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ORIGINAL ARTICLE

Impact of pre-hospital antibiotic therapy on mortality in invasive meningococcal disease: a propensity score study

Carmen Cabellos[1] · Ivan Pelegrín[1] · Eva Benavent[1] · Francesc Gudiol[1] · Fe Tubau[2] · Dolores Garcia-Somoza[2] · Ricard Verdaguer[2] · Javier Ariza[1] · Pedro Fernandez Viladrich[1]

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Abstract

The role of pre-hospital antibiotic therapy in invasive meningococcal diseases remains unclear with contradictory data. The aim was to determine this role in the outcome of invasive meningococcal disease. Observational cohort study of patients with/without pre-hospital antibiotic therapy in invasive meningococcal disease attended at the Hospital Universitari de Bellvitge (Barcelona) during the period 1977–2013. Univariate and multivariate analyses of mortality, corrected by propensity score used as a covariate to adjust for potential confounding, were performed. Patients with pre-hospital antibiotic therapy were also analyzed according to whether they had received oral (group A) or parenteral antibiotics (early therapy) (group B). Five hundred twenty-seven cases of invasive meningococcal disease were recorded and 125 (24%) of them received pre-hospital antibiotic therapy. Shock and age were the risk factors independently related to mortality. Mortality differed between patients with/without pre-hospital antibiotic therapy (0.8% vs. 8%, $p = 0.003$). Pre-hospital antibiotic therapy seemed to be a protective factor in the multivariate analysis of mortality ($p = 0.038$; OR, 0.188; 95% CI, 0.013–0.882). However, it was no longer protective when the propensity score was included in the analysis ($p = 0.103$; OR, 0.173; 95% CI, 0.021–1.423). Analysis of the oral and parenteral pre-hospital antibiotic groups revealed that there were no deaths in early therapy group. Patients able to receive oral antibiotics had less severe symptoms than those who did not receive pre-hospital antibiotics. Age and shock were the factors independently related to mortality. Early parenteral therapy was not associated with death. Oral antibiotic therapy in patients able to take it was associated with a beneficial effect in the prognosis of invasive meningococcal disease.

Keywords Invasive meningococcal disease · Antibiotic therapy · Prognostic factors, pre-hospital

Introduction

Invasive meningococcal disease (IMD), sepsis and/or meningitis, remains a serious health problem despite the effective implementation of vaccines in most countries. It is usually a severe infection with mortality ranging from 5 to 16%. Sepsis is more closely associated with mortality than meningitis, especially in cases of late therapy [1–6].

IMD may be extremely fast-acting, causing devastating disease or death in a previously healthy person, can spread from person to person via the air, can cause large outbreaks or be hyperendemic, so it is a dreaded disease and often the cause of tremendous public concern. Besides prevention, early recognition and aggressive treatment are the only effective measures against IMD. However, data on the role of antibiotic administration prior to hospital admission are discordant, with some studies recommending immediate administration since the microorganism can rapidly cause shock and death [7–16].

✉ Carmen Cabellos
ccabellos@bellvitgehospital.cat

[1] Infectious Diseases Service, IDIBELL-Hospital Universitari de Bellvitge, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

[2] Microbiology Service, IDIBELL-Hospital Universitari de Bellvitge, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

Table 1 Clinical characteristics, laboratory findings, and outcome of patients with IMD either treated or not treated with pre-hospital antibiotic

