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STANDARD · PROTOCOL · GUIDELINE

Recommendations on the diagnosis and the use of antibiotics for early-onset sepsis in preterm infants: consensus of the expert panel from Hunan Province

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Abstract: Preterm infants are at higher risk of developing early-onset sepsis (EOS). Due to non-specific clinical manifestations and lack of laboratory tests for prompt diagnosis of EOS, inappropriate use of antibiotics is common in preterm infants. Prolonged exposure to antibiotics can lead to antibiotic resistance and significantly increases the risk of mortality and morbidity. Based on the latest progress in the diagnosis and treatment for EOS, both in China and overseas, and considering the current condition in Hunan Province, the expert panel of neonatologists in Hunan have reached this consensus after many discussions. This consensus clarifies the risk factors, proposes the diagnostic criteria, and recommends the antibiotic use strategies for EOS in preterm infants. It is emphasized that blood culture results and clinical manifestations are the main basis for the diagnosis of EOS and the duration of antibiotics use in preterm infants.

Key words: Early-onset sepsis; Antibiotics; Expert consensus; Preterm infant

Neonatal sepsis is one of the major diseases for neonatal mortality and morbidity and the third leading cause of neonatal death in developing countries. The World Health Organization (WHO) has made it a priority in global health care in the next decade. Neonatal sepsis is usually classified as early-onset sepsis (EOS) or late-onset sepsis (LOS)[1]. Generally, the onset time of EOS is ≤3 days of life, and LOS is >3 days of life[2]. Antibiotics are the most effective method for the treatment of neonatal septicemia, but the inappropriate use of antibiotics will not only affect the treatment effect, but also lead to the increase of bacterial antibiotic resistance and the spread of antibiotic-resistant genes. This increases the cost of anti-infection treatment dramatically. Therefore, it is important for prompt diagnosis and the selection of appropriate antibiotics for neonatal sepsis. Over the years, several Chinese national experts' opinions have been published about the diagnosis and treatment of neonatal sepsis[3-4]. The latest "expert consensus on diagnosis and treatment of neonatal sepsis (2019)" was formulated and published jointly by the Subspeciality Group of Neonatology of Pediatric Society of Chinese Medical Association and the Infection Committee of the Chinese Neonatologists Association[5].

In the past 25 years, intrapartum antibiotic prophylaxis (IAP) against group B *streptococcus* (GBS) has significantly reduced the incidence of EOS in term infants, but has no significant impact on the incidence and mortality of EOS in preterm infants[6-10], suggesting that the pathogenesis of EOS in preterm infants may not be the same as that in term infants. Premature infants are the main population in neonatal intensive care unit (NICU). Clinical investigation has shown that more than 70% of the infants in NICU received antibiotic treatment, but only 5% of them might have true bacterial infections with positive blood cultures[11]. Due to non-specific clinical manifestations and lack of laboratory tests for prompt diagnosis of EOS, inappropriate use of antibiotics is common in preterm infants. Prolonged exposure to antibiotics can lead to antibiotic resistance

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and significantly increases the risk of mortality and morbidity[11].

A recent survey on the antibiotic use in the NICUs of Hunan Province revealed that the average antibiotic use time in very low birth weight (VLBW) infants was 57.1% of the total length of hospital stay, and highest was 91.4%. Half of the hospitals surveyed had an average antibiotic use time of more than 65.2% of the hospital stay (unpublished data). The data suggest that there are rooms to improve in Hunan Province in the use of antibiotics in preterm infants. According to the recent notice by the general office of the National Health Commission for the continuous improvement on the clinical management of antimicrobial agents (Guo Wei Ban Yi Fa [2019] No. 12), all health care institutions are required to formulate systematic and feasible technical specifications for the management of antimicrobial agents. The appropriate measures should be conscientiously implemented in accordance with the requirements for the management of antimicrobial agents in clinical practice. The latest guidelines of China on the diagnosis and treatment of neonatal sepsis was not specifically elaborated on EOS in premature infants[5]. According to the latest diagnosis and treatment progress of premature EOS in recent years in China and overseas, and combined with the actual situation in the Hunan Province, after several meetings and discussion, the members of the neonatal expert panel from Hunan Province reached this consensus. It is hoped that this consensus could help formulate the standard on the diagnosis and antibiotic management of EOS in premature infants, and further reduce the inappropriate use of antimicrobial agents in Hunan Province.

1 Incidence of EOS in neonates

In this consensus, EOS refers to the identification of pathogenic bacteria in blood or cerebrospinal fluid (CSF) culture taken within 72 hours of birth. Based on the data from the United States, after the widespread implementation of prenatal GBS screening and IAP, the overall incidence of EOS has decreased from 3-4/1 000 to 0.8/1 000 live births[6,12]. The clinical investigations have shown that the incidence of EOS was 0.5/1 000, 1/1 000 and 6/1 000 live births for gestational age greater than 37 weeks, 34 to 36 weeks, and less than 34 weeks, respectively. Especially, the incidence of EOS increased to 20/1 000 for less than 29 weeks, 32/1 000 for 22-24 weeks, and 9-11/1 000 for very low birth weight infants. It suggests that the smaller the gestational age and the lower the birth weight, the higher the incidence of EOS is[13-17]. In the past 25 years, the use of IAP against GBS has significantly reduced the incidence of EOS in term infants, but has no significant impact on the incidence and mortality of EOS in preterm infants[6-10]. There are few reports about the incidence of EOS in China. The recent data from Wenzhou Medical University demonstrated that the incidence of EOS in newborns was about 0.7/1 000 live births, suggesting that the incidence of EOS in China is similar to that in foreign countries[13].

2 Pathogenesis and risk factors of EOS in premature infants

Intrauterine infection or chorioamnionitis is considered a major risk factor for EOS in preterm infants[12]. EOS of term infants is caused by fetal inhalation of infected amniotic fluid or invasive infection due to the inherent colonized maternal flora in gastrointestinal tract and urogenital tract[6-7]. The pathogenesis of EOS in preterm infants is more complex. Maternal inflammation caused by microorganisms can cause fetal inflammatory reaction and preterm delivery. About 25% (especially in small gestational age) of preterm deliveries and premature rupture of membranes are caused by amnion cavity infection, suggesting that the infection of preterm infants occurs before delivery. Microorganisms isolated from the uterine cavity with preterm and/or premature rupture of membranes are mainly from the vagina, including Ureaplasma urealyticum, anaerobic

bacteria and known pathogens for neonatal sepsis, such as Escherichia coli (*E.coli*) and GBS[7-8,10]. However, preterm labor caused by inflammatory stimulation is not always caused by amnion cavity infections. Inflammation caused by placenta rejection due to maternal extrauterine infection, and stimulation by reproductive or non-reproductive microorganisms can also lead to preterm birth and premature rupture of membranes[11].

In conclusion, preterm birth itself is the strongest predictor of EOS, especially in the preterm birth less than 35 weeks of gestation, 2/3 of preterm birth may be related to maternal preterm labor, premature rupture of membranes or intrauterine infection. However, not all premature infants have EOS risk factors. Studies have shown that the incidence of EOS is very low in preterm infants who were delivered due to the mother's own reasons needed to terminate pregnancy and were delivered by elective cesarean section[15].

3 Laboratory investigations

3.1 Blood culture

Blood culture is the gold standard for diagnosing EOS. Modern blood culture system uses optimized enrichment culture medium, continuous reading detection system, and special pediatric culture bottle. The culture medium contains antibiotic neutralization elements that can effectively neutralize β- lactam antibiotics and gentamicin. This significantly improves the culture positive rate[16-17]. Studies have shown that the positive rate of this blood culture system is often not affected by the use of antibiotics during labor[18]. When the amount of bacteria in the blood is 1-10 colony units/mL, false negative results may occur when the amount of blood collected for culture is less than 1 mL. Therefore, the amount of blood drawn for blood culture shall be at least 1 mL to avoid false negative results. The positive results may be alarmed within 24 hours[19-20].

3.2 Cerebrospinal fluid examination

The incidence of meningitis in preterm infants is higher than that of the term newborns. The incidence of meningitis in preterm infants with gestational age 22-28 weeks is 0.7/1 000 live births, much higher than that of the term newborn infants (0.02-0.04/1 000 live births)[12]. The actual incidence of meningitis is not clear and may be underestimated because the lumbar puncture is usually performed after the use of empirical antibiotics. When EOS is highly suspected clinically and the patient can tolerate lumbar puncture, the spinal tap can be carried out at the same time with blood culture or be performed before the use of empirical antibiotics. Generally, when the blood culture is positive for the presence of pathogenic bacteria, routine CSF examination should be carried out to determine whether there is meningitis to guide the treatment.

3.3 PCR detection of bacterial nucleic acid

With the development of molecular biology, more and more PCR kits for detection of pathogen nucleic acids, such as 16SrRNA of bacteria, have been used in clinical trials. However, most of them are still in clinical research stage, and large-scale routine use of this technology still needs further study.

3.4 The whole blood cell count

Leukocyte count and the ratio of immature neutrophils to total neutrophils (I/T) are usually used to assess the risk of EOS, but they are affected by many clinical factors, such as gestational age, sex, mode of delivery, preeclampsia of mother, placental dysfunction, intrauterine growth environment and so on. Generally, the time of blood collection should be 6 hours after birth. It is considered abnormal if the white blood cell count $\geq 30\times10^9$/L or $<5\times10^9$/L, I/T≥0.20, the platelet count $<50\times10^9$/L[21]. Although the whole blood cell count is not sensitive to the prediction of EOS in preterm infants with gestational age less than 34 weeks, it is still widely used in clinical practice.

3.5 C-reactive protein and procalcitonin

C-reactive protein (CRP) and procalcitonin (PCT) are the most commonly used infection indexes in clinic. However, all kinds of stimulation (such as infection, asphyxia, pneumothorax, etc.) at or after

birth can increase the levels of CRP and PCT in blood, and the concentration of PCT in blood increases physiologically within 24-36 hours after birth. In the absence of culture confirmed infection, prolonging the treatment course of antibiotics only based on the abnormal values of CRP and PCT will lead to overuse of antibiotics[21]. Therefore, it is not recommended that antibiotics course of EOS is solely based on the abnormal values of CRP or PCT when blood cultures are negative. In case of suspected EOS, normal CRP and PCT values may be used to exclude infection. Normally, EOS can be excluded if two consecutive values of CRP are normal (12-24 h apart).

