ORIGINAL ARTICLE

Risk factors associated with serious bacterial infections among newborns with high body temperature

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Keywords

High body temperature • Fever • Newborns • Serious bacterial infection • Dehydration • Hyperthermia

Summary

Introduction. *Recognizing the importance of serious bacterial infections (SBIs), study aimed to identify factors associated with high body temperature in newborns.*
Methods. *A convenience sample of 54 newborns admitted to our hospital in Iran (March-July 2015) with rectal temperature > 38°C (100.4°F) were examined for clinical signs, blood cultures, complete blood counts, platelets, Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), renal function, chest/abdominal x-rays, spinal tap, and history of maternal infections.*
Results. *Newborns had either fever due to infections, or hyperthermia due to dehydration and/or extreme warm environment. Bacterial infections (37%) included: sepsis (15%) (coagulase-positive or coagulase-negative Staphylococci, Enterobacter, Klebsiella, Escherichia coli), meningitis (13%), and 3.5% UTI, 3.5% pneumonia, 2% cellulitis, and 2% omphalitis. Degrees of dehydration experienced by 55.6% included 37% of cases associated with hyperthermia caused by warm clothing/environment, while in 18.6% dehydration was secondary to fever. Viral infections (11%) included upper respiratory infections, gastroenteritis, while in remaining 13% cause of high body temperature was unknown. The group with SBIs had higher chance of having history of PROM (premature rupture of membrane) ($p = 0.023$), positive CRP ($p = 0.041$), and abnormal platelets count ($p = 0.021$) comparing all others.*
Conclusions. *High body temperature in newborns needs careful evaluation to identify fever due to SBIs. In sepsis cases, antibiotics should cover prevalent bacteria including Staphylococci and Enterobacter. Dehydration was prevalent among newborns with high body temperature due to hyperthermia or secondary to infections. To avoid hyperthermia, parents should know how to clothe their newborns appropriate for environmental temperature. Newborns' SBIs associated with positive CRP, abnormal platelet count, and maternal PROM.*

Introduction

High body temperature in newborns may be identified as either fever or hyperthermia.
Fever is caused by hyper-metabolism due to infection or stress. However, hyperthermia is caused by extreme warm environment. Fever in infants under three months old should be considered an emergency and receive appropriate treatment [1]. References have indicated that bacteremia develops in 2.2% to 5% of febrile infants under three months old [2, 3]. Premature babies born earlier than 37 weeks of pregnancy are 10 times more likely to develop sepsis. In premature babies who develop unstable temperatures or hypothermia rather than fever, these signs may be masked by incubator which holds the neonate. The need to increase the incubator's temperature may suggest that hypothermia is present [4, 5].
Hyperthermia as the result of dehydration during the second or third day of birth is prevalent, especially in breastfed neonates who are usually prone to receiving insufficient milk. Other causes of hyperthermia secondary to dehydration in newborns usually include warm environments such as an incubator, blankets covering the newborn, proximity to heat sources like heating radiator, or exposure to sunlight. Several differential diagnostic signs between hyperthermia due to dehydration versus fever caused by infections are the dehydration signs such as reduction in urine volume, reduced elasticity of skin, and fontanelle closure which is bulged inward. Neonate is eager to drink liquids and is not as ill as a neonate who is suffering from an infection. In that case, feeding the neonate with milk or liquids or providing parenteral liquid therapy as well as reducing the temperature of the baby's environment will help in reducing the baby's body temperature and improving baby's health. Untreated dehydration may develop hypernatremia that may cause convulsion [6]. In addition to infections and hyperthermia/dehydration, other reasons for development of high body temperature include central nervous system dysfunctions, hyperthyroidism, familial dysautonomia, and ectodermal dysplasia [5].
A publication from Greece in 2005 showed that half of the studied neonates with fever had a systemic bacterial infection while the other half had a viral infection [7].
Meanwhile, regardless of the cause of fever and hyperthermia in babies, it is important to correct any water and electrolytes imbalances.

Objectives

This study evaluated the factors associated with high body temperature in neonates admitted to our hospital

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in Iran while focusing on identifying serious bacterial infections.

Methods

In a prospective observational case-series study in an academic hospital in Iran, from March to July in 2015 neonates who had developed high body temperatures and were consecutively admitted to our hospital entered a pilot study.

