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Clinical Guideline Adaptation for Treatment of Neonatal Sepsis Based on Frequency of Microbial Agents

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ABSTRACT

Background: Sepsis is one of the most important causes of death in infants. The pattern of bacterial agents responsible for neonatal septicemia changes over time. The main aim of the present study was to provide a clinical guideline adapted for treatment of neonatal sepsis based on the frequency of microbial agents in the Neonatal Intensive Care Unit of Alzahra Hospital, Tabriz, Iran.

Methods: The clinical guideline adaptation is conducted based on the ADAPTE Resource Toolkit for Guideline Adaptation (version 2.0) from December 2016 to January 2018. For data collection, the specialized websites were identified, then an internet search method was used for gaining clinical guidelines and medical literature databases. A panel was established with members of multi-specialties and the obtained guidelines were examined and evaluated. In the end, the final guideline was selected and translated.

Results: Regarding the guideline, employing antibiotics should start when the neonate is < 35 weeks and premature rupture of membrane (PROM) happened < 18 h. Moreover, it could be employed when the neonate did not receive antibiotics, the gestational age (GA) is < 35 weeks with a PROM < 18 h or a GA < 37 weeks with a PROM ≥ 18 h.

Conclusion: Implementation of the neonatal sepsis treatment guideline leads to a unified method of treatment, reduces the risk of antibiotic resistance, and decreases the mortality and morbidity associated with sepsis.

Keywords: Antibiotic treatment, Clinical guideline, Microbial agents, Neonatal sepsis

Introduction

Sepsis is defined as systemic inflammatory response syndrome, an inflammatory cascade, which is initiated by a host in response to infection (1). Neonatal sepsis is a bacterial infection that initially affects blood flow in infants during the first four weeks of life (2, 3). The prevalence of sepsis was reported in different countries, in developed countries it is estimated to be 1-4 per 1,000 live births, while in poor and developing countries, it is reported to be almost ten times higher (4, 5).

Although, progress in medical technology has improved the survival of very low birth weight (VLBW) infants with birth weight < 1,500 g (6, 7). These infants are still at high risk of sepsis. Sepsis is the most common cause of neonatal mortality, which is responsible for 30-50% of the neonatal deaths in developing countries (8). Despite recent advances in healthcare and antibiotic therapy, of all children who died under 5 years of age, 51.8% died from infections and 44% died in the neonatal period (9, 10). In addition, these infants are at risk for infections and resistant organisms due to long-term hospitalization in the Neonatal Intensive Care Unit (NICU) and exposure to various invasive methods and interventions (5, 11).

According to the studies performed in this regard, causes of neonatal sepsis differ in different societies and even in different hospitals. In developed countries, the most common organism

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causing sepsis in the 1930s and 1940s was *group A Streptococcus beta-hemolytic*. This agent was replaced by *Staphylococcus aureus* and *Coliform bacteria* in the 1950s and since the late 1950s, *Escherichia coli* and *beta-hemolytic streptococcus group B* have been responsible for around 60-70% of the causative agents of the neonatal sepsis. Even in developed countries, the causes of sepsis have varied over time and in different regions (5, 12, 13).

Although different diagnostic methods were employed for neonatal sepsis, managing sepsis in neonates involves supportive care and antibiotic therapy, which in turn, includes early empirical therapy and specific microorganism treatment. Bang Atlante et al. (1999) found out that home visits by rural health personnel on the first day of birth and prescribing injection antibiotics could significantly reduce neonatal sepsis morbidity and mortality rates in low-income countries (14).

Since antibiotic therapy is considered to be the main way of neonatal sepsis management, empirical treatment is the subject of an ongoing discussion. Early intravenous administration of antibiotics in the case of infection is intended to reduce the delay in the treatment of sepsis, which is especially important in the neonates with symptoms and circulatory instabilities (15).

Experimental antibiotic therapy in early-onset sepsis is often an effective method for treating Gram-negative and Gram-positive microorganisms. Moreover, it should always be remembered that *Listeria* is a potential cause of early-onset sepsis in neonates. Compared to the administration of a single antibiotic at the time, it seems necessary to administer two antibiotics simultaneously to cover a broader spectrum of resistant bacteria (16).