4 Diagnostic criteria of EOS in preterm infants

Preterm infants (gestational age less than 37 weeks), especially those under 35 weeks, often need to be admitted into neonatal ward or NICU because of their immature organ functions. However, not all premature infants admitted to neonatal ward have risk factors of EOS. Because the pathogenesis of EOS may be different between preterm and term infants, the evaluation of EOS in preterm infants is mainly to determine which preterm infant is at low risk for EOS. Preterm infants meeting all of the following three conditions can be classified as EOS low-risk preterm infants[21]: i. preterm birth caused by the mother's need to terminate pregnancy, such as preeclampsia, placenta previa, other non-infectious diseases, or placental insufficiency; ii. delivered by cesarean delivery; iii. pregnant women have no preterm labor, no attempt to induce labor or rupture of membranes before cesarean section. Even if these premature infants need respiratory support, they do not necessarily need routine antibiotics and EOS laboratory evaluations right after birth.

Premature delivery caused by cervical insufficiency, premature rupture of membranes, chorioamnionitis, infection of amniotic cavity, acute or other fetal distress of unknown causes are all risk factors for EOS. These premature infants should be included in the high-risk group of EOS after birth and can be clinically diagnosed as suspected EOS. Necessary laboratory evaluations should be performed to rule out EOS. Only those with positive blood or cerebrospinal fluid culture (or other sterile cavity fluid, such as pleural fluid) with pathogenic bacteria within 72 hours after birth can be diagnosed as true EOS. Neonatal body surface culture, gastric content culture and sputum culture may not be used as the criteria for diagnosis of EOS.

For preterm infants with abnormal clinical manifestations but negative blood culture, the diagnosis of clinical sepsis can be made by referring to the standards set in the "consensus of experts on diagnosis and treatment of neonatal sepsis (2019)"[5]. The diagnosis of clinical EOS needs to meet any of the following conditions: i. ≥2 blood non-specific tests are abnormal; ii. cerebrospinal fluid examination showing purulent meningitis change; iii. detection of pathogenic bacteria DNA in blood[5]. However, we have to emphasize again that in the absence of pathogenic bacteria to diagnose infection, only based on the abnormal values of CRP, PCT and other inflammatory markers to prolong the treatment course of antibiotics will lead to overuse of antibiotics. There is no evidence to support the practice of the diagnosis of so-called clinical sepsis and prolonged use of broad-spectrum antibiotics just based on the abnormality of inflammatory markers in preterm infants.

5 Recommendations of antibiotics use for EOS in preterm infants

5.1 Distribution pathogenic bacteria of EOS in preterm infants

GBS and *E.coli* are the most common pathogens isolated from blood culture of EOS in late preterm infants, accounting for 40% to 45% and 10% to 15% respectively[22]. In the EOS of preterm infants less than 34 weeks, *E.coli* accounts for about 50%, GBS for about 20%, other Gram-positive bacteria (mainly

Streptococcus viridis and *Enterococcus*) account for about 10%, other Gram-negative bacteria account for about 20%, and fungi less than 1%. *Staphylococcus aureus* (about 1% - 2%) and *Listeria* (about 1%) are rare pathogens of EOS in premature infants. The distribution of pathogenic bacteria of EOS in China is still lacking of large-scale epidemiological data. Recent data from Wenzhou Medical University show that the microbiological characteristics of EOS pathogens in China are basically similar to that in the United States, with *E.coli* and GBS as the main pathogens, accounting for more than 50% of EOS pathogens, while *Enterococcus* and *Listeria* accounting for 10% and 3% respectively. *E.coli* is the main pathogen of EOS in premature infants in China, but its resistance rate to the third generation cephalosporins is increasing[13], which deserves our attention.

5.2 Selection of antibiotics for EOS in preterm infants

If sensitive antibiotics are not used promptly, serious consequences and even death will occur in EOS. Therefore, in addition to routine EOS laboratory tests, we also need to start empirical antibiotic treatment in infants at high-risk for EOS. According to the distribution of EOS pathogens, antibiotics selected should aim for the effective coverage of GBS, most other *Streptococcus*, *Enterococcus*, *E.coli* and *Listeria*. In the United States, extended spectrum beta-lactamase (ESBL)-producing bacteria are rare pathogen for EOS. Although two thirds of *E.coli* and most other gram-negative bacteria are resistant to ampicillin, most of them are still sensitive to gentamicin[23]. Therefore, ampicillin and gentamicin are still the recommended empiric antibiotics for EOS in western developed countries. Because of the possibility of ototoxicity and nephrotoxicity, "the expert consensus on diagnosis and treatment of neonatal sepsis (2019)" from China[5] points out that in principle, aminoglycoside antibiotics are not used in children under 6 years old. If the antibiotic sensitivity test indicates that the pathogen is only sensitive to this kind of antibiotic, it may still be used with informed consent from the parents.

