Scientific evidence on leg ulcers as leprosy sequel

Evidências científicas sobre as úlceras de pernas como sequela da hanseníase

Evidencias científicas sobre las úlceras de piernas como secuela de la lepra

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Abstract
Objective: To investigate the scientific evidence on leg ulcers as leprosy sequel.
Methods: This is an Integrative Literature Review (ILR). In order to identify the theme and research question, the PICo strategy was used, in the sequence the search was carried out in Index to Nursing and Allied Health Literature (CINAHL), Latin American & Caribbean Literature in Health Sciences (LILACS), (BDENF), EMBASE (Elsevier), PUBMED (National Library of Medicine), SCOPUS (Elsevier), Web of Science (Clarivate Analytics) databases. Specific descriptors were selected for each of them and respective search strategies were created. The languages considered were English, Portuguese and Spanish. The ILR period was indeterminate. For the study selection, the Ryyan tool was used and allowed two of the authors to independently include, exclude or remain undecided, disagreements were solved by a third party. The selected articles have been ranked according to the Agency for Healthcare Research and Quality (AHRQ). And for interpretation of results, the articles were grouped by similarity and categorized into author, country year, level of evidence, objectives and results, conclusion and recommendation.
Results: 415 studies were identified and 10 were included in the review. The main outcome was the topical treatment of ulcers, the vulnerabilities and the determinants that afflict those affected by leprosy were not studied.
Conclusion: There is no strong evidence on therapies for the treatment of leprosy-induced leg ulcers that support the reduction of disabling sequel caused by disease perpetuating stigma and social inequality.

Resumo
Objetivo: Investigar as evidências científicas sobre as úlceras de pernas como sequela da hanseníase.
Métodos: Revisão Integrativa da Literatura (RIL). Para identificação do tema e questão de pesquisa, utilizou-se a estratégia PICo, na sequencia procedeu-se a busca nas bases de dados: *Index to Nursing and Allied Health Literature (Cinahl)*, Literatura Latino-americana e do Caribe em Ciências da Saúde (Lilacs), Banco de dados em Enfermagem (BDENF), *EMBASE (Elsevier), PUBMED (National Library of Medicine), SCOPUS (Elsevier), Web of Science (Clarivate Analytics),* selecionados os descritores específicos para cada uma delas e elaboradas as respectivas estratégias de busca. Os idiomas considerados foram: inglês, português e espanhol. O período da RIL foi indeterminado. Para a seleção dos estudos, utilizou-se a ferramenta *Ryyan* que permitiu dois dos autores independentemente incluir, excluir, ou ficar indeciso, as discordâncias foram solucionadas por um terceiro. Os artigos selecionados foram classificados de acordo com a Agency for Healthcare Research and Quality (AHRQ). E para a interpretação dos resultados os artigos foram agrupados por semelhança e categorizados da seguinte maneira: autor, ano país, nível de evidência, objetivos e resultados, conclusão e recomendação.
Resultados: Identificou-se 415 estudos e 10 foram incluídos na revisão. O resultado principal obtido foi o tratamento tópico da úlcera, as vulnerabilidades e os determinantes que assolam os acometidos pela hanseníase não foram estudados.
Conclusão: Não há fortes evidências sobre as terapias para o tratamento de úlceras de pernas decorrentes da hanseníase que apoiem a diminuição de sequelas incapacitantes ocasionadas pela doença perpetuando o estigma e a desigualdade social.

