Readdressing Chloramphenicol: Data from a Paediatric Tertiary Care Centre

Revisitar o Cloranfenicol: Casuística da Enfermaria de Pediatria de um Hospital Terciário

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Abstract

Introduction: The use of chloramphenicol in developing countries is widely supported by the World Health Organization to treat bacterial infections, especially those caused by gram-negative bacteria. Wealthier regions favour other antibiotics, since there are concerns regarding chloramphenicol's adverse effects, such as aplastic anaemia. Nevertheless, the rise of multidrug resistant--bacteria has brought a growing interest on chloramphenicol as a new strategy to fight antimicrobial resistance, since current reports of its toxicity are very uncommon. This retrospective study intends to characterize the use of chloramphenicol in a tertiary care hospital in Brazil and report adverse reactions.

Methods: Retrospective analysis of clinical records from paediatric patients admitted to Paediatric Department of Instituto de Medicina Integral Professor Fernando Figueira, between May 2017 and April 2018, and treated with chloramphenicol.

Results: Results: One hundred and twenty-four patients were included, with a median age of 4.5 years (one month-14 years old) and male predominance (54%). Chloramphenicol was mostly used to treat respiratory infections (85%), skin and soft tissue infections (6%), or diseases of ear, nose and throat (6%). It was the first-line antibiotic in 42% of the patients, who presented a shorter length of stay (7.4 *versus* 11.1 days, p=0.02). Parenteral treatment was the choice for 91% of patients, for an average of 5.3 days. No adverse reactions were reported, either haematologic or other, and no late adverse effects were reported in the 13 patients evaluated one year after hospital discharge.

Conclusion: No early or late adverse effects to the use of chloramphenicol were reported in this study. Also, cloramphenicol's severe adverse effects are widely known and yet, rarely described among centres with current routine usage. While waiting for the research of new antimicrobials, old and abandoned antibiotics like chloramphenicol might foster interest as a tool to treat serious infections, especially those caused by multidrug resistant bacteria.

Resumo

Introdução: A utilização de cloranfenicol nas regiões em desenvolvimento é uma prática comum que, em idade pediátrica é suportada pela Organização Mundial de Saúde por ser importante no combate às infeções bacterianas, nomeadamente as causadas por agentes *gram* negativos. Nos países desenvolvidos, o receio de efeitos secundários graves, principalmente a aplasia medular, motiva até hoje a utilização de outros grupos de antibióticos. Todavia, a emergência de agentes multirresistentes tem concedido ao cloranfenicol um interesse renovado. Nos países onde ainda hoje se recorre amplamente ao cloranfenicol, os referidos efeitos

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adversos raramente são reportados. Este estudo retrospetivo propõe-se a caracterizar a utilização do cloranfenicol num hospital terciário localizado no Brasil, e descrever a ocorrência de efeitos secundários associados.

Métodos: Análises retrospetiva dos registos clínicos de crianças e adolescentes admitidos no Serviço de Pediatria do Instituto de Medicina Integral Professor Fernando Figueira, entre maio de 2017 a abril de 2018, e tratados com cloranfenicol.

Resultados: Foram incluídos um total de 124 doentes, com uma idade mediana de 4,5 anos (um mês – 14 anos) e predomínio do sexo masculino (54%). As principais patologias tratadas com cloranfenicol foram infeções respiratórias (85%), da pele e tecidos moles (6%), e otorrinolaringológicas (6%). O cloranfenicol foi usado como primeira-linha em 42% dos doentes, o que se associou a um internamento mais curto (*lenght of stay* de 7,4 dias *versus* 11,1 dias, *p*=0,02). Foi administrado maioritariamente por via endovenosa (91%), durante uma mediana de 5,3 dias. Não foram registados efeitos secundários, hematológicos ou outros, e não se registaram complicações tardias nos 13 doentes avaliados um ano após a alta hospitalar.

Conclusão: Não se registaram neste estudo reações adversas, imediatas ou tardias, associados à utilização do cloranfenicol. A rara ocorrência de efeitos adversos reportada pelos centros com maior experiência na utilização de cloranfenicol e a problemática atual de agentes resistentes aos antimicrobianos, especialmente os nosocomiais, pode fazer do cloranfenicol uma opção a ser revisitada em situações específicas.

Keywords: Child; Chloramphenicol/adverse effects.

Palavras chave: Cloranfenicol/efeitos adversos; Criança.

