CORRESPONDENCE

The Febrile Child: Diagnosis and Treatment

by Prof. Dr. med. Tim Niehues in Volume 45/2013

Pointers for the Examination Technique

With regard to physical examination, the article states that a child's throat and ears should be inspected, and the lungs and heart auscultated, and if the child is in pain, the site where the pain is felt should be localized. This strikes me as unsatisfactory in the context of such a seminal article. Important pointers in this setting should include:

The patient should be fully undressed during the examination (one sees increasingly often mothers who are apparently used to seeing their children auscultated above/through the neckline in their rompers, at the front and at the back, in a quasi-improvised fashion that only mimics a proper examination, even in pediatric practices).

Signs of meningitis should be excluded in all febrile children.

Palpation of the abdomen and the most important lymph nodes is, of course, one of the important steps in the examination.

A sentence in *Figure 2* in the article that irritates me, is "search for cause, urinalysis if cause is unclear". I wish to remind readers that we can identify genuine causes only in very rare cases, and it is a very subjective assessment on any pediatrician's part, whether they consider a cause as sufficiently confirmed in the concrete case scenario (for example, "viral infection," which is usually no more than an assumption). In other words, this means that in a febrile infant, urine testing is to be done as a matter of course; the younger the child, the more urgently (even though it may be slightly more laborious—it still can easily be organized in the outpatient setting).

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Conflict of interest statement

The author declares that no conflict of interest exists.

Consider Further Differential Diagnoses

Unfortunately the certified CME article (1) makes only passing reference to the fact that mere heat accumulation can result in body temperatures above 38 °C, and that not every fever is caused by pyrogens. I especially missed any mention of thirst fever owing to exsiccosis and hypohidrotic forms of ectodermal dysplasia, which are important differential diagnoses in childhood fever of unclear origin and can lead to fatalities (2, 3).

Thirst fever develops when a body has less water available than would be needed to regulate the body temperature through perspiration. Due to their more sensitive fluid balance, this is particularly common in infants. By contrast, most children with hypohidrotic ectodermal dysplasia are not capable of releasing surplus body heat through perspiration as they do not have sweat glands (4). In such cases, infant mortality—depending on the climate zone and healthcare provision—is between 2% and 20% (3). Antipyretic drugs are ineffective in this setting, in contrast to physical measures to lower the body temperature.

In fever of unknown origin, what also needs to be identified is whether the affected person is actually physically capable of sweating. The medical history and physical examination serve this purpose. For the most common form of hypohidrotic ectodermal dysplasia, there is a causal treatment approach that requires a diagnosis as early on as possible, and which is currently being evaluated in clinical studies (www.clinicaltrials.gov NCT01775462 und NCT01992289).

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Conflict of interest statement

Professor Schneider has received consultancy fees from Edimer Pharmaceuticals and Gerson Lehman Group.

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He co-owns a patent for the treatment of X-linked hypohidrotic ectodermal dysplasia.

Laboratory Tests Are Important

The medical standard for the diagnostic evaluation and treatment should be deduced from the published scientific literature, if possible. At least 5 studies published between 1982 and 1998 showed that the physical examination of a febrile infant has insufficient sensitivity to detect severe bacterial infections. To rely on this alone to determine the treatment of a child is therefore a mistake that we cannot really follow.

The answer to the question whether inpatient admission and immediate administration of antibiotics is necessary in sick children aged 1–3 months is a resounding yes. But when does an infant appear sick? The learning objective has to be: the physical examination alone is not enough to base decisions on as to whether outpatient treatment or admission to a pediatric hospital is needed

In terms of laboratory testing we wish to add that the interdisciplinary guideline on bacterial infections in neonates (No 024–008 in the registry of the Association of the Scientific Medical Societies [AWMF]) contains information on the sensitivity and specificity of the different variables that are appropriate for the early detection of bacterial infections and that have been deduced from 19 publications. Familiarity with this guideline and the approach to be concluded from it should be the learning objective

The last sentence in step 3: “The individual or combined testing [...] seems unnecessary and unjustified anywhere but in the intensive-care setting” remains without any scientific proof. It further suggests that there are differences in the urgency of laboratory diagnostic evaluation in neonates in intensive care units and in outpatient care. This is not the case: the urgency is always the same, because physical examination is not enough. Furthermore, the sentence contradicts the results of randomized studies in neonates (1–3).