Resumen
Objetivo: investigar las evidencias científicas sobre las úlceras de piernas como secuela de la lepra.
Métodos: revisión integradora de la literatura (RIL). Para la identificación del tema y pregunta de la investigación, se utilizó la estrategia PICo, luego se procedió a la búsqueda en las bases de datos: *Index to Nursing and Allied Health Literature (Cinahl)*, Literatura Latinoamericana y del Caribe en Ciencias de la Salud (Lilacs), Banco de dados em Enfermagem (BDENF), *EMBASE (Elsevier), PUBMED (National Library of Medicine), SCOPUS (Elsevier), Web of Science (Clarivate Analytics),* se seleccionaron los descriptores específicos para cada una y se elaboraron las respectivas estrategias de búsqueda. Se consideraron los idiomas inglés, portugués y español. El período de la RIL fue indeterminado. Para la selección de los estudios, se utilizó la herramienta *Ryyan*, que permitió dos de los autores independientemente incluir, excluir o estar indeciso, las discrepancias fueron resueltas por un tercero. Los artículos seleccionados se clasificaron según la Agency for Healthcare Research and Quality (AHRQ). Y para la interpretación de los resultados, los artículos se agruparon por semejanza y se categorizaron de la siguiente manera: autor, año, país, nivel de evidencia, objetivos y resultados, conclusión y recomendación.
Resultados: se identificaron 415 estudios y se incluyeron 10 en la revisión. El resultado principal obtenido fue el tratamiento tópico de la úlcera, las vulnerabilidades y los determinantes que asolaron a los afectados por la lepra no fueron estudiados.
Conclusión: no hay fuertes evidencias sobre las terapias para el tratamiento de úlceras de piernas resultantes de la lepra que justifiquen la reducción de secuelas incapacitantes provocadas por la enfermedad, perpetuando el estigma y la desigualdad social.

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Introduction

Although the prevalence of leprosy declined globally from five million in 1980 to two hundred thousand in 2015, Brazil in that same year registered 26,395 new cases.[1,2] In 2016, the national detection of new cases was 25,218, together with India and Indonesia, which reported more than 10,000 new cases per year.[3] These three countries account for 81.0% of newly diagnosed and reported patients worldwide.[4] Through these data, leprosy remains a disease of worldwide concern. The decrease in prevalence can be explained by the early detection of the disease and the implementation of treatment with multidrug therapy since the 1980s.

Leprosy is a multifactorial disease with social and biological components that affect the immune, dermatological, neurological and orthopedic systems and which can lead to numerous physical disabilities. The disease is caused by *Mycobacterium leprae*, an obligate intracellular parasite, which has high infectivity, low pathogenicity and virulence. The bacillus reaches the fibers of the peripheral nervous system, which can lead to weakness and muscular paralysis. The autonomic fibers affected lead to a decrease in the production of the sebaceous and sweat glands, which can render the skin inelastic, dry, with the presence of anhidrosis or hypohidrosis, and which, together with the alteration of the sensory fibers, causes a decrease or loss of the protective sensation. This makes the skin vulnerable to cracks, trauma and the risk of ulceration, especially in the eyes, hands, legs and feet. These factors constitute the genesis of deformities triggered in the majority of cases by mucosal, cutaneous and neurotrophic ulcers.[1,5,6]

Such changes are identified during clinical examination by means of tests that assess the decrease in tactile, thermal and pain sensitivity. Due to these proprioceptive changes and the long-term drug treatment, high rates of cutaneous ulcers are observed, which can lead to severe incapacities due to secondary physical deficiencies that only perpetuate the stigma that afflicts those affected by leprosy.

From the anatomical point of view, there is a narrow areolar cushion between the tibia and the covering skin on the lower third of the leg, and on the back a large set of tendons with a poor protection coating. Due to the orthostatic position in which the human being presents during the life cycle and the importance of lower limbs for human mobility and locomotion, leg ulcer becomes a serious problem for the person diagnosed with leprosy and a challenge for health professionals.[7]

The chronic condition of leg ulcer occurrence as leprosy sequel causes costly costs to the public health system, as well as the personal, physical, social, spiritual and psychological burden of their patients. This disastrous manifestation only perpetuates the stigma and marginalization suffered by people diagnosed with leprosy, in the family, society and even among health professionals.

The Brazilian Ministry of Health publishes manuals that address the treatment and control of leprosy and also discloses the simplified fact sheet of neural functions and degrees of physical disability in eyes, hands, feet and the prevention of complications.[8,9] In our professional practice we did not find consensus on the assessment and treatment used in patients with leg ulcer as leprosy sequel, as well as other factors that may contribute to this clinical situation, making it difficult to assess the effectiveness of treatment of these people. An analysis of the scientific production that deals with leg ulcer care as leprosy sequel is therefore opportune. By unveiling the scientific evidence on the subject it is possible to indicate therapeutic actions to implant advanced clinical practices of nursing and to subsidize the health professionals for a more adequate assistance to the patients with leprosy diagnosis with such sequel.

In view of the above, the objective of the study was to investigate in the national and international literature, scientific evidence on leg ulcers as leprosy sequel.

