Unveiling and understanding omphalitis: An obscure orphan disease in new-borns



Purva Godambe[1] , Savita Yadav[2] , Vividha Dhapte-Pawar[1,3] *

[1]Department of Industrial Pharmacy, Bharati Vidyapeeth (Deemed to be University), Poona College of Pharmacy, Erandwane, Pune 411038, Maharashtra
[2]Department of Pharmaceutical Chemistry, Bharati Vidyapeeth (Deemed to be University), Poona College of Pharmacy, Erandwane, Pune 411038, Maharashtra
[3]Department of Pharmaceutics, Bharati Vidyapeeth (Deemed to be University), Poona College of Pharmacy, Erandwane, Pune 411038, Maharashtra
Email: vividhadhapte@gmail.com

Abstract

Omphalitis is a serious infection of the umbilical cord stump, often caused by Staphylococcus aureus and other bacteria, leading to complications such as necrotizing fasciitis. This review highlights the etiology, and diagnostic approaches associated with omphalitis, with a particular focus on Staphylococcus aureus infections. Clinical cases from different countries illustrate variability in management of omphalitis. Additionally, insights into the potential use of umbilical cord blood stem cells as a future therapeutic approach are discussed, suggesting approach for personalized medicine.

Keywords: omphalitis, umbilical cord, bacteria, infants, clinical trial

1. Introduction

The umbilical cord is a tube-like structure that joins the newborn to the placenta of the mother (1). There are two methods for clamping the foetal cord: the standard (traditional method) and the delay clamping method. This procedure is performed within 30 to 60 seconds after birth. There are more benefits of delayed clamping. This reduces the risk of postpartum hemorrhage, enhances iron circulation, increases red blood cell volume, and helps regulate haemoglobin levels (2). After birth, the umbilical cord stump dries and falls off in 5-15 days. World Health Organization (WHO) states that care of dry cord for neonates is essential, due to rise in infections related to umbilical cord (3).

Omphalitis is a rare but severe postpartum localised infection of the umbilical cord stump and periumbilical soft tissue that occurs during the gestation period (4). If treated late, neonatal mortality rates from this illness could vary from 7% to 15% (5). According to a case report, periumbilical necrotizing fasciitis (NF) can result from neonatal omphalitis. The soft tissues of muscle fascia are primarily infected by bacteria. Compared to developing nations, developed nations have considerably better prediction statistics for NF bacterial infections. Despite therapy and prediction, the mortality rate is relatively high. Consequently, it is a rare infection that draws late attention from physicians (6).

2. Normal vs infected umbilical cord

The length of normal umbilical cord is approximately 55 cm in size. It gradually dries up and falls off in 3 weeks. Small mark of belly button is left behind. Infected neonatal umbilical cord is caused due to bacterial infection. Two factors create highly favourable milieu in necrotic tissues for bacteria to grow: (i) a typical spontaneous vaginal delivery; and (ii) the environment and treatment after delivery (4).

3. Etiology

Bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* are the root causes of omphalitis (7,8). *Bacteroides fragilis*, *Clostridium perfringens*, *Clostridium tetani*, and other facultative, anaerobic bacteria may sometimes be the cause of infection. Omphalitis and NF infections can potentially be caused by indirect maternal infection (chorioamnionitis)(9).Other factors include premature leakage of amniotic fluid, umbilical catheterization as well as home birth delivery still prevalent in underdeveloped countries. Cases of omphalitis may progress to umbilical melanoma owing to delayed or false diagnosis (10).

4. Signs-symptoms and diagnosis

Discoloration of skin or red patches surfaces as primary symptoms to infections usually observed for visual diagnosis of omphalitis. Thick peri-umbilical skin with fluid-leaky umbilical stump with foul odour is one of the distinguishing symptoms. Usually, it is observed that infants cry when the umbilical stump or skin around it is touched (9). Other symptoms like lethargy and high fever are also observed (10). Infection may be transfered from mother to child before birth or during delivery. This is due to various bacteria situated in vagina during gestational period, premature birth, infection in placenta, etc. Also, bacterial infection might spread around umbilical cord stump due to use of medical equipment like catheters, after birth. Detailed evaluation and confirmatory tests of neonatal sepsis are performed using tests as depicted in Figure 1.

