RADIOLOGICAL CASE

CLINICS IN DIAGNOSTIC IMAGING (9)

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SINGAPORE MED J 1996; Vol 37: 103-106

CASE REPORT

A 28-year-old Caucasian woman had a missed abortion, for which suction and evacuation were performed. She re-presented a few months later, having remained amenorrhoeic after the operation. Ultrasound revealed multiple vesicles in the uterus, compatible with molar pregnancy. Another suction and evacuation of her uterus was performed, histology of which was consistent with partial hydatidiform mole. Her serum level of ß-human chorionic gonadotropin (hCG) however remained high (4000 IU/L) on follow-up.

What does the pelvic angiograms Fig 1 & 2 show? What further investigation is indicated?

Fig 1 - Bilateral common iliac arteriogram: early phase (3.5 seconds).

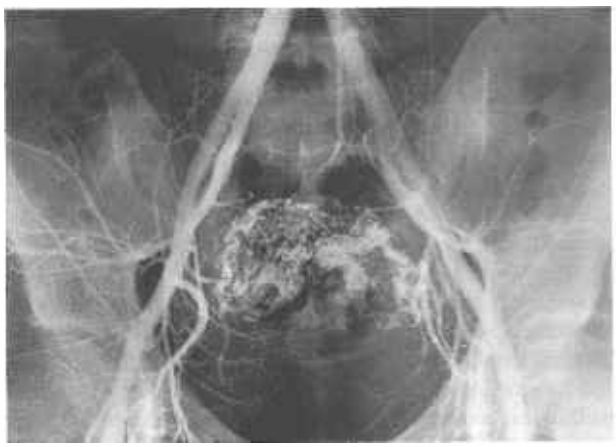

Fig 2 - Bilateral common iliac arteriogram: late phase (7 seconds).

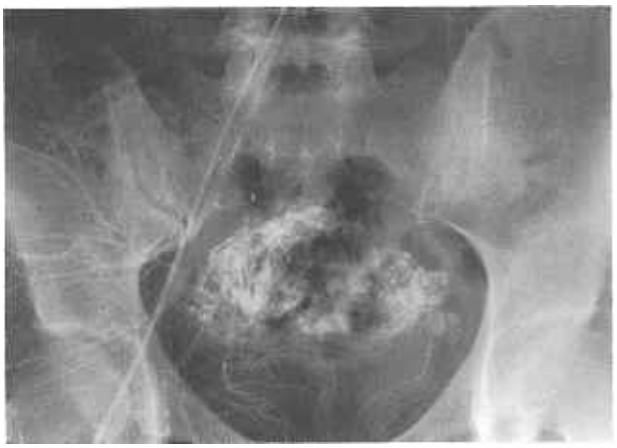

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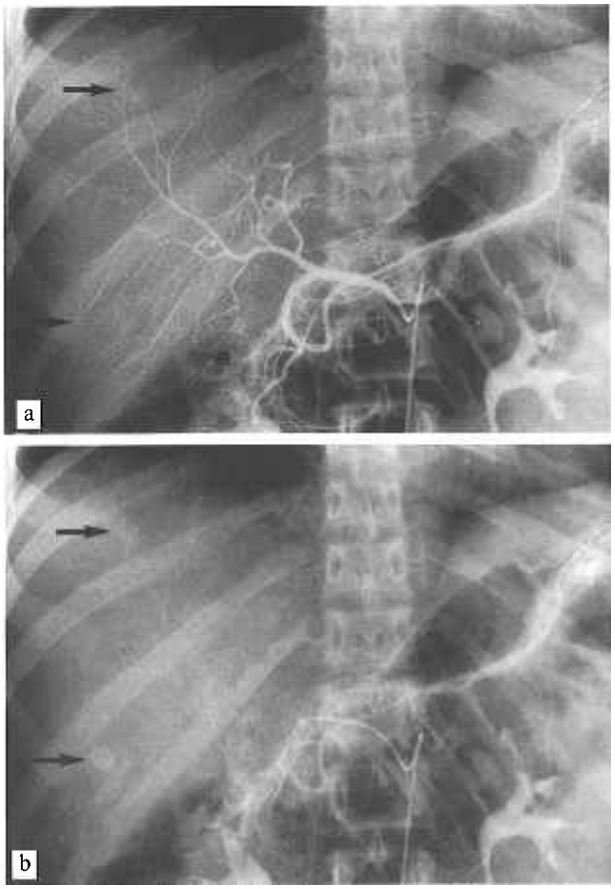
IMAGE INTERPRETATION

Early arterial phase of the pelvic angiogram demonstrated a large vascular tumour in the fundus of the uterus, supplied by dilated and tortuous uterine arteries (Fig 1). Areas of venous pooling on delayed films further confirmed tumour hypervascularity (Fig 2). No arteriovenous shunting was evident. Imaging appearances were that of residual uterine gestational trophoblastic disease (GTD).

