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Table of Contents: Volume 12 Number 4 29 January, 2018

ARTICLES

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Full Length Research Paper

In vitro antimicrobial activity of generic and brand-name Levofloxacin against clinical and ATCC strains *E. coli* and *S. aureus*

Carlos Sánchez-Hoyos[1], Antistio Alviz-Amador[2] and Marlene Duran-Lengua[1,3*]

[1]Farmabac Research Group, Faculty of Medicine, University of Cartagena, Cartagena, Colombia.
[2]Farmacologia y Terapeutica Group, Faculty of Pharmaceutical sciences, University of Cartagena, Cartagena, Colombia.
[3]Faculty of Medicine, University of Cartagena, Cartagena, Colombia.

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***In vitro* antimicrobial activity between generic and brand-name Levofloxacin was evaluated against isolated strains collected in 3 Colombia hospitals: *Staphylococcus aureus* and *Escherichia coli.* Initially, active substance was quantified using the methodologies identified by the United States Pharmacopeia (USP) 38 NF 32, chromatographic conditions were validated and standardized. The minimum inhibitory concentration (MIC) of Levofloxacin was determined in accordance with the Clinical and Laboratory Standards Institute (CLSI). Growth curves were then performed to determine the maximum growth time of the bacteria in order to determine the MIC at the maximum growth time. Different brands evaluated did not present any difference with MIC of 0.125, 0.062, 0.031, 0.062 and 0.125 µg/ml for *E. Coli* ATCC, *E. Coli* Tropical, *S aureus* sensible ATCC, *S aureus* resistant ATCC and *S. luteum*, respectively. The *in vitro* antibacterial activity of levofloxacin against *E coli* Tropically and *S luteum* are reported for the first time.**

Key words: Quinolones, levofloxacin, minimum inhibitory concentration (MIC), *Staphylococcus aureus* and *Escherichia coli* (MeSH).

INTRODUCTION

Fluoroquinolones are the fourth class of antibiotics used in human and veterinary medicine for the treatment of serious bacterial infections. Its broad spectrum of activity and favorable pharmacokinetic properties are the main characteristics that have increased its widespread clinical use throughout the world (Barreto et al., 2017). However, its irrational use has increased the resistance profile, for this reason, it is pertinent to conduct studies that evaluate pharmaceutical alternatives of Levofloxacin, against pathogenic microorganisms such as *S. aureus* and *E. coli* sensitive and resistant, as well as ATCC isolated from hospitals in Colombia (Carvalho et al., 2016; Fariña et al., 2007). Currently, the doubts that arise both in the users and health providers services are very evident

*Corresponding author. E-mail: marlene6817342@yahoo.es.

when it comes to the quality of any generic drug, and their replacement with brand name drugs (Artaza et al., 2016; Medina-Morales et al., 2015). For these reasons, it is necessary to demonstrate that the quality of a drug is not directly related to its value and to dispel the myth "the more expensive the product, the more effective", which may favor communities with less economic capabilities, allowing them access to effective and quality therapy, which until now would be the most affected due to the few numbers of studies.

Bacterial resistance to antibiotics is a global health problem, because the possibility of continuing to successfully treat infections that are now easily treated is in danger (Yılmaz and Aslantaş, 2017). Morbidity, mortality and treatment costs will increase, if these bacterial resistances are not controlled (Pastor-Sánchez, 2006; Jackson et al., 1998; Juste Díez de Pinos et al., 2000; Mandell et al., 2010). The irrational use of antibiotic therapy jeopardizes the possibility of continuing treating with success, infections that are treated with these drugs; to clear up the doubts, we must evaluate the behavior of these substances and certify the suitability of the products used for the therapies indicated, guaranteeing the interchangeability between generic Levofloxacin with its brand name in the treatment of the pathologies caused by *E. coli* and *S. aureus*.

For all drug generic or brand name, especially antibiotics, their efficacy and safety are infallible qualities, since in the opposite case; the patient health is put at risk due to the appearance of bacterial resistances (Sun et al., 2016). According to the surveillance programs in United States, a total of 2008 samples evaluated showed a resistance rate to Levofloxacin of 5% (Cercenado, 2011; Meléndez et al., 2005; Sato et al., 2011).

The aim of the study is to compare *in vitro* antibacterial activity of a generic and brand name of Levofloxacin previous substance active quantification, following USP38 NF 32 (Pharmacopeia, 2016). The activity of Levofloxacin was measured against 2 strains which are causes of nosocomial infections: *Escherichia coli* and *Staphylococcus aureus*, by determining the minimum inhibitory concentration (MIC), using broth microdilution method. The results obtained allow us to determine which drug offers the highest efficacy *in vitro*. In addition, this study will present results in strains which have not been evaluated microbiologically in Colombia: *Escherichia coli tropically* and *Staphylococcus luteum*.

MATERIALS AND METHODOLOGY

Reagents

Bacterial Culture Media

Solid media: Nutritious Agar, and Trypticase Soy Agar Merck Millipore. Liquid Medium: Thioglycolate Broth, Muller-Hinton Broth and Luria bertani broth Difco.

Antibiotics

Levofloxacin: 3 different batches of Pharmamedic, ADS PHARMA and Sanofi. USP standard of Levofloxacin Sigma Aldrich.

Microorganisms

ATCC: *S. aureus* 43300 (Met-R), *S. aureus* 25923 (Met-S), *E. coli* 25922, purchased from the authorized Techno medical distributor. Clinical isolations were obtained from 3 Colombian Hospitals. *S luteum* and *E coli Tropically* from Microkit SL laboratories

Active principle quantification

The active principle quantification was performed by high-performance liquid chromatography (HPLC) according to USP38 NF-33. Linearity, accuracy, repetitiveness, intermediate precision, selectivity of generic and brand names of levofloxacin drug were determined to validate the analytical methods.

Chromatographic conditions

The high resolution liquid chromatography (Elite Lachrom HITACHI I2350) equipment, equipped with a quaternary pump and a Diode Array Detector (DAD) was used. A reversed phase Merck® C18, 150 × 4.6 mm, particle size 5 µm was used as the analytical column. The mobile phase was a mixture of 0.1% solution of triethanolamine-acetonitrile (80:20), adjusted to a pH of 4.8 with phosphoric acid; filtered and degassed by 0.45 µm membrane. The wavelength was set at 296 nm, with flow rate of 1 ml/min and injection volume of 20 µl. Before using all solutions, the mobile phase was sonicated for 30 min and UV detection was performed at 296 nm for GTX.

Linearity

10 mg of Levofloxacin standard were weighed and taken to a 10 ml graduated volumetric flask, which was completed using mobile phase diluent, thus remaining at a concentration of 1000 ppm. This solution was labeled as standard stock solution. From the stock solution, aliquots of 0.25, 0.5, 0.75, 1.0, and 1.2 ml were taken to 10 ml graduated volumetric flask and adjusted with mobile phase, obtaining concentrations of 25, 50, 75, 100 and 120 ppm, respectively. Each solution was injected into the Chromatograph in triplicate.

Accuracy

Two milliliter of the drug Levofloxacin was taken, which was at a concentration of 5 mg/ml and taken to a 10 ml graduated volumetric flask, it was completed using mobile phase diluent, obtaining a concentration of 1000 ppm. It was labeled as the stock solution. From the stock solution, aliquots of 0.25, 0.5, 0.75 and 1.0 ml were taken to 10 ml graduated volumetric flask and adjusted with mobile phase, obtaining concentrations of 25, 50, 75 and 100 ppm, respectively. Each solution was injected into the chromatograph in triplicate. The obtained data were analyzed and the recovery percentage calculated.

Repetitiveness

From the stock standard and sample solutions, 1 ml aliquots were

Table 1. Percentage of recovery of Levofloxacin estimated by precision test, USP 38.

Levofloxacin accuracy				
Retention time	**Area**	**Theoretical concentration (ppm)**	**Real concentration (ppm)**	**Recovery %**
1.667	6908009	25	23.74732536	94.99
1.66	6886092	25	23.65993038	94.64
1.653	7079861	25	24.43259258	97.73
1.64	13030547	50	48.16120839	96.32
1.64	13264055	50	49.09233156	98.18
1.64	12953915	50	47.855635	95.71
1.633	19556758	75	74.18475483	98.91
1.633	19916697	75	75.62002704	100.83
1.633	19692647	75	74.72661805	99.64
1.633	25765870	100	98.9438554	98.94
1.633	25550126	100	98.08356694	98.08
1.633	25928682	100	99.59307523	99.59
Mean	97.8	Mean Standard Error	0.624928069	
Standard Deviation	1.976196	Variation coefficient	0.02	

taken to 10 ml graduated volumetric flask; mobile phase was adjusted and 100 ppm concentrations were obtained. These solutions were taken to the chromatograph and injected six times each. The obtained data were analyzed and the standard deviation and the coefficient of variation (RSD) were calculated; having an RSD ≤ 2% as acceptance criteria for the runs.

Intermediate precision

From the standard stock solution aliquots of 0.5, 0.75 and 1 ml were taken to 10 ml graduated volumetric flask, to which volume was completed with mobile phase and a solution was obtained with concentrations 50, 75 and 100 ppm, respectively. These solutions were injected in duplicate. This procedure was carried out by three different analysts on different days. The data obtained were analyzed and the relative standard deviation (RSD) obtained.

Antimicrobial activity

The minimum inhibitory concentration (MIC) of 2 generic, 1 USP standard and 1 brand name of levofloxacin drug were evaluated using the broth micro dilution method, described by the Clinical and Laboratory Standards Institute (CLSI, 2015). Ten dilutions were prepared for each drug, performing serial double dilutions from 64 to 0.0075 µg/ml on bacterial suspensions at a concentration of 5×10^5 CFU/ml, in 96-well microtiter plates CLSI (2011). Initially beginning with a concentration of levofloxacin drugs (5 mg/100 ml) which was diluted with Muller-Hinton broth at pH 7.3 to obtain a stock solution of 64 µg/ml, the solution was diluted to obtain an intermediate solution at a concentration of 8 µg/ml after which, doubling-dilution series of the antibiotic solutions of 8 µg/ml to 0.015 µg/ml were performed. 50 µl of each dilution was dispensed into the wells of the Microplates and 50 µl of the inoculum was added to each one, to obtain final bacterial concentrations of 5×10^5 CFU/ml. A well that contains inoculum without antibiotic was used as a positive control and one containing antibiotic dissolved in broth without inoculum as a negative control. The turbidity of the actively growing broth culture was adjusted to an optical density equivalent to a 0.5 McFarland standard using a Thermo Scientific Multiskan EX® spectrophotometer at 620 nm. All assays were conducted in triplicate.

