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ANÁLISE INTERINA DE SEGURANÇA E RESISTÊNCIA COM LEVOFLOXACINO COMO PROFILAXIA ANTIBIÓTICA EM CRIANÇAS COM LEUCEMIA LINFOBLÁSTICA AGUDA: UM ENSAIO CLÍNICO RANDOMIZADO

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Dedico esta dissertação aos pacientes, seus cuidadores e a todos os profissionais de saúde envolvidos em seus atendimentos. Espero contribuir para amenizar a dor relacionada ao tratamento desta doença.

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“Peço ao Senhor para que não caia mais os cabelinhos e que a quimio não faça mais feridinhas na minha boca, pois devido a elas, fico em isolamento”

Tirada do livro “Anjos do bem” de Gustavo Batista, 5 anos

RESUMO

Introdução: Apesar das altas taxas de cura, a mortalidade relacionada ao tratamento em crianças com leucemia linfoblástica aguda (LLA) permanece significativa. Cerca de 4% dos pacientes morrem durante a terapia de indução da remissão e aproximadamente dois terços das mortes relacionadas ao tratamento são devido a complicações infecciosas. Apesar destas, não está claro na literatura a o papel de medidas profiláticas **Objetivos:** Verificar o impacto do uso da levofloxacino profilática na incidência de efeitos adversos, colite por Clostridioides e emergência de germes multirresistentes, em crianças com LLA de novo **Métodos:** De maio de 2021 a junho de 2022, crianças de 1 a 18 anos, com diagnóstico recente de LLA, internadas em 3 centros de oncologia pediátrica no Brasil, foram incluídas neste ensaio clínico multicêntrico, aberto, randomizado, de fase 3. Os pacientes elegíveis foram divididos aleatoriamente em dois grupos, com base em uma proporção de alocação de 1:1, para receber ou não levofloxacino como agente profilático durante a fase de indução. Todos os pacientes foram tratados de acordo com o protocolo de quimioterapia IC-BFM 2009. Os desfechos primários foram colonização por Enterobacteriaceae produtoras de Carbapenemases (CPE), diarreia por *Clostridioides difficile* e outros eventos adversos relacionados ao uso de levofloxacino. O desfecho secundário foi neutropenia febril durante a indução. **Resultados:** 20 pacientes foram incluídos neste estudo, 10 em cada grupo (controle e levofloxacino). Reações adversas leves relacionadas ao levofloxacino foram observadas em 3 pacientes (30%). Três pacientes apresentaram diarreia por *Clostridioides difficile*, 2 no grupo levofloxacino e 1 no grupo controle (p>0,99). Apenas 1 paciente apresentou colonização por CPE. Este paciente pertencia ao grupo levofloxacino (P>0,99). Nove pacientes apresentaram neutropenia febril, 5 no grupo controle e 4 no grupo intervenção com levofloxacino (P>0,99), 1 paciente morreu de neutropenia febril. **Conclusão:** O uso de levofloxacino mostrou-se seguro na fase de indução em crianças com LLA de novo. O uso dessa medicação não aumentou a taxa de colonização por CPE nem a taxa de diarreia por *C. Difficile*. Todas as reações adversas foram leves e remitiram espontaneamente ou após a mudança da administração do medicamento da via oral para a intravenosa.

Palavras-chave: Leucemia Linfoide. Antibioticoprofilaxia. Criança. Quimioterapia de Indução. Levofloxacino. Neutropenia Febril.

ABSTRACT

Background: Despite high cure rates, treatment-related mortality in children with acute lymphoblastic leukemia (ALL) remains significant. About 4% of patients die during remission induction therapy and approximately two-thirds of treatment-related deaths are due to infectious complications. **Objectives:** to know the incidence of adverse effects, Clostridioides colitis and emergence of multidrug-resistant germs with the use of levofloxacin in children with de novo ALL. **Methods:** From May 2021 to June 2022, children ages 1 through 18 years, with a recent diagnosis of ALL, admitted to 3 pediatric oncology centers in Brazil, were enrolled in this multicentered, open, randomized, phase 3 clinical trial. Eligible patients were randomly divided into two groups, based on a 1:1 allocation ratio, to be given, or not, levofloxacin as a prophylactic agent during the induction phase. All patients were treated according to the IC-BFM 2009 chemotherapy protocol. Primary endpoints were carbapenemase-producing Enterobacteriaceae (CPE) colonization, *Clostridioides difficile* diarrhea, and other adverse events related to the use of levofloxacin. The secondary endpoint was febrile neutropenia during induction. **Results:** twenty patients were included in this trial, ten in each group (control and levofloxacin). Mild adverse reactions related to levofloxacin were observed in 3 patients (30%). three patients had *Clostridioides difficile* diarrhea, 2 in the levofloxacin group and 1 in the control group ($p>0.99$). Only 1 patient presented colonization by CPE. This patient belonged to the levofloxacin group ($P>0.99$). Nine patients presented febrile neutropenia, 5 in the control group and 4 in the levofloxacin intervention group ($P>0.99$), 1 patient died from febrile neutropenia. **Conclusion:** The use of levofloxacin showed to be safe in the induction phase in children with de novo ALL. The use of this medication did not increase the rate of colonization by CPE nor the rate of diarrhea by *C. Difficile*. All adverse reactions were mild and remitted either spontaneously or after switching medicine administration from oral to intravenous route.

Keywords: Leukemia Lymphoid. Antibiotic Prophylaxis. Child. Induction Chemotherapy. levofloxacin. Febrile Neutropenia.

LISTA DE QUADROS

LISTA DE ABREVIATURAS E SIGLAS

BFM	Berlin-Frankfurt-Muenster
CEP	Comitê de ética em pesquisa
DNA	Deoxyribonucleic acid
EPC	Enterobacter produtora de carbapenemase
FOI	Febre de origem obscura
FQ	Fluoroquinolonas
HCPA	Hospital de Clínicas de Porto Alegre
IC	Intercontinental
IFI	Infecção fúngica invasiva
Kg	Quilograma(s)
LA	Leucemia(s) aguda(s)
LMA	Leucemia(s) mieloide(s) aguda(s)
mg	Miligrama
NF	Neutropenia febril
NPIV	Neuropatia periférica induzida por vincristina
PCR	Polymerase chain reaction
PSS	*Power and sample size*
SPSS	Statistical Package for the Social Sciences
St.	Saint
TCTH	Transplante de células tronco hematopoiéticas
TMP-SMX	Trimetroprima-sulfametoxazol
UTI	Unidade de tratamento intensivo

SUMÁRIO

1 INTRODUÇÃO

As neoplasias malignas na infância são a principal causa de morte nessa faixa etária por doença e, dentre essas neoplasias, as leucemias linfoblásticas agudas (LLAs) são as mais prevalentes (SIEGEL; MILLER; JEMAL, 2018). As LLAs são um grupo heterogêneo de doenças que se manifestam pela proliferação de linfoblastos imaturos na medula ou outros tecidos e seu tratamento é basicamente poli quimioterapia em altas doses, seguido de uma fase de manutenção com quimioterapia em baixas doses (PIZZO *et al.*, 2016, p. 1062-1064).

Este tratamento tem evoluído nas últimas décadas, chegando a uma chance de sobrevida global beirando os 90 % (PUI *et al.*, 2015). Apesar das altas taxas de cura, existe uma taxa de mortalidade relacionada ao tratamento que impacta negativamente nesses números. Aproximadamente 4% dos pacientes vão a óbito por complicações relacionadas ao tratamento (PRUCKER *et al.*, 2009).

O protocolo quimioterápico utilizado pela maioria dos centros de tratamento no Brasil e preconizado pela Sociedade Brasileira de Oncologia Pediátrica é o protocolo Intercontinental BFM 2009. Neste protocolo os pacientes são estratificados segundo riscos de recaída e alocados em diferentes subgrupos. Todos eles são submetidos no primeiro mês de tratamento a um período de aproximadamente 30 dias de quimioterapia, período este chamado de indução à remissão. Aqueles que são alocados nos chamados grupos de alto risco, além da fase de indução, são expostos a 6 blocos de quimioterapia intensiva, todos com alto risco de neutropenia prolongada e, por consequência, de neutropenia febril, infecção da corrente sanguínea e óbito.

Infecções bacterianas são a maior causa de morbidade e mortalidade em pacientes neutropênicos secundariamente à quimioterapia, isto é, naqueles que apresentam contagem absoluta de neutrófilos menor do que 500/mm³. Aproximadamente dois terços das mortes relacionadas ao tratamento são de causa infecciosa (PRUCKER *et al.*, 2009). Em adultos, já se comprovaram benefícios do uso de antibioticoprofilaxia durante os períodos de neutropenia naqueles pacientes submetidos à quimioterapia. Nesta população, o uso da profilaxia reduziu infecções e mortalidade relacionada a infecções (GAFTER-GVILI *et al.*, 2005). Por estas razões, o uso de profilaxia antibiótica em pacientes adultos nos períodos de neutropenia afebril já é uma prática bem estabelecida. Porém, em crianças, não há evidências sólidas.

Entre as possibilidades de antibioticoprofilaxia, a levofloxacino, um antibiótico da classe das fluoroquinolonas de amplo espectro, já faz parte de diretrizes que orientam o uso em adultos com neutropenia afebril. Apesar disto, segundo diretriz publicada em julho de 2020 pela Infectious Diseases Society of America, a recomendação é que não se faça uso de antibioticoprofilaxia rotineiramente em crianças em primeiro diagnóstico de LLA na fase de indução devido ao baixo corpo de evidência até o momento. Quando indicado, o grupo sugere o uso de Levofloxacino como antibiótico de escolha e somente para aqueles pacientes que apresentam neutropenia grave (contagem absoluta de neutrófilos <500/mm3) por ao menos 7 dias (LEHRNBECHER *et al.*, 2020).

Em 2021 iniciou-se o ensaio clínico randomizado, aberto, multicêntrico chamado “profilaxia antibiótica com levofloxacino na indução quimioterápica em crianças com leucemia linfoblástica aguda – um ensaio clínico randomizado” (UTN U1111-1284-1338). Como parte desse ensaio clínico foi realizado um projeto objetivando avaliar a segurança do uso de levofloxacino como profilaxia antimicrobiana na fase de indução em crianças com LLA de novo. Desfechos como febre, colite por Clostridioides, efeitos adversos e surgimento de germes multirresistentes foram avaliados.

A análise interina de dados permitirá comparar a incidência de efeitos adversos, colite por Clostridioides e emergência de germes multirresistentes com o uso de levofloxacino nessa população, definindo assim a segurança do ensaio clínico e ampliação do número de pacientes incluídos.

2 REVISÃO DA LITERATURA

2.1 PROFILAXIA ANTIBIÓTICA E LAS NA INFÂNCIA

As características desejáveis para um antibiótico ser usado como profilaxia em pediatria são: amplo espectro de ação, boa biodisponibilidade, atividade bactericida, formulação oral com boa tolerabilidade, poucos efeitos adversos, baixa indução de resistência e baixo custo. Estudos metodológicos sólidos utilizando profilaxia antibiótica em crianças com LLA são escassos. Nos últimos 10 anos somente 7 estudos sobre profilaxia antibiótica com fluoroquinolonas (FQ) na LAs em crianças foram descritos, sendo 3 estudos observacionais e 4 ensaios clínicos randomizados (Quadro 1).

