SÃO PAULO Medical Journal
EVIDENCE FOR HEALTH CARE

December 5 - Volume 137 - Number 6

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Secondary prevention of cardiovascular disease in Brazil: lessons from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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In the 21st century, cardiovascular disease is the greatest cause of mortality worldwide, considering coronary heart disease and stroke together. It is also the leading cause of years of life lost, both worldwide and in Brazil.

Secondary prevention of cardiovascular disease encompasses all strategies such as changes in lifestyle, use of medications to treat cardiovascular disease and associated risk factors and rehabilitation after an event, among people who have previously suffered myocardial infarction or stroke. The objective is simple and clear: to prevent new cardiovascular events in a high-risk group, as proposed by Geoffrey Rose in the 1970s.[1]

Secondary prevention of coronary heart disease and stroke, especially using pharmacological therapy, has been effective in reducing the number of new fatal or nonfatal events worldwide. However, information about secondary prevention of cardiovascular diseases in Brazil is scarce. Previous studies in Brazil have identified the most formidable barriers preventing access to cardiac rehabilitation, which include transportation difficulties, low income, lack of insurance coverage and low educational level.[2-4] Regarding stroke, a previous study showed that less than 50% of patients with stroke who are attended in public hospitals and healthcare centers have any medical follow-up after their hospitalization at the time of the event.[5]

Recent data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) have presented similar results.[6,7] ELSA-Brasil is a prospective cohort study of 15,105 civil servants in six cities in Brazil (Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, São Paulo and Vitória). In this sample, 197 individuals (1.3%) reported at the baseline that they had previously had a stroke. Among them, 20% had then not used any medication for secondary prevention of stroke. Fifteen years after the event, only 39 participants (19.8%) were still using some type of medication for stroke prevention. The same was valid for secondary prevention of coronary heart diseases. Out of the 405 participants who reported at the baseline that they had previously had myocardial infarction, only 35% reported that they had then used drugs for secondary prevention of coronary heart disease. Drug use was more common among high-income participants than among low-income participants. Fifteen years after the stroke event, only 46 (11.6%) of the participants with a previous myocardial infarction were still using some type of medication for secondary prevention of coronary heart disease. Moreover, both studies highlighted a critical point: secondary prevention was less used among women than among men.[6,7]

This lack of secondary cardiovascular prevention is not a scientific secret, and also it is not an exclusively Brazilian problem. Some other studies have shown lower frequency of use of medication for secondary prevention of cardiovascular disease among women than among men.[8,9] Previous data from ELSA-Brasil showed that women were more conscious about their health status than men were, but also showed that they were receiving less prescription of medication for secondary prevention of coronary heart disease from healthcare professionals.[10,11]

The reasons that can explain these findings include higher frequency of atypical symptoms among women than among men, along with some underestimation of the severity of the disease in women. The pattern of statin use among the women in the ELSA-Brasil sample is similar

to the pattern reported in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. In that study, statin use was highest among white men, followed by black men, white women and black women.[8] Data from another study conducted in primary care settings also showed that more than 50% of primary care physicians did not use risk stratification tools in clinical practice, and that this may have led to lower frequency of statin use, especially among women.[9]

ELSA-Brasil also presented important data correlating the use of medication for secondary prevention with socioeconomic status. In both studies,[6,7] the use of secondary prevention was higher among participants with high socioeconomic status than among participants with low socioeconomic status. One crucial point needs to be noted here: the sample for ELSA-Brasil comprised civil servants with high educational attainment and monthly family income, compared with the general population in Brazil. Therefore, it can be suggested that the use of secondary prevention in the general population of Brazil, which has lower educational attainment and monthly family income than the ELSA-Brasil sample, is probably worse.

What is done for patients with myocardial infarction or stroke after they have been discharged from their hospitalization? It seems that not much is done for them, or at least much less than necessary. The solution lies in ensuring that every patient who has had a cardiovascular event is provided with an adequate level of follow-up with further access to secondary prevention. Achieving this is not easy, but it is the only thing to do right now.

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Adherence to antiretroviral therapy among people living with HIV/AIDS in northeastern Brazil: a cross-sectional study

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ABSTRACT

BACKGROUND: Nonadherence to antiretroviral therapy (ART) may lead to viral replication and development of antiretroviral resistance.

OBJECTIVE: To identify the factors associated with nonadherence to ART among people living with the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) (PLWHA).

DESIGN AND SETTING: Cross-sectional study in a tertiary-level hospital in northeastern Brazil.

METHODS: Intake of less than 90% of the antiretroviral drugs prescribed in the last week prior to the interview was defined as nonadherence. Intake was evaluated using a questionnaire. Descriptive and multivariate analyses were conducted on the study population, with estimation of the respective odds ratios and 95% confidence intervals.

RESULTS: The prevalence of nonadherence was 28.4%. Significant associations were found regarding the following variables: age less than 35 years, smoking, sedentary lifestyle, lack of medication and lack of knowledge regarding the patient's HIV status, on the part of the patient's partner or family.

CONCLUSIONS: Encouragement of adherence to antiretroviral therapy is one of the fundamental pillars of treatment for HIV-infected patients. The high proportion of nonadherence (28.4%) and the predictive factors related to this indicate that it is necessary to improve patients' adherence to antiretroviral therapy.

INTRODUCTION

Antiretroviral therapy (ART) decreases the viral load of the human immunodeficiency virus (HIV) or even renders it undetectable.[1,2] However, problems relating to adherence to this therapy are practically universal, and adherence is a complex process that requires a multifaceted approach for its improvement.[3] Nonadherence to antiretroviral drugs may consequently lead to development of viral resistance, which results in increased viral replication and development of opportunistic infections and other diseases, thereby increasing the morbidity and mortality associated with HIV infection.[4]

The ART adherence rates in Brazil vary from 20% to 84%.[5-9] However, the way in which this adherence to therapy is measured differs between studies. In a meta-analysis on ART adherence rates in Latin American and Caribbean countries, Costa et al.[10] found that they varied according to the length of time over which the measurement was made. Thus, individuals' adherence was found to be inversely proportional to the duration of the measurement period.

Data regarding adherence obtained through self-reporting has been identified as more reliable than data obtained through medical evaluation.[11] Moreover, it has been found that its accuracy can be amplified through use of questions that are less direct and with absence of prejudgment.[12]

Several factors have been correlated with nonadherence to ART among HIV-infected patients. Pinheiro et al.[13] found that elderly patients had a higher adherence rate and, consequently, that a higher proportion of these patients had an undetectable viral load. Additionally, nonadherence has been correlated with use of illicit drugs,[14,15] smoking,[14,16] alcohol consumption,[16] depressive symptoms,[17] lower schooling levels and economic status,[8,15] adverse reactions,[18] symptoms of opportunistic diseases[8] and longer time between infection and receiving the diagnosis of HIV and starting treatment.[15]

Interruption or irregularity of use of antiretroviral drugs is a public health problem in the fight against the HIV epidemic. Better adherence to therapy among patients not only leads to

virological failure but also reduces HIV resistance to antiretrovirals (ARVs).[19] Although several studies have been conducted in Brazil regarding ART adherence in the northeastern region of this country, more data is still needed, in order to broaden the notions about this issue and, thus, to enable creation of strategies elaborated on the basis of acquired knowledge.

OBJECTIVES

The aim of this study was to identify the predictive factors that might define the profile of individuals at the highest risk of interruption of treatment, at a large HIV/AIDS treatment center in the northeastern region of Brazil.

METHODS

Study design and population

This was a cross-sectional study that investigated nonadherence to antiretroviral treatment among people living with HIV/AIDS (PLWHA) who were treated at the infectious and parasitic diseases outpatient clinic of a tertiary-level hospital (Hospital das Clínicas, Federal University of Pernambuco, Brazil) in the northeastern region of Brazil between November 2012 and March 2013.

The study population consisted of PLWHA who had been diagnosed in accordance with the following criteria used by the Brazilian Ministry of Health:[20] individuals with a prescription for ART, aged 18 years or older, without mental illness, and who accepted participation in this study through signing a free and informed consent statement. A total of 253 people were interviewed.

Adherence to antiretroviral therapy and variables analyzed

The interview data were recorded in a questionnaire that had been elaborated in a previous study.[5] Nonadherence was defined as intake of less than 90% of the medications prescribed in the last week, considering the number of pills taken by asking the patients and the timetable for each intake.[5,21]

The outcome variable of this study was characterized as nonadherence in the week prior to the interview (self-reported). The independent variables were of three types, as follows:

- Sociodemographic variables and social behavior: region of residence, sex, age, schooling level, marital status, occupation, race, alcohol consumption, smoking, illicit drug use, religion and physical activity (defined as a minimum 30 minutes, three times a week);
- Variables relating to epidemiological data and support network: HIV transmission route, duration of infection, gender, stable or long-term relationship, number of stable or long-term partners, having casual partners, number of casual partners, HIV-infected partners, partners' knowledge of the subject's

HIV status, condom use before HIV infection, use of condoms after HIV diagnosis, family knowledge of the subject's HIV status, family support, support from friends/partners and level of knowledge about HIV/AIDS;

- Variables relating to antiretroviral therapy and pharmaceutical and medical care: duration of use of ART; current ARV scheme; reason for stopping taking ARVs; difficulty in obtaining the ARV from the dispensing pharmacist and what this difficulty was; difficulty in medical consultations and what this difficulty was; any other chronic illness; whether other medicines were being taken constantly and what these medicines were; whether the doctor had given explanations regarding the subject's health condition; whether the subject felt informed about HIV/AIDS; whether the subject talked to his/her doctor about his/her health condition; the subject's knowledge of ARV, including the names of ARVs; whether the subject's doctor talked about the ARV medications used; whether the pharmacy talked about the subject's use of ARV medicines; whether the subject felt secure about how to take his/her medications; and whether the subject would, if he/she had questions about the medicines, ask the doctor, the pharmacist or another professional.

Statistical analyses

The prevalence of nonadherence and the statistical association between the variables and the outcome were investigated using the chi-square test through the Epi Info software, version 3.5.3. $P < 0.05$ was considered statistically significant. For multivariate analysis, logistic regression was performed. The variables included were those that showed statistical significance in the bivariate analysis. The odds ratio, confidence interval and likelihood were calculated for each variable, with the respective significance tests. Regression analysis was performed using SPSS version 10.0.

Ethical considerations

The present work was approved, in accordance with the norms of Resolution 196/96 of the National Health Council, which regulates research activities on human beings, by the research ethics committees of Aggeu Magalhães Research Center, under the number 04911912.5.0000.5190, on September 5, 2012.

RESULTS

Among the 253 PLWHA who were assessed, 28.4% (n = 72) demonstrated nonadherence to ARVs. Among these individuals, 65% were men, 78% were over 35 years old, 78% practiced some type of religion, 58% had long-term partners and 26% had not informed their partners about living with HIV/AIDS. Nonadherence to ART was statistically associated with younger

age, smoking, use of illicit drugs and with having some religion or practicing physical activity (**Table 1**).

It was found that 32% and 38% of the nonadherent and adherent individuals, respectively, reported that there was a lack of antiretroviral medication. Furthermore, 30% of the nonadherent individuals had had some type of difficulty in obtaining their medications from the dispensing pharmacist and that they had had greater difficulties in making new appointments for medical consultations than the adherent individuals, thus revealing lapses in medical and pharmaceutical care.

Another important point was that adherent individuals reported receiving better information about ARVs from the attending physicians, which may have directly influenced the therapeutic results (**Table 2**).

Regarding epidemiological characteristics, nonadherent patients had a higher frequency of casual partnerships and their partners and families were not aware of their HIV status (**Table 3**).

The multivariate model revealed that the variables associated with nonadherence were younger age, smoking, sedentary lifestyle, lack of medication and alienation of the subject's partner and family regarding his/her HIV serological status (**Table 4**).

DISCUSSION

The rate of nonadherence detected among HIV-infected individuals undergoing ART at the Department of Infectious Diseases of Hospital das Clínicas, Federal University of Pernambuco, in the northeastern region of Brazil, was 28.4%. The multivariate analysis showed that there were statistical associations between nonadherence to ART and younger individuals, smokers, individuals with sedentary lifestyle, individuals whose partners and/or family were unaware of their HIV status and individuals who reported a lack of medication during treatment. Other studies[22,23] have also demonstrated an association between smoking and nonadherence. Regarding the association between nonadherence and younger individuals, there is a consensus in the literature that, in cases of chronic diseases, adherence increases with age.[24,25] Brazilian studies have ratified this type of association among HIV-positive individuals of younger age.[13,15]

Adults living with HIV can expect to gain many benefits from aerobic exercise, with improved cardiorespiratory function and psychological health.[26] Thus, the association between practicing exercise and adherence to therapy may be related to a possible improvement of psychological health, thereby leading to self-care. This conclusion has been confirmed through the observation that depressed patients or patients with other psychological disorders have less adherence to ARVs.[17,27]

The association between nonadherence and the variable of lack of knowledge among partners and relatives of the subject's HIV serological status may be related to social isolation. This is a common phenomenon among HIV-infected individuals and is caused by fear of social stigma. Hence, maintaining confidentiality seems to be the most adequate solution.[28] Self-imposed stigma can result in exclusion from social life and stable sexual relationships. Social support plays an important role in mitigating the negative consequences of stressful events, while insufficient support from people in the social and familial environment seems to negatively affect adherence.[29]

Table 1. Sociodemographic characteristics and social behavior of adults with human immunodeficiency virus (HIV) infection, in relation to nonadherence to treatment with antiretrovirals

Variables	Nonadherence		Adherence		χ^{2*}	P-value
	n = 72	%	n = 181	%		
Age (years)						
18-35	23	31.9	33	18.3	0.17	0.01
> 35	49	68.0	148	81.7		
Consumption of alcoholic beverage on a public holiday (glasses)						
1 to 12	30	66.7	66	80.5	3.01	0.08
> 13	15	33.3	16	19.5		
Smoking						
Yes	22	30.5	31	17.2	5.60	0.01
No	50	69.5	150	82.8		
Illicit drugs						
Yes	9	12.5	7	16.3	6.48	0.01
No	63	87.5	174	96.7		
Religious activity						
Yes	49	68.1	149	82.3	6.16	0.01
No	23	31.9	32	17.7		
Physical activity						
Yes	20	27.8	80	47.1	7.75	0.005
No	52	72.2	90	52.9		

*χ^2 = chi-square test.

Table 2. Characteristics of antiretroviral therapy and medical and pharmaceutical care, in relation to nonadherence to antiretroviral therapy

Variables	Nonadherence		Adherence		χ^{2*}	P-value
	n = 72	%	n = 181	%		
Antiretroviral (ARV) schemes						
2 NRTI + NNRTI	29	40.3	100	55.0	4.61	0.03
Others	43	59.7	81	45.0		
Reason for stopping taking ARVs						
Lack of medication	23	31.9	49	37.6	3.57	0.05
No reason/depression/forgetfulness	49	68.1	81	62.4		
Difficulty in obtaining medicines						
Yes	21	29.2	34	18.8	3.26	0.07
No	51	70.8	147	81.2		
Difficulty to getting a consultation with a doctor						
Yes	21	29.2	31	17.1	4.57	0.03
No	51	70.8	150	82.9		
Chronic illness						
Yes	13	18.3	51	28.2	2.62	0.10
No	58	81.7	130	71.8		
Do you use other medicines constantly?						
Yes	13	18.1	50	27.8	2.59	0.10
No	59	81.9	130	72.2		
Do you talk to your doctor about your medicines?						
Yes	30	41.7	93	51.4	1.95	0.16
No	42	58.3	88	48.6		
Does your doctor talk to you about your medications?						
Yes	45	62.5	137	75.7	4.44	0.03
No	27	37.5	44	24.3		
Do you think you should be more involved in decisions about your treatment?						
Yes	51	70.8	110	61.1	2.11	0.14
No	21	29.2	70	38.9		

*χ^2 = chi-square test.
NNRTIs = non-nucleoside reverse transcriptase inhibitors; NRTIs = nucleoside reverse transcriptase inhibitors.

Table 3. Epidemiological and supportive network characteristics of adults with human immunodeficiency virus (HIV) infection, in relation to nonadherence to antiretroviral therapy

Variables	Nonadherence		Adherence		χ^{2*}	P-value
	n = 72	%	n = 181	%		
Long-term partners						
Yes	49	69.1	98	57.9	2.56	0.10
No	22	30.9	71	42.1		
Casual partners over the last 12 months						
Yes	30	41.7	45	26.4	5.46	0.01
No	42	58.3	125	73.6		
Number of casual partners over the last 12 months						
1 to 9	23	76.6	42	89.4	2.24	0.13
≥ 10	7	23.3	5	10.6		
Partner infected with HIV						
Yes	26	41.9	74	60.5	5.81	0.01
Unknown HIV serological status	36	58.1	48	39.5		
Does your partner know about your serological status (HIV)?						
Yes	33	54.1	89	70.6	4.96	0.02
No	28	45.9	37	29.4		
Have you have spoken to someone in your family about your HIV status?						
Yes	49	72.1	153	85.0	5.47	0.01
No	19	27.9	27	15.0		

*χ^2 = chi-square test.

Individuals with greater difficulties in consulting their attending physicians and those who reported experiencing a lack of medications had higher nonadherence rates. Thus, it was seen that inaccessibility of healthcare services was a predictive factor for lack of correct adherence to ART. Additionally, approximately 32% of the nonadherent and 38% of the adherent patients reported experiencing a lack of medication at some time during their treatment. On the other hand, adherent individuals reported obtaining more information about ART from their attending physicians, which may have correlated with better treatment.

Thus, the role of the healthcare services is extremely important in relation to adherence. If dialogue with and communication from the service are available, a more reliable and committed relationship becomes possible. This broadens the understanding of adherence and, because of its multiple dimensions, a new adherence paradigm emerges. This consists of a model that is built between the patient, the healthcare team and the healthcare service.

One limitation of the present study relates to its use of information that only came from self-reports, although a check on the therapeutic schemes used was made available through the logistic control system for medicines (Sistema de Controle Logístico de Medicamentos, SICLOM) of the Brazilian Ministry of Health. For future studies, it is recommended that self-reporting should be confirmed through patient records, although this does not always address important issues regarding drug adherence.

Another limitation of the present study may have been its selection criterion, given that participation bias was present because the sampling was done according to convenience.

Encouragement of adherence to ART is one of the fundamental pillars of treatment for HIV-infected patients. Adequate adherence results in virological suppression, increased CD4+ T-cell counts and decreased morbidity and mortality. Additionally, nonadherence to ART is related to virological failure and antiretroviral resistance, with possible dispersion of resistant viruses. Therefore, working to promote adherence is also an important preventive tool within public health.[19]

Because of the policy of universal access to antiretroviral drugs in Brazil, the topic of adherence has been widely discussed in this country. However, there continues to be a lack of reports from the northeastern region, where the HIV epidemic is on the rise. Hence, studies on adherence to antiretroviral treatment remain extremely important, to enable better understanding of the problem and ensure adequate performance among multiprofessional teams.

CONCLUSIONS

This study showed that the prevalence of nonadherence was 28.4% and that the following factors presented statistical associations with it: age from 18 to 35 years, smoking, sedentary lifestyle, lack of knowledge among partners and families regarding the patient's serological status, lack of medication and difficulty in consulting a doctor. Identification of factors that are predictive of nonadherence will allow the multidisciplinary teams caring for PLWHA to adopt measures that increase drug adherence and will contribute towards establishment of information for a surveillance system.

Table 4. Multivariate analysis on associations with nonadherence to antiretroviral therapy among human immunodeficiency virus (HIV)-positive patients

Variables	OR	95% CI	P-value*
Age (years)			
18 to 35	2.105	(1.010-4.385)	0.047
> 35	1.0		
Smoking			
Yes	2.168	(1.046-4.491)	0.037
No	1.0		
Physical activity			
Yes	1.0	(1.059-4.085)	0.033
No	2.080		
Does your partner know about your HIV status?			
Yes	1.0	(1.278-4.927)	0.008
No	2.510		
Does your family know about your HIV status?			
Yes	1.0	(1.179-5.651)	0.018
No	2.581		
Lack of antiretrovirals			
Yes	2.434	(1.285-4.609)	0.006
No	1.0		

OR = odds ratio; CI = confidence interval; *χ^2 = chi-square test.

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Maternal exposure to benzene and toluene and preterm birth. A longitudinal study

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ABSTRACT

BACKGROUND: Exposure to air pollutants has several effects on human health, including during pregnancy.
OBJECTIVE: To identify whether exposure to benzene and toluene among pregnant women contributes to preterm delivery.
DESIGN AND SETTING: Longitudinal study using data on newborns from mothers living in São José dos Campos (SP) in 2016, who had been exposed to benzene and toluene.
METHODS: A logistic regression model with three hierarchical levels was constructed using maternal variables relating to newborns, and using benzene and toluene concentrations in quartiles. Occurrences of cesarean births, twins or malformations were excluded. Maternal exposure windows of 5, 10, 15, 30, 60 and 90 days prior to delivery were considered.
RESULTS: Out of the 9,562 live births, 3,671 newborns were included and 343 newborns were born at less than 37 weeks of gestation (9.3%). The average birth weight was 3,167.2 g. Exposure to benzene and toluene was significantly associated (P = 0.04) with preterm delivery in the five-day window. There was no association in any of the other exposure windows.
CONCLUSIONS: It was possible to identify that maternal exposure to benzene and toluene has an acute effect on preterm delivery.

INTRODUCTION

Preterm birth is defined as birth before 37 full weeks of gestation and is associated with higher neonatal morbidity and mortality,[1] along with diseases resulting from prematurity. The effects from preterm birth may extend into adulthood.[2]

In a multicenter study conducted in Brazil, the prematurity rate was estimated to be 11.7%. However, the rate reported through the national information system for live births (SINASC) was 7.1%.[3]

Many factors have been associated with preterm delivery, including pregnancies at ages of below 19 and above 34 years, low maternal schooling level, low number of prenatal visits, twin pregnancy, shortened cervix, premature rupture of the amniotic membrane, inflammation and recent exposure to environmental pollutants.[4,5]

Carbon monoxide (CO), ozone (O_3), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) are the gaseous pollutants that have been most studied.[6] Particulate matter with an aerodynamic diameter of less than 10 µm (PM_{10}) has also been investigated. This is composed of a mixture of solid and liquid particles that adsorb polycyclic aromatic hydrocarbons and ions such as sulphates, nitrates and metals.[7]

Besides these, reports have also shown that associations with benzene and toluene exist. These substances are emitted mainly by the petrochemical industry, but also come from the vehicular fleet. It has not been defined whether their effects occur in an acute or chronic manner, or what the mechanism of action for these effects might be. However, it is known that the action of air pollutants is associated with the pro-oxidant effects of lipids and proteins, along with formation of free radicals, which generate oxidative stress and inflammation.[8-11]

OBJECTIVE

The objectives of this study were to identify the possible effects of maternal exposure to benzene and toluene at the onset of preterm delivery and to evaluate whether these are acute or chronic.

METHODS

This was a longitudinal study that used data on live births from pregnant women living in São José dos Campos (SP), Brazil, in 2016. This municipality has a population of approximately 700,000 inhabitants. It is a regional center with several industries, including automobile, aerospace and petrochemical industries, among which the Petrobras oil refinery stands out. Via Dutra, the busiest highway in Brazil, connecting the metropolitan areas of São Paulo and Rio de Janeiro, crosses this municipality.

Data were obtained from birth certificates, i.e. declarations of live birth (Declaração de Nascido Vivo, DNV) that are recorded in the live birth information system (Sistema de Informação sobre Nascidos Vivos, SINASC).[12] Newborns weighing less than 500 grams, twin and trigeminal births and fetuses with congenital malformations were all excluded from this study because these occurrences are possibly associated with preterm birth. Cesarean deliveries were also excluded because of the possibility of iatrogenic prematurity.

Data on the pollutants benzene and toluene were obtained from the database of the Environmental Company of the State of São Paulo (Companhia Ambiental do Estado de São Paulo, CETESB), which is in the public domain.[13]

Statistical analysis was performed using a hierarchical logistic regression model. The pollutants were divided into quartiles and considered in relation to the first quartile (reference category).

The dependent variable was the presence of preterm birth. The independent variables were classified into three levels: distal, intermediate and proximal. The classification of the variables as such is described below.

The distal level included maternal age, marital status and schooling level. Maternal age was categorized as favorable when it was within the range from 20 to 34 years; or as unfavorable when it was 19 years or younger or 35 years or older, i.e. with greater risk of preterm birth. Marital status was categorized as single, separated or widowed (unfavorable); or as married or in a stable union (favorable). Schooling level was classified as elementary and high school only (unfavorable); or as tertiary-level, i.e. university or technical college (favorable).

The intermediate level included the number of prenatal visits, which was categorized as unfavorable when this number was between zero and six or as favorable when it was seven or more; and the time at which prenatal care began, which was categorized as favorable when this was no later than the third month or as unfavorable when this was from the fourth month onwards.

The proximal level included the sum of concentrations of the pollutants recorded in the 5, 10, 15, 30, 60 and 90-day windows prior to childbirth.

The pollutants benzene and toluene were analyzed in terms of daily averages, in $\mu g/m^3$. For analysis purposes, the sums of the concentrations in the 5, 10, 15, 30, 60 and 90-day windows before childbirth were considered. The aim of this procedure was to assess whether the cumulative effects of these pollutants on the onset of preterm delivery occurred in an acute or a chronic manner. Bivariate analysis was performed on the variables within the three levels, separately. At the distal level, variables with a P-value ≤ 0.20 were included in the multivariate analysis and variables that presented P-value < 0.05 at this level were maintained at the next phase of the analysis.

The same procedure was performed for intermediate-level variables, and then those with P-value < 0.05 were adjusted according to the variables of the previous level. At that moment, the hierarchical model contained two levels of variables: distal and intermediate. Lastly, for each of the pollutant exposure windows with P-value ≤ 0.20, the variables at this level were maintained for each window with P-value < 0.05, thus completing the three levels of this analysis.

For the exposure windows that continued to present P-values < 0.05 in the final model and thus were retained in the model, we also performed a χ^2 trend test to identify any possible dose-response effect.

For the statistical analysis, we used the Epi Info software, version 7.2. The significance level used in the analyses was alpha = 5%.

Because this study used data that are available online with public access, and it was impossible to identify the subjects analyzed, the study was not submitted to a research ethics committee.

RESULTS

Out of the total number of 9,562 live births in 2016 in São José dos Campos, Brazil, 3,671 (38.0%) that met the inclusion criteria were analyzed. There were 1,826 male newborns (50.9%) and 1,845 female newborns (49.1%). Their mean birth weight was 3,167.2 g (standard deviation, SD = 495.0 g). Among the live births that met the inclusion criteria, 343 (9.3%) were found to have taken place at a gestational age of less than 37 weeks.

The mean daily levels and respective standard deviations (SD) for the pollutants were as follows: benzene 6.56 $\mu g/m^3$ (SD = 4.83); and toluene 21.38 $\mu g/m^3$ (SD = 16.66).

The results from the bivariate analysis on the distal and intermediate levels showed that only the number of prenatal care consultations was significant (P-value < 0.01). These results are shown in **Table 1**.

In the final analysis, both of the pollutants were considered at the proximal level, adjusted for the number of prenatal care consultations. The odds ratios (ORs) and their respective 95% confidence interval (95% CI) for the accumulated 5, 10 and 15 days relating to benzene and toluene exposure, with emphasis on the accumulated five-day concentration regarding benzene (OR = 1.12; 95% CI: 1.01-1.23) and toluene (OR = 1.12; 95% CI: 1.01-1.23) are shown in **Table 2**.

Table 3 presents accumulation data for 30, 60 and 90 days, for benzene and toluene. No significant values were found for this range of exposure.

The χ^2 trend for the accumulated five-day periods is shown in **Table 4**. It shows that both benzene and toluene had significant cumulative effects.

DISCUSSION

This study identified an association between preterm birth and maternal exposure to benzene and toluene five days before delivery, after adjusting for the number of consultations attended by the pregnant woman during prenatal care. Thus, a possible acute effect was found.

It is known that exposure to air pollutants is associated with several respiratory and cardiovascular diseases, as well as with preterm birth.[8] Few studies in the literature have correlated exposure to benzene and toluene with premature delivery. In Brazil, to the best of our knowledge, this is the first study on this association.

The analysis on distal and intermediate factors (**Table 1**) showed that there was only an association with the number of visits made during prenatal care (P < 0.01). Pregnant women who made not more than six visits were more likely to have a premature delivery. This confirms the observations from a Brazilian multicenter study, which found similar results (OR = 2.13; 95% CI: 1.57-2.88).[5]

However, the factor of maternal age was not found to be associated with preterm birth, contrary to the findings from a Chinese study. In that study, two age groups were formed and the group older than 30 years presented higher risk of prematurity.[14]

There was also no association with maternal marital status, since women living without partners were not found to be at higher risk of preterm birth. This was discordant with the findings from an American study, which showed that those living without a partner presented significantly higher risk (relative risk, RR 10.67%; 95% CI: 10.23-11.12), in relation to those with a partner (RR = 7.21%; 95% CI: 6.92-7.50).[15]

Regarding schooling level as a risk factor for low birth weight, our findings were concordant with those from a Brazilian study carried out in the city of Rio de Janeiro, where no association between low schooling level and low birth weight (OR = 0.93) was found.[16] However, the results from the present study were contrary

Table 1. Descriptive analysis on distal and intermediate variables[#]. São José dos Campos (SP), 2016

Variable	Categories	Delivery at < 37 weeks (n)	Delivery at ≥ 37 weeks (n)	P-value
Age	20 to 34	2,128	6,371	0.61
	< 20 and > 34	265	763	
Marital status	Married	2651	5,799	0.54
	Unmarried	331	693	
Schooling	Tertiary-level	321	706	0.85
	High school	2,675	5,806	
Prenatal consultations	7 or more	1,357	7,136	< 0.01
	< 7	430	596	
Prenatal start	Not later than 3rd month	872	7,266	0.90
	4th month onwards	102	862	

[#]The differences between the total numbers of cases included in Table 1 and the total numbers of births result from lack of information about some variables.