A convenience sample of 54 recruited neonates had rectal temperatures over 38°C (100.4°F) or an axillary temperature over 37.5°C (99.5°F) at the time of admission [1]. Neonates were examined for causes of high body temperature to differentiate fever (due to infections) from hyperthermia. Both pre-mature and term newborns with high body temperature including newborns with fever due to early-onset sepsis (blood or cerebrospinal fluid (CSF) infections within the 3rd to 7th days of birth) and late-onset sepsis entered the study [8].

Samples from blood, urine, and CSF were collected before starting antibiotic therapy. Blood or urine culture, complete blood count (CBC), platelets (Plts), estimated sedimentation rate (ESR), C-reactive protein (CRP), renal function tests, chest or abdominal X-rays, and CSF tests were performed. The recorded data included family history, history of fever and maternal infections, and the results of clinical and laboratory evaluations.

Statistical analysis

Continuous data were averaged and compared between groups through t tests. Dichotomous data were presented as numbers and percentages and compared through chi-squared tests. All newborns were divided into two groups: serious bacterial infections (SBIs) and non-bacterial causes. Chi-square statistics compared those two categories.

No patient had any missing data. IBM SPSS Statistics 20 was used for statistical analysis. P values less than 0.05 defined statistical significance.

For seven patients who left the hospital earlier than their discharge date, their cultures came in afterward and their results were also included in the study.

Tables A-C in the Appendix explain the methods used to diagnose the etiologies for high body temperature in admitted newborns as well as show specific criteria for diagnosing SBI.

The study was approved and funded by our University based on prevailing ethical principles. Informed consents from the newborns' parents were obtained.

Results

We studied 54 newborns admitted to our hospital. Newborns' rectal temperatures at the admission time averaged 39.1°C (102.38°F), range of 38°C (100.04°F) to 41.5°C (106.7°F).

The average for baby's weight at the time of admission was 2,908 grams (1,650-4,600 grams range). Tables I and II show the numbers and percentages of attributes found in newborns.

Tables III and IV show the comparisons between newborns with and without SBIs.

Serious bacterial infections included sepsis (*coagulase-positive* and *coagulase-negative Staphylococci*, *Enterobacter*, *Klebsiella* and *Escherichia coli*), meningitis, urinary tract infections (UTI), pneumonia, cellulitis, and omphalitis. One newborn had both UTI and sepsis (positive culture). Mortality was 4 (7.4%).

Viral infections included upper respiratory infections and gastroenteritis. Different degrees of dehydration were experienced by 55.6% of newborns when dehydration was present secondary to infections in 18.6% of newborns but in 37% of newborns, dehydration was present due to warm clothing/environment which associated with hyperthermia (Tab. II; Fig. 1).

All viral/bacterial sepsis cases (8 or 14.8%) were preterm (two of them with positive culture), i.e., all preterm babies (8 or 14.8%) had sepsis.

Our data showed the group with SBI had higher chance of having history of premature rupture of membrane (PROM) ($p = 0.023$), positive CRP ($p = 0.041$), and abnormal platelet count ($p = 0.021$) compared to the rest of newborns (Tab. III).

T tests comparing the averages for absolute numbers of WBCs and polymorphonuclears among bacterial infections and non-bacterial cases showed no statistical significance (Tab. IV).

Tab. I. Attributes of neonates with high body temperature. .

Attributes	Percent	Frequency	Notes
GA (term babies) *	85.2%	46	Another 8 babies were pre-term
Sepsis	15%	8	All sepsis cases were pre-term (2 were culture positive)
PROM in mothers	5.6%	3	Longer than 24 hours
Presence of infection in mother	9.3%	5	
Presence of viral infection in family	9.3%	5	
Breast feeding	98.1%	53	

*Based on sonography findings, term newborns had gestational age range between 37 to 41 weeks with average of 38 weeks and 5 days. Preterm newborns had gestational age range between 33 weeks and 5 days to 36 weeks and 4 days with average of 35 weeks and 2 days. GA: gestational age; PROM: premature rupture of membranes. However, to avoid complexity, the overlaps of attributes in each newborn are not presented in this table (n = 54)

Tab. II. Findings in newborns with high body temperatures.