2.2 O PAPEL DAS FQS

FQs são uma classe de antibióticos que apresenta como características: amplo espectro de ação, boa penetração em tecidos e ação bactericida agindo na síntese do DNA bacteriano interferindo com a DNA girase e topoisomerase IV, ambas necessárias para a replicação do DNA. FQ tem ação antibacteriana contra gram positivos, gram negativos e bactérias atípicas (BOSSÙ *et al.*, 2021).

Apesar dessas vantagens teóricas, a preocupação com o uso de FQs em crianças vem de estudos em modelos animais jovens demonstrando diferentes graus de artropatias em diferentes animais. Apesar desses resultados, todos os estudos realizados posteriormente não conseguiram comprovar o aumento do risco de qualquer sequela em neonatos, lactentes e crianças com o uso dessa classe de medicamento (CHOI; KIM; KIM, 2013). Como exemplo, um estudo multicêntrico de Chalumeau *et al*. (2003) demonstrou que, apesar da maior frequência de eventos musculoesqueléticos com o uso do FQ em crianças, quando comparados aos adultos, a maioria desses eventos foi de intensidade moderada e transitória. A suspensão da medicação levou à interrupção completa dos sintomas.

Quadro 1 - Dados sumarizados com os diferentes regimes de profilaxia antibacteriana com FQ em crianças com LAs ou em TCTH nos últimos 10 anos

Estudo (ano)	Tipo de estudo	Pacientes e tratamentos	Regime Profilático	Resultados
Widjajanto *et al*. (2013)	Ensaio clínico randomizado, duplo cego	**- Diagnóstico:** LLA **- Nº pacientes:** 110 (0 - 14 anos) **- Protocolo:** (WK)-ALL-2000	Ciprofloxacino	**Febre (P = 0.07):** - Placebo: risco 2.7% - Intervenção: risco = 50% **Sepse (**P = 0.22): - Placebo: risks = 38.5% - Intervenção: risks = 50% **Mortalidade (P = 0.05):** - Placebo: risks = 5.8% - Intervenção: risks = 18.9% **Nadir (P= 0.01)** - Placebo: 270 (14–25.480) $\times 10^9$células/L - Intervenção: 62 (5–884) x10^9células/L
Laopraspopwattana *et al*. (2013)	Estudo prospectivo randomizado, duplo cego, placebo controlado	**- Diagnóstico:** LLA e linfoma **- Nº pacientes**: 95 (71 com LLA e 24 com linfoma) (3 meses - 18 anos) **- Protocolo:** fase de indução ou consolidação (não especificado)	Ciprofloxacino	**Febre:** - Placebo: 17/34 (50.0) - Intervenção: 27/37 (73.0) - Diferença absoluta de risco: -23.0 (–45.0 para –0.9) **P = 0.046** -LLA 13/24 (54.2) 24/30 (80.0) –25.8 (–50.4 para –1.3) **P = 0.042** -Linfoma 4/10 (40.0) 3/7 (42.9) –2.9 (–50.4 para 44.7) P <0.999
	Prospectivo	**- Diagnóstico:** LLA **- Nº pacientes:** 1.024 230 pacientes - (DFCI 11-001) 794 pacientes - (DFCI 05-001) (1–21 anos) **- Protocolo:** DFCI 11-001 (prophylaxis group) DFCI 05-001 (control group)	Levofloxacino ou moxifloxacino por via oral	**Taxa de infecção durante fase de indução P<0.0001** DFCI 11-001 14.3% DFCI 05-001 26.3% **Taxa de bacteremia durante fase de indução** ***P* < 0.0001** DFCI 11-001 10.9% DFCI 05-001 24.4%

Sulis *et al*. (2017)				**Taxa de morte durante indução** (0.9% vs. 2%) não teve diferença estatística significativa.
Yeh *et al*. (2014)	Estudo de coorte, centro único	**- Diagnóstico:** LLA e LMA **- Nº pacientes:** 149 (113 com LLA e 36 com LMA) (<18 anos) **- Protocolo:** LLA: Taiwan Pediatric Oncology Group-ALL-2002 protocol LMA: Taiwan Pediatric Oncology Group-AML-97A protocol	Ciprofloxacino e voriconazol via oral	LLA **Bacteremia I (P = 0.02)** Pre-prophylaxis: 19 Prophylaxis: 5 **IFI (P <0.01)** Pre-prophylaxis: 10 Prophylaxis: 0 **NF (P <0.01)** Pre-prophylaxis: 50 Prophylaxis: 19 **SG** Pre-prophylaxis: 86%±5% Prophylaxis: 98%±2% **SLE** Pre-prophylaxis: 78%±9% Prophylaxis: 87%±6,5% AML **Bacteremia (P <0.01)** Pre-prophylaxis: 25 Prophylaxis: 5 **IFI (P <0.01)** Pre-prophylaxis: 12 Prophylaxis: 0 **NF(P = 0.01)** Pre-prophylaxis: 24 Prophylaxis: 14 **SG** Pre-prophylaxis: 60%20% Prophylaxis: 68%±16% **SLE** Pre-prophylaxis: 50%±11% Prophylaxis: 55%±11%

Wolf *et al*. (2017)	Estudo de coorte, centro único	**- Diagnóstico:** LLA **- Nº pacientes:** 344 **- Protocolo:** TOTXVI and TOTXV	Levofloxacino (a partir de 08/14) (n=69) Cefepime, ciprofloxacino ou vancomicina mais cefepime ou ciprofloxacino (de 2007 a 07/2014) (n=102)	**Eficácia de profilaxia primária** NF - OR (95% CI): 0.23 (0.14–.40) P <.001 Bacteremia - OR (95% CI): 0.30 (0.13–0.73) P = 0.008 Infecção por *Clostridioides difficile* - (95% CI): 0.38 (0.16–0.93) P = 0.04 **Levofloxacino vs nenhuma profilaxia** NF - OR (95% CI): 0.28 (0.15–0.52) P <.001 Bacteremia - (95% CI): 0.42 (0.15–1.16) P = 0.09 Infecção por *Clostridioides difficile* - OR (95% CI): 0.03 (<.01 to .24) P <.001 **Levofloxacino vs outras profilaxias** NF - OR (95% CI): 1.17 (0.64–2.14) P = 0.60 Bacteremia - OR (95% CI): 1.85 (.54–6.35) P = 0.33 Infecção por *Clostridioides difficile* - OR (95% CI): 0.04 (<0.01-0.36) P= <.001
Alexander *et al*. (2018)	Ensaio clínico randomizado, aberto, multicêntrico	**- Diagnóstico:** LAs e pacientes submetidos a TCTH. **- Nº pacientes:** 624 200 (LAs) 424 (TCTH) (6 meses - 21 anos) **- Protocolo:** LMA: Citarabina, daunorrubicina, etoposídeo Citarabina, etoposídeo Mitoxantrona, Citarabina, outros LLA: Mitoxantrona, vincristina, dexametasona, asparaginase citarabina, asparaginase ciclofosfamida, etoposídeo, outros	Levofloxacino	**Probabilidade de bacteremia** **LAs** Grupo profilaxia: 21.9% Grupo controle: 43.4% Diferença de risco (95%CI); 21.6% (8.8%-34.4%) P = 0.001 **TCTH** Grupo profilaxia: 11.0% Grupo controle: 17.3%; Diferença de risco (95%CI): 6.3% (0.3%-13.0%) P = 0.06 Quando todos os pacientes combinados, levofloxacino reduz significativamente a probabilidade de bacteremia; diferença de risco (95%CI): 11.4%;(5.1%-17.6%) P < .001 **Febre e neutropenia** Grupo profilaxia: 71,2% Grupo controle: 82,1% Diferença de risco (95%CI): 10.8% (4.2%-17.5%) P = 0.002 **Infecção Grave**

		TCTH autólogo: Bussulfano/ melfalano carboplatina outros TCTH alogênico: Radioterapia, bussulfano outros		Grupo profilaxia: 3.6% Grupo controle: 5.9% Diferença de risco (95%CI): 2,3% (−1.1- 5.6%) P = 0.204
Feng *et al*. (2013)	Prospectivo	**- Diagnóstico:** LMA **- Nº pacientes:** 38 (2-16 anos) **- Protocolo:** NOPHO 2004	Vancomicina/ Cefepime ou Piperacilina/ Tazobactam	**Frequência de febre (eventos) P<0.001** Grupo profilaxia: 0.4±0.1 Grupo controle: 0.9±0.1 **Intervalo entre agranulocitose e febre (dias) P=0.07** Grupo profilaxia: 6.4±0.9 Grupo controle: 3.8±0.4 **Hospitalização (dias) P<0.001** Grupo profilaxia: 21.5±0.7 Grupo controle: 28.5±1.7 **Infecção pulmonar P<0.001** Grupo profilaxia: 80% Grupo controle: 39%

Abreviações: LLA (leucemia linfóide aguda); LMA (leucemia mielóide aguda); (WK)-ALL-2000 (Indonesian Wijaya Kusuma (WK)-ALL-2000); DFCI 11-001 (Dana-Farber Cancer Institute ALL Consortium Protocol 11-001); DFCI 05-001 (Dana-Farber Cancer Institute ALL Consortium Protocol 05-001); IFI (infecção fúngica invasiva); NF (neutropenia febril); SG (sobrevida geral); SLE (sobrevida livre de eventos); TOTXVI and XV (Total Therapy Study XVI and XV); TCTH (transplantes de células-tronco hematopoiéticas); LAs (leucemia agudas); NOPHO (Nordic Society of Pediatric Hematology and Oncology).
Fonte: Elaboração própria.

Além disso, o fato de as FQs serem conhecidas pelo risco aumentado de levar à neuropatia periférica em adultos, gera preocupação com o uso dessa classe de antibióticos em neoplasias que também fazem uso de medicamentos com potencial de causar lesão neuropática, como a vincristina, rotineiramente presentes no tratamento da LLA na infância.

No entanto, Karol *et al*. demonstraram, em uma coorte observacional com 598 crianças, que não houve aumento do risco de neuropatia periférica em pacientes diagnosticados com LLA e que utilizaram levofloxacino na indução de remissão. Não houve evidência de associação entre exposição a FQ e neurotoxicidade periférica induzida por vincristina subsequente (taxa de risco [HR] 0,8, intervalo de confiança de 95% [CI] 0,5-1,04, P = 0,08) ou NPIV de alto grau (RH 1,1, 95% CI 0,4-2,2, P = 0,87) (KAROL *et al.*, 2020).