Table 2. Odds ratio (OR) with 95% confidence interval (95% CI) and significance level (P-value) for maternal exposure to benzene and toluene in relation to preterm delivery, for benzene and toluene exposure windows of 5, 10 and 15 days prior to delivery. São José dos Campos (SP), 2016*

	OR	95% CI	P-value
Benzene 5 days (µg/m³)	1.12	1.01-1.23	0.04
Benzene 10 days (µg/m³)	1.07	0.97-1.19	0.16
Benzene 15 days (µg/m³)	1.04	0.94-1.15	0.46
Toluene 5 days (µg/m³)	1.12	1.01-1.23	0.04
Toluene 10 days (µg/m³)	1.10	0.99-1.22	0.06
Toluene 15 days (µg/m³)	1.07	0.97-1.19	1.18

*Adjusted for the number of prenatal consultations.

Table 3. Odds ratio (OR) with 95% confidence interval (95% CI) and significance level (P-value) for maternal exposure to benzene and toluene in relation to preterm labor and delivery, for benzene and toluene exposure windows of 30, 60 and 90 days prior to delivery. São José dos Campos (SP), 2016*

Pollutant (µg/m³)	Window of exposure	OR	95% CI	P-value
Benzene	30 days	1.06	0.95-1.17	0.30
	60 days	1.03	0.92-1.14	0.61
	90 days	1.02	0.92-1.13	0.93
Toluene	30 days	1.09	0.99-1.21	0.07
	60 days	1.01	0.91-1.21	0.81
	90 days	0.99	0.89-1.10	0.93

*Adjusted for the number of prenatal consultations.

Table 4. χ^2 trend for accumulation of 5 days of benzene and toluene exposure, in quartiles of level of concentration (Q1, Q2, Q3 and Q4). São José dos Campos (SP), 2016*

Pollutant and time of exposure	Quartile	Number of cases	Number of controls	OR	P-value
Benzene 5 days (µg/m³)	Q1[#]	78	883	1.00	
	Q2	84	856	1.11	0.04
	Q3	80	753	1.20	
	Q4	101	836	1.37	
Toluene 5 days (µg/m³)	Q1[#]	70	801	1.00	
	Q2	83	849	1.12	0.05
	Q3	92	843	1.25	
	Q4	98	835	1.34	

*Adjusted for the number of prenatal consultations; [#]Reference category.

to the findings from a study conducted in Spain (OR = 2.05)[17] and to those from a Brazilian study conducted in the city of São José do Rio Preto (P < 0.01), which found strong associations between maternal schooling level and low birth weight.[18]

Other comparisons with the Brazilian literature are very difficult, given the scarcity of studies on the effect of maternal exposure to air pollutants and occurrence of premature delivery. In a single study conducted by Lima et al.,[19] a significant association between premature delivery and exposure to PM_{10} was found on the day of delivery (lag 0), the day before delivery (lag 1) and three days prior to delivery. However, a different approach was used in their study.

Analysis on acute exposure (**Table 2**) showed that there were associations with premature delivery for the sum of five days prior to delivery, regarding maternal exposure to benzene (OR = 1.12; 95% CI: 1.01-1.23) and to toluene (OR = 1.12; 95% CI: 1.01-1.23). The results relating to benzene were partly concordant with findings from another study conducted in Spain, which found associations between maternal exposure to benzene and occurrence of premature delivery, from analysis on the whole gestational period, when the levels exceeded 2.7 µg/m³ (OR = 1.38; 95% CI: 1.03-1.84).[8] In the present study, the acute effect of exposure was identified, but no data on the acute effect of these pollutants are available in the literature.

In a study conducted in Canada, Poirier et al. showed that there was an association between exposure of pregnant women to toluene in the second quartile of toluene concentrations (OR = 1.35; 95% CI: 1.12-1.63) and preterm delivery. In this Canadian study, exposure was considered throughout the gestational period and the findings are partially concordant with our results, in which we found an association with maternal exposure for five days.[10]

On the other hand, there was no significant association between maternal exposure to benzene and toluene over other exposure windows such as 30, 60 and 90 days.

The χ^2 trend analysis on the five-day windows, with adjustment for the number of consultations, showed that the higher the concentrations of benzene and toluene were, the greater the chance of birth of a preterm fetus was. This highlights the possible cumulative effect of exposure.

One possible mechanism for the onset of preterm birth caused by exposure to air pollutants is thought to relate to release of cytokines and reactive oxygen species, thereby causing oxidative stress.[20] In the case of benzene and toluene, there are no studies that explain the mechanism of action of these two pollutants in triggering preterm birth. Moreover, there are no World Health Organization (WHO) guidelines for acceptable values for benzene or toluene, unlike in relation to other air pollutants.[6]

This study had certain limitations. The mothers' socioeconomic conditions, home address, living conditions, preexisting diseases and smoking status were not available through SINASC. The concentrations of the air pollutants were considered homogeneous throughout the city, which might not reflect the reality. Moreover, the pregnant women had been free to circulate during their pregnancies. Another possible limitation of the present study may have been its non-inclusion of other air pollutants. However, a previous analysis had not shown any correlation between these air pollutants and the outcome.

CONCLUSIONS

Despite the limitations of the present study, it was possible to identify the deleterious effect of maternal exposure to benzene and toluene on the preterm delivery in a medium-sized city in Brazil, and to ascertain that this was an acute effect. The results presented here may be useful for public policy implementation, with the aim of reducing these concentrations.

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Epidemiological profile, referral routes and diagnostic accuracy of cases of acute cholangitis among individuals with obstructive jaundice admitted to a tertiary-level university hospital: a cross-sectional study

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ABSTRACT

BACKGROUND: Obstructive jaundice may lead to ominous complications and requires complex diagnostic evaluations and therapies that are not widely available.

OBJECTIVE: To analyze the epidemiological profile, referral routes and diagnostic accuracy at admittance of cases of acute cholangitis among patients with obstructive jaundice treated at a referral unit.

DESIGN AND SETTING: Cross-sectional study at a tertiary-level university hospital.

METHODS: Patients with obstructive jaundice who were treated by means of endoscopic retrograde cholangiopancreatography, resection and/or surgical biliary drainage were evaluated. The main variables analyzed were epidemiological data, referral route, bilirubin levels and time elapsed between symptom onset and admittance and diagnosing of acute cholangitis at the referral unit. The accuracy of the clinical diagnosis of acute cholangitis was compared with a retrospective analysis on the medical records in accordance with the Tokyo criteria.

RESULTS: Female patients predominated (58%), with an average age of 56 years. Acute cholangitis was detected in 9.9% of the individuals; application of the Tokyo criteria showed that the real prevalence was approximately 43%. The main referral route was direct contact (31.8%) and emergency care (29.7%); routing via official referral through the public healthcare system accounted for 17.6%, and internal referral from other specialties, 20%. The direct route with unofficial referral was the most important route for cases of neoplastic etiology (P < 0.01) and was the fastest route (P < 0.01).

CONCLUSIONS: There is a deficiency in the official referral routes for patients with obstructive jaundice. The accuracy of the clinical diagnosis of acute cholangitis was poor. Wider dissemination of the Tokyo criteria is essential.

INTRODUCTION

Jaundice is a clinical sign characterized by abnormal yellow coloring of the skin, mucous membranes and sclera. It is caused by increased bilirubin levels in the blood.[1]

Most bilirubin is produced when hemoglobin is metabolized to indirect bilirubin, which then binds to albumin and is transported in the plasma to the liver, where it is conjugated with glucuronic acid to become water-soluble and is referred to as direct bilirubin. This is excreted in bile, in the duodenum. In the intestine, bacteria metabolize bilirubin to form urobilinogen. Part of this urobilinogen is eliminated in feces and part is reabsorbed, reprocessed and excreted in bile (enterohepatic cycle).[2-4]

Cholestasis is the condition in which the conjugated bile in the liver encounters an obstacle to its elimination in the duodenum. This may be due to disturbances of excretion such as hepatocellular injury (drug or viral hepatitis, pregnancy or sepsis) or abnormalities of the flow between the hepatocyte and the ampulla of Vater, such as gallstones of the main bile duct, periampullary neoplasm or pancreatitis.[4,7,8]

The clinical sign of jaundice has a broad spectrum of etiologies and can range in severity from asymptomatic cases that do not require intervention, to others in which there may even be an imminent risk of death.[4] Individuals with jaundice but without infectious signs may experience

weight loss or itching. Jaundiced patients presenting acute diseases, often of infectious causes, may seek medical care for treatment of fever, chills, abdominal pain or flu-like symptoms.[4,9]

Regarding imaging methods in the context of obstructive jaundice, ultrasound of the abdomen presents sensitivity of 46% and specificity of 96% for diagnosing dilatation of the common bile duct; and sensitivity of 38% and specificity of 100% for diagnosing gallstones. It has the advantages of being an inexpensive and accessible examination. However, it is operator-dependent and may be impaired through occurrences of distension of intestinal loops, agitation and obesity, which are common findings in these patients. Magnetic resonance imaging is the test with the best accuracy for evaluation of the bile ducts, both for benign and malignant diseases, with sensitivity and specificity of up to 98%.[10-11]

Contamination associated with infection of stagnant bile leads to inflammation of the biliary tract, and this condition characterizes cholangitis, a medical emergency. Biliary tract obstruction can occur due to benign strictures, malignant strictures, obstruction of bile stents, hemobilia or parasitic infection. The main cause of obstruction of the bile duct is choledocholithiasis.[12,13] The diagnosis of acute cholangitis was established by Charcot in 1877 as an association of abdominal pain in the right hypochondrium with fever and jaundice (Charcot's triad). Although classical, the presentation of Charcot's triad is unusual.[14-16] Hence, in 2007, the Tokyo guidelines for diagnosis and gradation of acute cholangitis were developed, and then revised in 2013 and again in 2018, in its third review.[17,18]

The pinnacle of the treatment hierarchy for this serious complication consists of use of antibiotics and decompression of the biliary tract. The therapy of choice for biliary tract drainage is endoscopic retrograde cholangiopancreatography (ERCP), and the degree of urgency of the procedure is based on the severity of cholangitis according to the Tokyo guidelines.[18] Transhepatic percutaneous cholangiography and endoscopic ultrasonography can be used for biliary tract drainage. Surgical drainage, in the context of cholangitis, is performed in cases of failure or contraindication of the less invasive procedures cited above.[19] In cases of obstructive jaundice due to neoplastic causes, R0 resection of the tumor is the ideal treatment, when feasible. There is still no consensus in the current literature regarding preoperative use of biliary tract drainage.[20-23]

According to the hierarchy of healthcare services proposed within the Brazilian National Health System (Sistema Único de Saúde, SUS), appropriate screening of individuals with diseases that require specialized treatment in tertiary-level healthcare services, to differentiate them from other individuals whose treatment can be appropriately conducted at primary healthcare units, is essential in order to avoid wasting resources. According to Santos et al., there are frequent misconceptions in Brazil regarding the management of patients with obstructive jaundice, ranging from inaccurate diagnoses at the healthcare services of origin to difficulty in

identifying the best available treatment for these patients in tertiary-level referral services.[24]

Thus, an analysis on the referral routes of patients with obstructive jaundice who are admitted to referral services is essential. This makes it possible to define the main weaknesses observed in the initial management of these patients, ascertain the average time taken to provide referral care and define ways to optimize specialized care for these patients, based on the most prevalent etiologies and the clinical state that these patients present upon admission to the tertiary-level unit.

OBJECTIVE

The aim of this study was to critically analyze the referrals of patients with obstructive jaundice who were treated by means of ERCP or surgery at a tertiary-level hospital in Brazil. This analysis included identifying the main referral routes among patients with obstructive jaundice; identifying the main causes of referral and the time that elapsed between the initial care and admission to this hospital; and reviewing the diagnosis of cases with acute cholangitis at admission to the tertiary-level unit.

METHODS

A cross-sectional, retrospective and descriptive study was carried out to evaluate all consecutive adult patients with obstructive jaundice who were treated by means of ERCP and/or resection or biliary drainage surgery at Hospital de Clínicas, UNICAMP, Campinas, Brazil.

The study participants were identified and selected through the electronic scheduling systems of the outpatient unit for biliary tract surgery, digestive endoscopy unit and main surgical center. These patients underwent ERCP or pancreatic or biliary resection surgery, and internal biliary drainage operations, between September 2017 and August 2018.

The inclusion criteria were that the patients needed to present: 1. bile duct obstruction with radiological evidence (computed tomography [CT], magnetic resonance imaging [MRI] or ERCP); or 2. jaundice defined by the presence of total bilirubin ≥ 2.5 mg/dl. The exclusion criteria were: 1. absence of laboratory jaundice reported in this hospital service or recorded in medical records; or 2. indication of ERCP or biliary drainage for other non-obstructive causes (stent replacement, primary sclerosing cholangitis or liver transplantation). A flowchart of the study population is presented in **Figure 1**.

The variables analyzed were the following: 1. age (expressed in years); 2. sex (male or female); 3. etiology (neoplastic or non-neoplastic); 4. referral routes, which could be through SUS regulations (regional health departments [DRS] or the regulatory center for healthcare service provision [CROSS]), referral from an emergency care unit, direct contact with the biliary surgery team or internal

referral; 5. time that elapsed between symptom onset and provision of care at HC-UNICAMP; 6. maximum total and direct bilirubin levels up to the time of the definitive treatment (ERCP or surgery); and 7. registration of the clinical diagnosis of acute cholangitis.

The criteria considered for making the diagnosis of acute cholangitis at the outpatient unit were those of Charcot's triad (jaundice, fever and abdominal pain reported on the chart). The gold standard considered for this diagnosis was the criteria of the 2018 Tokyo protocol (**Table 1**).

The medical records were reviewed and the diagnosis of cholangitis was reevaluated. The criteria of the Tokyo protocol were independently reapplied by the present authors based on the medical records, since there was no mention of these criteria in the records. The laboratory and radiological examinations performed in all cases of obstructive jaundice were also reviewed to identify the diagnosis of cholangitis in accordance with the criteria of the Tokyo protocol and were then compared with the clinical diagnosis at the time of admission.[18]

This research protocol was approved by our institution's research ethics committee under the reference number UNICAMP-2.924.828/2018, on September 28, 2018.

Statistical analysis

The chi-square test, or Fisher's exact test when necessary, was used to compare proportions. Diagnostic accuracy tests (sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy) were used to evaluate the

diagnostic methods. The diagnosis of cholangitis in accordance with the Tokyo protocol was considered to be the gold standard.[18] Normality was assessed using the Shapiro-Wilk test.

To compare continuous measurements, analysis of variance (ANOVA) was used for variables with normal distribution and the Mann-Whitney test was used for those with non-Gaussian distribution. To compare continuous measurements between three or

Table 1. Diagnostic criteria for cholangitis according to the 2018 Tokyo guidelines*

A. Systemic inflammation	
A-1. Fever and/or chills	Axillary temperature > 38º
A-2 Laboratory studies with evidence of systemic inflammation	White blood cell count (x 1000/µl) < 4 or > 10 C-reactive protein (mg/dl) > 1
B. Cholestasis	
B-1. Jaundice	Total bilirubin > 2 (mg/dl)
B-2. Abnormal liver enzymes	AST, ALT, ALP or GGT > 1.5 reference value
C. Imaging	
C-1. Biliary dilatation	
C-2. Etiology evidence from imaging	Strictures, stones, cancer, etc.
Suspected diagnosis: One item in A + one item either in B or C.	
Definite diagnosis: One item in A + one item in B + one item in C.	

*Adapted from Miura et al.[18]

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; GGT = gamma glutamyl transferase.
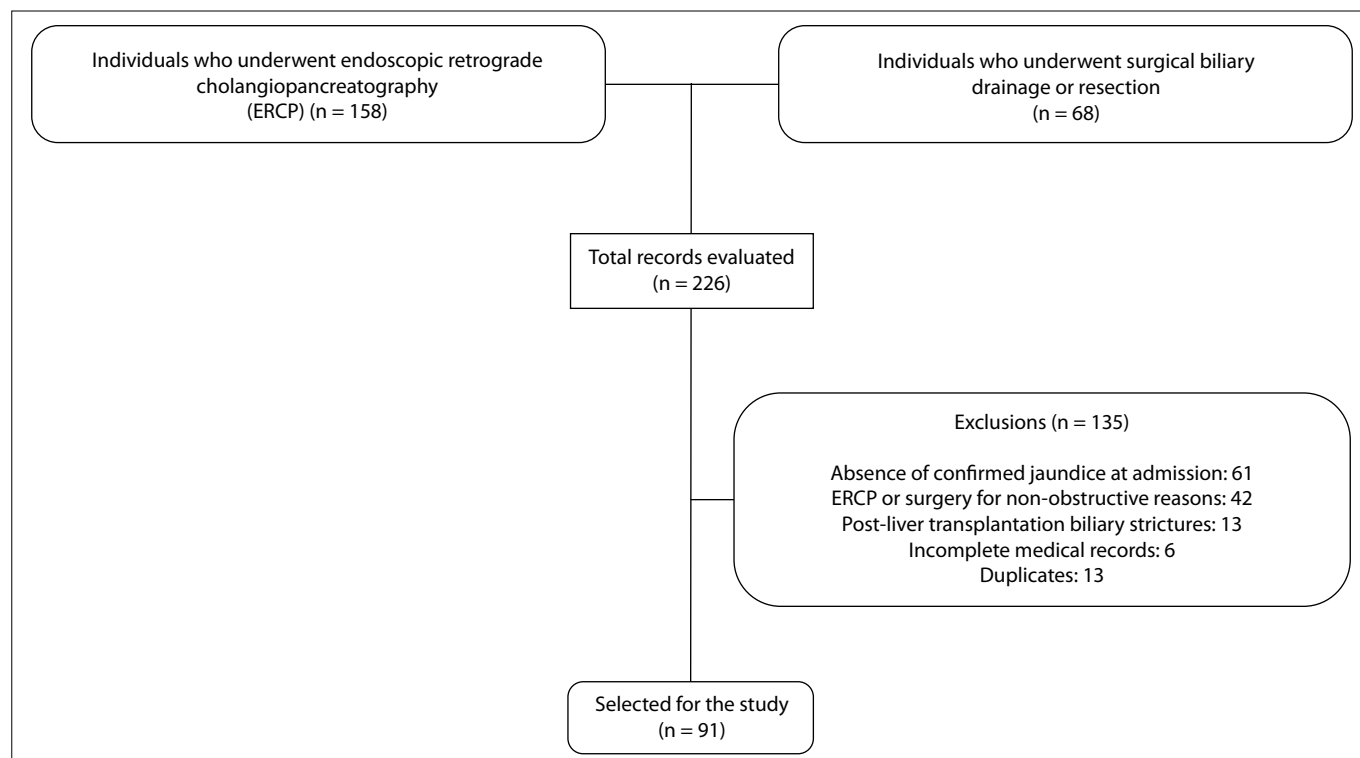
Figure 1. Flowchart of the study population.

more groups, the Kruskal-Wallis test was used and, when a significant difference was observed, Tukey's post-test was used to determine the groups between which the difference was significant.

The significance level was taken to be 5% (P < 0.05). The Statistical Analysis System (SAS) for Windows, version 9.2 (SAS Institute Inc., 2002-2008, Cary, NC, USA) was used for the calculations of the statistical analysis.

RESULTS

The demographic and clinical characteristics of the study population are presented in **Table 2**. Female patients predominated in the sample of this study (58%). The patients were in their fifth decade of age onwards, with a mean age of 56 years. Benign etiologies were slightly more prevalent (52% of the cases).

Acute cholangitis was originally recorded in 9.9% of the cases of obstructive jaundice, but the review of the cases with application of the 2018 Tokyo criteria showed that the prevalence was approximately 43%. The overall accuracy of the clinical diagnosis of cholangitis at admission was estimated to be 67%, with sensitivity of 23% and specificity of 100% (**Table 3**).

Table 2. Clinical characteristics of the population studied

N	91
Gender	Male: 38 (41.8%)
	Female: 53 (58.2%)
Age (years)	56.6 ± 16.3
Etiology	Non-neoplastic: 47 (51.6%)
	Neoplastic: 44 (48.4%)
Type of treatment	Endoscopic: 61 (67%)
	Surgery: 17 (18.7%)
	Both: 13 (14.3%)
Bilirubin level (mg/dl)	15.8 ± 8.1
Referral route	Unofficial direct contact: 29 (31.8%)
	Official regulations: 27 (29.7%)
	Internal referral: 16 (17.6%)
	Emergency care: 19 (20.9%)

Table 3. Accuracy of clinical diagnosis of acute cholangitis reported in the medical records, in comparison with the review of these reports using the 2018 Tokyo guidelines

Cholangitis			
Clinical Diagnosis	Present	Absent	Total
Positive	True positive (a = 9)	False positive (c = 0)	a + c = 9
Negative	False negative (b = 30)	True negative (d = 52)	b + d = 82
Total	a + b = 39	c + d = 52	

Diagnostic accuracy test values and 95% confidence intervals:
Sensitivity: 23.1% (11.1%-39.3%)
Specificity: 100% (93.2%-100%)
Positive likelihood ratio: not applicable
Negative likelihood ratio: 0.8 (0.7-0.9)
Positive predictive value: 100%
Negative predictive value: 63.4% (59.3%-67.3%)
Overall accuracy: 67% (56.4%-76.5%)

Regarding the referral routes among the patients with obstructive jaundice, the main routes were through direct contact (31.8%) and emergency care (29.7%). Routing via SUS regulations accounted for 17.6% of the cases and internal referral from other specialties, 20% (**Table 2**). The mean bilirubin levels of the patients with referrals was 15.8 mg/dl.

The direct route through unofficial referral was the most important route for cases of neoplastic etiology (P < 0.01) and was the fastest route (P < 0.01). However, there was no statistical difference in bilirubin levels among the routes (**Figures 2** to **4**).
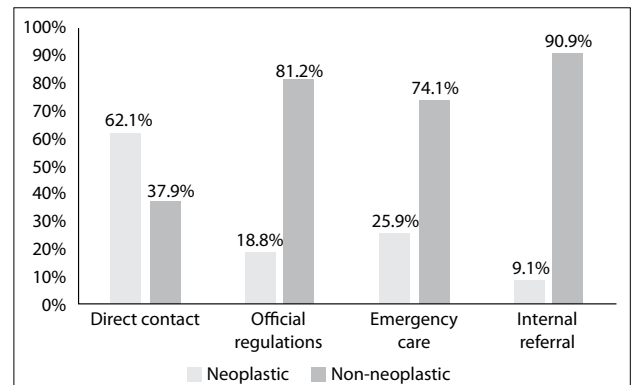
Figure 2. Etiology according to the referral route among individuals with obstructive jaundice who were referred to a tertiary-level hospital.

Kruskal-Wallis: P < 0.01
Tukey's post-test:
Direct contact < Official regulations (P < 0.01)
Emergency care < Official regulations (P < 0.05)
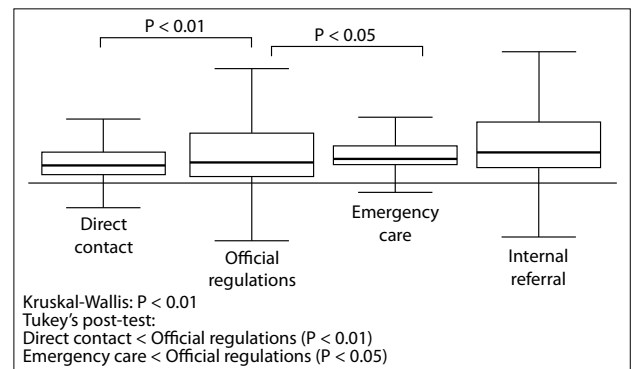
Figure 3. Time that elapsed between the beginning of symptoms and admission to the tertiary-level hospital (months).

Kruskal-Wallis: P = 0.5
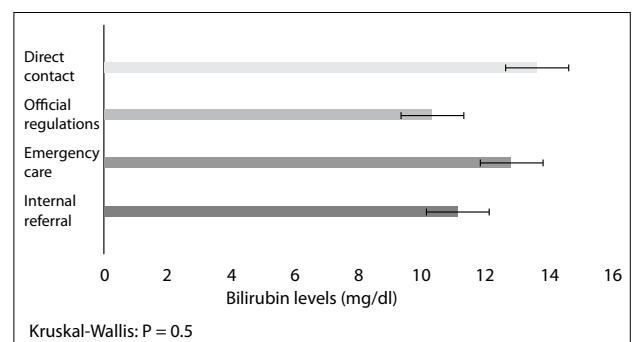
Figure 4. Bilirubin levels according to referral route among individuals with obstructive jaundice.

DISCUSSION

The present sample had a predominance of female patients (58%), with ages from the fifth decade onwards (mean of 56 years). Benign etiologies were slightly more prevalent (52% of the cases).

Among the previous evidence in the literature, Whitehead et al. evaluated 121 patients with jaundice in Wales, except for neonates, and found that malignant etiology was more prevalent. The pancreatobiliary system was most commonly affected. However, the etiology related to gallstones in only 13% of the cases.[25] Björnsson et al., in Sweden, evaluated 241 patients with obstructive jaundice, among whom 53% were female. The obstructive jaundice was of benign etiology in 36% of the cases, with a mean age of 69 years and mean bilirubin level of 7.1 mg/dl. In 64% of the cases, the etiology was malignant, and these patients had a mean age of 74 years and mean total bilirubin level of 13.8 mg/dl.[26]

In the current series, there was higher prevalence of jaundice caused by stones. This was probably related to the greater difficulty that patients in Brazil experience with regard to being able to undergo diagnostic tests that might detect early gallbladder stones and, thus, avoid migration of stones to the main bile duct. Likewise, it was observed that the bilirubin levels in our series were higher at admission. This can also be correlated with difficulty in accessing healthcare services and complementary tests, which leads to greater delay in diagnosing the condition and consequently obtaining treatment.

A diagnosis of cholangitis was registered in the medical records of 9.9% of the cases reviewed in this series. After laboratory and radiological review on all of the cases of obstructive jaundice, 42.9% of the patients were found to present the criteria for a diagnosis of cholangitis, according to the 2018 Tokyo protocol.[18] This discrepancy in the results was probably due to low dissemination of the Tokyo diagnostic criteria and also to widespread use of the clinical diagnostic criteria of Charcot's triad and Reynolds's pentad, which, although specific, are ineffective because of their low sensitivity.[14-16] Comparison between the diagnostic criteria among the current cases showed a result consistent with the previous evidence, i.e. that Charcot's criteria present high specificity and low sensitivity, and that their accuracy is below the level required for this complication of high morbidity and mortality. Charcot's triad is more important for cases of greater immediate severity.

Karvellas et al. showed that delayed introduction of antibiotic therapy in cases of septic shock due to cholangitis caused a 1.15-fold increase in mortality for each hour of delay. Moreover, another factor that was also correlated with higher mortality was delay of more than 12 hours in decompression of the biliary tract.[27] According to Khashab et al., a three-day delay in performing ERCP in cases of cholangitis resulted in increased length of hospital stay, increased cost of hospitalization and worsened clinical outcome (persistence of organ failure, length of intensive hospitalization and death).[28] Navaneethan et al. correlated time delays of more than 48 hours between admission and ERCP as an independent factor for rehospitalization within 30 days, and noted that this was the main cause of failure to diagnose cholangitis.[29]

Regarding the referral routes among patients with obstructive jaundice, the main routes were through direct contact (31.8%) and emergency care (29.7%), which can both be considered to be unofficial routes of referral. Routing via the official regulations accounted for only 17.6% of the cases and internal referral from other specialties, 20%. Direct referral was significantly more frequent among patients with neoplastic diseases, who accounted for 62% of direct referrals. Among the cases that came via the other referral routes, non-neoplastic disease was the main etiology. There was no statistical difference in bilirubin levels among the routes of referral. The time that elapsed between the onset of symptoms and receiving care in our referral service was statistically shorter among the cases that came via the unofficial routes. This time was significantly shorter among cases referred through direct contact than among cases referred through all other routes.

The great volume of cases and demand for care at our hospital service stems from the structuring of the healthcare service and the scarcity of specialized services providing high-complexity biliopancreatic surgery in our region. The regional health division of the Metropolitan Region of Campinas belongs to Regional Health Department (Departamento Regional de Saúde, DRS) VII, which has an estimated total population of three million inhabitants.[30]

Regarding the diagnostic imaging methods available in this DRS, it has been estimated that there are 8.3 CT and 3.8 MRI machines in the public system per million inhabitants. This is slightly higher than the average for the state of São Paulo, which is 7.9 CT and 3.4 MRI machines per million inhabitants.[31] Within the worldwide context, these rates reach 107 CT and 56 MRI machines per million inhabitants in Japan. In emerging South American countries like Chile (14 CT and 9.43 MRI machines per million), these rates are also higher than those of our region.

Regarding the main therapy, ERCP, it has been estimated that in Brazil there is an average of 2.98 procedures per 100,000 inhabitants, a rate that is far below the ideal.[32] In the United States, for example, this rate is 74 procedures per 100,000 inhabitants, and in China, an emerging country with a larger population, this rate is 14 per 100,000 inhabitants.[33,34]

Regarding surgical procedures for resection of neoplasms, which are the main cause of extra-official referral routes, our hospital is the only public one in this region that has a sufficiently periodic and steady flow of patients for it to be possible to accomplish such procedures. Thus, the low availability of diagnostic examinations and therapeutic procedures (whether surgical or endoscopic) in other healthcare facilities ends up creating a flow of referrals of these patients.

Moreover, the clinically stigmatizing sign of jaundice, the rapid evolution of periampullary neoplasms and the already-discussed

low availability of referral centers in this region that can resolve these cases, combined with the slowness and inefficiency of the official referral pathways, have led to potential alternative referral routes. Given the situation outlined above, these alternative referral routes are important for enabling rapid attendance of these patients. However, their existence attests to the organizational failure of the regional healthcare system in relation to allowing individuals access to the necessary resources in a timely manner through official channels.