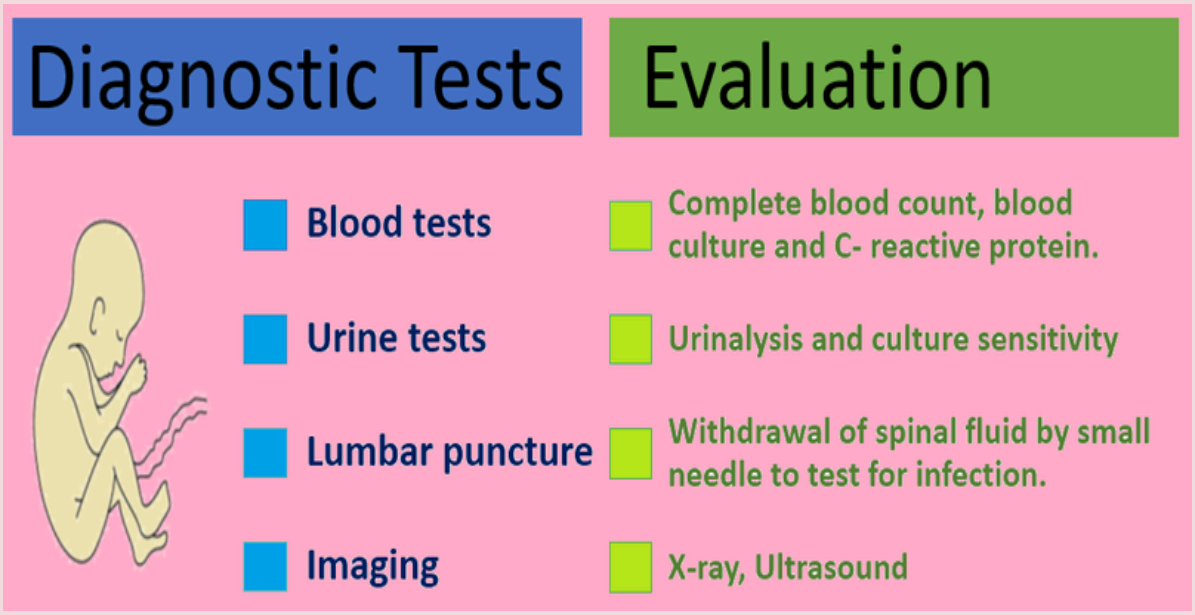

Figure 1. Diagnostic evaluation tests for Omphalitis and NF infections

5. Treatment

If umbilical infection is observed in infants, hospitalization in a tertiary health institution is necessary for treatment (4). Antibiotics like ampicillin, cloxacillin, gentamicin, amikacin, cefotaxime, vancomycin and imipenem are mostly prescribed; yet, employing their judicious therapeutic regimen is challenging. Also, these may cause high antibiotic resistance to isolated organisms. The primary cause of omphalitis is usually Staphylococcus aureus, which is fairly responsive to drugs like imipenem and cefotaxime. For omphalitis, combination antibiotic therapy is therefore highly recommended in order to minimise antimicrobial resistance (11). For sepsis treatment, antiseptic agents are used as it has bactericidal and bacteriostatic properties. Chlorhexidine known for its antiseptic property is recommended in safe concentrations. It strongly binds to negatively charged cell wall of microorganisms and alters the osmotic balance of the causative pathogen (12). Broad-spectrum applications for methylated spirit include bactericidal, mycobacterial, fungicidal, and viricidal effects. It causes lipid coagulation, denatures the protein, impairs cellular metabolism, and ultimately kills microorganisms (13).Thus, both chlorhexidine and methylated spirit can be used in the treatment of omphalitis and NF. Researchers and healthcare experts recommend parental education, awareness following treatment and discharge to lower the rate of morbidities, and ultimately decrease mortality (14). Few questions about the hand washing habits of birth assistants, clean delivery kits, skincare routines, mother-infant contacts, and use of various other applications like mustard oil, ash, mud, antiseptics as they are used in home-based deliveries were observed when data on risk factors for omphalitis was collected from Nepal (15).

6. Clinical trials in different countries

An estimated 3.7 million new-born deaths annually are attributed to various infections (3). Tokyo medical professionals described a case involving a 6-day-old female new born. Her umbilical cord was seen to be dry, black in colour, with redness and swelling surrounding it without pus. After a number of laboratory tests, omphalitis was identified. Thus, intravenous cefotaxime and vancomycin treatment were initiated. A variety of cultures of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and Entero bacteriaceae were used to examine the peri-umbilical swab and blood sample. Swelling around the abdomen appeared to be expanding. Consequently, meropenem was used instead of antibiotics in treatment. With hypotensive shock and hypothermia, the condition of the new-born worsened. NF was confirmed by computed tomography (CT). The area of perfusion was assessed intravenously using indocyanine green. Necrotic skin was surgically treated. Physicians handled the case of omphalitis with surgery followed by apt treatment of antibiotics. The case report highlights the need for physicians as well as pharmacists to be knowledgeable about the risk factors and possibility of getting NF (6). Different countries have already conducted clinical trials for omphalitis as exhibited in the tabulated data represented in Table 1.

