Arch Pediatr Infect Dis. 2020 April; 8(2):e92212. doi: 10.5812/pedinfect.92212.

Published online 2020 May 6. **Systematic Review**

Bacterial Causative Agents of Neonatal Sepsis and Their Antibiotic Susceptibility in Neonatal Intensive Care Units (NICUs) and Neonatal Wards in Iran: A Systematic Review

Alisha Akya [1], Mosayeb Rostamian [1], Shahab Rezaeian [1], Mahnaz Ahmadi [2], Maryam Janatolmakan [2], Seyed Amirabbas Sharif [3], Amir Ahmadi [1], Sajad Weisi [1] and Roya Chegene Lorestani [1, *]

[1] Infectious Diseases Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran
[2] Clinical Research Development Center, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
[3] Infectious Diseases Research Centre, Kashan University of Medical Sciences, Kashan, Iran

[*] *Corresponding author*: Infectious Diseases Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran. Email: lorestani25@gmail.com

Received 2019 April 13; **Revised** 2020 April 09; **Accepted** 2020 April 12.

Abstract

Context: Sepsis is one of the most common causes of neonatal mortality, especially in developing countries. The purpose of this study was to systematically review the bacterial causative agents of neonatal sepsis and their antibiotic susceptibility in Iran.
Material and Methods: We searched all previously published papers to gather related information on Iranian neonatal sepsis in international and national databases (in both Persian and English) from 2006 to 2018. The standard STROBE checklist was used for quality assessment. The data were analyzed by statistical methods with a random-effects model using Stata 14 software.
Results: A total of 89,472 neonates with sepsis (presented in 17 studies) were included in this systematic review. The mortality rate of neonates was 28.0%. The proportions of neonatal sepsis caused by Gram-negative and Gram-positive bacteria were 66.0% and 33.0%, respectively. The most common bacteria causing neonatal sepsis were *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (Gram-negative) and coagulase-negative staphylococci and *Staphylococcus aureus* (Gram-positive).
Conclusions: Gram-negative bacteria are the most common causes of neonatal sepsis in Iran. Imipenem is the most effective antibiotic against Gram-negative bacilli and vancomycin against Gram-positive cocci causing neonatal sepsis in Iran.

Keywords: Septicemia, Neonates, Antibiotic Susceptibility, Iran

1. Context

Sepsis is a systemic inflammatory response to infection in which microorganisms entering the bloodstream cause severe symptoms such as fever and shock (1). This disease is one of the most important causes of neonatal mortality, especially in premature newborns (2, 3). The prevalence of this disease is one to eight per 1000 newborns in developed countries (4), while this rate is quite higher in poor and developing countries. Therefore, sepsis is still among the most common causes of newborn death in developing countries (5).

Sepsis in younger than four-week-old newborns is diagnosed by clinical signs and positive bacterial blood culture. There are two types of sepsis based on the age of newborns when the symptoms appear, including early-onset sepsis and late-onset sepsis. Early-onset septicemia occurs shortly after birth by the organisms found in the maternal birth canal. Late-onset sepsis occurs 48 hours after the birth of neonates with the progression of clinical signs. The peak incidence for late-onset sepsis is usually around a week after birth, and it is usually caused by newborns' exposure to environmental microorganisms (4). In various studies in Iran, the incidence rate of sepsis has been reported from 16.6 to 24.65% (6).

Bacteria are of the most important causes of neonatal sepsis. Many studies have shown group B *Streptococci*, coagulase-negative staphylococci (CoNS), *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Pseudomonas aeruginosa*, and *Enterococci* as the most common bacterial agents causing neonatal sepsis (7-10). Several factors in the prenatal and postnatal periods can be involved in neonatal sepsis, such as the type of delivery, preterm birth, premature rupture of the fetal membrane, uterine inertia, and maternal infection. Furthermore, sepsis is more likely to occur in premature, low-birth-weight, and male neonates (11).

The common signs and symptoms of sepsis in newborns are usually non-specific. A delay in the treatment of neonatal sepsis is mostly associated with a higher mortality rate. Therefore, antibiotic therapy should quickly begin for newborns before reporting laboratory results. Given a variety of microorganisms causing neonatal sepsis in different regions, choosing appropriate antibiotics for empirical therapy depends on the epidemiological information of common circulating organisms and their susceptibility patterns in each area (12). Although there are few studies on bacterial agents causing sepsis in neonates in different parts of Iran, currently, there is no comprehensive investigation or systematic review on this topic. Therefore, the purpose of this study was to systematically review the bacterial agents causing neonatal sepsis and their antibiotic susceptibility in Iran.

2. Material and Methods

The present study was carried out by reviewing articles on neonatal bacterial sepsis in Neonatal Intensive Care units (NICUs) in Iran from 2006 to 2018. We searched several English keywords and their Persian equivalent including "neonatal septicemia", "neonatal sepsis", "antibiotic resistance in neonatal sepsis", "neonatal blood infections", and "bacterial agents of neonatal sepsis" in the title and abstract of published articles in various databases, including MEDLINE, EMBASE, Scopus, ISI, Google Scholar, MD Consult, BMJ Journals, Cochrane Library, Directory of Open Access Journals (DOAJ), BioMed Central, OvidSP, Oxford Journals, ProQuest, Ebscohost, and Emerald Journals, as well as Iranian databases such as SID, IranDoc, Iranmedex, Scimed, and RICeST. All published papers from 2006 to 2018 indexed in these databases were reviewed. To restrict the results to Iran, all the aforementioned keywords were applied with "AND Iran".

After creating a list of titles and abstracts of retrieved studies, the standard STROBE checklist was used to determine the quality of the studies. The STROBE checklist consists of 22 different sections that evaluate the various aspects of the methodology, including sampling method, statistical analysis, adjustment of confounders, measuring variables, the validity and reliability of tools, and the objectives of the study. In this study, an inclusion criterion was having a score of at least 15 on the 22 sections of the STROBE checklist. Accordingly, 88 articles were selected out of 280 primary retrieved articles. After the comprehensive examination of the articles, 17 articles were selected that were the most relevant studies to our objectives (Figure 1). The quality of the articles was checked by two researchers (AA and RCH) independently.

