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Background

The urinary tract infection (UTI) is defined as the presence of pathogenic organisms in the urine secondary to invasion of the urethra, bladder, kidney or prostate. It is extremely frequent, with an incidence of 250 million cases worldwide, representing between 1 to 5% of all medical consultations in a year. (Rafalsky 2006)

Three groups of patients that their frequency of occurrence is higher compared to the general population are recognized: A) infants with presence of anatomical or functional disorders of the urinary tract, B) adult women in reproductive age and C) older adults with urinary tract obstruction secondary to degeneration. (Linhares 2013)

In our country there has been an increase in the frequency of these infections in last years; according to the National Epidemiological Surveillance System in 2006 reported an incidence of 1,204,032 cases in adults between 25 and 44 years; however in 2010 the UTI was the main cause of health care for women of reproductive age and the third in overall morbidity in the country. (Calderon 2013)

The reasons of this health problem can be explained by the increase in imaging studies that invade the urinary tract (urodynamic studies, obtaining prostate biopsies, among others), and the placement of catheters, which modify the natural barriers of the urinary tract and promote access of pathogens favoring the development of the inflammatory process. (Booth 2013)

The symptoms of UTI can be diverse, from asymptomatic bacteriuria, cystitis, recurrent infections, prostatitis, pyelonephritis and complicated to infections which increase the risk of serious consequences and cost of care. (Domingo 2010)

Due these manifestations, there are different diagnostic methods to detect the UTI, it can be the analysis of signs and symptoms (dysuria, urgency, frequency and suprapubic pain), urine stick analysis, urinalysis and urine culture, considered the latter as the standard test because it has a specificity of 92%. (Grigoryan 2014)

The agents responsible for these infections are gram-negative bacteria belonging to the group of enterobacteria, among which are: Escherichia coli in 75-95% of cases, saprophytic Staphylococcus, Klebsiella sp, Proteus sp and Enterobacter sp. (Garcia-Viejo 2010, Duane 2013)
Therefore in last years, many researchers have analyzed the efficacy of new antibiotics schemes in order to improve the cure rate of patients and reduced resistance rates based on the type of antimicrobial agents, time of administration, severity of infection and patient tolerability. (Monroy 2010)

Among the most frequently used antimicrobial agents for treatment of these infections include trimethoprim-sulfamethoxazole, cotrimoxazole, nitrofurantoin, fosfomycin and the family of quinolones. (Schmiemann 2012)

These are synthetic agents whose action is the inhibition of bacterial topoisomerase II, which is necessary to avoid fragmentation of the genetic material of bacteria.

Thanks to the scientific advances, have been developed quinolones with improved bioavailability and antimicrobial spectrum, noting that those of the first generation (nalidixic acid and pipemidic acid) had adequate concentration in the urine, but his action was predominant gram-negative bacteria; however with the advent of new genetic techniques, they have been developed second generation quinolonas (norfloxacin, ciprofloxacin, ofloxacin, pefloxacin), third generation (lomefloxacin, levofoxacin) and fourth generation (gatifloxacin, moxifloxacin) with activity against both negative gram and gram positive bacteria. (Anderson 1999)

Because of different kind of quinolones, many researchers have conducted trials to identify the efficacy of each of them to establish the best therapy of urinary tract infections, according with duration of therapy, severity of infection and adverse effects:

By duration of therapy

In a systematic review by Milo in 2005, (32 trials and 9605 patients with UTI), reported no significant difference in the improvement of urinary symptoms between the administration of a short 3-day antibiotic therapy with quinolones compared to a scheme over 5 to 10 days of treatment, (RR1.06 95% CI 0.88-1.28); however when analyzing urine bacteriological eradication there was observed that the long scheme is more effective (RR 1.43 95% CI 1.19-1.73 P = 0.0002). (Milo 2005)

In 2008, a new scheme of therapy with a single dose for the treatment for UTI uncomplicated was evaluated, in order to improve adherence to treatment and reduced microbial resistance, so Lutters compared it to the short scheme through a systematic review in which 15 studies were included (1644 women over 60 years old) and observed that the short treatment regimen (3-6 days) and long scheme (5-14 days) were more effective in the cure rate compared to a single dose (RR 2.01 95% CI 1.05-3.84 and RR1.93, 95% CI 1.01-3.70, respectively); however the antibiotics administered in these studies were very diverse, making it difficult to establish an conclusion. (Lutters 2008)

