Clostridium tetani infections in newborn infants: a tetanus *neonatorum* review

Infecção por Clostridium tetani no recém-nascido: revisão sobre o tétano neonatorum

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ABSTRACT

Although tetanus is a preventable disease by vaccination, it continues to claim lives around the world. Whereas cases of accidental origin reflect insufficient population immunization, tetanus *neonatorum* reveals a double-nature fault—poor vaccination coverage of adults coupled with difficulties accessing appropriate prenatal care; this situation is aggravated by the extreme severity of tetanus in this age group in which the mortality rate can reach up to 80%. The early detection of tetanus in neonates is essential for immediately initiating the proper therapy. Therefore, although reaching an early diagnosis of tetanus is important, the most relevant aspect is related to the appropriate management and prophylaxis of this disease. Consequently, the aim of this article is to review *neonatorum* tetanus with an emphasis on its therapy and prevention.

Keywords: *Clostridium tetani;* Tetanus/prevention & control; Infant, newborn

INTRODUCTION

"Spasms after a wound are fatal".
Hippocrates of Cos

Tetanus is an acute infectious, non-contagious disease[1] that is triggered by the action of neurotoxins - in particular, tetanospasmin - that are produced by the gram-positive bacillus *Clostridium tetani,*[2,3] an anaerobic spore-forming bacterium. *C. tetani* is found throughout the environment[3,4] (e.g., in sand, dust, tree branches, bushes, putrid water, agriculture tools, animal or human stools), its multiplication is boosted by oxi-reductive substances,[2,3] and the bacteria can contaminate wounds.[4] Under ideal conditions, the spores can transform into a vegetative form that produces tetanospasmin. Another toxin that is produced by this bacillus is tetanolysin; however, based on our current knowledge, tetanolysin is not related to any of the clinical features of tetanus.[3]

In immunocompromised subjects, tetanus toxin can block inhibitory neurons, causing muscle hypertonia, hyperreflexia and muscle spasms; however, the patient remains lucid. Similarly, the toxin acts at the level of the preganglionic nerves, causing sympathetic hyperexcitability, increased circulating catecholamine levels, thereby leading to dysautonomia and consequent systemic blood pressure instability, heart arrhythmias, diaphoresis and hyperthermia.[2,3] In newborn infants, this disease manifests between three and 12 days after birth as progressively impaired feeding (e.g., sucking and

swallowing), thus resulting in hunger and inconsolable crying. In addition, the disease is characterized by palsy or reduced movements, touch hypertonia and spasms with or without opisthotonus.[2,3,5]

Tetanus is an immunopreventable, yet potentially, lethal disease. Its diagnosis is based fundamentally on clinical criteria, and a positive prognosis depends on both establishing an early diagnosis and providing adequate therapy. The control and eradication of tetanus can be achieved using relatively simple measures such as population education and vaccination. Vaccination of potential childbearing or pregnant women (during their prenatal care) is the best preventive strategy against tetanus *neonatorum*.[1,6-8]

In light of these considerations, the aims of this manuscript are to revise the ethiopathogenic, clinical, therapeutic and epidemiological aspects of the disease and to improve the control of neonatal tetanus.

Clostridium tetani

This pathogenic agent is a gram-positive, obligate anaerobic toxin-producing bacillus that measures approximately four microns in length. Its spore is described as having a tennis racket shape[2] and can be found in soil[3], animal stools (both human and non-human), putrid water and unsterilized surgical instruments. The spores are highly resistant to many agents, including disinfecting substances, and can survive for years. The vegetative forms are easily inactivated and susceptible to various antimicrobial compounds; however, these forms are responsible for the production of tetanospasmin,[2] the toxin that causes tetanus symptoms.[3]

PATHOGENESIS

Because of the ubiquitous environmental presence of tetanus bacilli, its contamination in wounds or the umbilical cord stump is relatively common. The organism's transformation into the vegetative form and its production of toxins requires proper conditions, including anaerobic conditions and the presence of substances with low oxi-reduction potential. Indeed, the disease can only occur in this context, which is often observed in wounds with devitalized or necrotic tissues, in the presence of foreign bodies or an infection by other organisms.[2] The toxin is released into the wound and reaches peripheral motor neuron terminals, where it progresses via the axons to the central nervous system, spinal cord and brainstem. The toxin crosses the synaptic terminals to reach the pre-synaptic membrane, where it blocks the release of the inhibitory neurotransmitters glycine and gamma-amino butyric acid (GABA). The firing rate of resting motor neurons is increased, thereby causing hyperreflexia and muscle spasms. Similarly, the inhibition of pre-ganglionic sympathetic neurons inhibition may be lost, thereby leading to sympathetic hyperexcitability and high levels of circulating catecholamines, contributing to dysautonomia.[3,5]

