Invasive Meningococcal Disease: Application of Base Excess and Platelets Score in a Portuguese Paediatric Intensive Care Unit

Doença Meningocócica Invasiva: Aplicação do Base Excess and Platelets Score numa Unidade de Cuidados Intensivos Pediátricos Portuguesa

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ABSTRACT

Introduction: Meningococcal infection has a high mortality and morbidity. Recently a new prognostic scoring system was developed for paediatric invasive meningococcal disease, based on platelet count and base excess – base excess and platelets score. The main objective of this study was to evaluate the accuracy of base excess and platelets score to predict mortality in children admitted to intensive care due to invasive meningococcal disease.

Material and Methods: Observational study, with retrospective data collection, during a 13.5 years period (01/2000 to 06/2013). Mortality by invasive meningococcal disease and related factors (organ dysfunction and multi-organ failure) were analysed. The base excess and platelets score was calculated retrospectively, to evaluate its accuracy in predicting mortality and compared with Paediatric Risk of Mortality and Paediatric Index of Mortality$_2$.

Results: Were admitted 76 children with invasive meningococcal disease. The most frequent type of dysfunction was cardiovascular (92%), followed by hematologic (55%). Of the total, 47 patients (62%) had criteria for multi-organ failure. The global mortality was 16%. Neurologic and renal dysfunction showed the strongest association with mortality, adjusted odds ratio 315 (26 - 3 804) and 155 (20 - 1 299). After application of receiver operating characteristic curves, Base Excess and Platelets score had an area under curve of 0.81, Paediatric Index of Mortality$_2$ of 0.91 and Paediatric Risk of Mortality of 0.96.

Discussion: The Base Excess and Platelets score showed good accuracy, although not as high as Paediatric Risk of Mortality or Paediatric Index of Mortality$_2$.

Conclusions: The Base Excess and Platelets score may be useful tool in invasive meningococcal disease because is highly sensitive and specific and is objectively measurable and readily available at presentation.

Keywords: Child; Intensive Care Units, Pediatric; Meningococcal Infections; Portugal; Predictive Value of Tests; Prognosis.

RESUMO

Introdução: A infeção meningocócica tem uma elevada mortalidade e morbilidade. Recentemente foi desenvolvido um *score* de prognóstico para a doença meningocócica invasiva em idade pediátrica, baseado na contagem plaquetar e no excesso de base - o *Base Excess and Platelets Score*. O objetivo principal desde estudo foi avaliar a precisão prognóstica do *Base Excess and Platelets Score* em doentes admitidos em cuidados intensivos pediátricos por doença meningocócica invasiva.

Material e Métodos: Estudo observacional, com colheita de dados retrospetiva, que incluiu um período de 13,5 anos (01/2000 a 06/2013). Foram analisados: mortalidade por doença meningocócica invasiva e fatores associados (disfunção de órgão e falência multi-órgão). Foi calculado o *Base Excess and Platelets Score* de forma retrospetiva, para avaliar a sua precisão na predição da mortalidade e foi comparado com o *Paediatric Risk of Mortality* e *Paediatric Index of Mortality*$_2$.

Resultados: Foram admitidas 76 crianças com doença meningocócica invasiva. O tipo de disfunção mais frequente foi a cardiovascular (92%), seguida da hematológica (55%). Cumpriram critérios de falência multi-órgão 47 doentes (62%). A mortalidade global foi de 16%. A disfunção neurológica e a renal foram as que apresentaram uma maior associação com a mortalidade, *odds ratio* ajustado 315 (26 - 3 804) e 155 (20 - 1 299). Após aplicação das curvas *receiver operating characteristic*, o *Base Excess and Platelets Score* tinha uma *area under curve* de 0,81, o *Paediatric Index of Mortality*$_2$ de 0,91 e o *Paediatric Risk of Mortality* de 0,96.

Discussão: O *Base Excess and Platelets Score* apresentou uma boa precisão apesar de não tão elevada como o *Paediatric Index of Mortality*$_2$ ou o *Paediatric Risk of Mortality*.

Conclusões: O *Base Excess and Platelets Score* pode ser útil como indicador prognóstico na doença meningocócica invasiva, por apresentar uma elevada sensibilidade e especificidade e ser objetivo e rapidamente disponível na admissão.