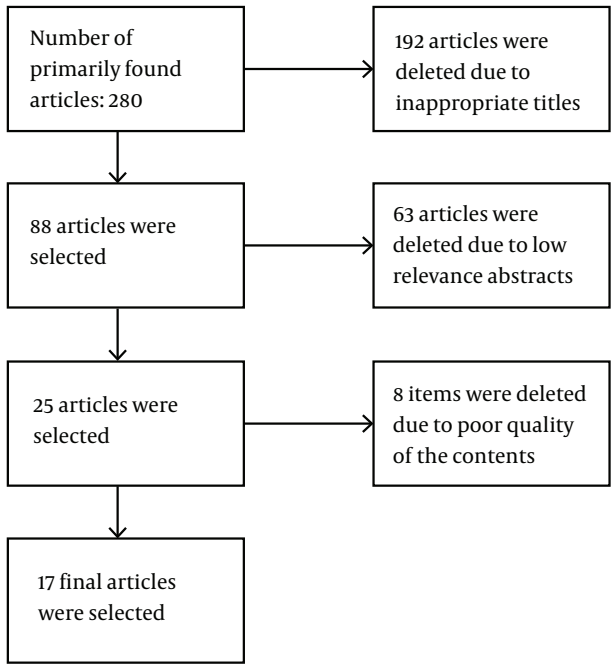

Figure 1. The flowchart of the selection steps of articles

Other inclusion criteria included studies that (1) were done on an Iranian population; (2) were performed during the last 12 years (2006 - 2018); (3) included bacterial agents causing neonatal sepsis; (4) conducted antibiotic susceptibility testing of bacterial isolates; and (5) measured the antibiotic resistance level by a standard method. The exclusion criteria included studies that (1) were available only in the abstract; (2) were review articles; (3) were Persian-language articles if their English language versions were also available (i.e., only the English version of articles were used); (4) were case studies; and (5) determined bacterial agents without antibiotic susceptibility testing.

The data for bacterial causative agents of sepsis and their antibiotic susceptibility were extracted from all neonatal cases of each study. Subsequently, the frequency of associated parameters of all studies was also was used to better estimate these criteria. Thus, the percentage of bacterial agents in 17 studies was calculated as an average number. Furthermore, the antibiotic susceptibility results of bacteria were extracted from studies, and the sensitivity of each bacterium to each antibiotic was determined and expressed as the mean $\pm$ standard deviation.

The characteristics of each study were recorded for data analysis, including the authors' names, publication year, study location, patient numbers and gender, neonatal weight and age, type of delivery, the mortality rate of

newborns, bacterial agents, and antibiotic resistance rates. All data were presented in tables or figures. The heterogeneity among studies was checked using the chi-square test and quantified using the I^2 index. All analyses were done using a random-effects model with a 95% confidence interval by Stata 14 statistical software (Stata Corp., College Station, TX, USA). Finally, the data were interpreted by considering the results of other studies from several countries.

3. Results

Table 1 shows the general data of all 17 studies. A total of 89,472 neonates with sepsis had been assessed in the 17 selected articles. Only 12 articles (with 75,336 neonates) reported the gender of the neonates in which 40.99 $\pm$ 12.35% of the neonates were female, and 59 $\pm$ 11.92% of them were male (Figure 2). The average age of the neonates in eight studies, with 875 neonates, was less than three days, three to seven days, and more than seven days for 211 (28.3%), 294 (31.9%), and 370 (39.8%) neonates, respectively. The distribution of studies based on Iran regional locations was 29.4% in the West, 5.8% in the East, 11.7% in the North, 5.8% in the South, 41.1% in the Center, and 5.8% in the Northwest.

The pooled proportion for neonatal sepsis prevalence in Iran was 14% (95% CI = 0.10, 0.18) with a significant heterogeneity (I^2 = 99.42%, P < 0.001). The proportions were 13%, 18%, 15%, 12%, 15%, and 14% in the Center, East, North, Northwest, South, and West of Iran, respectively (Figure 3).

The pooled proportion of early and late-onset neonatal sepsis in Iran was 50% (95% CI = 37.0, 63.0) with a significant heterogeneity (I^2 = 95.6%, P < 0.001). The proportions were 56% and 44% for the early and late sepsis, respectively (Figure 4).

Klebsiella pneumoniae (24.2 $\pm$ 29.33%) and *Pseudomonas aeruginosa* (16.6 $\pm$ 11.91%) were the most common Gram-negative bacteria causing neonatal sepsis in Iran. On the other hand, coagulase-negative staphylococci (15.17 $\pm$ 19.6%) and *Staphylococcus aureus* (8.41 $\pm$ 10.51%) were the most common Gram-positive bacteria isolated from neonatal sepsis in Iran (Figure 5). The overall antibiotic susceptibility results of Gram-negative and Gram-positive bacteria are presented in Tables 2 and 3, respectively.

The proportions of Gram-negative and Gram-positive bacteria causing neonatal sepsis were 66.0% and 33.0%, respectively, with considerable evidence of heterogeneity (Gram-negative bacteria: I^2 = 98.9%, P > 0.001; Gram-positive bacteria: I^2 = 98.7%, P > 0.001). The estimated mortality rate of neonates was 28.0% (95% CI = 10.0, 46.0) (Figure 6).

4. Discussion

Sepsis is one of the most serious infectious diseases of neonates (1). Due to the small number of studies and lack of their proper distribution in the geographical areas of Iran, it is not conceivable to compare the rates of neonatal sepsis in different regions of the country. In a review of eight studies on neonatal sepsis from India, USA, Thailand, South Korea, Myanmar, and Guatemala, the lowest prevalence was in the USA with 450 cases in 100,000 births while the highest prevalence was in India with 17,000 cases in 100,000 births. Furthermore, the overall prevalence of neonatal sepsis was reported as 2,202 cases in 100,000 births in seven countries (28). The reason for the difference in the sepsis prevalence in various parts of the world may be the factors such as socioeconomic status, quality of health care, climatic conditions, race, the level of technology, and medical knowledge (29).