Outro aspecto importante é que, dentro das limitações associadas ao uso profilático de antibióticos, muito se tem falado recentemente sobre o impacto na microbiota normal. Já se sabe que a profilaxia antimicrobiana altera a microbiota intestinal de crianças com câncer. A microbiota consiste em várias espécies de bactérias que povoam o lúmen intestinal compartilhando uma relação simbiótica com seu hospedeiro. É estabelecido nos primeiros estágios da vida e é único para cada indivíduo. Muitos fatores são responsáveis por alterar a taxa microbiana intestinal humana, um dos quais é o uso de antibióticos, mesmo por curtos períodos. Essa alteração é chamada de disbiose e tem se mostrado relacionada ao desenvolvimento de diversas doenças, como asma, síndrome de Kawasaki, autismo, doença inflamatória intestinal e, principalmente, câncer, além de outros fatores de risco.

Alguns efeitos do uso de FQs na microbiota intestinal já são conhecidos, como redução da abundância de Enterobacteriaceae, *Bacillus* spp., *Corynebacterium spp*., depleção de algumas bactérias anaeróbias (*Bacterioides* spp., *Bifidobacterium* spp., *Lactobacillus* spp., *Peptostreptococcus* spp., *Veilonella* spp.) e aumento da abundância de *Citrobacter spp*., *Enterobacter* e *Klebsiella* spp. (13). De acordo com uma revisão recente de Bossù *et al*. pouco se sabe hoje sobre a interação da microbiota com o antibiótico profilático e se esse aspecto pode realmente influenciar o prognóstico de crianças com LAs (BOSSÙ *et al.*, 2021).

Apesar dos poucos estudos com FQs, alguns resultados foram importantes para orientar novas pesquisas nessa classe de antibióticos. Laoprasopwattana *et al*., em 2013, em estudo randomizado com ciprofloxacino em 95 crianças, demonstraram

que seu uso é capaz de prevenir episódios febris em crianças neutropênicas com LLA (P=0,046). No entanto, esse efeito só foi identificado na fase de indução da remissão. Em outras fases de tratamento, e em pacientes com linfoma, esse efeito não foi observado. Todavia, houve um aumento na porcentagem de *Escherichia coli* e *Klebsiella pneumoniae* resistentes à ciprofloxacino em swab retal controle (LAOPRASOPWATTANA *et al.*, 2013).

No ano seguinte, outro estudo investigou a eficácia na prevenção de infecção da corrente sanguínea e infecção fúngica invasiva (IFI) com antibióticos e agentes antifúngicos. Um estudo de coorte em Taiwan foi realizado entre 113 pacientes com diagnóstico inicial de LLA e LMA. Profilaxia com ciprofloxacino e antifúngicos foram administrados nos períodos de indução e quimioterapia de alta intensidade. A profilaxia combinada foi capaz de reduzir as taxas de infecção da corrente sanguínea, IFI, NF e tempo de internação em UTI de pacientes com LLA. Também foi capaz de reduzir as taxas de infecção da corrente sanguínea, FN, IFI e mortes relacionadas à infecção em crianças com LMA. O estudo também se mostrou custo-efetivo e não demonstrou aumento da taxa de resistência à ciprofloxacino durante o tratamento (YEH *et al.*, 2014).

No entanto, nem todos os estudos de ciprofloxacino foram na mesma direção. Anteriormente, um ensaio clínico randomizado duplo-cego na Indonésia com 110 crianças com diagnóstico inicial de LLA concluiu que a ciprofloxacino, quando usada durante a indução da quimioterapia, levou a um nadir mais alto de contagem de neutrófilos (mediana de 62 vs. 270, P <0,01) e risco aumentado de mortalidade (18,9% versus 5,8%, P=0,05) quando comparado ao placebo. Os autores destacaram a desnutrição não balanceada entre o grupo placebo e o grupo intervenção (WIDJAJANTO *et al.*, 2013).

2.3 LEVOFLOXACINA E PROFILAXIA

É importante ressaltar que os benefícios do uso de antibioticoprofilaxia durante os períodos de neutropenia em pacientes em quimioterapia já foram comprovados em adultos com LA. A profilaxia reduz infecções e mortalidade relacionada à infecção. Por esses motivos, seu uso em períodos de neutropenia afebril já é uma prática bem estabelecida nessa faixa etária. Dentre os possíveis antibióticos, a levofloxacino já faz

parte das diretrizes internacionais para adultos com neutropenia (GAFTER-GVILI *et al.*, 2005).

Entre os poucos dados existentes sobre o uso de levofloxacino em crianças, um estudo de coorte realizado em 2017 no St. Jude Children's Research Hospital (Memphis/Tennessee) com 344 pacientes identificou que a profilaxia foi capaz de prevenir significativamente a NF e a infecção sistêmica durante a quimioterapia de indução por ≥ 70%. O uso de levofloxacino nessas crianças também minimizou o uso de antibioticoterapia com cefepime/ceftazidime, vancomicina e aminoglicosídeos. Inesperadamente, a profilaxia com levofloxacino reduziu drasticamente as taxas de infecção por colite causada por *Clostridioides difficile* e outras enterocolites (WOLF *et al.*, 2017). Dados extremamente relevantes, uma vez que a infecção por *Clostridioides difficile* está relacionada à maior mortalidade em crianças hospitalizadas, maiores custos hospitalares e tempo de internação hospitalar (SAMMONS *et al.*, 2013).

No mesmo ano, Sulis *et al*. (2018) corroboraram esses achados demonstrando que o uso de FQ para o tratamento inicial da febre, bem como para a profilaxia em 230 crianças com diagnóstico inicial de LLA recebendo quimioterapia de indução é eficaz na redução de bacteremia por gram-negativos e alguns gram-positivos. Além disso, foi demonstrado que a levofloxacino não levou a um aumento da incidência de germes multirresistentes ou infecção por *Clostridioides difficile* ou fungos.

Além de prevenir a NF, a levofloxacino também poderia ser utilizada para prevenir a bacteremia na LA, importante fator de morbimortalidade nesses pacientes. Da mesma forma, Alexander *et al*. em ensaio clínico randomizado com 195 crianças com LA e 418 crianças submetidas ao TCTH demonstraram efeito protetor em crianças com LA que usaram levofloxacino durante o período de neutropenia. A probabilidade de febre e neutropenia foi menor no grupo de profilaxia com levofloxacino do que no grupo controle (71,2% vs. 82,1%; IC 95%, P=0,002), assim como o risco de bacteremia (21,9% vs. 43,4%; IC 95%, P=0,01). No entanto, o mesmo estudo não demonstrou esse mesmo efeito na redução do risco de bacteremia em crianças submetidas ao TCTH (ALEXANDER *et al.*, 2018).

Atualmente, a prevenção da NF não é o único objetivo de implementação da profilaxia antibiótica. Também é importante considerar o custo-benefício de seu uso, uma vez que um episódio de NF pode ter um impacto orçamentário importante devido à internação em UTI, uso de antibióticos caros e óbito. Em alguns estudos, a levofloxacino foi eficaz na prevenção de infecção bacteriana com custo-efetividade

comprovada em crianças com LMA e LLA recidivante recebendo quimioterapia intensiva (MASER *et al.*, 2020; MCCORMICK *et al.*, 2020).

Esses dados apoiaram a publicação de uma diretriz, em julho de 2020, pela Infectious Diseases Society of America sobre profilaxia antibacteriana em câncer pediátrico e transplante de células-tronco hematopoiéticas. A recomendação é que a antibioticoprofilaxia não seja usada rotineiramente em crianças diagnosticadas com LLA na fase de indução, devido ao baixo corpo de evidências apresentado até o momento. Apesar dessa consideração, o grupo sugere o uso de levofloxacino como antibiótico de escolha para aqueles pacientes que apresentam neutropenia grave (contagem absoluta de neutrófilos <500/mm3) por pelo menos 7 dias (LEHRNBECHER *et al.*, 2020).

2.4 REGIMES PROFILÁTICOS QUE NÃO SEJAM FQS

Os estudos mais recentes se concentram no uso de FQs na profilaxia de infecções durante períodos neutropênicos em pacientes pediátricos com câncer, mas outras classes de antibióticos foram investigadas anteriormente (AVRIL *et al.*, 1994; CECINATI *et al.*, 2014). Os regimes baseados em trimetoprima-sulfametoxazol (TMP-SMX) foram uma das combinações testadas nesses ensaios.

O TMP-SMX tem atividade bactericida contra várias bactérias cepas como Klebsiella, *Escherichia coli*, Salmonella (bactérias Gram-negativas), *Streptococcus pyogenes*, *Staphylococcus aureus*, *Streptococcus pneumoniae* (bactérias Gram-positivas), como também *Pneumocystis jiroveci* e *Nocardia* (RUNGOE *et al.*, 2010).

Os estudos que testaram a profilaxia antibiótica em crianças tratadas para malignidades hematológicas agudas têm resultados conflitantes sobre a eficácia do TMP-SMX. Gorin *et al*., entre 1979 e 1982, em estudo duplo-cego, avaliaram a eficácia do uso da profilaxia TMP-SMX em crianças com LLA. O grupo de dados foi capaz de mostrar menor incidência de infecções bacterianas (como otite média p=0,004) e menos episódios de internação hospitalar no grupo tratado (p=0,01), mas a diferença no número de bacteremias no grupo profilático não foi estatisticamente significante (p=0,08). Eles também demonstraram a emergência de bastonetes gram-negativos resistentes a TMP-SMX (p=0,05) (GOORIN *et al.*, 1985). Em 2010, Rungoe *et al*. publicaram um estudo de coorte retrospectivo não randomizado de crianças com LLA (n=171) para comparar a taxa de infecções entre 2 grupos, dos quais um recebeu

profilaxia SMX-TMP. Eles conseguiram demonstrar que o grupo de profilaxia desenvolveu menos episódios de febre (p<0,002) e bacteremia (p<0,0003), apesar de não ser um estudo randomizado (RUNGOE *et al.*, 2010).

A superioridade do TMP-SMX na prevenção de infecções em crianças neutropênicas recebendo quimioterapia de indução de LLA não foi demonstrada em outros estudos. Cruciani *et al*., em um estudo prospectivo randomizado, compararam a eficácia de norfloxacino oral versus TMP-SMX oral e Van Eys *et al*., em outro estudo prospectivo randomizado, também verificaram o uso de profilaxia com TMP-SMX em crianças com LLA. Ambos foram incapazes de demonstrar uma diferença estatisticamente significativa entre os grupos de tratamento e controle. Da mesma forma, Cruciani *et al*. observaram uma grande seleção de cepas gram-negativas resistentes no grupo de profilaxia com TMP-SMX (CRUCIANI *et al.*, 1989). Em outro estudo, Lange *et al*., embora tenham mostrado diminuição do número de dias de internação no grupo de tratamento (p<0,001), não demonstraram diferença significativa no número de episódios de infecção ou febre de origem desconhecida (LANGE *et al.*, 1984).