Introduction

Widespread overuse of antibiotics is associated with antimicrobial resistance among bacteria, posing a major public health threat worldwide.[1] This led to a renewed interest in agents that were left in the past, with chloramphenicol being one of the examples.[1] It is a semisynthetic broad – spectrum antibiotic, widely used in the 1950s to treat severe bacterial infections.[1-4] Although considered bacteriostatic, it also has bactericidal activity in high doses or against *S. pneumoniae*, *N. meningitidis* and *H. influenza*, the three main causes of severe infection in children.[1,2,4] Chloramphenicol is also extremely active against *gram*-positive and *gram*-negative bacteria, *spirochetes, rickettsiae, chlamydiae* and *mycoplasma*.[1,2,4] It has great oral availability and tissue penetration, including to the central nervous system, as well as a good cost – effectiveness ratio.[1-3,5] Chloramphenicol is recommended by the World Health Organization (WHO) whenever the system lacks modern alternatives, which is very common in low-income countries.[6-8]

Haematotoxicity secondary to chloramphenicol was firstly reported in 1949, with three cases of severe but reversible granulocytopenia.[9] Soon reports of fatal aplasia rapidly followed worldwide, limiting its use in medium and high – income regions.[2,3,5,10] Adverse reactions occur either through a dose-related bone marrow suppression after seven days of treatment; or as an idiosyncratic reaction, often irreversible and fatal.[2] The first mechanism results from direct toxicity in the marrow's erythroid and myeloid precursors, and reversible it's with discontinuation; the latter, is unknown, very rare (apparently occurs 1 in 30 000 or more courses of oral chloramphenicol), cannot be predicted and emerges weeks, months or even years post-therapy.[2,11,12] Another often fatal reaction is the grey baby syndrome, a rare condition almost exclusive to newborns, culminating in severe metabolic acidosis, cyanosis and cardiorespiratory failure.[2,13-16]

There are, however, some facts to consider regarding chloramphenicol – related adverse effects. Reliable data on this matter goes back to the 1960's to late 1980's and therefore, can be obsolete. Also, by that time, reports on the incidence of chloramphenicol – associated severe aplastic anaemia ranged from 1/40 800 to 11/11 500 cases, which is 13 times the background incidence of idiopathic aplastic anemia.[17-19]

Nowadays, secondary myelotoxicity seems to be uncommon and its reports are anecdotal, particularly in countries with wide use of chloramphenicol.[3,7,8] Nonetheless, there is lack of current literature describing chloramphenicol adverse effects and the mechanisms underneath.[2,3,17,20,21]

Multi-drug resistant (MDR) pathogens have been pressuring the scientific community to find alternative options, and one of the most promising is the use of abandoned antibiotics like chloramphenicol. Since medium and high-income countries use it in such low-levels, chloramphenicol remains active against a large number of prevalent MDR bacteria. Currently, it appears to be useful in specific situations, as a salvage therapy for serious infections.[10,19]

This study aimed to characterize the use of chloramphenicol and report the occurrence of haematotoxicity or any other adverse reaction, within paediatric patients hospitalized in a tertiary care centre, in the northeast region of Brazil.

Methods

This work was carried out at the Paediatric Department of Instituto de Medicina Integral Professor Fernando Figueira, a public tertiary care centre that serves a population of 1.2 million children and adolescents under the age of fourteen. We enrolled an observational study comprising patients admitted to paediatric intensive care and general wards, treated with chloramphenicol from May 1st, 2017 to April 30th, 2018. Defined variables included demographic and clinical information, and also whether chloramphenicol was first-line therapy or not, in combination or monotherapy, duration of therapy, length of hospital stay, route of administration and outcome (favourable, discontinuation of therapy, death and adverse reaction, haematological or other). We also evaluated the number of patients with follow-up appointments and readmissions. Exclusion criteria comprised insufficient patient data or incomplete clinical records. The program used for data statistical analysis, was the "*Statistical Package for Social Science*" program (*IBM SPSS Statistics* 23.0 ®). Descriptive analysis was performed of continuous data and categories (mean, standard deviation, median, minimum and maximum, and relative frequency), and the nonparametric Mann-Whitney test was used, with a significance level of 5% (0.05) for all statistical tests. The Research Ethics Committee (CEP) of the Hospital allowed collection of the data, which enabled this work to be carried out.

Results

We analysed 175 clinical files from patients admitted throughout our defined interval (Fig. 1). From these, 52 cases were excluded due to insufficient or incomplete information, i.e., regarding the aim of chloramphenicol usage, route of administration, duration of therapy and reason for discontinuation. Therefore, a total of 124 cases were analysed, with one being a readmission of a patient who took a second course of chloramphenicol therapy within a six months period.