Studies in different parts of the world suggest that male neonates are more susceptible to bacterial sepsis than females so that the risk of sepsis is twofold higher in males (29-31), which is consistent with our results. This sex-dependent vulnerability is probably related to sex-linked factors in male neonates (29, 30). Given the relationship between sepsis frequency and neonatal weight, in our study, neonates with less than 2 kg weight showed a higher rate of sepsis, suggesting that low-birth-weight is an important factor in the development of sepsis, which is consistent with the literature review (31). Moreover, similar to the previous research (9), the majority of sepsis cases in our study were early-onset sepsis, indicating the importance of maternal factors and maternal health status in neonatal sepsis.

Regarding the frequency of isolated bacteria in our study, Gram-negative bacilli including *K. pneumoniae* and *P. aeruginosa* were the most common causes of neonatal sepsis in Iranian neonates. In a study carried out in Tehran (the capital of Iran), the most common cause of sepsis was *K. pneumonia* (32). In a study from India, *K. pneumonia* and *P. aeruginosa* were the most common causes of neonatal sepsis (7), which is similar to our results. On the other hand, in a study from Iran, *P. aeruginosa* and coagulase-negative staphylococci were the most common causes of neonatal sepsis (33). Furthermore, in a study from the USA, coagulase-negative staphylococci, *S. aureus*, and *K. pneumoniae* were the most common bacteria causing neonatal sepsis (34). In a review article in Nigeria from 1987 to 2017, S. aureus and *K. pneumonia* were reported as the most common agents of neonatal sepsis (35). These differences in the frequency of bacterial agents of neonatal sepsis in various regions can be explained by differences in socioeconomic

Table 1. General Data on Neonatal Sepsis From 17 Studies[a]

Authors' Name	Regional Location of the Study in Iran	Year of Study	Number of Neonates	Number of Neonatal Sepsis, %	Year of Publication	Hospital Ward	Prospective (P)/Retrospective (R) Study	Reference
Mohammadi et al.	East	2006	175	32 (18.2)	2007	NICU	p	(13)
Qrbany et al.	North	2007	298	31 (10.4)	2008	Neonatal Ward	R	(14)
Marzban et al.	Center	2007	124	12 (9.6)	2010	NICU	R	(15)
Dezfoolimanesh et al.	West	2008	2175	90 (4.13)	2011	NICU	R	(16)
Karambin and Zarkesh	Center	2008 - 2010	611	64 (10.6)	2011	Neonatal Ward	P	(17)
Ghasemi et al.	West	2014 - 2015	78	17 (21.9)	2018	NICU	P	(18)
Nikkhoo et al.	West	2010	472	30 (6.4)	2015	NICU	P	(19)
Rajabi and Soltan Dallal	Center	2012	120	20 (16.6)	2012	NICU	P	(20)
Yazdi et al.	Center	2012	216	55 (25.4)	2014	Neonatal Ward	P	(4)
Esmaeili et al.	West	2012	1897	563 (29.4)	2014	Neonatal Ward	P	(21)
Rafati et al.	North	2013	100	20 (20)	2014	Neonatal Ward	P	(11)
Ebrahim-Saraie et al.	South	2011 - 2013	491	74 (15.1)	2016	Neonatal Ward	R	(22)
Mahallei et al.	Northwest	2015 - 2016	838	102 (12.1)	2018	NICU	R	(23)
Maham et al.	Center	2014 - 2016	2054	433 (21.1)	2018	Neonatal Ward	R	(24)
Mahmoudi et al.	Center	2011 - 2016	68233	2325 (3.4)	2017	Neonatal Ward	R	(25)
Rabirad et al.	Center	2010 - 2011	11446	910 (7.95)	2014	Neonatal Ward	P	(26)
Nikpay et al.	West	2012 - 2017	144	15 (10.4)	2018	Neonatal Ward	R	(27)

[a]Values are expressed as No. (%).

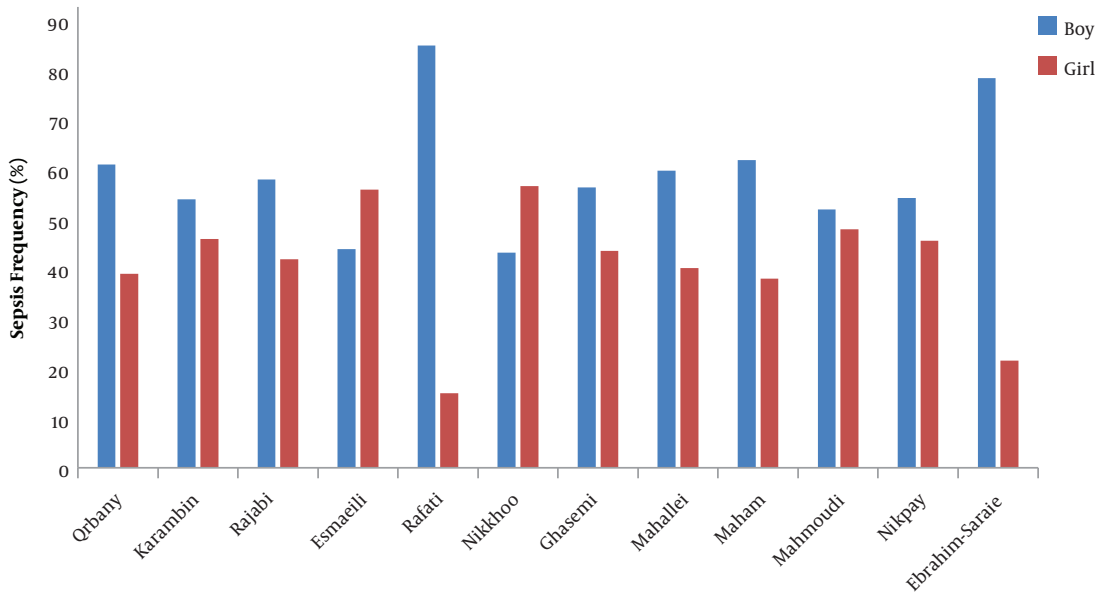

Figure 2. The frequency of sepsis based on patient gender

status, quality of health care, climatic conditions, race, the level of technology, and medical knowledge.

