The usefulness of infection biomarkers in patients with febrile neutropenia in the Emergency Department☆

Consideraciones sobre la utilidad de los biomarcadores de infección en el paciente con neutropenia febril en el Servicio de Urgencias

Dear Editor,

We have read with great interest the recent study published in your journal by Aguado et al.[1] in relation to the management of infection and febrile neutropenia in patients with solid cancer. We congratulate the authors on their great work and capacity for synthesis, which is sure to facilitate the management of these patients at all levels of care and, of course, in emergency departments (ED). This is the area where we work and it is where a very significant number of the febrile neutropenia episodes are initially treated. In fact, in the last 10 years there has been an increase in the incidence of infections in EDs, and very significantly ($p < 0.001$) in patients with neoplasia (from 3.6% to 9.3%) and neutropenia (from 1.3% to 4.6%), as well as the clinical severity[2] and mortality rates in these patient subgroups.[3] For these objective reasons and in order to adapt to and overcome situations in real clinical practice ("day-to-day") that often saturate or collapse our EDs,[4] tools of objective assistance have been sought, such as automatic alarm systems that prioritize the triage or first evaluation of the patient, to suspect and detect situations of severe sepsis[5] and, thus, perform in an early manner both the clinical assessment of the patient and obtain the lab work that includes lactate and procalcitonin,[6] especially in the patients most susceptible to infection and who have a more severe prognosis and evolution, such as, undoubtedly, patients with febrile neutropenia. In this regard, it has recently been published that both, and in combination, are helpful in predicting the severity and/or possibility of bacteraemia in these patients.[7] In fact, it has been published and strongly recommended that adult patients with infection in which lactate reaches concentrations ≥2–2.5 mmol/L and/or procalcitonin is ≥1 ng/ml should not be discharged (they should at least be kept under observation). And if the initial values of lactate are ≥4 and/or of procalcitonin ≥10 ng/ml they should be admitted to Intensive Care due to being considered serious patients (although they do not have hypotension) in need of resuscitation and intensive haemodynamic support.[6–8] Therefore, it is striking that the joint evaluation of lactate and procalcitonin in the initial algorithm for treatment of patients with neutropenia in the ED is not included in the work of Aguado et al.,[1] since it is a common recommendation for all patients with severe infection[6,8] and, therefore, especially indicated in the elderly, neonates and neutropenic patients, where the clinical manifestations may be more variable and subtle, resulting in a diagnostic-treatment delay, which may be fatal to the latter.

In recent years, various reviews[6,9] have confirmed the usefulness of these biomarkers for the detection of bacterial infection and severity in patients with febrile neutropenia, as well as their value in monitoring clinical evolution and treatment effectiveness. These are assertions that, specifically, Aguado et al.[1] quite rightly point out in their article and with which we agree. But these useful evaluations of initial stratification and subsequent monitoring cannot be carried out without the initial evaluation in the ED and the inclusion of these biomarkers in the algorithm or initial treatment recommendations in the ED.

Finally, we would like to make another observation. Although it is well known that C-reactive protein has, for patients with cancer and neutropenia, a false positive rate in >50% of cases (being higher without infection) and a significantly lower sensitivity and specificity than that offered by procalcitonin (for example, yielding areas under the ROC curve of 0.94, sensitivity of 91% and specificity of 89% to predict the presence of bacteraemia in neutropenic patients),[6,7,9] it has been proven that in the initial care of the patient with fever in the ED (and especially in immunosuppressed patients and patients with neutropenia) C-reactive protein is requested for the initial evaluation in more than 90% of cases, although later it is not useful, but lactate and procalcitonin are determined in only 10–20%,[10] which are really recommended. Therefore, we believe that their inclusion in the evaluation protocols and algorithms in EDs would promote their effective and efficient use. But, of course, on another important note, lactate and procalcitonin should only be requested if they will be useful in decision-making and patient assessment, and can never substitute clinical examination, microbiological testing or the clinical judgement of the doctor.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Reflections on the inappropriate use of antibiotic therapy in the emergency department☆

Consideraciones sobre la inadecuación de la antibioterapia en el servicio de urgencias