Table 1. Data on clinical trials for omphalitis cases

Country	Clinical study type	Etiology	Outcomes	Ref
Nepal	Cluster-randomized study (Community based trial)		• Cord care is divided into two types i.e. use of 4% chlorhexidine cleaning and other by soap-water or dry cord care. • These cares reflected the umbilical cord separation time in infants. • As per clinical study, cord separation duration was less for dry cord care / soap-water (4.25 days) compared to chlorhexidine (5.32 days).	(16)

Western Uganda	Cross-sectional study (Hospital-based trial)	*Staphylococcal aureus, Neisseria species E. coli Proteus species, Klebsiella species, Citrobacter species, Haemophilus species*	• Study was conducted in a hospital of western Uganda in which neonates with omphalitis infection were selected and clinical diagnosis was carried out. • Umbilical cord swab was assessed for etiology. • *Staphylococcal aureus* was primary reason to omphalitis infection. • Isolated species were resistant to ampicillin, gentamicin and cloxacillin antibiotics.	(11)
Eastern Turkey	Survey in department of paediatrics	*Staphylococcus aureus, Escherichia coli*	• The survey stated that nearly 7.7% cases occurred every year in hospital born neonates. Highest morbidity rate was reported to be 15%. • Infection increases with septic delivery (home delivery). • Clinical reports of WBC and neutrophil count in blood were in normal limits. • Pathological test reveal that *Staphylococcus aureus* was the most common microorganism detected. • Also, physicians concluded that aseptic delivery technique should be adapted with all the basic care of umbilical cord. • Antibiotic therapy was advised if infection was confirmed, in addition to umbilical stump care using alcohol, chlorhexidine, and hexachlorophene	(17)
North-Central Nigeria	A Randomized study (Non-inferiority Trial)		• A comparative analysis of 96% methylated spirit and an antiseptic agent with 4% chlorhexidine was done during 28 days trial. • 96% methylated spirit showed more effect than chlorhexidine. • It reported that 4% chlorhexidine showed the peri-umbilical cord acne (lesions with pus). • Thus, methylated spirit is more effective, safe, tolerable and cost effective than chlorhexidine in preventing omphalitis infection.	(13)
Pakistan	Community-based (cohort study)	*Staphylococcus aureus, Pseudomonas species, Aeromonas species, Klebsiella species*	• Infection cause due to *Staphylococcus aureus* species. • Preventive measures are required with proper diagnosis, proper medication. • This will eventually decrease the rate of neonatal mortality due to NF and omphalitis. • Use of chlorhexidine gels can help to avoid infections.	(18)

7. Future omphalitis therapy: Advancing stem cell therapies

Self-renewal and the capacity to develop into a particular adult cell type are the two distinct features that define stem cells. Pluripotent and multipotent stem cells are the two different types of stem cells. Pluripotent stem cells can develop into any type of adult cell; exists for a short period of time. Additionally, the cells differentiate further into strong tissues and cell lines. Pluripotent cells can therefore, develop into any type of multipotent stem cell. Researchers discovered that various diseases are treated by multipotent stem cells (19). Hematopoietic stem cells are multipotent stem cells found in umbilical cord blood. These can be transplanted for treatment of malignant and non-malignant disorders along with hematologic, immunologic and inherited metabolic disorders. As umbilical cord blood, high in CD34+ is widely used in immunotherapy (20). Therefore, transplanting hematopoietic stem cells is thought to be a form of therapy for treating omphalitis and NF.

The placenta and umbilical cord are discarded when neonates are born. However, blood remaining in the umbilical cord is extracted, examined and kept in a cord bank for future use in order to preserve stem cells. Many public and private umbilical cord blood banks are situated worldwide to get benefit of it. Cryopreservation is a technique in which the umbilical blood is stored in liquid nitrogen (−196°C) (21,22). Generally private and public cord banks are associated with storage of cord blood. Public cord banks of India are as follow:

- The Reliance Dhirubhai Ambani Life Sciences Center in Thane, Maharashtra
- Jeevan Stem Cell Bank, Tamil Nadu
- The School of Tropical Medicine (STM), Kolkata
- StemCyte Inc., Apollo Hospital Enterprises Ltd.

Thus, umbilical cord blood-derived hematopoietic stem cells exhibit considerable potential in omphalitis and NF treatment.

8. Conclusion

Omphalitis is a rare neonatal infection, often caused by *Staphylococcus aureus*, which can lead to severe complications such as necrotizing fasciitis. Understanding its etiology, diverse clinical presentations, and diagnostic approaches is crucial for effective management and timely treatment. Clinical cases from different regions highlight the global impact of omphalitis and the variability in treatment strategies. Furthermore, exploring the potential use of umbilical cord blood stem cells as a future therapeutic option offers promising prospects for personalized medicine in addressing omphalitis-related complications. Continued research and clinical efforts are necessary to improve outcomes and reduce the burden of this orphan disease.

