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ORIGINAL ARTICLE

Safety and effectiveness of colistin in a pediatric burn unit

Seguridad y eficacia del colistín en una unidad de quemados pediátrica

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What do we know about the subject matter of this study?

The increase in the incidence of multidrug-resistant gram-negative bacilli infections, especially in critical areas, has led to a reevaluation of the usefulness of old antibiotics such as colistin. Information on the use of colistin is particularly scarce in the pediatric population.

What does this study contribute to what is already known?

In this study, we evaluated the safety and efficacy of colistin use in pediatric burn patients. All burn patients who received colistin between May 2022 and October 2023 were included. There were no signs of nephrotoxicity or neurological alterations. Antibiotic treatment with colistin was effective in all cases.

Abstract

The increased incidence of infections by multidrug-resistant gram-negative bacteria, especially in critical care units, has required reevaluating the usefulness of old antibiotics such as colistin, from the polymyxin group. Its use in burned patients, especially in the pediatric population, has been scarcely studied. **Objective:** To evaluate the efficacy and neurological and renal toxicity of colistin in patients under 18 years of age admitted to a burn unit in a high-complexity hospital. **Patients and Method:** uncontrolled prospective cohort study. All burned patients who received colistin in the period between May 2022 and October 2023, empirically or due to a documented infection, were included. Demographic data, burn characteristics, microbiological isolation, treatment, and evolution were evaluated. Renal function was evaluated every 72 hours and neurological manifestations were evaluated daily. **Results:** 15 patients who received colistin with a total of 23 indications were included. Median age: 6 years (range (r): 0.7 to 15.0). Median colistin dose: 5.5 mg/kg/day (r: 4.0-7.5). In 10 indications, it was a treatment directed to a documented microorganism; in the others, it was an empirical treatment. There were no cases of nephrotoxicity or neurological alterations. All patients progressed favorably, except one who died of causes other than infection and colistin administration. **Conclusion:** Colistin appears to be a safe and effective drug in the management of burned patients. Prospective studies are required with a control group and a larger number of patients, in addition to pharmacokinetic studies, to support these results reliably.

Keywords:
Burns;
Colistin;
Infections;
Antibiotics;
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Introduction

Infection is the most frequent complication in burn patients[1]. Microbiological isolates vary by institution but follow a relatively predictable timeline, with gram-positive cocci predominating in the first week after the injury and gram-negative bacteria (GNB) appearing thereafter[2].

In a prospective cohort study carried out in the Burn Unit of the *Hospital Garrahan* that included 110 burned children, the most frequent clinical form was burn-related sepsis[3]. Bacterial infections were the most common and multidrug-resistant *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Acinetobacter* spp. were the main bacteria involved. Other burn units report similar results, with an overall increase in infections caused by multidrug-resistant GNB (MR-GNB)[4,1].

MR-GNB infections generate increased morbidity and mortality in ICUs and burn care centers[5]. In this epidemiological context, empirical and targeted treatment of burn patients with an infection represents a challenge, with colistin remaining a cornerstone in their treatment[6].

Colistin is a polypeptide antibiotic of the polymyxin group that binds to lipopolysaccharides and phospholipids of the GNB cell membrane and causes alteration of its outer membrane[7]. In addition to having a bactericidal effect, it enhances the activity of other antibiotics[8]. Colistin began to be used in 1950, but showed a considerable decline in its clinical use since the 1980s, due to reports of renal and neurological adverse events, and the development of safer and more effective antibiotics[9]. However, since the beginning of the 21st century, the lack of therapeutic alternatives for MR-GNB infections has re-evaluated its use[10]. Colistin is an active agent against aerobic GNBs that cause life-threatening infections, such as carbapenem-resistant *P. aeruginosa*, multidrug-resistant *Acinetobacter* spp, and species of the Enterobacter order[7].

Optimal dosing strategies for colistin[11,12], as well as its potential adverse effects and factors determining survival in burn patients with MR-GNB sepsis, are not yet fully defined[13] and information on colistin use is especially scarce in the pediatric population[14].

