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# Diagnostic Value of Hematologic and Inflammatory Profile in Adjunction to Blood Culture in Patients Suspected to Septicemia

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***Abstract***

***Background***
Septicemia is a serious condition in pediatric population which highly depends on immediate diagnosis and treatment in terms of mortality and morbidity rate. Developing adjunctive laboratory tests to help clinicians make appropriate decision is of great priority. In this study we aimed to evaluate the predictive value of each biomarker to find the most valuable one based of which a reasonable empiric therapy would be initiated prior to definite diagnosis by blood culture.

***Materials and Methods***
Hospital records of Patients who referred to the Hazrat-Masumeh hospital of Qom province were reviewed between March 2013 and March 2017. Diagnostic tests including blood culture and hematologic indices (WBC, ANC, ABC and Platelets) as well as inflammatory biomarkers (ESR, CRP) were measured for all participants. Patients over 6 year-old and those received antibiotic within a week prior to admission were excluded from the study.

***Results***
Total number of 378 patients was enrolled in this retrospective study, of which 200 (52.91%) were boys. Positive blood culture was achieved in 171 (45.23%) patients. Significant increase observed in ANC, ABC, Platelets, ESR and CRP levels among patients with positive blood culture compared with negative blood culture (P-value of 0.0012, <0.0001, <0.0001, 0.03 and 0.018, respectively). However, there was no significant difference in WBC counts between two groups (P-value = 0.1344). The most sensitive hematologic parameter (88.89%) and the most specific parameter in our evaluations was CRP (92.27%).

***Conclusion***
Measuring the ANC, ABC, Platelet, ESR, CRP levels as initial evaluation in adjunction to confirmative blood culture is reasonable approach with acceptable diagnostic value for patients suspected to septicemia.

***Key Words:*** Blood culture, C-reactive protein, Erythrocyte sedimentation, Septicemia.

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## 1- INTRODUCTION

When disease-causing organisms invade the body tissues, the reaction of body to these organisms or their toxins produced infectious disease. To evaluate the health status of a country the mortality rate of children is one of the main indicators. There are various reasons in pediatric for mortality but the major cause of mortality and morbidity in this age group is septicemia and this is much higher in developing countries (1). Septicemia is a life-threatening condition which demands an early diagnosis and subsequent treatment to restrain mortality and morbidity rate especially among pediatric population (2). Infection anywhere in the body might be the source of sepsis in susceptible patients (3, 4). Blood culture accounts the most valuable laboratory test, notwithstanding it might take long the result to be prepared (5).

Therefore, developing adjunctive tests which strengthen the diagnostic suspicion of septicemia in eligible patients is of the great importance (6). Accordingly, inflammatory biomarkers are widely employed in patients suspected to septicemia (7). C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), and hematologic indices are of the most widely used parameters in this context (8).

Nevertheless, their accuracy and preference depend on various circumstances and still remain unclear. In this study, we intend to evaluate the predictive value of each biomarker to find the most valuable one based of which a reasonable empiric therapy would be initiated prior to definite diagnosis by blood culture.

## 2- MATERIALS AND METHODS

### 2-1. Study design

Hospital records of patients with suspicious of septicemia were reviewed, retrospectively, in Hazrat Masumeh hospital of Qom province, Iran, between March 2013 and March 2017. A number of 419 patients include the study, 41 patients had missing data and therefor removed from the study; at last total number of 378 patients entered into the study. Diagnostic tests including blood culture and hematologic indices as well as inflammatory biomarkers were measured for all participants.

### 2-2. Instrumentation and Measurement

Total number of 378 cases admitted with suspicious septicemia had blood samples taken. White Blood Cells (WBC), Absolute Neutrophil Count (ANC), Absolute Band Count (ABC) and platelet counts were measured via flow-cytometry. ESR was also measured and documented less than an hour after blood sampling (9). CRP was measured with ELISA method. All data were documented.

### 2-3. Exclusion criteria

Patients were excluded if they were over 6 year-old or had a history of received antibiotic within a week before admission. Hospital records with incomplete data have not enrolled for further investigations.

### 2-4. Ethical considerations

The study proposal was approved by local ethical committee. Hospital records were kept confidential to consent with the principle of anonymity.

### 2-5. Statistical analysis

Data from pre-specified checklists were collected by an experienced medical staff at pediatric infection ward. Data were analyzed using SPSS version 24.0 software. P-value of $<0.05$ was considered to be statistical significant. Also, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and

diagnostic accuracy were calculated by MedCal software. The receiver operating characteristic (ROC) curves and the area under the curve (AUC) for each parameter were prepared using MedCal.