This study presents some limitations that need to be taken into consideration. Its retrospective design can possibly be correlated with lower quality among the data collected, along with potential loss of participants due to incomplete medical reports. Because this was a single-center study, the findings are not immediately reproducible in other hospital services. In addition, the small sample precludes ultimate conclusions. A multicenter study involving more hospital services that receive referrals of individuals with obstructive jaundice would be more appropriate.

CONCLUSION

There is a deficiency in the official referral route for patients with obstructive jaundice, since less than 20% of the patients were found to have arrived through the regulatory system. However, this deficiency was not found to significantly impact the time taken to attend patients, or their bilirubin levels, because of the existence of alternative routes and emergency care. The frequencies of referrals for neoplastic and non-neoplastic causes were similar. The accuracy of clinical diagnoses of acute cholangitis was found to be poor and, therefore, greater dissemination of the criteria of the Tokyo protocol is essential.

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Hospitalization costs and their determining factors among patients undergoing kidney transplantation: a cross-sectional descriptive study

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ABSTRACT

BACKGROUND: Cost evaluation is a key tool in monitoring expenditure for budget management. It increases the efficiency of possible changes through identifying potential savings and estimating the resources required to make such changes. However, there is a lack of knowledge of the total cost of hospitalization up to the clinical outcome, regarding patients admitted for kidney transplantation. Likewise, there is a lack of data on the factors that influence the amounts spent by hospital institutions and healthcare systems.

OBJECTIVES: To describe the costs and determining factors relating to hospitalization of patients undergoing kidney transplantation.

DESIGN AND SETTING: Cross-sectional descriptive study with a quantitative approach based on secondary data from 81 patients who were admitted for kidney transplantation at a leading transplantation center in southern Brazil.

METHODS: The direct costs of healthcare for patients who underwent kidney transplantation were the dependent variable, and included personnel, expenses, third-party services, materials and medicines. The factors that interfered in the cost of the procedure were indirect variables. The items that made up these variables were gathered from the records of the internal transplantation committee and from the electronic medical records. The billing sector provided information on the direct costs per patient.

RESULTS: The estimated total cost of patients' hospitalization was R$ 1,257,639.11 (US$ 571,010.44). Out of this amount, R$ 1,237,338.31 (US$ 561,793.20) was paid by the Brazilian National Health System and R$ 20,300.80 (US$ 9,217.24) by the transplantation center's own resources. The highest costs related to the length of hospital stay and clinical complications such as sepsis and pneumonia.

CONCLUSIONS: The costs of hospitalization for kidney transplantation relate to the length of hospital stay and clinical complications.

INTRODUCTION

Kidney transplantation is considered to be the best therapy for treating chronic kidney disease, which is increasing worryingly in the population.[1,2] It has been observed that kidney replacement therapies such as dialysis are costly and that transplantation is the most viable long-term cost-effective procedure.[1-4] In addition, kidney transplantation also implies improved quality of life.[5-7]

The United States is the country in which the highest absolute numbers of kidney transplantations are performed. There were more than 400,000 procedures in the United States between 1988 and 2017.[8] Brazil is considered to be the country with the second highest absolute numbers of transplantations and has the best transplantation system in the world.[2] It has been estimated that 6,000 transplantations are performed in Brazil every year, i.e. approximately 30 kidney transplantations per million population.[2]

However, since 2016, the numbers of kidney transplantations performed in many Brazilian states have been declining because the supply of donated organs from deceased donors has been decreasing. The exception to this is the states of Paraná, Rio Grande do Sul and São Paulo, where transplantation rates of more than 45 per million population have been maintained.[9]

For the Brazilian system to remain a global reference, the professionals involved in it need to undertake a chain of successful actions, from identification of potential donors to execution

of transplantations and outpatient follow-up.[10] Faced with the demands of society, managers need to have knowledge of the resources available and the strategies for qualifying patients and expanding access to organ transplants.[11] Such knowledge contributes towards cost management.

In this context, it is essential to know and evaluate the cost of transplantations from the perspective of public healthcare systems like the Brazilian National Health System. These systems are responsible for the costing of professional and hospital services and, hence, for identifying factors that influence expenditure[12] and adjusting this to the amounts paid to institutions. Furthermore, such knowledge contributes towards improvement of public policies and adjustment of the amounts paid by public healthcare systems for these procedures. In addition, cost evaluation is a key tool for monitoring expenditure and thus for managing the budget. This increases the efficiency of possible changes through identifying potential savings, estimating the resources required to make such changes and estimating the resources needed to extend the changes.[7] Research in Japan has recently identified a need to evaluate the cost of patient hospitalization and investigate the impact of clinical complications on the total cost of transplantation.[12]

However, there is a lack of knowledge of the total cost of hospitalization up to the time of the clinical outcomes among patients who are admitted for kidney transplantation, along with the factors that influence the amounts spent by hospital institutions and healthcare systems. Therefore, the aim of this study was to describe the cost and its determining factors relating to hospitalization of patients undergoing kidney transplantation.

METHODS

This was a cross-sectional descriptive study with a quantitative approach, on the costs and determining factors relating to hospitalization of patients for kidney transplantation. The study was developed in a Brazilian transplantation center, based on secondary data from all patients (n = 81) who had been admitted for kidney transplantation between January 2007 and December 2016. The inclusion criterion was that the transplantations needed to have been funded through the Brazilian public healthcare system.

The institution where this study was conducted is a 335-bed philanthropic hospital that provides services for the Brazilian National Health System. In terms of the complexity and comprehensiveness of the services provided, it is a tertiary-care hospital and is considered to be a type II transplantation center. It has an internal committee responsible for management of transplantations; it emphasizes the role of nurses; and it attends patients from all over the state of Paraná. Furthermore, this institution is a reference center for performing kidney and heart transplantations.

Information was gathered between November 2016 and July 2017. We prepared a spreadsheet, with adjustments after the initial data-gathering, in order to record items from the electronic medical records, data from the internal transplantation committee, records from the institution's billing sector and information from the remuneration table of the National Health System that was in force and which is updated each year.[13]

The direct costs of healthcare for patients who underwent kidney transplantation were considered to be the dependent variable. The direct costs included personnel, expenses, third-party services, materials and medicines.[14] They also included, as independent variables, the factors that interfered in the cost of the procedure. The items that made up these variables were gathered from the records of the internal transplantation committee and from the electronic medical records. These were divided into two groups: a) those relating to the patient, such as sex, age, date of admission, date of clinical outcome, clinical diagnosis and complementary clinical information; and b) those relating to the surgical procedure of transplantation, such as type of procedure, type of donor (living or deceased) and surgical complications. The billing sector provided information on the direct costs, along with the cost averages for the days of hospitalization and the estimated values for the surgical procedure and the period of hospitalization for each patient.

In order to measure the direct costs, the study followed the steps and guiding questions proposed by Silva:[7] definition of the overall proposal of the study, delimitation of the period under study, identification and measurement of costs, definition of the method for deciding cost values and temporal adjustments.

The total amount for hospital service items plus hospital stay values constitutes the total hospitalization cost per patient. The individual and total expenses were described in Brazilian reais (R$) and US dollars (US$), using estimates from quotations made in August 2017. To convert the costs into dollars, the amounts were calculated separately based on the average for each year. To calculate the average quotation for each year, the values from Brazilian financial indices were used. The Emerging Markets Bonds Index Plus, calculated by the United States bank JP Morgan, is used by financial companies for information on country risk.[15]

The data obtained were tabulated in an Excel spreadsheet and were then analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 18.0 (IBM, Chicago, IL, USA). The statistical analysis criteria that were established comprised a 95% confidence interval and a significance level of $P \leq 0.05$.

For descriptive analysis on the data, central trend measurements, medians and interquartile ranges were calculated, after the Shapiro-Wilk normality test was firstly done on all the main components. Multiple linear regression was performed to evaluate the influences of the independent variables relating to the patients and the procedures within the hospital costs. These variables were dependent on the model and the analysis.

This study was approved by our institution's ethics committee for research involving human subjects (procedural no. 1,883,141) on September 28, 2016. Its Brazilian certificate of presentation for ethics assessment (CAAE) number for public consultation is 61063116.0.0000.

RESULTS

Among the 81 cases of hospitalization that were assessed, 40 admissions (49.4%) were elective and 41 (50.6%) were urgent, for organ transplants from living and deceased donors respectively. Regarding the epidemiological variables, there were more men (54.3%), and the patients' ages ranged from 12 to 73 years, with an average of 37 years (± 15.29).

Regarding the patients' previous clinical history and their need for transplants, 69 (85.2%) presented unspecified chronic kidney failure, 12 (14.8%) had end-stage renal disease, 52 (66.7%) were undergoing weekly hemodialysis, 71 (87.7%) had systemic hypertension and 10 (12.3%) had diabetes mellitus. The median waiting time for the surgical procedure after hospital admission was one day, with a range from less than 24 hours (n = 36; 44.4%) to three days.

The total cost of the 81 hospitalizations was R$ 1,257,639.11 (US$ 571,010.44), with a minimum cost per patient of R$ 3,897.27 (US$ 1,769.49) and a maximum of R$ 86,716.58 (US$ 39,372.24).

Out of the total cost, R$ 720,198.08 (US $ 326,994.14) comprised expenditure relating to kidney transplantation from living donors and R$ 537,441.02 (US$ 244,016.29) was expenditure relating to deceased donors; R$ 536,828.84 (US$ 243,738.34) was for the surgical procedure, examinations, materials and medicines; and R$ 720,810.39 (US$ 327,336.70) was for the stay in the inpatient unit and intensive care unit.

Table 1 shows the time distribution of hospitalizations and annual costs relating to patients who were discharged from the hospital (n = 77) (the four dead patients are not included). Table 2 shows the amounts paid to the institution for the total cost of hospitalizations through the Brazilian public healthcare system per year, according to the current table of costs and annual adjustments.

Among the variables that that were found to influence costs through multiple bivariate linear regression (Table 3), multiple linear regression (Table 4) showed that only the lengths of hospital stay in the hospitalization units and in the intensive care unit had any bearing on the costs (P < 0.001).

The mean length of hospitalization (a variable that affects cost) was 17 days (± 11.02), with a range from three to 69 days and a median of 14 days. Out of the total number of patients, 64 had a long stay, consisting of more than 10 days of hospitalization. The mean length of stay in the intensive care unit was seven days

Table 1. Total cost of hospitalizations and time distribution of patients undergoing kidney transplantation. Paraná, Brazil, 2017

Year	n*	Total cost		Median (P 50%)			Interquartile range 1st (P 25%) to 3rd (P 75%)	
		R$	US$	R$	US$		R$	US$
2007	13	162,157.98	83,239.76	11,545.46	5,926.57	1st	10,147.56	5,209.00
						3rd	14,327.84	7,354.84
2008	5	103,280.61	56,286.27	15,468.96	8,430.33	1st	9,780.35	5,330.13
						3rd	34,125.47	18,597.83
2009	8	164,013.40	82,112.75	19,330.61	9,677.80	1st	16,595.57	8,308.51
						3rd	23,012.90	11,521.33
2010	3	21,453.43	12,187.14	7,899.00	4,487.22	1st	3,897.26	2,213.93
						3rd	7,899.00	4,487.22
2011	9	87,343.96	52,143.05	9,309.20	5,557.45	1st	7,432.08	4,436.84
						3rd	12,308.90	7,348.23
2012	6	114,441.73	58,547.94	15,759.15	8,062.32	1st	8,836.04	4,520.48
						3rd	27,548.80	14,093.86
2013	8	101,923.31	47,237.75	9,907.32	4,591.68	1st	8,047.57	3,729.76
						3rd	19,850.17	9,199.83
2014	12	147,338.83	62,612.99	11,135.77	4,732.25	1st	8,460,.60	3,595.41
						3rd	15,852.60	6,736.71
2015	7	144,020.67	43,236.47	20,271.67	6,085.76	1st	15,792.29	4,741.01
						3rd	23,809.31	7,147.80
2016	6	99,429.51	25,348.86	8,690.34	2,491.14	1st	5,241.82	1,502.60
						3rd	27,432.10	7,863.58
Total	**77**	**1,145,403.43**	**479,716.50**	**11,545.46**	**60,042.52**			

All amounts paid through the National Health System for kidney transplantation procedures from living and deceased donors per year, along with the adjustments made, can be obtained from: http://sigtap.datasus.gov.br/tabela-unificada/app/sec/procedure/display/0505020092/08/2017 and http://sigtap.datasus.gov.br/unitedtable/app/sec/procedure/exhibit/0505020106/08/2017.14.

*Number of patients undergoing kidney transplantation per year. Patients who died (n = 4) were not included because their values were considered to be outliers.

Table 2. Total cost paid through the Brazilian public healthcare system and coverage of hospital bills per year. Paraná, Brazil, 2017

Year	n	Total cost paid through the Brazilian public healthcare system		Coverage of hospital bills
		R$	US$	Percentage (%)
2007	13	154,570.70	79,345.03	95.32
2008	5	62,269.77	33,936.01	60.29
2009	8	103,863.50	51,998.91	63.32
2010	3	40,435.73	22,970.50	188.48
2011	9	120,237.50	71,780.02	137.66
2012	6	102,594.50	52,486.94	89.65
2013	8	145,728.80	67,539.99	142.98
2014	14	249,392.90	105,981.81	97.73
2015	8	127,381.30	38,241.16	85.86
2016	7	130,863.70	37,512.88	131.54
Total	**81**	**1,237,338.31**	**561,793.20**	

*All amounts paid through the National Health System for kidney transplantation procedures from living and deceased donors per year, along with the adjustments made, can be obtained from: http://sigtap.datasus.gov.br/tabela-unificada/app/sec/procedure/display/0505020092/08/2017 and http://sigtap.datasus.gov.br/unitedtable/app/sec/procedure/exhibit/0505020106/08/2017.[14]

Table 3. Bivariate linear regression model for the cost of hospitalization of patients undergoing kidney transplantation (n = 81). Paraná, Brazil

Variables	B	95% confidence interval	P-value
Age	-98,142	-265,610 to 69,326	0.247
Complications during the hospitalization period	11,126,968	6,634,340 to 15,619,595	< 0.001
Surgical complications	2,920,322	-7,725,767 to 13,566,410	0.587
Duration of ischemia in the transplanted organ	-313,480	-607,500 to -19,461	0.037
Length of stay in the hospitalization unit	552,595	265,472 to 839,717	< 0.001
Length of stay in the intensive care unit	1,014,198	818,191 to 1,210,205	< 0.001
Deceased or living donor	4,896,635	-119,156 to 9.912,426	0.056

B = unstandardized coefficient used in the regression model.

Table 4. Multiple linear regression model for the cost of hospitalization of patients undergoing kidney transplantation (n = 81). Paraná, Brazil

Variables	B	95% confidence interval	P-value
Complications during the hospitalization period	11,126.968	1.834,679 to 3.955,611	0.46
Duration of ischemia in the transplanted organ	313,480	171,710 to 348,788	0.49
Length of stay in the hospitalization unit	552,595	506,901 to 829,298	< 0.001
Length of stay in the intensive care unit	1,014,198	955,816 to 1,239,540	< 0.001
Deceased or living donor	4,896,635	10,903,239 to 448,004	0.07

B = unstandardized coefficient used in the regression model.

(± 8.61), ranging from one to 66 days and the mean length of hospitalization was 10.57 days (± 8.26), ranging from zero to 57 days.

The predominant clinical outcome was hospital discharge with a functioning graft (n = 72; 88.9%), followed by hospital discharge with a nonfunctioning graft (n = 5; 6.2%) and death (n = 4; 4.9%). The total cost of working grafts was R$ 1,046,618.25 (US$ 475,199.87) with a median of R$ 19,103.96 (US$ 8,481.78). The total amount spent on non-functioning transplant hospitalizations was R$ 87,785.16 (US$ 39,857.41) with a median of R$ 18,680.97 (US$ 8,483.46). Among the patients who died, the total cost was R$ 123,235.69 (US$ 55,953.15) with a median of R$ 48,887.71 (US$ 22,196.66).

Regarding the nonfunctioning grafts, the reasons for removal of the grafted organ were intraoperative complications (n = 1; 20%) or, during the hospitalization period (n = 4; 80%), organ thrombosis (n = 1), acute organ rejection (n = 2), acute rejection of the organ (n = 2) or healthcare-related infections (n = 1). Among the patients who died, the reasons also related to complications from the surgical procedure and hospitalization, caused by hemorrhagic shock, hypotension, renal ischemia and healthcare-related infections.

Among the 72 patients who were discharged from the hospital with functional grafts, three (4.2%) had intraoperative complications, with a diagnosis of moderate bleeding. The hospital stays of these patients ranged from 22 to 35 days. Out of the other 69 patients, 34 (49.3%) had some type of complication such as healthcare-related infections, sepsis, arterial hypertension, hemorrhage or acute rejection of the donated organ during the hospitalization period. These patients' length of hospitalization ranged from 13 to 65 days, and their intensive care unit stay from two to 43 days.

DISCUSSION

This study describes the costs and determining factors relating to hospitalization of patients who underwent kidney transplantation. The results showed that male patients predominated and that the average age among the patients who underwent kidney transplantation was 37 years. Likewise, other studies have found that greater numbers of transplantations were performed on men and that the predominant age group was the adult and elderly public.[16]

The data of the present study also indicated that the numbers of organ transplants from living and deceased donors were similar (40 versus 41) and that the procedures performed varied according to the year in which the patients were operated. Epidemiological information from 2016 showed that there had been a drop of up to 2.4% in the number of kidney transplantations from deceased donors over recent years, while the number of transplants coming from live donors had remained stable.[9]

Through highlighting this information, it can be seen that there is a need for healthcare system managers to develop strategies to increase the number of donors. Some studies have emphasized the importance of implementation of compensation programs for

kidney donors in order to increase the number of organs available for transplantation and reduce the costs relating to kidney replacement therapies.[17,18] In this case, kidney donors would receive a cash payment or other benefits established through healthcare programs, as recompense for the donated organ.

Regarding the data associated with the various stages of renal illness, comorbidities like arterial hypertension and diabetes mellitus are considered to be the dominant factors in this clinical condition. These comorbidities have also been correlated with longer hospitalization and death[6,16] and are reflected in hospitalization costs.[19]

The costs of carrying out hemodialysis prior to transplantation may result in costs that are higher than the cost of kidney transplantation.[3-5,7] Another study conducted in Brazil showed that over the four-year period studied, kidney transplantation from deceased and living donors gave rise to cost reductions per patient of approximately R$ 37,000 and R$ 46,000, in relation to hemodialysis, respectively.[7]

It should be noted that in the present study, it was not possible to identify the cost savings generated through kidney transplantation from deceased and living donors, compared with hemodialysis. This was because there was a lack of information on previous transplantation care and treatment, since most of the patients had been followed up at other healthcare units.

In relation to the values established within the Brazilian public healthcare system, it was necessary to make annual adjustments to the National Health System hospital services (**Table 2**). This was because of refusal by the transplantation centers to pay for the expenditure on transplants. The annual adjustments served to offset the expenditure borne by these hospital institutions.[13]

To identify the factors that made up the hospital costs, multiple linear regression was used. This showed that the length of the hospital stay was the main factor that influenced the total cost, as had been shown through the results from other studies.[12,20] The mean duration of hospitalization was longer than what had been estimated through the National Health System (17 days versus 10 days), including patient admission, surgical procedure and hospital discharge.[13]

The factors that contributed to the length of stay in the intensive care unit and hospitalization units related to the predominant clinical complications after transplantation and to preventable or minor reasons, especially among patients who acquired healthcare-related infections and developed sepsis. A study investigating the total cost of treatment before and after transplantation showed that clinical complications due to urinary tract infection, sepsis or pneumonia had a significant influence on the total transplantation cost and gave rise to long hospital stays. Patients with pneumonia had hospital costs and lengths of hospital stay that were greater than those of patients without clinical complications (50 days versus 44 days; P < 0.01).[12]

The results from the present study, along with those from other studies that investigated the hospital costs of other types of transplantation, such as liver transplantation, showed that complications after transplantation resulted in longer hospital stays, higher daily costs and more use of medication.[20] Infections are also a major cause of early hospitalization after hospital discharge.[21] Another study[22] showed that transplant recipients may be 6.4 times more likely to be hospitalized again after being discharged after transplantation.

The patients' clinical condition in relation to immunosuppression may also have influenced the outcomes and factors presented here. A study by Taminato[23] highlighted the challenge involved in management of infectious complications in patients who had received kidney transplantation, due to their compromised immune system. These results demonstrate that there is a need for the healthcare team to develop strategies for prevention of the more common clinical complications after the surgical procedure, such as healthcare-related infections, in order to reduce the costs incurred during hospitalization and after discharge.

Regarding the clinical outcome at discharge, approximately 90% of the patients were discharged with a functioning graft. Over the long term, costs incurred during hospitalization may be lower than those of other surrogate renal therapies, thus indicating the importance of further studies to analyze the efficiency, cost-effectiveness and quality of life of this target population after kidney transplantation.

The present study had limitations in terms of the lack of information in the medical records, even though they were computerized. Since these patients' treatments are funded through the National Health System, the average cost per day of the stays in the intensive care unit and inpatient units was considered to be a single amount. Moreover, the data referring to the drugs and examinations were made available together, without separating the costs relating to each item.

However, because of the payment policy adopted in the National Health System table of costs, the absence of minor details on each item did not interfere in the study results, given that the coverage of the accounts is for the total values, in packages established for each transplantation procedure.

CONCLUSION

Over the period from 2007 to 2016, the estimated hospital cost of hospitalization for patients undergoing kidney transplantation was R$ 1,257,639.11 (US$ 571,010.44). Out of this amount, R$ 1,237,338.31 (US$ 561,793.20) was paid through the Brazilian National Health System and R$ 20,300.80 (US$ 9,217.24) from the transplantation center's own resources. The highest costs related to the length of hospital stay and clinical complications.

The results from this study may help to consolidate the actions of healthcare managers, in order to identify the factors that relate to the cost of hospitalization of patients undergoing kidney transplants, to identify possible strategies for minimizing clinical complications and to stimulate an increase in the number of transplantations performed. It should be added that further studies need to be carried out in order to analyze the patients' quality of life and the amounts spent on patient follow-up after hospital discharge, especially within the field of supplementary healthcare.

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Potential life years not saved due to lack of access to anti-EGFR tyrosine kinase inhibitors for lung cancer treatment in the Brazilian public healthcare system: Budget impact and strategies to improve access. A pharmacoeconomic study

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ABSTRACT

BACKGROUND: Lung cancer is the fourth most common cancer in Brazil. In the 2000s, better understanding of molecular pathways led to development of epidermal growth factor receptor (EGFR)-targeted treatments that have improved outcomes. However, these treatments are unavailable in most Brazilian public healthcare services (Sistema Único de Saúde, SUS).

OBJECTIVE: To assess the potential number of years of life not saved, the budget impact of the treatment and strategies to improve access.

DESIGN AND SETTING: Pharmacoeconomic study assessing the potential societal and economic impact of adopting EGFR-targeted therapy within SUS.

METHODS: We estimated the number of cases eligible for treatment, using epidemiological data from the National Cancer Institute. We used data from a single meta-analysis and from the Lung Cancer Mutation Consortium (LCMC) study as the basis for assessing differences in patients' survival between use of targeted therapy and use of chemotherapy. The costs of targeted treatment were based on the national reference and were compared with the amount reimbursed for chemotherapy through SUS.

RESULTS: There was no life-year gain with EGFR-targeted therapy in the single meta-analysis (hazard ratio, HR, 1.01). The LCMC showed that 1,556 potential life-years were not saved annually. We estimated that the annual budget impact was 125 million Brazilian reais (BRL) with erlotinib, 48 million BRL with gefitinib and 52 million BRL with afatinib. Their incremental costs over chemotherapy per life-year saved were 80,329 BRL, 31,011 BRL and 33,225 BRL, respectively. A drug acquisition discount may decrease the budget impact by 30% (with a 20% discount). A fixed cost of 1,000 BRL may decrease the budget impact by 95%.

CONCLUSION: Reducing drug acquisition costs may improve access to EGFR-targeted therapy for lung cancer.

INTRODUCTION

Over recent decades, the incidence of cancer and the mortality that it causes have increased in developing countries such as Brazil.[1] Among all neoplasms, lung cancer presents major concern because it is a relatively frequent disease (i.e. the fourth most common type of cancer in Brazil) and presents high lethality. In Brazil, 28,220 new cases were expected in 2017; almost 25,000 were recorded in 2013.[2]

Studies on the molecular biology of advanced non-small cell lung cancer (NSCLC) have led to development of directed targeted therapies that have demonstrated better clinical outcomes and fewer collateral effects, compared with platinum-doublet chemotherapy.[3-5]

Epidermal growth factor receptor (EGFR) is a transmembrane receptor that conducts signals to promote cell proliferation, angiogenesis and cell immortality.[6] Treatment of advanced NSCLC with tyrosine kinase inhibitors (TKI) directed against the EGFR receptor leads to a response rate of over 50% (that of chemotherapy is approximately 35%), and a nearly 100% increase in median progression-free survival, compared with platinum-doublet chemotherapy.[3-5] On the other hand, no studies have demonstrated any increase in overall survival, compared with platinum-doublet chemotherapy, due to the high rate (about 70%) of treatment crossover between the arms of these studies. In other words, the majority of individuals included in such clinical studies received anti-EGFR TKI in first-line or second-line treatment.[3-5]

A Cochrane Library meta-analysis confirmed that anti-EGFR TKI was beneficial in relation to chemotherapy, in terms of response rate and progression-free survival. However, there was no improvement in terms of overall survival for any molecule.[7]

Although the Brazilian Ministry of Health considers that anti-EGFR TKI is a therapeutic option in cases of advanced lung cancer with the presence of EGFR mutation, the reimbursement offered by the Ministry of Health is insufficient for targeted therapy to be used. Consequently, the most common treatment among Brazilian public healthcare services is platinum-doublet chemotherapy, which does not provide median overall survival surpassing 12 months.[8,9]

Anti-EGFR TKIs cost as much as two to six times more than the 1,100.00 Brazilian reais (BRL) that are reimbursed by the Brazilian public healthcare system (Sistema Único de Saúde, SUS) for each month of treatment for metastatic lung cancer.[10,11] The progressive increase in the cost of cancer treatment is a growing concern worldwide. In Brazil, data from the Federal Court of Auditors show that the annual cost of cancer treatment within SUS doubled between 2002 and 2008, from about 250 million to 500 million BRL.[12] This increase in the costs of cancer treatment has outpaced the increase in average family income and inflation.[13] Consequently, the budget impact caused by cancer treatment can make healthcare systems unsustainable, thus provoking user coverage failures.[14] Consequently, choosing the best treatment at an accessible cost is a growing challenge for both clinics and managers.[15]

In view of this scenario, providers are placed in a difficult position with regard to acquiring anti-EGFR TKIs with reimbursement from the Ministry of Health. Consequently, there has been a loss of potential life-years that could have been saved through personalized treatment. Furthermore, several strategies can reduce the budget impact caused through incorporation of such medication, thereby making these agents available for treating SUS patients.

OBJECTIVE

The aim of this study was to assess the potential number of years of life not saved, the budget impact of the treatment and strategies to improve access.

METHODS

Estimation of the number of eligible patients

The number of patients eligible for treatment was calculated using the number of new cases estimated for Brazil from 2010 (the year in which the first anti-EGFR TKI was launched in Brazil) to 2017. The estimated number of new cases was published by INCA (the National Cancer Institute of Brazil).[2] The proportion of patients with the disease at an advanced stage and who were in a clinical condition to be able to receive first-line treatment was estimated based on the 2014 National Lung Cancer Audit in the United

Kingdom and the European study of real-world treatment data published by Moro-Sibilot et al.[16,17] The proportion of patients with activation of mutations in the EGFR gene was extracted from the largest database available in the literature.[18]

Clinical benefits of treatment

We evaluated the clinical benefit of targeted therapy by calculating the number of life-years saved, compared with chemotherapy. This was based on the hazard ratio retrieved from a single meta-analysis.[19] We also considered the areas under the overall survival curves of the American population study, Lung Cancer Mutation Consortium, since there are no data on the Brazilian population. The Lung Cancer Mutation Consortium study included 14 US centers and prospectively evaluated the overall survival of patients with metastatic NSCLC who either had or had not undergone molecular alterations appropriate for personalized treatment, and who either had or had not received targeted therapy directed against previously detected molecular alterations.[20] We considered a five-year timeline, which was estimated in accordance with the overall survival curve of the Lung Cancer Mutation Consortium study.

Costs of treatments and of the EGFR test

The Brazilian reference costs of acquisition of anti-EGFR TKI were considered.[10] On the other hand, treatment with chemotherapy was considered to have a monthly fixed cost of 1,100.00 BRL, which is the amount reimbursed through SUS.

The costs of the EGFR mutation test (Sanger DNA sequencing) were considered for analysis, even though this test is available at no cost from the pharmaceutical industry.

The median duration of each treatment was based on the area under the progression-free survival curve, as published in randomized clinical trials.[3-5,21]

The costs of treating adverse events, drug infusion, hospitalization and support care were extrapolated from Brazilian data available in the literature.[22-24]

To better understand the total potential economic impact of each treatment strategy, we assumed that the hypothetical market penetration of anti-EGFR TKIs after their release was 100%.

Endpoints

The primary objectives of this study were to evaluate the annual incremental cost (in millions of BRL) of incorporating anti-EGFR TKIs into routine use within SUS and the number of potential life-years not saved due to the unavailability of treatment using this medication within SUS since the time when the first EGFR TKI agent came into the market in 2010.