	No pre-hospital antibiotic, $N = 384$	Pre-hospital antibiotic, $N = 125$	P value
Meningitis	332 (87%)	122 (98%)	0.000
Age mean ± SD (median IQR)	33 ± 22 (21; IQR, 14, 54)	25 ± 17 (17; IQR, 14, 36)	0.007
Gender (female)	238 (62%)	79 (63%)	0.807
Underlying disease	68 (18%)	13 (10%)	0.052
Diabetes	42 (11%)	6 (5%)	0.041
Length of pre-hospital dis.			
Very fast disease < 12 h	83 (22%)	15 (12%)	0.018
Late consultation > 48 h	54 (14%)	21 (17%)	0.467
Clinical characteristics			
Cold symptoms	132 (35%)	62 (50%)	0.005
Odynophagia	142 (39%)	63 (51%)	0.016
Fever	354 (96%)	120 (97%)	0.591
Shock	53 (14%)	13 (10%)	0.325
Headache	332 (89%)	119 (96%)	0.015
Nuchal stiffness	305 (82%)	118 (94%)	0.001
Nausea/vomiting	298 (80%)	116 (94%)	0.000
Skin lesions	323 (84%)	106 (85%)	0.901
Altered mental status/coma on admission	234/63 (61%)/(17%)	58/15 (47%)/(12%)	0.005/0.239
Positive blood culture	201 (52%)	7 (6%)	0.000
Thrombocytopenia	80 (22%)	12 (10%)	0.004
Prothrombin time > 1.3 min	174 (48%)	50 (43%)	0.303
CSF hypoglycorrhachia	208 (61%)	69 (60%)	0.852
CSF protein >5 g	90 (27%)	21 (18%)	0.084
Positive CSF Gram stain	223 (63%)	46 (38%)	0.000
Positive CSF culture	256 (73%)	48 (40%)	0.000
Outcome			
Mechanical ventilation	48 (13%)	6 (5%)	0.015
Arthritis	36 (9%)	4 (3%)	0.025
Pericarditis	6 (2%)	4 (3%)	0.259
DIC	62 (16%)	11 (9%)	0.039
Median hospital days	(9; IQR, 7, 11)	(9; IQR, 7, 10)	0.922
Relapse	0 (0%)	0 (0%)	
Sequelae			
Cutaneous necrosis	17 (4%)	0 (0%)	0.008
Neurological	22 (6%)	10 (8%)	0.364
Total mortality	32 (8%)	1 (0.8%)	0.003
Early neurological	6 (2%)	0 (0%)	
Late neurological	2 (1%)	0 (0%)	
Early sepsis	17 (4%)	1 (1%)	0.047
Late non-neurological	7 (2%)	0 (0%)	
Early mortality	23 (6%)	1 (1%)	0.021
Late mortality	9 (2%)	0 (0%)	0.085

Underlying diseases include alcoholism, chronic hepatic disease, solid or hematologic neoplasm, immunodeficiency, systemic lupus erythematosus, splenectomy, myeloma, glomerulonephritis, chemotherapy, corticosteroids therapy

The objective of the present study was to determine the role of pre-hospital antibiotic therapy (PHAT) in prognosis in a large series of cases of IMD over a long timescale in a cohort with a high percentage of adult patients.

Patients and methods

This was an observational cohort study of patients admitted to our hospital with IMD from 1977 to 2013. Since 1977, all cases of bacterial meningitis or IMD have been routinely recorded. For the purpose of the study, we selected all episodes of IMD, with or without meningitis. An episode was considered to have occurred when there were clinical findings of sepsis and/or meningitis and *Neisseria meningitidis* was isolated in blood, CSF, pharyngeal swab or joint fluid, or, in the absence of positive cultures, when Gram-negative diplococci were detected in the CSF Gram stain, or in the hyperendemic period when patients presented findings of acute bacterial meningitis or sepsis with characteristic skin lesions even with negative cultures. Patients with IMD were classified as having sepsis (meningococcal disease without meningitis) or meningitis. Meningitis was diagnosed by inflammatory parameters in CSF or a positive CSF culture. Meningitis patients manifested varying symptoms and signs of the sepsis criteria, ranging from none to septic shock.

From 1977 to 1994, our hospital admitted patients as young as 7 years old. Since 1994, however, only patients aged 14 years or older have been admitted.

Mortality during hospitalization was recorded. The mechanism of death was classified as early sepsis (first 48 h), early neurological, late neurological, and late non-neurological.