At present, the combination of ampicillin (or penicillin) + a third generation cephalosporin is widely used for EOS in China. Although the third generation cephalosporins have a wider antimicrobial spectrum than aminoglycosides, they are more likely to induce resistant bacteria and secondary fungal infections. Thus far, data from China show that GBS is generally sensitive to ampicillin (or penicillin). Although the surveillance data of bacterial resistance in children and newborn patients in China from 2014 to 2017 show that the resistance rate of *E.coli* to ampicillin is about 15%[24], but the survey data shows that *E.coli* from neonates are generally resistant to ampicillin[25-26]. The antibiotic resistant rate of *E.coli* isolated from newborn to third generation cephalosporin was over 30%[24-26]. Thus, the combination of ampicillin (or penicillin) + a third generation cephalosporin as the first-line empirical antibiotics for EOS may have poor therapeutic effect. Therefore, ampicillin or amoxicillin plus β-lactamase inhibitor compound preparation, such as ampicillin with sulbactam or amoxicillin with clavulanate potassium, may be selected as the first-line empirical antibiotics. The alternative use of these first-line antimicrobial agents in a particular unit may reduce the production of antibiotic-resistant bacteria in the NICU.

5.3 Antibiotic course for the treatment of EOS in preterm infants

5.3.1 In infants with negative blood culture

When the initial blood culture result is negative, and the clinical condition is stable, except for infants with evidence of specific site infection, it is recommended that the empirical antibiotic treatment should be discontinued after 36 to 72 hours of negative culture. Persistent cardiopulmonary instability is common in very low birth weight infants, so the need for respiratory support is not the reason for continuing empirical antibiotic use.

5.3.2 In infants with confirmed EOS by positive blood culture

When the initial blood culture is positive, then the blood culture should be repeated within 24 hours until the repeat culture is confirmed

to be negative. If lumbar puncture has not been done, the lumbar puncture should be performed as soon as possible. Sensitive antibiotics should be selected for treatment based on the microbial susceptibility test result after the pathogen is determined, and the dosage and treatment duration should be adjusted under the guidance of specialists.

Duration of antibiotic course should be based on the results of cerebrospinal fluid analysis, blood and cerebrospinal fluid culture. Considering the latest consensus of neonatal septicemia management[5], it is suggested that:

(1) EOS with positive bacterial culture: the course of antimicrobial treatment is usually 10-14 days, and the blood culture should turn negative after 2-3 days. If repeat culture continues to be positive, it is necessary to consider changing antibiotics.

(2) Infants with GBS or Listeria meningitis: the course of treatment of ampicillin (or penicillin) needs 14-21 days (calculated from the time of negative cerebrospinal fluid culture). Generally, there is no need to change to more broad spectrum antibiotics.

(3) Infants with *E.coli* meningitis: antibiotics should be continued for 21 days after CSF culture is negative. For those with multiple drug resistance *E.coli*, a combined therapy with sensitive antibiotics should be used. A longer course of antibiotics may be necessary for patients with complications (ependymositis, encephalitis, subdural effusion, etc.).

5.3.3 In infants with clinical diagnosis of EOS

When the blood culture is negative and the clinical EOS is diagnosed based on the abnormal laboratory values, the use of antibiotics is still controversial. The latest guidelines from China suggests that, in term infants, if there is only abnormal laboratory values in those infants without a positive blood culture, routine CSF examination is not necessary unless there is clinical manifestation of meningitis[5]. We suggest that this principle may also be applied in preterm infants. More and more experts believe that when the blood culture is negative, it is unreasonable to continue antibiotics only for the abnormal laboratory values. The latest guidelines of the American Academy of Pediatrics suggest that the diagnosis of clinical sepsis in neonates should be abandoned[21,27]. In view of the actual situation in our province, we suggest that the initial course of antibiotics should not exceed 7 days for preterm infants with diagnosis of clinical EOS. Because of the high incidence of LOS in preterm infants after 7 days, we need to observe the condition closely after antibiotics have been discontinued. If necessary, we should perform laboratory tests such as blood culture again before starting appropriate antibiotics for possible blood stream infections.

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标准·方案·指南

早产儿早发型败血症的诊断与抗生素使用建议：湖南省新生儿科专家共识

湖南省新生儿医疗质量控制中心；湖南省医学会围产医学专业委员会新生儿学组

［摘要］ 早产儿是新生儿早发型败血症（EOS）的高危人群。EOS 临床表现和实验室检查缺乏特异性，易导致抗生素使用不合理或使用时间过长，进而引起耐药菌株产生，使早产儿病死率和不良预后的发生风险明显升高，严重影响早产儿的远期预后。湖南省新生儿科专家根据该省的实际情况，参考国内外近年来早产儿 EOS 最新的诊疗进展，经多次讨论达成此共识。该共识重点介绍了早产儿 EOS 高危因素的识别、诊断和抗生素治疗，特别强调了血培养和临床表现是早产儿 EOS 诊断及抗生素使用疗程的主要依据。

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［关键词］ 早发型败血症；抗生素；专家共识；早产儿

Recommendations on the diagnosis and the use of antibiotics for early-onset sepsis in preterm infant: consensus of the expert panel from Hunan Province

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Abstract: Preterm infants are at higher risk of developing early-onset sepsis (EOS). Due to non-specific clinical manifestations and lack of laboratory tests for prompt diagnosis of EOS, inappropriate use of antibiotics is common in preterm infants. Prolonged exposure to antibiotics can lead to antibiotic resistance and significantly increases the risk of mortality and morbidity. Based on the latest progress in the diagnosis and treatment for EOS, both in China and overseas, and considering the current condition in Hunan Province, the expert panel of neonatologists in Hunan have reached this consensus after many discussions. This consensus clarifies the risk factors, proposes the diagnostic criteria, and recommends the antibiotic use strategies for EOS in preterm infants. It is emphasized that blood culture results and clinical manifestations are the main basis for the diagnosis of EOS and the duration of antibiotics use in preterm infants.

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Key words: Early-onset sepsis; Antibiotics; Expert consensus; Preterm infant

新生儿败血症是威胁新生儿生命的主要疾病之一，是发展中国家引起新生儿死亡的第三大原因，世界卫生组织（WHO）已将其作为未来十年全球医疗保健中需优先干预的事项[1]。根据出生后发病日龄将新生儿败血症分为早发型败血症（early-onset sepsis, EOS）和晚发型败血症（late-onset sepsis, LOS），一般 EOS 指发病时间≤ 3 日龄，LOS 指发病时间 >3 日龄[2]。抗生素是治疗新生儿败血症最有效的药物，但抗生素的不规范使用不仅会影响治疗效果，而且会导致耐药菌株的增加和耐药基因蔓延，并使抗感染的治疗成本急剧增加。因此，及时诊断新生儿败血症及规范抗生素治疗是新生儿领域关注的重点之一。我国新生儿专家曾多次发表新生儿败血症诊疗方案[3-4]，中华医学会儿科学分会新生儿学组和中国医师协会新生儿科医师分会感染专业委员会根据新生儿败血症诊治的最新进展，于 2019 年重新制定了“新生儿败血症诊断及治疗专家共识（2019 版）”[5]。

在过去的 25 年，针对 B 族链球菌（GBS）产前预防性使用抗生素虽使足月儿 EOS 发病率明显

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下降，但对早产儿 EOS 的发病率和病死率无明显影响[6-10]，提示早产儿 EOS 的发生机制与足月儿可能并不完全相同。早产儿是新生儿重症监护病房（neonatal intensive care unit, NICU）的主要人群，临床研究显示在 NICU 住院的患儿 70% 以上均接受过抗生素治疗，但血细菌培养阳性者仅占 5%[11]。由于 EOS 临床表现和实验室检查缺乏特异性，易导致抗生素使用不合理或使用时间过长，不仅导致耐药菌株产生，而且严重影响早产儿的远期预后[11]。

湖南省新生儿医疗质量控制中心对湖南省 24 家三级医院新生儿病房和 NICU 早产儿抗生素使用情况进行调查，发现湖南省极低和超低出生体重儿平均抗生素使用时间占住院时间的 57.1%，最高达 91.4%；接受调查的医院有一半的 NICU 抗生素平均使用时间超过住院时间的 65.2%（资料待发表）。以上结果提示我省早产儿抗生素的使用有待进一步规范。最近《国家卫生健康委办公厅关于持续做好抗菌药物临床应用管理工作的通知（国卫办医发 [2019]12）号》中特别强调各医疗机构要按照《抗菌药物临床应用管理办法》中的各项要求，制订系统的、可操作的抗菌药物管理技术规范并认真落实，优化抗菌药物的管理模式及提高抗菌药物合理应用的能力。基于我国新生儿专家制定的有关新生儿败血症诊治方案主要是针对整个新生儿群体，对早产儿 EOS 的诊疗未做进一步的阐述，湖南省新生儿科专家根据国内外近年来早产儿 EOS 最新的诊疗进展，结合湖南省实际情况，对早产儿EOS的诊断和抗生素使用进行多次讨论，达成此共识。此共识对湖南省早产儿 EOS 的诊断与抗生素的规范使用提出了建议，希望对临床减少不合理和不必要的抗生素使用有些指导作用。

1　新生儿 EOS 发病率

本共识中 EOS 是指新生儿出生后 72 h 内采集的血液或脑脊液培养出致病细菌。美国研究的数据显示，在产前广泛进行围产期 GBS 筛查并使用抗生素预防以后，美国 EOS 总发病率已从 3~4/1 000 活产婴儿降至 0.8/1 000 活产婴儿[6,12]。临床观察发现胎龄 >37 周新生儿 EOS 发病率为 0.5/1 000 活产婴儿，胎龄 34~36 周新生儿发病率为 1/1 000 活产婴儿，胎龄 <34 周为 6/1 000 活产婴儿，胎龄 <29 周为 20/1 000 活产婴儿，胎龄 22~24 周则高达 32/1 000 活产婴儿，极低出生体重儿（出生体重 <1 500 g）EOS 发生率为 9~11/1 000 活产婴儿，表明胎龄越小、出生体重越轻 EOS 发生率越高[13-17]。在过去的 25 年，针对 GBS 的产前预防性抗生素使用使足月儿 EOS 发病率有明显下降，但对早产儿 EOS 的发病率和病死率无明显影响[6-10]。我国有关 EOS 发病率的报道很少。最近来自温州医科大学的研究数据显示，新生儿 EOS 发生率约为 0.7/1 000 活产婴儿，提示我国 EOS 的发病率和国外类似[13]。