In 2009, a study was carried out in the same Burn Unit as the one conducted for this study, in which no adverse renal or neurological effects were observed in 45 burned children treated with intravenous (IV) colistin[15]. In this study, we re-evaluated its use in pediatric burn patients, 15 years later, and under the implementation of an updated protocol, to evaluate the efficacy and neurological and renal toxicity of colistin use in patients under 18 years of age admitted to a burn unit in a high complexity hospital.

Patients and Method

Prospective descriptive study. Inclusion criteria were patients between 1 month and 18 years of age admitted to the burn unit between May 2022 and October 2023 who received complete treatment with IV colistin (at least 7 days of treatment). Exclusion criteria were established as referral of patients to other centers before completion of colistin treatment and death within the first 48 hours of treatment.

IV colistin was indicated in a targeted manner for a documented infection by microorganisms only sensitive to colistin or empirically in patients with negative cultures but with clinical manifestations compatible with sepsis and admission time ≥ 72 hours in the unit. In the first group, the duration of treatment depends on the site of isolation of the microorganism and the clearance of positive cultures. In the second group, the hospital protocol indicates the completion of 7 days of treatment.

This study was conducted at the *Hospital Garrahan*, a tertiary pediatric center located in the Autonomous City of Buenos Aires, Argentina. It admits patients who consult spontaneously, as well as children referred from other institutions throughout the country. The Burn Unit has 6 intensive care beds and 10 intermediate care beds.

Antibiotic sensitivity testing of the isolated microorganisms was performed according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI)[16]. Microorganisms that showed *in vitro* acquired resistance to at least 1 antimicrobial in 3 or more antibiotic families[17] were considered multidrug resistant. To evaluate colistin sensitivity, the colistin drop test was performed. The colistin drop test is a screening method used for assessing sensitivity to colistin. It is based on adding a single 10 µl drop of a 16 µg/ml colistin solution onto a Muller-Hinton Agar (MHA) plate previously swabbed with a standard 0.5 McFarland inoculum. The plates were left for 15 min at room temperature (the droplet should be completely absorbed before moving the plate), then inverted and incubated for 16 to 18 hours at 35°C. After incubation, the presence or absence of an inhibition zone was observed by careful examination with transmitted light.

For standardization purposes, inhibition halos were recorded. An isolate was classified as colistin-sensitive if any zone of inhibition was observed, regardless of diameter (median zones for sensitive isolates are approximately 10 mm for *Acinetobacter* spp. and enterobacterales, and 8 mm for *P. aeruginosa*). An isolate was considered colistin-resistant when there was no halo around the droplet or when colonies were observed within the zone of inhibition, indicative of resistant subpopulations. The stability of the colistin solution was tested monthly for 12 months[18,19].

IV colistin solutions were prepared from 100 mg vials of colistin methanesulfonate (*Laboratorios Richet S.A.*, Buenos Aires, Argentina) at the Intravenous Mixtures Unit of the Pharmacy Area of the *Hospital Garrahan*, following institutional guidelines.

The dosage of IV colistin was 5-7.5 mg/kg/day divided into 2 or 3 doses (maximum dose for > 60 kg: 160 mg every 8 hours). According to clinical and infectological criteria, in patients with severe infection, a dosage every 8 hours was used[20]. The solutions were administered IV, in all cases, within 30 minutes, and any changes that did not comply with this time were recorded.

In each case, the following were evaluated: age, sex, type of burn, Garcés index, isolated microorganism, place of isolation, days of treatment, concomitant nephrotoxic drugs received, presence of alterations in renal or neurological function, and progression.

The Garcés index establishes four groups (mild, moderate, severe, and critical), refers to the severity and prediction of mortality, and relates the patient's age, the depth and extent of the burn injury[21] (table 1).

The evolution of the patients was evaluated based on culture clearance, laboratory studies, and clinical characteristics.