Hepatic angiogram revealed two small metastases in the mid and inferior right lobe of the liver (Fig 3). These were not detectable on either ultrasound or computerised tomography (CT). Subsequently performed CT of the thorax was negative for metastasis.

Fig 3 - Hepatic angiogram (a) Early phase study shows 2 tiny areas of neovascularity in the mid- and inferior right lobe (arrows). (b) The staining of these 2 hypervascular nodules is better appreciated on the delayed films (arrows).



DIAGNOSIS

Gestational trophoblastic disease with liver metastases

CLINICAL COURSE

The tumour was staged as GTD of International Federation of Gynaecology and Obstetrics (FIGO) stage IV, due to the presence of liver metastases. Multiagent chemotherapy, consisting of 3 cycles of hydroxyurea, vincristine, methotrexate, actinomycin-D and cyclophosphamide, was administered for a three-month period. The patient responded well, with β-hCG levels regressing to normal levels (< 5 IU/L). At the last follow-up, the patient remained in remission.

DISCUSSION

GTD describes a spectrum of tumours that arise from the foetal chorion of the placenta, encompassing molar pregnancy or hydatidiform mole (benign), invasive mole and choriocarcinoma (malignant). GTD possesses three biologically unique characteristics, namely curability with chemotherapy, even with widespread metastases; production of hCG; and origin in tissue genetically different from the host. Although rare, GTD has received much attention, being the first solid tumour to be cured by chemotherapy, with hCG being the first reliable tumour marker. GTD is estimated to occur 7 to 20 times more frequently in Asia compared to the developed countries of the western hemisphere[1-3].

Early detection of GTD is usually successful in patients presenting as a molar pregnancy and having the complete form of hydatidiform mole. Partial hydatidiform mole, with the potential of giving rise to persistent GTD or undergoing malignant transformation, may not be readily recognised. The identification of choriocarcinoma, especially after a normal delivery, abortion or ectopic pregnancy, is normally difficult. Choriocarcinoma may present late with symptoms from metastases[3].

To date, a single classification scheme for GTD has not yet been agreed upon. Reasons for this difficulty include change of histopathology of disease with time (for example, malignant transformation) and the practice of not obtaining biopsy specimens of metastatic lesions for the sole purpose of establishing the histological pattern. The FIGO staging is based on tumour location. This classification is useful in identifying metastatic disease for surgical treatment and emphasises the relative benignity of lung metastases.

Stage I : disease confined to uterus;
Stage II : extra-uterine intra-pelvic tumour;
Stage III : metastases to lung;
Stage IV : distant metastases (for example, to brain, kidney and liver).

The World Health Organisation scoring system, based on prognostic factors, is gaining acceptance and allows selection of chemotherapy depending on risk category. The selection of initial chemotherapy, with or without surgery, is dependent upon the risk category assigned. Even for high-risk patients with distant metastases, combination chemotherapy can achieve cure rates of about 80%[3].

Prior to the ultrasound era, diagnosis of GTD was made either upon vaginal passage of characteristic hydatidiform tissue (Fig 4) or using the invasive method of intra-amniotic injection of radio-opaque contrast material. In a patient presenting with abnormal uterine bleeding in the first trimester of pregnancy, the combination of elevated serum hCG and typical sonographic appearances is highly suggestive of GTD. Diffuse swelling of the chorionic villi produces a homogeneous vesicular or "snowstorm" pattern (Fig 5). Internal haemorrhage or degeneration leads to irregular-shaped, sonolucent areas. Foetal growth within a molar mass and myometrial invasion can also be detected sonographically[4] (Fig 6). Ultrasound may help differentiate partial mole from first trimester missed abortion[5]. Transvaginal ultrasound has recently been found to be useful in localising foci of invasive trophoblastic tissue, with applications in diagnosis as well as monitoring of lesions during therapy[6]. Doppler studies have been shown to increase the accuracy of diagnosing persistent GTD, due to the high vascularity of these tumours[7].

