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Fever without apparent source on clinical examination

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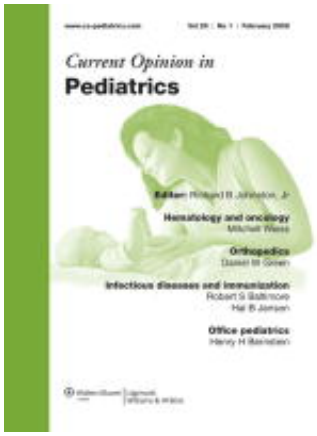

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Table of Contents:

≪ Promotion of physical activity in children.

≫ Case report: WT1 exon 6 truncation mutation and ambiguous genitalia in a patient with Denys-Drash syndrome.

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Full Text (PDF) 109 K Email Jumpstart Find Citing Articles ≪ Table of Contents About this Journal ≫

Links

Abstract

Complete Reference

Outline

Abstract

Purpose of review: Routine immunization of children with the heptavalent pneumococcal conjugate (PCV7) vaccine and rapid tests for identification of viruses since the last review in 2002 make this review timely and relevant.

Recent findings: Since the introduction of the PCV7 vaccine, the incidence of true bacteremia has decreased to 1% and has impacted the epidemiology of fever in the under-3-year-old population, making urinary tract infection the most common cause. Polymerase chain reaction testing for viruses helps in early diagnosis and serves to decrease the unnecessary use of antibiotics. Serious infections are dependent not only on the virulence of the agent, but also on host susceptibility, which has been getting more attention recently. Kawasaki disease in the very young infant is also discussed and awareness is increasing among physicians.

Summary: The decrease in the rate of bacteremia since the PCV7 vaccine was introduced means that the management guidelines for fever in the under-3-year-old population need to be reviewed. In addition, better markers are required to predict serious bacterial infection in this population. Further research into the understanding of the host immune response is also needed.

Introduction

This review focuses on febrile children in whom a source of fever is not readily apparent on clinical examination. This is discussed under the following headings:

1. host susceptibility and pathophysiology of infections;
2. evaluation and management of children from 0 to 36 months of age with fever;
3. children with prolonged fever of unknown origin.

Several articles that discuss the epidemiology, diagnosis and therapy of fever in children are reviewed below.

Host susceptibility and pathophysiology

Eagle and Trowsdale [1] discussed the role of natural-killer group 2 member D (NKG2D) ligands in the immune response to infections. NKG2D is a powerful activating receptor, expressed by natural killer (NK) cells and T cells, which regulates immune responses during infection, cancer and autoimmunity. NKG2D ligands comprise a diverse array of MHC class-1-related proteins that are upregulated by cellular stress. They propose that NKG2D-ligand diversity gives the host an advantage in an ancient evolutionary battle with viruses driven by an immunological arms race with pathogens. Both the host and the pathogen are under natural selection pressure to diversify and refine their defense strategies in response to improvements made by their competitor. In-vivo experiments have shown that NK cells are instrumental in driving viral evolution. The authors opine that the selection pressure exerted by the virus in return could select for retention of mutations and gene duplications in NK-cell receptor and ligands that are beneficial in protection against the virus. Thus clinical disease in some individuals and absence of disease in others despite identical exposures to pathogens are related to the variability in the host-pathogen interactions due to differences in the host immune response.

Genetic susceptibility to infectious diseases in an individual is very complex. Janssen *et al.* [2] studied the complexity of respiratory syncytial virus (RSV) susceptibility in young children using gene associations of 220 genes involved in airway mucosal responses, innate immunity, chemotaxis, adaptive immunity and allergic asthma. They enrolled 480 children with RSV bronchiolitis, their parents and 1008 random population controls. Single nucleotide polymorphisms in the innate immune genes involved in signal transduction, interferon pathway and the proinflammatory response demonstrated the strongest association with bronchiolitis. An in-depth understanding of both the innate and the adaptive immune response could lead to the development of better strategies for prevention.

Children 0 to 36 months of age with fever

Some articles of interest discussing the epidemiology, clinical features, management, predictors of serious bacterial infection (SBI), laboratory diagnosis, and therapy of fever in children under 36 months of age are reviewed in the following pages.

