Research, Society and Development, v. 11, n. 14, e130111436040, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i14.36040

Amoxicillin dosing and pharmacokinetics in obesity for the treatment of bacterial respiratory infection secondary to COVID-19: a systematic review

Dose e farmacocinética de amoxicilina na obesidade para o tratamento de infecção respiratória bacteriana secundária ao COVID-19: uma revisão sistemática

Dosis y farmacocinética de amoxicilina en obesidad para el tratamiento de la infección respiratoria bacteriana secundaria a COVID-19: una revisión sistemática

Received: 10/01/2022 | Revised: 10/16/2022 | Accepted: 10/17/2022 | Published: 10/21/2022

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Abstract
*Objective***:** To conduct a systematic review of Amoxicillin (AMX) dosing and pharmacokinetics (PK) in obese subjects for the treatment of the outpatient respiratory tract infection which may be a secondary co-infection with COVID-19. *Methodology***:** A systematic review was performed up to January 2022 on MEDLINE, EMBASE, and Web of Science. Full-text manuscripts describing AMX dosing for respiratory infection or PK in obese children, adults, and RYGB bariatric patients treated with AMX were included. *Results***:** A total of 179 records were screened, of which 8 met the inclusion criteria. Four studies described AMX dosing in obese children and adults, while 4 described PK in obese adults and RYGB bariatric subjects. Overall, in the dosing studies, 54% of children >20 kg and 10% <40 kg with respiratory infection were considered underdosed, according to guidelines or recommendations. Underdosing of 10% occurred in both overweight and non-obese children's groups. For morbidly obese adults, 70% were considered underdosed. In the PK studies, obese and bariatric adult subjects showed reduced exposure compared to normal weight patients for all AMX formulations. *Conclusion***:** More PK studies are needed to confirm the optimal dose of AMX for obese patients, particularly in children. However, considering that all obese and bariatric adults had reduced exposure compared to subjects of normal weight, 1 g 8/8h should be recommended and liquid formulations are preferable for bariatric patients. To minimize the risks of therapeutic failure and avoid toxicity, a higher threshold of doses should be prescribed for obese children.
Keywords: Amoxicillin; Obesity; Pharmacokinetics; Dosage; Child.

Resumo
*Objetivo***:** Realizar uma revisão sistemática de dose e farmacocinética (PK) da Amoxicilina (AMX) em obesos para o tratamento de infecção comunitária do trato respiratório que pode ser uma coinfecção secundária ao COVID-19. *Metodologia***:** Uma revisão sistemática foi realizada até janeiro de 2022 no MEDLINE, EMBASE e Web of Science. Artigos completos descrevendo a dose de AMX para infecção respiratória ou PK em crianças obesas, adultos e bariátricos RYGB tratados com AMX foram incluídos. *Resultados***:** Um total de 179 estudos foram selecionados, dos

quais 8 atenderam aos critérios de inclusão. Quatro estudos descreveram a dose de AMX em crianças e adultos obesos, enquanto 4 descreveram PK em adultos obesos e bariátricos RYGB. Nos estudos de dose, 54% das crianças >20 kg e 10% <40 kg com infecção respiratória foram consideradas em subdose, de acordo com as diretrizes ou recomendações. Crianças não obesas ou com sobrepeso apresentaram 10% de subdose. Para adultos obesos mórbidos, 70% estavam em subdose. Nos estudos farmacocinéticos, adultos obesos e bariátricos apresentaram exposição reduzida em comparação com indivíduos de peso normal para todas as formulações de AMX. *Conclusão***:** Mais estudos farmacocinéticos são necessários para confirmar a dose ideal de AMX para pacientes obesos, principalmente em crianças. No entanto, considerando que todos os adultos obesos e bariátricos tiveram exposição reduzida em comparação aos de peso normal, 1 g 8/8h deve ser recomendado, e se bariátricos, preferir formulações líquidas. Para minimizar os riscos de falha terapêutica e evitar toxicidade, a faixa de dose superior deve ser prescrita para crianças obesas.
Palavras-chave: Amoxicilina; Obesidade; Farmacocinética; Dosagem; Criança.

Resumen
*Objetivo***:** Realizar una revisión sistemática de la dosificación y farmacocinética (PK) de Amoxicilina (AMX) en obesos para el tratamiento de la infección del tracto respiratorio comunitario que puede ser una coinfección secundaria de COVID-19. *Metodología***:** Se realizó una revisión sistemática hasta enero de 2022 en MEDLINE, EMBASE y Web of Science. Artículos completos seleccionados describieron la dosis de AMX para infecciones respiratorias o PK en niños obesos, adultos y bariátricos RYGB tratados con AMX. *Resultados***:** De 179 estudios, 8 cumplieron con los criterios de inclusión. Cuatro revelaron dosis de AMX en niños y adultos obesos, mientras que 4 revelaron PK en adultos obesos y bariátricos. En los estudios de dosis, 54% de los niños > 20 kg y 10% < 40 kg con infección respiratoria se consideraron infra dosificados, de acuerdo con guías o recomendaciones. Los niños, non obesos o con sobrepeso, tuvieron una sub dosificación del 10%. Para los adultos con obesidad mórbida, 70% recibió sub dosis. En estudios farmacocinéticos, los adultos obesos y bariátricos tuvieron una exposición reducida en comparación con los sujetos de peso normal para todas las formulaciones de AMX. *Conclusión***:** Se necesitan más estudios farmacocinéticos para confirmar la dosis óptima de AMX para pacientes obesos, especialmente niños. Sin embargo, considerando que todos los adultos obesos y bariátricos tuvieron una exposición reducida de AMX, se debe recomendar 1 g 8/8 h y, en bariátricos, preferir formulaciones líquidas. Para minimizar el riesgo de fracaso del tratamiento o toxicidad, prescribir el régimen de dosis superior para niños obesos.
Palabras clave: Amoxicilina; Obesidad; Farmacocinética; Dosificación; Niño.

1. Introduction

Obesity is a global chronic pandemic that affects over 13% of the world's adult population (De Lorenzo et al., 2020), around 340 million children and adolescents aged 5-19 years, and 38.2 million children under 5 (World Health Organization [WHO], 2021a). It accounts for approximately annual medical care costs of more than 1 trillion dollars, representing around 9.3% of the gross domestic product only in the United States (De Lorenzo et al., 2020).