In generalized tetanus, the toxin reaches the blood and lymph and is then disseminated to other nerve terminals. Shorter nerves are affected first, thus explaining the sequential involvement of the head, trunk and finally the extremities. In the localized and cephalic forms of tetanus, only a select number of nerves are affected, resulting in localized muscle spasms.[2,5]

CLINICAL FEATURES

Tetanus *neonatorum* occurs in the umbilical cord stump and results from non-aseptic conditions and handling. In remote regions of Brazil, the popular names of the disease can be roughly translated into English as "seven-day evil" or "navel disease".[7,9] Home birth is still common in these regions, and a number of substances are often applied to the umbilical cord stump, including dust, coffee powder and spider webs, all of which are believed to promote healing or are used as part of a deeply rooted ritual.[9,10] In addition, shortcomings in the vaccination program (including vaccinations for pregnant women) and in prenatal care culminate in illness in the neonatal child. The clinical features of tetanus *neonatorum* manifest after a 5–13-day incubation time and begin as difficulty feeding from the breast due to an inability to suck, progressing to trismus and an inability to swallow. Subsequently, hypertonia, opisthotonus and generalized spasms occur. Table 1 summarizes Bazin's[10] categorization of tetanus *neonatorum*. Tetanus *neonatorum* is an extremely severe disease with a mortality rate that can exceed 90% without adequate therapy. Death is usually due to a perturbed hydro-electrolytic balance or asphyxia and can occur even with adequate therapy; in the case of adequate therapy, hemodynamic instability is a common cause of death.[9]

Incubation is the time that passes from germ implantation (e.g., in a wound) until the first clinical signs and symptoms and averages seven days, although it can last from 5 to 15 days after infection with *C. tetani.*[2,3] Another factor that is vital for managing the patient is the progression of time, which includes the time period between the first signs and the onset of generalized spasms.

Table 1 – Categorization of therapy and prognosis

Score	Age	Progression time	Type of spasm
5 (five)	< 7 days	< 12 hours	Frequent or sub-penetrant, high intensity, long-lasting, apnea.
3 (three)	7–10 days	12–24 hours	Strong, frequent, short induration, spontaneous or stimulus-elicited.
2 (two)	> 10 day	> 24 hours	Absent or weak, short in duration, usually elicited by stimuli.

Categorization: moderate tetanus – total score 6; severe tetanus – total score 7–10; very severe tetanus – total score above 10.

Source: Bazin AR. Estudo clínico e anatomopatológico do tétano neonatal no Estado do Rio de Janeiro [tese]. Rio de Janeiro: Faculdade de Medicina da Universidade Federal do Rio de Janeiro; 1976.[10]

A shorter incubation and progression time correlates with a more severe disease course.[2,3] Lastly, this disease provides no immunity to the host.[1]

DIAGNOSIS

A diagnosis of tetanus *neonatorum* is based on clinical findings, including muscle stiffness and painful muscle spasms.[9] The presence of a causative agent does not confirm the diagnosis, nor does its absence preclude a diagnosis in patients who manifest the clinical features of tetanus. Cultures of material from the infective focus or blood cultures have no diagnostic value.[2]

In the differential diagnosis of tetanus *neonatorum*, one should consider an adverse drug effect (e.g., to metoclopramide), a metabolic or hydro-electrolytic disorder (e.g., hypocalcemia), labor-acquired neurological injury and meningoencephalitis.[2,11,12]

THERAPY

The therapeutic targets should include the following: a) neutralization of circulating (i.e., not bound to receptors) toxins; b) the elimination of the toxin-producing source (i.e., the vegetative *C. tetani* forms); and in particular, c) management of clinical features using ventilation, nutrition and hemodynamic support in addition to treatment of muscle spasms.[6,10-13]

Neutralizing toxin activity

Unbound tetanus toxin can be found in organ fluids, in particular, in blood and tissues surrounding the wound. For neutralization purposes, heterologous anti-tetanus serum (ATS) or hyperimmune human tetanus immunoglobulin (TIG) should be administered as soon as possible, ideally before the tetanus toxin has begun its axonal migration toward the spinal cord, after which neutralization is no longer possible. There is no apparent difference in clinical effectiveness between ATS and TIG. TIG is able to maintain serum levels longer, whereas ATS requires previous sensitivity testing due to the risk of developing a heterologous serum reaction. Although the reported doses that can be used vary in the medical literature,[2,5,14-16] the Brazilian Ministry of Health recommends the following doses: ATS, between 10,000 and 20,000 IU given intravenously; TIG, between 1,000 and 3,000 IU given intramuscularly, with the dose divided into two different muscle masses. Currently, intrathecal TIG administration is not generally recommended.[1,17]