Methods

This is an Integrative Literature Review (ILR). Integrative review is a specific method that comprises the past of the empirical and theoretical literature of the subject in question.[12] The method was chosen aiming to provide an analysis and synthesis of the phenomenon studied, generating knowledge supported by previous research and pointing out gaps to be studied.

ILR comprises six methodological steps: identification of the theme and research question; establishment of criteria for inclusion and exclusion of studies/sampling or search in the literature; definition of the information to be extracted from the selected studies/categorization of the studies, assessment of the studies included in the integrative review; interpretation of results, presentation of knowledge review/synthesis.[10]

In order to identify the theme and the research question, the PICo strategy was used, being P (population), I (interest phenomenon), Co (context of the study). These elements are essential for the elaboration of the research question, since it systematically directs the search in databases.[14] In view of this concept, the following guiding question was elaborated: what are the scientific evidence identified in the literature about the related factors of people affected by leg ulcer as leprosy sequel?

In the sequence, the Brazilian and international databases were searched. The databases searched were: Index to Nursing and Allied Health Literature (CINAHL), Latin American & Caribbean Literature in Health Sciences (LILACS), Database of Nursing (BDENF), EMBASE (Elsevier), PUBMED (National Library of Medicine), SCOPUS (Elsevier), Web of Science (Clarivate Analytics). For the elaboration of the search strategy, the descriptors specific to each database were selected, as well as free terms for retrieval and identification of a greater number of articles, thus favoring sensitivity (Chart 1). The languages considered were English, Portuguese and Spanish. In relation to the date of publication, in consensus, the authors did not specify a period, thus allowing to scan all the literature registered in the databases.[13]

Chart 1. Search strategy in databases

Databases	Strategy
CINHAL	(leprosy OR "hansen diseases") AND (ulcer OR wound OR "chronic wounds")
EMBASE	(leprosy OR "hansen diseases") AND (ulcer OR wound OR "chronic wounds")
LILAC's/BDENF	(mh:*hanseníase* OR tw:*hanseniase* OR tw:*lepra*$) AND (mh:"*ulcera da perna* OR tw: "*ulcera da perna*") (Portuguese)
PUBMED	("hansen diseases" [all field] OR "leprosy"[MeSH Terms] OR "leprosy"[All Fields]) AND (ulcer"[MeSH Terms] OR "ulcer"[All Fields]) AND ("leg"[MeSH Terms] OR "leg"[All Fields])
SCOPUS	(leprosy OR "Hansen diseases") AND ulcer AND leg
Web of science	(leprosy OR "Hansen diseases") AND ulcer AND leg

LILAC's/BDENF - $ it allows recovery of the root of the term

As inclusion criterion, studies addressing leprosy patients with leg ulcers in humans older than 18 years were considered. Articles that deal with associations of leprosy and other diseases such as carcinoma, chromoblastomycosis, HIV, cutaneous tuberculosis, syphilis, Buruli ulcer, and ulcers with surgical follow-up such as grafts, amputations and other types of surgeries were excluded.

For study selection, the Ryyan tool was used for this step, through which two authors of the study could independently choose to include, exclude and or be undecided when reading titles and abstracts.[15] The disagreements were solved by a third author. In this way, the articles that should be read in full were selected. After this reading, a new round between the three researchers constituted the final sample of articles included in the review.

To classify the studies, there was selection of levels of evidence from the Agency for Healthcare Research and Quality (AHRQ): level 1 meta-analysis of multiple controlled and randomized clinical trials; level 2 individual studies with experimental design; level 3 almost experimental studies; level 4 descriptive (non-experimental) studies or qualitative approach; level 5 case or experience reports; and finally level 6 expert opinions.[16]

For interpretation of results, the selected articles were ordered according to the objective, results and conclusion of each study. Subsequently, the articles were grouped by similarity and categorized as follows: author, country year, level of evidence, objectives and results, and conclusion and recommendation.

