ARCHIVES OF Health Sciences

Artigo Original
ISSN 2318-3691

DOI: 10.17696/2318-3691.31.01.2025.254

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Congenital Toxoplasmosis in Brazil: A Document Analysis of Government Guidelines for the Prescription and Medicine Use

Toxoplasmose congênita no Brasil: uma análise das orientações governamentais sobre a prescrição e o uso de medicamentos

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RESUMO

Introdução: A toxoplasmose congênita pode resultar em manifestações clínicas graves e complicações de longo prazo em recém-nascidos. O tratamento padrão geralmente compreende uma combinação de três medicamentos, com a possível adição de um quarto temporariamente. No entanto, a falta de formulações pediátricas disponíveis comercialmente no Brasil requer manipulação farmacêutica ou métodos alternativos para ajustar comprimidos de dose adulta para uso neonatal. **Objetivo:** Este estudo tem como objetivo examinar as orientações governamentais sobre a prescrição e uso de medicamentos para o tratamento da toxoplasmose congênita. **Métodos:** A análise documental foi usada neste estudo descritivo, qualitativo e exploratório. Buscas manuais foram realizadas nos sites das Secretarias Municipais de Saúde de todas as capitais, Secretarias Estaduais de Saúde e no portal do Ministério da Saúde. Os critérios de inclusão foram documentos que continham orientações para a prescrição e/ou uso de medicamentos para toxoplasmose congênita. As informações sobre medicamentos foram compiladas em uma planilha, detalhando a fonte e as orientações governamentais relacionadas à prescrição e/ou uso de medicamentos para toxoplasmose congênita. Resultados: A busca inicial gerou 1.640 documentos. Após a triagem, 1.615 foram excluídos com base nos títulos; e apenas 25 seguiram para uma segunda seleção. Destes, apenas cinco preencheram os critérios de inclusão. Todos os documentos incluídos forneceram informações sobre o regime terapêutico e dosagem, porém apenas um abordou orientações para a adaptação de comprimidos adultos para recém-nascidos. Isso ressalta a falta de orientações relevantes para o uso racional de medicamentos e para a garantia dos resultados terapêuticos esperados. **Conclusão:** Este estudo ressalta a urgência de estabelecer orientações mais claras e completas sobre o uso apropriado de medicamentos para tratamento de toxoplasmose em recém-nascidos no Brasil.

Descritores: toxoplasmose congênita, uso racional de medicamentos, Brasil.

ABSTRACT

Introduction: Congenital toxoplasmosis can result in severe clinical manifestations and long-term complications in newborns. Standard treatment typically comprises a combination of three medications, with the potential addition of a fourth temporarily. However, the lack of commercially available pediatric formulations in Brazil requires pharmacy compounding or alternative methods to adjust adult-dose tablets for neonatal use. **Objective:** This study aims to examine government guidelines on the prescription and use of medications for the treatment of congenital toxoplasmosis. **Methods:** Document analysis was used in this descriptive, qualitative, and exploratory study. Manual searches were conducted on the websites of Municipal Health Departments from all state capitals, State Health Departments, and the Ministry of Health portal. The inclusion criteria focused on documents containing guidelines for the prescription and/or use of medications for congenital toxoplasmosis. Medication information was compiled into a spreadsheet, detailing the source and specific government guidelines related to the prescription and/or use of medications for congenital toxoplasmosis. **Results:** The initial search yielded 1,640 documents. After screening, 1,615 were excluded based on the titles; 25 for detailed analysis were investigated. Of these, only five met the inclusion criteria. While all included documents provided information on the therapeutic regimen and dosage, only one addressed guideline for adapting adult tablets for newborns. This underscores the lack of relevant guidelines for the rational use of medicines and the need to ensure the expected therapeutic outcomes. **Conclusion:** This study underscores the urgency of establishing clearer and more comprehensive guidelines regarding the appropriate use of medications for treating toxoplasmosis in newborns in Brazil.

Descriptors: Toxoplasmosis Congenital, Rational Use of Medicines, Brazil.

Authors' contributions: LAC study design, tabulation, discussion of findings, and writing of the manuscript. ZRSS collection, tabulation, discussion of findings and writing of the manuscript. IPDG, CBD, LMGBO, MMD discussion of findings and writing of the manuscript. DMSSS project supervision, discussion of findings and writing of the manuscript.