Clinical guidelines are systematic set of the latest and most prestigious scientific evidence, categorizing clinical approaches for a patient are according to their priorities, effectiveness, and cost-effectiveness. In developing countries, it is always argued that the number of credible indigenous evidences limited and if the evidences are supposed to be taken from developed countries, why bother to do what has already been conducted? In response to this argument, guideline adaptation was suggested. Guideline adaptation is a systematic look at the available guidelines to find the most relevant ones for the patient circumstances and integrate it with the cultural and regional requirements of the target population, as well as the health facilities (17).

Due to changing pattern of bacterial agents responsible for neonatal septicemia, usage of different antibiotics develop antibiotic resistance, varying prevalence and causes of septicemia in different societies, it is necessary to perform continuous epidemiological monitoring in hospitals, especially in NICU, and employing an antibiotic guideline based on the relevant microbial agents. Currently, in most treatment centers, treating neonatal sepsis is carried out based on received information from studies conducted in developed countries. However, due to social, cultural, and geographic differences the septic bacteria pattern in our region is likely to differ. On the other hand, the absence of an agreed-upon clinical guideline by all the neonatology faculty members leads to different opinions on the prescription of antibiotic medications and other supportive therapies for patients with sepsis. The current study aimed at adapting a clinical guideline for treating neonatal sepsis based on the frequency of microbial agents.

Methods

Study design and population

This study was carried out in four main stages from December 2016 to January 2018. To present a clinical guideline for the cases of neonatal sepsis in the NICU Department of the Al-Zahra Hospital, Tabriz, Iran. The materials of this study were the articles and clinical guidelines proposed for treating neonatal sepsis available in various sources. The process of adapting the clinical guideline is shown in Figure 1.

Methods

The clinical guideline adaptation was conducted based on ADAPTE Resource Toolkit for Guideline Adaptation (version 2.0). The target users for this clinical guideline consisted of neonatologist, laboratory experts, and specialists. At the first stage of the adaptation, the clinical guideline for antibiotic treatment of sepsis, all published clinical guidelines, and medical literature databases on neonatal sepsis treatment were studied and evaluated. Then, several clinical guidelines were selected, including 14 related databases, consisting of 7 clinical guideline databases and 7 medical literature databases (Table 1).

In the second step, the obtained guidelines were critically correlated with the clinical questions and the items that were less relevant to the key question were eliminated. At the third stage, after the initial screening of the guidelines, the quality, validity, content and compatibility, and availability of the full version, update and

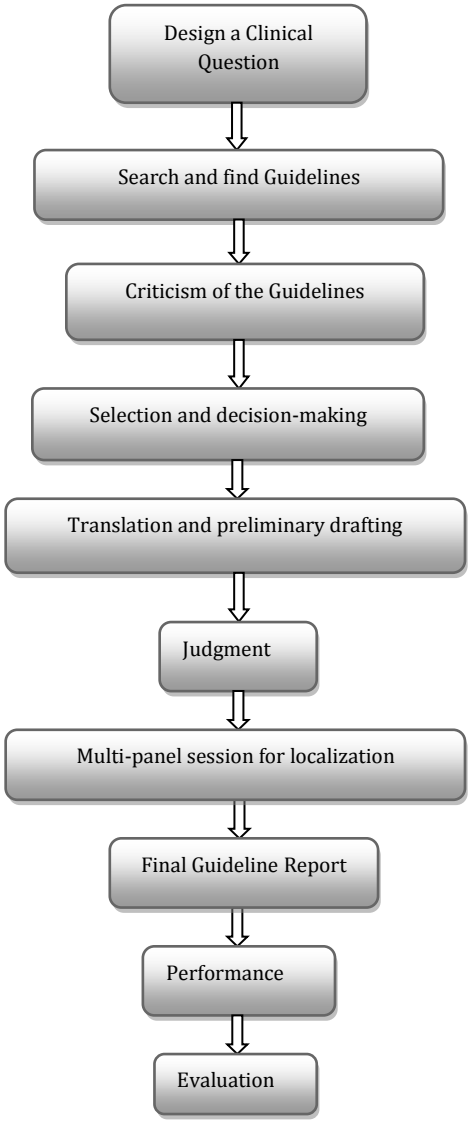

Figure 1. Process of the clinical guideline adaptation

Table 1. Searchable Databases

Clinical Guideline Database	Medical Literature Database
National Guideline Clearing house	PubMed
Guidelines International Network	Scopus
National Institute for Health and Clinical Excellence	Up to Date
Scottish Intercollegiate Guidelines Network (SIGN)	Trip Database
Guidelines Advisory Committee	Google Scholar
National Health and Medical Research Council	Magiran
WHO | World Health Organization	SID