Obesity is likely to cause several morbidities including hypertension, diabetes, cardiovascular diseases, and pulmonary arterial hypertension among other (De Lorenzo et al., 2020; Tchang et al., 2021; Caci et al., 2020). In order to mitigate complications of obesity-related comorbidities, patients may undergo bariatric surgery, although with limited success as most of them remain obese or regain the weight lost after 2 or more years post-surgery (Davis & Saunders, 2020). In addition, other issues related to the bariatric procedures may also arise, given that the gastrointestinal physiology relevant for oral drug absorption (stomach, duodenum, and part of jejunum) is altered, especially after Roux-en-Y Gastric Bypass (RYGB).

It is already known that obese patients are more susceptible to increased severity conditions and mortality after infection with H1N1 (Caci et al., 2020). The recent COVID-19 outbreak also revealed that overweight and obese patients are associated with an increased risk of multifactorial treatment failures, severity, and mortality (Oboza et al., 2022; Vasheghani et al., 2022). Although COVID-19 is a viral infection, obese patients are vulnerable to secondary bacterial pneumonia following the initial phase of viral infection (Wu et al., 2020). As consequence, an excessive prescription of antibiotics occurred leading to the emergence of antimicrobial resistance (AMR) (Khan et al., 2021).

Even before the COVID-19 outbreak, respiratory infections were responsible for more than 1.5 million deaths as a result of antimicrobial resistance, therefore, it became the most expensive infective syndrome worldwide (Antimicrobial Resistance Collaborators, 2022). As such, rational use of antimicrobials was already challenging for the general population, which should follow the main guidelines and recommendations by the National Health Services of each country.

The first choice of antimicrobial for the treatment of pneumonia recommended by the WHO (2021b) is amoxicillin and this antimicrobial was one of the most prescribed antibiotics to avoid bacterial secondary respiratory infection in hospitalized COVID-19 infected patients (Seaton et al., 2021; Buehrle et al., 2020). Nevertheless, no specific dose information is available for different populations such as obese children, obese adults, bariatric patients, older adults, or pregnant women (Amoxil, 2006).

In view of the multiple issues presented by obese patients, the use of the "one-dose-fits-all" approach may lead to underdosing or overdosing in these patients. Amoxicillin therapy can sometimes follow this approach, by being prescribed for children as a fixed dose according to the age described in the British National Formulary (National Institute for Health and Care Excellence, 2020) although dosing recommendations as mg/kg/day or mg/kg/dose also exist in other countries (Bielicki et al., 2015; IBM Micromedex Drug Ref, 2018).

The treatment failure of upper respiratory infections with AMX associated with COVID-19, as a consequence of inappropriate dosing for obese patients, will aggravate the infection, will require hospitalization, and the use of parenteral antibiotics (Longo et al., 2013).

Considering that the obese population is more vulnerable to the severity of COVID-19 and bacterial co-infections with a high risk of mortality, this study aimed to identify the optimal dosing recommendation for the treatment of respiratory infections for obese children, adults, and RYGB bariatric patients. For that, a review of AMX drug dosing and pharmacokinetic (PK) data available in the literature was performed in order to provide reliable information about the rational dosing of AMX for obese patients.

2. Methodology

2.1 Protocol

The methodology used was based on the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Liberati et al., 2009).

2.2 Eligibility criteria

PICOS (participants, intervention, comparator, outcome, study design) criteria were used in the selection of the studies. Participants: obese, bariatric (RYGB surgery); Intervention: amoxicillin dosing to treat a respiratory infection, including upper respiratory tract infections like otitis and complications from SARS-COV-2, or any AMX pharmacokinetic study in obese patients; Comparator: healthy subjects treated with amoxicillin; Outcomes: appropriate dose, underdose or overdose or pharmacokinetics parameters; Study design: randomized clinical trials, observational studies, retrospective, descriptive, case reports, case series, cohort studies. No language or publication date restrictions were imposed. Participants of any age, except new-born, infants, and pregnant women, were considered eligible. The main exclusion criteria were animal studies, diseases other than respiratory infection, drugs other than amoxicillin, reviews or systematic reviews, abstracts in congress, drug discovery, prophylaxis, physiologically-based pharmacokinetic (PBPK) simulations, protocol, and microbiota.

2.3 Information sources

Studies were selected based on searches of the MEDLINE (1992 to January, week 3, 2022), EMBASE (1989 to January, week 3, 2022), and Web of Science (1945 to January, week 3, 2022) databases. The database searches were carried out on January 20th, 2022, using terms divided into three blocks according to: Group 1 (amoxicillin) AND Group 2 (obese OR obesity OR bariatric surgery OR Gastric bypass OR Bypass surgery OR RYGB OR Roux-en-Y) AND Group 3 (Pharmacokinetics OR Bioavailability OR Therapeutic drug monitoring OR Drug disposition OR Drug dosing).

2.4 Study selection

Articles were initially screened based on title and abstract according to the eligibility criteria. Subsequently, the respective full papers were accessed, and only relevant studies were included. Two independent reviewers were involved in each step, and, in the event of disagreements, a third reviewer was brought in.

2.5 Data collection process

One of the reviewers performed data extraction, which was then independently checked by the second reviewer for accuracy. Regarding outcomes, the pharmacokinetic parameters and studies on the appropriate dose, underdose, or overdose were recorded in different spreadsheets using Microsoft Excel® version 2016.

2.6 Data collection for main variables

The data extraction for appropriateness of AMX dosing for obese patients were: (1) characteristics of subjects (age, BMI, obese, overweight, bariatric); (2) treatment with amoxicillin or amoxicillin + clavulanic acid (dose); and (3) outcome measurement defined according to each author´s criteria for underdosing, appropriate dosing or overdosing.

The main anthropometric, clinical, and PK data extracted from each article were: (1) characteristics of trial participants (including age, obese or bariatric patient, weight, body mass index (BMI)); (2) use of amoxicillin (dose and formulation/dosage form); and (3) outcome (area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$), maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), elimination half-life ($t_{1/2}$), and volume of distribution (Vd/F)).

2.7 Risk of bias in individual studies

The three reviewers checked the completeness of the outcome data: participant exclusions, attrition, and incomplete or missing outcome data.