## 3- RESULTS

An entire number of 378 patients were reviewed in various age groups of neonate (n=109, 28.83%), 0-1 year (n=107, 28.3%), 1-2 years (n=76, 20.1%), 2-3 years (n=51, 13.49%), 3-4 years (n=13, 3.43%), 4-5 years (n=13, 3.43%), and 5-6 years (n=9, 2.38%). Of these, 200 were boys (52.91%) and remaining 178 (47.08%) were girls. Positive blood culture was obtained from 171 patients (45.23%) and 207 patients (54.76%) had negative blood culture.

The results of hematologic and inflammatory profile including WBC, ANC, ABC, Platelets, ESR and CRP indicate a significant difference in ANC, ABC, Platelets, ESR and CRP levels between patients with positive and negative blood culture (P-value of 0.0012, <0.0001, <0.0001, 0.03 and 0.018, respectively). However, the association was not significant for WBC counts between two groups of positive and negative blood culture (P = 0.1344) (**Table.1**).

After subgroup analysis to find the precise correlation between leukocyte composition and culture results, no significant difference was found also for percentage of PMN (P = 0.013). Nevertheless, outstanding information on distribution of isolated microorganism within each percentage spectrum of PMN is shown in **Figure.2**. Accordingly, it is witnessed that patients with Escherichia coli and Klebsiella, as the most common pathogens, prevalently have the PMN percentage of more than 40%, with the most within the spectrum of 40-60% and 60-80%, respectively (P-value = 0.035 and 0.016, respectively). For each hematologic and inflammatory parameters sensitivity and specificity calculated separately.

WBC was the most sensitive hematologic parameter (88.89%) followed by ANC (84.21%), platelets (82.46%), ESR (72.51%), ABC (70.18%) and CRP (57.31%). The most specific parameter in our evaluations was CRP (92.27%) followed by ABC (86.96%), WBC (80.68%), ANC (79.59%), ESR (76.33%) and platelets (67.15%). Other diagnostic properties are summarized in **Table.2**.

The diagnostic performance of a test or the accuracy of a test to discriminate diseased cases from normal cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis. Each point on the ROC plot represents a sensitivity/specificity pair corresponding to a particular decision threshold. The ROC curves for each hematologic and inflammatory parameter are shown in **Figure.3**.

The ABC had the highest AUC (AUC: 0.937), in the ROC analysis, among all hematologic and inflammatory laboratory measures. The second place is platelets (AUC=0.935) and it follows by ANC (0.836), CRP (0.758), ESR (0.680) and WBC (0.621). The average value of sensitivity for all possible values of specificity for all hematological parameters and inflammatory markers are shown in **Table.3**.

**Table-1**: Hematologic and inflammatory profile of the patients in association with blood culture results.

| Variables | Blood culture | Mean | Standard Deviation | P-value |
|---|---|---|---|---|
| WBC | Positive | 14897.8 | 6709.4 | 0.1344 |
| | Negative | 11580.7 | 8203.5 | |
| ANC | Positive | 7473.27 | 1225.71 | 0.0012 |
| | Negative | 5983.51 | 979.53 | |
| ABC | Positive | 1622.93 | 157.77 | <0.0001 |
| | Negative | 1320.1 | 133.35 | |
| PLT | Positive | 216.66 | 17.52 | <0.0001 |
| | Negative | 255.56 | 19.71 | |
| ESR | Positive | 49.27 | 27.13 | 0.03 |
| | Negative | 30.4 | 28.23 | |
| CRP | Positive | 34.56 | 19.04 | 0.018 |
| | Negative | 18.86 | 19.99 | |
| WBC: White Blood Cells, ANC: Absolute Neutrophil Count, ABC: Absolute Band Count, PLT: Platelate, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein. | | | | |