In sum, the learning objective is that the outpatient treatment of a febrile infant meets the medical standard only once bacterial infection has been excluded by means of laboratory testing. DOI: 10.3238/arztebl.2014.0252a

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Conflict of interest statement

The author is the guideline representative of the German Society for Neonatology and Pediatric Intensive Care Medicine (GNPI).

Do not Administer Free Glucose Solution

The article was interesting. I have worked in neonatology, pediatrics, and intensive care medicine, but not every doctor has such a training background. If a doctor administers parenteral “saline or glucose solution to a child (in children <1st year of life, about 100 mL/kg body weight” [1], p 771) then the child may die because of the glucose solution. The problem in the setting is the “free” water, which may lead to cerebral edema and convulsions. This case has actually occurred—the child in question died with convulsions. DOI: 10.3238/arztebl.2014.0252b

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The author declares no conflict of interests.

Economicalness of Outpatient Laboratory Diagnostics

The author, Professor Niehues, deserves thanks for this review article (1), which may be extremely useful for everyone working with children. For pediatricians, no change in their daily routine would be expected as identifying the cause of a fever in a child is clinical routine. For those doctors, however, who do treat children, but for whom pediatrics is not the core element of their training, the described algorithms may be useful.

It is of note that the author does not see laboratory diagnostic evaluation (blood count, C-reactive protein [CRP], and urine, *Figure 2*) as within the outpatient sector but sets it within the hospital. This gives rise to two conclusions: firstly, the author does not trust physicians in private practice to perform such diagnostic evaluations. Secondly, the author has realized that outpatient laboratory diagnostic evaluation—according to the guideline of the German Medical Association and within the context of EBM reimbursement, especially in relation to point of care testing—is in no way economically viable, and he therefore concludes that such diagnostic tests can be undertaken only in the inpatient setting.

In my experience with the authors, I can definitely rule out the first conclusion. The second one definitely applies, although, for consistency’s sake, all children who meet the criteria will now need to be admitted as inpatients in order to undergo laboratory tests. DOI: 10.3238/arztebl.2014.0252c

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Additional Comments Regarding Diagnosis and Treatment

From the perspective of a pediatrician in private practice, I wish to add 5 short points to the article (1).

The degree of the fever is never a measure for the severity of the illness in infants. The recommendation to administer an antipyretic above a certain temperature—in the article, that is $>40^{\circ}\text{C}$ —is misleading and supports doctors' and parents' fever phobia.

In clinical practice, antipyretics can be used like a test in case of uncertainty. Within 45 minutes after the administration of a weight-appropriate medication, a child that was seemingly seriously ill before will be well. A child with pneumonia will certainly be afebrile, but clinically it is still ill.

Metamizole was unjustifiably not mentioned as an antipyretic. It offers a wide range of use after the third month of life and can be used without restriction in children (2). In our own experience it is notably more potent in fever than paracetamol/acetaminophen or ibuprofen (3).

A febrile child will always have abnormal, ie accelerated, breathing. Parents need to be instructed that the breathing should return to normal roughly three quarters of an hour after an antipyretic drug has been administered.

The cause of fever in children is usually an inflammation of the upper respiratory tract. Since paracetamol is not an anti-inflammatory substance, pediatricians in private practice should always prefer a preparation containing ibuprofen, especially because of better responsiveness of further inflammation-dependent symptoms, such as nausea, middle abdominal pain, sore eyes, vomiting, headache, and aching limbs.

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In Reply:

Müller comments with regard to the examination technique that children should always be completely undressed for a physical exam and that signs of meningismus should be actively excluded in every child. Undressing completely is an important prerequisite for the physical exam, in order to rule out heat accumu-

lation as the cause of the raised temperature and to detect findings in sites that are difficult to access, for example petechiae on the buttocks in meningitis. Unfortunately the meningismus signs are often not very reliable, and their investigation is not helpful especially in younger children.