2.8 Forest plot of area under the curve (AUC) of AMX

A forest plot graph was built using $AUC_{0\text{-}inf}$ data from obese and bariatric subjects found in the literature search compared against data for different generic brands of bioequivalence (BE) studies of AMX, developed since 2006. These BE data were kindly provided by the Brazilian Health Surveillance Agency. For the BE generic brands of AMX, the mean and relative standard deviation (RSD, %) of the $AUC_{0\text{-}inf}$ were compared to the respective reference brand data. In order to compare the obese and bariatric $AUC_{0\text{-}inf}$ data found in the literature with the normal-weight population from the BE studies, the average mean and RSD (%) of $AUC_{0\text{-}inf}$ of all reference brands of the BE studies according to their dosage forms were used. In studies where $AUC_{0\text{-}inf}$ was not provided, it was either calculated from the provided plasma concentration by time plots or calculated from the associated PK parameters using the formula AUC=(dose*F)/Cl, when possible. The $AUC_{0\text{-}inf}$ was divided by dose and then by weight for each study included in this review.

2.9 Forest plot of volume distribution (Vd/F) of AMX

A forest plot was built comparing the Vd/F of AMX of obese and bariatric patients with the observed data from bioequivalence (BE) studies in healthy subjects (average of all reference brands of the BE studies according to their dosage forms). In all studies that did not present Vd, but presented all plasma concentrations for the time, the calculation was done using the following formula: Vd = dose/(AUC0-inf.β). The Vd/F was divided by weight for each study included in this review.

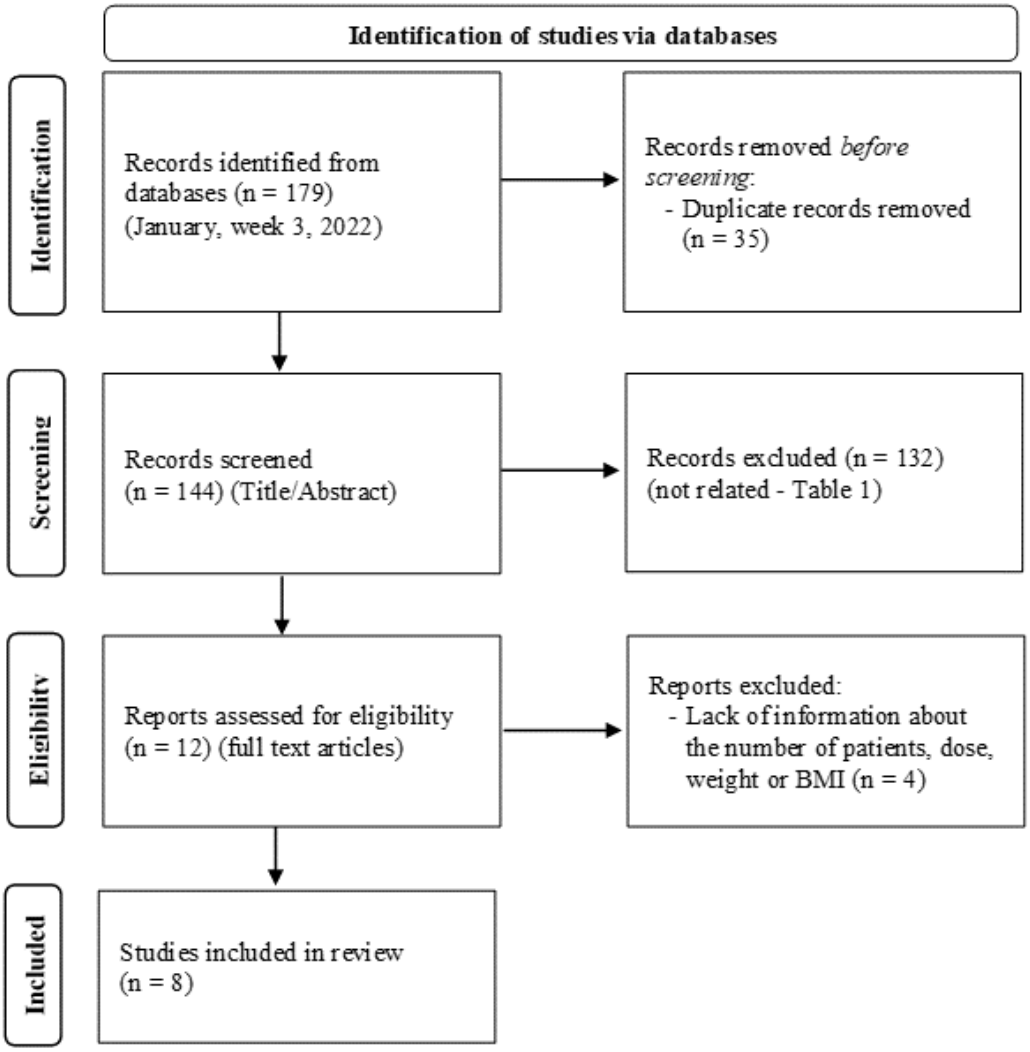
All forest plots were calculated using the tool for mean differences meta-analysis of Jamovi® version 1.6.21 software (The jamovi project, 2021).

3. Results

3.1 Study selection and characteristics

A total of 179 records were identified by the database searches, according to the study selection process is illustrated in the Figure 1.

Figure 1: Flow diagram of the study selection process.



Source: Authors.

Thirty-five duplicate articles were removed, giving a total of 144 articles for screening of title and abstract. Only 12 full-text articles were eligible, of which 4 were subsequently excluded for lack of information about the number of patients, dose, weight, or BMI. The articles which failed the eligibility criteria and the reasons for exclusion are listed in the Table 1.

Table 1: Articles excluded for failing the eligibility criteria.

Topic	N° of articles
Adverse reaction	1
Animal	3
Brain disease	1
Carrier drug	1
Computation platform	2
Congress abstract	5
Critical illness	3
Cystitis	1
Diabetic foot	1
Drug discovery	2
ECMO	2
Endocrine disease	1
Gastrointestinal disease	8
Gastrointestinal transit	1
Gout	2
Guideline	1
Heart disease	6
Influenza	1
Lipodystrophy	1
Liver disease	12
Microbiota	4
Newborn	3
Other drugs	36
PBPK simulation	2
Pregnant	4
Prescription practices	2
Pressure ulcer	1
Prophylaxis	3
Protocol	1
Publications on infectious diseases	1
Renal disease	2
Review	11
Surgical site infection	1
Systematic review	4
Urinary tract infection	1
Vaccine	1
TOTAL	**132**

Source: Authors.

Overall, eight publications fulfilled the inclusion criteria and were further analysed, 4 described AMX dosing regimens, and 4 reported PK studies.

