang JR, Pugh EJ. Meningococcal infections: reducing the case fatality rate by giving penicillin before admission to hospital. BMJ. 1992;305(6846):141-143.


Table 1. Symptoms recorded on history, with the corresponding OR for death.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>N (%)</th>
<th>Mean duration in hours (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>814 (96)</td>
<td>22 (21-23)</td>
<td>0.44 (0.14-1.3)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>647 (76.3)</td>
<td>18 (16-19)</td>
<td>0.47 (0.26-0.85)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>432 (50.9)</td>
<td>8 (6-9)</td>
<td>0.77 (0.43-1.38)</td>
</tr>
<tr>
<td>Headache</td>
<td>338 (39.9)</td>
<td>23 (21-26)</td>
<td>0.72 (0.39-1.33)</td>
</tr>
<tr>
<td>Low level of consciousness</td>
<td>334 (39.4)</td>
<td>15 (13-17)</td>
<td>0.6 (0.31-1.13)</td>
</tr>
<tr>
<td>Cold-like symptoms</td>
<td>127 (15)</td>
<td>60 h (48-72)</td>
<td>2.43 (1.27-4.66)</td>
</tr>
<tr>
<td>Pharyngoamygdalitis</td>
<td>119 (14)</td>
<td>35 (29-41)</td>
<td>1.2 (0.55-2.65)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>113 (13.3)</td>
<td>20 (16-25)</td>
<td>1.29 (0.58-2.83)</td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>71 (8.4)</td>
<td>16 (10-22)</td>
<td>0.45 (0.11-1.89)</td>
</tr>
<tr>
<td>Irritability</td>
<td>50 (5.9)</td>
<td>14 (11-18)</td>
<td>0.32 (0.04-2.36)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>37 (4.4)</td>
<td>3 (1-4)</td>
<td>2.72 (1.01-7.33)</td>
</tr>
</tbody>
</table>
Table 2. Physical signs on the initial examination at admission to the emergency room, with the OR of death for each.

<table>
<thead>
<tr>
<th>Physical sign</th>
<th>N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>621 (73.2)</td>
<td>0.82 (0.44-1.53)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>562 (66.3)</td>
<td>0.72 (0.4-1.3)</td>
</tr>
<tr>
<td>Kernig/Brudzinsky signs</td>
<td>405 (47.8)</td>
<td>0.68 (0.37-1.22)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>282 (33.3)</td>
<td>0.64 (0.33-1.24)</td>
</tr>
<tr>
<td>Pharyngoamygdalitis</td>
<td>259 (30.5)</td>
<td>0.3 (0.13-0.71)</td>
</tr>
<tr>
<td>Low level of consciousness</td>
<td>234 (27.6)</td>
<td>1.89 (1.04-3.4)</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>117 (13.8)</td>
<td>2.41 (1.24-4.7)</td>
</tr>
<tr>
<td>Irritability</td>
<td>110 (13)</td>
<td>0.93 (0.39-2.24)</td>
</tr>
<tr>
<td>Cold-like symptoms</td>
<td>75 (8.8)</td>
<td>0.66 (0.2-2.17)</td>
</tr>
<tr>
<td>Arthritis-arthralgia</td>
<td>61 (7.2)</td>
<td>0.53 (0.12-2.25)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>20 (2.4)</td>
<td>4.35 (1.4-13.55)</td>
</tr>
</tbody>
</table>