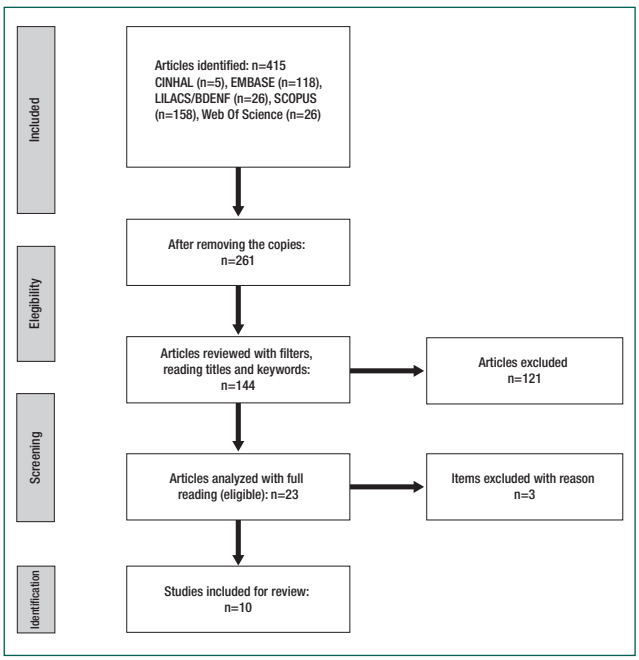

Figure 1. Flowchart of the integrative literature review on leg ulcer as leprosy sequel

Results

From the 415 articles identified in the literature, 10 were read in full, after the selection process, as shown in figure 1. Their data were transcribed for a tool with identification (author/year/country), category AHQR, objectives, results and conclusion described in figure 1.

The articles were published between 1966 and 2017, categorized according to the AHQR, five were considered level 3,[17-21] two 5 levels,[22,23] and the others of levels 1,[24] 2[25] and 4,[26] were published predominantly (80.0%) in English and the other 20.0% in Portuguese, the studies were of Domenican, Norwegian, American, Brazilian, Chinese, African and Indian origin (Chart 2).

Chart 2. Summary of articles found in ILR on leg ulcers with leprosy sequel

Author/year/country	Level of Evidence	Objectives and Results	Conclusion/ recommendation
Bogaert et al.[17] 1990. Domenican Republic	3	- To assess the efficacy of treatment of leprosy ulcer with topical and systemic phenytoin. At the first week, all ulcers showed decreased exudate and vast granulation tissue. Reassessed in 3-6 weeks, twenty patients had complete healing of lesions 2-4 cm in diameter. In lesions above four centimeters, seven showed a marked improvement in granulation.	The findings show that phenytoin is a valuable treatment option for this population.
Kaada B.et al.[18] 1988. Norway	3	- To describe a study using transcutaneous neural stimulation (TNS) aimed at accelerating the healing of ulcers of people with leprosy sequel. The 19 patients treated daily had complete healing.	TNS is a convenient method to use and can be applied by the patient himself.
Noe et al.[22]1974. United States	5	- To describe a case of leprosy with left leg ulcer sequel. With the Unna boot, there was complete healing.	Case of leprosy treated successfully.
Quege et al.[25] 2008. Brazil	2	- Compare the action of a latex biomembrane and EFA-based product on the microbiota of people with infected chronic wounds. The socio-demographic profile of patients was presented. The in vitro results showed absence of activity of both products on the microorganisms isolated from the lesions. The in vivo analysis that the EFA presented positive antimicrobial effect on *Enterobacter aerogenes* and the latex biomembrane on *Pseudomonas aeruginosa*.	The search for alternatives in the treatment of chronic infected wounds is important, because the systemic antibiotic therapy, because it leads to bacterial resistance.
Hu X, et al.[24] 2011. China	1	- To assess the effect of rhGM-CSF, growth factor on wound healing, topically applied was beneficial for ulcers such as leprosy sequel.	Controlled clinical studies are needed to support the therapeutic effect of rhGM-CSF.
Gomes et al.[26] .2007. Brazil	4	- To set the epidemiological profile of ulcerated and non-ulcerated leprosy treated at *Hospital das Clínicas de Ribeirão Preto* 2003/2004. Analysis showed 25 individuals (32%), 69.6% were males, 91.1% were white and smear positive (62%), had ulcerations located in the lower limbs (68%), classified as grade II disability (72%; p<0.01). In the operational classification, 80% of those who presented ulcers were multibacillary while 12% paucibacillary (p<0.05).	The Groups were epidemiologically similar. Ulcerations of leprosy appear to be related to the degree II of incapacity and to the positivity of the bacilloscopy, in classifications (spectral and operational).
Griffts, G et al.[23] 1966. Republic of Togo	5	- To describe two cases of people with ulcers in the lower limbs as leprosy sequel. One of the thighs treated with polybactrin (bacitracin, neomycin and polymyxin) spray, vaseline gauze, and dressing with daily exchange was completely healed in three months. The other ulcer in the leg, with nine months of healing healed almost completely. Using the above sequence of treatment and thereafter, cream and dressing.	The use of polybactrim was feasible for the healing of cases.
Nagaraju et al.[19] 2017. India	3	- Demonstrating the efficacy of the autologous Platelet-Rich Fibrin Matrix (PRFM) in unhealed trophic ulcers in patients treated for leprosy. Seven patients treated with leprosy, with nine unhealed trophic ulcers in more than six weeks, after receiving several treatments. With scanning, area measurements and volume. The ulcers received weekly treatment and healed (5 weeks).	The application of PRFM has brought satisfaction to the patient since it is easy to apply, simple and safe.
Mumford et al.[20]1988. India	3	- To assess the efficacy of a hydrocolloid occlusive dressing in the treatment of chronic leprosy ulcers. Seventy-seven ulcers were selected, four of which were legged in people sequestrated by leprosy. The occlusive hydrocolloid had an important role in the management of ulcers that did not respond to traditional treatments.	Randomized clinical trials are required to confirm the response of chronic ulcers to hydrocolloid use.
Malhota et al,[21] 1991. India	3	- To compare the action of zinc oxide (cream) and phenytoin (powder) on trophic leprosy ulcers with daily changes. None of the ulcers healed completely in the first six weeks. At 12 weeks, 79% of the ulcers treated with phenytoin had healed above 50% and in the zinc oxide group 29%.	The favorable results of this study suggest the completion of controlled study inpatients to investigate topical phenytoin compared to topical zinc therapy in the treatment of trophic ulcers