Palavras-chave: Criança; Cuidados Intensivos Pediátricos; Doença Meningocócica; Portugal; Prognóstico; Valor Preditivo dos Testes.

INTRODUCTION

Meningococcal infection may rapidly progress to sepsis, septic shock and multiple organ dysfunction syndrome.[1,2]

The development of prognostic scoring systems has two major aims: the identification of patients at high risk for quick clinical deterioration and risk stratification for future trials of new drugs or diagnostic tests.[3-5]

There are several prognostic scores combining clinical and laboratory data validated for invasive meningococcal disease (IMD). These include the *Glasgow Meningococcal Septicaemia Prognostic Score* (GMSPS)[6] and generic

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scores to be used in paediatric intensive care, such as the *Paediatric Risk of Mortality* (PRISM)[7] and the *Paediatric Index of Mortality* $_2$ (PIM_2).[8] There are also prognostic scores exclusively based in laboratory data, such as the Rotterdam score.[9]

The ideal score would include a minimum number of variables that could be quickly and objectively measurable at disease presentation and should be cost-effective.[3]

It should be mentioned that some scores, like PRISM or GMSPS, use clinical data that depend on a subjective assessment in many aspects, reducing reliability.[3,6,7]

A new prognostic score has been recently developed and validated by a group of researchers from different European paediatric intensive care centres, based on platelet count and base excess, the BEP (base excess and platelet count) score. This score is obtained by the formula:[3]

$$1 / (1 + e^{(0.18909 \times \text{Base Excess, mmol/L}) + (0.01015 \times \text{Platelet count, } 10^{*}12/L) + 3.07861})$$

Our study's main objective was to assess the BEP score's precision for mortality prediction in our population and to compare it with other scores used in intensive care. The secondary aims included an analysis of IMD-based mortality and related factors.

MATERIAL AND METHODS

This was an observational study involving retrospective data collection at the Intensive Care Unit of a reference paediatric hospital for the central region of Portugal.

All children diagnosed with IMD (confirmed or probable) admitted to the unit between January 2000 and June 2013 (13.5 years) were included in the study.

IMD was defined according to the 2010 CDC (Centers for Disease Control and Prevention) criteria.[10]

The following variables were obtained from the patient's clinical records as well as from the unit's database: year of hospital admission, patient's age, gender, meningoccus isolation and serogroup, type of organ dysfunction, mortality and outcome indicator (PRISM).

The BEP score was retrospectively calculated for all the patients in whom arterial blood gases (base excess quantification) and blood count (platelet count) were obtained on the first hour upon hospital admission. PIM_2 was also retrospectively calculated for the years before the score's publication.

Data's statistical analysis used the Statistical Package for the Social Science® version 20 software. Our population was characterised with central and dispersion measures calculated for quantitative variables and absolute and relative frequencies calculated for qualitative variables. Upon the application of a normality test (Kolmogorov-Smirnov), we found that quantitative variables did not follow a normal distribution and therefore these were characterised with median and interquartile range (IQR). Mann-Whitney's test was used for the comparison of nominal and quantitative variables with no normal distribution. Chi-square or Fisher exact test, according to Cochran rules, were used for the comparison of nominal variables.

The logistic regression was used for the inference of the association between the different types of organ dysfunction and mortality. A 5% significance level was considered. Receiver operating characteristic (ROC) curves for BEP, PRISM and PIM_2 scores were obtained and Youden's formula was applied in order to obtain a cut-off that would maximize mortality-related sensitivity and specificity.

This study fully complied with the ethical principles for human medical research substantiated in the World Medical Association's Helsinki Declaration.

RESULTS

During the study period, 76 children diagnosed with IMD were admitted to our unit, corresponding to 1.6% of the total admissions to intensive care. There was a variable distribution over the years, ranging from zero patients in 2011 to a maximum of 12 patients in 2002 (Fig. 1). A 2.2-year median age (IQR: 0.8 – 4.5) and a male predominance (43/76, 56.6%) were found.