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Conflict of interest statement: No

Funding: No funding was received for this research.

Received: 14/09/2024
Approved: 18/03/2024

INTRODUCTION

Toxoplasmosis is caused by the obligate intracellular protozoan parasite *Toxoplasma gondii* (*T. gondii*). In some countries, such as the United States of America (USA), it is recognized as a neglected disease, as it generally occurs

more frequently in low-income populations and due to the lack of interest from the pharmaceutical industry in producing medications for its treatment[1]. According to the Brazilian Ministry of Health (MS), toxoplasmosis is one of the most common zoonoses worldwide[2]. Data from the Centers for Disease Control and Prevention (CDC) revealed that approximately 11% of the USA population aged 6 years and older have been infected with *Toxoplasma*, and more than 60% of some populations in different countries have also been infected[3].

Toxoplasmosis is a globally preventable disease with a range of symptoms that can manifest acutely and chronically[4]. Prevalence is higher in Latin America compared to the United States of America and Canada; reaching up to 50% of the population[5]. According to the CDC[6], along with other literature studies[5,7,9], human transmission of toxoplasmosis can occur through the consumption of raw or undercooked meat containing cysts with bradyzoite forms, as well as through the consumption of oocysts present in water, seafood, vegetables, and fruits consumed raw, known as foodborne transmission. Additionally, congenital transmission can occur when a newly infected mother passes the infection to the fetus. Although rare in the epidemiological context, it has been established that vertical transmission of toxoplasmosis may occur when a genetically different *T. gondii* strain reinfects a previously infected immunocompetent woman during gestation[9], as well as when reactivation of latent toxoplasmosis occurs in immunocompromised women[10]. Other modes of transmission include, for example, infected organ transplants or transfusion of contaminated[5–8]. Notably, oocyst transmission in endemic regions has been linked to lower Human Development Index (HDI) scores in Brazil and other developing countries. Even in developed nations, a correlation between lower socioeconomic status and oocyst transmission has been observed[11-12].

Congenital Toxoplasmosis (CT) is a significant public health issue in Brazil. While the global incidence of CT is 1.5 cases per 1,000 live births, in Brazil this figure rises to 0.3 to 3.4 per 1,000 per 1,000 live births[8]. Most babies with CT are asymptomatic at birth, but many can develop sequelae during childhood, adolescence, and youth, with ocular and central nervous system complications[5]. It is estimated that 35% will develop neurological disease, 80% will suffer ocular lesions, and 40% will experience hearing loss[8]. According to MS data recorded in the Notifiable Diseases Information System (SINAN), from 2020 to 2023, there were 29,462 cases of CT reported nationwide, with notable figures in the states of São Paulo (4,043), Minas Gerais (3,409), Rio de Janeiro (2,034), Rio Grande do Sul (1,637), Ceará (1,546), and Paraná (1,506), which had the highest records for the evaluated period[13].

Early treatment for congenital toxoplasmosis is crucial as late diagnosis can lead to serious issues, as seen in a recent case where a symptomless baby developed severe neurological problems shortly after birth[14]. This points out the importance of early detection and intervention, sometimes even before birth. While early treatment can help, it may not fully prevent damage. Evidence shows that in-utero diagnosis and treatment can improve outcomes, making early action during pregnancy essential[15]. In some cases, significant congenital damage is already present at birth, which limits the effectiveness of postnatal treatment in preventing neurological, cognitive, visual, and motor sequelae of varying severity. Proof suggests that the French approach to in-utero diagnosis and treatment can significantly improve outcomes by limiting the adverse sequelae of congenital infection, as corroborated by internationally studied cases. Therefore, prevention, early diagnosis, and treatment strategies during pregnancy should be prioritized[15].

In response, the Ministry of Health (MS) has been making efforts to improve guidance on this issue through publications such as the "Protocol for Notification and Investigation: Gestational and Congenital Toxoplasmosis"[16] and, more recently, the "High-Risk Pregnancy Manual"[17]. Considering the social, clinical, and economic impact associated with this condition, in 2020, the National Commission for Technologies Incorporation (CONITEC - Comissão Nacional de Incorporação de Tecnologias) recognized the importance of expanding the newborn screening test to include CT screening, observing that the inclusion of this technology will aid in the early detection of this condition in newborns[18].