The clinical evaluation was performed daily to monitor the appearance of neurological abnormalities such as seizures, vertigo, dizziness, muscle weakness, paresthesia, confusion, ataxia, and neuromuscular blockade, which are the most frequently reported side effects in the literature[9,22,23].

Renal function assessment was performed every 72 hours until hospital discharge. The RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria were used according to the KDIGO Clinical Practice Guideline for Acute Kidney Injury 2012[24], which considers the serum creatinine (SCr) value and glomerular filtration rate (GFR), according to the revised Schwartz equation with coefficient K = 0.413[25].

Concomitant nephrotoxic drugs were considered to be any drug received during colistin treatment with the potential to cause an adverse effect at the renal level[22].

In order to evaluate clinical effectiveness, the following were considered: fever resolution, improvement of local infection signs, graft attachment in cases of skin infections, and the negative result of the cultures.

Statistical methodology

Categorical variables were expressed as percentages and continuous variables as median and range. To evaluate renal involvement, the difference between the final and initial values (Δ) of SCr and GFR was calculated for each patient, and it was verified whether the values were within or outside the RIFLE criteria according to the KDIGO guideline[24].

Ethical considerations

This study was approved by the Institutional Review Board of the *Hospital de Pediatría Prof. Dr. Juan P. Garrahan* (Protocol #1380). Written informed consent was obtained from the legal representatives of each patient.

Results

Fifteen patients were included in the study, with a median age of 6 years (range 0.7-15.0), and 8 of them were female. The main mechanism of injury was direct fire in 12 patients (80%), followed by hot liquids (13%), and flammable liquids (6.5%). The body surface area burned ranged from 15% to 90% (median 50%). 9 patients (60%) had type AB/B burns and 6 (40%) had type B burns. The Garcés index was II in 2 patients (13%), III in 2 patients (13%), and IV in 11 patients (73%). One patient presented an inhalation injury.

Seven patients received one complete treatment course with colistin, while the remaining 8 patients completed two treatment courses because they had two indications for targeted or empirical treatment. In total, 23 colistin regimens were considered for the study. The median length of hospitalization before initiation of colistin treatment was 9 days, ranging from 1 to 52 days (table 2).

In 10 cases, colistin was indicated as a targeted treatment for infections caused by multidrug-resistant bacteria. In the 13 cases in which a microorganism was not isolated, colistin was indicated as empirical treatment in septic patients with more than one week of hospitalization in the burn unit (considering the local epidemiology).

The most frequently isolated agent was *P. aeruginosa* (6 cases), and the main site of isolation was skin biopsy (9 cases). All cases involved multidrug-resistant bacteria (table 3).

Table 1. Garces Burn Index

(40-age in years) + %TBSA* type A+ % TBSA type AB x2 + % TBSA type B x3		
GROUP I	MILD	from 21 to 60 points
GROUP II	MODERATE	from 61 to 90 points
GROUP III	SEVERE	from 91 to 120 points
GROUP IV	CRITICAL	> 120 points

Table 2. Demographic and Clinical Characteristics

Variable	N
Female sex (%)	8 (53%)
Age (years), median (range)	6 (0,7-15,0)
Burned body surface (%), median (range)	50 (15-90)
Garcés Index III or IV	13 (86%)
Hospitalization time until start of treatment (days), median (range)	9 (1-52)

Table 3. Documented Microorganisms

Patient number	Isolation site	Microorganism
1	Skin	*Klebsiella pneumoniae*
2	blood	*Pseudomonas aeruginosa*
3	Skin	*Pseudomonas aeruginosa*
4	Skin	*Pseudomonas aeruginosa*
5	Skin, urine	*Pseudomonas aeruginosa*
6	Skin, CVC	*Pseudomonas aeruginosa*
7	Skin, urine	*Pseudomonas aeruginosa*
8	Skin	*Pseudomonas mosselii*
9	Skin	*Pseudomonas putida*
10	Skin	*Acinetobacter baumannii*

*CVC: central venous catheter

Regarding colistin treatment, the median dose used was 5.5 mg/kg/day (range 4.0-7.5). The frequency of administration was every 8 hours in 17 treatments (74%) and every 12 hours in the rest (26%). The median duration of treatment was 10 days (range 4-27), and the total length of hospital stay was 77.5 days (range 27.0-171.0).