Meningoccus was isolated upon sterile fluid culture in 57.9% of the patients (44/76). The *N. meningitidis* serogroup was identified in 21 patients (47.2%) and serogroup B was the most frequent (12), followed by C (eight patients) and Y (one patient). No serotype C has been isolated since 2005.

Most patients (50/76, 65.8%) presented with rapidly progressive purpura and 40.8% (31/76) with meningitis.

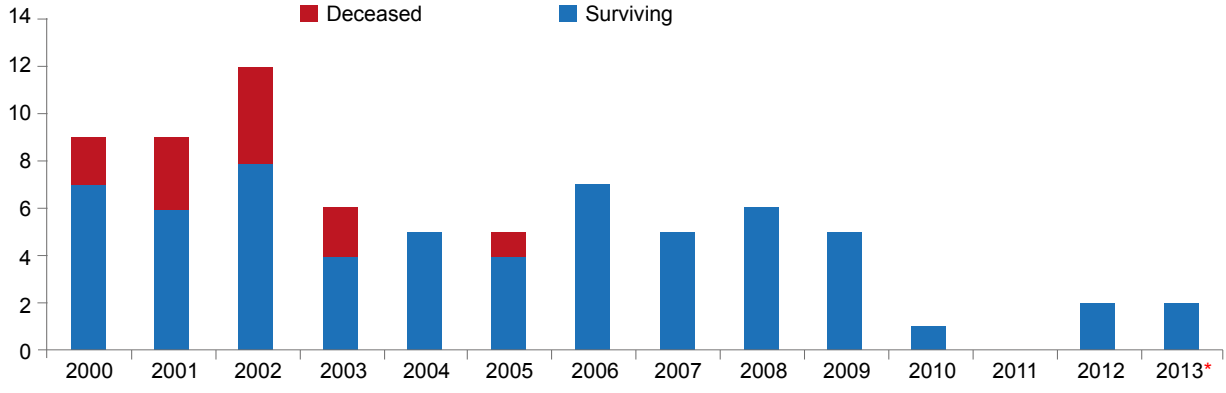

Figure 1 - Patients admitted to the paediatric intensive care by IMD (n = 76)

* Included only 6 months

Table 1 – Types of organ dysfunction in deceased and surviving patients (n = 76)

Type of organ dysfunction	Deceased (n = 12)	Surviving (n = 64)	*p*
Renal	83.3%	3.1%	**< 0.001** (Mann Whitney U)
Haematological	91.7%	48.4%	0.06 (Chi-square)
Neurological	83.3%	1.6%	0.71 (Mann Whitney)
Respiratory	91.7%	17.2%	**< 0.001** (Mann Whitney)
Cardiovascular	91.7%	92.2%	1 (Mann Whitney)
Multiple organ failure	100.0%	54.7%	0.02 (Mann Whitney)

In total, 47 patients (61.8%) met with multiple organ failure criteria. The most frequent type of dysfunction was cardiovascular (70/76, 92.1%), followed by haematological (42/76, 55.3%) and respiratory dysfunction (22/76, 28.9%). Most patients had cardiovascular support (71/76, 93.4%), some required invasive ventilation (21/76, 27.6%) and hemodiafiltration (3/76, 3.9%).

A 3.2% (IQR: 1.1; 20.4%) median PRISM score and 1.1% (IQR: 0.9-3.6%) median PIM_2 score were found in the 76 patients included in the study. We were able to get the BEP score calculated in 65 patients (85.5%). A 0.26 (IQR: 0.06 – 0.72) median value was obtained in these.

A 15.6% (12/76) global mortality was found.

A 1.6-year median age (IQR: 0.8 – 2.6) was found in deceased and 2.4-year (IQR: 0.9 – 5.3; $p = 0.176$, Mann-Whitney's test) in surviving patients.

Rapidly progressive purpura occurred in 91.7% of deceased and in 60.9% of surviving patients ($p = 0.049$; Fisher's test).

No significant differences were found regarding the presence of meningitis (deceased: 33.3% *versus* surviving patients: 42.2%; $p = 0.71$; Fisher's test).

As regards organ dysfunction, as shown in Table 1, all types were more frequent in deceased patients except cardiovascular dysfunction.

Upon logistic regression, the organ failure more closely associated to mortality was neurological, followed by renal (Table 2).