Epidemiology

The introduction of the heptavalent pneumococcal conjugate (PCV7) vaccine has accelerated the continuously evolving evaluation and management of the febrile child. Carstairs *et al.* [3•] compared the incidence of pneumococcal bacteremia between febrile children under 3 years of age who had and had not received the PCV7 vaccine. In the vaccinated group none (0/833) of the blood cultures were positive for pneumococcus compared with 2.4% (13/550) in the unvaccinated group [$P < 0.001$; 95% confidence interval (CI) 1.4-3.3%]. The etiology of true bacteremia in the unvaccinated group was all due to pneumococcus. Since urinary tract infection (UTI) was the next most common diagnosis in the truly bacteremic children between 3 and 36 months of age, it is increasingly important to include urine analysis in the evaluation of an immunized well-appearing febrile child aged 3-36 months.

Herz *et al.* [4••] retrospectively studied the change in the etiology and the incidence of bacteremia among previously healthy children aged 3-36 months. About 100 000 patients were analyzed per study year for 5 years (1998-2003). The investigators found that in the post-PCV7 period there was an 84% reduction of pneumococcal bacteremia and a 67% reduction in overall bacteremia. The number of blood cultures decreased by 35% in the outpatient pediatric clinics but remained unchanged in the emergency departments. In the post-PCV7 period one-third of all pathogenic organisms cultured were *Escherichia coli*, another third were nonvaccine serotype pneumococcus and the remaining third were *Staphylococcus aureus, Salmonella, Neisseria meningitidis* and *Streptococcus pyogenes*. The estimated occult bacteremia rate in the post-PCV7 period was 0.25%, which is well below the 0.5% bacteremia rate when it is no longer cost-effective to continue empiric testing and treatment based on current guidelines. In the post-PCV7 period, the white blood cell (WBC) count of over 15 000 had a sensitivity of 74%, specificity of 55%, positive predictive value of 1.5%, and negative predictive value of 99.5%, thus making it a less useful screening tool. We need prospective studies to help formulate new clinical sepsis guidelines in the post-PCV7 era to decrease the overuse of antibiotics and to identify the rare child who is at risk of bacteremia.

Clinical features

Bergman *et al.* [5•] examined the relationship between observed variability in the diagnosis and treatment of febrile infants and differences in clinical presentation, demographic features, practice/practitioner variables and geographic region. The Pediatric Research in Office settings network collected data and analyzed 2712 febrile infants up to 3 months of age examined by 484 pediatricians located in 194 practices. A statistical model was developed by the authors to quantify the independent effects of clinical presentation, demographic features, provider and practice characteristics, and regional variables on practice variability in the diagnosis and treatment of febrile infants. The clinical characteristics of the patient alone explained 29.7% of the overall variance and practice site fixed effects explained 15% of the overall variance. The authors concluded that the management of febrile infants up to 3 months of age depends more on the clinical presentation of the patient than on the characteristics of the provider/practice and the residential region. Of concern was the finding that 13% of infants up to 30 days of age who were assessed as being moderately or severely ill were not hospitalized, despite research showing that this is a particularly high-risk group for SBI.

Management

In the post-PCV7 era, new recommendations would likely include observation of immunized febrile children. Even with a highly efficacious vaccine, however, a subset of parents will prefer testing or treating presumptively. In addition, perceptions of risk affect physicians' practice styles and physicians may be uncomfortable with observation alone, either to avoid missing a case of bacteremia or from fear of a lawsuit. Madsen *et al.* [6••] explored the management strategy that would best suit parents based on their values for possible outcomes of fever of at least 39° C without apparent source among well-appearing children aged 3-36 months. A decision analysis was performed to compare the benefits and

outcomes of three management options (treat: blood culture and antibiotics, test: blood culture and complete blood count, and observe). Using a hypothetical cohort of 100 000 children for each strategy, they identified the treatment option that would best suit each parent's preferences for various interventions and outcomes at vaccine efficacies of 0-95%. They also performed survival analysis to assess the morbidity and mortality rates associated with each treatment strategy at various vaccine efficacies. At a vaccine efficacy of 0%, the majority of the parents' preferences suggested the treat option, the strategy with the lowest mortality rate. At a vaccine efficacy rate of 95%, mortality rates (about one in 100 000) were similar for all three management options, but parent preferences were still aligned with different options; 50% suggested observe, 42% suggested test and 8% suggested treat. Hence, in the post-PCV7 era, it is reasonable to incorporate parental preferences into the treatment decision.

Tools for predicting serious bacterial infection

Stathakis *et al.* [7] from Australia performed a retrospective review on febrile patients aged 3-36 months to determine the most reliable predictor of bacteremia. Among the 1488 patients studied, 43 (2.9%) were bacteremic and the most common organism was *Pneumococcus* (74.4%). The optimal logistic regression model identified neutrophil count as the variable that is most predictive of bacteremia. This is not surprising as pneumococcal bacteremia is associated with significant leukocytosis. It remains to be seen whether it will continue to be so in the post-PCV7 era. The PCV7 immunization rate was 50% until 2005; since then the vaccine has been distributed by the Australian government at no cost.