Duration of therapy was 7 days from 1977 until 1983 and 4 days from 1984 to 2013 [17, 18].

PHAT was considered any effective antibiotic by any route and at any dosage and duration administered once symptoms had started and before arrival at the hospital. Patients treated with PHAT were divided into two groups: group A, those treated with oral antibiotics; group B, those treated with parenteral (im or iv) beta-lactam antibiotics.

The isolates were identified and susceptibility defined using conventional microbiological methods and CLSI criteria [19, 20].

Statistical analysis Categorical data were compared using the chi-square test or Fisher exact test, and continuous data with the *t* test or Mann-Whitney test. A comparison was performed between patients who had or had not received PHAT. And also, analysis of risk factors for mortality was conducted via a logistic regression model performed after univariate analysis. To determine the predictors of mortality, logistic regression models were built to estimate odds ratios with 95% CI. Clinically relevant variables associated with the outcome in the univariate analysis were entered in the multivariate model avoiding collinearity. We completed the analysis of the impact of PHAT on mortality using a propensity score study.

First predictors for mortality were assessed in the entire population using a logistic regression model. In a second analysis, we calculated the propensity to have received or not received PHAT. The propensity score was estimated using a backward stepwise logistic regression model. The estimated propensity score was then used as a covariate in a multivariate analysis of mortality to adjust for potential confounding by factors associated with PHAT or no PHAT. All *p* values were two-sided and values of 0.05 or less were considered statistically significant. SPSS 15 for Windows was used in the statistical analysis.

Results

Between 1977 and 2013, 527 episodes of IMD were recorded: 57 cases of sepsis (11%) and 470 of meningitis with/without sepsis (89%). Of these, 325 patients (61%) were women and the median age was 19 (IQR, 14–50), ranging from 7 to 87 years old.

PHAT was recorded in 143 patients (28%) and consisted of iv penicillin/ampicillin 25, iv cephalosporin 3, im penicillin/ampicillin 29, im cephalosporin 5, oral amoxicillin/ampicillin/penicillin/cephalosporin 42, oral macrolides 9, other antibiotics 12, and unknown antibiotic 18; overall, 59% received beta-lactams before admission. Only patients receiving known antibiotics (125) were considered in the analysis, and these were divided into group A, 63 patients (previous oral antibiotics) and group B, 62 patients (parenteral early therapy).

Table 1 shows the characteristics of patients with and without PHAT. Some laboratory findings reflected the consequences of PHAT, with fewer positive blood cultures, CSF Gram stain and CSF cultures. Also, those patients treated with PHAT had a lower need for mechanical ventilation, less cutaneous necrosis, and lower mortality, especially lower early mortality.

Overall, 33 patients (6%) died: 8 of 57 sepsis patients (14%) and 25 of 470 meningitis patients (5%) ($p = 0.018$). The mechanism of death was early sepsis in 18 (3%), early neurological in 6 (1%), late neurological in 2 (0.4%), and late non-neurological in 7 (1%).

Table 2 Multivariate analysis of mortality including (B) or not including (A) the propensity score for pre-hospital antibiotic

	p	OR	CI 95%
A			
Age	0.000	1.046	1.025–1.067
Pre-hospital antibiotic	0.038	0.108	0.013–0.882
Shock	0.000	15.879	6.422–39.264
B			
Age	0.002	1.034	1.012–1.057
Pre-hospital antibiotic	0.103	0.173	0.021–1.423
Shock	0.000	13.528	4.732–38.670
Propensity score	0.479	0.192	0.002–18.527

Table 3 Clinical and laboratory characteristics and outcome of patients with IMD treated with pre-hospital antibiotic (oral group A or parenteral group B) or no pre-hospital antibiotic