By Severity

The complicated urinary tract infections are considered during pregnancy, in patients with anatomical abnormalities or functional urinary tract, Diabetes mellitus,
immunosuppression, among others; so the treatment must be very effective and with few adverse events; however there is few evidence that have analyzed the administration of quinolones, as the study performed by Garcia in 2010, in which he analyzed the urine cultures of 992 patients with complicated UTI and found that 22.8% were resistant to treatment with amoxicillin-clavulanate, 34.8% in the levofloxacin and 40.6% to ciprofloxacin. (Garcia-Viejo 2010), however in the trial of Wagenlehner in 2015 reported bacterial resistance to penicillin between 35-50%, but with a cure rate of 76.9% compared with 68.4% of patients treated with levofloxacin. (Wagenlehner 2015)

**By Tolerability**

Many trials have reported any adverse effects associated with the administration of quinolones including gastrointestinal and neuropsychiatric symptoms, tendinitis, arrhythmias and allergy. (Gobernado 1999), however Milo in 2005 did not identify significant gastrointestinal symptoms and rash with the administration of quinolones and beta-lactams, sulfonamides and trimethoprim as treatments for uncomplicated UTI (RR 1.20 95% CI 1.07-1.35). (Milo 2005)

In another study performed by Rafalsky in 2006, reported in narrative form, that the most common secondary side effects to the administration of norfloxacin, ciprofloxacin, ofloxacin, pefloxacin and levofloxacin as a treatment for uncomplicated women were acute cystitis, skin disorders, insomnia and neurological manifestations. (Rafalsky 2006)

However, despite these reports, there is insufficient evidence of adequate quality which has analyzed the efficacy and adverse effects between the different members of the family of quinolones for treatment of urinary tract infection, whereby, we will performed the following systematic review with network meta-analysis in order to rank them and suggest new therapy schemes, with which the rate of resistance and the risk of developing complications can be reduced and thus decrease the cost health care.

**Objetive**

To evaluate the efficacy and safety of the administration of quinolones for the treatment of urinary tract infection in adults.

**Métodos**

**Search strategy**

The information search will be made systematically for a documentary in the following databases: CENTRAL (*The Cochrane Central Register of Controlled Trials 2015*), MEDLINE (PubMed 2010 - 2015), Embase (Ovid 2010 - 2015), LILACS (august 2015) y World Health Organization International Clinical Trials Registry Platform (ICTRP) (august 2015); references cited in the studies and relevant information reported at conferences (*Infectious Diseases Society of America, European Association of Urology and American Urological Association*) It will be made by manual search of the past 5 years without language restriction. The search strategy included a validated filter to
identify clinical trials, which was combined with the strategy of specific topics using the following MeSH terms: (("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields])) OR "urinary tract infections"[All Fields]) AND ("quinolones"[MeSH Terms] OR "quinolones"[All Fields])) OR AND ((Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "2015/07/16"[PDat] AND "humans"[MeSH Terms] AND "adult"[MeSH Terms]).

Selection criteria for studies
All the randomized clinical trials comparing administration of quinolones for the therapy of urinary tract infection in adults, published until 2015 without language restriction will be included.

Criteria for selection of participants
They will be included clinical trials in which participants are over 18 years of age and who have diagnosis of urinary tract infection by any of the following methods: a) culture (> 105 colony forming units / ml) or b) urinalysis (> 20 leukocytes per field, > 3 erythrocytes per field and presence of nitrite) or c) the presence of bacteria and gram stain and / or clinical symptoms (cloudy or foul-smelling urine, dysuria, urinary urgency, urinary frequency and suprapubic pain)

Exclusion Criteria
They will not be eligible studies that has participants with immunosuppression, renal failure, cancer, chemotherapy or pregnancy, also studies that have been administered antibiotics as prophylaxis against invasive procedures urinary tract, prostate biopsy or recurrence of infection; further studies with cross-over design, quasi-experimental, observational, narrative, case report or consensus will be excluded in this review.

