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Umana, E., & Waterfield, T. (2021). Varying international practices regarding the evaluation of febrile young infants. *Archives of Disease in Childhood*. <https://doi.org/10.1136/archdischild-2021-323001>

Published in:
Archives of Disease in Childhood

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
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Varying international practices regarding the evaluation of febrile young infants

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Word Count: 1156

Identifying children with serious bacterial infection can be challenging. To aid clinicians in the UK and Ireland the National Institute for Health and Care Excellence (NICE) provides guidance on those children at greatest risk via NICE guideline (NG51) Sepsis: recognition, diagnosis and early management. One of those “high risk” groups are infants under three months of age presenting with a fever or history of fever over 38°C. For this high risk group NICE NG51 recommends extensive investigation and administration of broad-spectrum antibiotics to all within the hour [1]. Internationally however, approaches differ. In the United States and Europe validated clinical decision tools have been developed [2,3]. These tools allow for a tailored approach that reduces the need for painful interventions such as lumbar puncture, improves antimicrobial stewardship and reduces the need for hospital admission [2,3].

Although approaches to assessment and management vary internationally there are some areas where we do agree. The rates of serious bacterial infections are similar in the UK, Europe and the USA with between 10 and 20% of febrile young infants having a serious bacterial infection [2-4]. The majority of which (9-17%) will be urinary tract infections and (1-3%) will be invasive bacterial infections such as meningitis and bacterial sepsis [2-4]. We all agree that younger infants under 28 days of age are at higher risk for serious bacterial infections and finally we all agree that no pattern of clinical features or exam findings can be used to reliably predict the presence or absence of serious bacterial infections in this group [2-4].

In the USA the Pediatric Emergency Care Applied Research Network (PECARN) developed a clinical decision tool for the tailored management of febrile infants under 60 days of age [2]. In the study by Kupperman et al the team prospectively recorded clinical and laboratory data on 1821 infants to derive and validate a new clinical decision tool [2]. There were 170 (9.3%) of the infants diagnosed serious bacterial infections including 151 (8.3%) diagnosed with UTI, 26 (1.4%) with bacteremia and 10 (0.5%) with meningitis [2]. Kupperman et al report that the combination of normal urinalysis, an absolute neutrophil count of less than 4090/ μ l and a Procalcitonin of less than 1.71ng/ml could be used to safely identify infants at low risk of serious bacterial infection [2]. In the validation cohort 497/913 (54%) infants were identified as at low risk. Of these two were found to have urinary tract infections without bacteraemia or meningitis [2]. More recently a similar tailored approach has been suggested by the American Academy of Pediatrics. Validation data on this approach is keenly awaited [5].

In mainland Europe the Step-by-Step approach is a validated tool used to identify infants at low risk of serious bacterial infection suitable for a tailored approach to treatment [3]. Developed around the same time as the PECARN rule, the StepByStep rule defines infants at low risk as those who appear well, are over 21 days of age without leukocyturia, a Procalcitonin level of less than 0.5ng/ml, a CRP of less than 20mg/l and an absolute neutrophil count of less than 10,000/ mm^3 [3]. In the validation study published by Gomez et al the low risk group included 991/2185 (45%) infants [3]. Of these 11 (1%) had a serious bacterial infection including seven invasive bacterial infections [3]. Four of the seven invasive bacterial infections occurred in infants aged 28 days or younger [3].

In the UK, there are three suggested approaches to the assessment and management of febrile infants. The NICE Sepsis: recognition, diagnosis and early management guidance (NG51) advises that all febrile infants under three months of age are treated irrespective of their age, clinical appearance or laboratory features [1]. In contrast NICE Fever in under 5s: assessment and initial management (NG143) advises a tailored approach with low risk infants not requiring parenteral broad-spectrum antibiotics [6]. Low risk infants are defined as over one month of age, well appearing and with a total white cell count of between 5×10^9 /litre and 15×10^9 /litre [6]. Thirdly there is the recently proposed British Society for Antimicrobial Chemotherapy (BSAC) guidance that recommends that infants at low

risk of serious bacterial infection may not require parenteral broad-spectrum antibiotics [7]. The BSAC guidance identifies infants at low risk as well-appearing, over 28 days of age, with a CRP less than 20mg/l and with a negative urinalysis [7].

These different UK approaches were recently validated on behalf of the Paediatric Emergency Research UK and Ireland (PERUKI) network [4]. A total of 555 infants from six PERUKI sites were included in the validation cohort [4]. The NICE Fever in under 5s: assessment and initial management identified 51/555 (9%) of infants suitable for low risk management [4]. Of these infants deemed at low risk 7 (14%) were found to have serious bacterial infections [4]. The BSAC guidance identified 80/555 (14%) infants as at low risk of serious infection [4]. Of the 80 infants deemed at lower risk 14 (18%) were diagnosed with a serious bacterial infection [4]. The NICE NG51 guidance classified all infants as high risk.

The tailored approaches advocated by NICE NG143 and BSAC performed poorly when compared PECARN and StepByStep guidance. The low risk groups identified by NICE NG143 and BSAC had similar rates of serious bacterial infections (14% NICE NG143, 18% BSAC) as the overall study population (14%) [4]. The sensitivity and specificity of StepByStep and PECARN are reported as 0.92/0.47 and 0.98/0.60 respectively [2,3]. The sensitivity and specificity of NICE NG143 and BSAC guidance was 0.91/0.09 and 0.82/0.14 respectively [4]. Unlike the PECARN and StepByStep decision rules, the NICE NG143 and BSAC guidance were not developed using discovery and validation cohorts. Also, unlike PECARN and StepByStep, the NICE NG143 and BSAC guidance do not include the use of Procalcitonin as this is not widely available in the UK and Ireland.

What is clear is that further research is required to improve the care of febrile infants in the UK. None of the UK clinical decision tools are ideal. The NICE NG51 guidance is safe in that all serious bacterial infections are treated but results in the over investigation of many infants and the excessive use of broad-spectrum antibiotics. Conversely NICE NG143 and the proposed BSAC guidance lack the necessary sensitivity to exclude SBI. These issues have been recognised by NICE who have called for further research into the role of biomarkers and for the development of clinical decision rules in the UK [1]. Alongside this research is required to understand what happens to infants who have their initial treatment delayed due to being identified as being at low risk. Do they suffer harm from this delay? Is this potential harm sufficient to justify the treatment of all infants just-in-case? This research will involve engagement from clinicians as well as parents and patient groups. The outcomes of such research can advance the standard of care for febrile infant presenting to our emergency departments in the UK and Ireland.

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