proper organization by Appraisal of Guidelines Research & Evaluation (AGREE) software were examined by the experts. Considering ADAPTE, the most appropriate guideline was selected and translated. Based on this guideline, a primary draft of the sepsis treatment guideline was prepared. Then a panel was formed from the neonatology faculty members, gynecologists, pediatricians of infectious diseases, pathologists, bacteriologists, and pharmacologists. The next step was sharing the resulting information with the panel members. The data was examined and evaluated to exclude and eliminate cases that were less relevant to the key questions. Then final guideline and recommendation were written and the final report was prepared. Before the release of the final version, a copy of it was given to the multi-specialist panel members, while identifying

the strengths and weaknesses, modifications were made. Then, among four guidelines, the most appropriate one (Management of Neonates with Suspected Proven Early-Onset Bacterial Sepsis) published by the American Academy of Pediatrics was selected. At the fourth step, the final guideline was translated. After finalizing the guideline, it would be implemented for three months to evaluate the results.

Measuring tools

For data collection, first, the specialized websites were identified and an Internet search method was used for finding clinical guidelines and medical literature databases.

Inclusion criteria and exclusion criteria

In this study, the inclusion criteria were all the clinical guidelines and medical literature databases related to neonatal sepsis. Exclusion criteria were all the clinical guidelines and medical literature databases that were rejected in examination and evaluation by AGREE software or by experts for different reasons such as being unrelated or not being updated.

Ethical considerations

Ethical approval was received from the Ethics Committee of Tabriz University of Medical Sciences, Iran. Additionally, official permission was obtained from the hospital where the study was conducted. In order to perform the present study, a license was granted from Ethics Committee of Tabriz University of Medical Sciences with the registration number of IR.TBZMED.REC.1394.1045. Furthermore, collected information remained confidential and informed written consent was obtained from each family, who participated in the study.

Results

Despite the advances in neonatal and perinatal care, neonatal sepsis is still one of the major causes of mortality and morbidity among infants. In newborns, early warning signs of septicemia are often mild but its clinical course may be painful. Therefore, immediate antimicrobial therapy should begin in infants susceptible to sepsis and as long as the results of blood culture and antimicrobial sensitivity tests are not available, empirical treatment should begin with the aim of affecting potential pathogens. To guide the onset of empirical treatment, making changes in the pattern of agent organisms and antimicrobial sensitivity profile are vital (18-22).

According to studies carried out in developing countries, clinical sepsis is estimated to range from 49 to 170 per 1,000 live births, as well as the number of culture-positive sepsis, is estimated to be 16 per 1,000 live births (19-23).

Definitive sepsis

In this type of sepsis, the infant experiences at least one of the following signs or symptoms:

Temperature higher than 37.3°C, hypothermia (temperature<36°C), instability of temperature, changes in consciousness, change of tone, decrease in number of neonatal reflexes, seizure, apnea, cyanosis, respiratory distress (tachypnea with respiratory rate of >60 breaths per minute in term infants and more than 70 in preterm infants, grunting, nasal flaring, intercostal and subcostal retractions), new or progressive bradycardia, decreased blood pressure, vomiting, diarrhea, abdominal distension, and jaundice along with the growth of a specific pathogen from blood, urine, and cerebrospinal fluid (CSF).

Possible sepsis

This type of sepsis refers to the cases, showing at least one of the symptoms and clinical signs listed above. These symptoms are not related to another known cause, blood culture, other fluids, or finding microorganisms and antigens in blood and the other fluid. The infant will be diagnosed with this type of sepsis if at least one of the following two conditions is met:

- A test result indicating that the C-reactive protein (CRP) level is higher than 10 mg/l (more than 2 times in qualitative testing).
- Or 3 of the following criteria were present:
- The total number of white blood cells was lower than 5,000, while after 2 days the number was increased to be higher than 21,000.
- The total number of neutrophils is lower than 1,500 or higher than 10,000.
- The IT Ratio ≥ than 0.2.
- Degenerative changes in neutrophils (presence of vacuolization, toxic granulation or Dohle bodies).
- Thrombocytopenia ≤ 100,000.

Diagram of diagnosis and treatment of sepsis in the NICU Section of Al-Zahra Hospital of Tabriz is shown in Figures (2_4).