The treatment of Congenital Toxoplasmosis (CT) remains restricted to antiparasitic, and antibacterial drugs used since the 1950s, with the combination of pyrimethamine and sulfadiazine being the first-line therapy since then[4,5], associated with folinic acid. In cases of ocular and/or cerebral involvement, prednisolone (corticosteroids) is used. Currently, the most internationally recommended therapeutic regimen for CT, adopted by the Unified Health System (SUS) in Brazil, is the administration of pyrimethamine at a dose of 1 mg/kg/day, in a daily oral dose for two to six months, depending on the clinical presentation, followed by use three times a week until completing one year of treatment. Sulfadiazine should be administered at 100 mg/kg/day, in two daily oral doses for one year[19]. Folinic acid should always be administered together with pyrimethamine and sulfadiazine throughout the year of treatment to prevent the adverse effects of pyrimethamine, such as bone marrow depression. Therefore, it should not be replaced by folic acid. Corticosteroids should be administered in cases of active retinochoroiditis or when cerebrospinal fluid protein levels are equal to or greater than 1,000 mg/dL, at a dose of 1 mg/kg/day, always together with pyrimethamine and sulfadiazine, until the inflammatory process has subsided, and their withdrawal should be gradual under medical guidance[19].

Notably, the major challenge in treating CT is the absence of pediatric pharmaceutical forms in Brazil. The sulfadiazine available on the market comes in 500 mg tablets, pyrimethamine in 25 mg tablets, and folinic acid in 15 mg tablets. Of all the medications for CT treatment in Brazil, only corticosteroids (prednisolone) have liquid formulations offered by the pharmaceutical industry, being used in various other pediatric disorders conditions. In tablet form, the medications have doses far above those recommended for newborns, and pharmaceutical forms are unsuitable for this population. Thus, for their administration in CT treatment; dose adaptation is necessary, and therefore, it is essential to provide adequate information to ensure safe and effective treatment. The need to crush tablets followed by dilution in water, even with good guidance, implies the possibility of contamination and dosage errors, as homogeneous solutions cannot be achieved with this practice. This practice can lead to overdosing or underdosing if the mixture is aspirated without prior and immediate agitation, for example.

Therefore, considering the epidemiological importance of CT and the lack of pediatric formulations for its treatment in the Brazilian market; this study aims to investigate the government guidelines for the prescription and use of these medications in Brazil.

METHODS

This study, a document analysis research[20], exploratory, cross-sectional, and qualitative, aimed at answering the following question:

- How have governmental authorities in Brazil regulated the prescription and use of medications for congenital toxoplasmosis?"

To address this issue, a manual search was conducted on the websites of all State Health Departments (SES), Municipal Health Departments (SMS) of state capitals, and the Ministry of Health (MS). A list of the website addresses is provided in supplementary table 1. As this research comprises publicly accessible documents; approval from the Research Ethics Committee (CEP) was not required.

The first step of this study comprised searching the MS website using the keywords: Toxoplasmosis, *Toxoplasma gondii*, congenital toxoplasmosis, and medicine manipulation for congenital toxoplasmosis. Afterward, the same search was conducted on the websites of the 27 State Health Departments and the Municipal Health Departments of the state capitals, following a similar approach to the search on the Ministry of Health's website.

The inclusion criteria for document selection encompassed any type of document issued by the Ministry of Health, State Health Departments, or Municipal Health Departments that provided guidelines on the prescription and/or use of medications for congenital toxoplasmosis in Brazil."

Selection was performed through a preliminary analysis based on the titles of the documents. Documents meeting the inclusion criteria were downloaded and recorded in a spreadsheet. Afterward, these documents were read in full, and if their inclusion was confirmed, they were selected for analysis in this study.

After these two selection steps, data extraction was carried out. All included documents were properly identified with the following details: origin, document date, and the subsequent information: federative entity responsible for document dissemination (state, municipality, or federal government -referred to as the Union in some countries); the name of the municipality or state; year of the document; type of document; suggested treatment regimen for CT (medication, dosage, and treatment duration); whether there was guidance on medicine manipulation for pediatric dosing (yes/no); description of manipulation guidance, if available; whether there was guidance on partitioning and diluting adult tablets for pediatric use; and finally, the description of dilution and/or partitioning guidance, if applicable. The extracted data were presented descriptively and qualitatively, highlighting their main information and identifying gaps.