Findings in newborns with high body temperature	Percent	Number
Asphyxia	5.6%	3
Cerebral bleeding	3.7%	2
Kernicterus	0%	0
Dehydration of the neonate	55.6%	30
History of maternal hyperthyroidism in mother	0%	0
History of diabetes insipidus in mother	0%	0
Hyperglycemia in mother	3.7%	2
Blood culture		
Sterile blood culture	81.5%	44
Staphylococcus coagulase negative (2 contamination)*	7.4%	4
Staphylococcus coagulase positive	3.7%	2
Enterobacter	3.7%	2
Klebsiella	1.9%	1
Escherichia coli	1.9%	1
Positive urine culture	3.7%	2
Lumbar puncture (no cerebrospinal fluid smear was tested, all sterile cultures)		
Positive cerebrospinal fluid culture	0%	0
Abnormal cell counts, glucose, and protein levels	13%	7
Cultures performed based on the suspicion of local infection		
Positive eye secretions	9.3%	5
Positive peri-umbilical secretions	1.9%	1
Positive for pseudomonas aeruginosa (secretions from intubation tube)	1.9%	1
Abnormal urinalysis (includes 2 UTIs from above)	16.7%	9
Abnormal creatinine for the age of newborn	24.1%	13
Abnormal urea	31.5%	17
CRP		
Normal	83.3%	45
+	7.4%	4
++	1.9%	1
+++	3.7%	2
++++	3.7%	2
CBC		
Leukopenia	1.9%	1
Leukocytosis	3.7%	2
Platelet counts (normal)	90.7%	49
Thrombocytosis	1.9%	1
Thrombocytopenia	7.4%	4
ABG		
Normal ABG	68.5%	37
Acidosis	29.6%	16
Alkalosis	1.9%	1
Abnormal ESR	14.8%	8
Sodium		
Normal	83.3%	45
Hyponatremia	1.9%	1
Hypernatremia	14.8%	8
Main complaint at admission time		
Poor feeding	25.9%	14
Respiratory (distress, tachypnea, apnea, wheezing)	25.9%	14
Irritability	14.8%	8
Being ill, lethargic, poor health condition	13%	7
Dehydration and diarrhea	11.1%	6
Convulsion	11.1%	6
Icterus	9.3%	5
Fever only	3.7%	2
Others	16.7%	9

*Blood culture: if the laboratory results came positive for coagulase negative staphylococcus, the diagnosis was performed based on the clinical condition of the patients to identify the false positive cultures due to contamination. This row includes 2 newborns having contamination. PROM (including preterm or pre-labor): when the sac containing the fetus and the amniotic fluid develops a hole or bursts prior to the start of labor. UTI: urinary tract infection; CRP: C-reactive protein; CBC: complete blood count; ABG: arterial blood gas; ESR: erythrocyte sedimentation rate. However, to avoid complexity, the overlaps of attributes in each newborn are not presented in this table (n = 54).

Tab. III. Descriptive and comparative results for causes of high temperature in neonates (N = 54).

Factors	Attributes	Serious bacterial infections (N = 20)	Non-bacterial causes (N = 34)	Chi-square	P value
GA (Gestational Age)	Term Pre-term	90% (18) 10% (2)	82.4% (28) 17.6% (6)	0.58	0.441
PROM (Premature Rupture of Membranes)	Positive history Negative history	15% (3) 85% (17)	0% (0) 100% (34)	5.40	0.023*
Maternal infection	Positive history Negative history	10% (2) 90% (18)	8.8% (3) 91.8% (31)	0.02	0.890
Rectal temperature	≥ 39°c < 39°c	60% (12) 40% (8)	67.6% (23) 32.4% (11)	0.32	0.571
APX (Asphyxia)	Positive history Negative history	5% (1) 95% (19)	5.9% (2) 94.1% (32)	0.02	0.891
ESR (erythrocyte sedimentation rate)	Normal Abnormal	75% (15) 25% (5)	91.2% (31) 8.8% (3)	2.61	0.112
CRP (C-Reactive Protein)	Positive Negative	30% (6) 70% (14)	8.8% (3) 91.2% (31)	4.07	0.041*
PLT (Platelet Count)	Thrombocytopenia Normal PLT Thrombocytosis	20% (4) 80% (16) 0% (0)	0% (0) 97.1% (33) 2.9% (1)	7.79	0.021*
CBC (Complete Blood Count)	Leukopenia Normal leukocyte Leukocytosis	5% (1) 90% (18) 5% (1)	0% (0) 97.1% (33) 2.9% (1)	1.91	0.384
ABG (Arterial blood gas)	Normal Abnormal	75% (15) 25% (5)	64.7% (22) 35.3 % (12)	0.62	0.432
Creatinine	Normal Abnormal	70% (14) 30% (6)	79.4% (27) 20.6% (7)	0.61	0.433
Urea	Normal Abnormal	65% (13) 35% (7)	70.6% (24) 29.4% (10)	0.18	0.671