Andreola *et al.* [8•] assessed the value of procalcitonin and C-reactive protein (CRP) levels, compared with total WBC and absolute neutrophil count (ANC), in predicting SBI in febrile children in the emergency department. Analysis of the data on 408 children between 7 weeks and 36 months revealed that SBI was diagnosed in 94 (23.1%) and viral infection was confirmed in 36 (8.8%). Procalcitonin, CRP, WBC and ANC were significantly higher in patients with SBI. Procalcitonin differed significantly in relation to different organ involvement ($P < 0.001$), with the highest values found in sepsis and meningitis. Only procalcitonin [odds ratio (OR) 1.32; 95% CI 1.11-1.57; $P < 0.001$] and CRP (OR 1.02; 95% CI 0.60-0.87; $P < 0.001$) were retained as significant predictors of SBI in a multiple regression model. In children with fever less than 8 h ($n = 45$) before admission procalcitonin, CRP and ANC were significantly higher in the group with SBI. The authors conclude that procalcitonin and CRP perform better than WBC and ANC in predicting SBI in children with fever without source. Further studies are required for confirmation.

A reliable prediction tool for SBI is needed to assist clinicians in identifying children at high risk for SBI. Bleeker *et al.* [9•] from The Netherlands externally validated and updated a previously developed tool for predicting SBI in children with fever without apparent source. In the original study a stepwise multivariable logistic regression analysis yielded a final prediction tool including two models: the ‘clinical model’ (based on patient history and physical examination) and the ‘clinical plus lab model’ (including laboratory characteristics). The clinical model had poor discriminatory ability when used in the new set of patients and so the original prediction tool required updating. This was accomplished using all the available patient data ($n = 381$). Both models were translated into a ‘clinical score’, which was derived from the updated ‘clinical model’, and a ‘lab score’ from the updated ‘clinical plus lab model’. The clinical predictors were duration of fever, vomiting, ill clinical appearance, chest wall retractions, poor peripheral circulation, and laboratory predictors included WBC count, CRP and the presence of at least 70 WBCs in dipstick urine analysis. The updated prediction tool did not have perfect discriminatory power and could only be used as a screening tool. We concur with the authors that this updated tool could be used to support decision making in conjunction with clinical experience and should never be used as an independent diagnostic tool.

Laboratory diagnosis

Peltola *et al.* [10] analyzed WBC and CRP levels in children aged over 1 month of age with laboratory-confirmed bacterial and viral infections. They selected *S. pneumoniae, S. aureus*, and *E. coli* bacteremia for bacterial infections, and respiratory syncytial virus (RSV), rhinovirus, adenovirus and enterovirus respiratory infections, enterovirus meningitis, and influenza A and B infections for viral infections. They conducted a retrospective chart review and the median WBC and CRP levels were 18 600 cells/mm^3 and 84 mg/l, respectively, in children with bacteremia, compared with 9500 cells/mm^3 and 12 mg/l, respectively, in children with viral infections ($P < 0.001$). Among viral infections, respiratory adenovirus infection was associated with increase in WBC, CRP or both in 67% of the children and was significant when compared with the other viral infections ($P < 0.001$). The median WBC and CRP levels are higher in invasive bacterial infections than in viral infections, but the values are widely distributed. Thus they are not reliable indicators and we do need better predictors of SBI.

A reliable test to distinguish between bacterial and viral infections is needed to avoid the use of unnecessary antibiotics. Nuutila *et al.* [11•] investigated a novel marker of bacterial infection designated 'clinical infection score (CIS) point', which incorporated standard clinical laboratory data and quantitative analysis of expression of neutrophil complement receptors CR1 and CR3 as predictors. After microbiological confirmation or clinical diagnosis, 135 patients were found to have either bacterial ($n = 89$) or viral ($n = 46$) infection. All measured variables (WBC, ANC, CRP, erythrocyte sedimentation rate and neutrophil CR1 and CR3 levels) were significantly increased in bacterial infections; particularly the expression of neutrophil CR1 and CR3. The CIS point varied between 0 and 8, and displayed 98% sensitivity and 97% specificity in distinguishing between bacterial and viral infections. The laboratory testing of neutrophil CR1 and CR3 needs further innovations to lengthen sample storage time. The authors suggest that, with additional investigation, the CIS-based diagnostic test could potentially assist physicians in the appropriate use of antibiotics.