Laboratory tests

Definitive diagnosis is necessary to isolate the pathogen from a sterile environment of the body

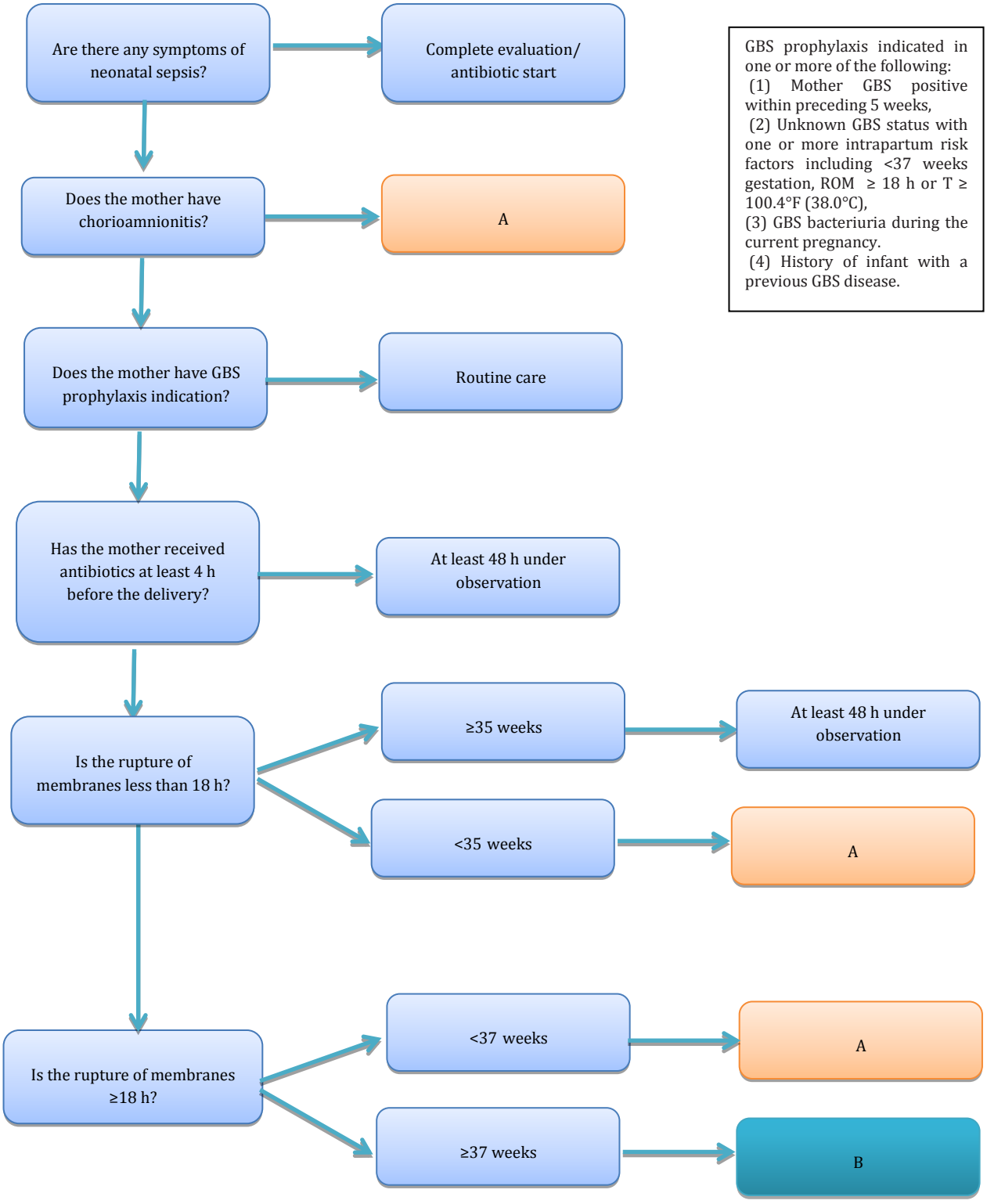

Figure 2. Diagnosis and treatment of sepsis in the Neonatal Intensive Care Unit Department of Al-Zahra Hospital in Tabriz, Iran

(blood, CSF, and urine) (23).

- *B/C*: Blood culture screening should be conducted in newborns suspected for neonatal sepsis, a sample of one cc is sufficient (24).
- Lumbar puncture**:** In cases of late sepsis, it should be performed (19).