Em uma recente meta-análise de diretrizes para profilaxia antibacteriana em câncer pediátrico e transplante de células-tronco hematopoiéticas, publicada por Lehrnbecher *et al*., embora tenham sido encontradas evidências de que a profilaxia TMP-SMX reduziu a mortalidade relacionada à infecção (razão de risco [RR], 0,61 ;95% CI, 0,39-0,94) e bacteremia (RR, 0,59; 95/5 CI, 0,41-0,85) e que a profilaxia com cefalosporina reduziu a bacteremia (RR, 0,30; 95% CI, 0,15-. 58), seu uso não foi recomendado devido ao fato de que os estudos podem ter viés e a observação de que a profilaxia TMP-SMX pode causar mielossupressão induzida por drogas e selecionar bactérias multirresistentes (LEHRNBECHER *et al.*, 2020).

Outra combinação de antibióticos já testados na profilaxia foi a teicoplanina com uma cefalosporina de terceira geração. Em um estudo randomizado com crianças tratadas com altas doses de quimioterapia e TCTH (n=60), Avril *et al*. (1994) apresentaram menor incidência de septicemia (p<0,05), atraso do primeiro episódio de febre (p<0,005) e aumento do intervalo de tempo entre o TCTH e o início da FOI no grupo de profilaxia (p<0,001).

Nesse contexto, a amoxicilina/clavulanato também foi testada para prevenir infecção em crianças neutropênicas. Em um estudo multicêntrico randomizado, duplo-cego controlado por placebo, Castagnola *et al*. (2003) testaram

amoxicilina/clavulanato oral para prevenir infecção e/ou febre em crianças neutropênicas (n=167). O estudo não foi capaz de demonstrar que a profilaxia com amoxicilina/clavulanato foi superior ao placebo na prevenção de febre ou infecção.

3 JUSTIFICATIVA

Não há nenhum ensaio clínico randomizado até o momento que tenha avaliado o uso de levofloxacino na indução quimioterápica e blocos de alto risco de neutropenia febril em crianças com LLA em primeiro diagnóstico, objetivando avaliar desfechos infecciosos e de segurança. Como este é um estudo prospectivo envolvendo pacientes de alta gravidade, faz-se necessária uma análise interina que avalie a segurança da exposição desses pacientes com levofloxacino para definirmos o seguimento ou não do estudo.

4 HIPÓTESE

O uso de levofloxacino em crianças com primeiro diagnóstico de LLA na fase de indução quimioterápica é seguro, não é capaz de induzir à emergência de *Enterobacter* produtora de carbapenemases e não aumenta o risco para colite por *Clostridioides difficile.*

5 OBJETIVOS

5.1 GERAL

Avaliar a segurança do uso de levofloxacino em crianças com primeiro diagnóstico de LLA na fase de indução quimioterápica.

5.2 ESPECÍFICOS

- Avaliar o impacto da antibioticoprofilaxia nas taxas de colonização por Enterobactérias Produtoras de Carbapenemases (EPC).
- Avaliar o impacto da antibioticoprofilaxia nas taxas de diarréia relacionada a *Clostridioides difficile*.
- Avaliar efeitos adversos agudos relacionados ao uso de levofloxacino.
- Avaliar o impacto da antibioticoprofilaxia nas taxas de neutropenia febril.

6 METODOLOGIA

6.1 TIPO E NATUREZA DO ESTUDO (DELINEAMENTO)

Este é um ensaio clínico de fase III, randomizado, multicêntrico, aberto.

6.2 LOCAL OU CENÁRIO

Este ensaio clínico está sendo realizado nos seguintes hospitais:

- Hospital da Criança Santo Antônio, Porto Alegre, RS.
- Hospital Amaral Carvalho, Jaú, SP.
- Hospital de Clínicas de Porto Alegre, Porto Alegre, RS.

6.3 POPULAÇÃO E AMOSTRA

6.3.1 Critérios de inclusão

Foram incluídos todos os pacientes, de um ano a dezoito anos incompletos, com diagnóstico inicial de leucemia linfoblástica aguda admitidos nos três hospitais pediátricos a partir da data da aprovação do estudo no comitê de ética de cada hospital. Todos os pacientes que participaram do estudo foram submetidos a Terapia de indução que inclui 4 semanas de prednisona oral, 4 doses de vincristina semanais, 2 ou 4 doses de daunorrubicina semanais e 2 doses de PEG-asparaginase. Os lactentes menores de um ano de idade são submetidos a protocolo específico para esta faixa etária e, portanto, não foram incluídos neste estudo.

Crianças com infecção clínica ou microbiologicamente documentada antes do início da indução ou com febre antes da terapia de indução que requereu uso de antibioticoterapia prolongada (> 5 dias) para tratar infecção não foram incluídos no estudo para evitar confusão entre tratamento antibiótico com profilaxia antibiótica. Crianças com qualquer tipo de histórico de alergia ao uso de quinolonas e histórico de artrite crônica em tratamento também não participaram do estudo.

6.3.2 Critérios de exclusão

Pacientes que desenvolveram neutropenia febril nos primeiros 7 dias de indução ou após <2 dias de neutropenia serão excluídos pela ausência de oportunidade suficiente para atividade da antibioticoprofilaxia.

6.3.3 Cálculo amostral

Foi calculado o tamanho de amostra para detectar diferenças entre as proporções de neutropenia febril entre os grupos intervenção controle, por meio da ferramenta PSS-health (BORGES *et al*., 2021). Considerando poder de 80%, nível de significância de 5% e uma proporção de neutropenia febril no Tratamento de 40% e no Controle de 61% como é referida em Wolf (2017), chegou-se ao tamanho de amostra total de 196 sujeitos, sendo 98 em cada grupo. Acrescentando 10% para possíveis perdas e recusas o tamanho da amostra deverá ser 218 pacientes.

Para este estudo, o cálculo amostral não foi realizado por se tratar de um estudo com amostra por conveniência.

6.4 INTERVENÇÃO

A randomização entre os grupos de estudo foi aleatória por bloco de quatro pacientes e foi utilizado o programa online *Research Randomizer*. A população foi dividida em dois grupos descritos a seguir.

6.4.1 Grupo intervenção (grupo 1)

Neste grupo, o uso de Levofloxacino inicia-se no terceiro dia na indução quimioterápica para todos os pacientes. A opção por só iniciar no terceiro dia foi para facilitar o recrutamento destes pacientes.

O uso foi contínuo até que qualquer um dos critérios a seguir fossem atendidos: (a) contagem absoluta de neutrófilos maior ou igual a 500/μL após nadir; (b) início do próximo ciclo quimioterápico. Levofloxacino era suspenso se antibioticoterapia parenteral foi iniciada por qualquer razão.

A dose do levofloxacino usada para crianças entre um ano e < cinco anos é de 10 mg/kg/dose 2x ao dia e, para aqueles maiores de 5 anos, é de 10 mg/kg/dose 1x ao dia, dose máxima de 750 mg/dia. Levofloxacino é administrada oralmente, caso

não seja tolerada a via oral o mesmo pode ser administrado endovenoso na mesma dose e esquema.

6.4.2 Grupo intervenção (grupo 2)

Os pacientes deste grupo não serão expostos a nenhum tipo de intervenção.

6.5 COLETA E PROCESSAMENTO DE DADOS

Os dados foram registrados através do *software* Redcap®, garantindo, assim, o sigilo das informações e permitindo a integração com as demais instituições nacionais participantes. Cada centro teve acesso às informações de seu próprio centro. Somente o centro coordenador tem acesso aos dados globais. A forma de acesso aos dados do paciente foi por consulta direta ao prontuário.

A análise estatística foi realizada com o software SPSS (*Statistical Package for the Social Science*, v. 18). As variáveis contínuas foram avaliadas com o teste de normalidade de Shapiro-Wilk; aqueles com distribuição assimétrica foram expressos em medianas e intervalos interquartis. As variáveis qualitativas foram resumidas em frequências absolutas e relativas. O teste exato de Fisher e o teste do qui-quadrado de Pearson foram usados para variáveis categóricas e o teste U de Mann-Whitney para variáveis quantitativas.

6.6 VARIÁVEIS UTILIZADAS

As variáveis analisadas foram idade, sexo, tipo de leucemia linfoblástica aguda, uso ou não de levofloxacino durante a indução, diagnóstico de síndrome de down, colonização por EPC, diarreia por clostridioides, toxicidade relacionada ao uso de levofloxacino e neutropenia febril durante a indução.

A Neutropenia febril foi definida pela presença de temperatura corporal maior ou igual a 37,8 oC em pacientes cuja contagem total de neutrófilos foi menor que 500/µL.

Diarreia por *Clostridiodes Difficile* foi definida pela presença de diarreia e identificação, nas fezes, da presença de *Clostridioides difficile* por PCR ou identificação de suas toxinas.

A monitorização da colonização por EPC foi realizada por swab retal no momento da admissão hospitalar – para identificarmos que o paciente não está colonizado antes do início do tratamento – e ao final das internações e do bloco de indução. A coleta de swab adicional à exceção desses critérios foi de escolha do médico ou Controle de Infecção Hospitalar de cada centro.

Efeitos adversos foram definidos quanto a causalidade sendo classificadas como: possível, provável ou definitiva e descritos quanto a gravidade de cada sistema fisiológico como: leve, moderada, grave ou fatal, segundo critérios modificados da Organização Mundial de Saúde (Quadro 2 e Quadro 3).

Quadro 2 – Classificação da toxicidade quanto a causalidade

Possível	Ocorre onde dois ou mais medicamentos podem ser envolvidos, ou ainda se pode inferir relação com a doença
Provável	Ocorre onde somente um medicamento pode ser envolvido
Definida	ocorre durante a infusão e/ou reexposição

Fonte: Elaboração própria.

Quadro 3 – Classificação da toxicidade quanto a gravidade

Leve	Pequena importância clínica e de curta duração, podendo requerer tratamento, não afetando substancialmente a vida do paciente
Moderada	Altera as atividades usuais do paciente, resultando em incapacidade transitória sem sequelas. Necessita de intervenção
Grave	Ameaça diretamente a vida do paciente, provoca hospitalização e pode causar sequelas permanentes
Fatal	Resulta em óbito

Fonte: Elaboração própria.

6.7 ANÁLISE ESTATÍSTICA

A análise estatística foi realizada com o software SPSS (Statistical Package for the Social Science, v. 18). Os dados categóricos foram expressos em frequências e percentuais.

6.8 CONSIDERAÇÕES ÉTICAS

O projeto foi aprovado pelo Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre CAAE 43076621.8.1001.5327 e pelos respectivos CEPs de todos os centros participantes.

A equipe de pesquisa assinou o termo de compromisso para utilização dos dados dos prontuários como garantia da confidencialidade das informações obtidas.

Ausência de conflitos de interesse.

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7 RESULTADOS

7.1 ARTIGO 1

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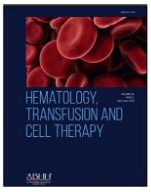

Review article

Antibiotic prophylaxis in acute childhood leukemia: What is known so far?