3.2 AMX dosing studies for upper respiratory infections

The 4 articles on dosing regimens were observational and retrospective studies, ages ranged from 2 to 83 years, comprising 2 investigations in primary care children, 1 in inpatient children, and 1 in inpatient adults (Table 2). The appropriateness of the dose calculation based on the guidelines or recommendations for the adult and pediatric populations are highlighted.

Table 2: Amoxicillin dosing studies.

Study; Year	Population	Patient (N)	Age, y	BMI, kg/m²	Dose, mg/kg/day	Underdose, N (%)	Appropriate dose, N (%)	Overdose, N (%)
Christian-Kopp et al., 2010	Children	< 20 kg (274)	3.2 (4.0) [2-18]	ND	74.2 (14.7)	ND	ND	3
		> 20 kg (85)	3.2 (4.0) [2-18]	ND	40.4 (16.6)	46 (54.1)	31 (36.5)	8 (9.4)
Miller et al., 2010		Control (561)	8.1 [5-12]	15.8 [6-22]	ND	4 (9.8)	36 (87.8)	1 (2.4)
		Overweight (278)	8.4 [5-12]	22.9 [16.9-52.8]	ND	3 (11.5)	23 (88.5)	0 (0)
Rann et al., 2017		< 40 kg (881)	[2-18]	ND	ND	91 (10.3)	ND	ND
		> 40 kg (675)	[2-18]	ND	ND	ND	675 (100)	ND
Serra Soler et al., 2009	Adult	Morbidly obese (13)	56 [23-83]	48 [40-68]	ND	9 (70)	ND	ND

Mean (standard deviation) [range], BMI, body mass index; SD, standard deviation; ND, not described. Source: Authors.

The study by Christian-Kopp et al. (2010) reviewed the medical records of children diagnosed with acute otitis media (OM) treated with AMX. The authors showed that, due to dose capping based on the adult dosing of 1500 mg/day, children weighing ≤20 kg received higher weight-based doses of amoxicillin compared to children >20 kg (74.2 mg/kg/day *vs* 40.4 mg/kg/day, respectively). The children >20 kg received approximately half (54.1%) of the recommended dose of 80 - 90 mg/kg/day. Overall, 7 of 359 children had treatment failures, and 4 of them had reinfection. This study also reported the opinion of the members of the Subcommittee on the Management of Acute Otitis Media of the American Academy of Paediatrics (AAP) on the maximum dose specification of AMX in cases where doses exceeded the adult dosing of 1500 mg/day. Most AAP members (66.7%) would prescribe the adult dose of 1500 mg/day, while 33.3% would follow the recommendation of 80 - 90 mg/kg/day, even when exceeding the adult dose (Christian-Kopp et al., 2010).

The study carried out by Miller et al. (2010), which used weight-based dosing, analyzed the hospital admissions of children aged 5-12 years. The authors classified children with %BMI ≥ the 85th percentile for age and sex as overweight and compared them with children with BMI < the 85th percentile. Overdose in the study was defined as: (1) total mg/kg/day or mg/kg/dose ≥110% of the maximum recommended pediatric dose; or (2) total mg/day > adult maximum recommended dose, or (3) greater than the recommended daily dosing interval. Underdose was defined as: (1) total mg/kg/day or mg/kg/dose ≤90% of the minimum recommended pediatric dose; or (2) less than the recommended daily dosing interval. A third of the total 699 children included were overweight, but irrespective of weight, around 10% were underdosed. The clinical outcomes regarding therapeutic failure or relapse were described (Miller et al., 2010).

Ran et al. (2017), in a study of AMX dosing based on age, gender, and BMI evaluated the suitability of AMX doses after the changes made in the British National Formulary (BNF) guidance in 2014, which doubled AMX doses for children aged 1 month to 12 years old and established the dose of 500 mg three times daily for 5 - 18 years old. The authors found that 500 mg doses for children aged 5 - 18 years with body weight >40 kg received the recommended dose based on 90 mg/kg/day (not exceeding 3 g/day), while children <40 kg aged around 4 years were still underdosing with this change. This paper only evaluated the percentage of children who would theoretically receive a dose outside the suggested summary of product characteristics (Rann et al., 2017).

One study was found for dosing in obese adult patients investigated the appropriateness of the dose calculation for morbidly obese patients. The investigation included only 62 morbidly obese inpatients (BMI 40 – 68) treated with different drugs, of which 13 were treated with AMX + clavulanic acid. The authors reported that 70% of these subjects were underdosed and concluded that dosing prescribed for this population is inappropriate, with underdosing proving more frequent than overdosing in obese patients. No clinical outcome was described (Serra Soler et al., 2009) and nor studies investigating AMX dosing in bariatric patients were found.

3.3 AMX PK studies

The four PK studies included in the review described AMX PK in obese and bariatric RYGB subjects (Montanha et al., 2019; Rocha et al., 2019; Mellon et al., 2020; Soares et al., 2021) (Table 3). No studies describing AMX PK in children were found, nor AMX PK in obese with an upper respiratory infection.

Table 3: Pharmacokinetics studies of amoxicillin in obese and RYGB bariatric patients.