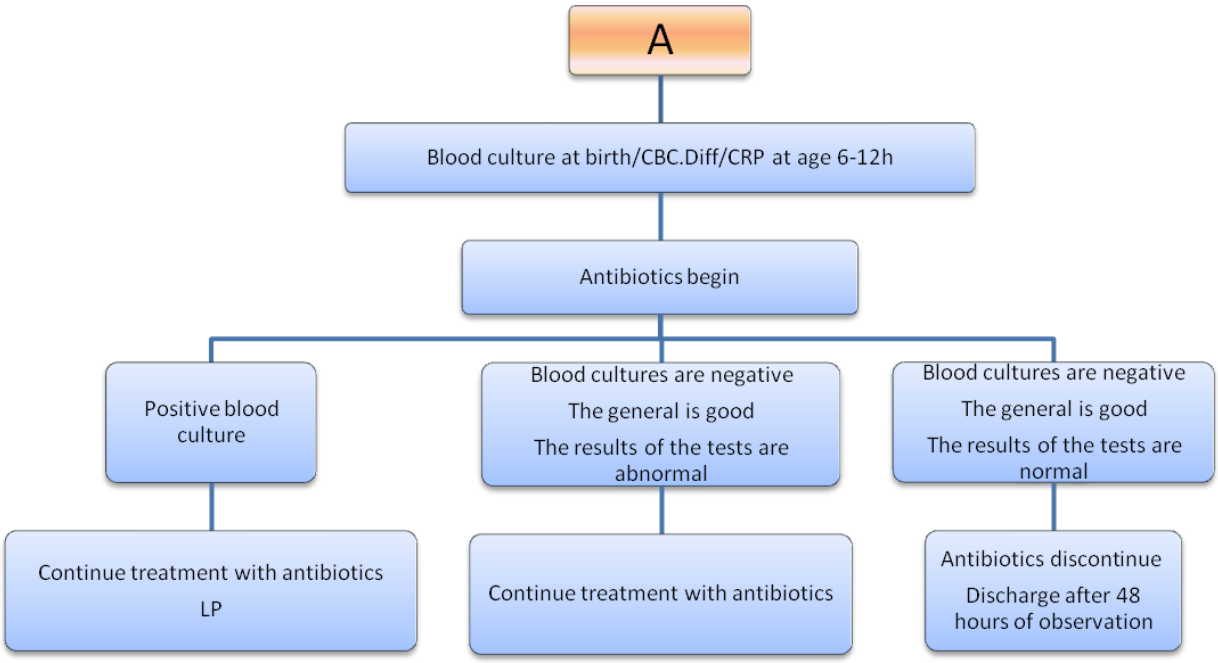

Figure 3. Chart A

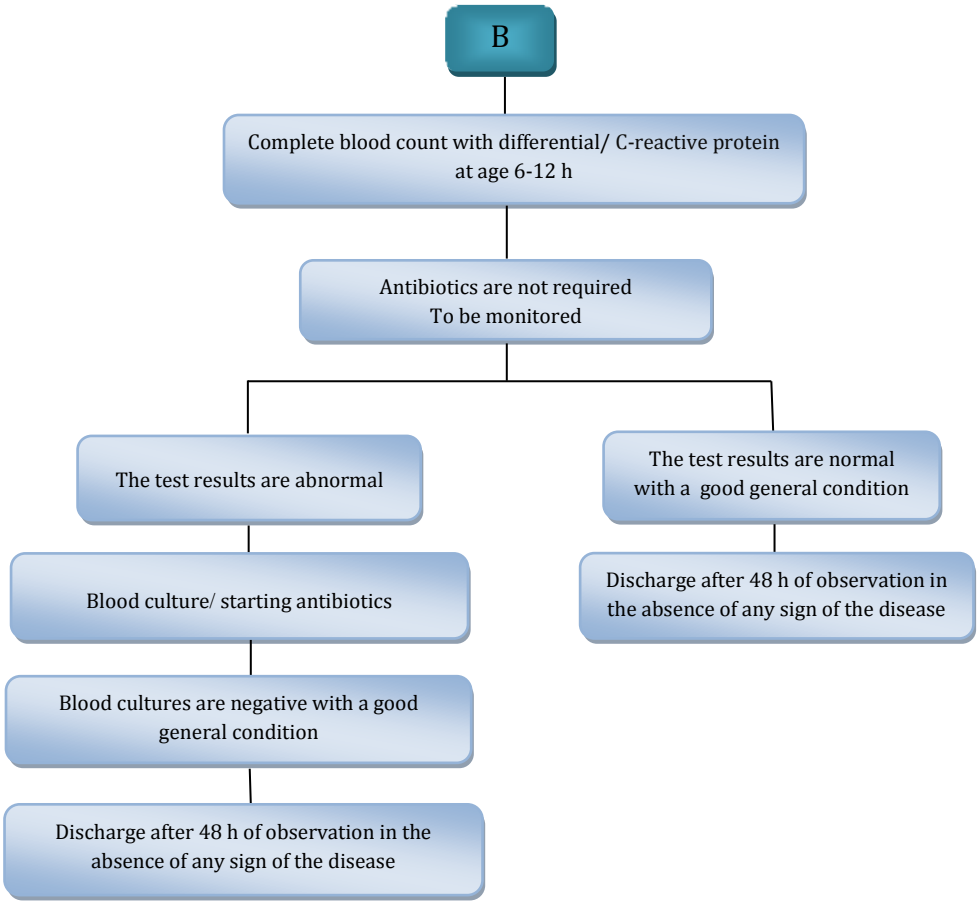

Figure 4. Charts B

Table 2. Antibiotic treatment protocol at the NICU section of the Alzahra Hospital, Tabriz, Iran

Ampicillin+Gentamicin
Vancomycin+Amikacin
Vancomycin+piperacillin/tazobactam(Tazocin)
Vancomycin+Meropenem
Vancomycin+Meropenem±Amikacin ±Amphotericin B (Amphotericin is added when there is no response to treatment or any culture is positive for fungi)

NICU: Neonatal Intensive Care Unit

The followings are indications of early sepsis:

1. Positive blood culture.
2. Clinical evidence (clinical symptoms) or laboratory evidence strongly suggesting a case of sepsis.
3. Deterioration of the condition despite the onset of treatment.

- *Urine Analysis:* it should be performed in case of late sepsis (preferably suprapubic or sterile catheterization) (25). There is no need to conduct urine analysis in case of early sepsis.

Complete Blood Count with Differential

- Complete Blood Count with Differential: It should be carried out 6 to 12 h after birth (if the case of early sepsis is not certain yet) (24).

The following results are considering to be abnormal:

1. Leukocyte < 5,000 or > 20,000 (cells/mm^3).
2. Total neutrophil count of < 1,500 cells/ mm^3.
3. I/T RATIO >0.2.
4. Platelet <100,000 cells/ mm^3.

No single marker carries the necessary sensitivity to reject sepsis, the following measures should be performed:

