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Biomarkers to guide antibiotic timing and administration in infected patients presenting to the emergency department

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Antibiotics are often prescribed in the emergency department (ED) to patients presenting with a suspected infection before any definitive diagnosis can be made [1]. However, increasing antibiotic resistance and detrimental effects on the microbiota require their use to be limited to those with a high likelihood of bacterial infection or the potential for further clinical deterioration. Conversely, withheld or delayed treatment in higher severity patients may lead to increased morbidity and mortality rates [2]. Thus, an accurate assessment of antibiotic requirement and speed of administration is crucial.

Current tools to aid clinical decision-making include the use of procalcitonin (PCT) and C-reactive protein (CRP). However, recent interventional evidence in the ED has shown few differences between conventional biomarker-guided therapy and standard practice [1, 3], despite protocol compliance, patient selection and cut-off concerns. This post hoc analysis of a patient subset (Malmö, Sweden) from our previous investigation [4] compared the use of PCT, CRP and lactate to the novel biomarker mid-regional proadrenomedullin (MR-proADM) in guiding antibiotic administration during treatment within the ED.

Within this subset ($N = 213$), 26 (12.2%), patients were prescribed antibiotics < 48 h prior to presentation, whilst 187 (87.8%) were administered antibiotics during ED assessment. Of these patients, 164 (77.0%) were treated with intravenous (i.v.) and 23 (10.8%) with oral antibiotics. The median time to initial administration was 93 [28–160] min, with 71 (43.8%) patients receiving therapy within 60 min. Univariate and multivariate logistic regression found that MR-proADM had the strongest association with the requirement for antibiotic administration during ED treatment (Table 1). Interestingly, MR-proADM (Spearman $\rho = -0.31$, $p < 0.001$) and lactate (Spearman $\rho = -0.25$, $p = 0.002$) were the only parameters to be significantly negatively correlated with the time to antibiotic administration, with significant differences found at optimised MR-proADM cut-offs for antibiotic administration (1.27 nmol/L: 139 [76–211] vs 43 [26–135] min; $p < 0.001$) or pre-established [4] cut-offs for mortality prediction (1.54 nmol/L: 124 [33–199] vs 42 [26–122] min; $p = 0.002$). Similar results were also found for MR-proADM within previously established PCT concentration ranges [5] (Table 2), with an absence of ICU admission or 28-day mortality in patients with low MR-proADM concentrations, despite lower antibiotic administration rates and a significantly longer time to administration.

Results suggest that delayed antibiotic administration in patients with low MR-proADM concentrations may result in few adverse effects, potentially allowing for a more detailed clinical assessment prior to any subsequent initiation. Further studies in larger patient populations are required to confirm these initial findings.

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Table 1 Univariate and Multivariate analyses found that MR-proADM had the strongest correlation with the requirement for antibiotic administration during ED treatment

Biomarker	Patient population (*N*)	Antibiotic administration (*N*)	*p* value	C index	Univariate OR [95% CI]	Multivariate OR [95% CI]
MR-proADM	213	164	< 0.001	0.76	3.1 [1.9–4.9]	3.3 [1.9–5.9]
PCT	213	164	< 0.001	0.74	2.7 [1.7–4.3]	2.7 [1.7–4.5]
CRP	207	159	< 0.001	0.68	1.8 [1.3–2.5]	1.9 [1.4–2.8]
Lactate	204	158	0.002	0.66	1.8 [1.2–2.6]	1.6 [1.1–2.5]

Age, cardiovascular, neurological, renal and malignancy comorbidities were used as adjusting variables within the multivariate regression analysis, as previously outlined [4]. Univariate and multivariate odds ratios were expressed per 1 SD increment of the log-transformed value for each respective biomarker. *CI* confidence interval, *CRP* C-reactive protein, *DF* degrees of freedom, *MR-proADM* mid-regional proadrenomedullin, *N* number, *OR* odds ratio, *PCT* procalcitonin

Table 2 Low MR-proADM concentrations resulted in an absence of ICU admission or 28-day mortality, despite lower antibiotic administration rates and a significantly longer time to administration, irrespective of corresponding PCT concentration

Patient subgroups	MR-proADM concentration	
	< 1.27 (nmol/L)	≥ 1.27 (nmol/L)
Subgroup 1: PCT concentration: < 0.25 μg/L (*N* = 106)		
Patients (*N*)	65	41
Antibiotic administration (*N*, %)	35 (53.8%)	34 (82.9%)
Time to antibiotic administration (min) (median, Q1-Q3)	127 [45.0–220]	42 [25.8–116]
Composite of 28-day mortality and ICU admission (*N*, %)	0 (0.0%)	7 (17.1%)
Subgroup 2: PCT concentration: ≥ 0.25 and < 0.50 μg/L (*N* = 24)		
Patients (*N*)	8	16
Antibiotic administration (*N*, %)	7 (87.5%)	15 (93.8%)
Time to antibiotic administration (min) (median, Q1–Q3)	165 [88–305]	50 [19.3–186]
Composite of 28-day mortality and ICU admission (*N*, %)	0 (0.0%)	1 (6.3%)
Subgroup 3: PCT concentration: ≥ 0.50 μg/L (*N* = 83)		
Patients (*N*)	21	62
Antibiotic administration (*N*, %)	15 (71.4%)	59 (95.2%)
Time to antibiotic administration (min) (median, Q1–Q3)	131 [92.8–166]	45 [26–136.5]
Composite of 28-day mortality and ICU admission (*N*, %)	0 (0.0%)	15 (24.2%)

MR-proADM mid-regional proadrenomedullin, *N* number, *PCT* procalcitonin, *Q* quartile

Abbreviations

CI: Confidence interval; CRP: C-reactive protein; ED: Emergency department; i.v.: Intravenous; ICU: Intensive care unit; MR-proADM: Mid-regional proadrenomedullin; N: Number; OR: Odds ratio; PCT: Procalcitonin

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Availability of data and materials

The datasets used and/or analysed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

MR was the primary author and editor of the manuscript. OM was the principal investigator. MR, LT, MBT, MP and OM collected the study data and, in collaboration with DCW (up until January 2019), KS and JGdC, contributed to the evaluation and interpretation of the data as well as writing and editing of the manuscript. MR and OM performed the statistical analysis of the data. All authors critically reviewed and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Regional Ethical Review Board at Lund University, Sweden (2013/635), and was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all patients or their next of kin.

Consent for publication

No individual participant data is reported that would require consent to publish from the participant (or legal parent or guardian for children).

Competing interests

All authors have provided information on potential conflicts of interests directly or indirectly related to the work submitted in the journal's disclosure forms. At the time of initial analysis, interpretation and writing, DCW was an employee of BRAHMS GmbH, which holds patent rights on the procalcitonin and mid-regional proadrenomedullin assay. All other authors declare that they have no competing interests.

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