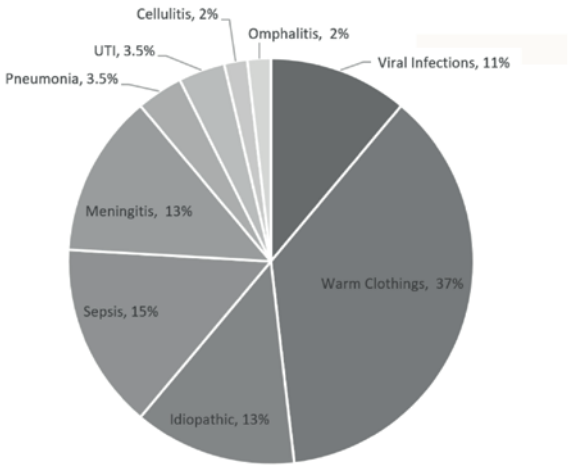
*P values less than 0.05 are statistically significant, in 2x2 tables with degree of freedom of 1, the X2 values higher than 3.84, and in 2x3 tables with degree of freedom of 2, X2 > 5.99. In the above cases, the p values < 0.05 were considered significant to address 95% confidence level. However, if the confidence level decreased to 90%, the difference between ESR levels between the two groups showed that high level of ESR was correlated with the presence of bacterial infection in neonate (p = 0.11).

Tab. IV. Differences in white blood cell and neutrophil counts between bacterial and non-bacterial cases of high body temperature in neonates (n = 54).

	Serious bacterial infections mean (SD)	Non-bacterial cases mean (SD)	T value	P value
WBC	11,042.50 (5,095.23)	11,070.59 (513.045)	0.02	0.985
Neutrophil	5,748.35 (3,235.35)	8,279.70 (8,521.27)	1.27	0.210

Degree of freedom (DF) is 52, p values less than 0.05 and t values higher than 1.68 are significant. SD: standard deviation; WBC: white blood cell.

Fig. 1. Diagnosed factors which were associated with high body temperature in newborns (n = 54). Bacterial infections comprised 20 (37%) of total patients. One newborn had both urinary tract infection and sepsis. Cases diagnosed as sepsis included three categories: 2 were certain sepsis, 5 were probable sepsis, and 1 was clinical sepsis. Viral infections included upper respiratory infections 5 (9.3%) and gastroenteritis 1 (1.8%).



Discussion

This study described the factors that associated with high body temperature among 54 newborns. Since infections are one of the most important causes of mortality in newborns [9], we prioritized the detection of SBIs among newborns to start proper treatment. However, dehydration and/or hyperthermia were the most prevalent factors associated with high body temperature in our patients. Cases diagnosed as fever included bacterial sepsis (*coagulase-positive* and *coagulase-negative Staphylococci*, *Enterobacter*, *Klebsiella*, and uro-sepsis due to *Escherichia coli*), meningitis, viral infections (upper respiratory infections and gastroenteritis), urinary tract infections, pneumonia, omphalitis, and cellulitis. Secretions from an intubation tube came positive for pseudomonas aeruginosa. In 7 cases (13%) no reason for fever was identified.

Our data showed the group with SBIs had higher chance of having history of PROM, positive CRP, and abnormal platelets count [10] compared to the rest of newborns with high body temperatures.

Similar to our results, other studies have shown PROM is a risk factor for developing bacterial infection such that the incidence of sepsis in newborns following PROM longer than 24 hours increased to 8.1% in another study [11-13].