Surveillance after evacuation of molar disease consists of monitoring hCG levels and detection of metastatic disease. Continued hCG elevation may indicate persistent GTD or transformation to malignant choriocarcinoma[3]. Arteriography

from bacterial, viral and fungal components. They cause release of endogenous pyrogens from host cells and, thus, fever. Examples are endotoxin from Gram– negative bacilli peptidoglycan of the bacterial cell wall and exotoxins.

b. **Endogenous Pyrogens** – Endogenous pyrogens are derived from the host's cells. They are produced in peripheral tissues and do not actually penetrate the blood-brain barrier but have their effect on the rich vascular network in the preoptic-anterior hypothalamus area. Cytokines thus far found to be endogenous pyrogens are IL-1 (interleukin-1), tumour-necrosis factor TNF, IL-6, IL-2, IL-8, alpha-beta-gamma-interferons and macrophage - inflammatory protein-1[16].

c. **Prostaglandins** – The effect of endogenous pyrogens on the hypothalamus is presumably due to an increase in prostaglandin E_1, the mechanism of which is currently unknown.

d. During fever, not only are pyrogens being produced but also antipyretic substances. Two of them are arginine vasopressin and melanocyte-stimulating hormone[16].

FEVER PATTERNS

Three main types of fever patterns are described:

1. **Continuous** – the T° is increased throughout the 24 hour. The total range of variation is < 0.3°C eg typhoid fever, *P. falciparum* infection, rickettsia infection and brucellosis.

2. **Intermittent** – the T° remains above normal but the daily range is > 1.4°C. If the swings are very wide the fever is referred to as hectic/spiking eg
   a) pyogenic abscesses, pyelonephritis
   b) double fever spike in one day (double quotidien): salmonellosis, double malaria, meningococcal endocarditis.

3. **Remittent** – the T° is normal for part of the day, or for several days eg *P. vivax/ovale P. malariae,* Hodgkin's lymphoma (Pel-Ebstein fever).

The height of the febrile response is not helpful in identifying a given disease or group of diseases. In general, if a disorder is capable of producing fever, it is capable of producing high fever.

BENEFITS OF FEVER

Animal studies have shown an enhanced resistance to infection and improved survival associated with temperature elevation[16,17]. Fever causes a general increase in immune system function eg increased proliferation of lymphocytes, increased Gamma-interferon production, increased chemotaxis of polymorphs, increased alternative complement pathway activation and increased antibody production[17]. Also, some antimicrobials are more active at febrile temperatures[18]. Some pathogens such as *Streptococcus pneumoniae* may be directly inhibited by elevated temperatures while others become more susceptible to the bactericidal effect of serum and/or antimicrobials[19,20].

COMPLICATIONS OF FEVER

Fever itself causes no harm unless it reaches at least 41.7°C. Seldom do children have fever > 40°C, especially if they are < 3 months old. Fortunately, the brain's thermostat keeps almost all untreated fevers due to infection below 41.7°C.

1. **Dehydration.** Children have a greater surface area per weight than adults, this leads to greater fluid losses through the skin. Thus when fluid intake is interrupted eg during gastroenteritis, dehydration is a more likely consequence in the child.

2. **Febrile fit.** Whereas all children will experience fevers, only 4% will have a febrile convulsion. For most normal children the seizure threshold is about 41.1°C. If the child is neurologically abnormal, seizures may occur at lower temperatures. Febrile seizures are caused by the height of the fever and not the rapidity of the rise. The seizure frequently is the first sign of the febrile episode. If the child has experienced fevers without a seizure and has not had a febrile seizure by 3 years of age, he will probably never have one[21]. The following factors would favour admission after a first convulsion:

   a. a complex febrile convulsion ie lasting more than 20 minutes, with focal features, repeated in the same episode of illness or with incomplete recovery after 1 hour;
   b. aged less than 18 months
   c. early review by a doctor at home not possible
   d. clinical signs of meningism
   e. child is unduly irritable or drowsy or systemically ill
   f. home circumstances inadequate or more than usual parental anxiety or parent's inability to cope.

   It should be remembered that a history of febrile fits does not exclude the possibility of meningitis[22]. Occasionally febrile status epilepticus can occur.

3. **Heat strokes.** Most heat strokes in children are due to inadvertent heat overload eg overwrapping, being left in a car in direct sunlight and are preventable[23].

   Fever can be detrimental to patients with congestive cardiac failure (due to increased metabolic requirements and increased cardiac output), respiratory failure, acute neurologic disease or endotoxic shock.