	No pre-hospital antibiotic, $N = 384$	Group A, $n = 63$	Group B, $n = 62$
Meningitis	332 (87%)	62 (98%)*	60 (97%)*
Age mean ± SD (median and IQR)	33 ± 22 (21; IQR, 14, 54)	24 ± 17 × 17 (IQR, 13 38)	25 ± 17 × 18 (IQR, 14, 33)
Gender (female)	238 (62%)	41 (65%)	38 (61%)
Underlying disease	68 (18%)	6 (10%)	7 (11%)
Diabetes	42 (11%)	2 (3%)	4 (7%)
Length of pre-hospital dis.			
Very fast disease < 12 h	83 (22%)	7 (11%)	8 (13%)
Late consultation > 48 h	54 (14%)	12 (19%)	9 (15%)
Clinical characteristics			
Cold symptoms	132 (35%)	27 (43%)	35 (57%)
Odynophagia	142 (39%)	28 (45%)	35 (57%)*
Fever	354 (96%)	61 (97%)	59 (97%)
Shock	53 (14%)	4 (7%)	9 (15%)
Headache	332 (89%)	60 (97%)	59 (95%)
Nuchal stiffness	305 (82%)	60 (95%)*	58 (94%)*
Nausea/vomiting	298 (80%)	60 (97%)*	56 (92%)*
Skin lesions	323 (84%)	54 (86%)	52 (84%)
Altered mental status/coma admission	234/63 (61%)/(17%)	22/9 (36%)*/(7%)	36/6 (58%)/(10%)
Positive blood culture	201 (52%)	6 (10%)	1 (2%)
Thrombocytopenia	80 (22%)	4 (7%)*	8 (13%)
Prothrombin time > 1.3 min	174 (48%)	22 (39%)	28 (46%)
CSF hypoglycorrhachia	208 (61%)	30 (51%)	39 (68%)
CSF protein > 5 g	90 (27%)	10 (17%)	11 (20%)
Positive CSF Gram stain	223 (63%)	25 (40%)	21 (35%)
Positive CSF culture	256 (73%)	27 (43%)	21 (36%)
Outcome			
Mechanical ventilation	48 (13%)	2 (3%)	4 (7%)
Arthritis	36 (9%)	2 (3%)	2 (3%)
Pericarditis	6 (2%)	0 (0%)	4 (7%)
DIC	62 (16%)	3 (5%)*	8 (13%)
Median hospital days	9 (IQR, 7, 11)	9 (IQR, 6, 10)	9 (IQR, 7, 10)
Relapse	0 (0%)	0%	0%
Sequelae			
Cutaneous necrosis	17 (4%)	0 (0%)	0 (0%)
Neurological	22 (6%)	3 (5%)	7 (11%)
Total mortality	32 (8%)	1 (1.6%)*	0 (0%)*
Early neurological	6 (2%)	0 (0%)	0 (0%)
Late neurological	2 (1%)	0 (0%)	0 (0%)
Early sepsis	17 (4%)	1 (2%)	0 (0%)
Late non-neurological	7 (2%)	0 (0%)	0 (0%)
Early mortality	23 (6%)	1 (2%)	0 (0%)
Late mortality	9 (2%)	0 (0%)	0 (0%)

*$p < 0.05$ vs. no pre-hospital antibiotic

Underlying diseases include alcoholism, chronic hepatic disease, solid or hematologic neoplasm, immunodeficiency, systemic lupus erythematosus, splenectomy, myeloma, glomerulonephritis, chemotherapy, corticosteroids therapy

A comparison was also made between dead and alive patients. In the univariate analysis, variables statistically related to mortality were as follows: presentation as sepsis without meningitis, age, presence of any underlying disease, diabetes mellitus, very fast disease (< 12 h), shock, ecchymosis, coma on admission, seizures at any moment or post-therapy, positive blood culture, low CSF WBC, > 1 g proteinorrachia, and positive CSF culture, thrombocytopenia, prothrombin time > 1.3, hypernatremia, heart failure, renal failure, DIC , and gastrointestinal complications. The same variables were also related to mortality in the group of meningitis patients. Among the group with sepsis without meningitis, variables related to mortality in the univariate analysis were as follows: presence of shock, ecchymosis, coma on admission, positive blood cultures, thrombocytopenia, prothrombin time > 1.3, hypokalemia, heart or renal failure, DIC, and gastrointestinal complications.