Among the bedside tests for predicting the occurrence of serious bacterial infections, when no source of infection was identified, blood procalcitonin (PCT) and CRP performed better than interleukin 6 (IL-6), WBC, and/or band count in a study in Geneva on febrile children younger than 36 months old [14].

Another study showed that compared to CRP level and the ratio of pre-mature neutrophils to the total neutrophil count, ESR level had less specificity for diagnostic purposes [13]. False positive ESR tests in hemolysis and false negative response in DIC have been observed [15].

Baby's physiologic responses to warm environment include vasodilation of blood circulation in the surface skin and perspiration to lose heat. Although in premature neonates, perspiration system may not be fully functional. When there is a fever developed due to hypermetabolism caused by either infection or some stimulating drugs, the rectal temperature will be higher than the skin temperature. In this case, since vasoconstriction reduces blood circulation in lower extremities, the feet will be more than 3°C colder compared to the skin temperature in the abdominal area. However, if the body's high temperature is due to staying in warm environment, the rectal temperature will be lower compared to the skin temperature while the temperatures of feet and abdominal skin are close [16].

Other researchers have reported that frequency of SBI is about 10% among newborns, 5% among infants under 3 months old, and between 0.5 to 1% among older infants and toddlers [16]. The mortality of SBI among newborns is about 10%. The degree of concern of either the parents and/or the physician is important warning signs for SBI. Clinical signs of SBI include tachypnea, cyanosis, impaired peripheral perfusion, petechiae, and a rectal temperature above 40°C. Antipyretic drugs can be used only in special, selected situations [16]. More than 40% of cases of fever of unknown origin (FUO) are due to infections. For over 30% of cases, the cause of fever is never determined [17].

Due to the importance of timely diagnosis of SBI, it is essential that the newborn having fever receives repeated physical examinations. Parent counseling in addition to making sure that medical and nursing staff have received education about the warning signs for SBI are important aspects in management of fever in newborns [18].

In this study, 37% of neonates had fever caused by SBIs which shows a higher rate compared to other studies reporting 10% prevalence of bacterial infections in hospitalized febrile neonates [5]. In another study, in febrile infants younger than three months old, pathogen bacteria were found in 27% of those cases [4]. A study in France showed that in febrile infants younger than three months old, SBIs including meningitis, osteoarthritis, cellulitis, UTI, pulmonary infections, and gastroenteritis comprised 10% of the cases while two third of fever cases were reported to be due to viral agents [18].

Our results showed higher prevalence of SBIs in febrile neonates compared to research results from the Western countries. However, our results were close to research results in Taiwan which is an Asian country and showed higher rates of sepsis among neonates [19].

Yet, fever can be a sign rather than an illness since it may even benefit the body in battling against the infections. Providing cold environment to bring down the body's temperature has been proved to benefit the neonates who have developed high body temperature due to exposure to hot environments. However, it is less clear if cooling down methods can similarly benefit neonates that have developed fever due to sepsis or other internal stresses.

Since the incidence of meningitis in neonatal period is higher compared to any other period of life, a neonate with septicemia should be evaluated for meningitis also. Less than one third of septicemia cases in neonates are due to meningitis. Neonatal fever due to pneumonia may develop following aspiration in birth canal during delivery, transferred germs from mother (trans placental), or acquired from the environment. Also, in 3% of pre-term and 1% of term neonates fever may develop due to urinary tract infections [20].

Limitations

Since data collection was not through randomized-controlled trial, factors associated with high body temperature were identified rather than factors causing it. Also, larger sample size may increase the power of the statistical calculations.

Stratification of the neonates according to their age could have provided more information. Also, as other researchers have reported the presence of fungal infections in Neonatal Intensive Care Units (NICUs), we missed to test and to look for possible fungal infections [21].

Conclusions

In newborns with high body temperature identifying bacterial fever is urgent. Dehydration was prevalent due to either hyperthermia or secondary to an infection. To reduce neonatal hyperthermia/dehydration, parents should learn how to clothe their newborns appropriate for the temperature in their environment.

For sepsis, antibiotics should cover prevalent bacteria (*Staphylococci* and *Enterobacter*).