Discussion

Concern for a holistic approach to care for the person with leprosy is critical. The highly incapacitating power of the disease makes it feared, stigmatized, distancing the patients from the treatment in the face of the patient's acceptance difficulty, culminating in a greater probability of abandonment or refusal of therapy. Conformation and models of care for people with chronic ulcers due to leprosy have been a major challenge for the leprosy care line. It is long ago that care is centered on disease, the context and biomedical model, and not on the comprehensive perspective with the focus on the person. The Global Strategy launched by WHO for Leprosy Control between 2016 and 2020 emphasizes the human aspects, aiming at the inclusiveness of people with leprosy and thus promoting the reduction of the stigma caused. It aims to enable people affected by leprosy to participate in promoting their health, creating psychosocial support networks to minimize social and economic losses.[2]

Most of the studies identified in this review pointed to the topical treatment of leg ulcers. The first study conducted in 1966 was highlighted, which used polybactrin ointment, vaseline gauze with daily changes with positive healing in two patients studied.[23] Currently, topical antibiotic therapy is used with great caution in ulcers infected by increased colonization of resistant, gram negative and positive agents, in addition to the presence of devitalized tissues, dead space, and serous collection.[27-29]

Another study of 1974 reported the use of Unna boot, with weekly change, usual practice until the present day.[24] The Unna boot is an inelastic dressing composed of zinc paste and constitutes the best evidence for ulcers of venous etiology.[30]

The 1991 study comparing zinc oxide ointment with phenytoin obtained favorable results and suggested new controlled clinical studies with inpatients, it did not report concentrations of either phenytoin or zinc oxide.[21]

A study that included 40 patients with trophic ulcers in the feet and legs examined the daily use of a zinc oxide paste mixed with macerated tablets of phenytoin sodium. Of the patients treated, 55% achieved total healing within four weeks and in the others it was evidenced granulation tissue formation in the ulcer bed.[31] In another study it points out the advances of this therapy although it is little used in the services that attend people with ulcers resulting from leprosy.[32]

In 2008, the publication comparing the biomembrane of vegetable latex and products based on Essential Fatty Acids (EFA) in lesions infected and recurrent leprosy showed that EFA showed positive antimicrobial effect for *Enterobacter aerogenes* and latex biomembrane on *Pseudomonas aeruginosa*.[25] This membrane is impermeable, has a vascular endothelial growth factor, has antigenic properties and accelerates the formation of granulation tissue.[33]

In 2011, the rhGM-CSF growth factor[24] was applied topically to burns and leprosy leg ulcers with beneficial.