We also estimated the impact on the budget of the following strategies: cost sharing (giving the first two months of treatment at no charge), risk sharing (the corresponding manufacturer would

reimburse 50% of the cost to non-responders), payment according to results (reimbursement of 100% of the cost in cases of progressive disease) and discounts (10% or 20%). Strategically, we also evaluated a hypothetical scenario in which the anti-EGFR TKI had a fixed cost of 1,000.00 BRL, i.e. a hypothetical value below the Brazilian Ministry of Health reimbursement level.

The secondary objectives of this study were to estimate the incremental cost for each year of life saved through using each anti-EGFR TKI and the additional cost per citizen of incorporation of each treatment, assuming a Brazilian population of 200 million inhabitants.

RESULTS

Estimated number of eligible cases
In 2017, the estimated number of patients with advanced or metastatic NSCLC was 20,261 in Brazil. Out of this total, a little more than half (57.4%) satisfied the clinical conditions for receiving any first-line treatment; and about one in four (25.5%) presented activation of mutations in the EGFR gene. Considering that 75% of the Brazilian population is treated through SUS, 2,224 cases were estimated to be eligible to receive anti-EGFR TKI in 2017.

Budget impact
The annual investment necessary for incorporating anti-EGFR TKIs into SUS was estimated to be 125.1 million BRL for erlotinib, 48.3 million BRL for gefitinib and 51.7 BRL for afatinib. These amounts represent proportional increases, compared with the current SUS costs of acquiring antineoplastic agents, of 5.2%, 2.0% and 2.2%, respectively. The incremental costs per SUS user for incorporating these treatments were estimated to be 0.83 BRL, 0.32 BRL and 0.34 BRL, respectively.

Cost sharing
The cost-sharing strategy, in which the first two months of treatment would be provided by the manufacturer of the medication, led to a 20% reduction in incremental cost. Through this strategy, the investments to incorporate erlotinib, gefitinib or afatinib to the SUS would be 100.2 million BRL, 36.2 million BRL or 39.1 million BRL, respectively.

Risk sharing and payment according to results
The risk-sharing strategy would reduce the annual budget impact by 25 million BRL for use of erlotinib, 9 million BRL for gefitinib and 16 million BRL for afatinib. These amounts represent reductions of 27%, 17% and 32%, respectively.

Payment according to results presented more modest results, with a reduction in the annual incremental cost of erlotinib, gefitinib and afatinib of approximately 4 million BRL for each drug.

Proportionally, payment according to results gave rise to reductions of 2%, 7% and 9%, respectively.

Discounts and fixed cost at 1,000.00 BRL
With a 10% reduction in the cost of anti-EGFR TKIs, the annual incremental cost of their incorporation into SUS was reduced by 12% for use of erlotinib, 15% for gefitinib and 14% for afatinib.

A 20% discount resulted in annual savings of 30 million BRL for use of erlotinib and 15 million BRL for gefitinib and afatinib each. These amounts represent reductions of 24%, 30% and 29%, respectively.

The greatest reduction in the budget impact of the treatment was observed through setting the cost of anti-EGFR TKIs at 1,000.00 BRL. Through this strategy, it would be possible to save more than 90% of the funds required to incorporate the NSCLC targeted therapy into SUS. The annual incremental costs of erlotinib, gefitinib and afatinib would be 2.88 million BRL, 2.9 million BRL and 3.0 million BRL, respectively. These values represent an additional investment of 0.1%, compared with the current cost to SUS of acquiring antineoplastic drugs. The incremental cost per user of this strategy is 0.02 BRL.

Figure 1 summarizes the incremental costs of incorporating anti-EFGR TKIs at baseline, and when using the various strategies presented.

Potential life-years not saved
The data from the single meta-analysis did not show any difference in overall survival for patients treated with anti-EGFR TKI, in comparison with those receiving chemotherapy (hazard ratio 1.01, 95% CI 0.88 to 1.17, P = 0.84). Considering the data from the Lung Cancer Mutation Consortium, the lack of access to targeted anti-EGFR therapy within SUS has resulted in around 1,556 potential life-years not saved annually. Over the last seven years since the launch of gefitinib in Brazil, 10,892 potential life-years have not been saved.

Cost-effectiveness
The data from the Lung Cancer Mutation Consortium study show that the strategy of offering molecular targeted therapy to eligible patients resulted in 0.70 life-years saved in comparison with chemotherapy alone.

In the base case, the average incremental cost per patient treated with erlotinib was 56,230.33 BRL, resulting in an incremental cost per year of life saved of 80,329.05 BRL. Gefitinib had an incremental cost per patient of 21,707.77 BRL, thus resulting in 31,011.10 BRL per life-year saved. Use of afatinib increased the cost per patient by 23,257.88 BRL, and the cost per life-year saved was 33,225.55 BRL. **Table 1** summarizes the costs considered and the cost-effectiveness findings.

DISCUSSION

Historically, cancer patients have had few therapeutic options and a poor prognosis. However, oncology has advanced over recent decades, especially in terms of secondary prevention, either through early detection of disease or through development of new therapies that have increased patient survival.[25] Although these advances are to be commended, they have been made at a high cost financially, sometimes making them inaccessible for developing countries.

Between 2010 and 2014, 25 new drugs were approved for cancer treatment in the United States.[26] This figure represented half of all the new medications that had been approved over the previous four decades.[26] Access to new cancer treatments in developing countries is made more complicated through the fact that these new therapies generally cost more than the reference drugs and are administered over longer periods of time.[26]

One major goal of doctors and public healthcare administrators in Brazil is to ensure that resources for acquiring antineoplastic agents are allocated efficiently. Cost-effectiveness studies are the most widely used tool for establishing the value of a treatment, considering the effectiveness of the drug and its direct and indirect costs.[15]

Several Brazilian studies have evaluated whether anti-EGFR TKIs are cost-effective for treating lung cancer.[22-24] The study that

defined the SUS policy was conducted by the National Commission on Incorporation of Technologies in SUS (CONITEC). It concluded that targeted therapy was not cost-effective, mainly based on the absence of an overall gain in life-years survived.[22] However, the CONITEC study relied on data from a randomized clinical study in which most individuals included were exposed to targeted therapy at some phase of treatment (first-line or second-line). However, the crossover rate between the treatment arms was nearly 70%.

Interestingly, despite the lack of overall survival benefit, anti-EGFR TKI can improve quality-adjusted life-years (QALY), compared with chemotherapy.[27] A previous study by our group found a gain of 0.18 QALY, considering the data from the single

Table 1. Estimated costs and cost-effectiveness, in Brazilian reais (BRL)

	Erlotinib	Gefitinib	Afatinib
Price	5,581.55	2,701.94	2,824.43
Cost of treatment	66,978.60	32,423.28	33,893.16
Cost of adverse events	54,74	87,50	167,74
Cost of monitoring	5,384.64	5,384.64	5,384.64
Additional life-years	0.70	0.70	0.70
Incremental cost	56,230.33	21,707.77	23,257.88
Cost per additional life-year	80,329.05	31,011.10	33,225.55
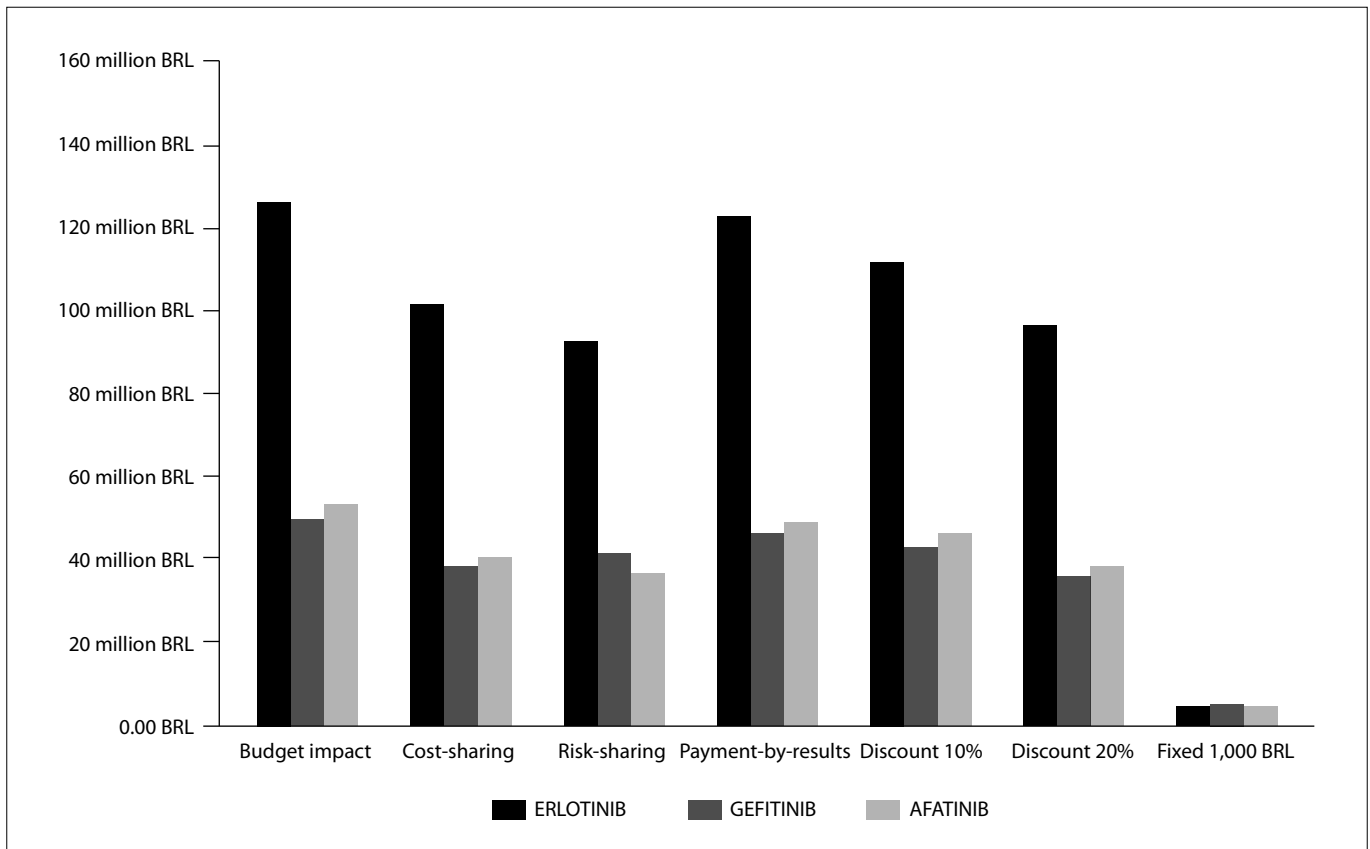
Figure 1. Budget impact in the base case and with strategies to reduce the incremental cost. Amounts in Brazilian reais (BRL).

meta-analysis, and a gain of 0.50 QALY considering the Lung Cancer Mutation Consortium data.[27] In terms of cost-effectiveness, the incremental costs per QALY (ICER) were 30,000 BRL and 70,000 BRL, respectively.[27] Curiously, the lower ICER observed in the single meta-analysis, compared with the Lung Cancer Mutation Consortium, was due to the crossover between the arms. In other words, everybody received TKI and consequently the same amount of money was spent on every case.

The consequence of a situation in which a given treatment is unavailable through the healthcare system is an increase in "judicialization" of healthcare. This practice, even if it does democratize access to new therapies, also raises costs and ultimately engenders more inequality.[28] Over a recent five-year period, the Brazilian federal government's expenditure on medicines obtained through court orders increased by 517%, from 42.8 million BRL in 2010 to 259.4 million BRL in 2014.[28]

We believe that measures to facilitate universal access to innovative medicines can reduce the costs associated with lawsuits and allow healthcare systems to negotiate prices with the industry through obtaining volume discounts. In our study, we found that the practice of offering discounts for acquiring medicines was an effective strategy, as this reduced the budget impact by 15% and 30%, for discounts of 10% and 20%, respectively. Setting the cost of medication below the amount currently reimbursed through SUS for chemotherapy reduced the budget impact by more than 90%, thus making it possible for the SUS investment in incorporating these agents to remain below inflation (a 0.1% increase in the cost of acquisition of antineoplastic agents).

Other strategies to reduce the budget impact of a treatment include cost sharing and risk sharing. In our study, compared with obtaining discounts, cost sharing and risk sharing presented only modest benefits in relation to acquiring drugs. Our hypothesis to explain the failure of cost sharing relates to the fact that patients receive treatment for an average period of 12 months, which makes receiving the initial months without cost proportionally less relevant.

The high rate of disease control (around 90%) achieved through anti-EFGR TKIs makes risk sharing a poor option for decreasing the budget impact. Furthermore, Brazil does not have laws or regulatory mechanisms that would permit implementation of a strategy of shared risks. The Italian experience has shown that systems for managing risk sharing have significant costs (almost one million euros annually), and up to one third of cases are not reimbursed by manufacturers because of administrative issues like errors or delays in completing reimbursement forms.[29]

The main limitation of the present study lay in our attempt to make estimates for the Brazilian population based on potentially underestimated epidemiological data, and on clinical data that was extrapolated from a study on the United States population. Ideally, a prospective randomized study on the Brazilian population, comparing anti-EGFR TKI for EGFR-mutated advanced NSCLC patients with platinum-doublet chemotherapy for patients who do not undergo the molecular test, should be conducted. However, a study with this design would not be authorized by any research ethics committee, given that the benefits of using targeted molecular therapy have already been established in the literature.

CONCLUSIONS

We believe that targeted anti-EGFR therapy for metastatic NSCLC is a cost-effective treatment in terms of cost per life-year saved. An investment of 2% of the amount paid for acquiring antineoplastic agents, or additional expenditure of around 0.30 BRL per user, could improve patient access to anti-EGFR therapy. Moreover, negotiation of discounts with manufacturers or implementation of a price control policy can reduce the budget impact by 90%. Improving the access of SUS patients to anti-EGFR therapy could potentially save more than 1,500 life-years annually.

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Wide diversity of fungal species found in wellwater for human consumption: an analytical cross-sectional study

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KEY WORDS (MeSH terms):
Water quality.
Water wells.
Fungi.
Chlorine.

AUTHOR KEY WORDS:
pH.
Free residual chlorine.
Microorganisms.

ABSTRACT

BACKGROUND: Fungi are ubiquitous in the environment. They are able to grow in water and many of them may be opportunistic pathogens.
OBJECTIVE: The aims were to identify fungi in registered wells (RWs) and nonregistered wells (NRWs) that tap into groundwater; and to correlate the results from physicochemical assays on this water (free residual chlorine and pH) with the presence of fungi.
DATA AND SETTING: Analytical cross-sectional quantitative study on groundwater wells in São José do Rio Preto, São Paulo, Brazil.
METHODS: 52 samples of 500 ml of water were collected from RWs and 107 from NRWs. These were sent to a microbiology laboratory to identify any fungi that were present. In addition, free residual chlorine and pH were measured immediately after sample collection. Several statistical analysis tests were used.
RESULTS: Fungal contamination was present in 78.8% of the samples from RWs and 81.3% from NRWs. Filamentous fungi were more prevalent than yeast in both types of wells. There was no significant difference in presence of fungi according to whether chloride and pH were within recommended levels in RWs; or according to whether pH was within recommended levels in NRWs. Furthermore, there was no statistical difference in the levels of fungal contamination between RWs and NRWs.
CONCLUSION: Both RWs and NRWs are potential reservoirs for many types of fungi. Many of these may become opportunistic pathogens if they infect immunosuppressed individuals. Furthermore, this study confirms that fungi are able to grow even when chlorine and pH parameters are within the standards recommended.

INTRODUCTION

Ensuring human health is directly related to water quality. The water supply needs to meet microbiological, physical and chemical standards, for it to be in an optimal condition for consumption.[1]

Underground water is one of the various types of drinking water sources. Although it is considered safe, given the filtration power of the soil, contamination with external microbes may be present. This event is common when water collection wells are constructed irregularly, thus favoring the entry of microorganisms and representing a risk to the health of the population.[2,3]

In the municipality of the present study, the municipal health surveillance agency is responsible for enforcing the quality of underground water from wells. All wells drilled need to be registered in the health surveillance system for monitoring to verify water quality.

However, irregular settlements exist within this municipality, which became inhabited by their populations at a time before the mandatory documentation came into existence. Thus, there is no legal basis for provision of a municipal water supply to these settlements. For this reason, wells have been drilled to obtain local water supplies. But because these are irregular settlements, the wells drilled there are also irregular, i.e. they are not registered in the health surveillance system. As a consequence of these irregularities, the water quality of these places is not monitored by the agency that should be responsible for this. This endangers the health of the local population, given that its water supply is left susceptible to contamination by microorganisms.

Within this context, it is known that fungi are ubiquitous in the environment. The fact that many of them may be opportunistic pathogens, causing many types of health problems, including allergies, mycosis and presence of biofilm and mycotoxins, is a subject of growing interest.[4,5]

Although the evidence is scarce, some studies have proven that correlations exist between fungi found in hospitalized patients and the same fungi found in the water from taps (faucets) and showers in hospitals.[6,7]

Aquatic environments favor the survival of fungi, because under these ideal nutrient and temperature conditions, fungi are capable of reproducing.[8] Consequently, water supply networks, reservoirs, tanks, faucets and showerheads may harbor different species, on inanimate surfaces. Thus, such environments are potential disease-transmitting vehicles.[6]

In addition to these parameters, it is also important that the quantity of chlorine in water should be monitored, since chlorine is the most effective agent against the growth of microorganisms.[1]

Therefore, research evaluating the occurrence and distribution of fungi in drinking water is necessary, since contamination by these agents may be harmful to health, especially among the most vulnerable individuals.

OBJECTIVE

The objectives of this study were to identify the presence of fungi in wells that tap into groundwater, i.e. both registered wells that are within the local health surveillance system and nonregistered wells in irregular or illegal settlements (unsupervised wells outside of the health surveillance system); and to correlate the results from physicochemical assays on this water (free residual chlorine and pH) with the presence of fungi.

METHODS

Study design, period, setting

This analytical cross-sectional study was conducted in São José do Rio Preto, São Paulo, Brazil, from September 2011 to June 2012.

The locations of registered wells were ascertained through consulting the list of these wells that is held in the health surveillance system. In relation to irregularly drilled wells, i.e. nonregistered wells, a list with addresses of the irregular settlements was passed on from the municipal authorities to the health surveillance professionals so that water could be collected from these places.

One 500 ml sample was collected per well: 52 from registered wells and 107 from nonregistered wells (a greater number of nonregistered wells was included in the study because there were more of them in the municipality).

Sample collection procedures

The water samples collected came from taps that provided a water supply from their respective well. Before the sample was collected, each tap was disinfected with 70% alcohol and then the water was allowed to flow continuously for two minutes. Following this, 500 ml were collected in a sterile container containing 1.8% sodium thiosulfate. These containers were then transported in isothermal boxes to a microbiology laboratory for mycological analysis.[9]

Sample analysis

For sample analysis, the membrane filter method was used. This method stands out as the most viable laboratory procedure for counting microorganism colonies in water. The protocol for this method is described in the "*Standard Methods for the Examination of Water Protocol and Wastewater*".[9]

The whole volume of water that had been collected was filtered through sterile cellulose membranes (47 mm; 0.45 μm). These filters have the capacity to retain various types of microorganisms such as fungi that are isolated from water.

The membranes were then placed on the surface of Petri dishes containing Sabouraud dextrose (containing chloramphenicol) for culturing, with incubation for 15 days at 30 °C. After this period, all colonies of morphologically distinct fungi were selected; if identical, only one isolate was considered.[10,11]

The filamentous fungi were identified through their macroscopic and microscopic features and through microculturing to stimulate development of fruiting bodies. For this, a small piece of Sabouraud dextrose agar was placed on a sterilized slide lying in a sterilized Petri dish. Fungi from a recent subculture were grown on all four sides of the agar block, which was covered with a sterilized coverslip. Next, 2 ml of sterile distilled water were added to the dish to prevent desiccation of the growth medium. A top was placed on the dish and its contents were left to incubate at 25 °C for seven to ten days, until development of hyphae was detected. After this fungal growth, the coverslip was removed using tweezers and a drop of lactophenol cotton blue stain was added to the material in order to view spores and hyphae using an optical microscope.[10]

In order to identify any yeasts that were isolated from the water, physiological tests consisting of assimilation of different carbohydrates (maltose, sucrose, lactose, galactose, melibiose, cellobiose, dextrose, inositol, xylose, raffinose, trehalose and dulcitol) and nitrogen sources (peptone and potassium nitrate) were performed. These tests were done using the pour-plate technique: 2 ml of a suspension of each yeast were homogenized in each mixed medium (yeast nitrogen base and yeast carbon base) and were distributed into two Petri dishes for culturing.

Small aliquots of each different carbohydrate were added to the surface of the carbon-free medium to serve as carbon sources. In another dish, nitrogen sources were placed on the surface of the nitrogen-free medium. After incubation at 30 °C for 24 to 48 hours, the results were read.[11]

Physical and chemical analysis

The water-free residual chlorine content and pH were measured immediately after the water sample collection, by professionals from the local health surveillance system. To determine the free residual chlorine content, 10 ml of each sample and 0.5 ml of *N, N*-diethyl-*p*-paraphenylenediamine reactant (DPD) were added

to a cuvette. The mixture was stirred to ensure homogeneity, and measurement was done using an electronic colorimeter device (HI96711C; Hanna Instruments). For the free residual chlorine levels to be within the range recommended by the World Health Organization (WHO),[1] the concentrations needed to be between 0.2 mg/l and 2 mg/l. pH was determined with the aid of a benchtop pH meter (PH250; Policontrol), which had previously been calibrated using standard solutions. The electrode of the device was immersed in an aliquot from each sample. The recommended water pH range was 6.0 to 9.5.[1]

Statistical analysis

The association between presence of fungi and free residual chlorine levels and pH parameters within the recommendations (for both wells) was investigated using the Mann-Whitney nonparametric test (which compares the medians of independent groups). The G-test (used to evaluate whether variables are associated or not) was used to investigate whether there was any association between the status of the well (registered or nonregistered) and the presence of fungi. The significance level was set at $P \leq 0.05$.

RESULTS

Most of the samples showed fungal contamination: 80% (128/159) overall; 78.8% (41/52) for registered wells; and 81.3% (87/107) for nonregistered wells. A wide variety of fungi were observed, regardless of the source of the water (**Table 1**). In registered wells,

75% (39/52) and 7.7% (4/52) of the samples were positive for filamentous fungi and yeast, respectively. In nonregistered wells, filamentous fungi were recovered from 74.7% (80/107) of the wells and yeast in 25.2% (27/107).

Aspergillus fumigatus was most prevalent in both types of wells, followed by *Penicillium commune* in the nonregistered wells. Regarding yeasts, *Candida guilliermondii* was the species most found in registered wells and the second in nonregistered wells, while *Aureobasidium pullulans* was the species most found in nonregistered wells.

Table 2 shows the numbers of samples with presence of fungi, correlated with the chloride and pH levels in both types of well.

The statistical results indicated that there was no significant difference in presence of fungi according to whether chloride levels ($P = 0.3804$) and pH levels ($P = 0.3187$) within the recommendations, in registered wells. Similarly, there was no

Table 2. Numbers of samples with presence of fungi, correlated with chloride and pH levels

Sampled	Chlorine (0.2 to 2.0 mg/l)		pH 6.0 to 9.5	
	RW	NRW	RW	NRW
Within recommended levels	20	0	40	87
Exceeded recommended levels	21	87	1	0
Total	41	87	41	87

RW = registered well; NRW = nonregistered well.

Table 1. Distribution of fungal isolates from registered and nonregistered wells

Registered wells (RWs)				Nonregistered wells (NRWs)			
Filamentous	**N**	**Yeasts**	**n**	**Filamentous**	**n**	**Yeasts**	**n**
Aspergillus fumigatus	28	*Candida guilliermondii*	3	*Aspergillus fumigatus*	21	*Aureobasidium pullulans*	7
Acremonium hyalinulum	4	*Candida parapsilosis*	1	*Penicillium commune*	19	*Candida guilliermondii*	5
Aspergillus penicillioides	3	*Blastoschizomyces capitatus*	1	*Penicillium decumbens*	8	*Candida intermedia*	4
Aspergillus japonicus	2	*Aureobasidium pullulans*	1	*Penicillium expansum*	6	*Trichosporon asahii*	4
Penicillium marneffei	2			*Fusarium incarnatum*	6	*Candida tropicalis*	3
Curvularia clavata	1			*Aspergillus penicillioides*	5	*Candida glabrata*	2
Fusarium incarnatum	1			*Basidiobolus ranarum*	5	*Candida lusitaniae*	2
Penicillium marquandii	1			*Penicillium citrinum*	4	*Candida parapsilosis*	2
Penicillium expansum	1			*Penicillium spinulosum*	4	*Trichosporon mucoides*	2
Aspergillus caesiellus	1			*Aspergillus japonicus*	4	*Candida famata*	2
Aspergillus flavus	1			*Acremonium hyalinulum*	4	*Candida silvicola*	1
				Penicillium purpurogenum	3	*Kodamaea ohmeri*	1
				Aspergillus flavus	3	*Rhodotorula minuta*	1
				Scytalidium hyalinum	3	*Rhodotorula glutinis*	1
				Curvularia clavata	2	*Zygosaccharomyces florentinus*	1
				Aspergillus clavatus	2		
				Curvularia clavata	1		
				Other genera/species*	16		
Total	**45**	**Total**	**6**	**Total**	**116**	**Total**	**38**

n = total number of isolates.

Fusarium solani, Acremonium potronii, Alternaria alternata, Mucor racemosus, Fusarium sacchari, Fusarium hyalinum, Penicillium marquandii, Absidia cylindrospora, Scedosporium dehoogii, Scedosporium apiospermum, Trichoderma harzianum, Penicillium lilacinus, Penicillium verruculosum, Aspergillus versicolor, Aspergillus candidus, Aspergillus caesiellus.

statistical difference in presence of fungi according to whether pH levels (P = 0.1396) were within the recommendations, in nonregistered wells.

Furthermore, no statistical difference regarding the presence of fungi was observed between registered and nonregistered wells (P = 0.7146).

DISCUSSION

The diversity of fungi in drinking water has been documented and is a concern for researchers, scientists, institutions and organizations around the world. However, the scarcity of large-scale studies and the lack of uniformity of the available research make it difficult to have an exact notion of the complexity of this phenomenon worldwide.[4,5] It is known that the fungi *Aspergillus* spp. and *Penicillium* spp. have greater adaptation to aquatic environments, and that they commonly have the ability to survive in treated water. This was seen in the present study, in which both of these genera had high survival rates.[4,6]

The most common species in both wells was *Aspergillus fumigatus*. Presence of this fungus may expose the human or animal host to the risk of diseases: pneumonia, systemic diseases, acute or chronic infections and allergies, especially in vulnerable individuals.[12,13]

In addition, special attention should be given to the large number of *Penicillium commune* isolates in the present study. Kadaifciler and Demirel reported that *Penicillium* spp. were the predominant group in the water system, with the capacity to produce mycotoxins.[5] Among immunocompromised patients, this fungus may lead to severe diseases, especially those that are acquired through inhalation, even if it is only present in small amounts.[4,5]

Although yeast species were less commonly found in the present investigation, their diversity is corroborated by data from other studies, involving water from different sources.[14] Like filamentous fungi, yeasts can also cause various kinds of diseases. After ingestion of water containing yeast, this yeast reaches the bloodstream through translocation, and then reaches other organs. Yeast also gives rise to a risk of infection when in contact with open wounds.[14,15]

Similarly, *Aureobasidium pullulans*, which was detected in water from both types of wells (**Table 1**), poses a risk to the health of immunosuppressed consumers, because this species can survival in water distribution systems.[16] *Candida guilliermondii* was commonly found concomitantly in the present study, regardless of the origin, which may indicate a potential risk to health. Presence of this species in the water of dental care units, in another study.[14]

Chlorine is the most common sanitizing agent used in water to eliminate disease-causing bacteria.[1] However, it did not have the same effect on fungi, since fungi were recovered from samples that had been correctly chlorinated. The present study showed that *A. fumigatus* was the most frequently found filamentous fungus in both types of wells. This prevalence may also have occurred because of

its resistance to chlorine, as demonstrated in a previous study, in which survival of this species in chlorinated waters was reported.[17]

Another study showed that *Aspergillus* spp. was also able to grow in treated water, and demonstrated the occurrence of chlorine-resistant *Candida* isolates.[18] This was also observed in the present study, especially in relation to *A. pullulans* and *C guilliermondii*, which are yeasts with greater numbers of isolates and probable resistance to chlorine.

Moreover, no association was observed between fungal growth and chloride parameters (P = 0.3804), indicating that the fungi were capable of developing in both chlorinated and non-chlorinated water (**Table 2**).

Most microorganisms multiply better within a particular pH range, called the optimal range, and this differs between species. There are fungi that have the ability to grow in media ranging from basic to acidic. Thus, if their nutritional requirements are met, it is likely that fungi will develop in different types of environments.[19] This was observed in the present study, in which there was high incidence of fungi in most of the samples in which the pH was within the recommended range (**Table 2**).

Even though there was no statistical difference in the presence of fungi in water with the recommended pH parameters (for both types of wells), growth of these microorganisms under the physical conditions studied was demonstrated.

We did not observe any statistical difference in fungal growth (P = 0.7146) between the registered and nonregistered wells (**Table 2**), even though it had been expected that nonregistered wells (which are unsupervised) would have had higher levels of contamination. This observation strengthens the importance of the present study, which showed contamination even in the registered wells. The fungi isolated from both types of wells may cause disease, especially among immunocompromised patients. Thus, these findings have an important impact on public health and emphasize the need to monitor these environments.

CONCLUSIONS

Both registered wells and nonregistered wells were shown to be potential reservoirs of many types of fungi, including filamentous fungi and yeast. Many of these may become opportunistic pathogens when they infect immunosuppressed individuals. Furthermore, it was confirmed in this study that fungi were able to grow even when the chlorine and pH levels were within the standards recommended.

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Tocilizumab for juvenile idiopathic arthritis: a single-center case series

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ABSTRACT

BACKGROUND: Juvenile idiopathic arthritis (JIA) is the commonest chronic rheumatic disease among children. When not treated effectively, JIA can lead to functional disability, due to joint damage, along with long-term morbidities.

OBJECTIVES: To describe the use of tocilizumab therapy for 11 patients with polyarticular JIA (pJIA) and systemic JIA (sJIA) who presented inadequate response or were refractory to disease-modifying anti-rheumatic drugs (DMARDs) and/or other biological therapies; and to evaluate its benefits, safety and tolerability.

DESIGN AND SETTING: Observational retrospective case series at a tertiary-level training and research hospital.

METHODS: We reviewed the medical records of 11 consecutive patients with JIA who received tocilizumab (anti-IL-6) therapy in our pediatric nephrology and rheumatology outpatient clinic. We analyzed their demographic data, clinical and laboratory findings, treatment response and adverse reactions. We determined the efficacy of tocilizumab treatment using the American College of Rheumatology (ACR) pediatric (Pedi) response criteria, including ACR Pedi 30, 50, 70 and 90 scores. We used the Wilcoxon test to compare measurements before and after treatment.

RESULTS: Tocilizumab was given to seven patients with sJIA and four with pJIA (one of the pJIA patients was rheumatoid factor-positive). In most patients, we observed improvement of symptoms, absence of articular and extra-articular inflammation and continued inactive disease. ACR Pedi 30, 50 and 70 scores were achieved by 90.9% of the patients. Five patients showed minor side effects, possibly due to use of tocilizumab.

CONCLUSIONS: Tocilizumab therapy should be considered for treating patients with diagnoses of pJIA or sJIA who are resistant to non-biological DMARDs and/or other biological therapies.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in the pediatric population. JIA is characterized by unknown etiology and onset before the age of 16 years. Systemic JIA (sJIA) and polyarticular JIA (pJIA) are associated with increased joint damage, treatment refractoriness, prolonged course and poor outcome.[1-3] pJIA is defined as arthritis in five or more joints during the first six months of the disease. sJIA is defined as arthritis and intermittent fever for two or more weeks, plus any of the following: typical rash, generalized lymphadenopathy, hepatosplenomegaly or serositis.[4] Currently, sJIA is classified as a multifactorial autoinflammatory disease.[5] Patients with these two subtypes of JIA generally have inadequate responses to non-steroidal anti-inflammatory drugs (NSAIDs) and non-biological disease-modifying anti-rheumatic drugs (DMARDs).[6]

IL-6 is a proinflammatory cytokine that plays an important role in the articular and extra-articular manifestations of JIA, as well as in the chronic complications of the disease.[7] The clinical symptoms of sJIA are attributed to overproduction of IL-6.[8] It is known that IL-6 increases in both the serum and the synovial fluid of patients with pJIA, and that the serum concentration of IL-6 is also positively correlated with the severity of joint involvement.[9,10]

Tocilizumab (an anti-IL-6 drug) is a recombinant, humanized monoclonal antibody that binds to IL-6 receptors and is commonly used for treating patients with active sJIA, alone or in combination with methotrexate.[11] Inhibition of IL-6 signaling in response to tocilizumab can significantly improve the symptoms of sJIA. Phase II[12,13] and phase III[14] clinical trials that included children with sJIA showed significant reductions in inflammatory response, with improvement in osteoporosis and growth retardation.

Tocilizumab is an effective treatment that reduces the signs and symptoms of disease, and improves quality of life (QoL) and physical functioning in patients with pJIA.[15] This drug is indicated for patients aged two or more years, for treating active sJIA and moderate to severe active pJIA, in situations of insufficient response to or intolerance of NSAIDs and DMARDs.

We aimed to describe the use of tocilizumab therapy for 11 patients with polyarticular JIA (pJIA) and systemic JIA (sJIA) who presented inadequate response or were refractory to disease-modifying anti-rheumatic drugs (DMARDs) and/or other biological therapies; and to evaluate its benefits, safety, and tolerability.

METHODS

We retrospectively reviewed the medical records of patients diagnosed as presenting JIA who were followed up at the Pediatric Nephrology and Rheumatology Outpatient Clinic of Dr. Sami Ulus Çocuk Hospital, Ankara, Turkey, between September 2014 and October 2017. There were 11 JIA patients aged 3-18 years who were treated with tocilizumab. The tocilizumab treatment was administered via intravenous infusion: 8-10 mg/kg once every month for pJIA patients; and 8-12 mg/kg every 14 days for sJIA patients.

JIA was diagnosed based on the classification criteria of the International League of Associations for Rheumatology (ILAR).[16] All the patients were treated in accordance with the standardized medication of the consensus-based treatment plans of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) for pJIA and sJIA.[17,18] These patients had presented treatment failure when other therapies (both biological and non-biological) had been used previously. Treatment failure was defined as an inadequate response or refractoriness or intolerance to other drugs that had been administered for at least three months.

Demographic data, clinical and laboratory findings, acute phase reactants, concomitant medications, response to treatment and adverse reactions were recorded in relation to all patients. All of them underwent laboratory analyses before tocilizumab treatment was started, along with evaluation for tuberculosis, including chest X-ray, tuberculin skin test (TST) and/or interferon-gamma release assay (IGRA).[19] Cases of macrophage activation syndrome (MAS) were diagnosed based on clinical symptoms and laboratory findings, in accordance with the guidelines proposed by Ravelli et al.[20]

Disease activity was measured by means of the American College of Rheumatology pediatric response criteria (ACR Pedi), including ACR Pedi 30, 50, 70 and 90 scores.[14,15] The clinical response was defined by using the core set, which include six markers, as follows: (1) number of joints with active arthritis; (2) functional ability; (3) number of joints with limited range of motion; (4) parent/patient's overall assessment on a visual analogue scale (VAS) (scored on a 10-cm VAS); (5) physician's overall assessment

on a visual analogue scale (VAS); and (6) erythrocyte sedimentation rate. The ACR Pedi 30, 50 and 70 responses were defined as at least 30%, 50% and 70% improvement in three or more markers of the JIA core set, compared with the baseline, while no more than one of the remaining markers worsened by more than 30%.

Use of tocilizumab was started for treatment of signs and symptoms of active JIA in patients who had not shown any ACR Pedi 30 response and had responded inadequately to previous therapy with disease-modifying antirheumatic drugs, corticosteroids and other biological medications.

For the JIA patients who failed to respond to the current (or existing) treatment due to clinical unresponsiveness or toxicity to previous treatments, the treatment was changed to one using medication with a different mechanism of action. The treatment response was assessed in accordance with the definitions of the Classification and Response Criteria Subcommittee of the American College of Rheumatology Committee on Quality Measures.[21]

This retrospective study was approved by the ethics committee of Ankara Numune Training and Research Hospital (date: March 8, 2018; decision no: E. Kurul-E-18-1825). It was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed using the SPSS software, version 20. The Kolmogorov-Smirnov test was used to assess the normality assumption for continuous variables. Non-normally distributed variables were presented as the median with the interquartile range (25th to 75th percentile). Categorical variables were presented as the number (with the percentage). The Wilcoxon test was used to compare the measurements from before and to after the treatment. P-values less than 0.05 were considered statistically significant.

RESULTS

Among the 350 JIA patients in the hospital's database, the case series consisted of 11 children with JIA (seven with sJIA and four with pJIA) who were treated with tocilizumab. At the onset of the disease, the patients were aged between 1 and 16 years (median: 4 years). At the onset of tocilizumab therapy, the patients were aged 3-18 years. The demographic data, clinical findings and treatment responses are shown in **Table 1** and **Table 2**.

In all the sJIA patients, the systemic signs of the disease (rash, arthritis, fever, lymphadenopathy, hepatomegaly and splenomegaly) completely disappeared after a few days, following injection of tocilizumab. This improvement was then maintained throughout the tocilizumab treatment.

Following this treatment, there were significant decreases in the median white blood cell count (P < 0.01) and platelet count

(P = 0.021), and significant increases in the median hemoglobin level (P < 0.01) and mean platelet volume (P = 0.046) (**Table 3**). There were also statistically significant decreases in the median erythrocyte sedimentation rate (ESR) and the median C-reactive

protein (CRP) level (P < 0.01 for each). Anemia was noted in seven patients (63.6%) before the treatment with tocilizumab, of whom four were sJIA patients. However, only one patient with pJIA had anemia following the treatment with tocilizumab. This patient was the only one who did not respond to this treatment.

The pre-tocilizumab evaluation showed that three of the patients (one of them was a sJIA patient) were TST and IGRA-positive. Latent tuberculosis treatment (isoniazid) was given for six months. and the tests were negative after treatment with isoniazid. After treatment with tocilizumab, TST and IGRA tests on all 11 patients were negative and no tuberculosis was observed in any of the patients.

The results from pain assessments before tocilizumab treatment were the following: the median VAS on the parent/patient's overall assessment of wellbeing was 10 cm (range 6-10 cm); and the median VAS on the physician's overall assessment of disease activity was 10 cm (range 8-10 cm). Treatment with tocilizumab was associated with better parent/patient VAS and physician VAS: median of 2 cm (range 0-3) for each of them (P < 0.01).

Clinical remission was achieved following commencement of use of tocilizumab in all the sJIA patients but in only three of the four pJIA patients (75%). We observed that treatment with tocilizumab led to a decrease in the number of actively arthritic joints (**Table 1**). The median duration of use of tocilizumab was 16 months (range 12-28 months). Use of tocilizumab was discontinued in only one patient during this study, while 90.9% (10/11) of the patients continued to receive tocilizumab. Thus, in total, 90.9% of the patients who had not responded to earlier biological therapy achieved ACR Pedi 30, 50 and 70 scores through use of tocilizumab.

Table 1. Patients' data and baseline characteristics

Patient characteristics	Value
Age in years at juvenile idiopathic arthritis onset, median (range)	4.2 (1-16)
Time in months that elapsed until administration of tocilizumab, median (range)	40.9 (6-150)
Sex, n (%)	
Male	4 (36.3)
Female	7 (63.7)
Subtype of juvenile idiopathic arthritis, n (%)	
Systemic	7 (63.7)
Polyarticular	4 (36.3)
Age in years at tocilizumab onset, median (interquartile range)	10 (5-14)
Disease duration in months, median (interquartile range)	32 (21-90)
Clinical findings at onset, n (%)	
Rash	6 (54.5)
Arthritis	11 (100)
Fever	7 (63.7)
Lymphadenopathy	5 (45.4)
Hepatomegaly	5 (45.4)
Splenomegaly	5 (45.4)
Macrophage activation syndrome	3 (27.2)
Number of joints with active arthritis at the start of tocilizumab therapy, median (interquartile range)	8 (1-18)
Number of joints with active arthritis after tocilizumab therapy, median (interquartile range)	0 (0)

Table 2. Patients' characteristics and possible side effects associated with treatment

Patient number	Diagnosis	Sex	Age at diagnosis (years)	Disease duration (months)	Duration of tocilizumab use (months)*	Previous treatments	VAS1	VAS2	Adverse effect with tocilizumab
1	sJIA	M	9	15	5	NSAIDs-MTX-CS	10	2	
2	sJIA	F	10	58	31	NSAIDs-MTX-CS-CAN	10	3	
3	sJIA	F	5	28	12	NSAIDs-MTX-CS	10	0	
4	sJIA	F	4	21	12	NSAIDs-MTX-CS-CAN	10	0	
5	sJIA	F	13	32	13	MTX-CS-CAN	6	2	
6	sJIA	M	2	21	16	NSAIDs-CS	10	0	Diarrhea, fungal skin infection, nasopharyngitis, bronchitis
7	sJIA	F	4	90	37	NSAIDs-MTX-CS-Anti-TNF	10	3	
8	pJIA	F	3	118	17	NSAIDs-MTX-Anti-TNF	10	3	Nasopharyngitis
9	pJIA	M	1	70	17	NSAIDs-MTX-CS-Anti-TNF	8	2	Nasopharyngitis, epistaxis
10	pJIA	M	2	178	28	NSAIDs-MTX-CS-Anti-TNF	10	0	
11	pJIA	F	16	19	7	NSAIDs-MTX-CS-Anti-TNF	8	4	

*Duration of tocilizumab use: defined as the time from the beginning of the treatment with tocilizumab to the last dose of tocilizumab or to the time of writing this manuscript.
VAS1 = visual analogue scale before treatment with tocilizumab; VAS2 = visual analogue scale after treatment with tocilizumab.
sJIA = systemic juvenile idiopathic arthritis; pJIA = polyarticular juvenile idiopathic arthritis; DMARDs = disease-modifying antirheumatic drugs; CAN = canakinumab; NSAIDs = nonsteroidal anti-inflammatory drugs; MTX = methotrexate; CS = corticosteroids; Anti-TNF = anti-tumor necrosis factor; VAS = visual analogue scale.

All of the patients had been treated with non-biological DMARDs and/or NSAIDs before starting to receive tocilizumab, as follows: methotrexate: n = 10 (i.e. all patients except for one with sJIA); NSAIDs: n = 10 (i.e. all patients except for one with sJIA); and corticosteroids: n = 10 (i.e. all patients except for one with pJIA). Some of the patients had been taking more than one type of medicine.

In addition, seven patients had previously also used another biological agent and one patient had previously used more than two biological agents. In total, four sJIA patients used only tocilizumab as biological therapy, and the other three sJIA patients switched to tocilizumab after having used canakinumab. For four pJIA patients, the biological treatment agent was switched from etanercept to tocilizumab. One of these patients was subsequently switched from tocilizumab to rituximab during the follow-up.

Among the ten patients who had taken corticosteroids at the baseline and during treatment with tocilizumab, eight (80%) discontinued their use of corticosteroids (three pJIA and five sJIA patients). Moreover, four patients (one of them presenting pJIA) did not receive any drugs concomitantly with tocilizumab. However, some patients continued to receive treatment with non-biological DMARDs after they started to receive tocilizumab: five used methotrexate (two of these were pJIA patients), three used NSAIDs (all of these were pJIA patients) and two used corticosteroids (one of these was a pJIA patient).

One patient who was seropositive for both rheumatoid factor and anti-cyclic citrulline peptide did not respond to tocilizumab treatment, which was used for seven months. This patient was subsequently switched to rituximab therapy. Unfortunately, in the case of this patient, there was also no successful response to rituximab therapy.

In all, five patients (45.4%) (one of these was a sJIA patient) experienced a range of possible minor adverse events. None of the patients were reported to have had uveitis before or after treatment with tocilizumab. One of the sJIA patients had diarrhea, but without any organisms isolated, and this patient additionally presented

fungal skin infection, nasopharyngitis and bronchitis. Other adverse events observed included nasopharyngitis (three patients in total, of whom two were pJIA patients) and epistaxis (one pJIA patient). No anaphylaxis-like reactions developed in any of the patients and none of the patients had to discontinue tocilizumab due to side effects. None of the patients developed any infection requiring intravenous antibiotics or hospitalization, malignancy, autoimmune diseases, uveitis, high liver function test results, hypothyroidism, diverticulitis or kidney stones during their treatment with tocilizumab. None of the patients developed neutropenia. None of the patients developed amyloidosis and/or proteinuria, and none of the patients presented elevated cholesterol levels following treatment with tocilizumab. None of the patients died during this treatment.

Two patients had three episodes of macrophage activation syndrome (MAS) (in one patient, this occurred twice; and only one had bone marrow alterations), before the treatment with tocilizumab. However, MAS did not develop in any patients after the treatment with tocilizumab.

DISCUSSION

The findings from the present retrospective observational case series showed that intravenous tocilizumab may be acceptable for treating sJIA and pJIA. The percentage of patients with sJIA-associated symptoms, such as fever, rash, lymphadenopathy, hepatomegaly, splenomegaly or arthritis, significantly decreased after treatment with tocilizumab. Clinical improvement was observed in the majority of the patients (90.9%) after treatment with tocilizumab, which is a higher success rate than previously reported.[22-26] In the present study, in total, ACR Pedi 30, 50 and 70 scores were achieved in 10 (90.9%) of our JIA patients. Different ACR Pedi 30, 50 and 70 scores in response to use of tocilizumab have been reported in the literature.[14,15,22,24-26]

Adverse events were seen in 45.4% of our patients who used tocilizumab, including nasopharyngitis, diarrhea, skin fungal infection, nasopharyngitis, bronchitis and epistaxis, as previously reported.[22,24] There was a decrease in the mean number of joints

Table 3. Laboratory analyses on children with juvenile idiopathic arthritis who were treated with tocilizumab

Parameters	At onset of tocilizumab use* Median (range)	After tocilizumab use* Median (range)	P-value
Hemoglobin, g/dl	11.3 (10.0-11.9)	12.5 (12.15-13.10)	< 0.01
White blood cells, 10⁹ cells/l	11.5 (10.1-17.5)	7.29 (5.43-8.70)	< 0.01
Granulocyte count	8.22 (6.92-10.19)	3.07 (2.29-4.88)	< 0.01
Lymphocyte count	2.3 (1.18-4.6)	2.47 (1.67-3.09)	0.859
Platelet count, 10⁹/l	457 (345-536)	278 (243-285)	0.021
Mean platelet volume, fl	7.3 (6.8-7.8)	7.9 (7.3-8.1)	0.046
Alanine aminotransferase level, U/l	12 (10-23)	15 (13-18)	0.895
C-reactive protein level (mg/l)*	45.6 (17.3-101)	3.1 (< 3.1)	< 0.01
Erythrocyte sedimentation rate (mm/hour)	42 (30-48)	3 (2-5)	< 0.01

*In our laboratory, the lowest measurable C-reactive protein (CRP) value was < 3.1 mg/l. CRP level after tocilizumab treatment was < 3.1 mg/l in all patients.

with active arthritis among our patients, during treatment with tocilizumab. Most of the patients (90.9%) did not have any joints with active arthritis after their treatment with tocilizumab, which was a much higher rate than had previously been reported in relation to sJIA and pJIA.[22-26]

The CRP and ESR levels decreased significantly in our patients after they started to receive treatment with tocilizumab. These levels then remained within normal limits throughout the therapy period, which was concordant with earlier reports.[22-26] Use of corticosteroids was successfully tapered off through tocilizumab therapy, even though they could not be completely withdrawn in the cases of eight patients (80%). These findings were much better than those observed in some clinical trials.[27,28]

As also previously reported, we observed that the treatment with tocilizumab in our patients increased their hemoglobin levels and percentage lymphocyte counts, and decreased the neutrophil, platelet and white blood cell counts.[15,28] Güneş et al.[29] reported that there was a significant association between mean platelet volume (MPV) and disease activity in JIA patients. There was a statistically significant increase in MPV after the treatment with tocilizumab in our patients.

The major limitation of the present case series was its single-center retrospective design. The small number of patients, short follow-up and the absence of a control group limited the evaluation of the effect of treatment in this case series.

CONCLUSIONS

This observational retrospective small series described patients with juvenile idiopathic arthritis that had been refractory to the usual treatment or had not responded to it. The present findings showed that the overall risk/benefit profile of tocilizumab used among JIA patients was acceptable, given the severity of the disease, the observed improvement in clinical symptoms and laboratory findings, and the possibility of tapering off the use of corticosteroids concomitantly with the treatment with tocilizumab.

Our findings are encouraging with regard to use of tocilizumab, as a possible viable alternative for JIA patients who have presented an inadequate response or been refractory to other therapies. Additional research is required to confirm the present findings and to determine the optimum duration of tocilizumab treatment in JIA patients.

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Effects of hyperuricemia on incident renal replacement therapy and all-cause mortality among patients with chronic kidney disease stages 3-5: a retrospective cohort study

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ABSTRACT

BACKGROUND: Findings regarding the effects of hyperuricemia on renal function and mortality have been inconsistent.
OBJECTIVES: To investigate the effects of hyperuricemia on incident renal replacement therapy and all-cause mortality among patients with chronic kidney disease (CKD).
DESIGN AND SETTING: Retrospective cohort study conducted in a medical center in Taiwan.
METHODS: Patients with CKD in stages 3-5, without histories of renal replacement therapy, were consecutively recruited from 2007 to 2013. Their medical history, laboratory and medication data were collected from hospital records. The mean uric acid level in the first year of follow-up was used for analyses. Hyperuricemia was defined as mean uric acid level ≥ 7.0 mg/dl in men or ≥ 6.0 mg/dl in women. The primary outcomes were incident renal replacement therapy and all-cause mortality, and these data were retrospectively collected from hospital records until the end of 2015.
RESULTS: A total of 4,381 patients were analyzed (mean age 71.0 ± 14.8 years; males 62.7%), and the median follow-up period was 2.5 years. Patients with hyperuricemia were at increased risk of incident renal replacement therapy and all-cause mortality, especially those with CKD in stages 4 or 5. Compared with patients with CKD in stage 3 and normouricemia, patients with CKD in stages 4 or 5 presented significantly higher risk of all-cause mortality only if they had hyperuricemia.
CONCLUSIONS: In patients with CKD in stages 3-5, hyperuricemia was associated with higher risk of incident renal replacement therapy and all-cause mortality. Whether treatment with uric acid-lowering drugs in these patients would improve their outcomes merits further investigation.

INTRODUCTION

Hyperuricemia, defined as a uric acid level higher than 7.0 mg/dl in men or higher than 6.0 mg/dl in women,[1] has been associated with cardiovascular risk factors[2-3] and cardiovascular diseases.[4,5] Hyperinsulinemia, a known consequence of insulin resistance, has been shown to reduce urinary excretion of uric acid.[6] Meanwhile, uric acid retention due to renal vasoconstriction is common in patients with hypertension.[7] In a meta-analysis on 25 observational studies with nearly 100,000 participants,[8] it was demonstrated that hyperuricemia independently increased the risk of incident hypertension. In another meta-analysis on 17 prospective observational studies with more than 160,000 participants,[9] a uric acid level that was one standard deviation higher was associated with an odds ratio for coronary heart disease of 1.07 (95% confidence interval, CI 1.04-1.10).

With regard to the risk of kidney disease, hyperuricemia has been associated with incident chronic kidney disease (CKD). In a prospective cohort study on more than 21,000 healthy volunteers,[10] a uric acid level ≥ 7.0 mg/dl at baseline was associated with a higher risk of incident kidney disease (defined as an estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2) during a median follow-up duration of 7 years. Similar findings were noted in another prospective study[11] on more than 13,000 participants pooled from two community-based cohorts with a mean follow-up duration of 8.5 years. These results were consistent with the findings from a meta-analysis[12] on 15 cohort studies with a total of nearly 100,000 relatively healthy individuals and nearly 3,500 incident CKD cases (defined as eGFR < 60 ml/min/1.73 m^2).

However, among patients with CKD who were not on dialysis, the data regarding the effects of hyperuricemia on renal function and mortality have been limited and the findings have been inconsistent. Among patients with CKD in stages 3-4 who were on chronic allopurinol therapy

for hyperuricemia,[13] withdrawal of allopurinol led to a significant increase in serum uric acid level and a significant deterioration in renal function, especially in those who were not on blockers of the renin-angiotensin system. In contrast, uric acid was not associated with the rate of decline in renal function in another cohort study[14] on patients with CKD in stages 3-5. With regard to risk of mortality, hyperuricemia was an independent risk factor for all-cause and cardiovascular mortality (but not kidney failure) in a cohort of patients with CKD in stages 3-4 during a median follow-up of 10 years.[15] In contrast, hyperuricemia was not associated with cardiovascular diseases and all-cause mortality in another cohort of patients with CKD in stages 3-4 during a median follow-up of 9 years.[16]

OBJECTIVE

In this study, we aimed to investigate the effects of hyperuricemia on incident renal replacement therapy (RRT) and all-cause mortality, among patients with CKD in stages 3-5 who were not on dialysis at the baseline.

METHODS

This was a retrospective cohort study conducted in a medical center in central Taiwan. Patients with CKD in stages 3-5 with no history of RRT were consecutively recruited in a CKD care program from January 2007 to December 2013. The patients' medical history, laboratory and medication data were collected from hospital records. The primary outcomes of this study were incident RRT and all-cause mortality, and these data were collected from hospital records until the end of 2015. We included patients for whom information about their vital status (records of follow-up visits or mortality events) were available in the analyses. This study was approved by the Local Institutional Review Board in Taichung, Taiwan (approval number CE16253A; approval date Oct 21, 2016). This report complied with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Baseline eGFR was determined using the Modification of Diet in Renal Disease (MDRD) equation (GFR = $186.3 \times$ serum creatinine$^{-1.154}$ $\times$ age$^{-0.203} \times 0.742$ if female $\times 1.21$ if black).[17] We divided our patients into CKD in stages 3-5 according to their baseline eGFR (CKD stage 3 = eGFR 30 to < 60 ml/min/1.73 m²; CKD stage 4 = eGFR 15 to < 30 ml/min/1.73 m²; and CKD stage 5 = eGFR < 15 ml/min/1.73 m² with no RRT). The patients' systolic and diastolic blood pressure and uric acid levels were collected from hospital records, and the mean blood pressure and uric acid levels in the first year of follow-up were used for analyses. Hyperuricemia was defined as a mean uric acid level ≥ 7.0 mg/dl in men or ≥ 6.0 mg/dl in women. The uric acid-lowering drugs used included allopurinol and benzbromarone.

RRT was defined as hemodialysis, peritoneal dialysis or renal transplantation. We classified patients' cause of death into cardiovascular or non-cardiovascular death[18] by reviewing the medical records. Cardiovascular death included sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke and death due to other cardiovascular causes. The codes for cardiovascular deaths that we used were International Classification of Diseases (ICD)-9 390-448. Non-cardiovascular death was defined as any death not covered by cardiac death or vascular death.[18] All causes of death were independently reviewed by two board-certified physicians of internal medicine. In the event of an inconsistency, an independent cardiologist reviewed the medical records and made the final classification.

All of the statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Inc., Cary, NC, USA). Continuous variables were reported as the mean ± standard deviation (SD), while categorical data were given as numbers (with percentages). The differences in clinical variables between groups were tested for statistical significance using the chi-square test for categorical variables; or using an independent-sample t test or one-way analysis of variance (ANOVA) for continuous variables.

We used Cox's proportional hazards model to compare the hazard ratios (HRs) of RRT, all-cause mortality and cardiovascular and non-cardiovascular death among patients with different CKD stages or uric acid levels. Since mortality was an event that competed with RRT, an extended Cox's proportional hazards model was used to calculate the subdistribution hazard ratio (SHR) as a sensitivity test.[19] For cause-specific mortality, we considered non-cardiovascular death to be an event competing with cardiovascular death, and vice versa. Therefore, an extended Cox's proportional hazards model was used to determine the SHR of cardiovascular and non-cardiovascular death among patients with different CKD stages or uric acid levels. The variables that were adjusted for in the analyses included factors that were known to be associated with the risk of mortality or with uric acid levels (age, sex, systolic blood pressure, smoking history, diabetes and use of uric acid-lowering drugs and statins). In all of the statistical analyses, a two-sided P-value < 0.05 was considered statistically significant.

RESULTS

A total of 4,381 patients were included in the analyses (mean age 71.0 ± 14.8 years; males 62.7%), and the median follow-up period was 2.5 years. **Table 1** shows the baseline characteristics of the study patients according to CKD stages and uric acid levels. The patients who were at a later stage of CKD were younger, were more frequently female, had higher systolic and diastolic blood pressure, were less likely to have a smoking history, were more likely to have diabetes, had higher uric acid levels and were less likely to be on a statin, compared with those at CKD stage 3. The patients who had hyperuricemia (defined as a mean uric acid level ≥ 7.0 mg/dl in men or ≥ 6.0 mg/dl in women) were younger, were more frequently female, had higher systolic and diastolic blood pressure, were less likely to have a smoking history, had lower eGFR and were more likely to be on uric acid-lowering treatment, compared with those presenting normouricemia.

Overall, 1229 patients (28.1%) were undergoing treatment with uric acid-lowering drugs. They were more frequently male (75.2% versus 57.8%; P < 0.001), more likely to have a smoking history (45.5% versus 35.8%; P < 0.001), less likely to have diabetes (33.6% versus 43.2%; P < 0.001) and had higher uric acid levels (8.4 ± 2.1 versus 7.8 ± 2.1 mg/dl; P < 0.001), compared with those who were not on uric acid-lowering treatment.

Table 2 shows the effects of CKD and uric acid levels on incident RRT and mortality. During a median follow-up period of 2.5 years, 21.3% of the patients (n = 932) received RRT, while the mortality rate was 8.1% (n = 356). Compared with patients at CKD stage 3,

those at CKD stage 4 or stage 5 presented significantly higher risk of incident RRT (all P < 0.001). The findings remained significant when multiple factors were adjusted for (all P < 0.001) and the competing risk of mortality was considered (all P < 0.001). Similar findings were noted when patients with hyperuricemia were compared with those with normouricemia, with regard to the risk of incident RRT. Patients at a later stage of CKD were also at higher risk of all-cause mortality, as well as cardiovascular and non-cardiovascular death, compared with those at CKD stage 3. Similarly, patients with hyperuricemia were at higher risk of all-cause mortality and non-cardiovascular death, compared with normouricemic patients (Table 2).

