Editorial

Diagnosis of bacteraemia in well-appearing children who present to the paediatric emergency department for fever.

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Short title: Blood culture in well-appearing feverish children.

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Fever is one of the most common reasons for visits to paediatric emergency rooms and departments, and the methodology for evaluating febrile children remains a challenge, especially in those with occult bacteraemia who appear well without any clinical evidence of severe infection. In the current issue of Acta paediatrica, Renana Gelernter et al publish their interesting results on the characteristics of 68 children with positive blood cultures who were discharged to home, as compared with those 182 who were hospitalised [1]. The design of the study was a retrospective review of the records of a teaching hospital in Tel Aviv, Israel. During nine years, blood cultures were taken from 31,444 children at the emergency department and 2,103(6.7%) cultures were positive, but only 289(0.9%) were considered as true-positive [1]. Finally, 250 cases with positive blood cultures were included in the analysis on clinical and laboratory characteristics, and among them, 68(27.2%) were discharged to home and 182 were admitted to hospital.

Twelve (17.6%) discharged children re-visited the emergency department and were hospitalised for clinical reasons before blood cultures were ready, and 46 children were recalled and re-examined because of confirmed positive blood cultures. Thirteen children were discharged and 33 were hospitalised. These 33 cases form 48.5% of those 68 originally discharged, 11.4% of those 289 with true-positive blood cultures, 1.6% of those 2,105 with positive blood cultures, and 0.3% of those 31,444 with blood cultures taken. None of the 46 recalled children presented with any complication [1].

In our teaching hospital in Tampere, Finland, the direct laboratory charge of one blood culture, when taken in a child at the emergency department, is €15.3 if the primary culturing in the bottle is negative. An additional €55 will be charged, if the primary culturing is positive and further culturing in plates for identification of the bacterium and its antibiotic susceptibility are needed. When the charge of €15.3 is multiplied by the figure of 31,444, the sum is €481,093. When the charge of €55 is multiplied by the figure of 2,103, the sum is €115,665. This calculation suggests that €596,758 are needed to identify 289 children with true-positive results from 31,444 blood cultures. For one such case, the estimated charge is €2,065, which is however, much lower than $20 000 for one positive blood culture in an American retrospective study inckluyding 454 inpatient and outpatient children, where nearly 99% of taken blood cultures were negative [2]. The laboratory charges applied in the American study were much higher than the charge of blood culture in our hospital, being $300 for the primary blood culture and additionally $250 if the primary culture was positive [2]. When applying the American prices, the total sum for 31,444 blood cultures would be $9,959,000 (€7,496,000, by the average rate of €1=$1.3285 in 2014) and the charge for identifying one positive blood culture would be $34,500 (€25,900). If the discharged child is recalled to the emergency department for the positive blood culture, there are also other costs to the families, such as traveling costs, hospital fees and costs due to time losses. In addition, recalling patients causes extra costs to the health care organisations because of more work and spent resources.

In the study from Israel [1], the 68 discharged children presented with lower fever (mean 38.2 ^{O}C), lower frequencies of dyspnoea (6.7%) and looking ill (3.0%), lower white blood cell (WBC) counts (mean 13.8x10^{9}/L) and lower serum C-reactive protein (CRP) concentrations (mean 50.5 mg/L), compared to those 182 who were hospitalised. Only lower serum CRP concentration remained as statistically significant in adjusted analyses. The rarity of the warning marks, and the rather low

WBC counts and CRP concentrations in discharged children [3] mean that their abilities either alone or as combined are poor in the screening of bacteraemia that is not clinically suspected.

Our criticism concerns the clinical practice to obtain blood cultures from children who are discharged from the outpatient clinic. That practice is expensive leading to large numbers of negative or false-positive results. In the study from Israel [1], true-positive findings were present in <1% of taken cultures. In addition, the usefulness of even true-positive finding is questionable, if the child is primarily discharged to home. The results of the cultures are ready after two days that is too late to help in the diagnosis of severe infection. By that time, some children have been hospitalised for clinical reasons, and some children have improved, either spontaneously or due to oral antibiotics. In the study from Israel [1], about 40% of children with true-positive blood cultures who were primarily discharged, belonged to either of these two groups. Two-thirds of those recalled due to positive blood cultures were hospitalised, but the design of the study did not allow any evaluation how necessary these hospitalisations were.

Renana Gelernter et al concluded that larger prospective studies are needed to define the characteristics and outcomes of children with unsuspected bacteraemia [1]. Their results showed, that there are no clinical symptoms or signs, and no laboratory markers, which could either alone or as combined offer a solution to this screening problem. The result would probably be similar in larger prospectively collected materials. Such pessimistic conclusion was to be drawn also from a large multi-centre study from America including 7,509 children hospitalised for suspected pneumonia with 2,568 blood cultures performed on the first day of hospitalisation [4].

In recent years, artificial intelligence and machine learning have been under active discussion in medicine, including also screening of bacteraemia in children. In Taiwan, the authors conducted a retrospective case-control study on 16,967 febrile children with blood cultures available, who presented to the pediatric emergency department of a teaching hospital during an eight-year surveillance period [5]. Only 146 febrile children had a true-positive and 462 had a false-positive result in blood culture. Machine learning and cost-sensitive learning methods were applied to build up a model for prediction of bacteremia. The extra cost of performing blood culture was settled to 0 for true positive and true negative results, and to 1 (real costs of primary bottle and further plate culturing) for false-positive results, and the extra costs between 7-13 were considered optimal for false-negative results. By the prices of our hospital, this range means that avoidance of one false-negative result in blood culture would mean extra costs from €492 to €914.

In the Taiwanese study [5], the final model consisted of serum CRP and nine characteristics of blood counts, which were included because they were significant predictors of true-positive blood cultures in crude analyses. Since the authors applied the case-control design, age and gender were not included in the model. This model was able to divide febrile children into five classes: class-1 with no risk, class-2 with minor risk, class-3 with modest risk and class-4 with high risk of bacteremia, and class-5 with bacteremia [5]. Sensitivity of the model to predict bacteremia was 0.92, specificity was 0.96, and positive and negative predictive values were 0.013 and 0.99, at different but optimal cost levels of 12, 7, 8 and 9 for false-negative results, respectively [5].

Combining of clinical decision-making with evidence-based algorithms, in future constructed by applying machine learning and cost-sensitive analyses, may optimize the clinical diagnostics of bacteraemic infections, highlighting both of the two

perspectives: usefulness for the child patients, and cost-effectiveness for the health care system.

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