RESULTS

The search on the websites of the Ministry of Health (MS), Municipal Health Departments (SMS), and State Health Departments (SES) was conducted from January to June 2023, resulting in 1,640 documents. After applying the eligibility criteria described in the Methods section; 1,615 documents were excluded. Subsequently, the review and analysis of titles led to the exclusion of an additional 13 that did not meet the inclusion criteria. During the full-text screening stage, 12 documents were included. However, a thorough peer review conducted during the extraction phase revealed that, while these documents addressed congenital toxoplasmosis (CT) and its diagnostic criteria, they did not fully meet our inclusion criteria and were therefore excluded (figure 1).

Of the five documents included in this study, one was from the MS, three were from State Health Departments (SES), and one was from a Municipal Health Department. The MS document includes a flowchart guiding the diagnosis and treatment of CT[21]. The three documents from the SES consisted of technical notes, including one from the state of Santa Catarina[22], one from Tocantins[23], and one from Paraíba[24]. These technical notes are protocols guiding the diagnostic and treatment flow for CT. Finally, the only municipal document included was a technical note from São Paulo[25]. The characteristics of the included documents are summarized in table 1.

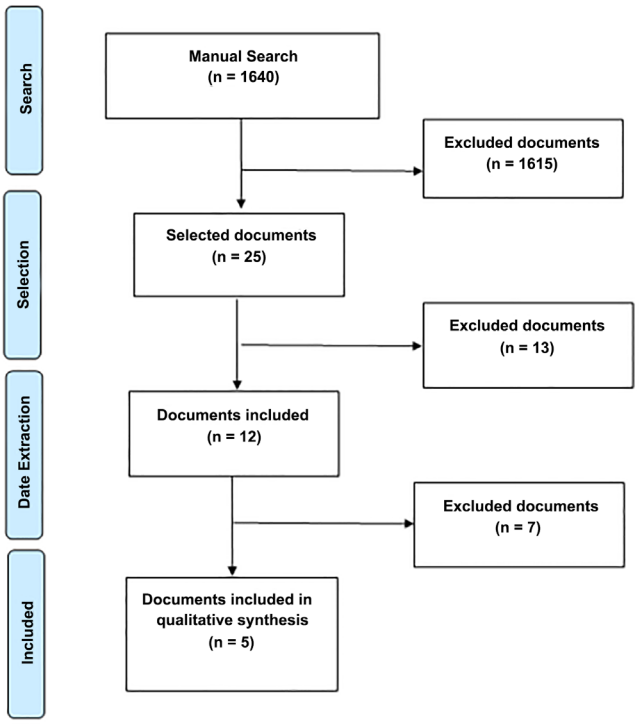

Figure 1. Flowchart of the search and selection phases of governmental documents guiding the use and prescription of medications for congenital toxoplasmosis in Brazil, 2023.

Table 1. Description of the authors, year, and type of documents included in the document analysis on medications use and prescription for congenital toxoplasmosis in Brazil, 2023.

Federative Entity	State	Municipality	Title	Document Type	Year
Ministry of Health	-	-	Flowchart for the management and treatment of the newborn	Flowchart	2014
SES	PB	-	Technical Note on Toxoplasmosis	Technical Note	2020
SES	SC	-	Joint Technical Note No. 008/2019 DAPS/ DIAF/DIVE/LACEN	Technical Note	2019/2020
SES	TO	-	Technical Note - 4/2020/SES/SVS	Technical Note	2020
SMS	SP	São Paulo	Guidelines for the Dispensation of Medicines for Toxo-plasmosis Cases with Treatment Indication	Technical Note	2023

The document from the MS included a flowchart that provided information on the treatment of CT and highlighted that sulfadiazine should be compounded at a concentration of 100 mg/mL, pyrimethamine at 2 mg/mL, and folinic acid at 5 mg/mL. It is recommended to carefully monitor clinical jaundice and bilirubin levels when sulfadiazine is used in newborns. Additionally, the document provided information on the dosage of medications used for congenital toxoplasmosis (CT), highlighting the need for compounding for pediatric administration. However, it lacked details on dose adaptation and specific administration instructions[21].