CAUSES OF FEVER

Fever is often accompanied by symptoms/signs that suggest a diagnosis or at least point to an organ system such as headache, cough, diarrhoea, dysuria, etc. However, this is not always the case. This distinction provides a convenient means of categorising causes of fever in children:

1) Localising symptoms or signs, (Table I)
2) Associated presentation eg rash. The approach to a child with fever and a rash requires consideration of the type of rash (Type II)
3) No localising signs (Table III)

Febrile infants < 3 months old

A serious bacterial illness can still occur in 5%-8%[24,25] of these patients despite unremarkable findings on clinical examination. 0.3%–5.4% of patients with serious bacterial infection were still not detected whether with screening tests or physical examination. As the height of fever increases, so also the likelihood of bacteremia[26].

A full history must be taken including perinatal history: prematurity, premature rupture of membranes, prolonged rupture of membranes, maternal fever, maternal urinary tract infection, invasive procedures in the neonate, birth asphyxia – these are associated with high risk of neonatal sepsis. In the postnatal history, the following 6 symptoms were found by Hewson[27] to be the most indicative of serious bacterial infection:

Table I – Causes of fever with localising symptoms or signs

Symptoms	Diseases		Comments
	Common	Uncommon	
Respiratory eg. Cough, rhinorrhoea	common cold, influenza, pharyngitis are by far the most common causes of fever	Otitis media, croup sinusitis	Normal children may experience up to 12 viral infections (mostly respiratory) a year. If all symptoms clear in between episodes, immunodeficiency is unlikely.
Urinary eg. dysuria frequency of micturition	urinary tract infection (UTI)	vulvitis balanoposthitis	All children (males any age, eg. females < 5 years or recurrent UTI if > 5 years old) with confirmed UTI need to be further evaluated.
Gastrointestinal			
Vomiting	Viral gastritis gastroenteritis food poisoning	Typhoid fever, acute (ac) appendicitis, acute hepatitis, acute meningitis	
Diarrhoea	Viral gastritis gastroenteritis food poisoning	Dysentery, cholera, acute appendicitis	Risk for bacterial diarrhoea are: a. a history of blood in the stools b. T° > 39°C c. > 10 stools in 24 hours.
Abdominal pain	Gastroenteritis – *Shigella,* – *Campylobacter jejuni* – *Yersinia Enterocolitica*	Acute appendicitis, acute hepatitis	
Central Nervous System			
Sensory changes	None	Acute meningoencephalitis acute encephalitis including mycoplasma, acute gastroenteritis with dehydration	
Headache	Acute sinusitis	Acute meningitis	
Neck stiffness	None	Meningitis	
Bulging fontanelle	None	Meningitis, benign intracranial hypertension	
Orthopaedic			
Joint pain/ swelling	Viral arthritis, mumps, rubella, enteroviral? infections	Septic arthritis, juvenile rheumatoid arthritis, systemic lupus erthyematosus	
Bone pain/ refusal to move the limb	Osteomyelitis septic arthritis		
Cardiac murmur	Functional due to tachycardia	Bacterial endocarditis, rheumatic fever acute myocarditis	

Table II – Causes of febrile rashes

Type of Rash	Causes	Comments
Erythematous eruptions	measles, rubella, roseola infantum/ exanthem subitum, erythema infectiosum/ Fifth disease, infectious mononucleosis, dengue fever, cellulitis, drug eruptions, erythema multiforme, connective tissue disease, Kawasaki's disease.	Exanthem subitum is a common exanthem caused by human herpes virus 6 and often mis-diagnosed as a drug allergy. Measles infection can still occur despite immunisation, especially in the school-going age due to primary vaccine failures (vaccine success is 95-97%).
Vesiculo-pustular eruptions	chicken-pox, hand-foot-mouth disease, Staphylococcus scalded skin syndrome, Herpes simplex, bullous impetigo	
Vasculitic/purpuric eruptions	Bacterial sepsis, subacute bacterial endocarditis, Henoch-Schonlein purpura	

Table III – Causes of fever with no localising symptoms or signs

Common	Uncommon	Comments
Urinary tract infection Viral fever	Sepsis syndrome, Typhoid fever, Malaria, Drug fever	Children < 3 months old or with immunodeficiency, asplenia, steroid therapy are at high risk for sepsis
	Immunisation reactions Hypothalamic lesion eg. intracranial haemorrhage encephalitis, brain tumour, Guillain-Barré syndrome Metabolic eg hyperthyroidism, dehydration from diabetes inspidus	
	Factitious	

1. Decreased feeding < 50% of normal in the past 24 hours,
2. Decreased activity,
3. Breathing difficulty/respiratory distress,
4. < 4 wet nappies in the past 24 hours,
5. Drowsiness,
6. Pale and hot.