Hsiao *et al.* [12•] investigated the epidemiology of febrile illness and evaluated the usefulness of screening tests in infants 2-6 months of age. SBI was diagnosed in 44 (10.3%) of 429 infants studied: 41 with bacteruria and four (0.9%) with bacteremia. One patient had pneumococcal bacteremia (0.2%) and that is consistent with the rates in the post-PCV7 era. Direct fluorescent antigen (DFA) for viruses was positive in 163 (38%) and the majority were RSV or influenza A. Concurrent SBI was seen in 4.9% (eight of 163; 95% CI 2.1-9.4) of patients who had a positive DFA which was significantly ($P < 0.001$) lower than the 13.5% (34 of 251; 95% CI 9.6-18.4) in those with a negative DFA. The rate of bacteruria was not influenced by gender but the risk for uncircumcised males was at least 13 times higher than for circumcised males. The epidemiology of febrile illness in infants in the post-PCV7 era is changing and reliable tests for viruses have further improved our diagnostic capabilities.

Since rapid influenza testing has become freely available it is not clear whether knowing if a patient tested positive for influenza or not influenced additional diagnostic testing by physicians. Abanses *et al.* [13•] studied the impact of triage-based rapid influenza A and B testing of febrile infants and children aged 3-36 months. The patients belonged to one of two groups: one that was tested at triage (288 patients) and the others who followed the standard protocol (719 patients). In the group tested at triage 81 (28%) tested positive while in the standard protocol group 75 (30%) of 252 patients tested were positive. Complete blood count, blood culture, RSV testing, urine analysis and chest radiographs were ordered significantly more in the standard protocol group among those patients who tested positive for influenza. None of the influenza-positive patients who were tested for bacteremia or bacteruria were positive. The authors summarize that instituting an emergency department protocol for rapidly identifying influenza in previously healthy febrile infants with no obvious focus of infection results in significant decreases in additional diagnostic testing, time in the emergency department and charges.

King *et al.* [14•] report on the duration of hospitalization and antibiotic use in infants less than 3 months of age who were tested for enterovirus in the cerebrospinal fluid. One hundred and fifty-four (34.8%) of 478 patients tested were positive and the mean length of stay was 3.64 days with a median test turnaround time of 23 h. In multivariate analysis, having a positive cerebrospinal fluid enterovirus PCR test result was associated with a 1.54-day decrease in the length of stay and a 33.7% shorter duration of antibiotic use. It is likely that we are now seeing the benefits of rapid PCR testing and we support the routine use of these tests in patients after appropriate clinical evaluation.

Treatment

Sarrell *et al.* [15•] conducted a randomized double-blinded clinical trial on the efficacy of the antipyretics acetaminophen, ibuprofen or both alternating in the treatment of fever in children 6-36 months of age. A total of 464 children were randomized and equally distributed to one of three groups: acetaminophen every 6 h; ibuprofen every 8 h or alternating acetaminophen and ibuprofen every 4 h for 3 days after a loading dose of either drug. The alternating regimen had lower mean temperature, more rapid reduction of fever and less absenteeism from day care ($P < 0.001$). From this study the efficacy was confirmed but the adverse events need careful consideration and further investigation. A concern with the alternating regimen is accidental overdosing.

Australian parents' medication practice and influences on medication use for childhood fever were surveyed by Walsh *et al.* [16•] using 401 parents with children aged between 6 months and 5 years. The results are interesting and concerning: 91% used over-the-counter medications, 94% reported using acetaminophen and 77% reported ibuprofen. Dosage was predominantly determined by weight (86.3%) or age (84.3%) and frequency by instructions on the medication label (55.3%) or temperature (40.6%); 52% had alternated medications, 65.8% of these for temperatures below 38.5°C. Decisions to alternate were influenced by information from doctors/hospitals (49.5%), and children remaining febrile postantipyretic (41.7%). The authors conclude that the belief that these medications were harmful was overridden by fears of harmful outcomes from fever. It is likely that in the face of increasing cost of healthcare, more parents may turn to over-the-counter medications before bringing the child to the physician office for evaluation.

Doganis *et al.* [17] conducted a prospective study to evaluate whether delay in therapy of UTI in febrile children aged between 2 weeks and 24 months influences the development of acute inflammatory changes and the subsequent development of renal scars as documented by dimercaptosuccinic acid (DMSA) scan. A total of 278 infants with their first UTI (confirmed by suprapubic aspiration) were enrolled in the study. The median time between onset of symptoms and antimicrobial therapy was 2 days (range 1-8 days).