Our results indicated that the most common Gram-negative bacterial isolates (*K. pneumoniae* and

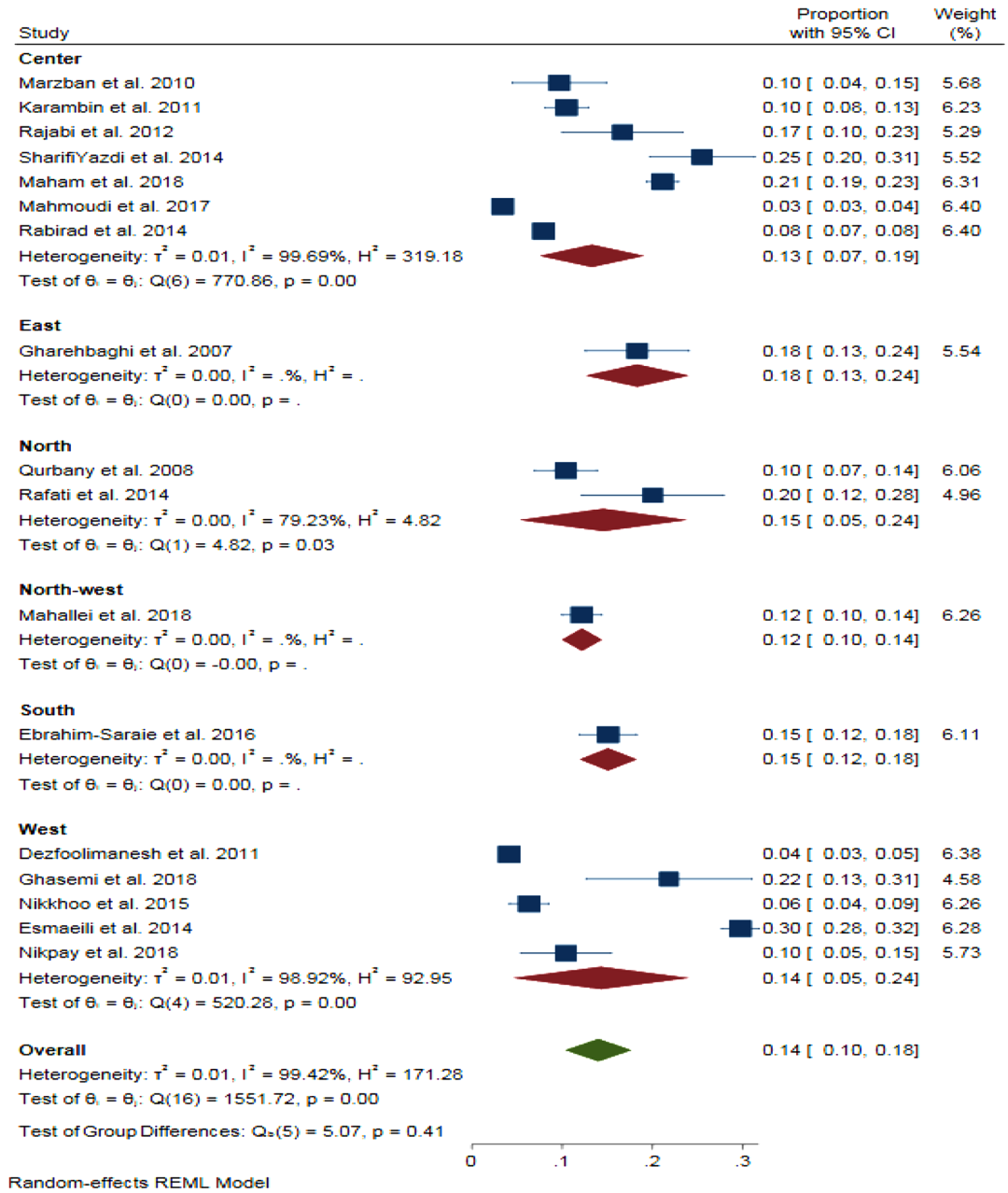

Figure 3. The pooled proportion of neonatal sepsis in Iran

Pseudomonas aeruginosa) were mostly susceptible to imipenem, suggesting this antibiotic as a good choice for empirical therapy. This is supported by the results of another study from Iran (7). The most common Gram-positive bacteria of neonatal sepsis were susceptible to vancomycin, which is consistent with the results of other studies (36, 37).

Here, we should declare some limitations to our study. We lacked relevant information to assess the relationship between neonatal weight, age, gender, and the type of childbirth and mortality rates for sepsis in several articles used in this study. Further, it is notable that all studies

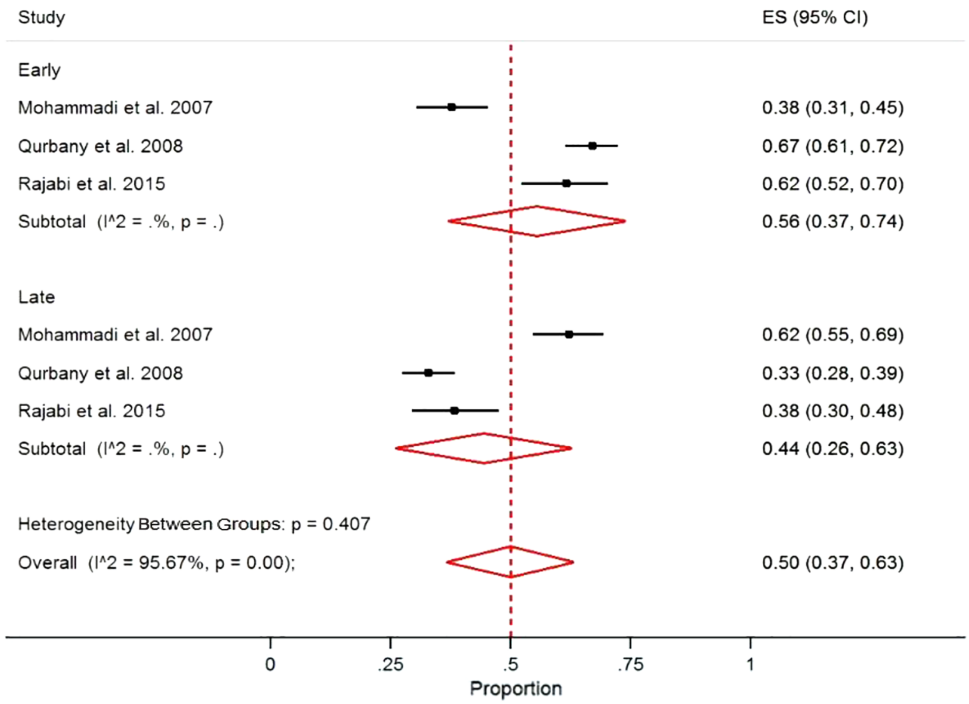

Figure 4. The pooled proportion of early and late neonatal sepsis in Iran

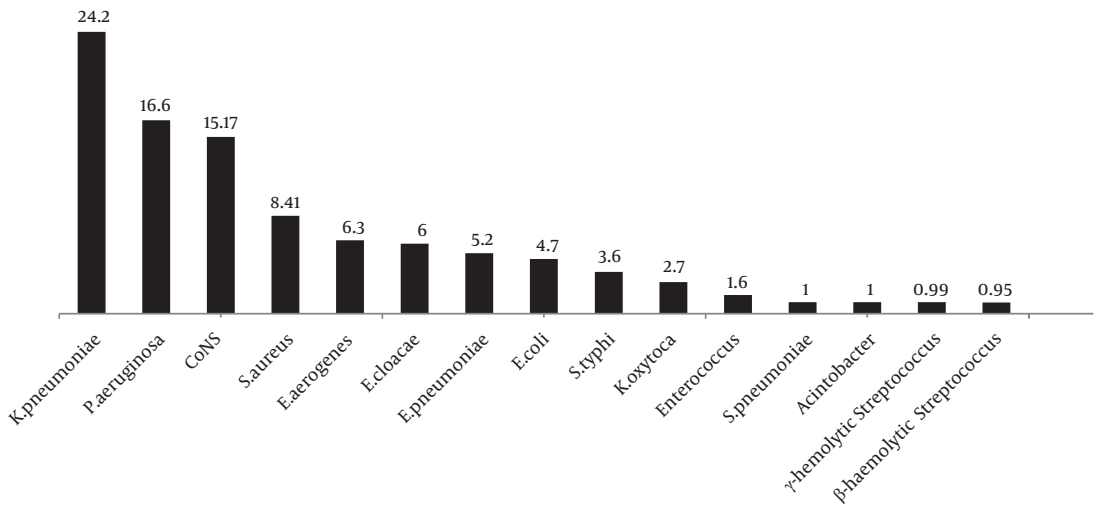

Figure 5. The frequency of bacteria causing neonatal sepsis in Iranian neonates. The numbers above each bar show the frequency percentage of each bacterium.

had used the disc diffusion method for evaluating the antibiotic susceptibility of bacteria, which is not appropriate for some types of antibiotics against particular bacteria. Some fastidious bacteria, which are among the common agents of neonatal sepsis such as *Streptococcus*, were not isolated in the selected studies. the survivors of a sepsis episode may be readmitted to the hospital again for sepsis (38). Here, no or little information was found on the repeated sepsis episodes in the included articles. Therefore, we did not consider this information for analysis in this

Table 2. The Pooled Proportion of Antibiotic Resistance of Common Gram-Negative Bacteria Causing Neonatal Sepsis in Iran

Antibiotics	*Klebsiella pneumonia*, Pr (95% CI)	*Escherichia coli*, Pr (95% CI)	*Pseudomonas aeruginosa*, Pr (95% CI)	*Enterobacter*, Pr (95% CI)
Imipenem	0.13 (0.07, 0.19)	0.15 (0.10, 0.20)	0.21 (0.21, 0.22)	0.27 (0.07, 0.46)
Ciprofloxacine	0.13(0.11, 0.14)	0.36 (0.34, 0.39)	0.98 (0.98, 0.98)	0.08 (0.07, 0.09)
Ampicilin	0.83(0.66-1.00)	0.78 (0.74, 0.82)	0.27 (0.27, 0.28)	0.77 (0.45, 1.10)
Tobramycin	0.18 (0.17, 0.20)	0.06 (0.05, 0.07)	0.09 (0.09, 0.10)	-
Gentamicin	0.49 (0.39, 0.60)	0.38 (0.30, 0.46)	0.40 (0.11, 0.70)	0.42 (0.20, 0.64)
Amikacin	0.42 (0.15, 0.69)	0.25 (0.20, 0.29)	0.30 (0.20, 0.40)	0.48 (0.25, 0.70)
Chloramphenicol	0.52 (0.43, 0.61)	0.68 (0.35, 1.00)	0.65 (0.60, 0.70)	-
Cefotaxime	0.58 (0.36, 0.80)	0.54 (0.37, 0.71)	0.49 (0.47, 0.50)	0.60 (0.47, 0.72)
Ceftriaxone	0.26 (0.24, 0.28)	0.32 (0.09, 0.56)	0.19 (0.19, 0.19)	0.19 (0.18, 0.21)
Ceftazidime	0.81 (0.80, 0.81)	0.54 (0.45, 0.63)	0.29 (0.24, 0.34)	0.50 (0.50, 0.50)
Ceftizoxime	0.20 (0.14, 0.27)	0.37 (0.33, 0.41)	-	-
Cefixime	0.74 (0.72, 0.76)	0.54 (0.15, 0.92)	0.52 (0.51, 0.52)	0.56 (0.54, 0.58)
Cotrimoxazole	0.55 (0.47, 0.64)	0.63 (0.56, 0.70)	0.20 (0.20, 0.21)	0.33 (0.15, 0.52)
Cefalotin	-	0.67 (0.62, 0.71)	-	0.88 (0.84, 0.90)
Overall	0.49 (0.40, 0.58)	0.45 (0.35, 0.56)	0.39 (0.24, 0.54)	0.47 (0.31, 0.62)