The most predictive signs of serious bacterial infection were:

1. Chest wall retraction,
2. Tender abdomen,
3. Respiratory grunting,
4. Cold calves.

A variety of test algorithms have been devised to predict risks of serious bacterial infection in well-looking infants eg total white cell count < 5000 /mL, or > 20,000/mL, immature/mature neutrophil ratio > 0.2, absolute neutrophil count < 1000 /uL, C-reactive protein, positive haptoglobin, positive micro-ESR > 15 mm/hr. Even with a combination of 5 tests by Philip[28], not all septic patients were identified.

Pyrexia of unknown origin

Definition: Fever > 2 weeks without a known cause.
Causes: Urinary tract infection, typhoid fever, malaria, subacute bacterial endocarditis, cyclical neutropenia, inflammatory bowel disease, postransfusion Cytomegalovirus infection. Antibiotic fever.

Investigations for fever

1. Full blood count – The total Wbc count or band count is elevated in 30% – 55% of well-looking young infants with bacteremia or UTI[24].

2. Urinanalysis – Up to 50% of children with UTI have normal urinanalysis, with Gram stain slightly more sensitive than dipstick or leukocyte esterase. Screening for UTI using Microstix which depends on bacteria to reduce nitrate to nitrite has a false-negative rate of 4%–20%. Proper urine cultures must be taken either by midstream, suprapubic aspiration (if < 6 months old) or catheter.

3. Chest radiograph – Only 1% of asymptomatic febrile infants had abnormal CXR[29], thus in the absence of respiratory signs or symptoms, febrile young infants are unlikely to require a CXR.

4. Other specialised investigations. These may need to be done in the hospital, eg blood cultures.

Managing fever

With regard to managing fever, the factors to consider include: toxicity of patient, immune status, age (an older child is better equipped to contain infections), and source of infection.

1) **Antipyretic drugs**
Zealous overprescription of antipyretics in children needs to be avoided with attention being redirected to the cause of the fever and the child's capacity to cope with the illness. Overuse of antipyretics can lead to delayed prescription of antimicrobial drugs. Antipyretics should only be used if the temperature is >38.5°C[21] or if associated with discomfort or the child has had febrile seizures before or has cardiac disease. Caution should be exercised regarding the use of antipyretics – the correct dose for the child's age or weight (paracetamol: 10-15mg/kg every 4-6 hourly and <90mg/kg/24 hours; ibuprofen: 5-10mg/kg every 6 hourly). These drugs will reduce the fever but will not normalise it. Do not use antipyretics if the child is <3 months old. Aspirin should not be given to children with influenza, chickenpox or any febrile infection because of the risk of Reye's Syndrome.

2) **Sponging**
Sponging should be used for T° > 38.5°C and after administration of antipyretic drugs. If the fever is >38.5°C half an hour after drugs have been given, sponge the child for 30 minutes in lukewarm water (temperature of the water: 29.5°C – 32°C). Sponge immediately if the child is delirious or fitting from fever. Sponging works much faster than immersion. Sit the child in 2 inches of water and keep wetting the skin surface. If the child shivers, raise the water temperature. Do not expect to lower the child's temperature below 38.3°C. One study found that sponging febrile children with tepid water after antipyretic therapy had no more effect on defervescene than the antipyretic drugs alone[30].

3) **Other measures** include light clothing, hydration and antibiotics. Blind treatment with antibiotics can mask physical signs, resulting in delay in making a correct diagnosis, increase bacterial resistance, cause drug fever, induce potentially toxic side-effects, and vitiate subsequent bacterial investigations. Judicious use of antibiotics is therefore recommended.

CONCLUSION

Fever in a child is a common problem encountered in the clinic or hospital. It is important to define the cause of the fever instead of just treating the fever empirically. Persistent fever reported by parents may be a series of self-limited viral illnesses rather

than a persistent pyrexia. In other instances the parent has a misunderstanding of what constitutes fever, the normal diurnal variation of fever or the effect of activity on core temperature. Parental education regarding fever is important. It is worth emphasising that strict attention to clinical detail and an understanding of symptoms and signs in the young infant still play a role in illness detection.