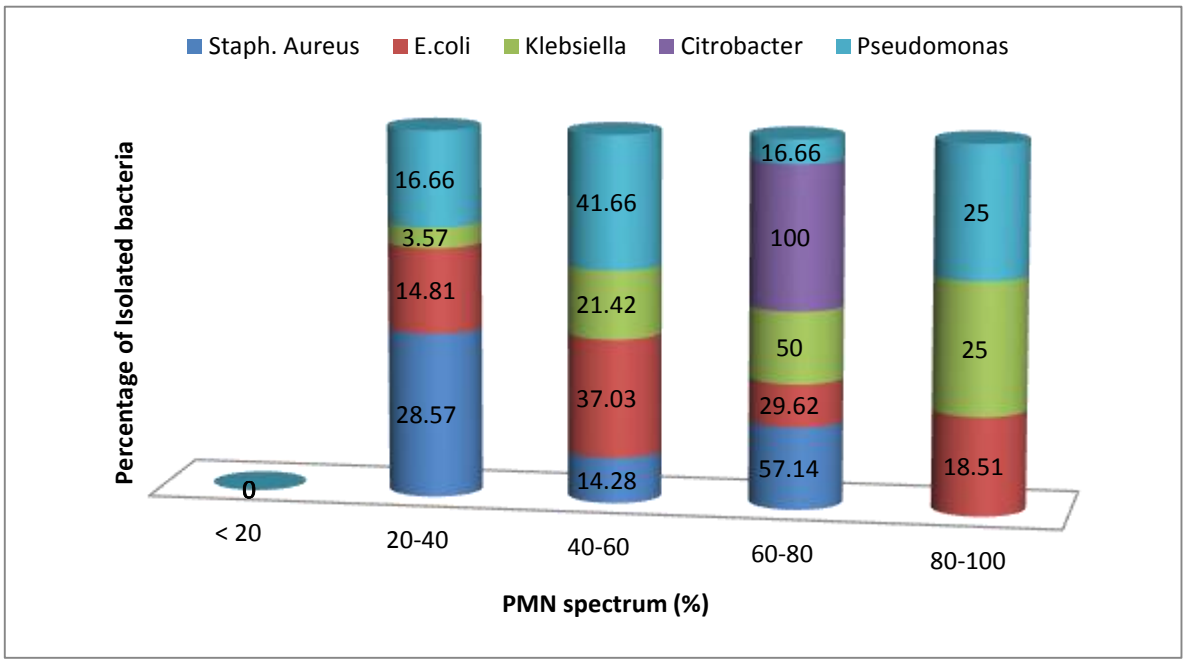


**Fig.2**: Percentage of isolated bacteria within each PMN spectrum. The diagram shows that the Staph. Aureus, Klebsiella and Citrobacter are mostly associated with a PMN percentage of 60-80%. This value is 40-60% for E.coli and Pseudomonas. PMN: Polymorphonuclear, E.coli: Escherichia coli.

**Table-2**: Diagnostic properties of hematologic and inflammatory profile in children suspected to septicemia.

| Variables | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | PLR (95% CI) | NLR (95% CI) | Diagnostic Accuracy (95% CI) |
|---|---|---|---|---|---|---|---|
| ESR | 72.51% (65.18%-79.05%) | 76.33% (69.94%-81.95%) | 71.68% (66.08%-76.67%) | 77.07% (72.26%-81.27%) | 3.06 (2.36-3.98) | 0.36 (0.28-0.46) | 74.6% (69.9%-78.92%) |
| CRP | 57.31% (49.53%-64.83%) | 92.27% (87.75%-95.52%) | 85.96% (78.99%-90.89%) | 72.35% (68.65%-75.77%) | 7.41 (4.55-12.08) | 0.46 (0.39-0.55) | 76.46% (71.85%-80.64%) |
| WBC | 88.89% (83.19%-93.18%) | 80.68% (74.63%-85.82%) | 79.17% (74.11%-83.46%) | 85.78% (85.12%-93.10%) | 4.60 (3.46-6.11) | 0.14 (0.09-0.21) | 84.39% (80.33%-87.90%) |
| ANC | 84.21% (77.86%-89.33%) | 79.59% (73.26%-85%) | 78.26% (73.05%-82.71%) | 85.25% (80.23%-89.16%) | 4.14 (3.11-5.48) | 0.2 (0.14-0.28) | 81.74% (77.4%-85.56%) |
| PLT | 82.46% (75.91%-87.84%) | 67.15% (60.3%-73.5%) | 67.46% (62.77%-71.83%) | 82.25% (76.76%-86.67%) | 2.51 (2.04-3.09) | 0.26 (0.19-0.37) | 74.07% (69.35%-78.42%) |
| ABC | 70.18% (62.72%-76.92%) | 86.96% (81.59%-91.23%) | 81.63% (75.52%-86.49%) | 77.92% (73.6%-81.71%) | 5.38 (3.73-7.75) | 0.34 (0.27-0.43) | 79.37% (74.93%-83.33%) |

PPV: Positive Predictive Value, NPV: Negative Predictive Value, PLR: Positive Likelihood Ratio, NLR: Negative Likelihood Ratio; CI: confidence interval, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein**,** WBC: White Blood Cells, ANC: Absolute Neutrophil Count, PLT: Platelate, ABC: Absolute Band Count.