Dear Editor,

We have read with interest the recent work published in your journal by González-del Castillo et al.,[1] in relation to the impact of the emergency department's (ED) inappropriate administration of antibiotic therapy on the efficiency of hospitalisation. We congratulate the authors for their work and for "bringing to the forefront" one of the clearly defined and unresolved areas of improvement for EDs; the early and appropriate administration of antibiotic treatment (AB).[2–4] We share many of the views presented in their discussion, as well as their conclusions when it is stated that, in their experience, the inappropriate prescribing of empiric AB treatment in patients admitted from the ED leads to prolonged stays. But we cannot agree when they say that there is no increase in complications, readmissions or even mortality. Thus, in line with this statement, we would like to present some comments about the need to implement programs to optimise the use of AB (PROA)[2] in EDs, and thus move away from a possible deceptive message of relaxation for the clinician that may have made him think that "things are being done correctly", when, in fact we must assume that the rate of inappropriateness of antibiotic therapy in both primary care,[5] and in some EDs, is significant.[6] And this has to be improved, to ensure that the result is efficiency, but also efficacy and effectiveness, both for the system and for the patient's progression (and here we include both those who are admitted and those who do not need to be admitted.[6] And in order to do this, there are experiences and strategies that have shown a very significant improvement in the overall care of the patient with infection in the ED from their triage[7] and, in particular, in the increase of appropriate (empirical indication according to local guidelines and resistance, route of administration, dosage, no need for later change of AB, etc.) and early (in the ED itself in the first hour if the patient has severity criteria or when making the clinical diagnosis in the remainder) administration.[8,9]

We think that the study by González-del Castillo et al.[1] has an intrinsic characteristic, recognised by the authors themselves, that determines its results, and which restricts its external validity. It shows an inappropriate AB treatment in only 10% of patients (not comparable to the 80% published in primary care[5] or approx. 40% in various EDs).[6] However, this fact is specifically due to the excellent results of implementing therapeutic guides in their own ED, agreed with a multidisciplinary team (from the Infection Commission), and training activities included in the PROAs,

Table 1
Related factors and indicators of antibiotic management in patients with community-acquired pneumonia and urinary tract infections in the emergency department.

Results	Community-acquired pneumonia[a] Pre group/Post group n (%) *p* value n (%)	Urinary tract infections[b] Pre group/Post group n (%) *p* value n (%)
Administration of antibiotics in the ED	313 (78.25)/396 (99) $p < 0.001$	173 (57.66)/259 (86.33) $p < 0.001$
Early administration of antibiotics (in less than 4 hours or less than 1 hour if S, SG or SS)	242 (60.5)/355 (88.75) $p < 0.001$	112 (37.33)/188 (62.66) $p < 0.001$
Prescribed antimicrobial treatment, appropriate according to the clinical practice guide (including family, dose, route of administration and treatment time)	238 (59.5)/346 (86.5) $p < 0.001$	140 (46.66)/208 (69.33) $p < 0.01$
Subsequent need for change of antimicrobial regimen (at the hospital or at home)	178 (44.5)/27 (6.75) $p < 0.001$	149 (49.66)/36 (12) $p < 0.001$
Reconsultation in emergency department for discharged patients (adjusted for n, only those discharged from the emergency department)	15 (9.2)/4 (2.98) $p < 0.05$	29 (12.5)/9 (3.89) $p < 0.05$
Time ± SD (days) of hospital stay (adjusted for n, only those hospitalised from the emergency department)	9.06 ± 5.76/7.03 ± 3.98 $p < 0.001$	6.43 ± 4.46/5.12 ± 3.28 $p < 0.05$
Total cumulative mortality at 30 days (of all cases)	53 (13.25)/22 (5.5) $p < 0.05$	23 (7.9)/13 (4.33) $p < 0.05$
Total cumulative mortality at 30 days in inappropriately treated patients	39 (24.07)/14 (25.92) $p > 0.05$	14 (8.75)/6 (6.52) $p > 0.05$

For the comparative analysis, the program IBM®-SPSS® Statistics v.19 for Windows, was used, with a p value < 0.05 considered significant. Fisher's test, Chi-square test for proportions and Student t or Mann–Whitney U test were used to compare the parameters between the 2 groups, as applicable.
SD: standard deviation; S: sepsis; SG: severe sepsis; SS: septic shock; ED: emergency department.
[a] Community-acquired pneumonia (data collected from January 2008 to July 2012, pre-PROA group 400 cases, post-PROA group 400 cases).
[b] Urinary tract infections (data collected from August 2012 to January 2015, pre-PROA group 300 cases, post-PROA group 300 cases).

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