Renal changes in the DMSA scan were documented in 57%. Forty-one percent ($n = 105$) of the patients who received antimicrobial therapy in the first 24 h after onset of fever showed changes in the DMSA scan versus 59% ($n = 73$) when therapy was started on day 2 and 72% ($n = 100$) when therapy was started between days 3 and 8. The frequency of scarring remained unchanged and was independent of timing of therapy. It is important to understand that acute inflammatory changes in the kidneys can worsen as treatment is delayed, but may not affect the long-term changes like renal scarring.

A multicenter randomized controlled noninferiority study was conducted by Montini *et al.* [18•] in Italy to compare the efficacy of oral antibiotic treatment alone versus parenteral followed by oral therapy in children during the first episode of acute pyelonephritis. A total of 502 children aged between 1 month and under 7 years with clinical pyelonephritis were randomized to receive either only oral amoxicillin-clavulanic acid or parenteral ceftriaxone for 3 days followed by amoxicillin-clavulanic acid for 7 days. There was no significant difference between

the groups for the time to defervesce or in the rate of renal scarring. Oral therapy is an option but should be used with caution and with close follow-up in the appropriate patient.

Prolonged fever of unknown origin

Some articles of interest relating to prolonged fever of unknown origin in children are reviewed below.

Epidemiology

Pasic *et al.* [19] prospectively investigated the causes and outcome of childhood fever of unknown origin (FUO) in 185 patients referred to a single tertiary-care pediatric center in Belgrade, Serbia and Montenegro. Etiological cause was established in 71% and 38% had infectious diseases. The most common infection was Epstein-Barr virus infection, followed by visceral leishmaniasis, which is endemic to the area. Autoimmune disorders were the next common cause, accounting for 13% of patients, Kawasaki disease 6% and a similar number with malignancy. The etiology was unknown in 29%. About 15% developed significant organ system dysfunction during investigation of FUO and five (2.5%) patients died. Mortality was associated with prolonged symptomatic therapy and significant organ system dysfunction at the time of admission. This study reiterates that infectious diseases are the leading cause of FUO in children.

Kawasaki disease

The clinical features, laboratory findings and outcome were compared retrospectively by Lee *et al.* [20•] at ages up to 6 months, 7 months to 4 years (typical age for Kawasaki disease) and at least 5 years. A total of 136 children were studied, with 10 (7.4%) children aged up to 6 months and 12 (8.8%) aged at least 5 years. Children aged at least 5 years had longer duration of fever, cervical adenopathy, more common occurrence of coronary artery lesions and higher ANC. Children aged up to 6 months were diagnosed with incomplete Kawasaki disease, had a higher incidence of thrombocytosis, and coronary artery lesions that responded to intravenous immunoglobin (IVIG) therapy. Healthcare providers should not limit themselves to the typical age range because prompt therapy with IVIG will decrease morbidity and mortality due to coronary artery lesions.

Chang *et al.* [21•] investigated the clinical and laboratory characteristics of Kawasaki disease in infants under 6 months of age. Twenty (17%) of 120 patients were under 6 months and 100 (83%) were over 6 months of age. In infants under 6 months, hydrops of the gall bladder was significantly higher ($P < 0.001$) and in children over 6 months the WBC was significantly higher ($P < 0.001$). In this study the infants under 6 months were more likely to have incomplete presentation (35% versus 12%, $P = 0.025$), coronary involvement (65% versus 19%, $P < 0.001$), late IVIG therapy and relatively poor outcome. One should suspect Kawasaki disease in infants under 6 months who present with prolonged febrile illness despite incomplete clinical presentation. An echocardiogram is important in the diagnostic evaluation and early IVIG therapy in view of the high risk of coronary lesions.

Nigrovic *et al.* [22•] investigated the value of an extremely elevated platelet count (>800 000 cells/mm^3) to help identify febrile infants with Kawasaki disease. The authors retrospectively reviewed the charts of 26 500 children under 1 year who had a platelet count performed as part of an emergency department evaluation; 8.5% of the infants who had platelet counts greater than 800 000 cells/mm^3 had Kawasaki disease compared with 0.4% with platelet counts less than 800 000 cells/mm^3 (likelihood ratio 17; CI 8-34). We agree with the authors that children, especially those under 6 months of age, with prolonged fever, extreme elevation of platelet count and no compelling alternative diagnosis should

be evaluated for Kawasaki disease.