Schneider points out exsiccosis (thirst fever) with regard to differential diagnoses in febrile children, and hypohidrotic forms of ectodermal dysplasia (ED). His working group has contributed to the elucidation of ED in crucial ways (see the reference list of his letter to the editor). Infants with ED are subject to high mortality, and it is possible that there is a certain unknown number of ED that remain undiagnosed. In infancy, the stigmata of ED may not yet be recognizable, for example, conical teeth; thin/sparse hair/eyebrows, reduced lacrimal secretion.

With regard to laboratory tests, Müller pointed out that urine tests should always be conducted in febrile children. We cannot emphasize enough the importance of urinalysis. However, situations are common in which the cause of the fever can be identified without urine testing (for example, otitis, tonsillitis, gastroenteritis). In such obvious cases, rational diagnostic evaluation is indicated. In my view, initially leaving out urine tests is justified in the sense of putting less stress on the child and saving costs.

Pohlandt points out that it should be a learning objective that physical examination alone is not enough to base a decision on regarding outpatient treatment or admission to a pediatric hospital, and that, with regard to laboratory diagnostic evaluation, the guideline on bacterial infections in neonates (AWMF 24–008, set out in June 1997) and the therapeutic approach to be concluded from this guideline should be a learning objective. The guideline was last updated 8 years ago, is not listed in the AWMF register, and is thus not appropriate as an up-to-date recommendation. Clearly, physical examination alone is not sufficient in premature babies and neonates. The history is of crucial importance in this context ([1] Box). Complementary laboratory tests (especially IL-6) are certainly required, especially in preterm infants and neonates. Their significance, however, is overestimated since all markers (CRP, procalcitonin, IL-6) are raised as a matter of course, in the context of the physiological acute-phase reaction up to 36 hours post partum. In recent years, many scientific proofs have been identified for the limited study data regarding the significance of laboratory tests as predictors of severe bacterial infections (2, 3).

Aliani points out that outpatient laboratory testing in the context of EBM reimbursement is not justifiable in terms of economicalness. As a consequence, all children will have to be admitted as inpatients for the purpose of laboratory tests. We intentionally did not further define the term “children without any other signs of severe illness.” The suspicion that a child has abnormal symptoms leads to laboratory investigations in day to day practice. Specialist doctors in private

practice order laboratory investigations and interpret them on a daily basis and in a competent manner. Laboratory tests are, however, only one of the pieces of the puzzle in deciding the pros and cons of a hospital admission or administration of antibiotics. In my experience, the significance of laboratory tests for assessing febrile children is overestimated, while the history and physical examination are underestimated. A rational approach to taking blood spares the children and our resources.

Staus (glucose solution) and Röhnelt (indication for and selection of antipyretic drug) wrote regarding the treatment of febrile children. In text books and guidelines the term “glucose solution” is used in isolation, without mentioning any added electrolyte. Obviously, children (and adults) must never be given free glucose solution, as this may cause severe harm to the patient.

Röhnelt writes that the degree of fever in infants is never a measure for the severity of disease. This contradicts a meta-analysis of 30 studies, in which a body temperature $>40^{\circ}\text{C}$ is regarded as a red flag symptom of a serious bacterial infection ([1] Box). Standard references and textbooks recommend using antipyretics in very high temperatures $>40^{\circ}\text{C}$, because the hope is for an improvement in the child's conditions (4, 5). Röhnelt mentions tests from his own clinical practice of many years (for example, lowering a fever, but lacking clinical response to antipyretics as a sign of pneumonia). In my opinion, using antipyretics *ex juvantibus* is questionable, since studies or long term observations are lacking. Röhnelt's experience of the innocuousness of metamizole in treating febrile children from the 3rd month of life is not shared by some (6). Metamizole still accounts for the majority of medication induced cases of the extremely rare, but po-

tentially life-threatening, agranulocytosis (7). The safety profile of ibuprofen or paracetamol/acetaminophen is far more favorable, either of those two drugs is preferred in febrile children (4, 5).

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