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ABSTRACT

Introduction: The treatment of acute lymphoblastic leukemia (ALL) has evolved in recent decades, reaching an overall survival rate close to 90%. Currently, approximately 4% of patients with ALL die from secondary complications of chemotherapy. Among these complications, the most frequent is febrile neutropenia (FN). The treatment of acute myeloid leukemias (AMLs) is even more aggressive, being consequently related to a considerable amount of treatment-related toxicity with a high risk of severe infection and death.
Method: In order to reduce the infection-related risks in these groups of patients, systemic antibacterial prophylaxis has emerged as a possible approach.
Results: Antibiotic prophylaxis during neutropenia periods in those undergoing chemotherapy have .already been proven in adults with acute leukemias (ALs). Among the possible available therapeutic options for bacterial prophylaxis in children with cancer, fluoroquinolones emerged with the most amount of evidence. Within this class, levofloxacin became the best choice.
Conclusion: Therefore, the use of levofloxacin seems to be indicated in very specific situations: in children who are known to be neutropenic for a long time, secondary to intensive chemotherapy; in children with AL undergoing chemotherapy to induce remission; or in children undergoing hematopoietic stem cell transplantation (HSCT). This article aims to describe recent evidence focusing on antibiotic prophylaxis in children with ALs.

por favor (1) pedir que o autor confirme o endereço institucional (2) pedir que o autor corrija algumas dúvidas do revisor de inglês marcadas no texto em azul

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Introduction

Malignant neoplasms in pediatric patients are the main cause of death not related to accidents in this age group and, among them, acute leukemias (ALs) are the most prevalent.[1] The ALs can be classified as acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), according to the hematopoietic origin of the leukemic blast

The treatment of ALLs has evolved in recent decades, reaching an overall survival rate close to 90%.[2] Although there are several chemotherapy protocols, most of them are based on a remission induction period, followed by a post-induction/intensification/consolidation and maintenance phase.

Due to the high cure rates in ALLs, the percentage of treatment-related deaths should be reduced to the lowest possible number. Today, approximately 4% of patients die from secondary complications of chemotherapy. Among these complications, the most frequent is febrile neutropenia (FN) followed by infections of the respiratory tract, ear, bloodstream and gastrointestinal tract, which occur mainly in more intensive chemotherapy periods, such as the induction phase.[3] Infections not only directly increase the death rate, but can also cause delays in chemotherapy treatment, which can, in turn, lead to an increase in relapse rates. It is noteworthy that, among all etiologies, bacterial infections are the major cause of morbidity and mortality in neutropenic patients after chemotherapy in this group of patients.[4]

The treatment of AML, different from ALL, consists of sequential blocks of high-intensity chemotherapy that can be associated with allogeneic hematopoietic stem cell transplantation (HSCT). These high-intensity chemotherapy blocks lead to near-myeloablation and, consequently, to a considerable amount of treatment-related toxicity with a high risk of severe infection and death.[3]

Despite this, survival rates have increased in the last decade, reaching 70% in developed countries, mainly due to the improvement of supportive care and the adaptation of therapy based on risk factors, such as genetic alterations and response.[5]

Because of the causes described above (intensity of chemotherapy regimen and need for HSCT), infection and treatment-related mortality rates in children with AML are generally higher than in those with ALL.[3,6,7]

In order to reduce the risks related to infection in these groups of patients, systemic antibacterial prophylaxis has emerged as a possible approach. To establish the regular use of this approach, risks and benefits must be evaluated, as the use of antibiotics is related to acute and chronic adverse effects, induction of antibacterial resistance, increased *Clostridium difficile* infection and invasive fungal infection (IFI).[8] At the same time, these negative events may be overcome by potential positive effects, such as a reduction in fever and infections, lower hospitalization rates in intensive care units (ICUs), reduction in overall mortality and infection-related costs.[9] This review will seek to evaluate these aspects by describing what is known today about the use of antibiotic prophylaxis in children with AL undergoing chemotherapy.

Antibiotic prophylaxis and ALs in childhood

The desirable characteristics for an antibiotic to be used as prophylaxis in pediatrics are a broad spectrum of action, good bioavailability, bactericidal activity, oral formulation with good tolerability, few adverse effects, low induction of resistance and low cost. Solid methodological studies using antibiotic prophylaxis in children with ALs are scarce. In the last 10 years, 7 studies on the impact of antibiotic prophylaxis with fluoroquinolones (FQs) in AL in children were described in the literature, of which 3 were observational analyses and 4, randomized clinical trials. (See Table 1).

The role of FQs

The FQs are a class of antibiotics with the main necessary characteristics for a good prophylactic agent in pediatrics: broad spectrum of action (antibacterial action against gram positive, gram negative and atypical bacteria), good penetration into tissues and bactericidal action, action on bacterial DNA synthesis, interfering with DNA gyrase and topoisomerase IV, and oral formulation.[11]

Despite these theoretical advantages, the concern regarding the use of FQs in children originates from studies in young animal models demonstrating different degrees of arthropathies in various subjects. Despite these previous results, all studies performed later failed to prove the increased risk of any sequel in neonates, infants and children with the use of this drug.[11] As an example, a multicenter study by Chalumeau et al. demonstrated that, despite a higher frequency of musculoskeletal events with the use of FQ in children, when compared to adults, most of these events were of moderate intensity and transient. The discontinuation of the medication led to the complete cessation of symptoms.[12]

In addition, the fact that FQs are known for their increased risk of leading to peripheral neuropathy in adults raises concern about the usage of this class of antibiotics in neoplasms that also make use of neuropathic medications, such as vincristine, applied in the treatment of childhood ALL.

However, Karol et al. demonstrated, in an observational cohort with 598 children, that there was no increase in risk of peripheral neuropathy in patients diagnosed with ALL who used it in the remission induction. There was no evidence of an association between FQ exposure and subsequent vincristine-induced peripheral neurotoxicity (VIPN) (hazard ratio [HR] 0.8, 95% confidence interval [CI] 0.5 - 1.04, $p = .08$) or high-grade VIPN (HR 1.1, 95% CI 0.4 - 2.2, $p = 0.87$).[13]

Another important aspect is that, within the associated limitations of the prophylactic antibiotics use, much has been recently stated about the impact on the normal microbiota. It is already known that antimicrobial prophylaxis alters the intestinal microbiota of children with cancer. The microbiota consists of several species of bacteria that populate the intestinal lumen, sharing a symbiotic relationship with their host. It is established in the early stages of life and it is unique to each individual. Many factors are responsible for altering the human intestinal microbial rate, one of which is the use of

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Table 1 – Summary data with different FQ regimes of antibacterial prophylaxis in children with AL or undergoing HSCT in the last 10 years.

Study (year)	Type of study	Diagnostic	Patients	Treatment	Prophylactic regimens	Results	Comments
Alexander *et al.* (2018)	Multicenter open label randomized trial	ALs and patients undergoing HSCT	624 patients (6 months - 21 years old) 200 (ALL) 424 (HSCT)	**Protocol:** AML: Cytarabine, daunorubicin, etoposide cytarabine, etoposide mitoxantrone, cytarabine, others ALL: Mitoxantrone, vincristine, dexamethasone, asparaginase cytarabine, asparaginase cyclophosphamide, etoposide, others Autologous HSCT: Busulfan/melphalan carboplatin based/ others Allogeneic HSCT: Total body irradiation based, busulfan based, others	Levofloxacin	**Bacteremia** ALs Prophylaxis group: 21.9% Control group: 43.4% risk difference (95%CI); 21.6% (8.8% - 34.4%) $p = 0.001$ Patients undergoing HSCT Prophylaxis group: 11.0% Control group: 17.3%. risk difference (95%CI): 6.3% (0.3% - 13.0%) $p = 0.06$ When all patients combined, levofloxacin significantly reduced the likelihood of bacteremia: risk difference (95%CI): 11.4%;(5.1% - 17.6%) $p < .001$ **Fever and neutropenia** Prophylaxis group: 71.2% Control group: 82.1% risk difference (95%CI): 10.8% (4.2% - 17.5%) $p = 0.002$ **Severe infection** Prophylaxis group: 3.6% Control group: 5.9% risk difference (95%CI): 2.3% (−1.1 - 5.6%) $p = 0.204$	The likelihood of fever and neutropenia was lower in the levofloxacin prophylaxis group than in the control group in children with AL (71.2% *vs.* 82.1%; 95% IC, $p = 0,002$) as was the risk of bacteremia (21.9% *vs.* 43.4%; 95% IC, $p = 0.01$). However, the study did not demonstrate this same effect in reducing the risk of bacteremia in children undergoing HSCT.

Table 1 (*continued*)

Study (year)	Type of study	Diagnostic	Patients	Treatment	Prophylactic regimens	Results	Comments
Sulis *et al.* (2017)	Prospective	ALL	1,024 patients (1 – 21 years old) 230 patients - (DFCI 11-001) 794 patients - (DFCI 05-001)	**Protocol:** DFCI 11-001 (prophylaxis group) DFCI 05-001 (control group)	Oral levofloxacin or moxifloxacin	**Bacteremia during induction** **P < 0.0001** DFCI 11-001 10.9% DFCI 05-001 24.4% **Infection during induction** **P<0.0001** DFCI 11-001 14.3% DFCI 05-001 26.3% **Induction death** (0.9% *vs.* 2%) was not significantly different	The study demonstrated that FQ use for prophylaxis is effective in reducing gram-negative and some gram-positive bacteremia. Also shown that levofloxacin did not lead to an incidence increase of multi resistant germs or infection by *Clostridium difficile* or fungi.
Wolf *et al.* (2017)	Single-center observational cohort study	ALL	344 patients	**Protocol:** TOTXVI and TOTXV	Levofloxacin (from August 2014) (n=69) Cefepime, ciprofloxacin or vancomycin plus cefepime or ciprofloxacin (2007 - July 2014) (n = 102)	**Effectiveness of Primary Prophylaxis** FN - adjusted OR (95% CI): 0.23 (0.14 −.40) $p < .001$ BSI - adjusted OR (95% CI): 0.30 (0.13 −0.73) $p = 0.008$ *Clostridium difficile* infection - adjusted OR (95% CI): 0.38 (0.16 − 0.93) $p = 0.04$ **Levofloxacin vs no prophylaxis** FN - adjusted OR (95% CI): 0.28 (0.15 − 0.52) $p < .001$ BSI - adjusted OR (95% CI): 0.42 (0.15 − 1.16) $p = 0.09$ *Clostridium difficile* infection - adjusted OR (95% CI): 0.03 (< .01 to .24) $p < .001$ **Levofloxacin vs**	The article identified that prophylaxis was able to significantly prevent FN and systemic infection during induction chemotherapy by ≥ 70%. The use of levofloxacin also minimized the use of antibiotic treatment with cefepime/ceftazidime, vancomycin and aminoglycosides.