Table 3. The Pooled Proportion of Antibiotic Resistance of Common Gram-Positive Bacteria Causing Neonatal Sepsis in Iran

Antibiotics	*Staphylococcus aureus*, Pr (95% CI)	*Staphylococcus epidermidis*, Pr (95% CI)	Coagulase-Negative Staphylococci, Pr (95% CI)
Vancomycin	0	0	0
Ampicilin	0.89 (0.89, 0.90)	0.75 (0.74, 0.76)	0.82 (0.80, 0.84)
Oxacillin	-	0.53 (0.50, 0.56)	-
Gentamicin	0.38 (0.20, 0.57)	0.41 (0.14, 0.69)	0.35 (0.25, 0.45)
Amikacin	0.37 (-0.06, 0.80)	0.12 (0.11, 0.14)	0.28 (0.26, 0.31)
Tobramycin	0.44 (0.42, 0.47)	-	-
Cefotaxime	-	0.60 (0.55, 0.64)	0.40 (0.37, 0.43)
Ceftriaxone	0.05 (0.02, 0.11)	0.04 (0.03, 0.05)	-
Ceftizoxime	-	0.25 (0.19, 0.32)	0.25 (0.19, 0.32)
Cefixime	-	0.40 (0.36, 0.45)	-
Ciprofloxacine	0.37 (0.36, 0.37)	0.78 (0.75, 0.80)	0.34 (0.32, 0.36)
Cotrimoxazole	0.65 (0.53, 0.77)	0.53 (0.14, 0.91)	0.74 (0.72, 0.76)
Chloramphenicol	0.26 (0.24, 0.28)	0.27 (0.25, 0.28)	-
Cefalotin	0.88 (0.87, 0.90)	0.25 (0.21, 0.29)	-
Overall	0.49 (0.35, 0.62)	0.44 (0.28, 0.60)	0.42 (0.26, 0.58)

study, which may produce bias as a limitation of this study.

5. Conclusions

The prevalence of sepsis is still high in NICUs and neonatal wards of hospitals in Iran. Low-birth-weight and male gender are among the risk factors of neonatal sepsis in Iran. Gram-negative bacteria, including *K. pneumonia* and *P. aeruginosa*, are the most common bacterial agents of neonatal sepsis with good susceptibility to imipenem. Coagulase-negative staphylococci and *S. aureus* are common Gram-positive bacteria and vancomycin is the most effective drug for them. It seems that further studies of neonatal sepsis are required to more accurately determine maternal and neonatal risk factors and bacterial agents with their susceptibility to available antibiotics.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Acknowledgments

The authors would like to thank the Kermanshah University of Medical Sciences for providing facilities for this work.

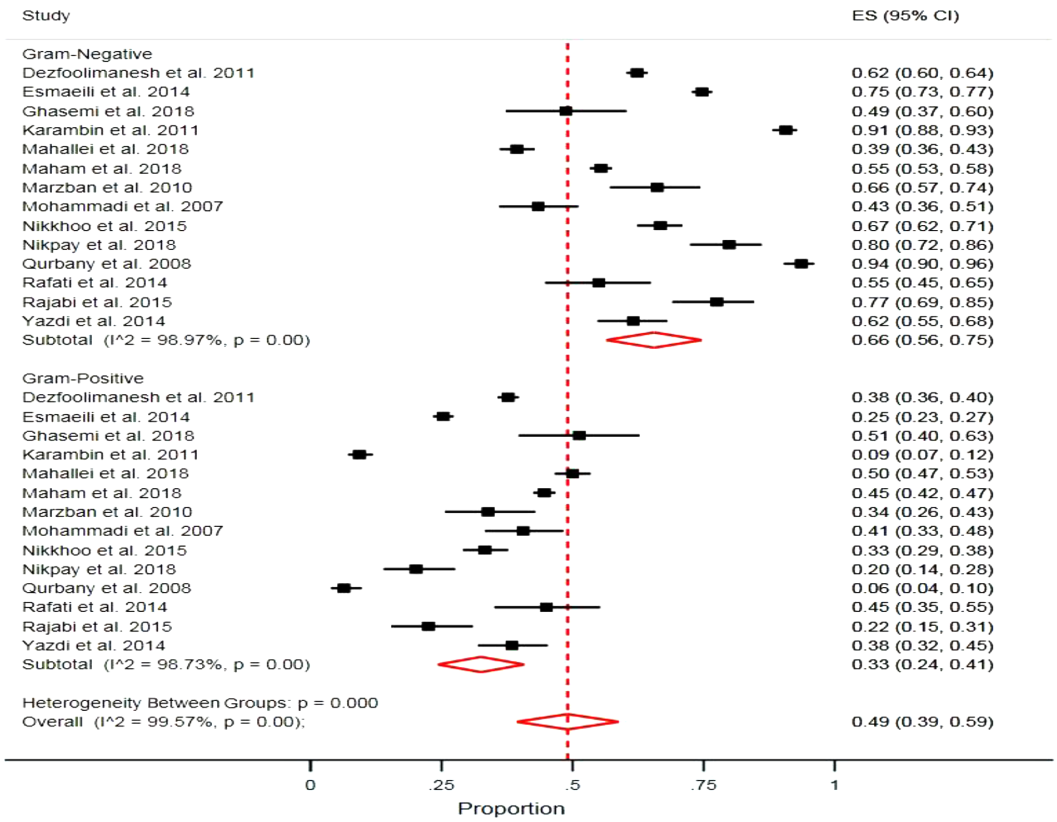

Figure 6. The pooled proportion of Gram-negative and Gram-positive bacteria causing neonatal sepsis

Footnotes

Authors' Contribution: Design: AA and RC. Data collecting or processing: RC, MR, and AA. Analysis or interpretation: RC and SR. Literature search: MA, AA, RC, MJ, SW, and SAS. Writing: RC.