Statistical analysis

The analytical datas, such as linearity, accuracy, repetitiveness and intermediate precision, were tested for each alternative through descriptive statistics. MIC values between doubling-dilution series of the antibiotic solutions, positive control and negative control for each alternatives, were tested using one-way analysis of variance (ANOVA), followed by a tukey test for multiple comparisons with significant statistical difference at $p < 0.05$.

RESULTS AND DISCUSSION

Linearity

The results obtained indicate that the system for determining levofloxacin is able to explain the response (Area) from the use of the concentration variable. Therefore, in the concentration range between 25 and 120 ppm the linearity conditions of the analytical system are satisfied, this is demonstrated by obtaining a correlation coefficient r = 0.9982 and a determination coefficient $R^2 = 0.9965$.

Accuracy

Table 1 shows the levofloxacin recovery percentage values, which reached between 94.64 and 100.83%, which are within the acceptance criteria of 92% as a minimum. The values of RSD remained below 2%, this

Table 2. Percentage of recovery of Levofloxacin estimated by system repeatability test, USP 38.

Standard Levofloxacin				
Retention time	**Área**	**Theoretical concentration (ppm)**	**Real Concentration (ppm)**	**Recovery %**
1.827	24370246	100	93.3787448	93.3787448
1.82	24311355	100	93.14391441	93.14391441
1.82	24385487	100	93.43951894	93.43951894
1.813	24337761	100	93.24920947	93.24920947
1.813	24415376	100	93.55870261	93.55870261
1.813	24302249	100	93.10760385	93.10760385
Mean	93.31294	Standard deviation	0.176377963	
Variation Coefficient	0.001890177	Mean Standard Error	0.055775609	

Table 3. Percentage of recovery of Levofloxacin estimated by method's repeatability test, USP 38.

Levofloxacin Sample				
Retention time	**Área**	**Theoretical concentration (ppm)**	**Real Concentration (ppm)**	**Recovery %**
1.83	24695054	100	94.67393064	94.67393064
1.82	24718643	100	94.76799279	94.76799279
1.813	24204589	100	92.7181804	92.7181804
1.802	24405801	100	93.52052189	93.52052189
1.813	24382798	100	93.42879644	93.42879644
1.82	24438024	100	93.64901248	93.64901248
Mean 94.0	Standard Deviation	0.788607358		
Variation Coefficient	0.008407949	Mean Standard Error	0.249379543	

indicates that the methodology yields acceptable results according to USP 38 (Van et al., 2017). These results are similar to those shown by Aragon-Martinez in a study conducted on plasma samples (Aragon-Martinez et al., 2017).

Repetitiveness

The recovery percentage for each injection were calculated, and average values of 93.31% for the system and 93.79% for the method were obtained, indicating that the method and system met the requirements to perform the test (Tables 2 and 3).

Intermediate precision

The RSD values obtained were between 0.01% and 0.05%. Likewise, the calculation of the recovery percentage was made for each run; the average value obtained was 102.58% (Tables 4, 5 and 6), this is due to analyst linked errors during the preparation of the solutions, evidenced when finding the real concentration of these solutions. These results show that the analytical method is accurate, since the USP38 accepts as a minimum value or acceptance criterion for this parameter, an RSD less than or equal to 4% and a recovery percentage greater than or equal to 95%.

Generic and brand name comparison

The comparison test between generic and brands name levofloxacin drug yielded very similar results in terms of areas under the curve and the recovery percentage, with an average of 97.76% for the generic drug and 97.11% for the commercial one. Both cases had a variation coefficient (RSD) of 0.01. The generic and brand name drug vials concentration were determined using the formula described in the methodology, obtaining a concentration of 4.861 mg/ml for the generic drug and 4.826 mg/ml for the brand name one (Tables 7 and 8), corresponding to 97.22% for the generic drug and 96.52% for the brand name one of the reported concentration (5 mg/ml). In this study, the analytical quantification of active principle of generic and brand names levofloxacin shows that there were no differences from the point of view of the concentration reported in the tag of the different drugs evaluated. This is directly

Table 4. Percentage of recovery of Levofloxacin estimated by intermediate precision test, day 1, USP 38.

Levofloxacin intermediate precision day 1				
Retention time	**Área**	**Theoretical concentration (ppm)**	**Real Concentration (ppm)**	**Recovery %**
1.667	14893895	50	55.5913885	111.18
1.66	14543607	50	54.19460007	108.39
1.653	21842411	75	83.29889425	111.07
1.64	21754631	75	82.94886774	110.60
1.64	28145689	100	108.4334858	108.43
1.64	28042377	100	108.0215248	108.02
Mean	109.62	Standard Deviation	1.480942954	
Variation Coefficient	0.01	Mean Standard Error	0.468315282	

Table 5. Percentage of recovery of Levofloxacin estimated by intermediate precision test, day 2, USP 38.

Levofloxacin intermediate precision day 2				
Retention time	**Área**	**Theoretical concentration (ppm)**	**Real concentration (ppm)**	**Recovery %**
1.612	13323093	50	49.32774811	98.66
1.62	14140852	50	52.58859722	105.18
1.613	20695054	75	78.72375898	104.97
1.613	20718643	75	78.81782113	105.09
1.64	24782798	100	95.02381361	95.02
1.653	25038024	100	96.04153823	96.04
Mean	100.83	Standard deviation	4.806603534	
Variation Coefficient	0.05	Mean Standard Error	1.519981498	

Table 6. Percentage of recovery of Levofloxacin estimated by intermediate precision test, day 3, USP 38.

Levofloxacin intermediate precision day 3				
Retention time	**Área**	**Theoretical concentration (ppm)**	**Real concentration (ppm)**	**Recovery %**
1.613	13003039	50	48.05151905	96.10
1.6	12607513	50	46.47434216	92.95
1.593	19428611	75	73.67376316	98.23
1.587	20121383	75	76.43622124	101.91
1.573	25563412	100	98.13654543	98.14
1.583	25145610	100	96.47054203	96.47
Mean	97.30	Standard deviation	2.96379407	
Variation Coefficient	0.03	Mean Standard Error	0.937233978	

related to the quality of levofloxacin used for *in vitro* antibacterial activity assay. In the Figure 1 you can see the recovery percentage means between generic and brandname levofloxacin drugs without significant differences

Hospital strains growth curves

E. coli and *S. aureus* ATCC strains, both sensitive and resistant, showed a maximum growth from 5 and up to 15 h, which is consistent with what was reported by the CLSI (2014) and computer simulated methods (Jorgensen and Turnidge, 2015; Cattaneo et al 2009). On the other hand, *E. coli tropically* and *S. luteum* canariensis strains reached up to 23 h, which is also compatible with that reported by Microkit SL laboratories in the technical annexes provided. Microkit laboratories strains grow faster in time than ATCC strains. Hospital strains presented the following timing of maximum growth; 16 h

Table 7. Percentage of recovery of Levofloxacin generic drug, USP 38.

Generic levofloxacin				
Retention time	**Área**	**Theoretical concentration (ppm)**	**Real concentration (ppm)**	**Recovery %**
1.787	13197225	50	48.82584406	9765
1.78	13246582	50	49.02265722	98.05
1.773	19307821	75	73.19210786	97.59
1.773	19536842	75	74.10533892	98.81
1.767	25526874	100	97.99084859	9799
1.76	25142543	100	96.45831223	96.46
Mean	97.76	Standard deviation	0.770234	
Variation Coefficient	0.01	Mean Standard Error	0.243569	

Table 8. Percentage of recovery of Levofloxacin brand name drug. USP 38.

Brand name levofloxacin				
Retention time	**Área**	**Theoretical concentration (ppm)**	**Real Concentration (ppm)**	**Recovery %**
1.74	13051547	50	48.24494679	96.49
1.74	12936915	50	47.78784677	95.58
1.74	19534091	75	74.09436919	98.79
1.733	19529731	75	74.0769835	98.77
1.733	25119726	100	96.36732847	96.37
1.733	25197243	100	96.67643083	96.68
Mean	97.11	Standard deviation	1.34627227	
Variation Coefficient	0.01	Mean Standard Error	0.425728672	

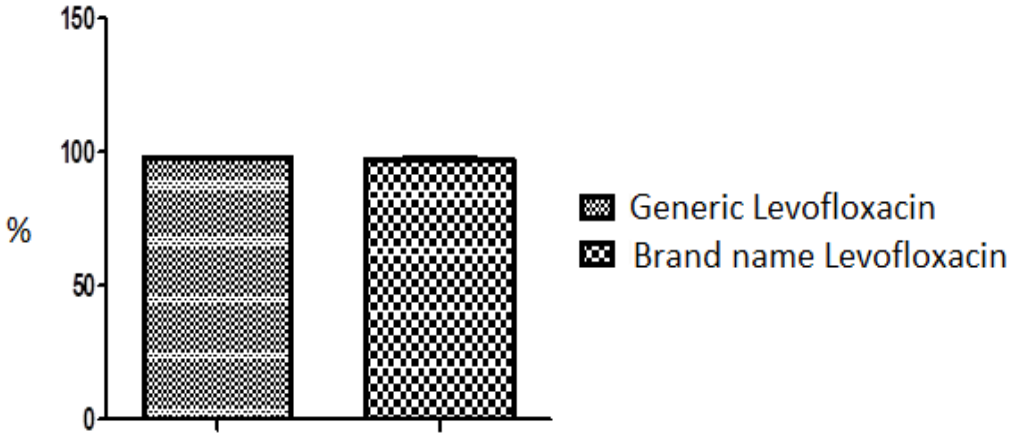

Figure 1. Recovery percentage between generic and Brand name levofloxacin drugs.