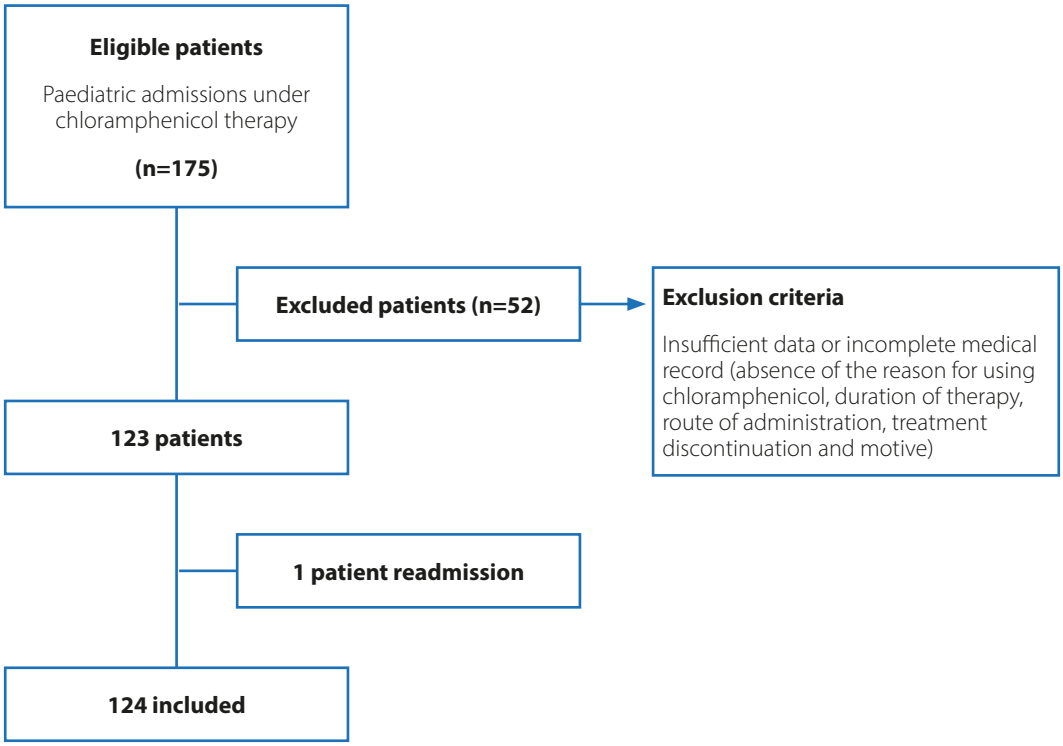

Figure 1. Flow chart of selection process, based on exclusion criteria

Table 1 outlines baseline demographic and clinical characteristics of the children enrolled in the study. Patients were predominantly male (54%) with a median age of 4.5 years, ranging from one month to 14 years old. Fifty-six per cent of the patients had a chronic disease, mainly a genetic syndrome or congenital malformation, a neurological disorder or a respiratory disease. Chloramphenicol (Table 2) was mostly used to treat respiratory infections (about 85% of all the cases, with pneumonia in 96% of these), infections of skin and soft tissue (6%), otorhinolaryngological (6%), and the remainder, acute gastroenteritis and fever of unknown origin (3%). All patients had a moderate or severe clinical condition, especially those with complicated pneumonia, five of whom required intensive care and five have come to die (two in the general ward and

three in the intensive care unit). In this series there were no deaths from other causes.

Table 1. Demographic and clinical characterization of patients treated with chloramphenicol between May 2017 and April 2018

		n	%
Sex			
Male		67	(54%)
Female		57	(46%)
Age			
≤ 12 months		9	(7%)
> 12 months		115	(93%)
Co-morbidity		70	(56%)
Chronic respiratory disease		9	
Neurological disorder		29	
Genetic/Malformation syndrome		10	
Gastrointestinal disease		4	
Nephro-urological disorder		4	
Immunodeficiency		2	
Haematological disorder		5	
Rheumatological disease		3	
Cardiovascular disease		4	
Patient Origin			
IMIP	ER	89	(72%)
	PA	3	(2%)
Other hospital		32	(26%)
Hospital admission			
General paediatric ward		119	(96%)
Intensive Care Unit		5	(4%)

ER - Emergency room; IMIP - Instituto de Medicina Integral Prof. Fernando Figueira, Recife, Brazil; PA – Paediatric appointments.

