

University of Medicine and Pharmacy Tîrgu Mureş

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Abstract of the PhD thesis

The diagnosis of serious bacterial infections through biomarkers in infants and young children with fever

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Fever is still one of the main complaints encountered in children visiting the Emergency Departments (ED). Clinicians are facing the difficulty to distinguish between febrile children with serious bacterial infections (SBI) and children with self limited viral infections. The identification of children with fever without localizing signs of infection (FWLS) who are at risk for SBI through the use of new surrogate biomarkers has been widely researched in the past years. Among the many proposed, C-reactive protein (CRP) and Procalcitonin (PCT) have gained most interest. They have also been considered for developing scores and predicting models for SBI detection. Interleukin-6 (IL-6) proved good perspectives on early neonatal sepsis detection but so far showed lower performance when compared to CRP or PCT for SBI detection, and it was asserted that this may be related to their different kinetics.

The thesis is divided into a first part comprising the current knowledge on the subject and a second part comprising the personal contribution consisting in two clinical studies.

The first study was entitled “**Diagnostic accuracy of CRP, PCT and IL-6 in identifying SBI in children younger than 36 months with fever without localizing signs of infection**”.

The aim of the study was to evaluate and compare the accuracy of CRP, PCT and IL-6 in identifying SBI in children with FWLS. Additionally, white blood cell count (WBC) was tested, as it still is widely used for evaluating febrile children.

Method. Children aged 7 days to 36 months with FWLS, who visited the ED from Tîrgu Mureş Emergency Clinical County Hospital, during January until September 2013, were included. CRP, PCT, IL-6, WBC and urinalysis were determined for every patient included. SBI diagnosis was supported by presence of positive cultures and chest radiographs. All children had clinical follow up. The final diagnosis was established after the final follow-up in conjunction with the results of cultures and chest radiographs.

Results. Of 159 children identified with FWS, 139 patients (73 males) were analysed. 31 patients (22.3%) had SBI: 17 UTI, 11 pneumonia, 1 bacteraemia and UTI, 1 bacterial enterocolitis, 1 sepsis. In the UTI group the most frequently isolated pathogen was *E. Coli*. For identifying SBI, AUC returned the best result for CRP [AUC: 0.87 (95%CI: 0.81-0.92)], followed closely by PCT [AUC: 0.83 (95%CI: 0.76-0.89)]. We found that IL-6 [AUC 0.77 (95%CI: 0.69-0.84)] performed better than WBC [AUC 0.69 (95%CI: 0.61-0.76)], but was

inferior to CRP and PCT. The optimal cut-off value for prediction of SBI was 12900/mm³ for WBC, 21mg/l for CRP, 0,5ng/ml for PCT and 40,6ng/ml for IL-6. In the group with fever lasting less than 12 hours, CRP and PCT performed similarly and both were inferior to IL-6. IL-6 performed increasingly better when utilised for the patient groups with less than 8 hours [AUC: 0.88 (0.76-0.95)] and 6 hours [AUC: 0.88 (0.75-0.96)] of fever, respectively.

Conclusions. In our study group, both C-reactive protein and Procalcitonin are strong and similar predictors for SBI, and Interleukin-6 might be a better SBI screening tool for children with shorter duration of fever.

The second study was entitled “**Utility of a laboratory score (Lab-score) and a Clinical Prediction Model (CPM) for identifying SBI in children with fever without localizing signs of infection**”

The aim was to evaluate and compare the utility of the two new tools for predicting SBI in young febrile children: The Lab-score and the Clinical Prediction Model (CPM). A second objective was to assess the Lab-score performance in comparison with independent variables (CRP, PCT).

Method. Children from the first study group were exposed to a secondary analysis by calculating the Lab-score and the CPM for every patient. The Lab-score combines CRP, PCT and urinalysis for identifying SBI in febrile children. According to the Lab-score, 2 points are given for PCT ≥ 0.5 ng/ml, 4 points for PCT ≥ 2 ng/ml; 2 points are given if CRP value ranges between 40mg/l and 99mg/l and 4 points for CRP ≥ 100 mg/l. 1 point is given for positive urine dipstick (positive leukocyte esterase and/or nitrates). The Lab-score values range from 0 to 9, and the cut-off of ≥ 3 points was proposed as optimal for SBI prediction. The CPM combines several clinical variables and the value of CRP, for the same purpose. The outcome categories were pneumonia and other SBI. Diagnostic performance of the model was tested for several risk thresholds and low risk thresholds less than 2.5% were able to rule out, and high risk thresholds of 10% or more were able to rule in pneumonia and other SBI, respectively.

Results: From 134 patients analysed, 31 (23.1%) had SBI, 11 pneumonia and 20 other SBI. For detecting pneumonia, the Lab-score [AUC 0.87 (95%CI: 0.80-0.92)] modestly outperformed the CPM [AUC 0.81 (95%CI 0.73-0.87)]. For a low risk threshold of 2.5% used for ruling out pneumonia, CPM had a sensitivity of 90.9% (95%CI: 58.7 – 99.8) and a negative LR of 0.1 (0.02-0.8). For diagnosing other SBI, both the Lab-score [AUC 0.89 (95%CI: 0.82-0.93)], and the CPM [AUC 0.89 (0.83-0.94)] were similar predictors. For detecting SBI overall, AUC for the Lab-score was 0.93 (95% CI: 0.87-0.96), higher than for CRP 0.87 (95%CI: 0.80-0.92) and PCT 0.83 (95%CI: 0.76-0.89).

Conclusions. The Lab-score and the CPM are easy-to-use models in clinical practice for identifying SBI in febrile children and proved strong and similar prediction value. The Lab-score proved superior performance in detecting SBI, in comparison with both CRP and PCT.

Key words: C-reactive protein, Procalcitonin, Interleukin-6, children, fever