2　早产儿 EOS 的发病机制及危险因素

宫内感染或绒毛膜羊膜炎被认为是早产儿 EOS 的主要危险因素[12]。足月儿 EOS 是在分娩过程中由于母体胃肠道和泌尿生殖道中固有定植和感染的菌群，导致胎儿定植及侵袭性感染或胎儿吸入感染的羊水所致[6-7]。而早产儿 EOS 的发病机制则更为复杂，由微生物引起的母体炎症可引起胎儿炎症反应及早产，约 25%（特别是小胎龄儿）的早产及胎膜早破是由羊膜腔感染所致，提示早产儿的感染发生在分娩前。从早产和 / 或胎膜早破的母亲宫腔中分离出来的微生物主要来自阴道，包括解脲支原体、厌氧菌和公认的新生儿败血症病原体，如大肠杆菌（*E.coli*）和 GBS[7-8,10]。但炎症刺激所致的早产并不总是由羊膜腔感染引起，来自母体宫外感染所致的胎盘排斥反应引起的炎症，以及生殖或非生殖道微生物群的刺激，都可导致早产和胎膜早破[11]。

总之，早产本身就是 EOS 的最强预测因素，特别是在胎龄 <35 周的早产中有 2/3 的早产可能与母亲早产、胎膜早破或宫内感染有关。但是，不是所有的早产儿都具有 EOS 的危险因素。研究表明，因母亲本身原因需终止妊娠并为择期剖宫分娩的早产儿，EOS 的发生率极低[15]。

3　实验室检查

3.1　血培养

血培养是诊断 EOS 的金标准。现代血培养系

统使用具有抗菌中和特性的优化富集培养基、连续读取检测系统和专用的儿科培养瓶，培养基含有抗菌中和元素可有效地中和 β- 内酰胺类抗生素和庆大霉素，使培养阳性率明显提升 [16-17]。研究表明这种血培养系统培养的阳性率不受产时抗生素使用的影响 [18]。血中含菌量为 1~10 个菌落单位 /mL 时，抽血量少于 1 mL 可出现假阴性。因此，血培养时抽血量至少 1 mL，以避免出现假阴性结果，阳性结果可在 24 h 内报警 [19-20]。

3.2 脑脊液检查

早产儿脑膜炎的发生率高于新生儿总体水平，胎龄 22~28 周的发生率为 0.7/1 000 活产婴儿，远高于新生儿总体水平（0.02~0.04/1 000 活产婴儿）[12]。由于腰穿多在经验性抗生素使用后完成，因此，脑膜炎实际发病率并不清楚，且可能低估。在临床高度怀疑 EOS 且患儿可以耐受的情况下，腰穿脑脊液培养可与血培养同时进行，或在经验性抗生素使用前完成。一般情况下，当血培养明确有病原菌存在时应常规行脑脊液检查，以确定是否有脑膜炎以指导治疗。

3.3 细菌核酸 PCR 检测

随着分子生物学的发展，越来越多的检测病原体核酸，如检测细菌 16SrRNA 基因的 PCR 试剂盒开始在临床试用。但目前大部分仍在临床研究阶段，大规模常规使用还有待进一步的研究。

3.4 全血细胞计数

白细胞计数和未成熟中性粒细胞 / 中性粒细胞总数比值（immature/total neutrophil, I/T）通常用于评估 EOS 的风险，但其受很多临床因素，如胎龄、性别、生产方式、母亲先兆子痫、胎盘功能不良、胎儿宫内生长环境等影响。采血时间一般应在出生 6 h 以后，白细胞计数 $\geq 30\times10^9$ 或 $<5\times10^9$ 提示异常，白细胞计数减少比增高更有价值；I/T $\geq$ 0.20、血小板计数 $<50\times10^9$ 为异常 [21]。尽管全血细胞计数对胎龄小于 34 周早产儿 EOS 的预测缺乏敏感性，但该项检查在临床上仍然被广泛采用。

3.5 C 反应蛋白和降钙素原

C 反应蛋白（CRP）和降钙素原（PCT）是临床上最常用的感染指标，但新生儿期间各种刺激（如感染、窒息和气胸等）均可使血 CRP 和 PCT 浓度增高，在生后 24~36 h 内 PCT 血浓度也会出现生理性增加。在没有培养确诊感染的情况下，仅根据 CRP 和 PCT 的异常值来延长抗生素的治疗时间会导致抗生素过度使用 [21]。因此，不建议出生后用单一 CRP 或 PCT 来评估 EOS 风险或指导 EOS 的治疗。在疑似 EOS 病例，CRP 和 PCT 正常可以用来排除感染，一般连续 2 次（间隔 12~24 h）正常可排除 EOS。