It is important to note that most of the other included documents were based on the same MS flowchart and, similarly, did not provide guidance on how to adapt the dose from the tablet available at SUS. The technical notes addressed information on diagnosis and therapeutic regimen and mentioned the need for compounding, but they did not provide instructions on how to carry out this compounding.

Finally, the only document that guided the adapting adult-dose medicines for pediatric use was the technical note from the Municipal Health Department (SMS) of São Paulo. As previously mentioned, medications used for treating CT are available in the Brazilian market in adult-dose tablet form, requiring adaptations for pediatric administration. Technical note No. 02/2023 from the Pharmaceutical Services Department outlines the extemporaneous preparations of CT medications. It instructs the administration of a 15 mg folinic acid or calcium folinate tablet, with 10 mg orally, once a day, three times a week. The caregiver is instructed to crush the tablet in a clean container, add 3 mL of filtered water, and wait approximately three minutes for dissolution. The note also guides administering pyrimethamine 25 mg, with a dose of 1 mg/kg/day for two to six months, followed by 1 mg/kg in an oral dose three times a week until completing one year of treatment. The procedure for pyrimethamine is similar to that described for folinic acid. Additionally, it advises discarding any remainder after administration[25].

DISCUSSION

This study reveals a significant institutional gap in the guidance on the use of medications for Congenital Toxoplasmosis (CT) in Brazil, particularly regarding the pharmaceutical form and dosage available in the Unified Health System (SUS). Although all the documents analyzed have provided information on the therapeutic regimen and dosage, only one contains information on the use of adult-dose tablets for administration in newborns. Thus, although these results cannot be extrapolated to all of Brazil—given that the manual search was limited to municipalities that are state capitals—it can be inferred that this situation is prevalent in most cities across the country. In most cases, to address the issue, tablets undergo a pharmaceutical form adaptation, a pharmaco-technical operation that modifies the original industrial medicine. In this case, the tablets are fragmented and diluted in oral liquids[26], as guided by the technical note from the municipality of São Paulo[25]. This process is referred to as "dose unitarization" by the Brazilian Health Regulatory Agency (ANVISA)[27].

Thus, the physician's only option is to issue two prescriptions: one for the tablets and another specifying the appropriate dilutions and doses based on the child's weight.

This approach allows caregivers to either take the medications to a compounding pharmacy for preparation or attempt to prepare the correct dilutions at home. However, it is important to note that only in 2023 did a single Brazilian municipality publish this guidance, which was not found in any other document that met the inclusion criteria of this study.

Considering that four medications may be necessary for the treatment of congenital toxoplasmosis — sulfadiazine and pyrimethamine; essential for controlling the growth of parasites, in addition to folinic acid, which prevents bone marrow depression, and corticosteroids to control inflammation in the retina or brain — significant challenges may arise due to the lack of pediatric formulations. Practical and clinical risks can emerge when only corticosteroids are available in pediatric form.

The absence of pediatric formulations can lead to incorrect dosages, especially when pyrimethamine and sulfadiazine tablets are divided at home. This practice increases the risk of underdosing these medications, which have antiparasitic and antibiotic functions. Additionally, there is the risk of complete abandonment of administration, as the correct dosing of sulfadiazine and pyrimethamine can become an insurmountable challenge.

In cases in which the use of antiparasitic and antibiotic treatments in conjunction with corticosteroids is necessary, such as in certain instances of treating toxoplasmosis in newborns, exists a potential intrinsic risk that discontinuation or underdosing of antiparasitic treatment, while corticosteroid therapy continues, could lead to increased parasite proliferation. This risk is based on the understanding that an intact immune system is crucial in managing *T. gondii* infection, as demonstrated in contexts like hematopoietic stem cell transplantation (HSCT) in pediatric patients. In these cases, toxoplasmosis represents a medical emergency with high fatality rates if untreated, underscoring the importance of an early and adequate immune response[28]. The role of corticosteroids in potentially altering host-parasite dynamics[29] further supports the need for careful management of antiparasitic regimens to avoid compromising the immune system's ability to maintain parasites in a latent state. This includes the reduction in the production of cytokines, such as gamma interferon, which plays a pivotal role in containing the replication of *T. gondii*[30-31].