Conflict of Interests: The authors declare that there is no conflict of interest to publish this article.

Ethical Approval: The study was reviewed by the Ethics Committee of Kermanshah University of Medical Sciences.

Funding/Support: The research reported in this article was supported by grants (no.: 95630) from the Kermanshah University of Medical Sciences, Kermanshah, Iran.

References

1. Randolph AG, McCulloh RJ. Pediatric sepsis: important considerations for diagnosing and managing severe infections in infants, children, and adolescents. *Virulence*. 2014;**5**(1):179–89. doi: 10.4161/viru.27045. [PubMed: 24225404]. [PubMed Central: PMC3916372].
2. Jiang JH, Chiu NC, Huang FY, Kao HA, Hsu CH, Hung HY, et al. Neonatal sepsis in the neonatal intensive care unit: characteristics of early versus late onset. *J Microbiol Immunol Infect*. 2004;**37**(5):301–6. [PubMed: 15497012].
3. Mosayebi Z, Movahedian AH, Soori T. Clinical and Bacteriological Characteristics of Neonatal Sepsis in an Intensive Care Unitin Kashan, Iran: A2YearDescriptiveStudy. *Arch Pediatr Infect Dis*. 2013;**1**(2):61–4.
4. Yazdi SH, Haghi Ashtiyani MT, Nikmanesh B, Sultandalal MM. Comparative study of antibiotic resistance in bacterial septicemia children and infants. *Iran South Med J*. 2014;**2**(17):223–32.
5. Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics-systematic review and meta-analysis. *Arch Dis Child*. 2013;**98**(2):146–54. doi: 10.1136/archdischild-2012-302033. [PubMed: 23142784].
6. Goldmann DA, Freeman J, Durbin WA, Jr. Nosocomial infection and death in a neonatal intensive care unit. *J Infect Dis*. 1983;**147**(4):635–41. doi: 10.1093/infdis/147.4.635. [PubMed: 6842004].
7. Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: an international perspective. *Arch Dis Child Fetal Neonatal Ed*. 2005;**90**(3):F220–4. doi: 10.1136/adc.2002.022863. [PubMed: 15846011]. [PubMed Central: PMC1721871].
8. Saez-Lorens X, Cracken GH. Prenatal bacterial diseases. In: Feigin RD, Cherry JD, Demler GL, Keplan SL, editors. *Textbook of pediatric infectious diseases*. Philadelphia: Saunders Co; 2004.