Table 2. Duration of chloramphenicol therapy and length of hospital stay of treated patients throughout May 2017 and April 2018

	n
Duration of chloramphenicol therapy (median, days)	
Exclusively used during inpatient treatment	5.3 [1;16]
Inpatient followed by outpatient treatment	8.3 [2,6;10]
Length of hospital stay (days)	
As 1st line-treatment	7.4 [1;25]
As 2nd line-treatment	11.1[2;45] p=0.002)

Chloramphenicol was not the first therapeutic regime in 57% of the patients (Table 2), and after a median of 3.2 days of treatment with the first-line antibiotic, these patients were given chloramphenicol due to an insufficient or worsening clinical response. Therapy with chloramphenicol lasted a median of 5.3 days [1;16] when completed throughout hospital stay and 8.3 days [2,6;10] when completed at home, beyond hospital stay.

Table 3. Characterization of therapeutic regimens with chloramphenicol, from May 2017 to April 2018

	n	(%)
Chloramphenicol		
1st line- treatment	53	(43%)
2nd line- treatment	71	(57%)
Other antibiotics		
Cephalosporins[1]	30	
Aminopenicillins[2]	33	
Piperacillin + tazobactam	1	
Oxacillin	6	
Macrolide[3]	1	
Therapeutic regimen		
Monotherapy	49	(40%)
Combination treatment: oxacillin, cephalosporins or clindamycin	75	(60%)
Condition, diagnosis (ICD-10)		
Respiratory (pneumonia, with/without pleural effusion)	106	(85%)
Skin and soft tissue infections (periorbital cellulitis)	7	(6%)
Otorhinolaryngologic (acute mastoiditis, peritonsillar abscess)	7	(6%)
Gastrointestinal (typhoid fever)	2	(1.5%)
Fever of unknown origin	2	(1.5%)
Administration route		
Exclusively parenteral	81	(65%)
Parenteral followed by oral therapy	32	(26%)
Exclusively oral therapy	11	(9%)
Outcome		
Favourable	87	(70%)
Discontinuation of chloramphenicol	37	(30%)
Readjustment according to AST or local epidemiology	28	
Insufficient clinical response	9	
Death	5	(4%)
Respiratory failure	4	
Sepsis	1	
Adverse reaction	0	
Readmission	1	(<1%)
Follow-up appointments (chronic illness)	13	(10%)

AST - antibiotic susceptibility test; ICD-10 - International Classification of Diseases 10th revision; ẋ - arithmetic mean, *vs – versus*. Notes: [1] Cephalosporins: ceftriaxone, cephalexin or cephalothin; [2] aminopenicillins: amoxicillin, amoxicillin + clavulanate and ampicillin; [3] macrolide: azithromycin.

The predominant route of administration was parenteral (91%), of which 65% were treated exclusively with a parenteral regime and 26% parenteral followed by oral therapy (Table 2). Length of stay was shorter in patients who started chloramphenicol within the first 24 hours of hospitalization, as a first--line option (7.4 days versus 11.1 days, p=0.002). However, it was longer in cases where chloramphenicol was administered exclusively *per os* (median of 9 [1;45] days versus 4 [1;13] days, p=0.017). Seventy per cent of the patients had an adequate clinical response; among the remainder 30% (n=37), in 28 patients chloramphenicol was suspended once the antibiotics susceptibility test was known and nine patients suspended due to clinical worsening. In this series, there were no complications after treatment with chloramphenicol, including in seven patients who had anaemia on admission (two of them with sickle cell disease); in all patients and especially amongst these seven, there were no reports of worsening haemoglobin levels or other erythrocyte indices, neither reports of haematotoxicity or death related to chloramphenicol. One patient readmitted within a six-month period and both times after community-acquired pneumonia, was given another course of therapy and did not have any adverse reaction. Within a year after hospital discharge, thirteen patients required paediatric appointments (related to their chronic illnesses), and none presented haematological or other long-term complication caused by therapy with chloramphenicol.

Discussion

Approaching an infectious disease can pose a challenge, and it surely exposes the substantial differences between high and low-income countries, with resources being provided at a different pace. Countries that regularly turn to chloramphenicol as an essential weapon against bacterial infections usually lack the means to access newer antibiotic options.

The present study was conducted in a public hospital of the northeastern region of Brazil. Usually, it serves a poor population from the State of Pernambuco, comprising about 1.2 million inhabitants under the age of fourteen. This hospital follows the WHO's policy on the use of antibiotics, carefully considering the most likely bacterial agent, clinical severity of the disease, the associated costs and the impact on the regional public health system.[6]

This centre has a vast experience using chloramphenicol and that motivated the present study, aiming to describe the possibility of harmful effects, especially those of greater severity. It is also worthy of notice that most patients (56%) had chronic illnesses, and to some-extent one can deduce that probably they have had previous antibiotic courses, some with chloramphenicol, allowing it to be used safely throughout the current hospital stay.