Study; Year	Study type	Patients (N)	Age, y	Wt, kg	BMI, kg/m²	Body fatness by BMI[a]	Dose (dosage form)	$AUC_{0\text{-}inf}$, mg.h/L	$AUC_{0\text{-}inf}$ for 1g dose	T_{max}, h	C_{max}, mg/L	$T_{1/2}$, h	Vd, L	Vd/Wt, L/kg
Montanha et al., 2019	Single-centre, randomized, double-blind, crossover, after RYGB surgery	Bariatric (20)	42.65 (7.21) [18 - 55]	79.76 (12.55)	29.88 (4.36)	Overweight	875 mg (tablet)	23.10 (7.41)	26.4	2 [1 - 4]	7.42 (2.99)	1.4 (0.68)	88.54 (69.30)	1.11 (0.87)
							800 mg (suspension)	25.22 (7.61)	31.52	1.7 [1 - 5]	7.98 (2.98)	1.32 (0.31)	62.92 (27.16)	0.79 (0.34)
Rocha et al., 2019	Single-centre, randomized, open-label, single-dose, before and after RYGB surgery	Obese (8)	40.4 (8.9) [28 - 59]	119.44 (22.4)	46.21 (2.82)	Obese class 3	500 mg (capsule)	2.15 (0.87)	4.3	2.31 (0.59)	0.62 (0.14)	1.30 (0.22)	462.82 (129.39)	3.87 (1.08)
		Bariatric (8)	40.4 (8.9) [28 - 59]	102.41 (19.5)	39.82 (3.32)	Obese class 2	500 mg (capsule)	7.98 (5.49)	15.96	2.75 (1.13)	1.77 (1.19)	1.96 (1.16)	364.42 (630.92)	3.56 (6.16)
Mellon et al., 2020	Single-centre, prospective, open-label, crossover, population PK model, obese	Obese (27)	51.7 [22.9 - 62.9]	109.3 [88 - 151.5]	40.6 [35.2 - 67.3]	Obese class 3	1000 mg (injectable)	68.5 (18.5)	68.5	ND	69.77	ND	31.2 (19.7)	0.28 (0.18)
							1000 mg (suspension)	54,6 (15.7)	54.6	1.56	17.97	1.48 (0.84)	39.2 (25)	0.36 (0.23)
Soares et al., 2021	Single-centre, prospective, open-label, clinical study, normal and obese	Non-obese (10)	30.6 (7.12)	60.19 (7.47)	21.56 (1.95)	Healthy weight	875 mg (tablet)	34.18 (12.94)	39.06	1.5 [1 – 3]	12.12 (4.06)	0.86 (0.44)	27.57 (12.96)	0.46 (0.21)
		Obese (19)	34.47 (7.03)	93.25 (10.87)	33.17 (2.38)	Obese Class 1	875 mg (tablet)	26.88 (9.24)	30.72	2.5 [1 – 4]	9.66 (2.93)	0.86 (0.26)	44.20 (17.85)	0.47 (0.19)

Mean (standard deviation) [range], Wt, weight; BMI, body mass index; SD, standard deviation; ND, not described; AUC, area under the plasma concentration-time curve; Cmax, maximum plasma concentration; Tmax, time to reach Cmax; T1/2, elimination half-life; a, Body fatness by BMI according to Centers for Disease Control and Prevention (2020): BMI < 18.5, underweight; BMI 18.5 to <25, healthy weight; BMI 25.0 to <30, overweight; BMI 30.0 or higher, obese (Class 1: BMI of 30 to < 35; Class 2: BMI of 35 to < 40; Class 3, "extreme" or "severe" obesity: BMI of 40 or higher). Source: Authors.

Two studies included morbidly obese subjects (BMI >40) (Rocha et al., 2019; Mellon et al., 2020), while another included healthy obese class I subjects (Soares et al., 2021).

Soares et al. (2021) conducted a PK study in which a single oral dose of 875 mg AMX tablets was administered to 10 normal-weight subjects and 19 obese class I (BMI 30 - 35) subjects. The obese class I group had around 21% lower AMX exposure than the normal-weight group, with a C_{max} of 9.66 mg/L *vs* 12.12 mg/L and $AUC_{0\text{-}inf}$ of 26.88 mg.h/L *vs* 34.18 mg.h/L, respectively. Given the high variability between subjects, no significant differences were identified. Vd/F was the only PK parameter displaying a significant difference in obese subjects, proving 1.6 times higher in obese patients than in normal-weight subjects (44.20 L *vs* 27.57 L) (Soares et al., 2021). However, when Vd/F was calculated as L/Kg they were similar (0.47 and 0.46 L/kg) meaning that Vd was following the typical allometric weight-related behavior for this PK parameter.

A study investigating population PK and dosing simulations of AMX in obese class III (BMI >40) adults were carried out by Mellon et al. (2020). A single intravenous (IV) dose of 1000/200 mg of AMX/clavulanate was administered, followed by a second dose of an oral suspension of 1000/125 mg of AMX/clavulanate. Oral bioavailability was 79.7% with an $AUC_{0\text{-}inf}$ of 68.5 mg.h/L (IV) and 54.6 mg.h/L (PO). The dosing simulation predicted that most of the obese population would attain the pharmacodynamics target (40% of time free plasma drug concentration > MIC - fT>MIC≥40%) at doses of 1000 mg AMX (Mellon et al., 2020).

The subjects enrolled in the PK study carried out by Rocha et al. (2019) were morbidly obese class III (BMI >40) and received a single oral dose of 500 mg AMX capsules just before, and 2 months after, RYGB bariatric surgery. The PK parameters of C_{max} and $AUC_{0\text{-}inf}$ before the surgery were very low, with 0.62 mg/L and 2.15 mg.h/L, respectively.

Two PK studies included RYGB bariatric surgery patients. Rocha et al. (2019) described the AMX PK in morbidly obese patients pre- and post-RYGB surgery, and Montanha et al. (2019) described the relative bioavailability of suspension and tablets in healthy overweight RYGB patients (Table 3).