No patient presented renal damage associated with the use of colistin, both in the period of drug use and in the total hospitalization until discharge.

When analyzing the differences between the final and initial renal function values, a median SCr before colistin use was 0.32 mg/dL (range 0.20-0.67) and 0.29 mg/dL (range 0.15-0.62) after it was used. The Δ in all cases was less than 2 mg/dL, with 0.58 mg/dL being the highest Δ value calculated.

The GFR before the use of colistin was 156.0 ml/min/1.73 m2 (range 66.6-238.3) and at the end of treatment it was 180.6 ml/min/1.73 m2 (range 91.8-302.9). When decreases in values were recorded throughout treatment, in all cases they were less than 25%.

These results, i.e. the Δ calculated for both variables associated with renal function, showed results compatible with preserved renal function. All patients received at least one nephrotoxic drug concomitant with colistin, with a median of 4 nephrotoxic drugs per patient (range 1-10), including amikacin, liposomal amphotericin, furosemide, ibuprofen, morphine, naproxen, trimethoprim-sulfamethoxazole, and vancomycin.

No neurological adverse effects associated with the use of colistin were reported.

One patient died, although unrelated to colistin administration.

Discussion

The current expansion of MR-GNB, which includes *A. baumannii* and *P. aeruginosa*, has led to renewed interest in some older antibiotics, such as polymyxins because the limited use of these agents between the 1980s and the beginning of the 21st century has allowed them to preserve their activity against these pathogens[26]. Montero et al. demonstrated the safety of colistin in the treatment of infections caused by *P. aeruginosa*, the main agent responsible for infections in burn patients[27].

The use of colistin has been restricted in the past due to its associated adverse effects. Its administration may result in increased urea and creatinine levels, as well as the presence of tubular necrosis. Signs of neurological toxicity include seizures, vertigo, paresthesia, muscle weakness, confusion, lack of coordination, visual disturbances, and neuromuscular blockade with episodes of apnea[9,28]. However, improvements in pharmaceutical formulations and new dosing strategies have considerably reduced the toxicity previously attributed to these drugs[29]. Studies in adults propose that short courses of treatment, with controlled cumulative doses, can achieve a favorable clinical progression without associated renal alterations[30,31].

In pediatrics, colistin is proposed as a reasonable alternative when choosing empirical treatment in burn patients, in contexts of high rates of MR-GNB infections, given the low resistance detected to it[32]. Its use as monotherapy is suggested since no benefits were found in the use of combined treatments with carbapenems or other drugs in patients with infections caused by multidrug-sensitive multidrug-resistant microorganisms[33].

Evidence on adverse effects is scarce. In a retrospective investigation covering 11 years and focusing on 14 burn patients, Goverman and his team reported that renal alterations were observed in 14.3% of the cases, with no cases of neurotoxicity reported[14]. More recently, in a study of children in ICUs, adverse effects at the renal level were found in 10.5% of pa-

tients[34]. In this cohort, no patient died in relation to the use of colistin, either from infectious causes or from the progression of the burn, despite that most of them had a Garcés index of III or IV, indicative of severe or critical injury[21].

The limitation of this work is that it is a study with few patients, without a control group, and from a single center. However, its strength lies in the fact that it deals with burn patients, where the effects of the use of this drug are poorly known.

Conclusions

In line with the results of the study previously published by our group, no renal or neurological alterations were evidenced in this work, which makes colistin an alternative, safe, and effective drug in the management of pediatric burn patients in which there are no other therapeutic alternatives according to the sensitivity of the pathogen and the local epidemiology. It is crucial to constantly monitor renal function and possible neurotoxicity. Given the limited number of patients in this study and the lack of a control group, further prospective and pharmacokinetic investigations are needed to conclusively support these claims.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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