In this series, no side effects of chloramphenicol were recorded, whether related to bone marrow toxicity or any other kind. However, some factors need to be considered when interpreting these results, especially its limitations like the size of the sample, inferior to the *number needed to harm* (NNH) and a relatively short period under analysis.[18] Nevertheless, in this low-income setting, it appears that limiting the use of chloramphenicol to very few specific situations might be a wise practice, where benefits outweigh the potential risks.

In our series, chloramphenicol was mostly used to treat moderate or refractory community-acquired pneumonia, with or without parapneumonic effusion, as well as suspected aspiration pneumonia, and in these cases, in association with oxacillin. This emphasizes the centre's current strategy for the treatment of severe infections, which lies on the preferential use of other antibiotic groups, like third-generation cephalosporins or fluoroquinolones. Therefore, it is comprehensible that in our study, there were only two cases of typhoid fever and no records of central nervous system infections. Currently, this hospital's internal guideline recommends chloramphenicol as a second-choice treatment for acute bacterial meningitis and enteric fever in children older than 2 years, thus promoting a wise management of the available resources.[22]

Chloramphenicol was predominantly used as a first-line therapy in respiratory infections that did not require intensive care, and therefore this might justify the shorter length-of-stay observed in our series, when chloramphenicol was the initial option. We also highlight that in these cases, the most commonly responsible agents are usually susceptible to chloramphenicol, which favours a good prognosis.

Chloramphenicol is very effective as a parenteral or oral treatment, with excellent tissue penetration. In our series though, parenteral therapy was the most common route and it was associated with longer hospital-stay, perhaps related with higher disease severity and a greater need for an intravenous choice in the first place.

The experience from this centre, together with similar reports from other developing countries, might be a source of information about chloramphenicol, as an antimicrobial drug with a growing role on the emergence of MDR agents, especially *gram*-negative bacteria.[7,8,20] Chloramphenicol is routinely used in this hospital since 1960, and it has proven to be an effective and economically viable option, without any record of haematological or other complications. Brazil is also a particular example among the developing regions of the world, since its public healthcare system manages to provide at some extent alternative antibiotics other than chloramphenicol. This was also shown in this series, where chloramphenicol was not

the first-line option in most cases (57%). Poorer regions of the globe have a larger chloramphenicol usage on a daily-basis, frequently not being able to discriminate between disease severity and clinical recommendation.

Both high and low – income countries face the problem of bacterial resistance to antibiotics, especially nosocomial agents. Wealthier regions cannot recommend chloramphenicol as a first-line choice; however, they should revisit it as a viable alternative, for a short course in the more severe cases, treated in highly differentiated settings under the supervision of experienced infectious diseases specialists, blood disorders experts and intensivists.

Available literature on this matter does not provide a full understanding or sufficient evidence concerning the morbidity and mortality associated with the use of chloramphenicol. In that sense, the current paradigm should motivate further studies, especially in places with greater experience and capacity to perform larger studies, to better clarify the causal relationship between chloramphenicol and the adverse events previously described.

Conclusion

Chloramphenicol is an antibiotic with remarkable features, such as its broad spectrum of action, and it plays an important role in the treatment of infections in developing countries. It is widely known for its potentially severe adverse effects, which appear to be rarely described in centres with great experience on its routinely usage. In limited and specific situations, chloramphenicol portrays an effective antibiotic, and when used appropriately it seems to be advantageous. The ongoing increase in antimicrobial resistance to currently available antibiotics, may lead to a larger use of chloramphenicol in the future. However, further randomized clinical trials are needed to describe more accurately the side effects of chloramphenicol, as well as the underlying mechanisms.

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CC: Contribuição intelectual substancial direta no desenho e elaboração do artigo, responsável pela análise e interpretação dos dados, elaboração do rascunho do manuscrito e da revisão crítica do conteúdo.
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Contributorship Statement

CC: Direct contribution to the writing and elaboration of the article, responsible for the substantial analysis and interpretation of data, elaboration of the manuscript draft and content criticism.

SA: Substantial direct intellectual contribution to the design and elaboration of the article, responsible for the analysis and interpretation of data, direct contribution to the writing of the manuscript draft and the critical review of the content.

RM and SV: Substantial direct intellectual contribution to the design and elaboration of the article, contribution to the analysis and interpretation of data, direct contribution to the writing of the draft and the critical review of the content.

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