References

1. Herzog LW. What is fever? Normal temperature in infants less than 3 months. Clin Pediatr 1993; 32: 142-6.
2. DuBoid EF. Fever and the regulation of body temperature. Springfield Illinois: Charles C Thomas, 1948.
3. Bayley N. Maturational changes in rectal temperatures of 6 infants from 1-36 months. Child Dev 1937; 8: 195-206.
4. Morley CJ. Axillary and rectal temperature measurements in infants. Arch Dis Child 1992; 67: 122-5.
5. David CB. Liquid crystal forehead temperature strips. Am J Dis Child 1983; 137: 87.
6. Reisinger KS, Kao J, Grant DM. Inaccuracy of the clinical skin thermometer. Pediatr 1979; 64: 4-6.
7. Scholefield J H, Gerber M A, Dwyer P. Liquid crystal forehead strips: a clinical appraisal. Am J Dis Child 1982; 136: 198-201.
8. Freed GL, Fraley JK. Lack of agreement of tympanic membrane temperature assessments with conventional methods in a private practice setting. Pediatr 1992; 89: 384-6.
9. Shenep JL. Infrared, thermistor and glass-mercury thermometry for measurement of body temperature in children with cancer. Clin Pediatr 1991; 30 (4 Suppl): 36-41.
10. Davis K. The accuracy of tympanic membrane temperature measurement in children. Pediatr Nursing 1993; 19: 267-72.
11. Selfridge J. The accuracy of the tympanic membrane thermometer in detecting fever in infants aged 3 months and younger in the emergency department setting. J Emerg Nursing 1993; 19: 127-30.
12. Stewart JV. Re-evaluation of the tympanic thermometer in the emergency department. Ann Emerg Med 1992; 21: 158-61.
13. Muma BK. Comparison of rectal, axillary and tympanic membrane temperatures in infants and young children. Ann Emerg Med 1991; 20: 421-4.
14. Pransky SM. The impact of technique and conditions of the tympanic membrane upon infrared tympanic thermometry. Clin Pediatr 1991; 30 (4 Suppl): 1-72.
15. Boulant JA. Fever: Basic mechanisms and management. In: Mackowiak PA. ed. New York: Raven Press, 1991: 219-23.
16. Kluger MJ. Fever: role of pyrogens and cryogens. Physiol Rev 1991; 71: 93-127.
17. Roberts NJ. Impact of temperature elevation on immunologic defenses. Rev Infect Dis 1991; 13: 462-72.
18. Kluger MJ. Is fever beneficial? Yale J Biol Med 1986; 59: 89-95.
19. Mackowiak PA. Direct effects of hyperthemia on pathogenic microorganisms: teleologic implications with regard to fever. Rev Infect Dis 1981; 3: 508-20.
20. Mackowiak PA, Marling-Cason M, Cohen RL. Effects of temperature on antimicrobial susceptibility of bacteria. J Infect Dis 1982; 145: 550-3.
21. Schmitt BD. Fever in childhood. Pediatr 1984; 74 (Suppl): 929-36.
22. Joint working group of the research unit of the Royal College of Physicians and the British Paediatric Association. Guidelines on the management of convulsions with fever. Br Med J 1991; 303: 634-5.
23. King K. Heat stress in motor vehicles: a problem in infancy. Pediatr 1981; 68: 579-82.
24. Baraff LJ. Probability of bacterial infections in febrile infants less than 3 months of age: a meta-analysis. Pediatr Infect J 1992, 11: 257-65.
25. Klassen TP. Selecting diagnostic tests to identify febrile infants less than 3 months of age as being at low risk for serious bacterial infection: a scientific overview. J Pediatr 1992; 121: 671-6.
26. McLellan D. Perspectives on occult bacteremia in children. J Pediatr 1986: 109: 1-8.
27. Hewson PH. Markers of serious illness in infants under 6 months old presenting to a children's hospital. Arch Dis Child 1990; 65: 750-6.
28. Philip AGS. Decreased use of antibiotics using a neonatal sepsis screening technique. J Pediatr 1981; 98 5: 795-9.
29. Crane EF. Is a chest radiograph necessary in the evaluation of every febrile infant less than 8 weeks of age? Pediatr 1991; 88: 821-4.
30. Newman J. Evaluation of sponging to reduce body temperature in febrile children. Can Med Assoc J 1985; 132: 641-2.