References

1. Benirschke K. The umbilical cord. NeoReviews. 2004;5(4):e134–41.
2. American College of Obstetricians and Gynecologists, Committee on Obstetric Practice. Delayed umbilical cord clamping after birth: ACOG Committee Opinion, Number 814. Obstet Gynecol. 2020;136(6):e100–6.
3. Mullany LC, El Arifeen S, Winch PJ, Shah R, Mannan I, Rahman SM, et al. Impact of 4.0% chlorhexidine cleansing of the umbilical cord on mortality and omphalitis among newborns of Sylhet, Bangladesh: design of a community-based cluster randomized trial. BMC Pediatr. 2009;9:1–9.
4. Sawardekar KP. Changing spectrum of neonatal omphalitis. Pediatr Infect Dis J. 2004;23(1):22–6.
5. Güvenç H, Aygün D, Yaşar F, Şoylu F, Güvenç M, Kocabay K. Omphalitis in term and preterm appropriate for gestational age and small for gestational age infants. J Trop Pediatr. 1997;43(6):368–72.
6. Sato J, Yotani N, Shoji K, Mori T, Fujino A, Hikosaka M, et al. Necrotizing fasciitis following rapidly deteriorating neonatal omphalitis with good initial presentation. IDCases. 2023;32:e01750.
7. Airede AI. Pathogens in neonatalomphalitis. J Trop Pediatr. 1992;38(3):129–31.
8. Celebi Celik F, Tuzun F, Duman N, Keskinoglu P, Kumral A, Ozkan H. Current factors affecting the risk of omphalitis in newborns: A prospective case-control study. Int J Clin Pract. 2021;75(5):e14071.
9. Brook I. Cutaneous and subcutaneous infections in newborns due to anaerobic bacteria. 2002;
10. Song Y, Xu D, Sun L, Ding K, Hu Y, Yuan Y. Diagnosis and management of primary umbilical melanoma with omphalitis features. Case Rep Oncol. 2013;6(1):154–7.
11. Turyasiima M, Nduwimana M, Kiconco G, Egesa WI, Manuel SA, Kalubi P, et al. Bacteriology and antibiotic susceptibility patterns among neonates diagnosed of omphalitis at a tertiary special care baby unit in western uganda. Int J Pediatr. 2020;2020.
12. Matthijs S, Adriaens P. Chlorhexidine varnishes: a review. J Clin Periodontol. 2002;29(1):1–8.
13. Shwe D, Afolaranmi T, Egbodo C, Musa J, Oguche S, Bode-Thomas F. Methylated spirit versus chlorhexidine gel: A randomized non-inferiority trial for prevention of neonatal umbilical cord infection in Jos, North-Central Nigeria. Niger J Clin Pract. 2021;24(5):762–9.
14. Stewart D, Benitz W. Umbilical cord care in the newborn infant. Pediatrics. 2016;138(3).
15. Mullany LC, Darmstadt GL, Katz J, Khatry SK, LeClerq SC, Adhikari RK, et al. Risk factors for umbilical cord infection among newborns of southern Nepal. Am J Epidemiol. 2007;165(2):203–11.
16. Mullany LC, Darmstadt GL, Khatry SK, LeClerq SC, Katz J, Tielsch JM. Impact of umbilical cord cleansing with 4.0% chlorhexidine on time to cord separation among newborns in southern Nepal: a cluster-randomized, community-based trial. Pediatrics. 2006;118(5):1864–71.
17. Güvenç Hüs, Güvenç Müz, Yenioglu H, Ayata A, Kocabay K, Bektasl S. Neonatal omphalitis is still common in eastern Turkey. Scand J Infect Dis. 1991;23(5):613–6.
18. Mir F, Tikmani SS, Shakoor S, Warraich HJ, Sultana S, Ali SA, et al. Incidence and etiology of omphalitis in Pakistan: a community-based cohort study. J Infect Dev Ctries. 2011;5(12):828–33.
19. Biehl JK, Russell B. Introduction to stem cell therapy. J Cardiovasc Nurs. 2009;24(2):98–103.
20. Gupta AO, Wagner JE. Umbilical cord blood transplants: current status and evolving therapies. Front Pediatr. 2020;8:570282.
21. Chen G, Yue A, Ruan Z, Yin Y, Wang R, Ren Y, et al. Comparison of the effects of different cryoprotectants on stem cells from umbilical cord blood. Stem Cells Int. 2016;2016.
22. Devi S, Bongale AM, Tefera MA, Dixit P, Bhanap P. Fresh Umbilical Cord Blood—A Source of Multipotent Stem Cells, Collection, Banking, Cryopreservation, and Ethical Concerns. Life. 2023;13(9):1794.