In the PRFM study in autologous platelets, treatment for trophic ulcers in patients treated with leprosy is a viable, safe and simple method.[19]

Regarding the other aspects addressed in the review, the epidemiological and clinical profile of participants were identified, indicating age, gender, color, disability, comorbidities, bacilloscopy, ulcers, location.[26] These data were also discussed later by another author.[27]

Social vulnerability was identified in the study where a large part of the patients studied did not develop paid activities, did not receive social security assistance, had family income between one and two minimum wages/month, evidencing the social inequalities of these patients.[26]

It is therefore necessary to identify early diagnosis in order to prevent physical disabilities, stigma and social isolation in these persons.[26,27] The clinical characteristics of the lesions constrain them, increasing social isolation.[3,28] In addition, most of the time they suffer from stigma in their families, in social life and even by professionals who segregate them within health institutions.[28]

Unveiling aspects related to social and disease-related characteristics are fundamental to indicate the need for action with advanced care practices in the treatment

of leprosy ulcers and, in fact, contribute to the reduction of the number of sequel that affect those affected by the disease only perpetuate stigma and social inequality.

Conclusion

A Brazilian and international overview was identified on the treatment of leg ulcers in people with leprosy. It emerged from researches by Brazilian, Norwegian, American, Brazilian, Chinese, African and Indian authors proposing topical and systemic phenytoin, zinc oxide, transcutaneous neural stimulation, growth factor (rhGM-CSF), the autologous Platelet-Rich Fibrin Matrix. However, there is no strong evidence that therapies for the treatment of leprosy-induced leg ulcers decrease the disabling sequel caused by the disease. Social inequality was little investigated and it became necessary to unveil the person affected by leprosy. It is necessary to develop controlled clinical research to find the best evidence to strengthen decision-making for treatment in the multidimensional aspects that affect people affected by leprosy.

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References

1. World Health Organization (WHO). Global leprosy update, 2014: need for early case detection. Wkly Epidemiol Rec. 2015;90(36):461-76.
2. Sistema de Informação de Agravos de Notificação (SINAM). Registro ativo: número e percentual, casos novos de hanseníase: número, coeficiente e percentual, faixa etária, classificação operacional, sexo, grau de incapacidade, contatos examinados, por estados e regiões, Brasil, 2015. Brasília, DF: Ministério da Saúde; 2016.
3. World Health Organization (WHO). Global leprosy update, 2016: accelerating reduction of disease burden. Wkly Epidemiol Rec. 2017;92(35):501-20
4. Organização Mundial da Saúde (OMS). Estratégia global para a Hanseníase 2016-2020: aceleração rumo a um mundo sem hanseníase. New Delhi: OMS; 2016.
5. Opromolla DV. Úlceras de perna. In: Jorge AS, Dantas SR. Abordagem multiprofissional do tratamento de feridas. São Paulo: Atheneu; 2003. p. 271-8.
6. Oda RM, Galan NGA, Opromolla DV. Úlceras de perna na hanseníase. In: Opromolla DA, Baccarelli R. Prevenção de incapacidades e reabilitação em hanseníase. Bauru (SP): Instituto Lauro de Souza Lima; 2003. p. 130-3.
7. Virmond MC. Ulcera de perna. In: Duerksen F, Virmond M. Cirurgia reparadora e reabilitação em hanseníase. Bauru: Centro de Estudos Dr. Reynaldo Quagliato; 1997. p. 294-303.
8. Brasil. Ministério da Saúde, Secretaria de Políticas de Saúde, Departamento de Atenção Básica. Guia para o Controle da Hanseníase [Internet]. Brasília (DF): Ministério da Saúde; 2002.
9. Brasil. Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis. Guia prático sobre a hanseníase. Brasília (DF): Ministério da Saúde; 2017.
10. Whittemore R, Knafl K. The integrative review: updated methodology. J Adv Nurs. 2005; 52(5):546-53.
11. Oliveira MS, Valle SC, Souza RM, Silva RP, Figueiredo EM, Taminato M, et al. Evidências científicas sobre a hepatite Delta no Brasil: revisão integrativa da literatura. Acta Paul Enferm. 2017;30(6): 658-66.
12. