DOI: 10.53469/jcmp.2024.06(11).55

Mycoplasma Hominis Meningitis Neonates: A Review

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Abstract: ***The review presents an analysis of the incidence of Mycoplasma hominis (M. hominis) infection in newborns, discusses the difficulties of laboratory diagnosis of neonatal menigitis caused by M. hominis, and examines risk factors for the development of this disease. The review contains data on the sensitivity and resistance spectra of M. hominis to antibiotics, and options for antibacterial therapy for meningitis in newborns are considered.***

Keywords: *Mycoplasma hominis*, meningitis, newborn, diagnosis, treatment

Mycoplasma hominis (*M. hominis)* is currently considered as an opportunistic pathogen that usually colonizes the organs of the genitourinary system and can be either an asymptomatic carrier or cause the development of infectious and inflammatory diseases. According to the latest data, it is found in the urogenital tract in women of childbearing age from 15% [1] to 22.5% [2, 3] and 25.1% [3] and is mainly involved in urogenital and postpartum infections.

The pathogen is associated with miscarriage, low fertility and infertility [2, 4, 5]. According to Shunobu Murakami et al., (2020), *M. hominis* was cultured in 21.3% of women aged 18 to 24 years, as well as in 25.6% with bacterial vaginosis. *M. hominis* was found in 40.5% of patients delivering by cesarean section who had a variety of infectious diseases, including chorioamnionitis, intrauterine infection and pelvic abscess. It is also known that this microorganism can contribute to the development of pyelonephritis, chorioamnionitis, postpartum endometritis, postpartum fever in women in labor, cause fetal growth retardation, spontaneous abortion, stillbirth, premature birth [1].

Many researchers have pointed out the relationship between *M. hominis* colonization or infection in a pregnant woman and intrauterine neonatal infection. Infection of the fetus can occur in utero or during childbirth when passing through the birth canal [1, 2, 4, 5, 6].

The authors also associate the development of *M. hominis* infection with the empirical administration of β - lactam antibiotics (cephalosporins, carbapenems) and glycopeptides to newborns against bacterial infection, to which *mycoplases* are naturally resistant, which leads to the selection of these pathogens, massive colonization and the formation of an infectious process [6, 7, 8, 9, 10].

M. hominis infection in newborns can manifest as conjunctivitis, abscess, urinary tract infection, pneumonia, chronic lung disease, meningitis, bacteremia and sepsis [11].

M. hominis meningitis in both neonates [12] and adults [8, 9] is a relatively uncommon but dangerous disease. Currently, this pathology is described in the literature in no less than 30 infants. However, the diagnosis and treatment of *M. hominis* meningitis should be paid attention to, as this pathology is associated with the possibility of lethal outcome in 28% of cases, as well as the development of severe complications from the central nervous system in 34% of cases, leading to disability [12]. Researchers have reported complications of the central nervous system (CNS), such as brain abscess, hydrocephalus, infarction, periventricular/intraventricular hemorrhage, hemiparesis [3, 10, 13, 14], serious disorders of neuropsychic development [13].

The low frequency of detection of *M. hominis* in the cerebrospinal fluid (CSF) of newborns with meningitis may be due to the difficulty of laboratory diagnosis, which may cause underdiagnosis of this disease. The gold standard for identifying *M. hominis* is microbiological culture. However, it has a significant drawback, namely, cultures are grown for a long time on special media (3 - 7 days), which significantly delays the timely administration of targeted antibacterial therapy [1, 2, 4, 8, 9, 10].

Culture studies are also carried out using test systems that allow the identification and assessment of the number of *M. hominis* based on the degree of arginine hydrolysis. Commercial kits for both culture and diagnosis are less labor - intensive to use than classical methods and have comparable sensitivity and specificity [10].

The difficulty of express diagnostics also lies in the fact that *mycoplasmas* do not stain with Gram, so they cannot be detected in CSF smears during routine examination [1]. Detection of mycoplasmas in native CSF preparations is possible using immunofluorescence staining.

To detect *mycoplasma* infection, real - time polymerase chain reaction (PCR) and 16S rRNA sequencing are currently used. [1, 2, 4, 8, 9, 11, 12]. The sensitivity of pathogen detection in CSF using 16S pR can reach 75 - 98% [10].