S. aureus, 18 h *E. coli*, showing a time of maximum growth greater than ATCC strains, previously evaluated and presenting no abnormalities with respect to growth. It is possible to observe and differentiate the stages from medium assimilation that is less than 5 h to the stage of death, which in the case of *S. aureus* is between 18 and 20 h, and for *E. coli* it is observed from 19 h. Hence, the timing of maximum growth of the isolates is greater than ATCC. Comparing Microkit SL laboratories strains to those isolated from hospitals and to ATCC, it was observed through absorbance performed by turbidimetry tests, that hospital strains had the highest cellular

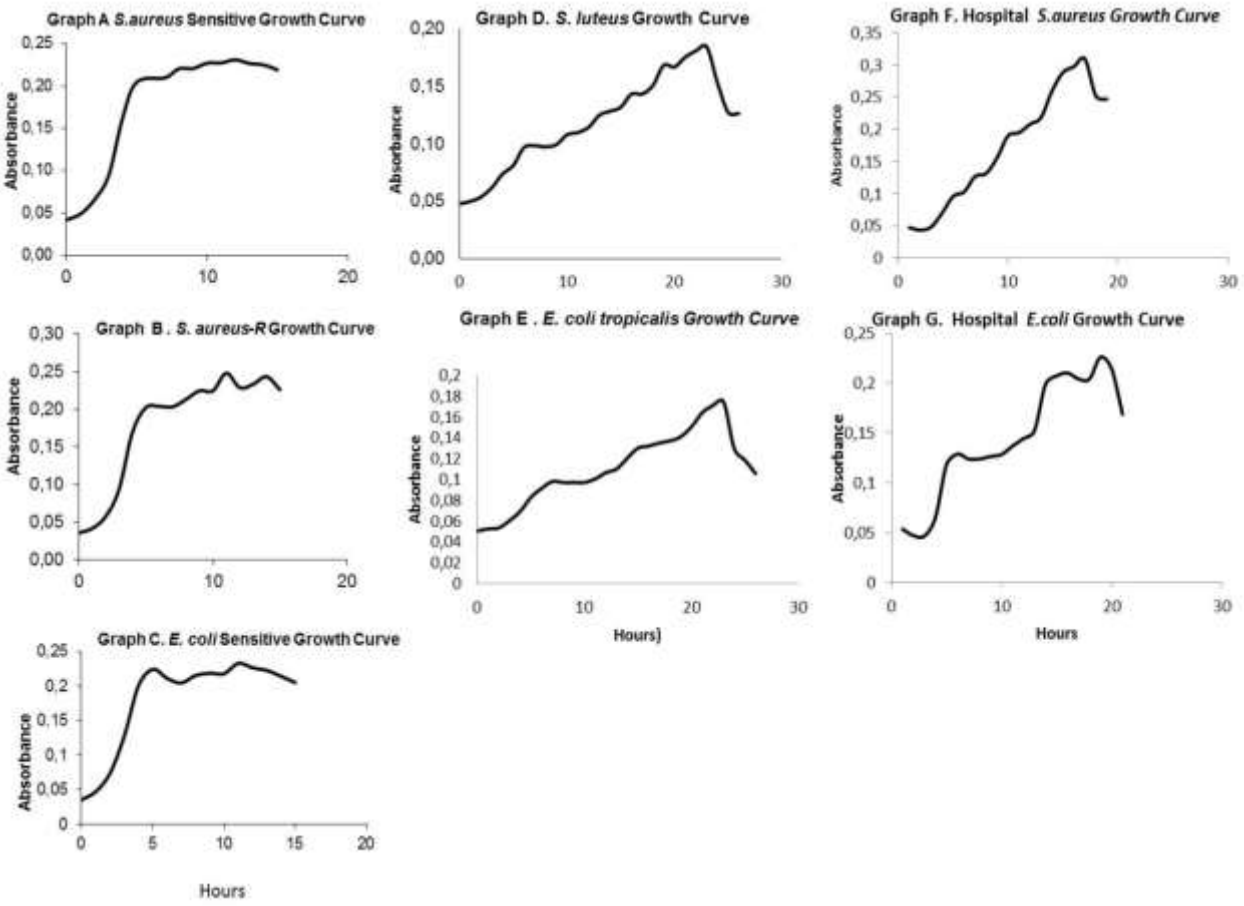

Figure 2. Growth curves A. *S aureus* sensitive ATCC B. *S aureus* resistant, ATCC C. *E coli* ATCC. D. *S luteum*, E. *E coli Tropically*, F and G. *S aureus* and *E coli clinical* isolated.

concentration over time of maximum growth (Figure 2). Although Microkit SL laboratories strains obtained the longest time of maximum growth, they presented less bacterial concentration. Thus, comparing hospital isolated strains; it can be concluded that those obtained from ICU had a higher bacterial concentration, in a smaller time unit. The MIC values of standard, generic and brand name of levofloxacin are presented in Tables 9 and 10. Overall, the MIC of different levofloxacin drugs against *S. aureus* and *E coli* evaluated were found much lower than that reported by Martínez et al. (2004) and Van Bambeke (2005). On the other hand, MIC of levofloxacin was determined against to *E. coli tropically* and *S. luteums*, for the first time in Colombia.

None of the strains exceeded the ranges reported by literature. However, we must take into account the significant difference between MIC values presented by Clinical Isolated strain of Colombian hospital, which were higher with respect to ATCC and MICROKIT SL laboratory strains. Although, they do not exceed the limits established by the above referenced studies, this outcome could be in relation with the increase of levofloxacin resistance (Kao et al., 2016), reason for which its use in clinic has decreased in Colombian Hospital.

Table 11 shows the results of confirmative tests confirming that the data obtained by turbidimetric method used in the present study were correct. Furthermore the MIC values remained the same as in the previous trials, confirming the low efficacy against clinical isolates compared with standard strains of *E coli* and *S aureus* for both generic and brand name of levofloxacin

Conclusions

No significant differences existed in active principle substance concentration between the different brands of levofloxacin evaluated by a precise, repetitive and accurate method. This is directly related to the quality of levofloxacin used for *in vitro* antibacterial activity assay. When comparing the differences between generic and brand name levofloxacin, the differences in MIC values were very minimal. It was possible to demonstrate that

Table 9. Standard, generic and commercial Levofloxacin MIC in the maximum growth time for each strain.

Strains	Levofloxacin MIC (µg/ml) (standard)	Levofloxacin MIC (µg/ml) (Generic) Ads pharma	Levofloxacin MIC (µg/ml) (Generic) Pharmedic	Levofloxacin MIC (µg/ml) (commercial) Sanofi
E. coli ATCC	0.125	0.125	0.125	0.125
S. aureus-R ATCC	0.0625	0.0625	0.0625	0.0625
S. aureus- S ATCC	0.03125	0.03125	0.03125	0.03125
*E. coli tropically**	0.0625	0.0625	0.0625	0.0625
*S. luteums**	0.125	0.125	0.125	0.125
*S. aureus***	4	4	4	4
*E. coli***	8	8	8	8

*MICROKIT SL laboratory strains, **Clinical Isolated strain.

Table 10. Standard, generic and commercial levofloxacin MIC, 24 hours after the maximum growth time for each strain.

Strains	Levofloxacin MIC (µg/ml) (Standard)	Levofloxacin MIC (µg/ml) (Generic) Ads Pharma	Levofloxacin MIC (µg/ml) (Generic) Pharmedic	Levofloxacin MIC (µg/ml) (Commercial) Sanofi
E. coli ATCC	0.25	0.25	0.25	0.25
S. aureus-R ATCC	0.125	0.125	0.125	0.125
S. aureus-S ATCC	0.0625	0.0625	0.0625	0.0625
E.coli tropically*	0.125	0.125	0.125	0.125
*S. luteums**	0.25	0.25	0.25	0.25
*S.aureus***	8	8	8	8
E.coli **	>8	>8	>8	>8

*MICROKIT SL laboratory strains, **Clinical Isolated strain.

Table 11. Results of all confirmative tests.

Strains	Levofloxacin MIC (µg/mL) (Standard)	Levofloxacin MIC (µg/mL) (Generic) Ads Pharma	Levofloxacin MIC (µg/mL) (Generic) Pharmedic	Levofloxacin MIC (µg/mL) (Commercial) Sanofi
E. coli ATCC	0.125	0.125	0.125	0.125
S. aureus-R ATCC	0.0625	0.0625	0.0625	0.0625
S. aureus-S ATCC	0.03125	0.03125	0.03125	0.03125
*E. coli tropically**	0.0625	0.0625	0.0625	0.0625
*S. luteums**	0,125	0.125	0.125	0.125
*S.aureus***	4	4	4	4
E. coli **	8	8	8	8

*MICROKIT SL laboratory strains, **Clinical Isolated strain.

generic and brand names levofloxacin showed similar *in vitro* antimicrobial activity against Clinical and ATC strain of *S. aureus* and *E. coli*.

However the clinical isolation strain presented MIC to be more elevated that ATCC strain for both generic and brand name levofloxacin, this outcome could be the relationship with the increase of levofloxacin resistance, and this would explain the low efficacy of quinolones in clinic. This study reported for the first time the levofloxacin MIC against two specific strains from Colombia that had never been evaluated against *E. coli tropically* and *S. luteum*.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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REFERENCES

(CLSI) CLSI. Clinical and Laboratory Standards Institute Standards Development Policies and Process. M07-A102011. Available at: https://clsi.org/standards/products/microbiology/documents/m07/

Aragon-Martinez OH, Isiordia-Espinoza MA, Galicia O, Romo SA, Gómez AG, Romano-Moreno S, Martinez-Morales F (2017). Measurement of levofloxacin in human plasma samples for a reliable and accessible drug monitoring. Clin. Biochem. 50(1):73-9.