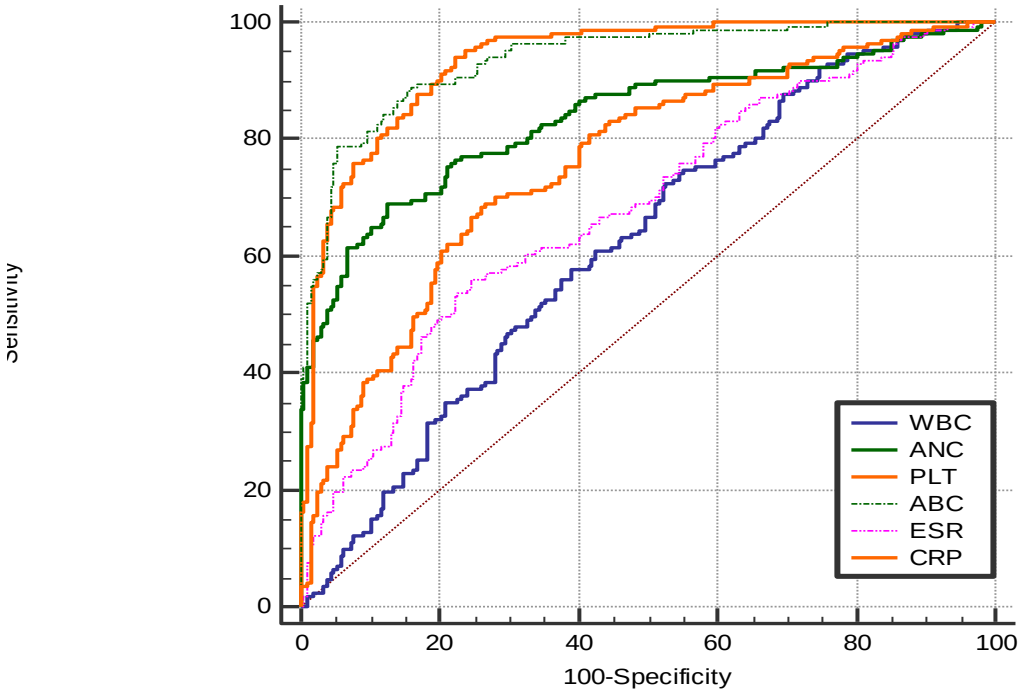


**Fig.3**: ROC curves in children suspected to septicemia younger than six years old showing sensitivity and specificity of WBC, ANC, PLT, ABC, ESR and CRP. (WBC: White Blood Cells, ANC: Absolute Neutrophil Count, PLT: Platelate, ABC: Absolute Band Count, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein).

**Table-3**: Comparison of AUC values from receiver operating characteristic curves.

| Variables | AUC | SE | 95% CI |
|---|---|---|---|
| WBC | 0.621 | 0.0286 | 0.570 to 0.670 |
| ANC | 0.836 | 0.0216 | 0.795 to 0.872 |
| PLT | 0.935 | 0.0119 | 0.906 to 0.958 |
| ABC | 0.937 | 0.0118 | 0.908 to 0.960 |
| ESR | 0.680 | 0.0275 | 0.631 to 0.727 |
| CRP | 0.758 | 0.0247 | 0.712 to 0.801 |
| AUC: Area Under Curve, SE: Standard Error, CI: Confidence Interval, a. DeLong et al., 1988 (10), b. Binomial exact. WBC: White Blood Cells, ANC: Absolute Neutrophil Count, PLT: Platelate, ABC: Absolute Band Count, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein. | | | |

## 4- DISCUSSION

Pediatric age group takes account a highly susceptible population to infection either primary or secondary to surgical complications (11-14), and other underlying disease (15, 16). Our results clearly illustrate the significance of measuring hematologic and inflammatory profile of patients with suspicious of bacteremia. Based on the current study, ANC, ABC, Platelets, ESR and CRP levels, are the most valuable laboratory tests which are easily applicable and widely available through in-patient setting. Nonetheless, there are contradictory believes in the literature regarding the best laboratory measurements adjunctive to standard choice of blood culture. Some authors support the importance of measuring inflammatory markers (7), albeit some authors suppose a little clinically relevant value (6, 17).