4 早产儿 EOS 的诊断

早产儿（胎龄 <37 周），特别是 35 周以下的早产儿由于器官功能不成熟，常需收住新生儿病房或 NICU。但不是所有收住新生儿病房的早产儿都具有 EOS 的危险因素。由于早产儿与足月儿 EOS 的发病机制不同，对于早产儿 EOS 的评估主要是确定哪些早产儿不易发生 EOS。同时符合下列 3 个条件的早产儿可列为 EOS 低风险早产儿 [21]：（1）因母亲的原因需要终止妊娠导致的早产，如子痫前期、前置胎盘、其他非感染性疾病或胎盘功能不全；（2）剖宫产分娩；（3）孕妇没有早产征兆、无试图引产或剖宫产前的胎膜破裂。这些早产儿即使需要呼吸支持，刚出生时也不需要常规使用抗生素及行 EOS 的实验室检查。

因宫颈功能不全、胎膜早破、绒毛膜羊膜炎、羊膜腔感染、急性或其他不明原因的胎儿状态不稳定引起的早产都是 EOS 发生的危险因素。这些早产儿应在出生后列入 EOS 高危儿行列并临床诊断疑似 EOS，进行必要的实验室检查以排除 EOS。只有那些在生后 72 h 内血液或脑脊液培养（或其他无菌腔液，如胸水）发现有致病细菌才可确诊。新生儿体表培养、胃液培养及痰培养不能作为确诊依据。

对于血培养阴性，而有临床异常表现的早产儿，可参考我国“新生儿败血症诊断及治疗专家共识（2019 版）”[5]。诊断临床 EOS 需要满足下列条件中任何一项：（1）血液非特异性检查 $\geq$ 2 项阳性；（2）脑脊液检查呈化脓性脑膜炎改变；（3）血中检出致病菌 DNA[5]。但我们再次强调，在没有培养出致病菌确诊感染的情况下，仅根据 CRP、PCT 等炎症因子的异常值来延长抗生素的治疗时间会导致抗生素的过度使用。根据炎症因子的异常而诊断临床败血症，并长期使用广谱抗生

素是没有任何临床研究证据支持的。

5 早产儿 EOS 抗生素使用建议

5.1 早产儿 EOS 的致病菌群分布情况

美国的数据显示，GBS 和 *E.coli* 是晚期早产儿 EOS 培养中最常见的病原菌，分别约占 40%~45% 和 10%~15%[22]。在 <34 周早产儿 EOS 中，*E.coli* 约占 50%，GBS 约占 20%，其他革兰阳性菌（主要是草绿色链球菌和肠球菌）约占 10%，其他革兰阴性菌约占 20%，真菌 <1%。金黄色葡萄球菌（约 1%~2%）和李斯特氏菌（约 1%）是早产儿 EOS 罕见病原体。我国新生儿 EOS 的致病菌群分布尚缺乏大规模的流行病学调查数据。最近来自温州医科大学的研究数据显示，我国新生儿 EOS 致病菌微生物学特征和美国基本类似，也是以 *E.coli* 和 GBS 为主，两者相加占 EOS 致病菌的 50% 以上，其他致病菌包括肠球菌占 10%，李斯特氏菌大约占 3%；*E.coli* 是我国早产儿 EOS 的主要致病菌，但对三代头孢的耐药率越来越高 [13]，值得我们高度重视。

5.2 早产儿 EOS 的抗生素选择

对于早产儿 EOS，如不及时使用敏感抗生素，会导致严重的后果甚至死亡。因此对于 EOS 高危儿在出生后除进行常规的 EOS 实验室检查，还需同时开始经验性抗生素治疗。抗生素的联合用药是经验性抗生素使用的常用方法。根据 EOS 菌群分布情况，联合用药需选用对 GBS、大多数其他链球菌、肠球菌、*E.coli* 及李斯特氏菌有效的抗生素。超广谱产 β- 内酰胺酶（$ESBL^+$）的细菌在美国 EOS 中很少见，尽管 2/3 的 *E.coli* 和大多数其他革兰阴性菌菌株对氨苄青霉素耐药，但大多数仍对庆大霉素敏感 [23]。因此，西方等发达国家，仍将氨苄青霉素加庆大霉素作为 EOS 的首选经验性治疗药物。因有发生耳毒性和肾毒性的可能性，“新生儿败血症诊断及治疗专家共识（2019 版）”[5] 指出，对于 <6 岁儿童，原则上不使用氨基糖苷类抗菌药物。若药物敏感试验提示病原菌仅对该类药物敏感，在取得家长知情同意的情况下可考虑使用。