A 52.4% median PRISM score was found in deceased (IQR: 23.7 – 82.5) and 2.2% in surviving patients (IQR: 1.0 – 10.1) ($p < 0.001$, Mann-Whitney's test).

A 13.3% median PIM_2 score was found in deceased (IQR: 3.0 – 76.1) and 1.1% in surviving patients (IQR: 0.9 – 2.3%) ($p < 0.001$, Mann-Whitney's test).

A 0.14 median BEP score was found in deceased (IQR: 1.0 – 10.1) and 0.02 in surviving patients (IQR: 0.01 – 0.04) ($p < 0.001$, Mann-Whitney's test).

Upon the application of ROC curves to PRISM score, a 0.96 area under curve (AUC) was obtained (0.91 – 1.00) with 100% sensitivity and 87.5% specificity, obtained through the Youden's formula for an 18.4% cut-off. A 0.91 AUC (0.84 – 0.98) was obtained for the PIM_2 score and a 100 and 70.3% sensitivity and specificity, respectively, for a 1.45 cut-off. A 0.81 (0.66 – 0.97) AUC was obtained for the BEP score and 83% sensitivity and specificity for a 0.06 cut-off (Fig. 2).

DISCUSSION

Despite the technical advances that included vaccine introduction and an improvement in patient's initial stabilisation, IMD remains a cause for mortality and morbidity in Paediatrics. However, mortality has been reduced in the central region of Portugal, in line with what has been described in other European countries[11-13] and since 2005 there have been no IMD-related death patients in our centre (Fig. 1).

The importance of scores lies in their capacity to objectively assess and identify more severe patients, allowing for decisions regarding hospital admission of

Table 2 – Organ dysfunction and mortality-adjusted odds ratio (n = 76)

	Adjusted odds ratio (95% CI)	*p*
Neurological	315.0 (26.1 - 3,804.1)	**< 0.001**
Renal	155.0 (19.5 - 1,299.1)	**< 0.001**
Respiratory	53.0 (6.2 - 453.9)	**< 0.001**
Haematological	11.7 (1.4 - 96.1)	**0.006**
Cardiovascular	0.931 (0.1 - 8.8)	0.95