Artaza O, Méndez C, Holder R, Suárez J (2016). Redes Integradas de Servicios de Salud: el desafío de los hospitales. Santiago, Chile: Organización Panamericana de la Salud/Organización Mundial de la Salud, 2011. Available at: http://www1.paho.org/chi/images/PDFs/redes_integrales_de_servicios.pdf

Barreto F, Ribeiro CBD, Hoff RB, Costa TD (2017) Development and validation of a high-throughput method for determination of nine fluoroquinolones residues in muscle of different animal species by liquid chromatography coupled to tandem mass spectrometry with low temperature clean up. J. Chromatograph. A.1521(Supplement C):131-9.

Carvalho M, Maia A, Tiritan M, Castro P (2016). Bacterial degradation of moxifloxacin in the presence of acetate as a bulk substrate. J. Environ. Manag. 168:219-28.

Cattaneo CA, Larcher LI, Acosta CA. Cattaneo CA, Larcher LI, Acosta CA.(2009) Aplicación de Dimensión Fractal al estudio de Sistemas Naturales. Mecánica Computacional, Numerical Methods for Simulation and Analysis in Bioengineering; Volume XXVII. (Number 44):2021-38.

Cercenado E (2011). Enterococcus: resistencias fenotípicas y genotípicas y epidemiología en España. Enferm. Infecc. Microbiol. Clin. 29:59-65.

Fariña N, Sanabria R, Laspina F, Samudio M, de Figueredo L, de Kaspar HM (2007) Actividad in vitro de fluoroquinolonas en bacilos gramnegativos aislados de urocultivos de pacientes ambulatorios. Memorias del Instituto de Investigaciones en Ciencias de la Salud. 5(1).

Jackson LC, Machado L, Hamilton ML (1998). Principios generales de la terapéutica antimicrobiana. Acta Méd. 8(1):13-27.

Jorgensen JH, Turnidge JD (2015). Susceptibility test methods: dilution and disk diffusion methods. In Manual of Clinical Microbiology, Eleventh Edition. Am. Soc. Microbiol. 1253-1273.

Juste Díez de Pinos JL, Adrover Rigó M, Ribas Sala J (2000). Levofloxacino, fluorquinolona de tercera generación. Farm Hospit. 24(5):288-295.

Kao CY, Wu HM, Lin WH, Tseng CC, Yan JJ, Wang MC, Teng CH, Wu JJ (2016). Plasmid-mediated quinolone resistance determinants in quinolone-resistant Escherichia coli isolated from patients with bacteremia in a university hospital in Taiwan, 2001–2015. Sci. Rep. 6:32281.

Mandell GL, Dolin JE, Mandell RL, Bennett JE, Dolin R, Mandell GL, Douglas JE, Mandell GL, DOLIN JE, Mandell RL, Bennett JE (2010). Enfermedades infecciosas: principios y práctica (No. 616.9). Elsevier

Martínez P, Mercado M, Máttar S (2004). Actividad *in vitro* de moxifloxacina comparada con otros antibióticos frente a aislamientos nosocomiales de dos hospitales de Colombia. Universitas Medicas. 45:101-9.

Medina-Morales DA, Machado-Duque ME, Machado-Alba JE (2015). Resistencia a antibióticos, una crisis global. Rev. Méd. Risaralda. 21(1):74-74.

Meléndez P, Díaz J, Silva E, González P, Moreno E, Amaya P, Serrato N, Sáenz E (2005). Estudio comparativo de la actividad antimicrobiana de diferentes presentaciones comerciales de antibióticos de administración intravenosa a través de métodos in vitro. Rev. Colombiana. Cien. Químico-Farm. 34(2).

Pastor-Sánchez R (2006). Alteraciones del nicho ecológico: resistencias bacterianas a los antibióticos. Gac. Sanit. 20:175-81.

Pharmacopeia (2016). United States Pharmacopeia and National Formulary (USP 38–NF 33). Vol Section. 2016; 2:35-117. Available at: http://www.uspnf.com/

Sato T, Yokota SI, Uchida I, Okubo T, Ishihara K, Fujii N, Tamura Y (2011). A fluoroquinolone-resistant *Escherichia coli* clinical isolate without quinolone resistance-determining region mutations found in Japan. Antimicrob. Agents Chemother. 55(8):3964-3965.

Sun HY, Liao HW, Sheng MH, Tai HM, Kuo CH, Sheng WH (2016). Bioequivalence and in vitro antimicrobial activity between generic and brand-name levofloxacin. Diagn. Microbiol. Infect. Dis. 85(3):347-51.

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM (2005). Quinolones in 2005: an update. Clin. Microbiol. Infect. 11(4):256-280.

Van Toi P, Pouplin T, Tho NDK, Phuong PN, Chau TTH, Thuong NTT, Heemskerk D, Hien TT, Thwaites GE (2017). High-performance liquid chromatography with time-programmed fluorescence detection for the quantification of Levofloxacin in human plasma and cerebrospinal fluid in adults with tuberculous meningitis. J. Chromatogr. B. 1061:256-262.

Yılmaz EŞ, Aslantaş Ö (2017). Antimicrobial resistance and underlying mechanisms in Staphylococcus aureus isolates. Asian Pac. J. Trop. Med. 10(11):1059-1064.

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Risk factors for, and treatment of, Stevens-Johnson syndrome and toxic epidermal necrolysis: Evidence from the literature

Ricardo Eccard da Silva[1,4*], Alice Garbi Novaes[2], Leila Bernarda Donato Göttems[2,3] and Maria Rita Carvalho Garbi Novaes[3,4]

[1]Brazilian Health Regulatory Agency (Anvisa), Brasilia, Brazil.
[2]Departamento de Enfermagem, Escola de Ciências da Saúde, Universidade Católica de Brasília, Brazil.
[3]Health Sciences Education and Research Foundation (FEPECS), Brasilia, Brazil.
[4]Faculty of Health Sciences, Post Graduation in Health Sciences, University of Brasilia, Brasilia, Brazil.

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are adverse drug reactions. They occur in the form of mild and sometimes severe cutaneous eruptions, with high morbidity and mortality, requiring fast and appropriate diagnosis and treatment. The aim of this study was to describe and discuss the evidence regarding the risk factors, complications and treatment of SJS and TEN in inpatients. The present study is a literature review of case reports published between January 1981 and December 2016, in the following databases: The Virtual Health Library (*Biblioteca Virtual da Saúde* - BVS), MEDLINE (National Library of Medicine, USA), LILACS (Latin American and Caribbean Health Sciences Literature), and PUBMED – NCBI (National Center for Biotechnology Information). A total of thirteen case reports were selected. Most of the cases (54%) developed adverse reactions to anticonvulsant drugs. The most common were valproic acid, lamotrigine and carbamazepine. In 69% of all cases, the patients were female. The patients' age range varied from 18 to 82 years old. In two cases which correspond to 15%, the patients were either infected with HIV or were receiving chemotherapy treatment for cancer. These patients had a higher possibility for immunosuppression. In relation to the actions taken as treatment, the suspension of the drugs or the treatment of the skin lesions occurred in 85 and 54% of the cases, respectively. A total of 6 cases, corresponding to 46%, occurred in the Latin American and Caribbean region. In conclusion, the use of anticonvulsants, and female gender, are among the main risk factors identified by the study. The main therapeutic action for SJS and TEN is the suspension of the use of the drug that triggered the inflammatory process and the topical treatment of the lesions caused.

Key words: Stevens-Johnson syndrome, toxic epidermal necrolysis, adverse drug reaction.

INTRODUCTION

An adverse drug reaction (ADR) is a harmful response to drugs, occurring in doses usually employed in the prophylaxis, diagnosis, treatment or modification of physiological functions (Walley, 2000). An ADR may appear as a reaction of mild intensity, of little clinical relevance, medium intensity, or severe intensity, and can lead to hospitalization, with incapacitating or even lethal sequelae (Upadhyaya et al., 2012).

Studies have shown that approximately 4% of hospital admissions in the United States of America are due to

ADR and that 57% of these reactions are not recognized at the time of the patients' admission; such reactions affect more than 2.2 million people per year (Pereira, 2012).

In Europe, approximately 3.6% of all hospital admissions are due to ADR. Moreover, the percentage of hospitalized patients who die from ADR is below 0.5%, which corresponds to 419,000 deaths annually from this cause in this region (Bouvy et al., 2015).

Stevens Johnson syndrome and TEN are serious conditions that can lead to death and are characterized mainly by blisters in the region of the skin and mucosa. The lesions generally affect the trunk. Although these conditions are rare worldwide, with an incidence of 0.4 to 6 cases per million people per year, the mortality rate are high: 5 to 12% for SJS, 30% for TEN, and 33.3% for the two conditions combined (Tangamornsuksan et al., 2013).

Approximately 2 to 3 people per million/year have SJS or TEN in Europe and the United States of America. In Brazil, Stevens-Johnson syndrome varies from 1.2 to 6 cases per million people/year, and TEN varies from 0.4 to 1.2 million per year (Bulisani, 2006). For 2005 to 2007, the incidence rate of TEN in Japan was 0.28 to 0.52 per million per year (Kinoshita, 2017).

The difference between SJS and TEN is related to the extent of the body surface where epidermis is peeling away. In SJS, TEN and the combination of both conditions, respectively, at least 10%, over 30%, and between 10 and 30% of the body's surface area is affected (Sun et al., 2014).

In approximately 80% of these cases, drugs are the primary cause. The classes of drugs associated most with these conditions are the antiepileptics, antibiotics, and the xanthine oxidase inhibitors. The use of carbamazepine is considered to be the most common cause. Other factors related to the emergence of these reactions are immunization, viral infections, chemical products and mycoplasma pneumoniae (Tangamornsuksan et al., 2013).

One overlapping feature in SJS and TEN is the presence of fever and malaise (Kumar et al., 2005; Yamane et al., 2016). Although, SJS and TEN affect patients of all ages, races and genders, it is mainly related to the use of drugs (Bulisani, 2006). ADR's cost to the health services is normally underestimated, as the majority of the reactions occur in patients who are not hospitalized, these reactions, therefore, is being under reported (Nagao-Dias et al., 2004).

Some factors may predispose patients to develop SJS and TEN. These include multiple morbidities and the use of drugs for treating the following: advanced age, genetic propensity, and diseases which affect the immune system (Bulisani, 2006). Mortality caused by SJS and TEN increases with age and according to the region of the body affected. SJS and TEN are conditions that can result in a severe cutaneous reaction, requiring rapid and appropriate diagnosis (Bulisani, 2006).