SBIs in neonates associated with having history of PROM, positive CRP, and abnormal platelet count.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

AN and NTT both contributed to designing the study and writing the manuscript.

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Appendix

Tab. A. Methods defining diagnostic criteria (n = 54).

Diagnostic criteria followed in this study to identify different disease conditions.	
Definite septicemia	Clinical signs, positive blood culture, with/without changes in CBC, ESR, and CRP
Probable septicemia	Clinical signs, negative blood culture, abnormal CBC, ESR, and CRP
Clinical septicemia	Strong clinical signs, negative blood culture, normal CBC, ESR, and CRP
Definite meningitis	Abnormal CSF and positive CSF culture
Probable meningitis	Abnormal CSF and negative CSF culture
Pneumonia	Clinical signs and positive chest X-ray
UTI	Positive urine culture collected through suprapubic aspiration method
Hyperthermia	Is the status when body's peripheral temperature is either the same or higher compared to body's central temperature. Hyperthermia associated with dehydration. Causes included the high temperature of the environment and/or wearing too warm clothing. There were no signs of sepsis/infections
Viral infections	The diagnosis was based on the presence of the signs for common cold, coryza, the history of recent viral infection in the family, or a mix of all above, or gastroenteritis with negative stool smear and culture for bacteria. The work up for sepsis was negative
Idiopathic high body temperature	When no clinical and para-clinical reasons for high body temperature were found
PROM	When membrane ruptures before the start of labor

ESR: erythrocyte sedimentation rate; CBC: complete blood count; CSF: cerebrospinal fluid; CRP: C-reactive protein; UTI: urinary tract infection; PROM: premature rupture of membrane.

Tab. B. Factors for identifying different states to diagnose disease conditions (n = 54).

Infection in mother	Fever around the time of delivery, signs of chorioamnionitis (maternal fever, tenderness of uterus, fetal tachycardia), or maternal urological infection towards the end of pregnancy and around the delivery, the history of viral infection (i.e. common cold or coryza) in the family
APX	The history of neonatal asphyxia at delivery reported by mothers (the timing of first cry, presence of cyanosis in baby, baby's breathing status) and/or presence of low Apgar number recorded in the birth card were evaluated
Kernicterus	Diagnosed based on clinical signs and high levels of serum bilirubin
Staying in a warm environment	Determined based on the parents' attitude towards the room temperature and evaluating their judgement
Clothing	The presence of too many layers or thickness of clothing were evaluated
Hyperglycemia	Serum glucose levels above 180 mg/dl in addition to glycosuria and dehydration were counted as hyperglycemia
WBC count	Between 4,000 to 25,000 per microliter during the first days after birth and after that period, the normal range based on baby's age were evaluated. The values above normal were counted as leukocytosis and the values below normal were considered leukopenia
PLts count	Between 100,000 to 450,000 per microliter were considered normal range. Less than 100,000 was considered thrombocytopenia and above 450,000 was considered thrombocytosis
Estimated ESR	The normal range for ESR was determined in relation to the baby's age based on number of days plus number 3, to the maximum number of 15
ABG	PH between 7.35 and 7.43 was considered normal. PH below 7.35 was considered acidosis and PH above 7.43 was considered alkalosis
Hypernatremia	Was determined when serum sodium level was above 150 mEq/L and hyponatremia was determined when it was below 130 mEq/L
Meningitis	Meningitis cases were diagnosed based on changes in cells, glucose, and proteins in CSF (all CSF cultures were negative and CSF smear was not tested due to limited logistics)

APX: asphyxia; WBC: white blood cell; PLts: platelets; ESR: erythrocyte sedimentation rate; ABG: arterial blood gas; CSF: cerebrospinal fluid.

Tab. C. Criteria to diagnose sepsis (n = 54).

Clinical examination
Increase or decrease in blood neutrophil count
Increase in band cell count
Increase in ESR and/or CRP
Blood culture of at least 1 milliliter blood sample from peripheral vein (and not from intravenous catheter)
Lumbar puncture to test cerebrospinal fluid
Urinalysis to detect bacterial antigens (urine was collected through suprapubic aspiration to avoid external contamination of sample)
Chest X-ray, simple abdominal X-ray
Granulocytopenia indicates that the body antimicrobial system is exhausted

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.