Recently, the possibility of using new methods for laboratory diagnosis of *M. hominis* infection has been discussed. Whole genome sequencing (WGS) can successfully identify the pathogen and evaluate the presence of genetic markers of antibiotic resistance. Matrix - assisted laser desorption/ionization time - of - flight mass

spectrometry (MALDI - TOF MS) is one of the latest microbial identification systems available to laboratories. It allows rapid identification of the pathogen, but has limitations because it requires the pathogen to be cultured and present in a database for identification [10]. There is also a report of the use of MALDI - TOF MS for the diagnosis of M. hominis meningitis in a premature newborn girl with a birth weight of 885 g. Sequencing of the 16S rRNA gene of the sample confirmed the presence of *M. hominis* [1].

Two articles examining the development of postoperative meningitis in adult men report the rapid detection of *M. hominis* in cerebrospinal fluid using metagenomic next - generation sequencing (mNGS) [8, 9] with confirmation of the pathogen by PCR [9]. Che Guanglu et al., (2023) also reported effective and rapid diagnosis of *M. hominis* meningitis in a newborn using mNGS.

The Researchers emphasize the importance of suspecting *M. hominis* as a cause of infection in neonates who 1) have clinical signs in the absence of growth on conventional bacterial media, 2) blood laboratory values and pleocytosis indicate the presence of inflammation, but the microorganisms may not be detected by microscopy of the CSF; 3) no improvement with empirical antibiotic treatment [1, 10, 12]. Currently, risk factors for the development of *M. hominis* meningitis in newborns are considered to be prematurity, low body weight, and low gestational age at birth [12, 13], neural tube defects [12], detection of *M. hominis* in the maternal birth canal [1 2, 4, 6], respiratory distress syndrome [13].

The clinical picture of *M. hominis* meningitis may include hypotension, temperature instability, lethargy, vomiting, irritability, decreased tone, twitching or convulsions, tachycardia, lethargy [12], episodes of apnea [12, 13], generalized tonic - clonic activity causing seizures [13],

Currently, the authors note a wide variety of antibiotic sensitivity spectra of *M. hominis* isolated from pregnant women and infants with perinatal infection. Thus, Shunobu Murakami et al., (2020), reported sensitivity of all *M. hominis* strains to clindamycin, minocycline, and quinolones and resistance to macrolides and fosfomycin. According to R. V. Lendamba et al., (2022) *M. hominis* isolated from the genitalia of pregnant and non - pregnant women of childbearing age were multiresistant to antibiotics. Thus, resistance was observed to ciprofloxacin in 97.41%, azithromycin 81.9%, ofloxacin 69.835, tetracycline in 68.9% of strains.

In an infant with ventriculitis, a strain of *M. hominis* isolated from the cerebrospinal fluid was sensitive to tetracyclines and quinolones but resistant to lincosamides and macrolides. Thus, the sequence of the 23S rRNA gene of *M. hominis* contained mutations G2063A and C2618U (the numbering is based on the sequence of 23S rRNA AF 44361.3 from an *M. hominis* isolate with known resistance to macrolides), which confer resistance to these antibiotics [11].

The development of resistance of *M. hominis* strains to macrolides, tetracyclines, fluoroquinolones, and aminoglycosides has also been reported [11]. R. V. Lendamba et al., (2022) found that *M. hominis* isolated from the vagina of women was resistant to ciprofloxacin (97.41%), azithromycin (81.9%), ofloxacin (69.83%) and tetracycline (68.97%).

Earlier in vitro studies showed the sensitivity of *M. hominis* to macrolides, chloramphenicol, tetracyclines, lincosamides and fluoroquinolones [1, 13].

The choice of antibiotic for the treatment of *M. hominis* meningitis in newborns is associated with certain difficulties. These include the natural resistance of this type of *mycoplasma* to beta - lactam antibiotics, the rapid development of resistance to macrolides, the selective natural sensitivity of strains to macrolides, and the oral dosage forms of most macrolides, which limits their use in neonatology. It is important to take into account the ability of antibiotics to create high concentrations in neutrophils, in which vegetation of *M. hominis* is possible due to incomplete phagocytosis [10]. The macrolides and the fluoroquinolones are distributed intracellularly. However, the use of the latter in neonatology is limited due to impaired formation of cartilage tissue in children. Tetracyclines have a bacteriostatic effect and are not used in children under 8 years of age due to the negative effect on the bones and teeth of a growing organism. It is important to consider the ability of antibiotics to penetrate the blood - brain barrier [10, 13].