Renal function, electrolyte fluid balance, eye and affected regions care, pain control and infection prevention are priority measures (Schneider, 2017). In addition, referral of patients to the intensive care unit or burn unit is recommended (Alerhand et al., 2016).

This article's objective is to describe and discuss the evidence regarding the risk factors, prevalence, mortality, complications, treatment and prevention of SJS and TEN; when these occur in hospitalized patients. In spite of the seriousness and high mortality of these reactions and the fact that they are not yet totally understood, few studies have yet been undertaken (Arantes et al., 2017). Besides the known risk factors such as infections and the use of drugs, there are probably other related factors which have not yet been identified (Mockenhaupt, 2011). The investigation of risk factors, clinical cases and treatment options could be useful for health teams in managing patients with SJS and TEN (Chantaphakul et al., 2015).

This study mainly investigates the population which is affected by these conditions and the discussion of the associated risk factors, based on the comparison of our results with those already published in the literature. The study of risk factors is fundamental in promoting policies aimed at preventing ill health and promoting clinical management.

METHODOLOGY

The study consists of a review of the scientific literature on the topic. The following databases were consulted for articles: MEDLINE (National Library of Medicine, USA), LILACS (Latin American and Caribbean Health Sciences Literature) and PUBMED – NCBI (National Center for Biotechnology Information), published between January 1981 and January 2016, and which included the following MeSH (Medical Subject Headings) and DeCS (*Descritores em Ciências da Saúde*) descriptors: Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug-related side effects and adverse reactions.

Selection criteria

Inclusion criteria: Only case reports were selected.
Exclusion criteria: clinical trial, systematic review, observational studies, reviews, letters to the editor and update articles. In the literature researched, the following were described and discussed: the evidence regarding risk factors, prevalence, mortality, complications, treatment and prevention of SJS and TEN in

*Corresponding author. E-mail: ricardo.eccard@gmail.com.

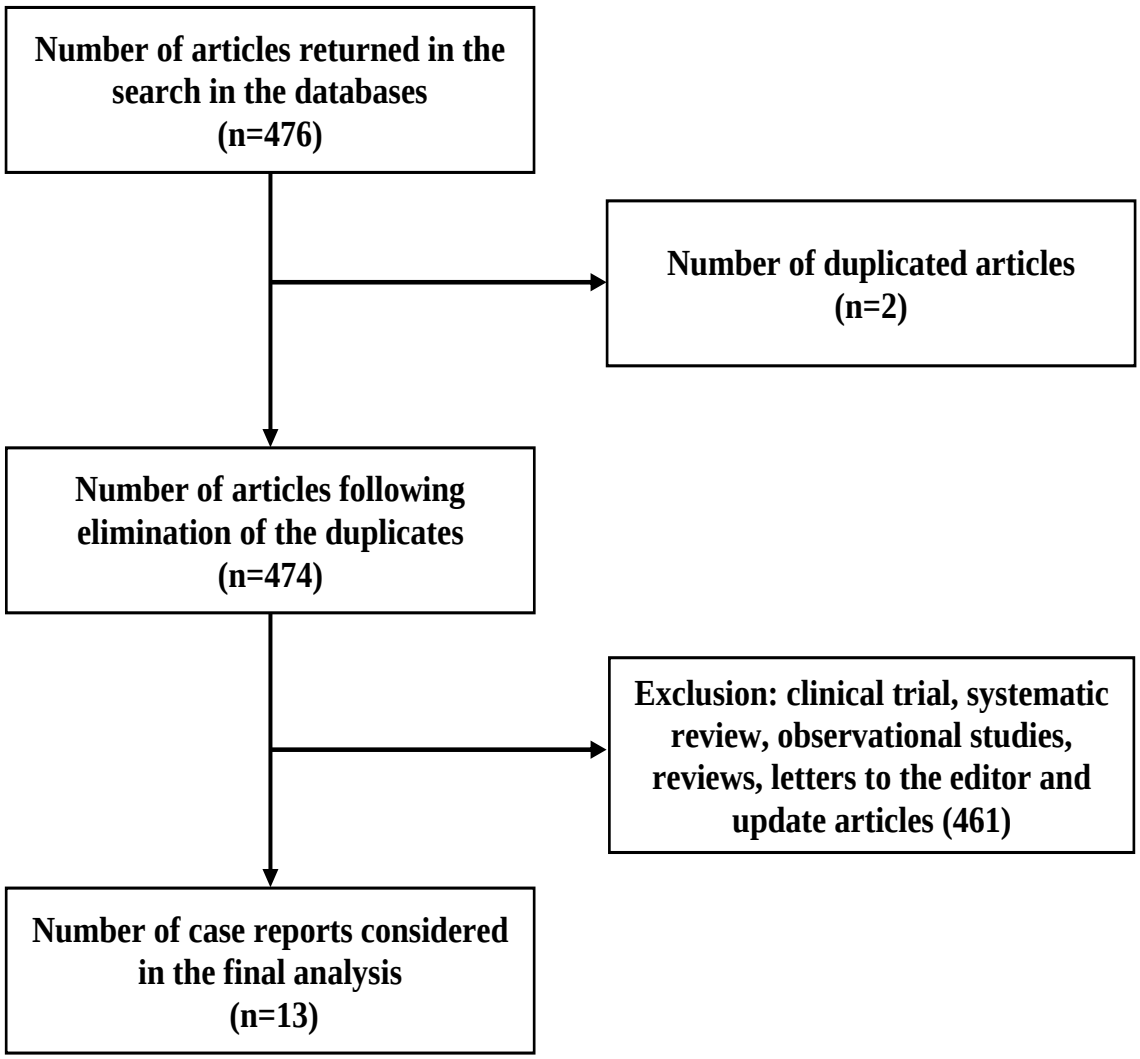

Figure 1. Process of study selection.
Source: Adapted figure: Galvão et al. (2015) and Williams et al. (2015).

hospitalized patients.

Study populations' ages were classified in accordance with the suggestions of the National Institute of Health. Age filters include: "80 and over: 80+ years; Aged: 65+ years; Middle Aged: 45-64 years; Adult: 19-44 years; Adolescent: 13-18 years; Child: 6-12 years; Preschool Child: 2-5 years; Infant: 1-23 months; Newborn: birth-1 month" (NIH, 2014).

Countries were classified according to economic development category as either 'High-income' (HI), 'Upper-middle income' (UMI), 'Lower-middle income' (LMI), or 'Low-income' (LI), depending on how they were categorized by the World Bank (2017).

The World Bank classifies countries into four income groups. Economies were divided according to 2016 Gross National Income (GNI) per capita with income being categorized as: "(i) Low income: per capita GNI of US$1,025 or less, (ii) Low-middle income: per capita GNI between US$1,026 and US$4,035, (iii) Upper-middle income: per capita GNI between US$4,036 and US$12,475, and (iv) High-income: per capita GNI of US$12,476 and over".

Countries were classified according to geographical regions (continental), based on their categorization by the United Nations (2016).

RESULTS

A total of 13 case reports were selected for the research (Figure 1). Five case reports were found in the LILACS database, four in MEDLINE, and four in PUBMED (Table 1). Reports on pediatric patients who suffered SJS and TEN were not found in the literature.

The data obtained from the case reports selected were grouped in Table 1, using the following information from each study: study's countries of origin, patient age, sex, etiology, diagnosis, drug which caused ADR and treatment. The countries with the highest number of studies published were India (2), Brazil (2), Colombia (2) and United States (2). In all of the cases reviewed, the lesion was treated topically and with corticosteroids in order to delay the unregulated immune response caused by SJS and TEN, in addition to removal of the drug that caused the ADR (Table 1). All the patients presented

Table 1. Description of the cases diagnosed as SJS, TEN and SJS/TEN in the MEDLINE, LILACS and PubMed databases (January 1981 - January 2016).

Reference	Occurrence	Years	Sex	History	Diagnosis	Drug	Treatment
Andreoli et al. (2008)	Argentina	20	F	Epilepsy.	SJS, TEN	Lamotrigine	-Suspension of lamotrigine; treatment of the lesions; venous hydration.
Falcão et al. (2008)	Brazil	26	M	Antibiotic use (72 h)	SJS	Trimethoprim-sulfamethoxazole	-Suspension of the drug; treatment with corticosteroids and surgery; treatment of the cutaneous lesions.
Jao et al. (2010)	USA	57	F	Patient with HIV	SJS and liver failure	Nevirapine	-Topical treatment of the cutaneous lesions; suspension of the drug; liver transplant.
Hsieh et al. (2009)	China	82	F	Patient receiving treatment for leukemia	SJS	Imatinib combined with allopurinol	-Intensive care; oral steroids with anti-histamines were used in the treatment of the severe cutaneous reaction.
Castana et al. (2009)	Greece	38	M	Epilepsy	SJS	Valproic acid	-Specific treatment for burns; interruption of the drug; steroids and topical antibiotics.
Salama (2009)	USA	29	M	Crohn's Disease and treatment with adalimumab (subcutaneous route). Progressed to cellulitis in a lower limb.	Non-specific ADR and SJS	Adalimumab	-Suspension of the drug; - Antibiotic therapy.
Mantilla et al. (2009)	Colombia	21	F	Epilepsy treated with valproic acid and phenytoin	TEN	Valproic acid	Suspension of the drug; -Venous hydration; -Administration of corticosteroids.
Garcia et al. (2010)	Brazil	61	F	Postherpetic neuralgia	SJS, TEN	Carbamazepine	-Suspension of the drug; -Venous hydration.
Quinones et al. (2011)	Cuba	69	F	Amygdalitis treated with antibiotics over two week.	SSJ, TEN.	Antibiotic - ciprofloxacin	-Clinical, dermatological and otorhinolaryngological monitoring; -Venous hydration.
Das et al. (2011)	India	18	F	Malaria	SJS	Chloroquine	-Surgery and superficial lamellar dissection of the cornea to separate conjunctival-corneal adhesions; -Suspension of the drug; -Topical treatment of the lesions.
Martínez-Pérez et al. (2012)	Spain	36	M	Epilepsy and alcoholism	SJS	Calcium carbimide - Tryptizol	Suspension of the drugs; -Use of intravenous corticoids; - Topical antibiotics; - Treatment of skin lesions.