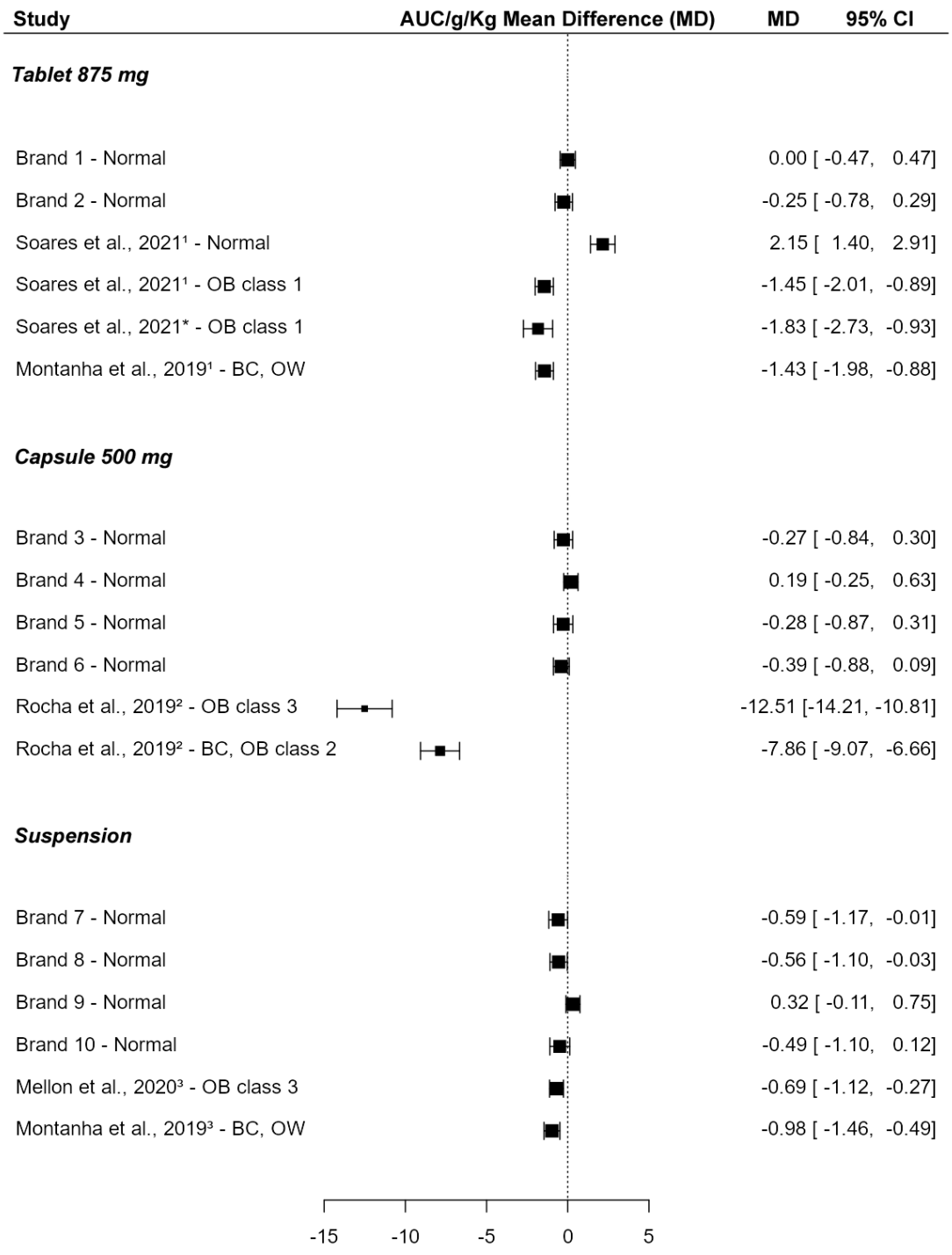
In the study carried out by Rocha et al. (2019), the PK parameters of C_{max} and $AUC_{0\text{-}inf}$ after the RYGB surgery were 1.77 mg/L and 7.98 mg.h/L, respectively, remaining unexpectedly very low. The weight loss recorded 2 months post-RYGB surgery was around 20 kg, with a resultant BMI of 35-40 (obesity class II).

These results by Rocha et al. (2019) contrast with the findings of a study of overweight post-RYGB subjects by Montanha et al. (2019). A total of 20 healthy overweight RYGB bariatric subjects (BMI 25-30) were enrolled and the amount of AMX absorbed was compared in a cross-over study. After the initial administration of 875 mg tablets, a dose of 800 mg as the suspension was also given after a sufficient washout between doses in the same subjects. The $AUC_{0\text{-}inf}$ values, after normalizing by dose, were almost twice as high as those reported by Rocha et al. (2019) (Table 3).

3.4 Forest plot of area under the curve (AUC) of AMX

The forest plot of the AUCs of the bioequivalence (BE) studies in different dosage forms with normal weight subjects, together with the AUCs of the obese and bariatric studies found in the literature are shown in Figure 2. A total of 10 BE studies were included, comprising 4 studies using AMX 500 mg capsules, 2 studies AMX 875 mg tablets, and 4 studies using suspension formulation (Table 4). As expected, all AMX AUCs from the BE studies were equivalent to their respective reference brands, independently of the dosage formulations. However, after normalizing AUC by dose and weight, the studies presented very different values between them, especially those of suspension.

Figure 2: Amoxicillin AUC mean differences (MD) in normal, obese, and bariatric subjects.



BC, bariatric; OB, obese; OW, overweight

Normal = non-obese health subject

¹ Compared with mean $AUC_{0\text{-inf}}$/g/Kg of reference from brand 1 to 2

² Compared with mean $AUC_{0\text{-inf}}$/g/Kg of reference from brand 3 to 6

³ Compared with mean $AUC_{0\text{-inf}}$/g/Kg of reference from brand 7 to 10

* Compared normal with obese from the study of Soares et al., 2021

Source: Authors.

Regarding the obese and bariatric AUC data, only Soares et al. (2021) enrolled normal-weight and obese subjects in their study.

Compared to normal patients in the BE studies, all obese showed reduced plasma concentration for all AMX dosing formulations. The obese class 1 had a 23% reduction in AUC when ingesting a tablet (Soares et al., 2021), while the obese class 3 had a 92% reduction for capsule (Rocha et al., 2019) and 31% for suspension (Mellon et al., 2020).

Table 4: Bioequivalence (BE) studies of amoxicillin in normal-weight subjects.

Study	Year	N	Wt, kg	Dose, mg	Dosage form	AUC_{0-inf}, mg.h/L		Vd/F, L	
						Test	Reference	Test	Reference
Brand 1	2008	35	68.27	875	Tablet	28.34 (7.48)	27.92 (9.13)	54.97 (17.05)	58.55 (21.78)
Brand 2	2007	27	64.84	875	Tablet	20.96 (7.02)	22.46 (6.66)	109.86 (56.72)	86.1 (35.53)
Brand 3	2008	24	66.44	500	Capsule	14.9 (3.99)	15.85 (3.22)	54 (14.34)	51.93 (10.74)
Brand 4	2016	40	70.3	500	Capsule	20.85 (5.56)	19.8 (5.1)	37.6 (10.7)	39.96 (13.18)
Brand 5	2009	22	69.69	500	Capsule	16.96 (3.46)	18.16 (3.74)	51.42 (13.16)	48.06 (12.99)
Brand 6	2016	33	74.09	500	Capsule	18.57 (4.62)	20.31 (4.72)	46.23 (9.91)	42.7 (8.39)
Brand 7	2008	24	64.86	400	Suspension	15.98 (1.17)	17.02 (1.95)	37.38 (5.54)	36 (8.38)
Brand 8	2011	28	68.41	500	Suspension	36.75 (6.89)	40.69 (7.38)	21.76 (4.29)	18.91 (3.31)
Brand 9	2009	42	67.84	500	Suspension	27.91 (5.48)	26.19 (5.22)	32.03 (8.96)	33.66 (6.63)
Brand 10	2016	21	69.32	500	Suspension	9.65 (2.02)	10.84 (2.25)	80.79 (21.31)	75.8 (23.74)

Mean (standard deviation); Wt, weight; N, number of subjects. Source: Authors.