- CRP: It should be conducted preferably 6 to 12 h after birth (the sensitivity increases) (24).
- To evaluate the response to CRP 2 treatment should be conducted after 3 days.
- Chest X-ray: should be performed in infants with respiratory distress**.**

Treatment

According to a study on septic germs conducted in the NICU of Alzahra Hospital, the prevalence of germs in early-onset sepsis is as follows: *coagulase-negative staph* (38.6%), *Enterobacter* and *Klebsiella*, and *Enterococcus* (10.6% each), *Acinetobacter* (8.8%). This prevalence in LOS, includes *coagulase-negative staph* (31%), *Acinetobacter* (22.3%), and *Klebsiella* (14.6%). Therefore, based on the sensitivity pattern of the germs and according to the results of antibiogram, antibiotic susceptibility and compliance, and also with regard to the results of similar studies, the following antibiotic lines are suggested in Table 2.

The clinical conditions and laboratory results should be checked; so that, if the patients clinical condition did not improve or become worse, the given antibiotics should change based on the suggested lines or according to the antibiogram (If available), then a blood culture should be examined.

Preferably, the new antibiotics shall be given to the patient within 48 h unless the clinical condition of the neonate does not allow it. If the neonate needs antibiotic treatment, 1-hour treatment should be started as soon as possible (19).