Table 1. Contd.

Dominguez et al. (2012)	Colombia	67	F	Treatment of epilepsy with phenytoin: 100 mg intravenous bolus and 300 mg/day (oral)	SJS	Phenytoin	-Suspension of the drug; -Correction of electrolyte disturbance; -Treatment of the skin lesions with dipyrone.
Kaur (2013)	India	47	F	Epilepsy	TEN	Valproic acid/lamotrigine	-Intensive care; -Suspension of the drug; -Clobazam 20 mg/day was initiated for prophylaxis of the epileptic crises.
Kaur (2013)	India	26	F	Bipolar and obsessive-compulsive disorder Treatment with lamotrigine	TEN	Valproic acid/propanalol/ risperidone/lamotrigine	Treated with prednisolone 40 mg/day; -Venous hydration.

sequelae and scars from the epidermal lesions. Those who were affected in the oral and ocular mucosa recovered more slowly than those who had been affected in other parts of the body.

Most of the cases (54%) developed adverse reactions to anticonvulsant drugs. The most common were valproic acid, lamotrigine and carbamazepine. The incidence of reactions with these drugs was higher in female patients (86%). Several cases (15%) were related to the use of antibiotics.

In 46% of the cases, the patients had a history of epilepsy. It can be confirmed that in only two cases (HIV, and a patient receiving chemotherapy treatment for cancer), corresponding to 15% of cases, was there a higher possibility of the patients' immunosuppression. Corticosteroid use was present in 46% of the cases. In 69% of all cases, the patients were female. The patients' age range varied from 18 to 82 years old. In relation to age groups, 54% of the cases were adult, 23% were middle-aged, 15% were aged, 8% were adolescents and 8% were aged, over 80 years old. Regarding the actions taken as treatment, the suspension of drugs and the treatment of skin lesions were undertaken in 85 and 54% of the cases, respectively. None of the evaluated studies were used as treatment for immunomodulating therapies.

A large proportion of the countries where the cases of SJS, TEN and the combination of both took place were high or upper middle income (Table 2). A total of six cases, corresponding to 46% of total cases, occurred in the Latin American and Caribbean region. SJS in association with TEN is concentrated in Latin America and the Caribbean, and in upper middle-income countries (Table 2). SJS affected patients in the following countries: Brazil (1), China (1), Greece (1), United States (2), India (1), Spain (1), and Colombia (1). TEN, on the other hand, was found in Colombia (1) and India (2). The combination of these two conditions was found in Argentina (1), Brazil (1) and Cuba (1).

DISCUSSION

The present study showed that the anticonvulsants were drugs suspected to be related to SJS and TEN conditions. Moreover, the antibiotics were involved in more than one case. The main drugs mentioned in the literature as triggers of the SJS and TEN reactions were the sulfonamides, anti-inflammatories, penicillin, barbiturates, allopurinol, antiepileptics and vaccines (French, 2006; Mendonça, 2009). Another study by Arantes et al. (2017), conducted in the city of Brasilia, Brazil, found that anticonvulsants, antibiotics and analgesics were the main drugs suspected to be related to these conditions. The study's results, therefore, appear to be consistent with the data in the already-published literature.

One possible explanation for the development of SJS and TEN reactions in patients seems to be related to thehuman leukocyte antigen (HLA) system, as a study by Adkinson Jr. et al. (2002) suggested that there is a correlation between the use of an anticonvulsant in the case of their study, carbamazepine and the activation of the unregulated cytotoxic response, via the HLA system, with consequent appearance of the characteristic SJS and TEN reactions.

Chloroquine and nevirapine were also drugs used by the patients who had these reactions, according to the present study's results. This finding too is consistent with already-published

Table 2. Countries where the cases of SJS, TEN and the combination of both took place were high or upper middle income .

Country	Geographic Region	Income Level	Number of cases
Argentina	Latin America	Upper middle income	1 case: SJS associated with TEN
Brazil	Latin America	Upper middle income	1 case: SJS; 1 case: SJS associated with TEN
China	Asia	Upper middle income	1 case: SJS
Colombia	Latin America	Upper middle income	1 case: SJS; 1 case: TEN
Cuba	Caribbean	Upper middle income	1 case: SJS associated with TEN
Greece	Europe	High Income	1 case: SJS
India	Asia	Lower middle income	1 case: SJS; 1 case:TEN
Spain	Europe	High income	1 case: SJS
The United States	Northern America	High income	2 cases: SJS

Source: United Nations (2016); World Bank (2017).

studies, as one systematic review by Patel et al. (2013) showed that chloroquine and nevirapine were associated with the conditions of SJS and TEN in 7 and 4% of cases, respectively.

Biological therapies such as Adalimumab have also been related to severe reactions. This study showed that one patient developed SJS after treatment with this drug. Another study, published by Owczarczyk-Saczonek et al. (2016) showed that etarnecept, which is of the same class as Adalimumab, that is to say, a tumor necrosis factor-α inhibitor, has been associated as a cause of severe reactions such as SJS and TEN. In the case of these reactions, both etarnecept and Adalimumab have been used for treating inflammatory diseases mediated by the immune system, such as rheumatoid arthritis and Crohn's disease (Kuek et al., 2007).

The use of calcium carbimide has been associated with unpleasant reactions, including dermatological reactions. There are also safety concerns related to effects on the liver (Verge et al., 2006). One of the studies selected (Martínez-Pérez et al., 2012), mention the case of a patient with SJS whose history included the use of calcium carbimide for treatment of alcoholism. In this case, the patient was prescribed paracetamol and amoxicillin for treating the effects of general malaise, fever, rash and itchiness in the eyes, which had first led the patient to seek medical attention. After some hours, following the use of these drugs, the patient presented the characteristic reactions of SJS. In this case, as the use of amoxicillin has been associated with SJS (Zaidi et al., 2017), the use of this product may be a confounding factor in the analysis of the causal relationship between calcium carbimide and SJS. In relation to paracetamol, on the other hand, one recently-published study by Lebrun-Vignes (2017) suggested that there is no evidence for a causal relationship between the use of paracetamol and the occurrence of SJS and TEN.

According to the present results, most patients had a history of epilepsy. This condition seems to be directly related not to the effects of SJS and TEN, but rather to the use of drugs for controlling epileptic crises, such as carbamazepine and phenytoin, which have an already well-established causal relationship with SJS and TEN (Trivedi et al., 2017). Approximately, 75% of cases of SJS and TEN are caused by drugs (Mockenhaupt, 2017).

The medical histories of the patients in the present study were consistent with the groups at risk of developing SJS and TEN. According to the present study's results, the medical history of some patients is related to infections, such as HIV, amygdalitis and antibiotic use. The patients with HIV and cancer identified in the present study, furthermore, had a higher possibility of presenting immunosuppression. According to the scientific literature, the condition of compromise of the immune system is considered to be a risk factor for SJS and TEN (Wong et al., 2016).

One study by Mockenhaupt (2017) suggested that other possible causes for the development of SJS and TEN are bacterial infections, nonspecific viral infections affecting the airways, human immunodeficiency virus, vaccination and graft-versus-host disease. There are also idiopathic cases, in which no adjacent cause is identified.

Regarding the complications reported, two of the patients studied died, as a result of sepsis and multiple organ failure (Garcia et al., 2010; Quinones et al., 2011), while one of the patients presented clinically relevant ocular complications (Das et al., 2011). The literature corroborates these results, as the most frequent complications resulting from SJS and TEN are sepsis, which can lead to death, and keratoconjunctivitis, which can lead to conjunctival retraction, scarring, and corneal lesions. In these cases, the sequelae are more common in the later phase of the development of TEN (Sotelo-Cruz et al., 2005).

The medical treatment of SJS and TEN is the immediate suppression of the use of the drugs which could have been causing the reactions, clinical, dermatological and otorhinolaryngological monitoring, correction of electrolyte disturbance, intensive care, venous hydration, liver transplant, clobazam for prophylaxis of the epileptic crises, and administration of systemic corticoids and topical antibiotics. The treatment

of the cutaneous lesions was also undertaken in all cases (Andreoli et al., 2008; Dominguez et al., 2012). According to our study's results, corticosteroids were not administered to all patients. One study by Chantaphakul et al. (2015) suggested that corticosteroid use was greater in a group of patients with SJS and TEN who survived, in comparison with a group of patients who did not. This same study, moreover, suggested that the use of corticosteroids in these patients prevents ocular complications. On the other hand, a separate study by Lee et al. (2012) suggested that it is necessary to undertake controlled clinical trials in order to assess the real benefits of corticosteroid use in patients with SJS and TEN.

According to the results of this study, immunomodulating therapies were not used in the patients' treatment. In a systematic review study published in the literature, treatment of patients with SJS and TEN with immunomodulating therapies, including glucocorticosteroids, intravenous immunoglobulins, cyclosporine, plasmapheresis, thalidomide, cyclophosphamide, hemoperfusion, tumor necrosis factor inhibitors, and granulocyte colony-stimulating factors, only glucocorticosteroids and cyclosporine were the most promising (Zimmermann et al., 2017). Another study showed that the use of cyclosporin in patients with SJS and TEM was associated with decreased mortality (Kirchhof et al., 2014). One systematic review with meta-analysis suggested that intravenous immunoglobulin combined with corticosteroid may reduce the recovery time of patients with SJS and TEN, mainly among Asians (Ye et al., 2016).

According to the results, the incidence of SJS and TEN was high in the age range from 18 to 82 years old. Furthermore, this incidence was greater among the adults. According to the NIH (2014), the adult age range is from 19 to 44 years old. According to Çekiç et al. (2016), the conditions of SJS and TEN affect all age groups, but have been observed more among adults. One study by Bequignon et al. (2015) showed that the incidence varied in the age range from 17 to 91 years old. The results of another study, this one by Lim et al. (2016), showed that SJS and TEN were more likely to affect women (56.6%) and that the patients' mean age was 54.3 years old. That is to say, in relation to gender, our results are in accordance with the literature; however, this study indicated that the age group made up of the middle-aged was affected most, which diverges from our results.