Table 1. Baseline characteristics of study patients according to CKD stages and uric acid levels

Variables	Overall	CKD stages				Uric acid levels		
		Stage 3	Stage 4	Stage 5	P	Normouricemia	Hyperuricemia[a]	P
Number of patients	4381	2076	1365	940		1151	3230	
Age, years	71.0 ± 14.8	72.2 ± 14.4	71.5 ± 15.0	67.7 ± 14.9	< 0.001	73.4 ± 13.8	70.2 ± 15.1	< 0.001
Male, n (%)	2747 (62.7)	1491 (71.8)	794 (58.2)	462 (49.2)	< 0.001	864 (75.1)	1883 (58.3)	< 0.001
Systolic BP, mm Hg[b]	134 ± 16	132 ± 15	134 ± 16	137 ± 17	< 0.001	133 ± 19	135 ± 19	0.041
Diastolic BP, mm Hg[b]	74 ± 9	74 ± 9	74 ± 10	76 ± 9	< 0.001	74 ± 11	75 ± 11	0.039
Smoking history, n (%)	1688 (38.5)	880 (42.4)	506 (37.1)	302 (32.1)	< 0.001	501 (43.5)	1187 (36.8)	< 0.001
Diabetes, n (%)	1776 (40.5)	784 (37.8)	614 (45.0)	378 (40.2)	< 0.001	479 (41.6)	1297 (40.2)	0.386
eGFR, ml/min/1.73 m²	28.1 ± 13.2	39.8 ± 6.4	23.1 ± 4.9	9.6 ± 3.4	< 0.001	31.8 ± 12.4	26.7 ± 13.3	< 0.001
Uric acid, mg/dl[b]	8.0 ± 2.1	7.6 ± 1.8	8.2 ± 2.3	8.5 ± 2.2	< 0.001	5.7 ± 0.9	8.7 ± 1.8	< 0.001
Uric acid-lowering drugs, n (%)	1229 (28.1)	556 (26.8)	403 (29.5)	270 (28.7)	0.189	279 (24.2)	950 (29.4)	< 0.001
Statins, n (%)	1523 (34.8)	768 (37.0)	492 (36.0)	263 (28.0)	< 0.001	383 (33.3)	1140 (35.3)	0.217

Continuous variables are expressed as mean ± standard deviation. Categorical data are presented as numbers (with percentages). [a]Defined as a mean uric acid level ≥ 7.0 mg/dl in men or ≥ 6.0 mg/dl in women. [b]Mean level within the first year of follow-up.
BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

Table 2. Cox proportional hazards models for renal replacement therapy and mortality according to CKD stages and uric acid levels

	Renal replacement therapy (n = 932)					
	Univariate HR (95% CI)	P	Multivariate[a] HR (95% CI)	P	Multivariate[b] SHR (95% CI)	P
CKD stages						
Stage 3	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Stage 4	4.13 (3.32-5.14)	< 0.001	4.34 (3.29-5.71)	< 0.001	4.10 (3.14-5.35)	< 0.001
Stage 5	22.43 (18.29-27.52)	< 0.001	24.23 (18.66-31.47)	< 0.001	21.68 (16.74-28.08)	< 0.001
Uric acid levels						
Normouricemia	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Hyperuricemia[c]	2.12 (1.78-2.53)	< 0.001	1.71 (1.37-2.13)	< 0.001	1.60 (1.26-2.04)	< 0.001

	All-cause mortality (n = 356)				CV death (n = 65)		Non-CV death (n = 291)	
	Univariate HR (95% CI)	P	Multivariate[a] HR (95% CI)	P	Multivariate[a] SHR (95% CI)	P	Multivariate[a] SHR (95% CI)	P
CKD stages								
Stage 3	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Stage 4	1.61 (1.27-2.04)	< 0.001	1.88 (1.42-2.48)	< 0.001	2.58 (1.28-5.22)	0.008	1.72 (1.27-2.32)	< 0.001
Stage 5	1.56 (1.19-2.05)	0.002	1.81 (1.28-2.58)	< 0.001	2.82 (1.19-6.68)	0.018	1.61 (1.09-2.39)	0.016
Uric acid levels								
Normouricemia	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Hyperuricemia[c]	1.21 (0.95-1.55)	< 0.001	1.58 (1.16-2.15)	0.004	1.61 (0.72-3.59)	0.246	1.56 (1.12-2.17)	0.009

[a]Adjusted for age, gender, systolic blood pressure, smoking history, diabetes and use of uric acid-lowering drugs and statins. [b]Considering the competing risk of mortality in addition to multivariate adjustment. [c]Defined as a mean uric acid level ≥ 7.0 mg/dl in men or ≥ 6.0 mg/dl in women. CKD = chronic kidney disease; CV = cardiovascular; HR = hazard ratio; SHR = subdistribution hazard ratio.

The effects of hyperuricemia on incident RRT and mortality across the CKD stages are shown in **Table 3**. The higher risk of incident RRT associated with hyperuricemia was statistically significant among patients at CKD stage 4 or stage 5, but not among patients at CKD stage 3. With regard to risk of mortality, hyperuricemia was associated with significantly higher risk of all-cause mortality among patients at CKD stage 4. Patients with hyperuricemia did not have significantly higher risk of cardiovascular death across the CKD stages. Hyperuricemia was associated with significantly higher risk of non-cardiovascular death among patients at CKD stage 4 or stage 5 (**Table 3**).

When we stratified our patients according to their CKD stages and uric acid levels (**Table 4**), the weighted event rate of incident RRT per 1000 person-years increased from 13.75 for patients at CKD stage 3 with normouricemia to 398.43 for patients at CKD stage 5 with hyperuricemia. With regard to the risk of mortality among patients with normouricemia, those at CKD stage 4 or stage 5 did not have significantly higher risk of all-cause mortality,

compared with patients at CKD stage 3. In contrast, patients at CKD stage 4 or stage 5 with hyperuricemia had significantly higher risk of all-cause mortality, as well as cardiovascular and non-cardiovascular death, compared with those at CKD stage 3 with normouricemia. These findings remained consistent after adjustment for multiple factors (**Table 4**).

DISCUSSION

In this study, we investigated patients with CKD in stages 3-5 and found that patients with hyperuricemia (defined as a mean uric acid level ≥ 7.0 mg/dl in men or ≥ 6.0 mg/dl in women) were at increased risk of incident RRT and all-cause mortality, independent of traditional risk factors such as age, gender, blood pressure, smoking, diabetes etc. (**Table 2**). Hyperuricemia was associated with worse outcomes mainly among patients at CKD stage 4 or stage 5 (significantly higher risk of incident RRT and non-cardiovascular mortality; **Table 3**).

Table 3. Cox proportional hazards model for renal replacement therapy and mortality according to uric acid levels at different CKD stages

		Renal replacement therapy				
		Univariate HR (95% CI)	Multivariate[a] HR (95% CI)	P	Multivariate[b] SHR (95% CI)	P
CKD stage 3	Normouricemia	1.00 (reference)	1.00 (reference)		1.00 (reference)	
	Hyperuricemia[c]	1.52 (0.99-2.32)	1.31 (0.76-2.26)	0.331	1.28 (0.75-2.22)	0.368
CKD stage 4	Normouricemia	1.00 (reference)	1.00 (reference)		1.00 (reference)	
	Hyperuricemia[c]	1.89 (1.35-2.65)	1.77 (1.15-2.72)	0.010	1.68 (1.10-2.57)	0.016
CKD stage 5	Normouricemia	1.00 (reference)	1.00 (reference)		1.00 (reference)	
	Hyperuricemia[c]	1.61 (1.26-2.04)	1.62 (1.20-2.17)	0.002	1.52 (1.12-2.06)	0.007
		All-cause mortality			CV death		Non-CV death	
		Univariate HR (95% CI)	Multivariate[a] HR (95% CI)	P	Multivariate[a] SHR (95% CI)	P	Multivariate[a] SHR (95% CI)	P
CKD stage 3	Normouricemia	1.00 (reference)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
	Hyperuricemia[c]	1.08 (0.75-1.55)	1.31 (0.86-2.01)	0.214	2.87 (0.62-13.25)	0.176	1.18 (0.75-1.85)	0.470
CKD stage 4	Normouricemia	1.00 (reference)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
	Hyperuricemia[c]	1.00 (0.67-1.50)	1.70 (1.02-2.85)	0.043	1.28 (0.41-3.99)	0.667	1.80 (1.01-3.22)	0.047
CKD stage 5	Normouricemia	1.00 (reference)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
	Hyperuricemia[c]	1.76 (0.88-3.52)	2.48 (0.89-6.95)	0.083	0.76 (0.14-4.25)	0.756	4.23 (1.02-17.50)	0.047

[a]Adjusted for age, gender, systolic blood pressure, smoking history, diabetes and use of uric acid-lowering drugs and statins. [b]Considering the competing risk of mortality in addition to multivariate adjustment. [c]Defined as a mean uric acid level ≥ 7.0 mg/dl in men or ≥ 6.0 mg/dl in women.
CKD = chronic kidney disease; HR = hazard ratio; CV = cardiovascular; SHR = subdistribution hazard ratio.

Table 4. Cox proportional hazards model for all-cause mortality and for CV and non-CV deaths

Uric acid levels	CKD stages	All-cause mortality				CV death		Non-CV death	
		Number of events	Weighted event rate[a]	Univariate HR (95% CI)	Multivariate[b] HR (95% CI)	Multivariate[b] SHR (95% CI)	P	Multivariate[b] SHR (95% CI)	P
Normouricemia	Stage 3	42	20.34	1.00 (reference)	1.00 (reference)	1.00 (reference)		1.00 (reference)	
	Stage 4	31	34.30	1.69 (1.06-2.68)	1.62 (0.90-2.90)	5.05 (0.92-27.83)	0.063	1.34 (0.71-2.53)	0.375
	Stage 5	9	20.54	1.01 (0.49-2.07)	1.01 (0.35-2.88)	7.86 (1.00-61.74)	0.050	0.52 (0.12-2.27)	0.387
Hyperuricemia[c]	Stage 3	94	21.91	1.08 (0.75-1.55)	1.36 (0.89-2.08)	3.10 (0.68-14.17)	0.144	1.23 (0.79-1.93)	0.363
	Stage 4	107	34.52	1.70 (1.19-2.43)	2.66 (1.75-4.05)	6.68 (1.52-29.38)	0.012	2.28 (1.46-3.58)	< 0.001
	Stage 5	73	36.14	1.78 (1.22-2.60)	2.73 (1.70-4.36)	7.15 (1.52-33.66)	0.013	2.33 (1.40-3.87)	0.001

[a]Per 1000 person-years. [b]Adjusted for age, gender, systolic blood pressure, smoking history, diabetes and use of uric acid-lowering drugs and statins. [c]Defined as a mean uric acid level ≥ 7.0 mg/dl in men or ≥ 6.0 mg/dl in women.
CKD = chronic kidney disease; CV = cardiovascular; HR = hazard ratio; SHR = subdistribution hazard ratio.

Patients with advanced CKD and hyperuricemia were at substantially increased risk of incident RRT. Moreover, compared with patients with CKD in stage 3 with normouricemia, patients at CKD stage 4 or stage 5 were at significantly higher risk of all-cause mortality only if they had hyperuricemia (**Table 4**).

Our findings are consistent with those of previous studies[10-12,20,21] that showed that hyperuricemia was an independent risk factor for decreased kidney function and presence of end-stage renal disease in general populations. Our results suggest that hyperuricemia was a risk factor for decreased kidney function requiring RRT among patients with CKD in stages 3-5. Several studies have reported that hyperuricemia was not associated with any decline in renal function[14] or kidney failure[14,15] among patients with CKD in stages 3-5.

Certain factors may account for these inconsistent findings. First, because uric acid is excreted by the kidney, a decrease in renal function is inevitably accompanied by an increase in serum uric acid level. This complicating phenomenon therefore makes it particularly challenging to study the role of uric acid in CKD. Second, patients with advanced CKD and/or hyperuricemia are at increased risk of mortality.[22-26] Thus, the lack of association between hyperuricemia and decreased kidney function in previous studies might be explained by the fact that the competing risk of mortality was not considered. In our study, we demonstrated that hyperuricemia was associated with incident RRT among patients with CKD (**Table 2**), especially those at CKD stage 4 or stage 5 (**Table 3**). Moreover, the risk remained significant after adjustment for multiple factors and consideration of the competing risk of mortality (**Tables 2** and **3**).

We also reported that hyperuricemia was associated with a higher risk of all-cause mortality (mainly non-cardiovascular death) among patients with CKD in stages 3-5 (**Table 2**). It is well known that patients with CKD are at increased risk of mortality and cardiovascular events.[22-24] Although occurrences of hyperuricemia had previously been correlated with risks of mortality and cardiovascular diseases,[25,26] conflicting data regarding this association had been reported in the general population[26-28] and among patients with diabetes[29,30] or CKD.[15,16] Our data support an association between hyperuricemia and higher risk of mortality among patients with CKD.[15,31,32]

Interestingly, less than 20% of the all-cause mortality comprised cardiovascular death among our patients (**Table 2**). Although patients with CKD are at increased risk of cardiovascular events,[22-24] it is worth noting that the majority of patients with CKD have died due to non-cardiovascular causes.[33,34] For example, in a large population of non-dialysis-dependent CKD patients,[33] less than 35% of the all-cause mortality was due to cardiovascular death during a median follow-up duration of 2.3 years. In another Asian population with CKD,[34] less than 20% of the all-cause mortality was due to cardiovascular death among patients with baseline eGFR < 45 ml/min/1.73 m², over the course of a median follow-up duration of 9.8 years. Thus, most patients with CKD died due to non-cardiovascular causes.[34] We found that hyperuricemia was associated with higher risk of all-cause mortality and non-cardiovascular death among patients with CKD in stages 3-5 (**Table 2**).

In line with previous reports,[33,34] the leading cause of non-cardiovascular death in our patients was malignancy (n = 202; 56.7% of the all-cause mortality). We found that hyperuricemia was associated with higher risk of non-cardiovascular death (**Table 2**), especially among patients with CKD in stage 4 or stage 5 (**Table 3**).

More than three decades ago, it was hypothesized that uric acid might protect against carcinogenesis, owing to its antioxidant properties.[35] However, studies in more recent decades have suggested that hyperuricemia was associated with higher risk of incidence of cancer and mortality.[36] Thus, despite the possible antioxidative effects of uric acid, this substance may play a contributory role in carcinogenesis. Since reactive oxygen species play a critical role in cell growth and survival, in both normal and cancer cells,[37] uric acid may promote cancer cell growth and survival by scavenging reactive oxygen species and reducing oxidative stress-induced apoptosis.[36,37]

Another mechanism through which hyperuricemia may be related to higher risk of incidence of cancer and mortality is inflammation. Uric acid has been found to induce the expression of several inflammatory mediators (such as monocyte chemoattractant protein-1 and C-reactive protein),[38] which may lead to a microenvironment with low-grade inflammation,[36] thus favoring transformation into cancer cells.

Taken together, a growing body of evidence suggests that hyperuricemia is associated with a higher risk of mortality due to cancer,[36] which is the leading cause of non-cardiovascular death among patients with CKD.[33,34] Our results suggest that hyperuricemia was associated with higher risk of non-cardiovascular death among patients with non-dialysis-dependent CKD.

Our study had some limitations. First, the causal relationship between hyperuricemia and incident RRT and mortality among patients with CKD could not be confirmed in this cohort study. Although several small studies have reported that treatment with the uric acid-lowering drug allopurinol slowed the progression of kidney disease and reduced cardiovascular risk in patients with CKD,[39,40] this effect needs to be confirmed in a large-scale prospective study. Second, the events of RRT and mortality among our patients were collected from our hospital records.

Third, this was a retrospective cohort study. Thus, we may have underestimated the event rates among our patients. In a large prospective cohort study[24] in which the mortality data were obtained from death certificate codes in Taiwan, the all-cause mortality rate among patients with CKD in stages 3-5 (n = 26,757) was 16.2% over a median follow-up period of 7.5 years. The all-cause mortality rate among our patients was 8.1% over a median follow-up period of 2.5 years. Although patients with CKD in stages 3-5 in the aforementioned study[24] were younger (mean age around 61.9 years) than our patients (mean age 71.0 years), the extent of underestimation of mortality events in our study was likely to have been small, and therefore probably did not confound the results.

Lastly, we investigated patients with CKD in stages 3-5 in this study. Whether our findings may be generalized to patients with early stages of CKD needs further investigation.

CONCLUSION

We demonstrated that in patients with CKD in stages 3-5, hyperuricemia was associated with higher risk of incident RRT and all-cause mortality (mainly non-cardiovascular death). Further studies are needed, to investigate whether treatment with uric acid-lowering drugs in such patients would improve their outcomes.

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What do Cochrane systematic reviews say about interventions for age-related macular degeneration?

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ABSTRACT

BACKGROUND: Age-related macular degeneration (AMD) is the third largest cause of blindness worldwide, accounting for 8.7% of all cases. A considerable number of preventive or therapeutic interventions have been used for AMD.
OBJECTIVE: This study presents a critical view of the interventions that have been assessed through Cochrane systematic reviews.
DESIGN AND SETTING: Review of systematic reviews, conducted in the Discipline of Evidence-Based Medicine, Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP).
METHODS: Review of Cochrane systematic reviews about interventions for AMD.
RESULTS: The 18 systematic reviews included assessed the effects of surgical techniques, laser/photo/radiotherapy, intravitreal injections, systemic drugs and phytotherapy/vitamins/supplements.
CONCLUSION: The Cochrane systematic reviews found evidence that use of bevacizumab, ranibizumab, pegaptanib, laser photocoagulation, photodynamic therapy and multivitamin compounds may present some benefits for treating AMD. There was insufficient evidence for supporting the use of macular translocation, submacular surgery, steroid implantation, radiotherapy, intravitreal aflibercept, interferon alfa, statins or omega-3 fatty acids for treating AMD; or the use of multivitamin antioxidant vitamins or mineral supplementation for preventing AMD. Future randomized controlled trials are imperative to reduce the uncertainty in several clinical questions regarding AMD.

INTRODUCTION

Age-related macular degeneration (AMD) is a degenerative disease of the macula (central region of the retina) that causes loss of central vision. This type of vision is essential for performing activities of daily living.[1]

AMD is the third largest cause of blindness worldwide, accounting for 8.7% of all cases of definitive loss of vision.[1] Currently, 15% to 24% of the population over the age of 65 years are affected by the early stages of AMD.[2]

AMD is differentiated into the early (often asymptomatic) or intermediate stages with drusen (amorphous extracellular sediments in the retina) and characteristic pigmentary changes, and the late stages. For clinical purposes, the late stages of AMD have been classified as dry (non-neovascular and atrophic) or wet (neovascular and exudative). In the wet stages, new blood vessels can lead to leakage and tissue lesions.[3] Although the neovascular form represents only 10% of the disease burden, it is responsible for 90% of AMD-related blindness.

A considerable number of preventive or therapeutic interventions are available and have been used for both types of AMD. This study presents a critical view of the interventions that have been assessed through Cochrane systematic reviews (SRs).

OBJECTIVE

To synthetize and present the results from Cochrane SRs assessing interventions for preventing and treating age-related macular degeneration.

METHODS

Design and setting

We carried out a narrative review of Cochrane SRs in the Discipline of Evidence-Based Medicine of Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP).

This manuscript was elaborated for the section Cochrane Highlights. This initiative is a formal collaboration between the São Paulo Medical Journal and Cochrane, and it is supported by Cochrane Brazil. The aim of this initiative is to disseminate the evidence from Cochrane SRs.

Inclusion criteria

Types of studies

We included only the latest published version of Cochrane SRs. We did not consider protocols, or any SR marked as "withdrawn" in the Cochrane Database of Systematic Reviews (CDSR).

Types of participants

In relation to reviews examining therapeutic methods, we considered any participant with the diagnosis of AMD, as defined by the review authors' criteria. SRs including cases of AMD and other clinical situations were included only if the subset of data on AMD participants was provided separately. In relation to reviews examining preventive methods, no restrictions on participants were applied.

Types of intervention

We considered any surgical or pharmacological (local or systemic) intervention, compared with placebo, no intervention or any other intervention.

Type of outcomes

We considered all clinical and laboratory outcomes addressed by the SRs.

Search for reviews

We carried out a systematic search in the Cochrane Database of SRs (via Wiley) on January 8, 2019. The search strategy is presented in **Table 1**.

Selection of systematic reviews

The selection process was performed by two authors (RLP and RR), who independently assessed all titles and abstracts that had initially been obtained through the electronic search for potential reviews. These authors confirmed the eligibility of these SRs by assessing their full texts. Any divergences in the selection process were resolved through reaching a consensus.

Presentation of the results

We summarized and presented the following characteristics from the SRs that were included: PICOs (population, intervention, comparator and outcomes), goals, methods, main findings, certainty of evidence in accordance with the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation)[4] and conclusions.

RESULTS

Search results

The initial search retrieved 90 abstracts of systematic reviews (SRs), and 18 of them fulfilled our inclusion criteria and were considered for the analysis.[5-22]

Results from systematic reviews

The 18 SRs included assessed the effects of surgical techniques (n = 4),[5-8] laser/photo/radiotherapy (n = 4),[9-12] intravitreal injections (n = 3),[13-15] systemic drugs (n = 3)[16-18] and phytotherapy/vitamins/supplements (n = 4)[19-22] for preventing AMD or treating participants with AMD. The main results from the SRs that were included and the certainty of the evidence (based on the GRADE approach)[4] are presented in **Table 2**. A brief narrative synthesis of each SR is presented below.

Surgical techniques

1. Implantable mini-telescope for diminishing loss of vision

A mini-telescope is an implantable ophthalmic device for amending visual acuity after impairment of vision due to AMD. It has been used to enlarge objects in the central visual field and focus them onto healthy areas of the retina, thus making it possible to view objects that otherwise could not be seen. This review[5] assessed the effects of an implantable ophthalmic mini-telescope in individuals with late or advanced AMD, but no randomized clinical trials (RCTs) or quasi-RCTs were found.

Table 1. Search strategy

#1 MeSH descriptor: [Macular Degeneration] explode all trees
#2 (Maculopathies, Age-Related) or (Macular Degeneration, Age-Related) or (Age Related Maculopathies) or (Age Related Maculopathy) or (Macular Degenerations, Age-Related) or (Age-Related Macular Degeneration) or (Macular Dystrophies) or (Dystrophies, Macular) or (Degeneration, Macular) or (Age-Related Macular Degenerations) or (Age-Related Maculopathy) or (Macular Degenerations) or (Maculopathies, Age Related) or (Dystrophy, Macular) or (Age-Related Maculopathies) or (Maculopathy, Age-Related) or (Macular Dystrophy) or (Degenerations, Macular) or (Degenerations, Age-Related Macular) or (Age Related Macular Degeneration) or (Degeneration, Age-Related Macular) or (Maculopathy, Age Related)
#3 #1 or #2
Filters: in Cochrane Reviews; *in Title, Abstract, Keywords*

Table 2. Characteristics, main results and certainty of evidence of the systematic reviews included

Surgical interventions				
Intervention	Population (sample)	Comparison	Main findings	Certainty of evidence (GRADE)*
Full macular translocation[6]	AMD (n = 50)	Full macular translocation versus PDT	Benefit of macular translocation: • Gain of three or more lines in the ETDRS test • Change of visual acuity • Change of near visual acuity score No difference between interventions groups: • Progression to loss of vision • Change of contrast sensitivity • Recurrence of choroidal neovascularization Benefit of PDT: • Complications were minor and less frequent in PDT Time point for measurement: 12 months	NA
Submacular surgery[7]	AMD with or without blood in the macula (n = 890)	Submacular surgery versus observation	No difference between groups: • Progression to loss of vision • Visual gain Benefit of observation: • Cataracts needing surgery • Retinal detachment Time point for measurement: 12 months	High Low NA NA
Steroid implantation (intra- and peri-ocular)[8]	AMD (n = 809)	Anecortave acetate versus placebo	• Progression to loss of vision: benefit over placebo for anecortave 15 mg**, but not for 3 mg or for 30 mg	NA
		Triamcinolone acetonide versus placebo	• Progression to loss of vision: no difference between groups	NA
		Anecortave acetate versus PDT	• Progression to loss of vision: no difference between groups Time point for measurement: 12 months	NA
Laser/photo/radiotherapy				
Intervention	Participants	Comparisons	Main findings	Certainty of evidence (GRADE)*
Laser photocoagulation	AMD with drusen (n = 2,159/3,580 eyes)[9]	Laser versus no intervention	Benefit of laser: • Reduction of drusen • Risk of choroidal neovascularization • Risk of geographic atrophy • Progression to loss of vision	High High Low Moderate
	AMD (n = 2,064)[10]	Direct photocoagulation of the entire choroidal neovascularization versus no intervention	Benefit of photocoagulation: • Progression to loss of vision at 24 months Benefit of no intervention: • Progression to loss of vision at three months	NA
		Perifoveal photocoagulation versus observation	Benefit of photocoagulation: • Progression to loss of vision at 24 months	NA

Table 2. Continuation.

Intervention	Participants	Comparisons	Main findings	Certainty of evidence (GRADE)*
PDT[11]	AMD (n = 1,429)	PDT with verteporfin versus PDT with 5% dextrose in water	Benefit of PDT/verteporfin • Progression to loss of vision Time point for measurement: 12 and 24 months	High
			No difference between groups: • Risk of severe decrease in visual acuity Time point for measurement: one week	Moderate
			Benefit of PDT/dextrose: Infusion-related back pain: higher with PDT/verteporfin (RR 9.93; 95% CI 2.82 to 35.02; 4 RCTs; 1439 participants; high certainty of evidence) Time point for measurement: one week	High
Radiotherapy[12]	AMD (n = 1,154)	External beam radiotherapy or plaque brachytherapy versus no intervention	Benefit of radiotherapy: • Progression of loss of vision at 24 months (only considering loss of six or more lines)	Low
			No difference between groups: • Progression of loss of vision at 24 months	Moderate

Intravitreal injections of anti-VEGF				
Intervention	**Participants**	**Comparisons**	**Main findings**	**Certainty of evidence (GRADE)***
Aflibercept[13]	Neovascular AMD with active subfoveal choroidal neovascular lesions (n = 2,412)	Aflibercept versus no intervention	No difference between groups: • Change in best-corrected visual acuity (BCVA) • Gain of 15 or more letters of BCVA • Loss of 15 or more letters of BCVA • Serious systemic adverse events Time points for measurement: 12 and 24 months	NA High High Moderate
Bevacizumab ***[14]	AMD (n = 159)	Bevacizumab versus standard therapy	Benefit of bevacizumab: • Gain of 15 or more letters of visual acuity at one year • Progression to loss of vision	Moderate Moderate
			No difference between groups: • Serious systemic adverse events	Low
Ranibizumab***[14]	AMD (n = 1,322)	Ranibizumab versus sham	Benefit of ranibizumab: • Progression to loss of vision at one year • Serious adverse events	High Moderate
Pegaptanib[14]	AMD (n = 1,186)	Pegaptanib versus sham	Benefit of pegaptanib: • Gain of 15 or more letters of visual acuity at one year • Loss of fewer than 15 letters of visual acuity at one year	High High
			No difference between groups: • Serious adverse events	Moderate

Systemic medication				
Intervention	**Population**	**Comparisons**	**Main findings**	**Certainty of evidence (GRADE)***
Interferon alpha[17]	AMD (481 participants)	Interferon alpha versus placebo	Benefit of placebo: • Progression to loss of vision at 52 weeks	NA
Statins[18]	Older people at high risk of developing AMD (drusen observed) (n = 144)	Simvastatin versus placebo	No difference between groups: • Visual acuity at three months of treatment, and at 45 days and 12 months after the completion of treatment • Drusen score at 12 months • Progression of AMD at 36 months • Adverse events	NA NA Low NA

Table 2. Continuation.

Phytotherapy/vitamins/supplements				
Intervention	Population	Comparisons	Main findings	Certainty of evidence (GRADE)*
Beta-carotene	Healthy individuals (n = 22,083)[19]	Beta-carotene versus placebo	No difference between groups: • Overall risk of AMD • Risk of late AMD Harm with beta-carotene: • Risk of lung cancer in people who smoked	High Moderate High
Lutein and/or zeaxanthin	AMD[20]	Lutein and/or zeaxanthin versus placebo	No difference between groups: • Progression to late AMD • Progression to loss of vision • Quality of life evidence • Mortality	Low Low Moderate Very low
Multivitamins	Healthy men (n = 14,233)[19]		Harm from multivitamins: • Overall risk of AMD • Risk of skin rashes No difference between groups: • Risk of late AMD Benefit of multivitamins: • Progression to late AMD • Progression to loss of vision • Quality of life	Moderate Moderate Moderate Moderate Moderate Low
	AMD (n = 2,445)[20]		No difference between groups: • Mortality Harm from multivitamins: • Risk of yellow skin	Very low Very low
Omega-3 fatty acids[22]	AMD (n = 2,343)		No difference between groups: • Progression to advanced AMD • Progression to loss of vision at 24 and 36 months • Adverse events	High Moderate High
Vitamin C	Healthy men (n = 14,236)[19]	Vitamin C versus placebo	No difference between groups: • Overall risk of AMD • Risk of late AMD	High Moderate
Vitamin E	Healthy individuals (n = 55,614)[19]	Vitamin E versus placebo	No difference between groups: • Overall risk of AMD: • Risk of late AMD • Overall risk of adverse events Harm from vitamin E: • Risk of hemorrhagic stroke	High Moderate NA Low
	AMD (n = 998)[20]	Vitamin E versus placebo	No difference between groups: • Progression to late AMD • Progression to loss of vision • Withdrawal due to adverse events No serious adverse events	Very low Low Very low
Zinc[20]	AMD (n = 3,790)	Zinc versus placebo	Benefit from zinc: • Progression to late AMD • Progression to loss of vision	Low Moderate

AMD = age-related macular degeneration; ETDRS = Early Treatment Diabetic Retinopathy Study; NA = not assessed; PDT = photodynamic therapy; RCTs = randomized clinical trials; VEGF = anti-vascular endothelial growth factor.

*GRADE (Grading of Recommendations Assessment, Development and Evaluation). This system assesses the certainty of the body of evidence. High certainty of evidence means that there is high confidence that the estimated effect is near to the true effect; moderate certainty means that it is very likely that the estimated effect is close to the real effect, but there is a possibility that it is not; low certainty means that there is only limited confidence in the effect estimate; and very low certainty means that the true effect is likely to be substantially different from the estimated effect.

**statistical benefit (clinical benefit is questionable); ***for ranibizumab versus bevacizumab, see the reviews relating to this, in the text.

The authors could not draw any conclusions regarding this clinical question. There is one ongoing RCT that is comparing the OriLens intraocular telescope with standard low-vision training for coping with end-stage AMD. The results from this trial are expected in 2020.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011140.pub2/full.