Previous studies have indicated that congenital toxoplasmosis in Brazil has a higher prevalence of cases with ocular involvement compared to Europe[32]. This difference is believed to be partly explained by the biodiversity of Brazilian strains, which may include strains of greater virulence[33]. However, the lack of consistent compliance treatment, along with the unavailability of adequate pediatric formulations of drugs used in the treatment of congenital toxoplasmosis (CT), may contribute to the high prevalence of cases with ocular involvement in Brazil, as described in the literature[32]. Although many newborns with CT already present ocular involvement at birth, limited adherence to postnatal treatment can exacerbate these ocular outcomes over time. Therefore, the potential ineffectiveness of treatment due to the lack of adequate pediatric formulations may be an important factor explaining this difference. There must be clear guidelines and practical solutions to ensure the safety and efficacy of treatment, addressing these critical gaps in disease management.

The lack of this guidance in institutional documents can be explained by ANVISA's resolution, which states that dose unitarization may only be carried out in hospitals or compounding pharmacies[27]. As a result, guiding dose unitarization in a home setting could be deemed inappropriate and contrary to the country's health regulations. This scenario complicates CT treatment, as it creates additional costs for the patient's caregivers when they have to rely on private compounding pharmacies. Conversely, when the caregiver performs the compounding, especially in a context with very little guidance on how to safely and correctly perform this adaptation at home, poses potential dosage errors and contamination risks.

To ensure the Rational Use of Medicines (RUM) and the effectiveness of pharmacological treatment, the correct dose must be administered to the patient[34]. Additionally, the National Medicines Policy and the Pharmaceutical Services Policy aim to ensure RUM and its access, as guaranteed by the Constitution and SUS organic laws[35–38]. These guidelines are crucial because there is no access to medications or guarantee of the right to health if medicines are not available in the appropriate dose and pharmaceutical form to ensure the safety and therapeutic effect of these technologies.

The adaptations for CT treatment discussed here, as exemplified by the technical note from the municipality of São Paulo, underscore the need for further governmental guidance. Such guidance would help address the challenges associated with the transformation process required due to the lack of an appropriate pharmaceutical form for

this population. We understand that, although it may be considered inappropriate due to Brazilian regulations for this sector to provide information for this transformation in a home setting, at least guidelines for its manipulation in pharmacies should be presented in the documents. However, these guidelines were also not found. Furthermore, it is crucial to consider initiatives that ensure medications available in the appropriate dose and pharmaceutical form without making patients solely responsible for the costs associated with the necessary pharmaco-technical transformation for its rational use. It is known that financial cost is one of the main barriers to accessing medications and that, in Brazil, access is a citizenship right guaranteed by law[35]. Therefore, the State and its federated entities should be responsible for informing and implementing strategies to ensure this right.

It is also well known that there are difficulties in the research and development (R&D) of pediatric medications[39]. The challenges in developing a more effective treatment for toxoplasmosis to reduce toxicity and achieve therapeutic concentrations in the brain and eyes are also recognized[40,41]. In the context of CT, these challenges may be even greater, considering all the particularities and care associated with pregnant women[40] and, especially, the need to create a formulation that is affordable and practical for use, particularly directed at newborns. Given all the difficulties and needs experienced in the clinical and therapeutic context of CT, the importance of conducting studies that better assess the possibilities and strategies is reinforced, for example, in the field of pharmaco-technology, since there are several questions and weaknesses in the treatment currently adopted and recommended for newborns.

CONCLUSIONS

To the best of our knowledge, this is the first study to reveal, through publicly available documentary evidence, a significant gap in governmental guidance on the use of medicines for the treatment of Congenital Toxoplasmosis (CT). Although governmental documents present guidelines for prescribing CT treatment, they do not provide adequate guidance for professionals and caregivers on the appropriate use of this medicine, especially regarding the necessary adaptations for pediatric doses.

This gap influences both the information provided to healthcare professionals and the caregivers of these patients. It constitutes a notable deficiency in promoting the Rational Use of Medicines (RUM) for managing this condition in Brazil, potentially undermining its efficacy and, as a result, affecting health outcomes. The lack of an industrially produced pediatric formulation on the Brazilian market hinders efforts to ensure that newborns receive their treatment accurately and appropriately, particularly in the absence of clear guidance on the administration of this therapy.

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