Another study by Wang (2017) showed that female gender, age above 70 years old and infection status were not significantly different between the patients who survived and those who died. In that same study, furthermore, the number of cases with SJS and TEN in the group aged 10 years old or less, and in the group aged between 81 and 91 years old, was low, with 1 and 2 patients, respectively. The age ranges with the most cases were 31 to 40 years old (20 patients), 21 to 30 years old (17 patients), and 51 to 60 years old (16 patients).

A study by Yang et al. (2016) showed age to be a risk factor for mortality from SJS and TEN. Mortality among patients aged 40 years old or over was significantly higher in comparison with groups of patients aged below 40 years old.

Although the results showed that more cases originate from countries in Latin America, the data from the literature suggests that few countries from Latin America have published scientific work on SJS and TEN. Although, Brazil and Mexico are on the list of countries publishing most worldwide, when one compares their production with that of countries from other continents, such as North America, Europe and Asia, it may be seen that they are among the last on the list (Sweileh, 2017).

It is believed that the low number of cases selected in this study is a limiting factor in the discussion and conclusion regarding the relationship between the occurrence of SJS and TEN and aspects relating to countries' levels of economic development and ethnic characteristics of the populations of different continents. According to Hsu et al. (2016), future studies should investigate different populations' ethnic, genetic and economic aspects as well as their access to health care and their use of drugs.

Asian countries, such as India and China, were among the countries where there were cases of SJS and TEN, according to the present study's results. Asians are more likely to develop these conditions because of the use of specific drugs, such as carbamazepine, due to specific genetic characteristics related to the HLA system. Hispanics, on the other hand, seem to be less affected by SJS and TEN (Blumenthal et al., 2015).

Infection by HIV is also a risk factor for developing SJS and TEN (Thong, 2013). Some countries of Africa and Asia, such as India, have a high number of people living with the virus. In India, for instance, over 2,100,000 people live with the virus (WHO, 2017). The population of South Africa is only 0.7% of the world's total population, but has 17% of the burden caused by the HIV virus.

In poorer countries, there is a paucity of data on SJS and TEN (Kannenberg et al., 2012). Generally speaking, studies on the incidence and prevalence of SJS and TEN are undertaken in the developed countries (Knight et al., 2015). The difficulties related to the precise diagnosis of SJS and TEN may be related to underestimating the number of cases (Lim et al., 2016).

The results showed that most countries where the cases occur are upper middle and high-income. However, in the Latin American and Caribbean region, where there were the most cases of SJS and TEN, according to the present study's results, in spite of the advances which have taken place over the last 60 years, inequalities in accessing the health services remain high (Barreto et al., 2012). One problem to be faced in less-developed countries is the limited access to medical resources,

which could stabilize the health conditions of patients affected by SJS and TEN (Thong, 2013). Asians may be more prone to developing SJS and TEN, due to genetic characteristics (Blumenthal et al., 2015). Some countries in the South of Asia, such as India, are among those where one finds the world's largest social and economic inequalities, which also have an impact on healthcare (Zaidi et al., 2017). It follows that the patients who are most vulnerable to reactions linked to SJS and TEN may experience difficulty accessing the health services. According to Ellender et al. (2014), patients with extensive skin involvement should be admitted to an intensive care unit or a burn unit if possible. In countries with fewer resources, intensive care units may lack adequate infrastructure for protecting the patients' lives.

As a limitation of this study, emphasis is placed on the fact that the clinical trials and systematic reviews have not been included. This study only included case reports. Despite being considered a low level of scientific evidence (Oxford Centre for Evidence-based Medicine, 2009), case reports are important for hypothesis generation and can lead to more controlled studies (Burns et al., 2011). Although this impact on the quality of the results generated, the study contributes to the discussion of important questions, such as the severity of these conditions, which have as yet been little studied. In addition to this, the low number of studies selected could compromise the generalization of the results.

Conclusions

Among the main risk factors identified by the study, one finds the use of anticonvulsants and female gender. The immunosuppressed, such as patients infected by HIV or who are receiving chemotherapy and individuals of middle age were also identified as being at-risk groups. Most cases of SJS and TEN were caused by drug use. Previously healthy people who were making use of drugs such as antibiotics and nonsteroidal anti-inflammatories may also develop adverse reactions. These reactions are not yet totally understood and there are cases without a defined cause. There may be other, currently unknown, factors acting in the development of these conditions. The main therapeutic action for SJS and TEN is the suspension of the use of the drug that triggered the inflammatory process, and the topical treatment of the lesions caused. SJS and TEN have been found in regions where the patients experience difficulty accessing the health services. This may be a problem, as patients affected by SJS and TEN require rapid attendance and the presence of available medical resources. Considering the impact that these conditions have on patients' health, it is important that further studies should be undertaken in order to investigate the risk factors, ethnic and genetic aspects, the costs associated, effective preventive and therapeutic measures, and access to healthcare among the different populations affected by these conditions.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES

Adkinson Jr NF, Essayan D, Gruchalla R, Haggerty H, Kawabata T, Sandler JD, Updyke L, Shear NH, Wierda D (2002). Task force report: future research needs for prevention and management of immune-mediated drug hypersensitivity reactions. J. Allergy Clin. Immunol. 109(3):461-478.

Alerhand S, Cassella C, Koyfman A (2016). Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the Pediatric Population: A Review. Pediatr. Emerg. Care 32(7):472-476.

Andreoli MX, Tellez M, Guglielmone A, Velásquez CM, Dilsizian VN (2008). Progresión a necrólisis epidérmica tóxica por uso de lamotrigina: A propósito de un caso. Rev. Argent. Dermatol. 89(3):188-192.

Arantes LB, Reis CS, Novaes AG, de Carvalho MR, Göttems LBD, Novaes MRCG (2017). Stevens-Johnson syndrome and toxic epidermal necrolysis: epidemiological and clinical outcomes analysis in public hospitals. An. Bras. Dermatol. 92(5):661-667.

Barreto SM, Miranda JJ, Figueroa JP, Schmidt MI, Munoz S, Kuri-Morales PP, Silva JB Jr (2012). Epidemiology in Latin America and the Caribbean: current situation and challenges. Int. J. Epidemiol. 41(2):557-571.

Bequignon E, Duong TA, Sbidian E, Valeyrie-Allanore L, Ingen-Housz-Oro S, Chatelin V, Coste A, Wolkenstein P, Chosidow O, Papon JF (2015). Stevens-Johnson Syndrome and Toxic Epidermal NecrolysisEar, Nose, and Throat Description at Acute Stage and After Remission. JAMA Dermatol. 151(3):302-307.

Blumenthal KG, Wickner PG, Lau JJ, Zhou L (2015). Stevens-Johnson syndrome and toxic epidermal necrolysis: A cross-sectional analysis of patients in an integrated allergy repository of a large healthcare system. J. Allergy Clin. Immunol. Pract. 3(2): 277-280.

Bouvy JC, De Bruin ML, Koopmanschap MA (2015). Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies. Drug Saf. 38(5):437-453.

Bulisani ACP (2006). Síndrome de Stevens-Johnson e necrólise epidérmica tóxica em medicina intensiva. Rev. Bras. Ter. Intensiva. 18(3).

Burns PB, Rohrich RJ, Chung KC (2011). The Levels of Evidence and their role in Evidence-Based Medicine. Plast Reconstr Surg.128(1):305–310.

Castana O, Rempelos G, Angiotos G, Apostopoulou C, Dimitrouli A, Alexakis D (2009). Stevens-Johnson Syndrome: a Case Report. Ann. Burns Fire Disasters 22(3):147-151.

Çekiç S, Canıtez Y, Sapan N (2016). Evaluation of the patients diagnosed with Stevens Johnson syndrome and toxic epidermal necrolysis: a single center experience. Turk. Pediatr. Ars. 51(3):152-158.

Chantaphakul H, Sanon T, Klaewsongkram J (2015). Clinical characteristics and treatment outcome of Stevens-Johnson syndrome and toxic epidermal necrolysis. Exp. Ther. Med. 10(2):519-524.

Das JK, Medhi J, Chakravart R, Soibam R (2011). Mucous membrane grafting for the post-Steven–Johnson syndrome symblepharon: A case report. Indian J. Ophthalmol. 59(3):231-233.

Dominguez CD, Briceño JF, Marin CB, Ospina CA (2012). Síndrome de Stevens Johnson asociado a fenitoína en una paciente colombiana con síndrome convulsivo focal. MÉDICAS UIS 245(2):155-162.

Ellender RP, Peters CW, Albritton HL, Garcia AJ, Kaye AD (2014). Clinical considerations for epidermal necrolysis. Ochsner. J. 14:413-417.

Falcão PGCB, Santos TS, Avelar RL, Antunes AA, Pita Neto IC, Dourado E (2008). Síndrome de Stevens-Johnson associada ao uso de antimicrobiano. Rev. Gaúcha. Odontol. 56(3): 337-340.

French LE (2006). Toxic Epidermal Necrolysis and Stevens Johnson Syndrome: Our Current Understanding. Allergol. Int. 55(1):9-16.

Galvão TF, Pansani TSA, Harrad D (2015). Principais itens para relatar Revisões sistemáticas e Meta-análises: A recomendação PRISMA.