2. Macular translocation

Macular translocation is a surgical procedure that includes displacement of the retina to a less-damaged area, which could improve vision. This review[6] aimed to assess the effects of this procedure for maintaining or improving vision in patients with AMD. The authors found only one small open study (n = 50) that compared full macular translocation versus photodynamic therapy (PDT) for AMD. After one year, macular translocation presented some benefit regarding the following outcomes:

- Gain of three or more lines read during the ETDRS (Early Treatment Diabetic Retinopathy Study) test (risk ratio [RR] 21; 95% confidence interval [CI] 1.30 to 340.02);
- Change of visual acuity (mean difference [MD] 14.60; 95% CI 5.39 to 23.81);
- Change of near visual acuity score (MD 17.80; 95% CI 3.98 to 31.62).

However, there was no difference between the interventions groups regarding these other outcomes:

- Progression of loss of vision (loss of three or more lines) (RR 0.56; 95% CI 0.22 to 1.43);
- Change of contrast sensitivity (MD: one letter favoring translocation; 95% CI -3.51 to 5.51);
- Recurrence of choroidal neovascularization (RR 1.56; 95% CI 0.83 to 2.91).

Complications were minor and less frequent in the PDT group. The complications observed in the macular translocation group included: retinal detachment (6/25 patients), diplopia requiring prismatic correction (5/25 patients), macular edema (11 eyes; six of them required surgery for retinal detachment) and need for muscle surgery (23 eyes).

The authors concluded that the current evidence was insufficient for them to be able to recommend macular translocation for AMD, which is also associated with significant harm. This technique is complicated and long surgical training is needed in order to be able to perform it.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006928.pub2/full.

3. Submacular surgery for choroidal neovascularization

Surgical removal of the submacular tissue underlying the macula (within which small new blood vessels grow) might limit the development of AMD. This review[7] aimed to assess the effectiveness of submacular surgery for preserving or improving vision in individuals with AMD and included three RCTs. Two RCTs comparing submacular surgery for AMD with observation were found, including patients with (n = 336) or without (n = 454) blood in the macula. After one year, no difference was found between the intervention arms in relation to:

- Prevention of loss of vision (RR: 0.96; 95% CI 0.84 to 1.09; risk difference [RD] -2%; 95% CI -10% to 5%; excluding a large benefit from surgery, in terms of absolute risk in this sample; high certainty of evidence);
- Probability of visual gain (RR: 1.06; 95% CI 0.75 to 1.51; RD 1%; 95% CI -4% to 6%; excluding a large benefit from surgery, in terms of absolute risk in this sample; low certainty of evidence).

However, cases of cataracts requiring surgery (RR: 8.69; 95% CI: 4.06 to 18.61) and retinal detachment (RR: 6.13; 95% CI: 2.81 to 13.38) were more frequent in the surgical group. Detachment was observed in 5% of the participants without extensive blood under the macula and in 18% of those with this.

In another small pilot RCT, submacular surgery was compared with laser photocoagulation (n = 70) and no difference was found for any of the outcomes measured.

The authors of the SR concluded that submacular surgery for choroidal neovascularization did not provide any benefit for individuals with AMD.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006931.pub2/full.

4. Steroid implantation (intra- and peri-ocular)

Steroids have anti-inflammatory and antiangiogenic properties that can be useful for treating AMD. This review[8] aimed to assess the effects of intra- and peri-ocular antiangiogenic steroids for treating neovascular AMD. Three clinically heterogeneous RCTs (809 participants) were found, comparing: (a) different doses of anecortave acetate versus placebo; (b) triamcinolone acetonide versus placebo; and (c) anecortave acetate versus photodynamic therapy (PDT). For the main outcome, i.e. progression to loss of vision (loss of three or more lines of vision), the results at 12 months were the following:

- Anecortave acetate (3 mg) versus placebo: no difference between the interventions (RR 0.8; 95% CI 0.45 to 1.45);
- Anecortave acetate (15 mg) versus placebo: slight difference favoring steroids, but clinical relevance needs to be discussed (RR 0.45; 95% CI 0.21 to 0.97);

- Anecortave acetate (30 mg) versus placebo: no difference between the interventions (RR 0.91; 95% CI 0.52 to 1.58);
- Triamcinolone acetonide versus placebo: no difference between the interventions (RR 0.97; 95% CI 0.74 to 1.26);
- Anecortave acetate versus PDT: no difference between the interventions (RR 1.08; 95% CI 0.91 to 1.29)

The authors of the SR did not find any evidence that antiangiogenic steroids prevented loss of vision due to AMD.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005022.pub3/full.

Laser/photo/radiotherapy

5. Laser photocoagulation of drusen in AMD

Drusen, which consist of an amorphous yellowish aggregate that accumulates under the retina, are considered to be risk factors for developing AMD. This review[9] evaluated the effects of laser photocoagulation of drusen in AMD and found 11 RCTs (2159 participants; 3580 eyes) comparing laser with control (no intervention). Overall, the risk of bias in the studies included was low. The secondary outcome of "probability of reducing the drusen" was reached more frequently with laser (OR 9.16; 95% CI 6.28 to 13.4; 3 RCTs; 570 participants; 944 eyes; high certainty of evidence). The results relating to primary and other secondary outcomes showed that there was no benefit from laser, considering the following:

- Risk of choroidal neovascularization at two years of follow-up: odds ratio (OR) 1.07; 95% CI 0.79 to 1.46; eleven RCTs; 2159 participants; 3580 eyes; high certainty of evidence.
- Risk of geographic atrophy: OR 1.30; 95% CI 0.38 to 4.51; two RCTs; 148 participants; 148 eyes; low certainty of evidence.
- Progression to loss of vision (loss of three or more lines of visual acuity): OR 0.99; 95% CI 0.81 to 1.22; nine RCTs; 2002 participants; 2386 eyes; moderate certainty of evidence.

No further adverse events (apart from development of choroidal neovascularization, geographic atrophy or loss of vision) were reported.

The authors of this SR concluded that laser photocoagulation of drusen led to their disappearance but did not reduce the risk of developing choroidal neovascularization, geographic atrophy or loss of visual acuity. Ongoing RCTs are being conducted to evaluate the effects of extremely short laser pulses (i.e. nanosecond laser treatment) and the results will be available in the future.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006537.pub3/full.

6. Laser photocoagulation for AMD

This review[10] aimed to assess the effects of laser photocoagulation for treating neovascular AMD and included 15 RCTs (2,064 participants) assessing the following: direct photocoagulation of the entire choroidal neovascularization (11 RCTs); perifoveal photocoagulation (one RCT); and grid photocoagulation (three RCTs). In 12 trials, the control group consisted of observation alone.

In comparing direct photocoagulation of the entire choroidal neovascularization versus no intervention, the risk of progression to loss of vision (loss of six or more lines of visual acuity) was found to be more frequent in the photocoagulation group at three months (RR 1.41; 95% CI 1.08 to 1.82), but less frequent at two years (RR 0.67; 95% CI 0.53 to 0.83). In comparing perifoveal photocoagulation versus observation, a benefit from the intervention was observed at two years (RR 0.36; 95% CI 0.18 to 0.72). For other comparisons, no other differences were found.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004763.pub2/full.

7. Photodynamic therapy (PDT)

PDT has been investigated as an option for managing neovascular membranes in cases of AMD without affecting the retina. This review[11] aimed to assess the effects of PDT for neovascular revascularization in patients with AMD and included four trials (1429 participants) comparing PDT with verteporfin versus PDT with 5% dextrose in water. Verteporfin (Visudyne) is a benzoporphyrin derivative that is used as a photosensitizer during PDT. The main findings from this review were the following:

- Progression of loss of vision at 24 months:
  - Loss of three or more lines of visual acuity: benefit with PDT/verteporfin (RR 0.80; 95% CI 0.73 to 0.88; four RCTs; 1381 participants; high certainty of evidence);
  - Loss of six or more lines on visual acuity test: benefit with PDT/verteporfin (RR 0.66; 95% CI 0.56 to 0.83; four RCTs; 1381 participants; high certainty of evidence).

The results at 12 months were similar to those at 24 months.
- Adverse outcome, within one week of treatment:
  - Risk of severe decrease of visual acuity: no difference between interventions (RR 3.75; 95% CI 0.87 to 16.12; three RCTs; 1075 participants; moderate certainty of evidence);
  - Infusion-related back pain: higher with PDT/verteporfin (RR 9.93; 95% CI 2.82 to 35.02; four RCTs; 1439 participants; high certainty of evidence).

Two other trials compared different treatment regimens: (a) standard versus delayed light application; and (b) retreatment every

two months versus every three months. No difference in effectiveness was found in either of these.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002030.pub3/full.

8. Radiotherapy

This review[12] had the aim of assessing the effects of radiotherapy for treating AMD. The review included 13 RCTs (1,154 participants) on external beam radiotherapy (dosages from 7.5 to 24 Gy) and one RCT (n = 88) on plaque brachytherapy (15 Gy at 1.75 mm for 54 minutes/12.6 Gy at 4 mm for 11 minutes). The main findings comparing radiotherapy versus control were:

- Progression of loss of vision:
  - Loss of three or more lines on visual acuity test: no difference between the groups at 24 months (RR 0.8; 95% CI 0.63 to 1.03); four RCTs, 428 participants; low certainty of evidence) or at 12 months (RR 0.90; 95% CI 0.74 to 1.1; eight RCTs; 759 participants; moderate certainty of evidence);
  - Loss of six or more lines on visual acuity test: no difference between the groups at 24 months (RR 0.81; 95% CI 0.64 to 1.03; four RCTs; 428 participants; moderate certainty of evidence), but lower occurrence with radiotherapy at 12 months (RR 0.81; 95% CI 0.44 to 0.87; seven RCTs; 576 participants; low certainty of evidence).

The frequency of adverse events was low and there were no reports of radiation retinopathy, optic neuropathy or malignancy.

The authors of this SR concluded that there was no convincing evidence that radiotherapy was an effective treatment for neovascular AMD.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004004.pub3/full.

Intravitreal injections

9. Aflibercept

Aflibercept is a biological drug that blocks the biological activity of vascular endothelial growth factor (VEGF) and inhibits abnormal growth of blood vessels. This review[13] assessed the effects of use of aflibercept for treating patients with AMD. Two RCTs, supported by the company that manufactures aflibercept, and comprising 2,457 participants with active subfoveal choroidal neovascular lesions, were included. The main findings were the following:

- Change in best-corrected visual acuity (BCVA): no difference between the groups at one year (MD -0.15 in Early Treatment

Diabetic Retinopathy Study [ETDRS] letters; 95% CI -1.47 to 1.17; two RCTs; 2412 participants; high certainty of evidence); and insufficient results for assessing the outcome at two years (MD 0.7 in ETDRS letters, but the data available were insufficient for calculation of the CI).

- Gain of 15 or more letters in BCVA test: no difference between the groups at one year (RR 0.97; 95% CI 0.85 to 1.11; two RCTs; 2412 participants; high certainty of evidence) or at two years (RR 0.98; 95% CI 0.85 to 1.12; two RCTs; 2412 participants; high certainty of evidence).
- Loss of 15 or more letters in BCVA test: no difference between the groups at one year (RR 0.89, 95% CI 0.61 to 1.30; two RCTs, 2412 participants; high certainty evidence).
- Serious systemic adverse events: no difference between the groups at one year (RR 0.99; 95% CI 0.79 to 1.25; two RCTs; 2419 participants; moderate certainty of evidence).
- Any serious ocular adverse event: no difference between the groups (RR 0.62; 95% CI 0.36 to 1.07; two RCTs; 2419 participants; moderate certainty of evidence).

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011346.pub2/full.

10. Anti-vascular endothelial growth factor

This review[14] assessed the use of anti-vascular endothelial growth factor in patients with AMD. This type of growth factor reduces proliferation of blood vessels, thus preventing AMD. Twelve RCTs were included (5,496 participants), comparing pegaptanib, ranibizumab or bevacizumab versus no administration of anti-vascular endothelial growth factor; and a comparison of ranibizumab versus bevacizumab.

Ranibizumab versus bevacizumab

- Visual acuity (assessed from the proportion of patients with a gain of 15 letters or more): no difference between the interventions after one year (RR 0.90; 95% CI 0.73 to 1.11; six RCTs; 2446 participants; high certainty of evidence);
- Progression to loss of vision (loss of 15 letters or more): no difference between the interventions after one year (RR 1.00; 95% CI 0.98 to 1.02; six RCTs; 2446 participants; high certainty of evidence);
- Number of serious systemic adverse events: higher with bevacizumab after one year (RR 1.27; 95% CI 1.06 to 1.52; 2597 participants; four RCTs; moderate certainty of evidence).

Pegaptanib versus sham

- Visual acuity (assessed from the proportion of patients with a gain of 15 letters or more): favored pegaptanib after one year

(RR 2.83; 95% CI 1.23 to 6.52; one RCT; 1,186 participants; high certainty of evidence);

- Progression to loss of vision (loss of 15 letters or more): favored pegaptanib after one year (RR 1.24; 95% CI 1.11 to 1.39; one RCT; 1,186 participants; high certainty of evidence);

- Proportion of participants with serious adverse events: no difference between the interventions after one year, although the estimate was very imprecise because of the low number of events (RR 1.25; 95% CI 0.93 to 1.70; one RCT; 1,190 participants; moderate certainty of evidence).

Ranibizumab versus sham

- Progression to loss of vision (loss of 15 letters or more): favored ranibizumab after one year (RR 1.53; 95% CI 1.41 to 1.64; three RCTs; 1,322 participants; high certainty of evidence);

- Proportion of participants with serious adverse events: no difference between the interventions after one year, but the evidence was imprecise and no important differences could be excluded (range of risk ratios [rRR] 0.17; 95% CI 0.01 to 4.24 for ischemic cardiomyopathy; 2.08; 95% CI 0.23 to 18.45 for myocardial infarction; two RCTs; 603 participants; moderate certainty of evidence).

Bevacizumab versus standard therapy

- Visual acuity (assessed from the proportion of patients with a gain of 15 letters or more): favored bevacizumab after one year (RR 7.80; 95% CI 2.44 to 24.98; two RCTs; 159 participants; moderate certainty of evidence);

- Progression to loss of vision (loss of 15 letters or more): favored bevacizumab after one year (RR 1.28; 95% CI 1.09 to 1.50; two RCTs; 159 participants; moderate certainty of evidence);

- Proportion of patients with serious systemic adverse events: no difference between the interventions after one year, but this result was very imprecise (RR 2.03; 95% CI 0.19 to 21.85; one RCT; 131 participants; low certainty of evidence).

The review authors concluded that the results indicated that there were benefits from use of anti-vascular endothelial growth factor, for patients with AMD. The assessment of adverse events was impaired by the low number of events.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005139.pub3/full.

11. Bevacizumab versus ranibizumab

This review[15] compared the systemic safety of bevacizumab versus ranibizumab and included nine RCTs (3,665 participants). There was no difference in the risk of death between the two drugs (RR 1.1; 95% CI 0.78 to 1.57; eight RCTs; 3,338 participants;

moderate quality of evidence). Regarding the number of serious systemic adverse events, no difference was found between the groups (RR 1.08; 95% CI 0.90 to 1.31; nine RCTs; 3,665 participants; low quality of evidence). These results were substantially different from the previous review, which found that use of bevacizumab led to a higher number of serious adverse events. This difference was mainly due to the difference in the number of RCTs included in the analysis (while the previous review only included four RCTs, this review included nine).

The authors of this SR concluded that there were no significant results that could support use of bevacizumab or ranibizumab.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011230.pub2/full.

Systemic medications

12. Complement inhibitors

This review[16] aimed to evaluate complement inhibitors for treating AMD. The authors found only two ongoing RCTs with no results available at time and therefore no numerical data assessing the effects of this intervention were included. So far, there is insufficient data for any conclusion to be reached regarding complement inhibitors for treating AMD and a future update of this review is warranted.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009300.pub2/full.

13. Interferon alpha

Interferon alpha is an antiangiogenic drug that inhibits migration and proliferation of vascular endothelial cells. This review[17] assessed the use of interferon alpha for treating AMD and included one RCT (481 participants). In comparison with placebo, use of interferon alpha was associated with worse results, consisting of loss of three or more lines of vision at 52 weeks (OR 1.60; 95% CI 1.01 to 2.53; one RCT; 391 participants). This review was published in 2006 and did not assessed the certainty of evidence.

Further RCTs are needed in order to increase confidence in this estimate. The next update of this review will probably assess the certainty of the evidence using the GRADE approach.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005138.pub2/full.

14. Statins

Recent studies have shown that AMD and atherosclerosis present some risk factors in common, and that statins may present

benefits for patients with AMD. This review[18] assessed the effects of statins for treating AMD and included two RCTs (144 participants) comparing simvastatin versus placebo among older people who were at high risk of developing AMD (drusen were observed in examinations). Overall, data regarding effectiveness and safety were underreported and the results from the RCTs were not pooled. The main findings were the following:

- Visual acuity: there was no difference between the groups at three months of treatment (decimal visual acuity 0.21 ± 0.56 for simvastatin versus 0.19 ± 0.40 for placebo; 30 participants); at 45 days after the completion of treatment (decimal visual acuity 0.20 ± 0.50 for simvastatin versus 0.19 ± 0.48 for placebo; 30 participants); or at 12 months (42 participants; numbers not provided).
- Drusen score and visual function results were reported to be similar between the groups at 12 months (42 participants), but no effect estimates or confidence intervals were provided.
- Progression of AMD: there was no difference between the groups at three years (OR 0.51; 95% CI 0.23 to 1.09; low certainty of evidence).
- Adverse events: only one RCT reported adverse outcomes, and it was stated that there were no differences between the groups regarding death, muscle aches or acute hepatitis.

The authors of this SR concluded that the current evidence from RCTs was insufficient to confirm that statins had any benefit with regard to preventing or delaying the onset or progression of AMD.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006927.pub5/full.

Phytotherapy/vitamins/supplements

15. Antioxidant vitamins and mineral supplements for prevention
Observational studies have suggested that a diet enriched with antioxidant vitamins (carotenoids and vitamins C and E) or minerals (selenium and zinc) may reduce the risk of development and progression of AMD. This review[19] assessed the effects of taking antioxidant vitamins and/or mineral supplements with regard to prevention of AMD, and it included five RCTs (76,756 participants) with low risk of bias.

Vitamin E versus placebo
- Overall risk of AMD: no difference between the groups (RR 0.97; 95% CI 0.90 to 1.06; four RCTs; 55,614 participants; high certainty of evidence);
- Risk of late AMD: no difference between the groups (RR 1.22; 95% CI 0.89 to 1.67; four RCTs; 55,614 participants; moderate certainty of evidence);

- Adverse events: two RCTs reported similar numbers of adverse events for both groups. A third RCT reported that there was higher risk of hemorrhagic strokes in the vitamin E group (HR 1.74; 95% CI 1.04 to 2.91; low certainty of evidence).

Beta-carotene versus placebo
- Overall risk of AMD: no difference between the groups (RR 1.00; 95% CI 0.88 to 1.14; two RCTs; 22,083 participants; high certainty of evidence);
- Risk of late AMD: no difference between the groups (RR 0.90; 95% CI 0.65 to 1.24; two RCTs; 22,083 participants; moderate certainty of evidence);
- Adverse events: use of beta-carotene was associated with increased risk of lung cancer among people who smoked (high certainty of evidence).

Vitamin C versus placebo
- Overall risk of AMD: no difference between the groups (RR 0.96; 95% CI 0.79 to 1.18; one RCT; 14,236 men; high certainty of evidence);
- Risk of late AMD: no difference between the groups (RR 0.94; 0.61 to 1.46; one RCT; 14,236 men; moderate certainty of evidence).

Multivitamin (Centrum Silver) versus placebo
Centrum Silver is composed of zinc (15 mg), vitamin E (45 IU), vitamin C (60 mg), beta-carotene (5000 IU), vitamin A (20% as beta carotene), folic acid (2.5 mg), vitamin B6 (50 mg) and vitamin B12 (1 mg).
- Overall risk of AMD: slightly higher with multivitamin (RR 1.21; 95% CI 1.02 to 1.43; one RCT; 14,233 men; moderate certainty of evidence);
- Risk of late AMD: no difference between the groups (RR 1.22; 95% CI 0.88 to 1.69; one RCT; 14,233 men; moderate certainty of evidence);
- Adverse events: skin rashes were slightly more frequent in the multivitamin group (HR 1.08; 95% CI 1.01 to 1.15; moderate certainty of evidence).

The authors of this SR concluded that vitamin E, beta-carotene, vitamin C and the multivitamin (Centrum Silver) did not reduce the risk of developing AMD. There was no evidence regarding other antioxidant supplements, such as lutein and zeaxanthin. Although vitamin supplements are commonly assumed to be safe, they may have harmful effects. Hence, sound evidence of benefit is needed before they can be recommended.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000253.pub4/full.

16. Antioxidant vitamins and mineral supplements for treatment

This review[20] assessed the effects of taking antioxidant vitamins and/or mineral supplements on the progression of AMD and included 19 RCTs (76,756 participants) with low or unclear risk of bias.

Multivitamins versus placebo/no treatment

- Progression to late AMD: less frequent with multivitamins (OR 0.72; 95% CI 0.58 to 0.90; 2445 participants; three RCTs; moderate certainty of evidence);
- Progression of loss of vision (loss of three or more lines on logMAR chart): lower with multivitamins (OR 0.77; 95% CI 0.62 to 0.96; one RCT; 1791 participants; moderate certainty of evidence);
- Quality of life (change in National Eye Institute Visual Function Questionnaire [NEI-VFQ] score, in which higher scores are better): higher with multivitamins (mean difference [MD] 12.30; 95% CI 4.24 to 20.36; one RCT; 110 participants; low certainty of evidence);
- Adverse events: no difference between the groups regarding mortality (HR 0.87; 95% CI 0.60 to 1.25), but participants in the antioxidant arms more commonly reported presenting yellow skin (8.3% versus 6.0%; P = 0.008; one RCT; 4203 participants; very low certainty of evidence).

Lutein and/or zeaxanthin versus placebo

- Progression to late AMD: no difference between the groups (RR 0.94; 95% CI 0.87 to 1.01; one RCT; 6891 eyes; low certainty of evidence);
- Progression to loss of vision (loss of three or more lines on logMAR chart): no difference between the groups (RR 0.98; 95% CI 0.91 to 1.05; one RCT; 6656 eyes; low certainty of evidence);
- Quality of life: no difference between the groups (MD 1.48; 95% CI -5.53 to 8.49 higher; one RCT; 110 participants; moderate certainty of evidence);
- Adverse events: no difference between the groups regarding mortality (HR 1.06; 95% CI 0.87 to 1.31; one RCT; very low certainty of evidence).

Vitamin E versus placebo

- Progression to late AMD: no difference between the groups (RR 1.36; 95% CI 0.31 to 6.05; one RCT; 998 participants; very low certainty of evidence);
- Progression to visual loss (loss of three or more lines on logMAR chart): no difference between the groups (RR 1.04; 95% CI 0.74 to 1.47; one RCT; 1179 participants; low certainty of evidence);
- Adverse events: no serious adverse events were reported. No difference between the groups was found regarding withdrawal due to adverse effects (four versus seven), any adverse events (91 versus 83) or ocular adverse events (105 versus 90) (very low certainty of evidence).

Zinc versus placebo

- Progression to late AMD: slightly lower with zinc (OR 0.83; 95% CI 0.70 to 0.98; three RCTs; 3790 participants; low certainty of evidence);
- Progression to loss of vision (loss of three or more lines on logMAR chart): no difference between the groups (OR 0.87; 95% CI 0.75 to 1.00; two RCTs; 3791 participants; moderate certainty of evidence);
- Adverse events: gastrointestinal symptoms was more frequently reported as a reason for withdrawal in the zinc group (5/146 versus 2/140; p-value not provided). Anemia was more common in the zinc group (13.2% versus 10.2%; P = 0.004). However, serum hematocrit levels were similar between the groups.

The authors concluded that use of multivitamins, antioxidant vitamins and mineral supplementation may delay the progression of AMD. This finding was based on a single large trial, including only American individuals, and the external validity considering different populations is uncertain. Although vitamin supplements are commonly assumed to be safe, they may have harmful effects.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000254.pub4/full.

17. Gingko biloba

Ginkgo biloba extracts are used for treating some health conditions, including peripheral vascular diseases, and may present benefits for treating AMD. This review[21] assessed ginkgo biloba extract for patients with AMD and included two RCTs (119 participants). In these RCTs, it was reported that ginkgo biloba provided some benefits, but there was insufficient data to pool the results.

The outcomes reported in the RCTs were generally different from those of relevance for the review, and the safety results were very sparse. The certainty of evidence was not assessed. Further RCTs are needed in order to reduce the uncertainty of the evidence and to provide a basis for practical recommendations.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001775.pub2.

18. Omega-3 fatty acids

This review[22] assessed supplementation using omega-3 fatty acids and included two placebo-controlled RCTs (2343 participants). The main findings were the following:

- Progression to advanced AMD: no difference between the groups (HR 0.96; 95% CI 0.84 to 1.1; two RCTs; 2343 participants; high certainty of evidence);
- Progression to loss of vision (loss of three or more lines): no difference between the groups at 24 months (RR 1.14; 95% CI

0.53 to 2.45; one RCT; 236 participants; moderate certainty of evidence) or at 36 months (RR 1.25; 95% CI 0.69 to 2.26; one RCT; 230 participants; moderate certainty of evidence);

- Adverse events: no difference between the groups (RR 1.01; 95% CI 0.94 to 1.09; two RCTs; 2343 participants; high certainty of evidence).

The authors concluded that there was no evidence of benefits from use of omega-3 among patients with AMD.

For further details and to access all the analyses, see the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010015.pub3/full.

DISCUSSION

This review included 18 Cochrane systematic reviews (SRs) that evaluated three surgical techniques, three interventions based on laser/photo/radiotherapy, four different drugs for use in intravitreal injections, three systemic drugs and four complementary interventions for preventing or treating age-related macular degeneration (AMD). The following interventions may present some benefits for AMD: (a) use of bevacizumab, ranibizumab or pegaptanib; (b) laser photocoagulation; (c) photodynamic therapy; and (d) use of multivitamin compounds.

The Cochrane SRs found insufficient evidence to support use of the following: (a) macular translocation (which was also associated with considerable harm); (b) submacular surgery; (c) steroid implantation; (d) radiotherapy; (e) aflibercept; (f) interferon alpha; (g) statins; (h) multivitamins, antioxidant vitamins and mineral supplementation as preventive interventions; and (i) omega-3 fatty acids.

No published RCT was found assessing: (a) use of an implantable ophthalmic mini-telescope device for improving visual acuity after impairment of vision due to AMD (results from an ongoing trial are expected to be published in 2020); and (b) use of complement inhibitors.

Among the 18 SRs included, four did not assess the certainty of the body of evidence based on the GRADE approach, since they were developed before this approach became recommended as mandatory in the Cochrane Handbook. It is strongly desirable that SRs should be updated after two years have elapsed, or more frequently if new studies are available. Indeed, the lack of an approach of this nature for supporting SR conclusions is a factor that limits practical applicability.

We observed an issue involving the comparison between ranibizumab and bevacizumab, which was addressed through two different SRs and led to an overlapping of safety assessments. The first SR focused on the overall effects (benefits and harm) of any intravitreal anti-VEGF drug.[14] The second SR focused on safety outcomes for the single comparison of ranibizumab versus bevacizumab.[15] Mainly because of differences between the methodological assumptions used for each SR, the findings regarding serious adverse events were inconsistent between these two reviews. Overlapping of PICOs in Cochrane SRs needs to be avoided, and it is uncommon. Specifically, in this context, considering the debate around off-label use of bevacizumab for treating AMD, a second Cochrane SR was developed in an attempt to address safety concerns.

Additional ongoing Cochrane SRs addressing other interventions for treating AMD will be available over the coming months and may contribute towards expanding the body of evidence available for management of AMD.

Further well-designed and well-conducted randomized controlled trials are still necessary, in order to reduce the uncertainties regarding the clinical questions that surround AMD.

CONCLUSION

This review found 18 Cochrane systematic reviews that evaluated interventions for preventing or treating AMD. Overall, use of bevacizumab, ranibizumab, pegaptanib, laser photocoagulation, photodynamic therapy and multivitamin compounds may present some benefits for treating AMD. Further randomized controlled trials are still necessary, in order to reduce the uncertainties regarding most clinical questions that surround AMD.

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What do Cochrane Systematic Reviews say about conservative and surgical therapeutic interventions for treating rotator cuff disease? Synthesis of evidence

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ABSTRACT

BACKGROUND: Shoulder pain is considered to be the third largest cause of musculoskeletal functional alterations in individuals presenting pain during movement.

OBJECTIVE: The purpose of this synthesis of evidence was to identify the clinical effectiveness of conservative and surgical treatments reported in Cochrane systematic reviews among individuals diagnosed with rotator cuff disease.

DESIGN AND SETTING: Review of systematic reviews, conducted in the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP).

METHODS: This synthesis of evidence included systematic reviews that had been published in the Cochrane database. The inclusion criteria were that these systematic reviews should involve individuals aged ≥ 16 years with rotator cuff disease, comparing surgical procedures with or without associated nonsurgical procedures versus placebo, no treatment or other nonsurgical interventions.

RESULTS: Thirty-one systematic reviews were included, involving comparisons between surgical procedures and conservative treatment; procedures either combined or not combined with drugs, versus other procedures; and procedures involving exercises, manual therapy and electrothermal or phototherapeutic resources.

CONCLUSIONS: The findings suggest that strengthening exercises, with or without associated manual therapy techniques and other resources, were the interventions with greatest power of treatment over the medium and long terms, for individuals with shoulder pain. These had greater therapeutic power than surgical procedures, electrotherapy or photobiomodulation.

PROTOCOL REGISTRATION NUMBER IN THE PROSPERO DATABASE: ID - CRD42018096578.