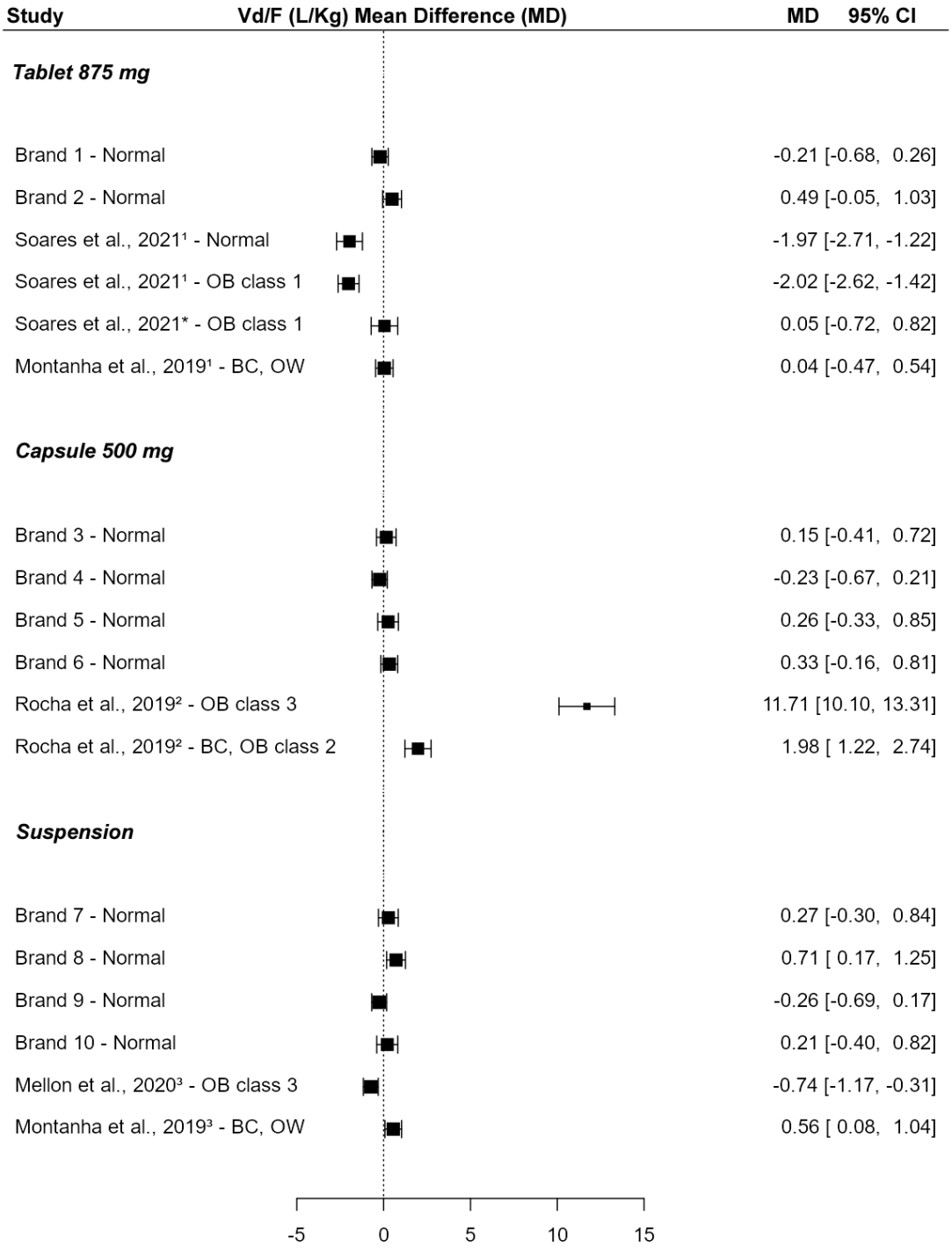
As for bariatrics, they also showed reduced exposure compared to normal patients in the BE studies for all AMX dosing formulations. The obese class 2 bariatric had a 70% reduction in AUC when he ingested a capsule (Rocha et al., 2019), and the overweight bariatric had a reduction of 23% for tablet and 45% for suspension (Montanha et al., 2019).

Finally, a direct comparison between the overweight subjects of the studies from the literature between themselves, resulted that both obese and bariatric subjects who used suspension had greater exposures (0.5 and 0.4, respectively) than those who used tablets (0.33 and 0.33, respectively) and capsules (0.04 and 0.16, respectively).

3.5 Forest plot of the volume of distribution (Vd/F) of AMX

The mean difference of Vd/F values divided by weight (L/Kg) from the BE studies was similar between the reference and test brands (Figure 3). However, the Vd/F values between the studies included in the review were quite discrepant.

Figure 3: Amoxicillin Vd/F mean differences (MD) in normal, obese, and bariatric subjects.



BC, bariatric; OB, obese; OW, overweight

Normal = non-obese health subject

¹ Compared with mean Vd/F (L/Kg) of reference from brand 1 to 2

² Compared with mean Vd/F (L/Kg) of reference from brand 3 to 6

³ Compared with mean Vd/F (L/Kg) of reference from brand 7 to 10

* Compared normal with obese from the study of Soares et al., 2021

Source: Authors.

Regarding the class 3 obese patients compared to normal subjects from the BE studies. While one study with capsule showed a Vd/F six times higher (Rocha et al., 2019), another showed a Vd/F reduction of around 50% with suspension (Mellon et al., 2020).

Increased Vd/F was also seen in the overweighted bariatric patients when administered AMX as suspension but not after tablets (Montanha et al., 2019).

4. Discussion

The association between obesity and the COVID-19 pandemic can cause a negative impact on the healthcare system, increasing the number of high severity patients hospitalized in the critical care units, leading to prolonged mechanical ventilation and high mortality, among other health issues, contributing to the poor outcome of COVID-19 (Caci et al., 2020).

The high consumption of antimicrobials in the first wave of COVID-19 and inappropriate drug dosing due to suspected or confirmed secondary co-infection in these patients lead to the emergence of antimicrobial resistance (AMR) (Khan et al., 2021). This scenario was more dramatic for obese patients to manage the viral infection associated with the lack of drug dosing information (Longo et al., 2013). Unfortunately, according to the results of this systematic review, the AMX dosing information for obese patients remains unclear.