Elimination of the toxin-producing source

Although surgical debridement and the removal of foreign bodies from wounds that are infected with *C. tetani* are essential for post-neonatal disease control, removing the umbilical cord stump is not recommended in neonatal tetanus. However, the following regimens are recommended: 1) rigorous cleansing of the umbilical stump and 2) systemic antibiotic therapy.[1] The drugs of choice are penicillin G or metronidazole, both of which are given intravenously.[1,5,14,16,18] Alternatively, oral cephalexin and erythromycin can be administered, particularly in less severe cases.[1,19]

Management of clinical features

The most important treatment aspect is assuring survival until the toxin is released from their receptors in the cells; the objectives are to maintain vital functions and nutrition and to prevent associated infections.[2,5]

Considering the disease's severity and high lethality rate, admission to an intensive care unit is recommended. In addition to the spasms that are typical of the disease, a newborn with neonatal tetanus can experience instability of several organ systems and may also experience respiratory failure, hemodynamic changes, sympathetic hyperactivity and heart arrhythmias; this combination can cause a hypercatabolic state with high potential for sequelae and even death. Some intensive care units report survival rates above 90%, whereas treatment outside of an intensive care unit carries a survival rate of 20–50%.[20,21] The newborn should receive minimal handling and should be kept in a quiet environment with low ambient light, as stimuli can trigger muscle spasms. Coordination

between the medical, nursing and physiotherapy teams—as well as other healthcare professionals—is recommended for providing both fast and effective patient care. Hydroelectrolytic and acid-base disorders should be controlled and corrected, and supplying appropriate nutrition is essential.[2,5]

Muscle spasms are controlled by an intravenous infusion of benzodiazepines, as these compounds provide anxiolytic, sedative and muscle-relaxing properties. A continuous midazolam infusion at doses of up to 6–8 mcg/kg/minute and diazepam at 0.3–2.0 mg/kg/minute are the most commonly used drugs, and their doses should be titrated based on the clinical response of the patient.[1,2,5,22] Muscle spasms are extremely painful; therefore, analgesic drugs should always be administered, with fentanyl as a good option. In cases in which benzodiazepines and analgesics fail to resolve the spasms, the patient must be curarized with pancuronium or vecuronium; in this case, the patient must already be ventilated mechanically.[1,23]

EPIDEMIOLOGY

Tetanus *neonatorum* is a cosmopolitan disease that affects newborn babies of both genders [1,14] and has both varying incidences worldwide and high lethality; the disease is more prevalent in regions with precarious health conditions and serious social and economic problems, thus preventing the dissemination of correct information and access to adequate healthcare services.[15]

In Brazil, the number of confirmed tetanus *neonatorum* cases has recently dropped significantly. In fact, compared with the past decade, the incidence of tetanus *neonatorum* has dropped by 89.0%, and the current lethality rate is 43.7%.[24,25] The risk factors for tetanus *neonatorum* are shown in table 2.

The use of vaccinations has significantly contributed to the reduction in the incidence of this disease. In the United States, the few cases that occur are related to unvaccinated or inappropriately vaccinated individuals or to elderly persons who failed to receive a booster vaccine within the appropriate interval. This situation is also observed in Europe.[26] Conversely, in developing countries, tetanus continues to affect elderly persons, young adults, newborn infants and children, thereby reflecting ineffective vaccination regimens and difficulties in accessing adequate healthcare services.[12]

PROPHYLAXIS AND CONTROL

Although there has been considerable progress toward the eradication of tetanus *neonatorum*, the World Health Organization (WHO) estimates that approximately 60,000 deaths could be ascribed to this disease in 2008, with more than half of these cases occurring in Africa.[27] Nations that have eradicated tetanus *neonatorum* used relatively simple strategies, such as improving their primary immunization regimens and providing appropriate care during delivery, including training traditional midwives, vaccinating pregnant women and using surveillance systems to track reports of tetanus *neonatorum*.[27-33]

The official data from the Brazilian Ministry of Health show a decrease of 89.0% in the incidence of tetanus *neonatorum* compared with the past decade, and this decrease is predominantly in the northern and northeastern regions, with no new cases reported in the central-western region since 2005.[24,25]

The eradication of tetanus *neonatorum* is feasible and depends on education and immunization measures; therefore, political willingness at various levels within the Brazilian Healthcare System (SUS) and the implementation of prevention and education measures—as appropriate for any society—are needed.[34,35] Indeed, tetanus *neonatorum* can occur in babies of mothers without sufficient levels of circulating antibodies, which would have been able to confer passive protection. Therefore, the most important form of prevention is through the