- The length of the treatment is based on the infection location and the patients clinical response.
- Untreated bacterial infections are usually treated between 7 to 10 days. (Preferably 10 to 14 days for 32>Gestational Age) (25).
- Uncomplicated Group B Strep (GBS) Meningitis is treated between 14 to 21 days. Other secondary GBS locally-acquired infections (cerebritis, osteomyelitis, endocarditis) need a longer treatment time (25).
- Gram-negative Meningitis is treated for a minimum of 21 or 14 days after obtaining a negative culture (whichever is longer) (26).
- Gram-negative bacteremia is treated after 10 to 14 days (25).
- If blood culture is negative and infant is in a good general condition, in addition, there is no clinical or laboratory evidence of infection, the treatment can be stopped within 72 h to 5 days (25).
- If the blood culture is negative but the case is strongly suspected of sepsis, the treatment should last for 7 days and if the treatment is not completed after this period, it should continue (19).
- If there is evidence of Necrotizing enterocolitis, Metronidazole should be added to the first and second lines but the other lines do not require adding medicines. The antibiotic dosage in this guideline line is shown in Table 3.

Table 3. Antibiotics dosage

Suggested dosage schedules for antibiotics used in newborns						
Antibiotic	Route	<7 days old	1-3 weeks		4 weeks or more	
Ampicillin	IV, IM	100q12h	100q8h		100q6h	
			Dosage (mg/kg) and interval of administration			
			Weight<1,200 g*	Weight 1,200-2,000g	Weight>2,000 g	
		Age 0-4 w	*Age 0-7 days*	*Age>7 days*	*Age 0-7 days*	*Age>7 days*
Amikacin†:						
SDD	IV, IM	7.5q12h	7.5q12h	7.5q8h	10q12h	10q8h
ODD	IV, IM	18q48h	16q36h	15q24h	15q24h	15q24h
Aztreonam	IV, IM	30q12h	30q12h	30q8h	30q8h	30q6h
Cefazolin	IV, IM	20q12h	20q12h	20q12h	20q12h	20q8h
Cefepime	IV, IM	50q12h	50q12h	50q8h	50q12h	50q8h
Cefotaxime	IV, IM	50q12h	50q12h	50q8h	50q12h	50q8h
Ceftazidime	IV, IM	50q12h	50q12h	50q8h	50q8h	50q8h
Ceftriaxone	IV, IM	50q24h	50q24h	50q24h	50q24h	75q24h
Cephalothin	IV	20q12h	20q12h	20q8h	20q8h	20q6h
Chloramphenicol†	IV, PO	25q24h	25q24h	25q24h	25q24h	25q12h
Ciprofloxacin‡	IV	—	—	10-20q24h	—	20-30q12h
Clindamycin	IV, IM, PO	5q12h	5q12h	5q8h	5q8h	5q6h
Erythromycin	PO	10q12h	10q12h	10q8h	10q12h	10q8h
Gentamicin†:						
ODD	IV, IM	5q48h	4q36h	4q24h	4q24h	4q24h
Imipenem	IV, IM	—	20q12h	20q12h	20q12h	20q8h
Linezolid	IV	—	10q12h	10q8h	10q12h	10q8h
Methicillin:						
Meningitis	IV, IM	50q12h	50q12h	50q8h	50q8h	50q6h
Other infections	IV, IM	25q12h	25q12h	25q8h	25q8h	25q6h
Metronidazole§	IV, PO	7.5q48h	7.5q24h	7.5q12h	7.5q12h	15q12h
Mezlocillin	IV, IM	75q12h	75q12h	75q8h	75q12h	75q8h
Meropenem	IV, IM	—	20q12h	20q12h	20q12h	20q8h
Nafcillin	IV	25q12h	25q12h	25q8h	25q8h	37.5q6h
Netilmicin:						
SDD†	IV, IM	2.5q18h	2.5q12h	2.5q8h	2.5q12h	2.5q8h
ODD	IV, IM			Same as for gentamicin		
Oxacillin	IV, IM	25q12h	25q12h	25q8h	25q8h	37.5q6h
Penicillin G (units):						
Meningitis	IV	50,000q12h	50,000q12h	50,000q8h	50,000q8h	50,000q6h
Other infections	IV	25,000q12h	25,000q12h	25,000q8h	25,000q8h	25,000q6h
Penicillin benzathine (units)	IM	—	50,000 (one dose)	50,000 (one dose)	50,000 (one dose)	50,000 (one dose)
Penicillin procaine (units)	IM		50,000q24h	50,000q24h	50,000q24h	50,000q24h
Piperacillin	IV, IM	—	50-75q12h	50-75q8h	50-75q8h	50-75q6h
Piperacillin/tazobactam				Same as for piperacillin		
Rifampin	PO, IV	—	10q24h	10q24h	10q24h	10q24h
Ticarcillin	IV, IM	75q12h	75q12h	75q8h	75q8h	75q6h
Ticarcillin-clavulanate				Sameas for ticarcillin		
Tobramycin:						
SDD†	IV, IM	2.5q18h	2q12h	2q8h	2q12h	2q8h
ODD	IV, IM			Same as for gentamicin		
Vancomycin†	IV	15q24h	10q12h	10q12h	10q8h	10q8h