Table 1 (*continued*)

Study (year)	Type of study	Diagnostic	Patients	Treatment	Prophylactic regimens	Results	Comments
						other prophylaxis FN - adjusted OR (95%CI): 1.17 (0.64 – 2.14) p = 0.60 BSI - adjusted OR (95%CI): 1.85 (.54 – 6.35) *p* = 0.33 *Clostridium difficile* infection - adjusted OR (95%CI): 0.04 (< 0.01 - 0.36) *p* = <. 001 (Shouldn't this be "≤"???)	
Yeh *et al.* (2014)	Single-center cohort study	ALL and AML	149 patients (< 18 years old) 113 with ALL 36 with AML	**Protocol:** ALL: Taiwan Pediatric Oncology Group-ALL-2002 protocol AML: Taiwan Pediatric Oncology Group-AML-97A protocol	Oral ciprofloxacin Oral voriconazole	**ALL** **BSI (P = 0.02)** Pre-prophylaxis: 19 Prophylaxis: 5 **IFI (*p* < 0.01)** Pre-prophylaxis: 10 Prophylaxis: 0 **FN (*p* < 0.01)** Pre-prophylaxis: 50 Prophylaxis: 19 **OS** Pre-prophylaxis: 86% ± 5% Prophylaxis: 98% ± 2% **EFS** Pre-prophylaxis: 78% ± 9% Prophylaxis: 87% ± 6,5% **AML** **BSI (*p* < 0.01)** Pre-prophylaxis: 25 Prophylaxis: 5 **IFI (*p* < 0.01)** Pre-prophylaxis: 12 Prophylaxis: 0 **FN (*p* = 0.01)** Pre-prophylaxis: 24 Prophylaxis: 14	The study demonstrated that the combined prophylaxis was able to reduce the rates of bloodstream infection, IFI, FN and length of stay (LOS) in ICU patients with ALL. It was also able to reduce rates of bloodstream infection, FN, IFI and infection-related deaths in children with AML. They did not demonstrate ciprofloxacin resistance rate increase during treatment.

Table 1 (*continued*)

Study (year)	Type of study	Diagnostic	Patients	Treatment	Prophylactic regimens	Results	Comments
						OS Pre-prophylaxis: 60% ± 20% Prophylaxis: 68% ± 16% **EFS** Pre-prophylaxis: 50% ± 11% Prophylaxis: 55% ± 11%	
Widjajanto *et al.* (2013)	Randomized double-blind study	ALL	110 patients (0 - 14 years old)	**Protocol:** (WK)-ALL-2000	Ciprofloxacin	**Fever (*p* = 0.07):** - Placebo: risks = 32.7% - Prophylaxis: risks = 50% **Clinical sepsis** (*p* = 0.22): - Placebo: risks = 38.5% - Prophylaxis: risks = 50% **Death (*p* = 0.05):** - Placebo: risks = 5.8% - Prophylaxis: risks = 18.9% **Nadir of absolute neutrophil count (*p* = 0.01)** - Placebo: 270 (range: 14 – 25,480) × 10^9 cells/L - Prophylaxis: 62 (range: 5 – 884) x 10^6 cells/L	The study concluded that ciprofloxacin, when used during chemotherapy induction, led to a higher nadir of neutrophil count (median of 62 *vs.* 270, *p* < 0.01) and increased risk of mortality (18.9% *vs.* 5.8%, *p* = 0.05), when compared to placebo.
Laoprasopwattana *et al.* (2013)	Prospective double-blind randomized placebo-controlled trial	ALL and lymphoma	95 patients (3 months - 18 years old) 71 had ALL 24 had lymphoma	**Protocol**: induction or consolidation phase chemotherapy (unspecified)	Ciprofloxacin	**Fever:** - Placebo: 17/34 (50.0) - Prophylaxis: 27/37 (73.0) - Absolute difference in risk: -23.0 (−45.0 to −0.9) ***p* = 0.046** -ALL 13/24 (54.2) 24/30 (80.0) −25.8 (−50.4 to −1.3)	The authors show that the ciprofloxacino was able to prevent febrile episodes in neutropenic children with ALL (P=0,046). However, this effect was only

Table 1 (*continued*)

Study (year)	Type of study	Diagnostic	Patients	Treatment	Prophylactic regimens	Results	Comments
						$p = 0.042$ -Lymphoma 4/10 (40.0) 3/7 (42.9) −2.9 (−50.4 to 44.7) $p < 0.999$	identified in the remission induction phase. And, there was an increase in the percentage of ciprofloxacin-resistant *Escherichia coli* and *Klebsiella pneumoniae* in a control rectal swab
Feng *et al.* (2013)	Prospective	AML	38 patients (2 - 16 years old)	**Protocol:** NOPHO 2004	Vancomycin/ Cefepime or Piperacillin/ Tazobactam	**Frequency of fever (events) $p < 0.001$** Prophylaxis group: 0.4 ± 0.1 Control group: 0.9 ± 0.1 **Interval between agranulocytosis and fever (days) $p = 0.07$** Prophylaxis group: 6.4 ± 0.9 Control group: 3.8± 0.4 **Hospitalization (days) $p < 0.001$** Prophylaxis group: 21.5 ± 0.7 Control group: 28.5 ± 1.7 **Lung Infection $p < 0.001$** Prophylaxis group: 80% Control group: 39%	Prophylactic antibiotics during the period of chemotherapy-induced agranulocytosis in this study reduced the incidence of infectious fever and shortened the mean length of hospital stay.[10]

Abbreviations: ALL: (acute lymphoblastic leukemia); AML: (acute myeloid leukemia); (WK)-ALL-2000: (Indonesian Wijaya Kusuma (WK)-ALL-2000); DFCI 11-001: (Dana-Farber Cancer Institute ALL Consortium Protocol 11-001); DFCI 05-001: (Dana-Farber Cancer Institute ALL Consortium Protocol 05-001); BSI: (Bloodstream infection); IFI: (invasive fungal infection); FN: (febrile neutropenia); OS: (Overall Survival); EFS: (Event Free Survival); TOTXVI and XV: (Total Therapy Study XVI and XV); HSCT: (hematopoietic stem cell transplantation); ALs: (acute leukemias); NOPHO: (Nordic Society of Pediatric Hematology and Oncology.

antibiotics, even for short periods of time. This change is called dysbiosis and it has been shown to be related to the development of several diseases, such as asthma, Kawasaki syndrome, autism, inflammatory bowel disease and, most importantly, cancer, in addition to other risk factors. For example, Rechtman et al. observed that the microbiota diversity and composition in carbapenem-resistant Enterobacteriaceae-colonized patients differed from those of the healthy participants.[14]

Some effects of the use of FQs in the intestinal microbiota are already known, such as reduction in the abundance of *Enterobacteriaceae, Bacillus spp., Corynebacterium spp*., depletion of some anaerobic bacteria (*Bacterioides spp., Bifidobacterium spp., Lactobacillus spp., Peptostreptococcus spp*. and *Veilonella spp*.) and increased abundance of *Citrobacter spp., Enterobacter* and *Klebsiella spp*.[15] According to a recent review by Bossù et al. little is known today about the microbiota interaction with the prophylactic antibiotic and whether this aspect may actually influence the prognosis of children with AL.

Despite the few studies with FQs, some results were important to guide further research in this class of antibiotics. Laoprasopwattana et al., in 2013, in a randomized study with ciprofloxacin in 95 children, demonstrated that its use is able to prevent febrile episodes in neutropenic children with ALL (p = 0,046). However, this effect was only identified in the remission induction phase. At other stages, and in patients with lymphoma, this effect was not observed. Nevertheless, there was an increase in the percentage of ciprofloxacin-resistant *Escherichia coli* and *Klebsiella pneumoniae* in a control rectal swab[16]

In the following year, another study investigated the effectiveness in preventing bloodstream infection and invasive fungal infection (IFI) with antibiotics and antifungal agents. A cohort study in Taiwan was conducted among 113 patients with an initial diagnosis of ALL and AML. Prophylaxis with ciprofloxacin and antifungal agents were administered in the induction periods and high-intensity chemotherapy. Combined prophylaxis was able to reduce the rates of bloodstream infection, IFI, FN and length of stay (LOS) in ICU patients with ALL. It was also able to reduce rates of bloodstream infection, FN, IFI and infection-related deaths in children with AML. The study also proved to be cost-effective and did not demonstrate ciprofloxacin resistance rate increase during treatment.[17]

However, not all ciprofloxacin studies have gone in the same direction. Earlier, a double-blind, randomized clinical trial in Indonesia with 110 children with an initial diagnosis of ALL concluded that ciprofloxacin, when used during chemotherapy induction, led to a higher nadir of neutrophil count (median of 62 *vs.* 270, $p < 0.01$) and increased risk of mortality (18.9% *vs.* 5.8%, $p = 0.05$), when compared to a placebo. The authors highlighted the non-balanced undernutrition between the placebo and the intervention groups[18]

Levofloxacin and prophylaxis

It is important to note that benefits from the use of antibiotic prophylaxis during neutropenia periods in those undergoing chemotherapy have already been proven in adults with AL. Prophylaxis reduces infections and infection-related mortality. For these reasons, its use in afebrile neutropenia periods is already a well-established practice in this age group. Among the possible antibiotics, levofloxacin is already part of international guidelines for adults with neutropenia.[19]

Among the few existing data regarding levofloxacin use in children, a cohort study carried out in 2017 at St. Jude Children's Research Hospital (Memphis/Tennessee) with 344 patients with newly diagnosed ALL identified that prophylaxis was able to significantly prevent FN and systemic infection during induction chemotherapy by ≥ 70%. The use of levofloxacin in these children also minimized the use of antibiotic treatment with cefepime/ceftazidime, vancomycin and aminoglycosides. Unexpectedly, the prophylaxis with levofloxacin dramatically reduced colitis infection rates caused by *Clostridioides difficile* and other enterocolitis.[20] This is extremely relevant data, as *Clostridioides difficile* infection (CDI) is related to higher mortality in hospitalized children, higher hospital costs and hospital LOS.[21]

In the same year, Sulis et al. corroborated these findings, demonstrating that FQ use for the initial treatment of fever, as well as for prophylaxis, in 230 children with an initial diagnosis of ALL receiving induction chemotherapy, is effective in reducing gram-negative and some gram-positive bacteremia. In addition, it was shown that levofloxacin did not lead to an incidence increase of multiresistant germs or infection by *Clostridium difficile* or fungi.[22]

In addition to preventing FN, levofloxacin could also be used to prevent bacteremia in AL, an important morbidity and mortality factor in these patients. In the same manner, Alexander et al., in a randomized clinical trial with 195 children with AL and 418 children undergoing HSCT, demonstrated a protective effect in those who used levofloxacin during the neutropenia period. The likelihood of fever and neutropenia was lower in the levofloxacin prophylaxis group than in the control group in children with AL (71.2% *vs.* 82.1%; 95% IC, p = 0,002), as was the risk of bacteremia (21.9% *vs.* 43.4%; 95% IC, p = 0.01). However, the same study did not demonstrate this same effect in reducing the risk of bacteremia in children undergoing HSCT.[9]

Currently, the FN prevention is not the only implementation goal of antibiotic prophylaxis. It is also important to consider the cost-effectiveness of its use, as an episode of FN can have an important budgetary impact due to hospitalization in an ICU, use of expensive antibiotics and death. In some studies, levofloxacin was effective in preventing bacterial infection with a proven cost-effectiveness in children with AML and relapsed ALL receiving intensive chemotherapy.[23,24]

These data supported the publication of a guideline, in July 2020, by the Infectious Diseases Society of America (IDSA) on antibacterial prophylaxis in pediatric cancer and hematopoietic stem cell transplantation. The recommendation is that antibiotic prophylaxis should not be routinely used in children who are first diagnosed with ALL in the induction phase, due to the low body of evidence presented so far. Despite this consideration, the group suggests the use of levofloxacin as the antibiotic of choice for those patients who have severe neutropenia (absolute neutrophil count [ANC] < 500/mm^3) for at least 7 days.[25]

Prophylactic regimens other than FQs

The most recent studies focus on FQs use in infection prophylaxis during neutropenic periods in pediatric cancer patients,

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but other classes of antibiotics have been priorly investigated.[26,27] Trimethoprim-sulfamethoxazole (TMP-SMX)-based regimens were one of the combinations tested in trials.