Articles from the last decade report the effectiveness of various groups of antibiotics used to treat *M. hominis* vaginosis in women and *M. hominis* meningitis in infants. The table shows various options for antibiotic therapy for *M. hominis* infection.

Table: Antibacterial therapy for *M. hominis* infection in women and infants

№	Antibiotics	Diagnosis	Patients	Authors
1	Macrolides	Vaginosis	Pregnant women	R. V. Lendamba et al., 2022
2	Tetracycline, fluoroquinolones	Vaginosis	Non - pregnant women	R. V. Lendamba et al., 2022
3	Clindamycin	Vaginosis	Pregnant women	Shunobu Murakami et al., 2020
4	Ciprofloxacin	Meningitis	Newborn	S. G. Kersin, et al., 2020
5	Moxifloxacin + doxycycline	Intraventricular hemorrhage	Newborn	K. M. Watt, et al., 2012
6	Moxifloxacin	Meningoencephalitis	Newborn	J. G. Wildenbeest et al., 2016
7	Gentamicin	Meningitis	Newborn	Jaweed Ahmed, et al., 2021
8	Azithromycin + doxycycline; Ciprofloxacin+ doxycycline	Meningitis	Newborn	F. Scaggs Huang, et al., 2019
9	Moxifloxacin + doxycycline	Meningitis Meningitis	Newborn	Quoting from Scaggs Huang. et al., 2019
10	Gentamicin	Meningitis	Newborn	Quoting from F. Scaggs Huang6 et al., 2019

11	Moxifloxacin + doxycycline	Meningitis	Newborn	Najmus Shehretal et al., 2021
12	Azithromycin	Meningitis	Newborn	Guanglu Che et al., 2023

A number of authors note that tetracyclines and fluoroquinolones can be used in newborns without obvious toxicity, even for a long time (up to 6 weeks) [11, 12], although this point of view requires confirmation by conducting special studies to identify side and undesirable reactions of these antibiotics.

According to some authors, the use of moxifloxacin in newborns with menigitis caused by *M. hominis* is promising [12, 13, 14]. This is due to the bactericidal effect of the antibiotic and its ability to concentrate in the CSF. A study of the pharmacokinetics of this antibiotic in a newborn with a birth weight of 813 g and a gestational age of 26 weeks showed the following results. The maximum concentration in the blood serum after intravenous administration of 5 mg/kg (at the time of initiation of treatment with moxifloxacin, body weight was 1164 g) was 1.7 mg/l, which was 27 times higher than the minimum inhibitory concentration for the pathogen (MIC), and 22 hours after the end of the infusion, the concentration was 0.18 mg/l, which was 2.9 times higher than the MIC. The authors noted that pharmacokinetics in newborns differed significantly from those in adults. The monotherapy with moxifloxacin was effective [13].

It should be noted that there is currently no consensus on optimal antibiotic therapy (antibiotic options and duration of treatment) for *M. hominis* meningitis in newborns due to the relative rarity of this disease [10, 11, 12, 13, 15]. Current recommendations are based on clinical experience and in vitro susceptibility testing results [12].

It must be said that some authors have reported the cure of a mild form of *M. hominis* infection without antibacterial treatment [7]. This may be due to the use of immunomodulatory or immunoreplacement therapy (for example, intravenous immunoglobulins), as well as the activation of one's own immune system under the influence of the pathogen.

Thus, despite the low incidence of *M. hominis* meningitis in newborns, this disease remains problematic due to complex diagnosis and treatment, which require further study and development of recommendations for practitioners.

Conclusion

1) To date, the fastest and most affordable method for detecting *M. hominis* in biofluids, including in the cerebrospinal fluid of infants with meningitis, is PCR with primers for *mycoplasma* 16S rRNA genes. The cultural method also retains its importance.
2) As a rule, *M. hominis* retains sensitivity to moxifloxacin and tetracycline series now. However, given the wide variety of the spectrum of *M. hominis* resistance to antibiotics and the lack of consensus on recommendations for antibacterial therapy of *M. hominis* neonatal meningitis, it is advisable to prescribe empirical treatment based on the sensitivity of the pathogen in the region and targeted therapy based on laboratory results.

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