9. Agnihotri N, Kaistha N, Gupta V. Antimicrobial susceptibility of isolates from neonatal septicemia. *Jpn J Infect Dis*. 2004;**57**(6):273–5. [PubMed: 15623955].
10. Ahmed AS, Chowdhury MA, Hoque M, Darmstadt GL. Clinical and bacteriological profile of neonatal septicemia in a tertiary level pediatric hospital in Bangladesh. *Indian Pediatr*. 2002;**39**(11):1034–9. [PubMed: 12466574].
11. Rafati MR, Farhadi R, Nemati-Hevelai E, Chabra A. Determination of Frequency and Antibiotic Resistance of Common Bacteria in Late Onset Sepsis at the Neonatal Ward in Booali-Sina Hospital of Sari, Iran. *Journal of Babol University Of Medical Sciences*. 2014;**16**(6):64–71. doi: 10.18869/acadpub.jbums.16.6.64.
12. Hematyar M, Najibpour R, Bayesh S, Hojjat A, Farshad A. Assessing the Role of Clinical Manifestations and Laboratory Findings in Neonatal Sepsis. *Arch Pediatr Infect Dis*. 2017;**5**(1). e29985.
13. Mohammadi N, Gharebaghi M, Maamuri GA. Determination of Bacterial Causes of Sepsis in Premature Newborns. *J Tabriz uni med sci*. 2007;**29**(4):67–71.
14. Qrbany M, Karmbin M, Sobhani A, Fasihi M, PrndakhJvshary S, Shahrami H. Compare bacterial newborns sepsis between Years 2007, 1998-1993 in Rasht hospital. *J GilanUniv Med Sci*. 2008;**69**(18):25–32.
15. Marzban A, Samaee H, Mosavinasab N. Changing trend of empirical antibiotic regimen: experience of two studies at different periods in a neonatal intensive care unit in Tehran, Iran. *Acta Med Iran*. 2010;**48**(5):312–5. [PubMed: 21287464].
16. Dezfoolimanesh J, Tohidinia R, Darabi F, Almasi A. Drug sensitivity prevalence of bacterial sepsis in neonates admitted in Imam Reza (AS) Kermanshah between 2008. *J Kermanshah Univ Med Sci*. 2011;**15**(2):132–8.
17. Karambin M, Zarkesh M. Entrobacter, the most common pathogen of neonatal septicemia in rasht, iran. *Iran J Pediatr*. 2011;**21**(1):83–7. [PubMed: 23056769]. [PubMed Central: PMC3446115].
18. Ghasemi SF, Valizadeh F, Almasian M, Firouzi M, Heydari H. Newborns and Sepsis: An Overview of the Condition of Neonates Hospitalized with a Diagnosis of Sepsis in Iran in 2014-2015. *World Family Medicine*. 2018;**16**(2):95–105.
19. Nikkhoo B, Lahurpur F, Delpisheh A, Rasouli MA, Afkhamzadeh A. Neonatal blood stream infections in tertiary referral hospitals in Kurdistan, Iran. *Ital J Pediatr*. 2015;**41**:43. doi: 10.1186/s13052-015-0136-4. [PubMed: 26051617]. [PubMed Central: PMC4470359].
20. Rajabi Z, Soltan Dallal MM. Study on Bacterial Strains Causing Blood and Urinary Tract Infections in the Neonatal Intensive Care Unit and Determination of Their Antibiotic Resistance Pattern. *Jundishapur J Microbiol*. 2015;**8**(8). e19654. doi: 10.5812/jjm.19654v2.
21. Esmaeili R, Yousefi MR, Moshtaghi A, Alikhani M. Frequency of Antibiotic Resistance Patterns in Bacteria Isolated from Children. *Med Lab J*. 2014;**7**(5):57–64.
22. Ebrahim-Saraie HS, Motamedifar M, Mansury D, Halaji M, Hashemizadeh Z, Mohammadi YA. Bacterial Etiology and Antibacterial Susceptibility Patterns of Pediatric Bloodstream Infections: A Two Year Study From Nemazee Hospital, Shiraz, Iran. *J Compr Ped*. 2016;**7**(1). e29929.
23. Mahallei M, Rezaee MA, Mehramuz B, Beheshtirooy S, Abdinia B. Clinical symptoms, laboratory, and microbial patterns of suspected neonatal sepsis cases in a children's referral hospital in northwestern Iran. *Medicine (Baltimore)*. 2018;**97**(25). e10630. doi: 10.1097/md.0000000000010630. [PubMed: 29923969]. [PubMed Central: PMCPmc6024470].
24. Maham S, Fallah F, Gholinejad Z, Seifi A, Hoseini-Alfatemi SM. Bacterial etiology and antibiotic resistance pattern of pediatric bloodstream infections: A multicenter based study in Tehran, Iran. *Ann Ig*. 2018;**30**(4):337–45. doi: 10.7416/ai.2018.2225. [PubMed: 29895051].
25. Mahmoudi S, Mahzari M, Banar M, Pourakbari B, Haghi Ashtiani MT, Mohammadi M, et al. Antimicrobial resistance patterns of Gram-negative bacteria isolated from bloodstream infections in an Iranian referral paediatric hospital: A 5.5-year study. *J Glob Antimicrob Resist*. 2017;**11**:17–22. doi: 10.1016/j.jgar.2017.04.013. [PubMed: 28729206].
26. Rabirad N, Mohammadpoor M, Lari AR, Shojaie A, Bayat R, Alebouyeh M. Antimicrobial susceptibility patterns of the gram-negative bacteria isolated from septicemia in Children's Medical Center, Tehran, Iran. *J Prev Med Hyg*. 2014;**55**(1):23–6. [PubMed: 25916028]. [PubMed Central: PMC4718336].
27. Nikpay S, YadegarAzadi A, Mohamadi J, Soleymani A, Badfar G. Epidemiologic Indicators of Neonatal Sepsis in Teaching Hospitals of Ilam, Western Iran during (2012-2017). *Int J Pediatr*. 2018;**6**(7):7947–58.
28. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. *Lancet Respir Med*. 2018;**6**(3):223–30. doi: 10.1016/S2213-2600(18)30063-8. [PubMed: 29508706].
29. Tsai MH, Chu SM, Hsu JF, Lien R, Huang HR, Chiang MC, et al. Risk factors and outcomes for multidrug-resistant Gram-negative bacteremia in the NICU. *Pediatrics*. 2014;**133**(2):e322–9. doi: 10.1542/peds.2013-1248. [PubMed: 24420803].
30. Shehab El-Din EM, El-Sokkary MM, Bassiouny MR, Hassan R. Epidemiology of Neonatal Sepsis and Implicated Pathogens: A Study from Egypt. *Biomed Res Int*. 2015;**2015**:509484. doi: 10.1155/2015/509484. [PubMed: 26146621]. [PubMed Central: PMC4471255].
31. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med*. 2003;**167**(5):695–701. doi: 10.1164/rccm.200207-682OC. [PubMed: 12433670].
32. Aletayeb SMH, Khosravi AD, Dehdashtian M, Kompani F, Mortazavi SM, Aramesh MR. Identification of bacterial agents and antimicrobial susceptibility of neonatal sepsis: A 54-month study in a tertiary hospital. *Afr J Microbiol Res*. 2011;**5**(5):528–31.
33. Haj Ebrahim Tehrani F, Moradi M, Ghorbani N. Bacterial Etiology and Antibiotic Resistance Patterns in Neonatal Sepsis in Tehran during 2006-2014. *Iran J Pathol*. 2017;**12**(4):356–61. [PubMed: 29563931]. [PubMed Central: PMC5844680].
34. Karlowsky JA, Jones ME, Draghi DC, Thornsberry C, Sahm DF, Volturo GA. Prevalence and antimicrobial susceptibilities of bacteria isolated from blood cultures of hospitalized patients in the United States in 2002. *Ann Clin Microbiol Antimicrob*. 2004;**3**:7. doi: 10.1186/1476-0711-3-7. [PubMed: 15134581]. [PubMed Central: PMC420484].
35. Medugu N, Iregbu K, Iroh Tam PY, Obaro S. Aetiology of neonatal sepsis in Nigeria, and relevance of Group b streptococcus: A systematic review. *PLoS One*. 2018;**13**(7). e0200350. doi: 10.1371/journal.pone.0200350. [PubMed: 30016358]. [PubMed Central: PMC6049915].
36. Foster DR, Rhoney DH. Enterobacter meningitis: organism susceptibilities, antimicrobial therapy and related outcomes. *Surg Neurol*. 2005;**63**(6):533–7. discussion 537. doi: 10.1016/j.surneu.2004.06.018. [PubMed: 15936376].
37. Qu Y, Daley AJ, Istivan TS, Garland SM, Deighton MA. Antibiotic susceptibility of coagulase-negative staphylococci isolated from very low birth weight babies: comprehensive comparisons of bacteria at different stages of biofilm formation. *Ann Clin Microbiol Antimicrob*. 2010;**9**:16. doi: 10.1186/1476-0711-9-16. [PubMed: 20504376]. [PubMed Central: PMC2902406].
38. Wang T, Derhovanessian A, De Cruz S, Belperio JA, Deng JC, Hoo GS. Subsequent infections in survivors of sepsis: epidemiology and outcomes. *J Intensive Care Med*. 2014;**29**(2):87–95. doi: 10.1177/0885066612467162. [PubMed: 23753224]. [PubMed Central: PMC4393330].