The TMP-SMX has bactericidal activity against several bacterial strains, such as *Klebsiella*, *Escherichia coli*, *Salmonella* (gram-negative bacteria), *Streptococcus pyogenes*, *Staphylococcus aureus* and *Streptococcus pneumoniae* (gram-positive bacteria), as well as *Pneumocystis jiroveci* and *Nocardia*.[28]

The studies that tested antibiotic prophylaxis in children treated for acute hematologic malignancy have conflicting results regarding the TMP-SMX efficacy. Gorin et al., between 1979 and 1982, in a double-blind trial, evaluated the efficacy of TMP-SMX prophylaxis use among children with ALL. The data group was able to show a lower incidence of bacterial infections (such as otitis media, $p = 0.004$) and fewer episodes requiring hospitalization in the treated group ($p = 0.01$), but the difference in the number of bacteremias in the prophylactic group was not statistically significant ($p = 0.08$). They also demonstrated an emergency of TMP-SMX resistant gram-negative rods ($p = 0.05$).[27] In 2010, Rungoe et al. published a retrospective non-randomized cohort study on children with ALL (n = 171) to compare the rate of infections between 2 groups, of which one received the SMX-TMP prophylaxis. They were able to demonstrate that the prophylaxis group developed fewer fever episodes ($p < 0.002$) and bacteremia ($p < 0.0003$), despite not being a randomized trial.[28]

The superiority of the TMP-SMX in preventing infections in neutropenic children receiving induction ALL chemotherapy was not demonstrated in other studies. Cruciani et al., in a prospective randomized study, compared the oral norfloxacin efficacy *vs.* oral TMP-SMX and Van Eys et al., in another prospective randomized trial, also checked the TMP-SMX prophylaxis use in children with ALL. Both were unable to demonstrate a statistically significant difference between treatment and control groups. Similarly, Cruciani et al. observed a large selection of resistant gram-negative strains in the TMP-SMX prophylaxis group.[29] In another study, Lange et al., although showing a decrease in the number of days spent in the hospital in the treatment group ($p < 0.001$), did not demonstrate a significant difference in the number of infection episodes or fever of unknown origin (FUO).[30]

In a recent guideline meta-analysis for antibacterial prophylaxis in pediatric cancer and hematopoietic stem cell transplantation, Lehrnbecher et al. demonstrated that the TMP-SMX prophylaxis reduced infection-related mortality (risk ratio [RR], 0.61; 95%CI, 0.39 - 0.94) and bacteremia (RR, 0.59; 95/5CI, 0.41 - 0.85), and that cephalosporin prophylaxis reduced bacteremia (RR, 0.30; 95%CI, 0.15 - 0.58); although they did not differentiate data from the HSCT *vs.* non-HSCT AL patients, these data are relevant to present. Even though this evidence has been found, its use has not been recommended because the studies may have bias and it has been observed that the TMP-SMX prophylaxis can cause drug-induced myelosuppression and select for resistant bacteria.[25]

Another combination of already-tested antibiotics in prophylaxis was teicoplanin plus a third-generation cephalosporin. In a randomized study with children treated with high-dose chemotherapy and HSCT (n = 60), Avril et al. showed a lower incidence of septicemia ($p < 0.05$), delay of the first episode of fever ($p < 0.005$) and increased time gap between the HSCT and the onset of the FUO in the prophylaxis group ($p < 0.001$).[27]

In this context, amoxicillin/clavulanate were also tested to prevent infection in neutropenic children. In a multicenter randomized, double-blind placebo-controlled trial, Castagnola et al. tested oral amoxicillin/clavulanate to prevent infection and/or fever in neutropenic children (n = 167). The study was not able to demonstrate that amoxicillin/clavulanate prophylaxis was superior to the placebo in preventing fever or infection.[31]

Conclusion

Antibiotic prophylaxis in pediatric cancer patients can be an important tool for reducing treatment-related morbidity and perhaps mortality, as it is in adults. However, the rarity of these diseases in the pediatric population and the small number of publications on the subject are still an obstacle in creating guidelines. For this reason, both The ECIL Pediatric Group and the Children's Oncology Group do not strongly recommend any systemic antibacterial prophylaxis in children with acute leukemias.[25,32]

Studies with the SMX-TMP and other regimens to prevent fever during neutropenia either demonstrated risk of myelosuppression and induction of multidrug-resistant strains or were ineffective. Among the possible available therapeutic options for bacterial prophylaxis in children with cancer, the FQs emerged with the greatest amount of evidence. Since ciprofloxacin, despite promising studies, does not show activity against Streptococcus, especially from the *viridans streptococci* group, levofloxacin became the best choice. Therefore, the use of levofloxacin seems to be indicated in very specific situations: in children who are known to be neutropenic for a long time, secondary to intensive chemotherapy; in children with AL undergoing chemotherapy to induce remission, or; in children undergoing HSCT. In cases where chemotherapy has a low risk of leading to neutropenia or generates short neutropenia periods, the use of antibiotic prophylaxis does not appear to be of benefit.

More studies are necessary to demonstrate the real benefits of using levofloxacin and/or other antibiotics as antimicrobial prophylaxis. Long-term monitoring to assess the emergence of multiresistant germs, Clostridioides difficile infection, invasive fungal infection and impact on child growth is required.

Conflicts of interest

The authors declare no conflicts of interest.

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7.2 ARTIGO 2

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Original Article

Safety of levofloxacin as an antibiotic prophylaxis in the induction phase of children newly diagnosed with acute lymphoblastic leukemia: an interim analysis of a randomized, open-label trial in Brazil

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ABSTRACT

Background: Despite high cure rates, treatment-related mortality in children with acute lymphoblastic leukemia (ALL) remains significant. About 4% of patients die during remission induction therapy and approximately two-thirds of treatment-related deaths are due to infectious complications.

Methods: From May 2021 to June 2022, children aged one through 18 years, with a recent diagnosis of ALL, admitted to three pediatric oncology centers in Brazil, were enrolled in this multicenter, open-label, randomized, phase 3 clinical trial. Eligible patients were randomly divided into two groups, based on a 1:1 allocation ratio, to receive, or not, levofloxacin as a prophylactic agent during the induction phase. All patients were treated according to the IC-BFM 2009 chemotherapy protocol. Primary endpoints were carbapenemase-producing Enterobacteriaceae (CPE) colonization, *Clostridioides difficile* diarrhea, and other adverse events related to the use of levofloxacin. The secondary endpoint was febrile neutropenia during induction. The median follow-up was 289 days.

Results: Twenty patients were included in this trial, 10 in each group (control and levofloxacin). Mild adverse reactions related to levofloxacin were observed in three patients (30%). Three patients had *Clostridioides difficile* diarrhea, two in the levofloxacin group and one in the control group ($p > 0.99$). Only one patient presented colonization by CPE. This patient belonged to the levofloxacin group ($p > 0.99$). Nine patients presented febrile neutropenia,

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five in the control group and four in the levofloxacin intervention group ($p > 0.99$), one patient died due to febrile neutropenia.

Conclusion: The use of levofloxacin was shown to be safe in the induction phase in children with *de novo* ALL. The use of this medication did not increase the rate of colonization by CPE nor the rate of diarrhea by *C. difficile*. All adverse reactions were mild and remitted either spontaneously or after switching medicine administration from oral to intravenous route.

Introduction

Malignant neoplasms are the leading cause of disease-related childhood deaths and, among them, acute lymphoblastic leukemias (ALLs) are the most prevalent.[1] ALLs can be defined as a heterogeneous group of diseases manifested by the proliferation of immature lymphoblasts in the marrow, in peripheral blood or on other tissues. It is basically treated with high-dose polychemotherapy, followed by a maintenance phase consisting of low-dose chemotherapy.[2]

Despite the positive evolution of treatment over the last decades –with a global survival rate close to 90%[3] – treatment-related mortality (TRM) remains significant: about 4% of patients die during remission induction therapy. Approximately two-thirds of these deaths are due to infectious causes.[4]

Bacteria can thus be perceived as one of the main causative agents of morbidity and mortality in patients with chemotherapy-related neutropenia. In adults, significant benefits were demonstrated with the use of antibiotic prophylaxis during these periods, as they reduced infections and lowered rates of infection-related mortality.[5] While the use of antibiotic prophylaxis in adult patients during periods of afebrile neutropenia is already a well-established practice, we lack solid evidence concerning its use in children.

Levofloxacin, a broad-spectrum fluoroquinolone antibiotic, is included in guidelines and indicated to afebrile neutropenic adult patients. According to a recommendation published by The Infectious Diseases Society of America (IDSA) in July 2020, the regular use of antibiotic prophylaxis for children with *de novo* ALL is not indicated during the induction phase precisely because of the low body of evidence that exists. When necessary, the IDSA suggests levofloxacin as the antibiotic of choice and only for patients with severe neutropenia (absolute neutrophil count < 500/mm^3) for at least seven days.[6]

In spite of the scarcity of currently available information, a few observational studies on the use of levofloxacin and one randomized trial in children with relapsed ALL have been published. Wolf et al. demonstrated that levofloxacin reduced the odds of febrile neutropenia, bacterial infection, and bloodstream infection during the induction therapy of children with LLA. Surprisingly, it also reduced the chances of infections from *C. difficile* without breakthrough infections with antibiotic-resistant organisms.[7] Similarly, Sulis et al. verified that the use of Fluoroquinolones (levofloxacin or moxifloxacin) for prophylaxis in children with an initial diagnosis of ALL receiving induction chemotherapy was effective in reducing Gram-negative and some Gram-positive bacteremia. Moreover, no increased incidence of multidrug-resistant microorganism, *C. difficile* infection, or fungi was observed.[8]

Considering the promising activity of levofloxacin in preventing febrile neutropenia and the lack of knowledge regarding its possible adverse effects in the induction phase, we conducted the present study to assess the safety and efficacy of this antibiotic medication in children newly-diagnosed with ALL during the induction phase. This preliminary interim analysis aims to ensure greater safety for the patients contemplated in this study and allows the continuation of the clinical trial.