Newburger *et al.* [23•], as part of the Pediatric Heart Network Investigators, conducted a multicenter, randomized, double-blind, placebo-controlled trial to determine whether intravenous methylprednisone in addition to conventional IVIG therapy further reduces the risk of coronary artery abnormalities. Patients with Kawasaki disease were randomized to receive either methylprednisone (*n* = 101) or placebo (*n* = 98) in addition to IVIG. The two groups had similar outcome with coronary artery lesions, days spent in hospital, number of days of fever, rates of retreatment with IVIG and number of adverse events. The data presented did not support the use of methylprednisone in addition to IVIG in Kawasaki disease.

Miscellaneous

Scagni *et al.* [24] describe two children with Kikuchi-Fujimoto disease (KFD) as a rare cause of lymphadenopathy and fever of unknown origin. KFD is a rare, benign, self-limiting histiocytic necrotizing lymphadenitis of unknown origin and should be considered in the differential diagnosis of lymphadenopathy and fever of unknown origin. Since there is no specific test for diagnosis, a high index of suspicion and careful histopathologic evaluation are necessary. An accurate diagnosis will minimize unnecessary investigations and inappropriate therapy.

Christie *et al.* [25•] report the high prevalence of *Mycoplasma pneumoniae*-associated encephalitis in 1988 patients with unexplained encephalitis. Of the 111 patients who showed evidence of *M. pneumoniae* based on serology or cerebrospinal fluid PCR, 84 (76%) were under 18 years of age. Eighty of the 84 patients were positive by serology alone and cerebrospinal fluid PCR was rarely positive (2%). Pediatric patients with *M. pneumoniae*-associated encephalitis had a median age of 11 years, progressed rapidly and were often in the ICU (55%) and required prolonged hospitalizations. Symptoms included fever (70%), lethargy (68%), and altered consciousness (58%). They had fewer seizures and less severe hospital courses. Testing for *M. pneumoniae* should be considered in any child with unexplained encephalitis.

Conclusion

Changing epidemiology of fever without an apparent source in the very young due to the PCV7 vaccine behooves a reassessment of our current guidelines. Rapid diagnostic tests and better predictors of disease should contribute to an improved approach to the diagnosis and management of the febrile child. Research towards enhancing our understanding of the immune system is much needed. Kawasaki disease continues to be an enigma and more research is required to understand the etiology and pathophysiology of the disease.

Acknowledgements

I would like to thank Lisa Nichols for the many well done literature searches and Avind Rampersad MD for his help with the manuscript.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- **• of special interest**
- **•• of outstanding interest**

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 114-115).

1 Eagle RA, Trowsdale J. Promiscuity and the single receptor: NKG2D. Nat Rev Immunol 2007; 7:737-744. **Srial Solutions 360 Bibliographic Links** [Context Link]

2 Janssen R, Bont L, Siezen CL, Hodemaekers HM, *et al*. Genetic susceptibility to respiratory syncytial virus bronchiolitis is predominantly associated with innate immune genes. J Infect Dis 2007; 196:826-834. **Srial Solutions 360 Bibliographic Links** [Context Link]

3• Carstairs KL, Tanen DA, Johnson AS, *et al*. Pneumococcal bacteremia in febrile infants presenting to the emergency department before and after the introduction of the heptavalent pneumococcal vaccine. Ann Emerg Med 2007; 49:772-777. This retrospective study compares the rate of bacteremia between those who did and did not receive the PCV7 vaccine. They demonstrate that the rates of true bacteremia due to pneumococcus had decreased in the immunized and that UTI was the next most common cause of fever in children 3-36 months of age. [Context Link]

4•• Herz AM, Greenhow TL, Alcantara J, *et al*. Changing epidemiology of outpatient bacteremia in 3- to 36-month-old children after the introduction of the heptavalent conjugated pneumococcal vaccine. Pediatr Infect Dis J 2006; 25:293-300. The findings of this study support the idea that the routine practice of obtaining blood cultures and complete blood counts may no longer be indicated in the previously healthy, immunized, well-appearing febrile child. [Context Link]

5• Bergman DA, Mayer ML, Pantell RH, *et al*. Does clinical presentation explain practice variability in the treatment of febrile infants? Pediatrics 2006; 117:787-795. **Srial Solutions 360 Bibliographic Links** This is an interesting study that analysed variation in practices among physicians in the treatment of febrile infants using a statistical model. Based on the model they could explain about 50% of the variability and about 30% of the overall variability was dependent on clinical presentation. [Context Link]