IV: Intravenous, IM: Intramuscular, ODD: Once-daily dosing, PO: Per oral, SDD: standard daily dosing

Discussion

The present study showed the stages of a clinical guideline adaptation for treating neonatal sepsis. In this study, in addition to considering the principles of evidence-based practice, all the recommendations of the guideline were integrated with priorities of cultural and social conditions, as well as macro policies of the health system (17).

Currently, in most treatment centers, managing neonatal sepsis is based on studies in developed countries. However, due to the social, cultural, and geographic differences the patterns

causing neonatal sepsis in these treatment centers are different (5).

High prevalence of neonatal sepsis is the main reason behind the need for an appropriate clinical guide to treat this condition. The main aim of the present study was to provide an appropriate clinical guideline, which was in line with the common microbial agents causing neonatal sepsis in infants admitted to Alzahra Hospital in Tabriz.

Doctors through using clinical guideline create an agreement to act in accordance with the proved recommendations and avoid ineffective interventions. It also provides easy and evidence-based monitoring for supervisory systems (27).

Antimicrobial treatments may alter the microbial flora of the body and potentially predispose the infant to opportunistic infections, which may lead to antibiotic-resistant organisms. In a retrospective study, empirical antibiotic administration (for over 5 days) in the first week of life in the VLBW newborns was associated with an increased incidence of late sepsis. Therefore, since there is no specific consensus procedure for the experimental antibiotic regimen, antibiotic selection for possible infectious sepsis should be performed in such a way that is suitable for organisms with high mortality. Moreover, antibiotic selection should be conducted in accordance with local resistance patterns (28).

Furthermore, due to increased antibiotic resistance and the chronicity of infectious agents, antibiotic selection should be carefully performed to reduce the antibiotic resistance of bacterial agents in NICUs (29). There is no clinical trial study on finding the best antibiotic regimen. Each antibiotic has its special benefits and side effects that will be shown over the course of time (30). Therefore, as mentioned, the experimental antibiotic therapy should be carried out based on native epidemiology and antimicrobial resistance pattern in the neonatal sepsis of the society (29). Instead of the unusual use of broad-spectrum antibiotics that lead to medication resistance, an appropriate guideline should be proposed in accordance with the microbial agents in the society to promote appropriate use of antibiotics with lesser treatment duration and fewer incidences.

In different studies, the antibiotic guideline is different depending on the type of agent present in different regions, the antibiotic susceptibility and resistance. For example, in a study conducted in Kasturba Hospital, Kasturba Medical College, Manipal, India in 2011, Ampicillin and Gentamicin antibiotics were determined as the first line and Amikacin as the second line of treatment in the neonatal sepsis treatment guideline (31). The similarity of their agents with that of our center is the reason for this choice of antibiotics.

In a study conducted in Shahid Arefian Hospital of Urmia, Iran in 2011, the bacteria were the most resistant to Ampicillin and Cefotaxime. The bacteria were most sensitive to Vancomycin and Ciprofloxacin. Therefore, these antibiotics are the first line of treatment in their guideline (32). In another study carried out in Mitford Hospital, Sir Salimullah Medical College, Dhaka, Bangladesh, in 2013, the most susceptible to the mass of Imipenem, Ceftazidime, Ciprofloxacin, and Amikacin were determined, and these antibiotics have been identified as a selective medicine in their guideline (33). The reason for this difference in the results is due to the different type of existing agents and their antibiogram.

Limitations and strengths

Lack of time for finding resources and not having access to some full-text articles were considered as limitations of this study.

Conclusion

In the present clinical guideline, we tried to provide the best evidence-based practices and recommendations for the clinical treatment of neonatal sepsis. This guideline is fully clear, accessible, and unambiguous; moreover, algorithms, instructions, checklists, and patient information are its inseparable parts. Employing this guideline in the treatment of the neonatal sepsis leads to a unified method of treatment and reduces the risk of antibiotic resistance, mortality, and morbidity associated with sepsis.

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Conflicts of interests

None.

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