Material and methods

Trial design, oversight, and participants

From May 2021 to June 2022, children aged one through 18 years, with newly-diagnosed ALL admitted at three pediatric oncology centers in Brazil, who completed induction therapy before 30 June 2022, were enrolled in this multicenter, open label, randomized, phase 3 clinical trial. Children with any type of allergy to the use of quinolones and a history of chronic arthritis undergoing treatment were not included in the study. Children with clinically or microbiologically documented infection prior to initiation of induction, as well as those with fever prior to induction therapy that required prolonged antibiotic therapy (> 5 days) to treat infection, were not included in the study in order to avoid confounding antibiotic treatment with antibiotic prophylaxis. Likewise, children with any form of allergy to quinolones or with a history of chronic arthritis treatment were not included in this trial. Patients who developed febrile neutropenia within the first seven days of induction or after up to two days of neutropenia were excluded due to the lack of sufficient time for antibiotic prophylaxis activity.

The trial protocol was approved by the ethics committee or institutional review board at each of the participating centers (CAAE 43,076,621.8.2001.5683). The children's parents or legally acceptable representatives provided written informed consent.

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Randomization

Eligible patients were randomly assigned in a 1:1 ratio by a computer-generated number. During the induction phase, patients would either be given levofloxacin (intervention group) as a prophylactic agent or no prophylaxis (control group).

Treatment

All patients were treated according to the IC-BFM 2009 chemotherapy protocol. Patients in the intervention group started using levofloxacin on the third day after the beginning of induction and its use was continued until any of the following criteria were met: (a) absolute neutrophil count greater than or equal to 500/μL after nadir; (b) start of the next cycle of chemotherapy; (c) use of parenteral antibiotic therapy for any reason.

Children aged 1 to < 5 years were given a dose of 10 mg/kg/dose of levofloxacin, twice a day; children older than five years were prescribed 10 mg/kg/dose once a day, with a maximum dose of 750 mg a day. Levofloxacin was administered orally but, if the oral route was not tolerated, it could be administered intravenously at the same dose and schedule.

Although the control group did not receive levofloxacin as primary prophylaxis, both groups received trimethoprim-sulfamethoxazole as primary prophylaxis for *Pneumocystis jirovecii*.

All patients from both groups received induction therapy that included four weeks of oral prednisone, fours weekly doses of vincristine, two or four weekly doses of daunorubicin, and two doses of PEG-asparaginase.

Outcomes and assessments

The primary endpoints were CPE colonization, *C. difficile* diarrhea, and adverse events related to the use of levofloxacin. The second endpoint was febrile neutropenia during induction.

C. difficile diarrhea was defined by the presence of diarrhea and identification of *C. difficile* in stools by PCR or presence of its toxins.

CPE colonization monitoring was performed by rectal swab at the time of admission to the hospital and at the end of the induction phase. Any additional swab collection was at the discretion of the physician or Hospital Infection Control team of each center.

Febrile neutropenia was defined by the presence of axillary body temperature greater than or equal to 37.8 °C in patients whose total neutrophil count was below 500/μL.

Adverse effects were defined in terms of causality and classified as: possible, likely, or certain. They were also described regarding the severity of each physiological system and classified as: mild, moderate, severe or fatal, according to modified criteria of the World Health Organization (Tables 1 and 2).[9]

Table 1 – WHO classification of toxicity as causality.

Possible	Occurs where two or more medications may be involved, or it can be inferred relationship with the disease
Likely	Occurs where only one drug may be involved
Certain	Occurs during infusion and/or re-exposure

Statistical methods

This study is ongoing and data for this interim analysis were collected on June 23, 2022 after 18 months of initiation. Efficacy and safety analyses included all patients who completed induction phase chemotherapy. Initial target enrollment for the main cohort of the study was 196 patients for the outcome febrile neutropenia, 98 in each group.

Qualitative variables were summarized as absolute and relative frequencies and differences were considered significant at $p < 0.05$ (2-tailed). Data were compiled using the REDCap® web application and analyzed using the PASW Statistics Version 18.0. Fisher's exact test and Pearson's chi-square test were used for categorical variables, and the Mann–Whitney U test for quantitative variables. The binomial proportion confidence interval for the occurrence of adverse events was calculated using the Clopper-Pearson interval.

Results

Twenty patients were included in the interim analysis: Ten in the control group and 10 in the intervention group, who received prophylaxis with levofloxacin. Table 3 shows the characteristics of each group. The median follow-up was 289 days (27 - 394 days). The median duration of levofloxacin use was 29 days (23 - 37 days).

Only one death, due to sepsis by *Pseudomonas aeruginosa*, was observed in the control group. The patient was a male with Down syndrome who died on the thirtieth day of induction. Among the 10 patients who received levofloxacin, three had adverse reactions classified as mild and probably related to levofloxacin. Two patients suffered from nausea, so it was necessary to switch administration of medication from oral to intravenous with cessation of symptoms. One (1) patient had a transient increase in hepatic transaminases, reaching levels up to five times the upper level of normality. Interruption of levofloxacin was not necessary (Table 4).

Three patients had *C. difficile* diarrhea, two in the levofloxacin group and one in the control group ($p > 0.99$). Only one

Table 2 – WHO Classification of toxicity as severity.

Mild	Small clinical and short-term importance, which may require treatment, not substantially affecting the patient's life
Moderate	Alters the patient's usual activities, resulting in transient disability without sequelae. Needs intervention
Severe	Directly threatens the patient's life, causes hospitalization, and can cause permanent sequelae
Fatal	Results in death

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Table 3 – Characteristics of the patients included in the analysis.

	Patients, No (%)[a]		
Characteristics	No Prophylaxis ($n = 10$)	Levofloxacin ($n = 10$)	p-Value[b]
Age, median (IQR), y	8.0 (2–13.5)	9.5 (2–14.0)	.971
Sex			>0.99
Male	6 (60)	7 (70)	
Female	4 (40)	3 (30)	
Down Syndrome	1 (10)	1 (10)	>0.99
ALL type			>0.99
B	8 (80)	9 (90)	
T	2 (20)	1 (10)	

Abbreviations. ALL, acute lymphoblastic leukemia; IQR, interquartile range; y, year(s).

[a] Data represent No. (%) of patients except otherwise specified.
[b] Fisher's exact test was used for categorical variables and the Mann–Whitney U test for quantitative variables.

Table 4 – Incidence of related adverse events.

	Patients, No (%)			
	No Prophylaxis	Levofloxacin		
Outcome	($n = 10$)	($n = 10$)	p-Value[a]	95% CI[b]
C. difficile diarrhea	1 (10)	2 (20)	>0.99	–
Febrile Neutropenia	5 (50)	4 (40)	>0.99	–
CPE colonization	0 (0)	1 (10)	>0.99	–
AEs related to levofloxacin	–	3 (30)	–	6.7 – 65.2

CPE, carbapenemase-producing Enterobacteriaceae; AEs, adverse events.

[a] Fisher's exact test was used.
[b] Clopper-Pearson Confidence Interval.

patient assigned to the levofloxacin group presented colonization by CPE in this study identified as *Klebsiella* spp. Similarly, no significant difference was observed between the groups ($p > 0.99$).

Nine patients presented febrile neutropenia in the study, five in the intervention group, and four in the control group. No significant difference between groups was observed ($p > 0.99$).

Discussion

In this preliminary multicenter analysis, the use of levofloxacin showed to be safe in children newly diagnosed with ALL during the induction phase. Its use did not increase the rate of colonization by CPE nor the rate of diarrhea by *C. difficile*. Despite the significant number of adverse reactions related to its use, all were mild and remitted either spontaneously or by switching administration of medication to the intravenous route.

Among the few available data on the use of levofloxacin with children, a cohort study carried out in 2017 at St. Jude Children's Research Hospital (Memphis/Tennessee) with 344 patients found that prophylaxis was able to significantly prevent FN and systemic infection during induction chemotherapy by ≥70%. The use of levofloxacin in these children also minimized the use of antibiotic treatment with cefepime/ceftazidime, vancomycin, and aminoglycosides. Unexpectedly, prophylaxis with levofloxacin also dramatically reduced colitis infection rates caused by *Clostridioides difficile* and other enterocolitis. This is extremely relevant information since infection with *Clostridioides difficile* is related to higher mortality in hospitalized children, higher hospital costs, and longer hospital stays.[7]

In the same year, Sulis et al. corroborated these findings by demonstrating that FQ use for the initial treatment of fever, as well as for prophylaxis in 230 children with an initial diagnosis of ALL receiving induction chemotherapy, was effective in reducing Gram-negative and some Gram-positive bacteremia. In addition, it was shown that levofloxacin did not lead to increased incidence of multiresistant microorganisms nor infections by *C. difficile* or fungi.[8]

The present study, a randomized clinical trial, is the first conducted in Brazil to assess safety and infectious outcomes with the use of levofloxacin in children with an initial diagnosis of ALL in the induction phase.

Due to the history of arthropathies in animal models, the potential to induce bacterial resistance, and fluoroquinolone-resistant *C. difficile* diarrhea, an interim analysis was essential to allow the clinical trial to continue, ensuring greater safety for the observed patients.

While long-term use of levofloxacin may increase the incidence of antibiotic resistance and the development of *C. difficile* diarrhea, the GIMEMA study and a recent meta-analysis of randomized controlled trials demonstrated that these potential facts did not impact infectious outcomes.[10-12]

The study has some limitations. It was not powered to detect differences between the evaluated outcomes. The high number of patients admitted with fever, requiring prolonged antibiotic therapy, significantly reduced sample size. Most importantly, the study was not blinded. Awareness of allocation could affect patient care decisions.

The results shown here allow for the continuity of the study, as acute toxicity or emergence of multidrug-resistant strains were not observed in the group undergoing intervention (use of FQ). Evidently, it is not possible to assess, at this time, any impact on rates of febrile neutropenia or ICU admissions, as the number of patients evaluated is insufficient to analyze these outcomes. Such aspects will be better approached at the end of the study.

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Conflicts of interest

The authors declare no conflicts of interest.

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8 CONCLUSÕES

Em conclusão, nesta análise multicêntrica preliminar, o uso de levofloxacino mostrou-se seguro na fase de indução em crianças recém-diagnosticadas com LLA. Seu uso não aumentou a taxa de colonização por CPE ou a taxa de diarreia por *Clostridioides*. Apesar do surgimento de algumas reações adversas com seu uso, todas foram leves, remitiram espontaneamente ou após troca para a via intravenosa.

9 CONSIDERAÇÕES FINAIS

Os resultados deste estudo vão permitir a expansão do projeto inicial para atingir um maior número de pacientes assegurando a segurança deles. A profilaxia antimicrobiana com levofloxacino já está bem sedimentada em adultos com LLA em primeiro diagnóstico, porém os dados são escassos na faixa etária pediátrica. Este é o primeiro ensaio clínico randomizado em crianças que objetiva avaliar desfechos infecciosos com o uso de levofloxacino nas fases de tratamento de maior risco infeccioso. Esperamos, com a continuidade do presente estudo, avaliar se o uso de antibioticoprofilaxia neste grupo de pacientes confirmará os resultados atuais de toxicidade e se irá contribuir para a redução da morbimortalidade relacionada ao tratamento destas crianças. A partir deste estudo pretende-se, futuramente, estudar também as alterações da flora bacteriana destes pacientes e aumentar os centros participantes.