In a recently published study by Asadi et al. (18), inflammatory biomarkers of ESR and CRP were compared with procalcitonin levels and the authors found the procalcitonin as a more reliable marker. However, applicability of measuring procalcitonin is restricted due to its higher cost, so that the CRP level is claimed to be preferred in evaluating an infection. Another study also conducted to compare the diagnostic accuracy of procalcitonin with CRP, ESR and WBC counts in which the authors revealed a better diagnostic accuracy for procalcitonin in patients with suspected septicemia (8). In another study also the importance of measuring inflammatory biomarkers is pointed out (6). The authors revealed that the with blood cell indicators have less diagnostic value and suggested the best diagnostic accuracy by combining CRP and procalcitonin. In contrary, Manzano et al. (19), reported that CRP, procalcitonin, WBC and absolute neutrophil counts have the same diagnostic value with superiority to clinical evaluation of patients. In the current study, we compared the diagnostic value of ESR, CRP, WBC, ANC, platelets and ABC counts in patients with bacteremia.

As mentioned above, and in accordance with the literature, we found CRP levels more valuable in prediction of septicemia. Running into patients with suspected septicemia, timely initiating a reasonable treatment is crucial to have the patient's circumstance on control. Thus, early initiating an empiric therapy until the definite diagnosis be confirmed by blood culture is an acceptable approach (20). In one study the ROC curve analysis showed that CRP and ESR had a powerful indicate to diagnose UTI in neonates. They also showed that WBC Counts had the highest sensitivity, specificity, accuracy and likelihood ratio to identify positive urine culture in infants (21). According to our study ROC analysis showed that ABC and platelets counts had the most powerful

indicators to identify septicemia in pediatric. In another study that evaluated the hematologic profiles in sepsis showed that in sepsis episodes there is a higher level of WBC, ANC and ABC, but lower platelets counts. They also showed that the ANC count had the highest NPV (93%) for ruling out the sepsis and 95% sensitivity to diagnose sepsis. In our study the highest NPV were for WBC (85.78%) and ANC (85.25%). We also find that the highest diagnostic accuracy is for WBC (84.39%).

### 4-1. Strengths and Limitations

The strength of our paper is to conduct the study within an approximately vast spectrum of age through which the prevalent age of septicemia in children is included. Our study, however, is restricted by evaluating a limited set of laboratory test as well as the potential restriction on retrospective design of the study which make further studies require to be performed.

## 5- CONCLUSION

Given the importance of strengthening paraclinical suspicion of septicemia, we recommend measuring hematologic and inflammatory biomarkers of ANC, ABC, platelets, CRP and ESR as an initial evaluation of patients suspected to bacteremia until the definite diagnosis is confirmed by blood culture. Measuring these biomarkers has the supremacy of being inexpensive and easy to perform which make them widely applicable in almost every hospital with any level of facilities.

## 6- ABBREVIATION

WBC: White Blood Cells,
ANC: Absolute Neutrophil Count,
ABC: Absolute Band Count,
ESR: Erythrocyte Sedimentation Rate,
CRP: C - reactive protein,
PMN: Polymorphonuclear,
AUC: Area under the curve,
UTI: Urinary Tract Infetion.

## 7- CONFLICT OF INTEREST: None.

## 8- REFERENCES

1. Allam NG, Metwally MA, Ibrahim WS, Abdelrazik RG. New approach in treatment of antibiotic resistant microorganisms causing septicemia in children and neonate. Australian Journal of Basic and Applied Sciences. 2017;11(9):96-104.

2. Wani K, Gattoo I, Ahmed K, Qadir W. Role of blood culture in critically sick paediatric patients and its clinical impact: a tertiary care hospital based study. International Journal of Research in Medical Sciences. 2017 Jan 10; 3(8):1863-67.

3. Boskabadi H, Maamouri G, Akhodian J, Zakerihamidi M, Sayedi SJ, Ghazvini K, Kiani MA, Boskabadi A, Reyhani T, Karbandi S, Behnam Vashani H. Neonatal Infections: a 5-Year Analysis in a Neonatal Care Unit in North East of Iran. International Journal of Pediatrics. 2016; 4(12):3989-98.

4. Pawar A, Raut A, Kalrao V, Jacob J, Godha I, Thomas R. Etiology and clinical outcomes of neonatal and pediatric sepsis. Archives of Pediatric Infectious Diseases. 2016;4(2): 11-15.

5. Sultana Q, Ansari H, Ansari WM. Bacteriological profile and antimicrobial susceptibility patterns of organisms responsible for blood stream infections. Indian J Microbiol Res. 2016; 3(2):113-7.

6. Dapaah-Siakwan F, Mehra S, Lodhi S, Mikhno A, Cameron G. White Cell Indices and CRP: Predictors of Meningitis in Neonatal Sepsis?. International Journal of Pediatrics. 2016; 4(2):1355-64.

7. Van den Bruel A, Thompson MJ, Haj-Hassan T, Stevens R, Moll H, Lakhanpaul M, Mant D. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. Bmj. 2011; 342(3082): 1-11.

8. Leli C, Cardaccia A, Ferranti M, Cesarini A, D'Alò F, Ferri C, Cenci E, Mencacci A. Procalcitonin better than C-reactive protein, erythrocyte sedimentationrate, and white blood cell count in predicting DNAemia in patients with sepsis. Scandinavian journal of infectious diseases. 2014; 46(11):745-52.

9. Bedell SE, Bush BT. Erythrocyte sedimentation rate. From folklore to facts. The American journal of medicine. 1985; 78(6):1001-9.

10. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988: 837-45.

11. Salimi A, Iranikhah A, Rashidi Nia S, Eftekhari SS, Shahmoradi S. First Report of A Unique Presentation of Hypertrophic Pyloric Stenosis Following Type I Esophageal Atresia; A Case Report. International Journal of Pediatrics. 2017; 5(6):5195-98.

12. Salimi A, Shahmoradi S, Rashidi Nia S, Eftekhari SS. Beneficial Impression of San-ligation over High-ligation during Orchidopexy; a Cross-Sectional of 2659 Patients. International Journal of Pediatrics. 2017; 5(6):5145-52.

13. Salimi, A., Besharati, M., Rashidi Nia, S., Shahmoradi, S., Eftekhari, S. Application of the Topical Hydrocortisone Ointment Decreases Post-Circumcision Meatal Stenosis in Neonates: A Cross-Sectional Study. International Journal of Pediatrics, 2017; 5(6): 5061-67.

14. Salimi A, Rashidi Nia S, Shahmoradi S, Eftekhari SS. The Role of Cremaster Muscle as a Cause of Ascending Testis after Inguinal Hernia/Hydrocele Repair. International Journal of Pediatrics. 2017; 5(5):4919-28.

15. Akhavan Sepahi M, Eftekhari SS, Shahmoradi S, Talebizadeh M, Rashidinia S, Hejazi SS. Metabolic and Anatomic Abnormalities Associated with Pediatric Nephrolithiasis: a Cross-Sectional Study. International Journal of Pediatrics. 2017; 5(5):4833-38.

16. Salimi A, Rashidinia S, Eftekhari SS, Shahmoradi S. Novel Presentation of Complete Coronal Urethral Duplication: a Case Report. International Journal of Pediatrics. 2017; 5(4): 4707-12.

17. Kool M, Elshout G, Koes BW, Bohnen AM, Berger MY. C-reactive protein level as diagnostic marker in young febrile children presenting in a general practice out-of-hours service. The Journal of the American Board of Family Medicine. 2016; 29(4):460-8.

18. Asadi F, Pourmoshtagh H, Mazloomzadeh S, Koosha A. Procalcitonin Levels Compared With CRP and ESR Levels in Septicemic Children Aged 3 Months to 13 Years in the Pediatric and PICU Wards of Ayatollah Mousavi Hospital, Zanjan. Archives of Pediatric Infectious Diseases. 2016; 4(4): e34435, 1-5.

19. Manzano S, Bailey B, Gervaix A, Cousineau J, Delvin E, Girodias JB. Markers for bacterial infection in children with fever without source. Archives of disease in childhood. 2011; 96(5): 440-6.

20. Eftekhari SS, Shahmoradi S, Rashidi Nia S, Heidari H. Age-Specific Bacteriological Profile of Pediatric Septicemia; A Population-Based Study. International Journal of Pediatrics. 2017; 5(6):5211-17.

21. Lin DS, Huang SH, Lin CC, Tung YC, Huang TT, Chiu NC, Koa HA, Hung HY, Hsu CH, Hsieh WS, Yang DI. Urinary tract infection in febrile infants younger than eight weeks of age. Pediatrics. 2000; 105(2):e20-23.