6•• Madsen KA, Bennett JE, Downs SM. The role of parental preferences in the management of fever without source among 3- to 36-month-old children: a decision analysis. Pediatrics 2006; 117:1067-1076. **Srial Solutions 360 Bibliographic Links** This is an elegantly conducted study which uses decision analysis to compare the benefits and outcomes of three management options (treat: blood culture and antibiotics, test: blood culture and complete blood count, and observe). The survival analysis model used is a must-read for all physicians taking care of febrile infants. Also, the exploration of parental preferences as the odds of SBI decrease in the post-PCV7 era is enlightening and probably

needs consideration in the management of the immunized febrile infant in the future. [Context Link]

7 Stathakis T, Acworth JP, Barnett AG. Prediction tool for bacteraemia in children aged 3-36 months. Emerg Med Australas 2007; 19:353-358. **Srial Solutions 360 Buy Now** [Context Link]

8• Andreola B, Bressan S, Callegaro S, *et al*. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. Pediatr Infect Dis J 2007; 26:672-677. **Ovid Full Text Bibliographic Links** In this study the value of procalcitonin and CRP levels was compared with total WBC and ANC in predicting SBI in febrile children in the emergency department. Although procalcitonin, CRP, WBC and ANC were significantly higher in patients with SBI, procalcitonin and CRP performed better than WBC and ANC in predicting SBI in children with fever without source. [Context Link]

9• Bleeker SE, Derksen-Lubsen G, Grobbee DE, *et al*. Validating and updating a prediction rule for serious bacterial infection in patients with fever without source. Acta Paediatr 2007; 96:100-104. **Srial Solutions 360 Bibliographic Links** The updated prediction tool did not have a perfect discrimination power and could be used as a screening tool to support decision-making in conjunction with clinical experience and should never be used as an independent diagnostic tool. [Context Link]

10 Peltola V, Mertsola J, Ruuskanen O. Comparison of total white blood cell count and serum C-reactive protein levels in confirmed bacterial and viral infections. J Pediatr 2006; 149:721-724. **Srial Solutions 360 Buy Now Bibliographic Links** [Context Link]

11• Nuutila J, Hohenthal U, Laitinen I, *et al*. Quantitative analysis of complement receptors, CR1 (CD35) and CR3 (CD11b), on neutrophils improves distinction between bacterial and viral infections in febrile patients: comparison with standard clinical laboratory data. J Immunol Methods 2006; 315:191-201. **Srial Solutions 360 Bibliographic Links** A novel marker of bacterial infection designated CIS point, which incorporated standard clinical laboratory data and quantitative analysis of neutrophil complement receptors CR1 and CR3, was presented in this report. The storage time of samples was found to affect the levels of CR1 and CR3. Despite the shortcomings, this novel approach needs further study. [Context Link]

12• Hsiao AL, Chen L, Baker MD. Incidence and predictors of serious bacterial infections among 57- to 180-day-old infants. Pediatrics 2006; 117:1695-1701. **Srial Solutions 360 Bibliographic Links** This study investigated the epidemiology of febrile illness and evaluated the usefulness of screening tests in the post-PCV7 era. WBC and CRP are no longer useful screening tests but reliable tests for viruses have improved our knowledge of the epidemiology of fever without source and helped in the appropriate use of antibiotics. [Context Link]

13• Abanses JC, Dowd MD, Simon SD, Sharma V. Impact of rapid influenza testing at triage on management of febrile infants and young children. Pediatr Emerg Care 2006; 22:145-149. **Ovid Full Text** The authors found that those who test positive at triage for influenza have shorter time in the emergency department and less diagnostic testing, and cost of care is less. The children who test positive, however, also need to be clinically evaluated by the physician for concurrent bacterial infections before being discharged from the emergency department. [Context Link]

14• King RL, Lorch SA, Cohen DM, *et al*. Routine cerebrospinal fluid enterovirus polymerase chain reaction testing reduces hospitalization and antibiotic use for infants 90 days of age or younger. Pediatrics 2007; 120:489-496. **Srial Solutions 360 Bibliographic Links** The impact of rapid PCR testing of viruses is seen in the management of the febrile infant. This study reports that a positive cerebrospinal fluid enterovirus PCR test result was associated with a 1.54-day decrease in the length of stay and a shorter duration of antibiotic therapy in the febrile infant. [Context Link]