我国目前 EOS 较多采用氨苄青霉素（或青霉素）+ 第三代头孢菌素作为一线抗菌药物组合。尽管第三代头孢菌素较氨基糖苷类药物抗菌谱更广，但诱导耐药菌产生以及继发真菌感染可能性也较高。我国的数据显示 GBS 对氨苄青霉素（或青霉素）普遍敏感；虽然 2014~2017 年中国儿童及新生儿患者细菌耐药监测研究数据显示 *E.coli* 对氨苄青霉素耐药率在 15% 左右 [24]，但在专门针对新生儿的调查数据则显示普遍耐药 [25-26]；我国近期多个报道均显示新生儿 *E.coli* 对头孢菌素类耐药率超过 30% [24-26]。因此，采用氨苄青霉素（或青霉素）+ 第三代头孢菌素作为 EOS 一线抗菌药物组合，可能治疗效果不佳。因此，可选用氨苄青霉素或阿莫西林加 β- 内酰胺酶抑制剂复方制剂，如氨苄青霉素 + 舒巴坦或者阿莫西林克拉维酸钾作为一线抗菌药物。这几种一线抗菌药物组合可以交替使用，以减少病房内耐药菌的产生。

5.3 早产儿 EOS 抗生素使用疗程

5.3.1 血培养阴性　最初的血液培养结果为阴性时，如果早产儿病情稳定，除有特定部位感染的证据，否则建议在培养 36~72 h 后停用经验性抗生素治疗。持续性心肺功能不稳定在极低出生体重患儿中很常见，因此需要呼吸支持不是长期经验性抗生素使用的理由。

5.3.2 血培养确诊为 EOS　对于血培养阳性者，应在 24 h 内复查血培养直至培养阴性。如果未做腰椎穿刺者，应立刻完善腰椎穿刺。在确定病原菌后应使用敏感的抗生素治疗，并在专家指导下进行剂量和治疗时长的调整。

抗生素疗程：应以脑脊液分析结果、血液和脑脊液培养的结果为依据。结合国内最新新生儿败血症管理专家共识 [5]，建议：

（1）细菌培养阳性 EOS：抗生素疗程为 10~14 d，血培养在用药 2~3 d 后应该转阴，如持续阳性则需要考虑换用抗生素。

（2）GBS 或李斯特氏菌脑膜炎：通常氨苄青霉素（或青霉素）疗程需要 14~21 d（从脑脊液培养阴性后计算），一般情况下不需要加用更高级的抗生素。

（3）*E.coli* 脑膜炎：脑脊液培养阴性后继续治疗 21 d。对多重耐药的 *E.coli*，需要联合使用敏感抗生素。少数有并发症（室管膜炎、脑炎、硬膜下积液等）者需使用更长时间。

5.3.3 临床败血症　当血培养阴性而因实验室

检查异常诊断为临床 EOS 时，其抗生素的使用仍存在争议。我国最新的指南认为足月儿除非临床提示有脑膜炎，若只有实验室检查异常（不包括血培养阳性）而无临床表现的 EOS，不需常规做脑脊液检查[5]。我们建议在早产儿中也可以遵循这一原则。越来越多的专家认为血培养阴性时，仅针对实验室检测异常而长期经验性使用抗生素是不合理的。美国儿科学会最新指南建议取消临床败血症这个诊断[21,27]。鉴于我省的实际情况，我们建议初次抗生素疗程不应该超过 7 d。由于 7 d 后早产儿 LOS 的发生率很高，因此，在停用抗生素后需要严密观察病情，必要时可再次进行血培养等实验室检查，根据检验结果使用合理的抗生素治疗。

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·消息·

2020 年《中国当代儿科杂志》征稿征订启事

《中国当代儿科杂志》是由中华人民共和国教育部主管，中南大学及中南大学湘雅医院主办的国家级儿科专业学术期刊。本刊为中国科技论文统计源期刊（中国科技核心期刊），中国科学引文数据库（CSCD）核心期刊，北京大学图书馆中文核心期刊和国际权威数据库美国 MEDLINE/PubMed、美国《化学文摘》（CA）、美国 EBSCO、荷兰《医学文摘》（EM）及世界卫生组织西太平洋地区医学索引（WPRIM）收录期刊，同时被中国学术期刊（光盘版）、中国科学院文献情报中心、中国社会科学院文献信息中心评定为《中国学术期刊综合评价数据库》来源期刊，并获评 2016 中国国际影响力优秀学术期刊。2019 年 9 月进入国家首批发布的临床医学领域高质量科技期刊目录，这将推动同等水平的国内外期刊等效使用。

本刊内容以儿科临床与基础研究并重，反映我国当代儿科领域的最新进展与最新动态。辟有论著（临床研究、罕见病 / 疑难病研究、病例分析、儿童保健、流行病学调查和实验研究）、临床经验、专家讲座、述评、综述及国外儿科动态等栏目。读者对象主要为从事儿科及相关学科的临床、教学和科研工作者。

本刊为月刊，每月 15 日出版，向国内外公开发行。欢迎全国各高等医学院校，各省、市、自治区、县医院和基层医疗单位，各级图书馆（室）、科技情报研究所及广大医务人员和医学科技人员订阅。每期定价 20 元，全年 240 元。邮发代号：国内 42-188；国外 3856（BM）。可通过全国各地邮局订阅或直接来函与本刊编辑部联系订阅。

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