INTRODUCTION

Shoulder pain is considered to be the third most important musculoskeletal complaint that leads individuals to seek some type of primary care. Its prevalence in the general population is 7% to 26%. Most complaints of shoulder pain relate to rotator cuff disease, which is responsible for 4.5 million cases per year, attended by healthcare professionals in the United States.[1,2]

The term "rotator cuff disease" is used to refer to a set of conditions, regardless of cause and specific area of the injury. It may encompass conditions ranging from partial to total ruptures, as well as tendinopathies and tendinosis.[3,4] This divergence in the definition of this term is closely related to the diversity of technical terms that have been described and used for such conditions. These have multifactorial causes (mechanical, biological and social factors) and, consequently, considerable influence on patients' performance.[3-5]

Rotator cuff injury leads to pain, functional impairment and psychological distress.[6-9] These conditions start a cascade of consequences involving increased symptoms and functional incapacity. The possibility of chronic injury caused by lack of ideal treatment for these types of lesions also needs to be considered. Chronicity often leads these individuals into scenarios of exclusion and worsening of the condition, both physically and mentally.[10,11]

OBJECTIVE

Thus, the purpose of this synthesis of evidence was to identify the clinical effectiveness of conservative and surgical treatments for individuals diagnosed with rotator cuff disease that are described in Cochrane systematic reviews.

METHODS

Design

This synthesis of evidence comprised a summary of systematic reviews that have been published in the Cochrane database. There were no restrictions on the date and language of publication of the studies included in this synthesis.

Inclusion criteria

Types of participants

Individuals aged ≥ 16 years with rotator cuff disease were considered, irrespective of the time of onset of the injury and the symptoms presented. Diagnostic confirmation of these participants' conditions was clarified in the body of the text. Systematic reviews involving only individuals with painful symptoms or any other symptom in the shoulder complex without diagnostic confirmation of rotator cuff disease were not considered for this synthesis of evidence.

Types of interventions

The interventions considered for this synthesis of evidence were the following: surgical procedures with or without associated nonsurgical procedures, compared with placebo, no treatment or other nonsurgical intervention; or nonsurgical procedures with or without associated surgical procedures, compared with placebo, no treatment or other non-surgical or surgical intervention.

The following studies were not included in this review: systematic reviews comparing two or more surgical procedures or techniques for shoulder problems (for example, open versus arthroscopic surgery) and systematic reviews that investigated the effects of revision surgeries on the shoulder complex or prosthesis placement in the glenohumeral joint.

Types of outcomes

We considered any outcomes (pain, function, range of motion etc.) that were found in the studies.

Types of comparison

The following comparisons regarding the intervention were considered: (1) surgical procedures versus conservative treatment; (2) procedures either combined or not combined with drugs, versus other procedures; and (3) comparisons between procedures involving exercises, manual therapy and electrothermal or phototherapeutic resources.

Search and study selection process

The search for systematic reviews was conducted between March 30, 2017, and February 3, 2019, by two authors (Franco ESB and Puga MES), using the official medical subject headings (MeSH) terminology, in the Cochrane Library database (via Wiley). The search strategy can be seen in **Table 1**. Two authors (Franco ESB and Mizusaki Imoto A) selected the studies, respecting the inclusion criteria described above. In cases of disagreement, discussions were held to arrive at a consensus. When this was not possible, the opinion of a third author was requested. Only reviews published in the Cochrane Library were included.

The selection process was carried out in two stages. Firstly, studies were selected according to their title and summary, using the PICOS criteria (population or problem, intervention, comparison, outcome and study design). Secondly, studies were selected from the full text. When the first step was deemed insufficient for the authors to make their decisions, the study was accessed and the analysis was based on the full text.

Data extraction was performed by two evaluators (Franco ESB and Mata V), from the original files of the systematic reviews, using a predetermined digital extraction sheet containing the following main points: year of publication, authors' names and name of periodical, number of primary studies included in the review, types and numbers of participants, interventions and outcomes, analysis of bias and adjustments made, details of intervention groups, duration and parameters of the study, follow-up period, assessment tools and, when present, statistical values expressed through meta-analysis, relative risk format, differences between standardized and non-standardized means or confidence intervals.

A single author (Franco ESB) used the Review Manager software (RevMan) 5.3 to compile all information extracted from the systematic reviews. For this review, the data were synthetized by the group of researchers involved (Franco ESB, Puga MES and Peccin S), using the RevMan 5.3 software. From the data extracted, subgroups of the systematic reviews with Cochrane methodology were created and a subdivision for each outcome was elaborated.

All the reviews included for the final synthesis incorporated the following features from the systematic reviews: project

Table 1. Search strategy

#1 MeSH descriptor: [Rotator Cuff Injuries] explode all trees
#2 Cuff Injury, Rotator or Injuries, Rotator Cuff or Injury, Rotator Cuff or Rotator Cuff Injury or Rotator Cuff Tears or Rotator Cuff Tear or Tear, Rotator Cuff or Tears, Rotator Cuff or Rotator Cuff Tendinosis or Rotator Cuff Tendinoses or Tendinoses, Rotator Cuff or Tendinosis, Rotator Cuff or Rotator Cuff Tendinitis or Rotator Cuff Tendinitides or Tendinitis, Rotator Cuff or Glenoid Labral Tears or Glenoid Labral Tear or Labral Tear, Glenoid or Labral Tears, Glenoid or Tear, Glenoid Labral or Tears, Glenoid Labral
#3 #1 OR #2

published a priori; selection and extraction of data from trials performed by two independent evaluators; electronic searches always performed using more than two sources, with search strategies presented in the body of the text; lists containing the primary studies included and excluded, with detailing of the characteristics of the studies included presented in the body of the text; analysis of the methodological quality of the primary studies through evaluation instruments; appropriate methods for combining the results of the primary studies, so as to ensure the homogeneity or heterogeneity of the final product; and conflicts of interest reported by the authors.

The quantitative analyses on continuous variables were grouped in terms of the mean difference (MD) or standardized mean difference (SMD) with the 95% confidence interval (CI). The heterogeneity presented was calculated in terms of I^2.

This study was approved by the Research Ethics Committee of the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP) under the number 4095131216 on January 16, 2017.

RESULTS

The search strategy found 783 studies in the Cochrane database, among which there were 31 systematic reviews, 9 protocols, 739 primary studies, one editorial and three clinical answers. In compliance with the inclusion criteria, eight studies were considered eligible for further qualitative analysis (**Table 2**).[1,12-18]

Table 2. Characteristics of the interventions and main findings from comparisons between them, seen in Cochrane systematic reviews in relation to the target population (i.e. individuals with rotator cuff disease)

Comparison	Results	Quality of evidence (GRADE)
Subacromial decompression versus conservative treatment	After 12 months of follow-up, there were no differences between the groups, in evaluations at 3, 6 and 12 months (outcome: function)	Not described
Corticosteroid versus placebo	Reduction of pain and improved function seen over the short term, favoring the group that used the drug.	Not described
Subacromial drugs guided via US versus undirected subacromial drugs	Pain reduction (after 6 weeks) and short-term active ROM improvement (after 1 and 2 weeks), favoring the group that used the guide	Moderate (pain after 6 weeks) Not described (active ROM)
Glycerin trinitrate versus placebo	Reduction favoring intervention within 24-48 hours after application	Low
Manual therapy + exercise versus exercise	Improvement of the pain and function symptoms for the group with manual therapy + exercise after 3 and 4 weeks	Not described
LLLT versus placebo	Reduction of pain and improvement of ROM after 2 and 3 weeks, favoring the LLLT group	Low (pain and active ROM after 2 and 3 weeks)
LLLT versus non-steroidal anti-inflammatory drugs	Reduction of pain after 2 weeks, favoring the LLLT group	Very low
TENS versus placebo	Reduction of pain after application, favoring the TENS group	Very low
Glucocorticoid + exercise versus TENS + exercise	Reduction of pain and improvement of function over the short term (1 week), favoring the group with drug + exercise	Not described
Naturopathy + medication versus exercise + manual therapy	Reduction of pain and improvement of function, favoring use of the naturopathic method, after 12 weeks	Low
*Diacutaneous fibrillation versus placebo	Pain reduction (immediately) and active ROM improvement, favoring the intervention group shortly after the procedure	Low
Massage versus no treatment	Reduction of pain and improvement of function, favoring the intervention group, after 2 weeks	Very low
FNP versus US	Pain reduction, favoring the intervention group shortly after the procedure (immediately)	Not described
Exercise versus subacromial decompression	After 12 months of follow-up, there were no differences between the groups, in evaluations at 6 and 12 months (outcome: pain and function)	Low (pain after 6 months) Low (function after 6 months)
Training based on exercise versus no treatment	Reduction of pain and improvement of function, favoring the intervention group, after 8 and 10 weeks	Very low (pain and function)
Specific exercises versus nonspecific exercises	Reduction of pain and improvement of function, favoring the specific group, after 3 months	High (pain and function after 3 months)
"Jing Luo" acupuncture versus traditional acupuncture	Improvement of the recovery level, favoring the "Jing Luo" method over the short term	Not described

*Diacutaneous fibrillation: a technique known as crocheting, in which therapeutic "hooks" are used.

PNF = proprioceptive neuromuscular facilitation; RCD = rotator cuff disease; ROM = range of motion; US = ultrasound; TENS = transcutaneous electrical nerve stimulation; LLLT = low-level laser therapy.

1) Surgical procedures versus conservative treatment

Pain

One systematic review investigated comparisons between surgical and conservative treatments among 90 participants with a mean age of 44 years. The surgical procedure comprised subacromial decompression (bursectomy with partial resection of the antero-inferior extremity of the acromion and the coracoacromial ligament) via an arthroscopic approach, followed by a rehabilitation process composed of physiotherapy and exercise. The conservative treatment comprised a process of 19 visits over a 12-week period. No differences between the groups were observed in evaluations at the 3rd, 6th and 12th months after these treatments (MD -4.6, 95% CI -12.48 to 3.28; MD -1.4, 95% CI -10.43 to 7.63; and MD -4.5, 95% CI -13.73 to 4.73, respectively).[12]

Treatment success

Comparative analysis was done on the open-ended acromioplasty followed by a physiotherapy process that started three months after surgery, in relation to the conservative treatment, which comprised exercises and guidance for the participants identified in that review.[12] At the end of the 6th and 12th months, there were no significant differences between the groups regarding treatment success, defined as reduction of pain symptoms by more than 50%. After six months, the relative risk (RR) was 1.07 (95% CI 0.34 to 3.4); 5 patients out of a total of 21 (surgical group) and 4 patients out of a total of 18 (non-surgical group) were evaluated. After 12 months, the RR was 1.89 (95% CI 0.81 to 4.41); 11 patients out of a total of 21 (surgical group) and 5 patients out of a total of 18 (non-surgical group) were evaluated.

2) Procedures either combined or not combined with drugs versus other procedures

We found five different systematic reviews addressing this subject, from which we could extract data.

Pain and range of motion

One review[13] addressed application of corticosteroids subacromially, compared with placebo, among 160 subjects. A small benefit was found regarding pain relief, measured four weeks after the intervention, compared with the placebo group (SMD 0.83; 95% CI 0.39 to 1.26); and regarding function, measured after the intervention (SMD 0.63; 95% CI 0.20 to 1.06).

Use of different types of drug application was assessed in another review,[14] in which data were gathered from three studies on 207 participants that compared the effect of ultrasound-guided subacromial application of drugs with the effect of application of these drugs without the presence of a guiding device. Based on the data from the three studies together, pain improvement was observed six weeks after drug application in the group in which the injection was guided (SMD -0.80; 95% CI -1.46 to -0.14). However, these studies presented a high degree of heterogeneity (I² = 79%).

In the same review,[14] it was found that 40 participants who received ultrasound-guided subacromial application of drugs presented significant improvement in measurements of active abduction between one and two weeks after the application, compared with unguided application (MD 39.29; 95% CI 27.40 to 51.18).[14]

In a third review,[15] the effect of application of topical glycerin trinitrate at a dosage of 5 mg per day was investigated in comparison with placebo for pain (after 24 hours: SMD -1.05; 95% CI -1.52 to -0.0%), and in the treatment group, 58 patients (after 48 hours: SMD -3.50; 95% CI -3.96 to -3.04), compared with the placebo group. After 15 days, the intervention group presented more participants without any symptoms (RR 1.91; 95% CI 1.04 to 3.50), although the control group suffered a loss of 50% of the participants.[15]

In a fourth review,[1] glucocorticoid use in association with physical exercise was compared with use of transcutaneous electrical nerve stimulation (TENS) in association with physical exercise. There were 40 participants. It was seen that the results favored use of glucocorticoid in association with home exercises, evaluated after one week (MD 2.10; 95% CI 0.92 to 3.28). Thus, after one week of treatment, the criterion of "treatment success" (number of participants indicating improvement) favored the group that used the drug: TENS group 20% (4/20) versus glucocorticoid group 70% (14/20); RR 0.29; 95% CI 0.11 to 0.72.

Also in this fourth review,[1] use of a naturopathic intervention in association with acupuncture plus the drug phlogenzym was compared with use of physical exercises in association with manual therapy, among 85 participants. It was shown that, after 12 weeks, there were significant differences that favored the naturopathic group regarding pain (MD 1.30; 95% CI 0.56 to 2.04; versus MD 20.94; 95% CI 6.40 to 35.48).

In a fifth review,[16] favorable effects regarding pain reduction through application of low-intensity laser were observed in comparison with use of non-steroidal anti-inflammatory drugs after two weeks (MD 2; 95% CI 1.00 to 3.50) in a sample of 40 patients. Another outcome was that the low-intensity laser resulted in some improvement compared with the non-steroidal anti-inflammatory drug group, regarding active shoulder abduction (MD 20 degrees of range of motion, 95% CI 10.00 to 40.00); shoulder flexion (MD 14.99 degrees, 95% CI 5.00 to 29.00); and extension (MD 6 degrees, 95% CI 0.00 to 20.00).

3) Comparison between procedures involving exercises, manual therapy and electrothermal and phototherapeutic resources

One review[17] assessed whether inclusion of a manual therapy program for physical exercise would generate greater benefits in relation to pain, compared with physical exercise alone, in two

non-comparable studies. It was found that, after three and four weeks, mobilization performed in association with an exercise program gave rise to greater effects than were seen through exercise alone (MD -186.23, 95% CI -319.34 to -53.12; versus MD -32.07, 95% CI -58.04 to -6.10).[17]

In the same review,[17] it was shown that application of low-intensity laser in the intervention group was favorable in relation to pain, compared with the placebo group, after two and three weeks of application seen in the primary studies: after two weeks: MD 2.5, 95% CI 2.01 to 3.00; after three weeks: 83% (10/12) versus 42% (5/12); RR 2.00, 95% CI 0.98 to 4.09. Moreover, there was improvement of the active ranges of motion of abduction, flexion and extension, measured in degrees, respectively: MD 20°, 95% CI 10.00 to 40.00; MD 15°, 95% CI 5.00 to 29.00; and MD 6°, 95% CI 0.00 to 20.00.[17]

In another review,[16] application of electrical currents for pain control was assessed. This review, with 20 participants, showed that application of TENS gave rise to better results shortly after the intervention, compared with placebo. In the intervention group, the mean was 34.8 (ranging from 12 to 68 points on a 100-point scale); and in the control group, the mean was 64.5 (ranging from 38 to 95 points on a 100-point scale).

Another review[1] involved 50 participants, and it analyzed the use of diacutaneous fibrillation by means of hooks (crocheting) in comparison with placebo (same material, but done superficially) gave rise to a significant difference between the groups. Pain reduction was favored in the intervention group after a single treatment session of approximately 15 minutes (RR 2.14; 95% CI 1.06 to 4.34). These improvements (expressed in degrees) were observed in relation to active abduction (MD 7.30°, 95% CI 2.22° to 12.38°), active flexion (MD 11.40°, 95% CI 5.86° to 16.94°), active extension (MD 1.9°, 95% CI -1.46° to 5.26°) and active medial rotation (MD 3.10°, 95% CI 0.17° to 6.03°).[1]

In the same review,[1] use of therapeutic massage was compared with a group without any type of treatment, among 29 participants. The massage was applied for 15 to 20 minutes and was administered six times over a two-week period. An evaluation after this two-week period showed that the massage had beneficial effects, compared with the group that did not receive any intervention, in relation to pain (MD -22.00, 95% CI -41.19 to -2.81) and function (MD 7.20, 95% CI 2.20 to 12.20).

The same review[1] evaluated other interventions: the use of mobilization in association with the proprioceptive neuromuscular facilitation technique was compared with use of therapeutic ultrasound. Among the 30 participants in this review, use of mobilization in association with proprioceptive neuromuscular facilitation was shown to have a positive effect regarding pain reduction immediately after the intervention, in comparison with the other group (MD -1.43, 95% CI -1.97 to -0.89).

The review[1] also made a comparison between a training group and a non-training group, considering 120 participants. Favorable results regarding pain reduction were found in the training group that performed strengthening exercises, compared with the control group (non-training group), after 8 weeks (MD -1.90, 95% CI -3.27 to -0.53) and 10 weeks (MD -1.30, 95% CI -2.10 to -0.50); and regarding function after 8 weeks (MD -15.50, 95% CI -28.94 to -2.06) and after 10 weeks (MD 6.90, 95% CI 0.59 to 13.21).

Again in the same review[1], use of specific exercises for treating tendinopathies of rotator cuff structures was compared with a nonspecific exercise program, among 97 participants evaluated on a 100-point scale regarding two outcomes: pain and function. After three months, there was a significant difference favoring the specific exercise group in relation to three types of pain: general pain (MD -10.00, 95% CI -18.18 to -1.82), night pain (MD -12.00, 95% CI -21.87 to -2.13) and pain on motion (MD -16.00, 95% CI -26.57 to -5.4); and in relation to function (MD 20.00, 95% CI 11.55 to 28.45). The group that did specific exercises had better results, characterized by a decrease in the symptoms (RR 2.87, 95% CI 1.66 to 4.96) and a smaller number of patients who needed to undergo surgery, 3 and 12 months after the treatment started (RR 0.37, 95% CI 0.22 to 0.64).

The same review[1] also compared the use of physical exercise in association with manual therapy, with non-treatment. Among the 85 participants in this review, favorable results regarding improved function were found in the intervention group six months after the therapy (MD 19.35).

Supervised exercises were also compared with two interventions:[1] 1) use of arthroscopic subacromial decompression; and 2) use of low-intensity laser in placebo (off) format. This analysis involved 125 participants. At the end of six months, favorable results were found in the supervised exercise group, compared with the other groups, in relation to pain (MD 10, on a 35-point scale) and in relation to function (MD 10, on a 30-point scale).

In another review,[18] use of acupuncture was analyzed among 98 participants through comparison of the distribution of points between the "Jing Luo" method and the traditional method. The results showed that there was significant improvement in the recovery level through the Jing Luo method, compared with application of traditional acupuncture (RR 1.50, 95% CI 1.08 to 2.09).

DISCUSSION

Using the inclusion criteria initially described, eight systematic reviews were considered eligible for this synthesis. All of these reviews included primary studies that involved participants presenting either rotator cuff disease or nonspecific shoulder joint pain. As a form of standardization, only the studies in which there was diagnostic confirmation of rotator cuff dysfunctions were included for the final synthesis. There were 34 primary

studies that, following the analysis in the reviews, showed some kind of statistically significant benefit in comparisons between two groups of interventions, but in which the methodological quality was uncertain and, in many cases, was not discussed by the authors of the systematic reviews.

In comparing the wide range of interventions involving subjects with rotator cuff disease, the treatments used some years ago seem to be divergent from what was used more recently. Recent studies have shown scenarios that are more favorable for use of conservative treatments instead of surgical treatment. Invasive procedures such as acromioplasty in association with soft tissue resection have not shown any benefit for patients in terms of pain levels and functionality over the short, medium and long terms. Thus, in keeping with the most recent clinical guidelines, conservative treatment, based mainly on therapeutic exercises either combined or not combined with electrothermal therapeutic devices, has been shown to be more efficient for treating rotator cuff disease.[19]

The risk of bias in the primary studies that was ascertained in the present review was closely linked with the low numbers of participants in many of these studies. It was also especially linked with the short follow-up periods of many interventions, which were often only evaluated over periods of between 24 hours and six weeks.

Standardization of samples of participants such that these subjects all present the same condition (rotator cuff dysfunction in the present study) and definition of post-treatment evaluation periods may enable syntheses involving larger numbers of studies with high degrees of homogeneity and, consequently, higher methodological quality. This will facilitate completion of systematic reviews, since the numbers of homogeneous studies will be higher.

CONCLUSION

The present review identified eight Cochrane systematic reviews that had assessed conservative and surgical treatments for rotator cuff dysfunctions. The findings suggested that strengthening exercises with or without associated techniques for manual therapy and use of electrothermal or phototherapeutic resources were the interventions with greatest power of treatment for individuals with this condition, over the medium and long terms. These approaches had greater therapeutic power than surgical procedures, which had previously been considered to be the standard treatment for many patients.

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Clone journals: a threat to medical research

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Dear Editor,

The scholarly world is currently facing various anomalous threats that include paid publishers and fake journals. There has been enough debate about the challenges of predatory publishers, which encourage authors to publish their work in unreliable peer-reviewed journals, for a price.

A new discussion has spread across the scholarly world regarding fake journals. This is a recent phenomenon of even more malevolent fraud that has broken into the realm of the academic world. This phenomenon is also commonly known as "hijacked journals" or "clone journals."

Clone journal web pages are a counterfeit mirror of an authentic journal that exploit the title and ISSN of legitimate journals.[1] In contrast to predatory journals, clone journals are more likely to accept papers from authors, since they have developed as the mirror image of reputable journals, including their domain name. Usually, they receive massive attention through claiming that they have earned high impact factors from reputable indexing agencies such as Web of Science and Scopus.[1]

Some of these counterfeit journals actively chase authors by trawling through the latest conference proceedings to acquire the e-mail addresses of participants. These people are then approached through a modified e-mail message that announces a fake call for papers in a current issue of the journal. Careless authors may be duped by these solicitations into paying an open-access publication fee, trusting that their work is about to be published in a reputable journal.

Once these authors have paid the publication fee, they may lose ownership over their submission because they will have signed it over to the clone publisher. Consequently, they will be unable to get a refund or withdraw the article from publication. Since the article has now been "officially" published, it no longer meets the legitimate criteria of most reputable journals, which have ethical guidelines regarding the submission process, which include a declaration that the article has not previously been published. In this regard, clone journals present a serious threat to the integrity of scientific publishing and place a big question mark on the peer review process.

The main apprehension regarding this new trend is that unreviewed manuscripts that are published on these clone websites may become sources of medical practice and health policy and might be incorporated into systematic reviews on the clinical literature.[2] Another major concern that these clone journals may impose on clinical sciences is that their unreviewed outcomes could become sources for novel hypotheses. These can be considered to be a severe threat to the reliability and validity of future medical research.[2]

The prominent journals relating to medical science that have fallen victim to this phenomenon over time have included "*Revista Brasileira de Medicina do Esporte (RBME)*", "*Emergencies*", "*Journal of the American Medical Association*", "*Vitae Revista*", "*Terapevticheskii Arkhiv*" and "*Kardiologiya*".[3] Dadkhah and Borchardt inspected 2,442 papers in just five clones of journals in which researchers and scientist thought that they had published their articles during the first quarter of 2015.[4] According to their report, there are various unknown clone journals that continuously transform their web domain addresses. The cybercriminals behind this phenomenon seem to develop new clone journals every day, thus targeting increasing numbers of authors who may be unaware of this threat.[4]

Many researchers have highlighted a range of threats to the reliability of the scientific process of deceitful publishers, but none of them have addressed how these cybercriminals process

their clone mechanism. Although publishers pay their registration charges for web domain services on a regular basis, any failure to do so could allow a waiting cyber intruder to swoop in and steal a domain for their own purposes and, at the same time, divert the entire web traffic towards the clone journal website. In the cyber world, the phenomenon of stealing web domains is known as "web swooping".[5]

In conclusion, issuing warnings to the world of medical sciences regarding this new threat and conducting rigorous scientific reviews of citations to and from medical research articles could form the most realistic measures for combating this phenomenon. The council of science editors has suggested some cautionary red flags with the aim of educating the worldwide scholarly publishing community before sending manuscript submissions.[6] These include the need for authors to be aware of the following, regarding clone journals: (1) False claims to be members of the Committee on Publication Ethics (COPE) and the Open Access Scholarly Publishing Association (OASPA); (2) False declarations of indexation in databases such as SCOPUS and Web of Science (WOS); (3) Manuscript publication charges that are not visible; (4) Non-transparency of the peer-review process, with unrealistically short peer review-to-publication turnaround times (e.g. one week); (5) Non-existent publisher contact details: fake publishers do not have authentic postal addresses or any active telephone number; and (6) Counterfeit publishers have small numbers of articles per year but have enormous editorial boards, or vice versa.

Nonetheless, these precautionary steps require long-term measures that would enable use of stricter and more advanced techniques with the aim of eliminating these threats, along with effective copyright measures that can protect the reliability and validity of published medical science articles.

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Leprosy elimination – Still a long way to go

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Elimination of leprosy as a public health problem at the global level was considered achieved in the year 2000, when the registered prevalence reached less than one case of the disease per 10,000 inhabitants.[1] The Global Leprosy Strategy 2016-2020 published by the World Health Organization (WHO) established a goal of further reduction of the leprosy burden. Moreover, the primary target of the strategy moved from elimination towards an emphasis on early detection, reduction of grade-2 disabilities (i.e. visible impairments/deformities at the time of diagnosis) and reduction of transmission.[1]

Although detection of new cases has shown a modest decline over the last five years, the grade-2 disabilities rate among new cases has remained almost static, thus indicating a continued delay in detection.[1-3] Efforts have been made in Brazil regarding early detection, such as active case search and continuous medical education for primary care workers, using tools such as e-learning and telemedicine.[4]

The state of Sao Paulo had a prevalence rate of 0.36 cases of leprosy/10,000 inhabitants in 2017. Therefore, leprosy is not considered endemic in this state.[5] Nonetheless, we continue to make diagnoses of multibacillary patients showing grade-2 disabilities in our hospital, which is a quaternary-level care facility in the largest city in Brazil. We present images of multibacillary individuals diagnosed in our hospital over the last five years (**Figures 1** and **2**). All of these patients authorized the use of their images. As can be seen, these patients presented numerous cutaneous and neurological features that made it mandatory to consider leprosy at least as a differential diagnosis in any medical consultation. Furthermore, most of these patients received the diagnosis only when they reached our service.

Out of 121 patients diagnosed with leprosy in our hospital, 20 (17.2%) already presented grade-2 disabilities at the time of the diagnosis, while 56 (46.3%) had grade-1 disabilities. Most of our patients were not born in the city of São Paulo, but they had been living in the city for at least ten years. In the state of São Paulo, within the last five years, a total of 515 patients, corresponding to 13% of the new diagnosed cases, presented grade-2 disabilities at the time of the diagnosis. Since multibacillary patients are responsible for sustaining the endemic status of leprosy in Brazil, we can conclude that we are still failing to reach the goal of early diagnosis.

The possible causes of late diagnosis are the following: (i) lack of education: most of these patients had never completed their formal schooling; (ii) poor sanitary conditions: some of these patients were homeless or lived in slums; (iii) history of alcohol abuse; (iv) difficulties in accessing healthcare; and (v) lack of suspicion of the diagnosis of leprosy among doctors: even when such patients reach a healthcare service, it is rare for leprosy to be suspected.

Despite all the efforts by healthcare providers and despite healthcare policies that focus on the disease itself, political measures towards providing social advances remain necessary. If the abovementioned causes of late diagnosis persist, undiagnosed multibacillary patients will still face long delays before proper treatment is implemented and will probably end up transmitting the disease, thus sustaining its endemic status. Evaluation of households is still probably the most accessible way to conduct an active search for cases, especially in endemic areas.

Figure 1. Advanced multibacillary leprosy presenting with madarosis and diffuse face infiltration.

Figure 2. Lesions on extremities leading to reabsorption of distal phalanges and skin ulcers relating to the lack of protective sensitivity; numerous lepromas in lower left image.

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5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

The following are considered to be full-text original articles: clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as Clinical-Trials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number in the PROSPERO database. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Sample size

All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Short communications

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page
The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);

2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;

3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;

4. Each author should present his/her ORCID identification number (as obtained from www.orcid.org);

5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;

6. Each author should indicate a valid, up-to-date email address for contact;

7. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);

8. Place or institution where the work was developed, city and country.

9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.

10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.

11. Description of any conflicts of interest held by the authors (see above).

12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
- Conclusions – Make a succinct statement about data interpretation, answering the research question presented previously. Check that this is concordant with the conclusions in the main text of the article;
- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh. These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the "doi" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of

sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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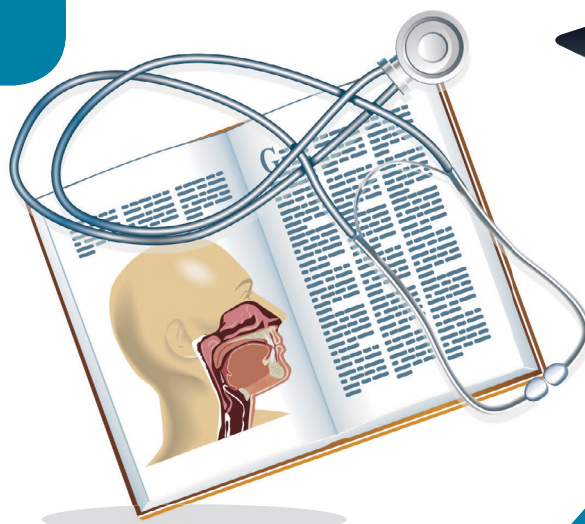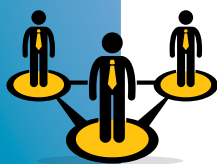
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