Table 2 – Risk factors for tetanus *neonatorum*

1) Low anti-tetanus vaccination coverage in potential childbearing women;
2) Home birth assisted by a traditional midwife or other non-capacitated provider without appropriate tools and personnel;
3) Inappropriate prenatal care (and/or poorly qualified caregivers) in remote areas;
4) Early hospital discharge and insufficient infant and mother postpartum follow-up;
5) Insufficient hygienic care of the umbilical cord stump and the newborn;
6) Low maternal education level;
7) Low family social and economic levels;
8) No access to health education.

Source: Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Guia de vigilância epidemiológica. 7a ed. Brasília: Ministério da Saúde; 2009. Tétano neonatal. Caderno 4. p. 27-36. Disponível em: http://portal.saude.gov.br/portal/arquivos/pdf/gve_7ed_web_atual.pdf.[1]

vaccination of potential childbearing women and pregnant women; the vaccination schedule should be updated or initiated during prenatal care using tetanus toxoid, a low-cost and effective measure.[1,8,36] Table 3 shows the basic immunization schedule that was proposed by the Brazilian Ministry of Health and the Brazilian Pediatrics Society. The addition of vaccinations and appropriate prenatal care to prevent tetanus *neonatorum* is possible based on the health education measures[1] that are summarized in tables 4 and 5.

From an epidemiologic standpoint, the control of an immunopreventable disease is usually achieved

Table 3 – Basic immunization schedule – Brazilian Ministry of Health and Sociedade Brasileira de Pediatria (2011)

Children	For children under six years of age: DPT, consisting of tetanus toxoid, diphtheria toxoid and *pertussis* component. Should be given as three initial doses at 4–8-week intervals, with at least one month between doses. Ideally, the doses should be given at the ages of two, four and six months. Two booster doses should be given, with the first at the age of 15 months and the second between the ages of four and six years.
Adolescents	For adolescents who previously received three or more doses of DPT, DT or dT, give one booster dose.
Remarks	In children older than six years of age, adolescents or adult patients, adult double vaccine is given (dT). The minimal inter-dose interval is 30 days. Booster doses should be given at 10-year intervals. In case of severe wounds, administer a booster dose within five years of the last dose.

DPT – triple bacterial vaccine (diphtheria, pertussis and tetanus; DT – double infantile vaccine; dT – double adult vaccine.

Sources: Sociedade Brasileira de Pediatria. Departamento de Infectologia. Calendário vacinal: manual 2011/2012. Rio de Janeiro: Sociedade Brasileira de Pediatria; 2011 [atualizado 2011; citado 2011 Out 19]. Disponível em: http://www.sbp.com.br/pdfs/calendario_vacinal_SBP2011.pdf. [41]

Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Ações Programáticas Estratégias. Caderneta de saúde da criança. 7a ed. Brasília: Ministério da Saúde; 2011.[42]

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Table 4 – Measures that are considered essential for tetanus *neonatorum* prophylaxis and control

Health education and communication actions	Publish preventive measures using expressions such as "umbilical tetanus", "navel evil" or "seven-days-evil" (the latter two expression are approximate English translations of popular Brazilian expressions) to provide clear communication to the general population.[9,44]
Prenatal care	Appropriate assessment of the vaccine status, guidance of aseptic delivery, breastfeeding, family planning and hygienic care of the newborn and the umbilical cord stump in particular. There is a direct relationship between partum and postpartum care and neonatal tetanus.[1,39,40]
Vaccination	Full dT schedules vaccinations for every potential childbearing woman—whether pregnant or not—between 12 and 49 years of age; for indigent women, the potential childbearing age should be considered between 10 and 49 years; the Pan-American Health Organization (PAHO) considers this age to be between 15 and 49 years; pregnant women who have not begun the schedule should be started as soon as possible. Immunity is provided to the newborn infant by appropriate maternal immunization with at least two doses. Children from mothers who were vaccinated with three doses within the past five years have transient passive immunity until two months of life (Table 5). Passive immunity via anti-tetanus serum (ATS) and human anti-tetanus immunoglobulin (HATIG) persist an average of two and three weeks, respectively.[1,39]
Birth care	Delivery under rigorous aseptic techniques with the use of sterilized tools and aseptic dressing of the umbilical cord stump.[10]
Postpartum care	Education for health and the use of sterile materials for the care of the umbilical cord and stump. Mothers and responsible persons should be educated at all opportunities regarding the care of the newborn infant and hygienic care of the umbilical stump using 70%. Postpartum consultations provide unique opportunities for the education and detection of disease-predisposing practices and for updating the vaccine calendar for both the mother and child.[1]