Epidemiol. Serv. 24(2):335-342.
Garcia JBS, Ferro LSG, Carvalho AB, Rocha RM, Souza LML (2010). Reação cutânea grave induzida por carbamazepina no tratamento da neuralgia pós-herpética: relato de caso. Rev. Bras. Anestesiol. 60(4):433-437.
Hsieh HJ, Chan ALF, Lin SJ (2009). Stevens-Johnson Syndrome Induced by Combination of Imatinib and Allopurinol. Chemother. 55(4):197-199.
Hsu DY, Brieva J, Silverberg NB, Silverberg JI (2016). Morbidity and Mortality of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in United States Adults. J. Investig. Dermatol. 136(7):1387-1397.
Jao J, Sturdevant M, Del Rio Martin J, Schiano T, Fiel MI, Huprikar S (2010). Nevirapine-Induced Stevens Johnson–Syndrome and Fulminant Hepatic Failure Requiring Liver Transplantation. Am. J. Transplant. 10(7):1713-1716.
Kannenberg SMH, Jordaan HF, Koegelenberg CFN, Groote-Bidlingmaier FV, Visser WI (2012). Toxic epidermal necrolysis and Stevens–Johnson syndrome in South Africa: a 3-year prospective study. Q. J. Med. 105:839-846.
Kaur S, Dogra A (2013). Toxic Epidermal Necrolysis Due to Concomitant Use of Lamotrigine and Valproic Acid. Ind. J. Dermatol. 58(5): 406.
Kinoshita Y, Saeki H (2017). A review of toxic epidermal necrolysis management in Japan. Allergol Int. 66(1): 36-41.
Kirchhof MG, Miliszewski MA, Sikora S, Papp A, Dutz JP (2014). Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine. J. Am. Acad. Dermatol. 71(5):941-947.
Knight L, Todd G, Muloiwa R, Matjila M, Lehloenya RJ (2015). Stevens Johnson Syndrome and Toxic Epidermal Necrolysis: Maternal and Foetal Outcomes in Twenty-Two Consecutive Pregnant HIV Infected Women. PLoS one 10(8):e0135501.
Kuek A, Hazleman BL, Östör AJK (2007). Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad. Med. J. 83(978):251-260.
Kumar PNS, Thomas B, Kumar K, Kumar S (2005). Stevens–Johnson syndrome–toxic epidermal necrolysis (SJS–TEN) overlap associated with carbamazepine use. Indian. J. Psychiatr. 47(2):121-123.
Lebrun-Vignes B, Guy C, Jean-Pastor MJ, Gras-Champel V, Zenut M (2017). The French Network of Regional Centres of Pharmacovigilance and the French Investigators for Adverse Skin Reactions to Drugs. Is acetaminophen associated with a risk of Stevens–Johnson syndrome and toxic epidermal necrolysis? Analysis of the French Pharmacovigilance Database. Br. J. Clin. Pharmacol. pp. 331-338.
Lee HY, Dunant A, Sekula P, Mockenhaupt M, Wolkenstein P, Valeyrie-Allanore L, Naldi L, Halevy S, Roujeau JC (2012). The role of prior corticosteroid use on the clinical course of Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control analysis of patients selected from the multinational EuroSCAR and RegiSCAR studies. Br J. Dermatol. 167:555-562.
Lim VM, Do A, Berger TG, Nguyen AH, DeweeseJ, Malone JD, Jordan K, Hom F, Tuffanelli L, Fillari P, Siu S, Grossman R (2016). A decade of burn unit experience with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: Clinical pathological diagnosis and risk factor awareness. Burns 42(4):836-843.
Mantilla JC, Pico-Espinosa OJ, Naranjo LFF, Ordóñez DLT, Castro NMM, Herrera NU (2009). Necrólisis epidérmica tóxica asociada a anticonvulsivantes. Presentación de un caso en el Hospital Universitario de Santander, Bucaramanga, Colombia. MÉDICAS UIS 22: 238-245.
Martínez-Pérez JD, Caldevilla-Bernardo R, Perales-Pardo F, Pérez-Gómez (2012). Síndrome de Stevens-Johnson, a propósito de un caso de fiebre y erupción cutánea. Rev. Semergen. 38(4): 245-247.
Mendonça RJ, Netto JC (2009). Aspectos Celulares Da Cicatrização. An. Bras. Dermatol. 84(3):257-262.
Mockenhaupt M (2011). The current understanding of Stevens–Johnson syndrome and toxic epidermal necrolysis. Expert Rev. Clin. Immunol. 7(6):803-815.
Mockenhaupt M, Hautreaktionen DS (2017). Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. National Organization for Rare Disorders (NORD). Available at: https://rarediseases.org/rare-diseases/stevens-johnson-syndrome-and-toxic-epidermal-necrolysis/
Nagao-Dias AT, Barros-Nunes P, Coelho HLL, Solé D (2004). Reações alérgicas a medicamentos. J. Pediatr. 80(4):259-266.
Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009). Available at: http://www.cebm.net/blog/2009/06/11/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
Owczarczyk-Saczonek A, Zdanowska N, Znajewska-Pander A, Placek W (2016). Stevens-Johnson syndrome in a patient with rheumatoid arthritis during long-term etanercept therapy. J. Dermatol. Case Rep. 10(1):14-16.
Patel TK, Barvaliya MJ, Sharma D, Tripathi C (2013). A systematic review of the drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Indian population. Indian J. Dermatol. Venereol. Leprol. 79(3):389-398.
Pereira JG (2012). Reações Adversas a Medicamentos. Secretaria de Ciência, Tecnologia e Insumo Estratégicos/MS-FTN. Available from: http://portal.saude.gov.br/portal/arquivos/multimedia/paginacartilha/docs/reacoes.pdf.
Quinones HJ, Chavez V, Ángel J, Hernandez OB (2011). Síndrome de Stevens-Johnson: presentación de un caso. AMC 15(3):576-584.
Salama M, Lawrance IC (2009). Stevens Johnson Syndrome complicating adalimumab therapy in Crohn's disease. World J. Gastroenterol. 15(35):4449-4452.
Schneider JA, Cohen PR (2017). Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Concise Review with a Comprehensive Summary of Therapeutic Interventions Emphasizing Supportive Measures. Adv. Ther. 34(6):1235-1244.
Sotelo-Cruz N, Hurtado-Valenzuela JG, Rascón-Alcantar A (2005). Síndrome de Stevens-Johnson. Informe de 7 casos. Bol. Med. Hosp. Infant. Mex. 62(1):25-32.
Sun J, Liu J, Gong QL, Ding GZ, Ma LW, Zhang LC, Lu Y (2014). Stevens–Johnson Syndrome and toxic epidermal necrolysis: a multi-aspect comparative 7-year study from the People's Republic of China. Drug Des. Dev. Ther. 8:2539-2547.
Sweileh WM (2017). Bibliometric analysis of literature on toxic epidermal necrolysis and Stevens-Johnson syndrome: 1940 – 2015. Orphanet. J Rare Dis. 12:14.
Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W (2013). Relationship Between the HLA-B*1502 Allele and Carbamazepine-Induced Stevens-Johnson Syndrome and Toxic Epidermal NecrolysisA Systematic Review and Meta-analysis. JAMA Dermatol.149(9):1025-1032.
Thong BYH (2013). Stevens-Johnson syndrome / toxic epidermal necrolysis: an Asia-Pacific perspective. Asia Pac. Allergy. 3(4):215-223.
Trivedi BS, Darji NH, Malhotra SD, Patel PR (2017). Antiepileptic Drugs-induced Stevens-Johnson syndrome: A case Series. J. Basic Clin. Pharma. 8:42-44.
United Nations (UN) (2016). Statistics Division. Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings. Available at: https://unstats.un.org/unsd/methods/m49/m49regin.htm#
Upadhyaya SK, Raina RS, Sharma A, Thawani V, Dimari D (2012). Carbamazepine-induced erythema multiforme major in an epileptic patient with bipolar affective disorder. J. Pharmacol. Pharmacother. 3(2): 202-204.
US National Institute of Health (NIH) (2014). Age filters. Available at: http://www.ncbi.nlm.nih.gov/books/NBK3827/. (Accessed 16 April 2016).
Verge C, Lucena MI, López-Torres E, Puche-García MJ, Fraga E, Romero-Gomez M, Andrade RJ (2006). Adverse hepatic reactions associated with calcium carbimide and disulfiram therapy: Is there still a role for these drugs. World J. Gastroenterol. 12(31): 5078-5080.
Walley T (2000). Davies Textbook of Adverse Drug Reactions. Postgrad. Med. J. 76(901):741.
Wang L, Mei XL (2017). Retrospective Analysis of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in 88 Chinese Patients. Chin. Med. J. 130(9):1062-1068.
Williams RJ, Tse T, Di Piazza K, Zarin DA (2015). Terminated Trials in the Clinical Trials.gov Results Database: Evaluation of Availability of.

Primary Outcome Data and Reasons for Termination. PLoS one 10(5): e0127242
Wong A, Malvestiti AA, Hafner MFS (2016). Stevens-Johnson syndrome and toxic epidermal necrolysis: a review. Rev. Assoc. Med. Bras. 62(5):468-473.
World Bank (2017). World Bank Open Data. Free and open access to global development data. Available at: https://data.worldbank.org Accessed on 24 December 2017.
World Health Organization (WHO) (2017). Number of people (all ages) living with HIV Estimates by country. Available at: http://apps.who.int/gho/data/view.main.22100?lang=en Accessed on 20 December 2017.
Yamane Y, Matsukura S, Watanabe Y, Yamaguchi Y, Nakamura K, Kambara T, Ikezawa Z, Aihara M (2016). Retrospective analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis in 87 Japanese patients - Treatment and outcome. Allergol Int. 65(1):74-81.
Yang MS, Lee JY, Kim J, Kim GW, Kim BK, Kim JY, Park HW, Cho SH, Min KU, Kang HR (2016). Incidence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Nationwide Population-Based Study Using National Health Insurance Database in Korea. PLoS One 11(11):e0165933.
Ye LP, Zhang C, Zhu QX (2016). The Effect of Intravenous Immunoglobulin Combined with Corticosteroid on the Progression of Stevens- Johnson Syndrome and Toxic Epidermal Necrolysis: A Meta-Analysis. PLoS ONE 11(11):e0167120.
Zaidi M, Zaidi SK, Bhutto M, Umer MY (2017). Amoxycillin and clavulanic acid induced Stevens-Johnson syndrome: A case report. EXCLI J. 16:748-751.
Zaidi S, Saligram P, Ahmed S, Sonderp E, Sheikh K (2017). Expanding access to healthcare in South Asia. BMJ. 357:j1645.
Zimmermann S, Sekula P, Venhoff M, Motschall E, Knaus J, Schumacher M, Mockenhaupt M (2017). Systemic Immunomodulating Therapies for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis. JAMA Dermatol. 153(6):514-522.

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