In the entire cohort, PHAT (group A + B) ($p = 0.003$) appeared to be protective.

A multivariate analysis (Table 2a) showed that age and presence of shock were independent factors related to mortality and PHAT as a protective factor.

To better assess the influence of PHAT on mortality and to account for the possibility that patients receiving PHAT differed from those that did not receive such therapy, we used the propensity score. The variables included producing the propensity score were chosen from those that were significant among patients receiving or not receiving PHAT and that could be present and known at the time of the decision to administer PHAT, and included the following: meningitis, underlying disease, very fast disease, odynophagia, headache, nuchal stiffness, nausea/vomiting, and changes in level of consciousness. The estimated propensity score was then used as a covariate in the multivariate analysis of mortality. This analysis revealed that PHAT was not significant, and thus could not be considered a protective factor, whereas age and shock remained significant and related to death (Table 2b).

When studying the two different groups of PHAT patients vs. non-PHAT patients (Table 3), mortality in group B was statistically significantly lower in the univariate analysis at 0% vs. 8% ($p = 0.018$), and thus, it could not be studied in the multivariate analysis since there were no deaths in patients receiving early therapy. Mortality in group A was also statistically significantly lower than in the non-PHAT group (1.6% vs. 8%; $p = 0.05$), but it was not a protective factor in the multivariate analysis.

Discussion

Our data emphasize the need for early therapy as the best way to improve prognosis, while they put into perspective the role of PHAT, since the population that received pre-hospital oral antibiotics seemed to be less sick in some aspects than those who did not receive such therapy. Overall, treatment with any antibiotic before arrival at the hospital seems to be a strong protective factor; but on further analysis, the protective effect disappears due to the different populations represented by the propensity score. This might partly explain why there have been conflicting results when studying the effect of PHAT. Some studies showed the advantage of rapidly reducing the burden of meningococci and endotoxins [7, 21–23], whereas another [8] showed a worse prognosis, maybe due to differences in severity among patients receiving or not receiving PHAT. A Cochrane meta-analysis [10] concluded that there were not enough data to reinforce or refute the use of PHAT but recent UK guidelines also recommend the practice of giving PHAT while ensuring that transfer to hospital is never delayed for this reason [24]. In our study, the fact that no patient died among those who received parenteral beta-lactams (group B), should reinforce the idea that IMD should be promptly recognized among health workers and that appropriate therapy should be started as soon as possible. The data from group A indicate that oral PHAT points to a less "rapidly sick patient," with less shock, underlying diseases and with statistically significant differences in thrombopenia, DIC, and level of consciousness, patients who effectively were able to receive oral antibiotics. All these might have contributed to their lower mortality; but still, the oral antibiotic performed well in this population and would have benefited them. Globally, the good results of PHAT might reflect the combination of less sick patients receiving oral antibiotics and early parenteral therapy in other patients. Of course, if the diagnostic of IMD is suspected, the really important issue is to start parenteral beta-lactam antibiotics as complete therapy as soon as possible. Since it would be impossible to perform a clinical trial on this issue, our data might help clarify the problem.

Our study confirmed that age and presence of shock are independently related to mortality, as previously reported [2, 23, 25, 26]. Both are impossible to change, but we could try to improve shock management.

Conclusion

Age and shock were the factors independently related to mortality. Early parenteral therapy was associated with no deaths. Oral antibiotic therapy in patients able to take it might have a beneficial effect in the prognosis of IMD. Rapid access to full antibiotic therapy may help to improve prognosis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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