Source: Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Guia de vigilância epidemiológica. 7a ed. Brasília: Ministério da Saúde; 2009. Tétano neonatal. Caderno 4. p. 27-36. Disponível em: http://portal.saude.gov.br/portal/arquivos/pdf/gve_7ed_web_atual.pdf.[1]

Table 5 – Immunization schedule for potential childbearing women

History of previous vaccination against tetanus	Potential childbearing women	
	Pregnant*	Non-pregnant
No recorded dose	Start the vaccination schedule as soon as possible with three doses, with 30–60-day intervals	Vaccine schedule of three doses with 30–60-day intervals
Fewer than three recorded doses	Complete the three doses as soon as possible at 30–60-day intervals	Complete the three doses with 30–60-day intervals
Three or more doses, with the last dose less than five years ago	No vaccination required	No vaccination required
Three or more doses, with the last dose 5–10 years ago	One booster dose	No vaccination required
Three or more doses, with the last dose more than 10 years ago	One booster dose	One booster dose

*If vaccination is started late, the second dT (double adult) vaccination dose should be given up to 20 days before the anticipated date of birth; this time is necessary for the formation of antibodies and their placental transference to the fetus (passive immunization). In this case, the third dose should be scheduled for after the delivery.

Sources: Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Guia de vigilância epidemiológica. 7a ed. Brasília: Ministério da Saúde; 2009. Tétano neonatal. Caderno 4. p. 27-36. Disponível em: http://portal.saude.gov.br/portal/arquivos/pdf/gve_7ed_web_atual.pdf.[1]

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by providing vaccination coverage to 70–80% of the susceptible population. In the context of tetanus *neonatorum*, strategies to increase vaccination coverage should be considered, with an emphasis on utilizing available opportunities to vaccinate children and adults - including pregnant women who were not appropriately vaccinated - during their visit to a healthcare facility; in this manner, the so-called 'lost opportunity to vaccinate' would therefore be prevented.[37,38] In addition, care of the umbilical cord stump should be emphasized; specifically, the stump should be handled using aseptic techniques both during and after the delivery, and the mother should be educated on proper postpartum care.[18]

The care of pregnancy and delivery has improved in Brazil; improved social and economic living conditions have led to advances, although some less-developed regions continue to remain deficient.[39] Studies in Brazil have identified lost opportunities and poor anti-tetanus coverage in children and pregnant women at 31.0% and 70.0%, respectively.[38] These findings indicate that all healthcare professionals who are involved in the care of pregnant women - both in public service and in private clinics - should be aware of the importance of providing tetanus vaccinations.[38] In addition, it should be highlighted that neonatal deaths are under-reported and remains a major issue in the Brazilian society, particularly in the northeastern region.[40]

CLOSING REMARKS

Although an early diagnosis of tetanus *neonatorum* is essential for adequate therapy and an improved prognosis, the importance of prophylaxis and control of the disease is clear. *Clostridium tetani* cannot be eradicated from the environment; however, tetanus is immunopreventable, and eliminating this disease requires political will (at the level of the SUS) and awareness by healthcare professionals. The eradication of tetanus *neonatorum* is feasible and depends on improving the levels of education and healthcare, particularly prenatal care.

It should be highlighted that measures to prevent tetanus *neonatorum* should be sustained in accordance with each site's particularities and should rely on active and continued surveillance and reporting. By maintaining high levels of vaccine coverage (which is both effective and affordable), mortality from tetanus *neonatorum* can be eliminated.

RESUMO

A despeito de ser uma doença imunopreveníveL, o tétano permanece ceifando vidas em diferentes regiões do planeta. Se para a doença de origem acidental a ocorrência de novos casos reflete a insuficiente imunização da população, no caso do tétano *neonatorum* o problema tem dupla natureza: a precária cobertura vacinal dos

adultos e as dificuldades de acesso ao pré-natal de qualidade, situação agudizada pela extrema gravidade da moléstia nesta faixa etária, cuja letalidade pode chegar a 80%. Deste modo, ainda que seja importante o reconhecimento precoce do tétano no recém-nato para seu pronto e adequado tratamento, o aspecto de maior relevância é, indubitavelmente, a implementação de adequadas medidas de profilaxia e controle. Com base nestas premissas, propõe-se, neste artigo, uma atualização sobre o tétano *neonatorum*, enfatizando-se, com mais vigor, o tratamento e a prevenção da moléstia.

Descritores: *Clostridium tetani;* Tétano/prevenção & controle; Recém-nascido

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