Regarding the dosing regimen for children, the BNF recommendation to use either a fixed dose of 500 mg AMX or the following mg/Kg seems reasonable, even for obese children (Rann et al., 2017). AMX is a safe drug and has a wide therapeutic window as shown by the maximum dosage range recommended for children. For instance: 1) the manufacturer's drug label recommends doses up to 6 g (3 g twice daily) for children above 10 years and over 40 kg (Amoxil, 2019); 2) the IBM Micromedex Drug Ref (2018) recommends a daily dose up to 4 g for children over 5 years; 3) the AAP members, AMX dosing in children should be 80 - 90 mg/kg/day, but the adult dosing of 3 g/day (Christian-Kopp et al., 2010) and 250 mg/kg for children should not be exceeded to avoid toxicity (IBM Micromedex Drug Ref, 2018). Therefore, higher dosing should be recommended for obese children, since AMX toxicity would achieve only with doses over 250 mg/Kg, causing crystalluria with hematuria and transient renal failure, in addition to nausea, vomiting, abdominal pain, diarrhea, skin rash, and urticarial (IBM Micromedex Drug Ref, 2018).

Allometric scaling has been used as a tool for drug dosing in children, based on body surface area (BSA), body weight, or BMI, together with patient physiology to avoid studies in children (Pai, 2012). However, these tools have limitations since, for some drugs, the use of BSA halved the expected AUC (Pai, 2012), while BMI failed to distinguish between adipose tissue and lean muscle mass (Anderson & Holford, 2017).

Comparing AMX PK data with other hydrophilic antibiotics such as vancomycin, gentamicin, and cefazolin (Sampson et al., 2013) in obese children, dosing in mg/kg calculated using total body weight (TBW) resulted in sub-therapeutic concentrations for vancomycin, while calculations using adjusted body weight (ABW) resulted in appropriate exposure for gentamicin and cefazolin. Hence, without a PK study in obese children, it is difficult to affirm whether AMX should be dosed using TBW or ABW. According to the 3 studies included in our review, around 10 to 54% of children above 20 Kg were referred to as AMX subdose using TBW (Christian-Kopp et al., 2010; Miller et al., 2010; Rann et al., 2017).

Regarding the dosing regimen in adult patients, for usual non-weight-based doses, AMX exposure in obese patients lies at the lower threshold limit of the pharmacokinetic and pharmacodynamic correlation of fT>MIC>40% (Jacobs, 2003). Therefore, for obese patients, both children and adults, it would be more rational to prescribe the upper threshold limit of the recommended dosing described in the guidelines. This slightly higher dose would guarantee AMX efficacy against secondary bacterial pneumonia in outpatient settings. Also, dosing in obese bariatric patients is of particular concern because of theoretically

lower AMX absorption compared to normal-weight subjects which can also explain the lower AUC exposures and higher Vd/F seen in Figures 2 and 3, respectively.

AMX doses of 1 g every 8h (q8h) were appropriate for morbidly obese patients, with the probability of target attainment (PTA) >90% for bacteria with MIC<2 mg/L (Mellon et al., 2020). Furthermore, according to Soares et al. (2021), AMX plasma concentration after 4h and 6h of oral intake of AMX 875 mg tablets in obese patients were below 3.99 mg/L and 0.84 mg/L, respectively, showing that shortening the AMX dosing interval from q12h to q8h would achieve the PK/PD target of fT>MIC>40%. Therefore, doses of 1g AMX q8h seem to be safer for obese patients to treat bacteria like S. pneumonia with MIC<2 mg/L.

It is known that the main physiologic changes influencing the absorption of drugs in the obese adult population comprise an increased gastric emptying time, intestinal permeability, splenic blood flow, and increased or decreased intestinal enzyme activity (Smit et al., 2018; Krekels & Knibbe, 2020). Amoxicillin is known to be absorbed by both passive and active transport processes but it is considered a BCS class 1/2, being eventually less influenced by these issues (Thambavita et al., 2017). In fact, lower AUC was seen in obese patients in the forest plot of our review, independently of the obesity class, and it was more pronounced in patients who had gastroparesis (Xing & Chen, 2004) or who had undergone bariatric surgery (Montanha et al., 2019). As such, changes in the absorption processes were more likely because of the modified gastrointestinal physiology as a result of the surgery procedure beyond obesity.

According to Smit et al. (2018), due to the poor tissue penetration and protein binding, the expected increased or decreased Vd of AMX in obese patients should remain unchanged. However, the Vd/Kg for the PK studies (Figure 3) found in this study, showed varied Vd according to both, formulation and obesity classification, compared to BE studies, making it difficult the clarification if the reasons for the observed changes were due to the absorption or the disposition process.

According to our knowledge, there are only a few studies examining the dosing and effect on the PK for the majority of the antimicrobials in obese patients (Alobaid et al., 2016) and most of these studies have suggested that obesity is likely to affect the PK, but none of them showed robust results (Montanha et al., 2019; Rocha et al., 2019; Mellon et al., 2020; Soares et al., 2021). Therefore, the use of a higher threshold of the standard AMX dose and dose based on safety should be used.

This review has some limitations and may rise some issues for the external validity of the conclusions: 1) the 4 studies on AMX dosing which fulfilled the inclusion criteria were observational, had low-grade evidence, and used local or national databases to compare subjects; 2) no AMX PK study in obese patients with any respiratory infection was identified; 3) the PK studies of bariatric patients included a small number of subjects, different obesity classes, and different postoperative time courses, contributing to high individual variability; 4) No consistent approach about the increased or decreased Vd of AMX in obese patients was possible since values between each study showed high variability; 5) increase the number of PK data to mitigate this variability.

5. Conclusion

More PK studies are needed to confirm the optimal dose of AMX for obese patients with respiratory infections, particularly in children. But considering that all obese and bariatric adults showed reduced plasma exposure of AMX compared to subjects of normal weight, this review arise the necessity of prescribing 1 g 8/8h for obese adults, and that if bariatric patients, liquid formulations are preferable. For the obese child, to minimize the risks of therapeutic failure and to avoid toxicity, the prescription of the highest threshold of the doses recommended by the main guidelines for children is indicated, not exceeding the adult dose. Higher dosing of AMX should be considered when prescribing to obese patients.

Acknowledgments

We would like to thank Dr. Gustavo Mendes Lima Santos from the Therapeutic Equivalence Coordination (CETER) of ANVISA who kindly supplied the data from the bioequivalence studies.

Competing interests

The authors declare no competing interests.

Funding

The author has no affiliations or financial involvement with any organization or entity with a financial interest or financial conflict with the subject matter discussed in this systematic review.

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