Interventions and outcomes
Interventions with quinolones will be compared with any antimicrobial agent administered to adult patients with urinary tract infection regardless of dose or route of administration.

Outcomes to be evaluated are:
- Primary: remission of symptoms, negative cultures, duration of treatment and adverse events (neurologic, hepatic, cardiovascular, musculoskeletal, gastrointestinal and allergy).
- Secondary: relapse and bacterial resistance.

Selection of studies
Two independent and blinded reviewers, will analyzed by title and summary the obtained clinical trials to determine their inclusion in this review; disagreements will
be resolved by discussion and consultation with a third reviewer, in cases where the information is unclear, we will contact the authors by email.

Assessment of risk of bias
The assessment of risk of bias of the studies that meet the inclusion criteria will be conducted by two independent reviewers, using the Cochrane Collaboration form which includes the following criteria: random sequence generation, allocation concealment, blinding of participants, staff and evaluators, incomplete data, and selective report of information; which are analyzed as (1) high risk of bias which undermines confidence in the results, (2) unclear risk of bias, where doubts about the results arises and (3) low risk which is unlikely the existence of biases that undermine the confidence of the results. In case of discrepancies will be resolved through discussion and consultation with a third reviewer. (Higgins 2011)

Data Extraction
This process is carried out independently by two researchers using a standardized format which included the following information: author’s name, year of publication, number of participants included in the test method used for the diagnosis of infection of urinary tract, treatment and dosage used, and time of follow up.

Statistical analysis
A) Effect measures. For dichotomous outcomes (remission of symptoms, negative cultures, adverse effects, relapse and resistance), they will be presented as relative risk (RR) and confidence interval 95% (95% CI); while for continuous outcomes (duration of treatment) were expressed as mean difference (MD) between the experimental and control groups, in case that the studies reports the effect measures in different scale, they will be transformed and the results are expressed with risk difference (RD) and standardized mean difference (SMD); this information will be reported in the summary table. (Higgins 2011)

B) Data lost. For all outcomes, we will take into account all participants assigned to groups and analyzed by intention to treat; in cases where the information is not reporting, it will contact the authors of the studies.

C) Assessment of heterogeneity. It will be analyzed statistically by testing T2, I2 and X2 it will be considered substantial heterogeneity if the value of I2 is greater than 30% and the value of T2 is greater than zero or the presence of p <0.10 in the X2 test for heterogeneity.

Statistical analysis will be conducted in STATA version 13.1 software. First direct comparisons through meta-analysis using the fixed effects model by the method of the inverse of the variance for comparing the same interventions, we will analyze the
presence of heterogeneity \cite{Higgins2011}; if this is substantial (I2> 30%), we will identify the potential sources: sex, dose, route of administration, urinary catheters and urinary malformations; if despite the stratified analysis cannot be reduced heterogeneity, the comparisons will be analyzed through meta-analysis by random effects model with the Laird Der Simonian method. \cite{DerSimonian1986}

The network meta-analysis is a method for synthesizing information from a number of clinical trials that address the same outcomes but involve different interventions analyzing a data set through indirect and mixed so comparisons increases the accuracy of the comparisons; for indirect comparisons use the command mvmeta \cite{White2012} and then the validity of the network will be analyzed by calculating the inconsistency factor by the method of Bucher \cite{Bucher1997} among all closed cycles and then the treatment interaction model to analyze the inconsistency of the network. \cite{Lu2006} Then the results of the meta-analysis in network meta-regression is produced for each intervention using a common comparator and the area under the curve will analyze the effects of interventions to sort hierarchically by Sucra command. \cite{Salanti2011}

For the assessment of publication bias, we will analyze a funnel plots their visually asymmetry; if it will be present, we will perform a formal statistical analysis using Harbord test for dichotomous data, while for continuous data Egger's test will be used. \cite{White2012, Higgins2011, Harbord2006}

**Declaration of interest**

Each author participated actively in all protocol sections of the manuscript, editing, and approving the final, submitted version. Alejandro González, Liliana Velasco, and Cecilia Solis (authors of the review) have not conflict of interest. This review is funded by Senosiain Laboratories

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