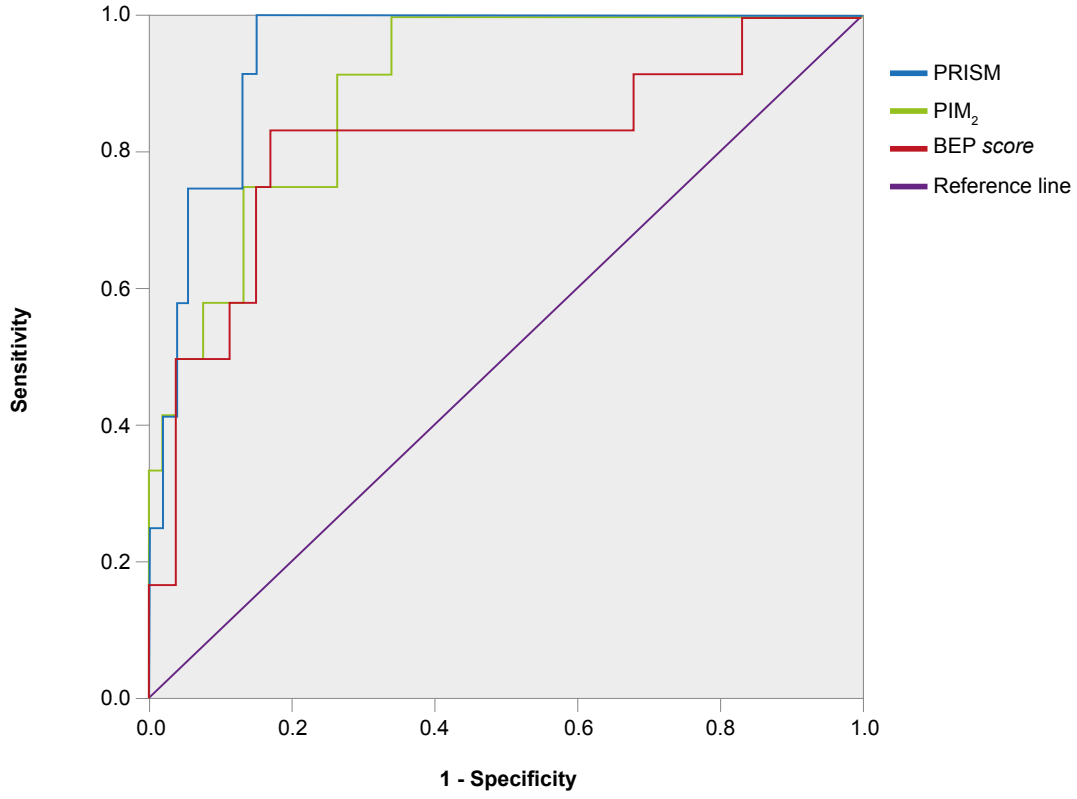

Figure 2 - ROC curves for PRISM (in blue). PIM_2 (in green) and BEP score (in red)

patients, as well as for guiding optimal intensive care therapeutic approach. Scores should allow for an adequate stratification in order to optimize patient inclusion in future clinical trials and to select those that may benefit from new therapies, avoiding patient heterogeneity that may have contributed to clinical trial failure in the past.[14-16]

Most prognostic scores combine clinical and laboratory data while some are only based on laboratorial markers. Not all are specifically designed and seem to currently overestimate mortality regarding healthcare improvement in meningococcal disease.[17]

The GMSPS score was used in intensive care for many years, with a sensitivity of approximately 100%.[18,19] However, it has some drawbacks, including the high number of analysed variables (seven) and the inclusion of subjective parameters such as the patient's parents opinion regarding the progression of the disease.

The PRISM score is a generic score used to compare the performance between healthcare centres. It allows for the assessment of mortality risk on the first 24 hours upon hospital admission in intensive care. It is a complex score and 14 clinical and laboratory parameters are required, including arterial blood gases, coagulation tests and serum biochemical tests.

The PIM_2 score has the advantage of allowing for its calculation on admission (first hour) although it is time-consuming and, as for the PRISM score, many variables are required. It is also used for comparison between healthcare centres.

PN product (platelet and neutrophil count) only includes two laboratorial parameters and is based on the extent of the inflammatory response. It does not depend on the observer it is quickly obtainable and in the original study it seemed to be accurate in children aged below five; however, it was validated in a small number of patients.[17]

The Rotterdam score has also no subjective factors involved, is based on base excess, platelet count, potassium and C-protein reactive, all of which are easily obtained on the first hour upon a patient's admission.

The BEP score only requires two laboratory values, easily obtainable and objective.

More recently, other scores based on biomarkers were proposed; however, these are not easily available in daily clinical practice and are solely reserved for research studies.

All the prognostic scores analysed in our study showed good precision with high sensitivity and specificity, as previously described, despite the small sample.[3,20] The PRISM score showed the best precision, followed by the PIM_2 score. The BEP score also showed a good precision, although not as high as the other scores. However, we should mention the fact that the BEP score is easily and quickly obtained upon admission from a simple formula, in contrast to the other scores, that require a higher number of observer-dependent data and variables to be obtained. Its specificity was higher in the PIM_2 score.[3,6-8]

The data retrospective collection, preventing the application of the BEP score in all the patients and the small

number of patients were limitations to our study, which may be solved with a further multi-centric study.

Despite these limitations, our study contributed to validate the use of the BEP score in the European population, as suggested on a recent review.[21] Addition of renal function tests to this score, as renal dysfunction was more associated to mortality in our analysis, would be useful to improve the precision of the BEP score.

CONCLUSION

Generic prognostic scores like PRISM or PIM_2 showed a good precision in mortality prediction of IMD. However, these are based in combining different clinical and laboratory data, some of which are difficult to obtain upon a patient's admission to intensive care.

Despite a lower precision when compared to the abovementioned scores, the BEP score has the advantage of being easily and quickly calculated upon a patient's admission.

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HUMAN AND ANIMAL PROTECTION

The authors declare that the procedures followed were in accordance to the regulations established by the responsible body of the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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