15• Sarrell EM, Wielunsky E, Cohen HA. Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized, double-blind study. Arch Pediatr Adolesc Med 2006; 160:197-202. **Srial Solutions 360 Buy Now Bibliographic Links** This study reports that the alternating regimen had lower mean temperature, more rapid reduction of fever and less absenteeism from day care ($P < 0.001$). One concern with the alternating regimen is accidental overdosing with either drug. Drug-related adverse events need further evaluation. [Context Link]

16• Walsh A, Edwards H, Fraser J. Over-the-counter medication use for childhood fever: a cross-sectional study of Australian parents. J Paediatr Child Health 2007; 43:601-606. The authors surveyed 401 Australian parents with children aged between 6 months and 5 years about their medication practice and influences on medication use for childhood fever management. They conclude that the belief that these medications were harmful was overridden by fears of harmful outcomes from fever. [Context Link]

17 Doganis D, Siafas K, Mavrikou M, *et al*. Does early treatment of urinary tract infection prevent renal damage? Pediatrics 2007; 120:e922-e928. **Srial Solutions 360 Bibliographic Links** [Context Link]

18• Montini G, Toffolo A, Zucchetta P, *et al*. Antibiotic treatment for pyelonephritis in children: multicenter randomized controlled noninferiority trial. BMJ 2007; 335:386. **Srial Solutions 360 Buy Now Bibliographic Links** This study is a noninferiority randomized controlled trial comparing the efficacy of oral antibiotic treatment alone with parenteral followed by oral therapy in children during the first episode of acute pyelonephritis. No significant difference was found between the groups for the time to defervesce or in the rate of renal scarring. Oral therapy is an option but should be used with caution in the appropriate patient. [Context Link]

19 Pasic S, Minic A, Djuric P, *et al*. Fever of unknown origin in 185 paediatric patients: a single-centre experience. Acta Paediatr 2006; 95:463-466. **Srial Solutions 360 Bibliographic Links** [Context Link]

20• Lee KY, Hong JH, Han JW, *et al*. Features of Kawasaki disease at the extremes of age. J Paediatr Child Health 2006; 42:423-427. **Srial Solutions 360 Buy Now** A total of 136 children were studied and 10 (7.4%) patients were up to 6 months of age and 12 (8.8%) were at least 5 years of age. The clinical features outside the typical age range are described. [Context Link]

21• Chang FY, Hwang B, Chen SJ, *et al*. Characteristics of Kawasaki disease in infants younger than six months of age. Pediatr Infect Dis J 2006; 25:241-244. **Ovid Full Text Bibliographic Links** This study reports the clinical and laboratory characteristics of Kawasaki disease in infants less than 6 months of age. The infants less than 6 months were more likely to have incomplete presentation (35% versus 12%, $P = 0.025$), coronary involvement (65% versus 19%, $P < 0.001$), late IVIG therapy and relatively poor outcome. [Context Link]

22• Nigrovic LE, Nigrovic PA, Harper MB, Chiang VW. Extreme thrombocytosis predicts Kawasaki disease in infants. Clin Pediatr (Phila) 2006; 45:446-452. **Srial Solutions 360** The authors investigated the value of an extremely elevated platelet count to help identify febrile infants with Kawasaki disease. Children less than 6 months of age with prolonged fever, extreme elevation of platelet count and no compelling alternative diagnosis should be evaluated for Kawasaki disease. [Context Link]

23• Newburger JW, Sleeper LA, McCrindle BW, *et al*. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. N Engl J Med 2007; 356:663-675. **Srial Solutions 360 Bibliographic Links** The data from a well conducted multicenter, randomized, double-blind, placebo-controlled trial did not support the use of methylprednisone in addition to IVIG in Kawasaki disease. [Context Link]

24 Scagni P, Peisino MG, Bianchi M, *et al*. Kikuchi-Fujimoto disease is a rare cause of lymphadenopathy and fever of unknown origin in children: report of two cases and review of the literature. J Pediatr Hemotol Oncol 2005; 27:337-340. [Context Link]

25• Christie LJ, Honarmand S, Talkington DF, *et al*. Pediatric encephalitis: what is the role of Mycoplasma pneumonia? Pediatrics 2007; 120:305-313. **Srial Solutions 360 Bibliographic Links** The authors report the high prevalence (111 of 1988) of *Mycoplasma pneumoniae*-associated encephalitis in patients with unexplained encephalitis. Eighty-four (76%) were less than 18 years of age. Testing for *M. pneumoniae* should be considered in any child with unexplained encephalitis. [Context Link]

Ovid: Fever without apparent source on clinical examination.

Keywords: fever; Kawasaki disease; serious bacterial infection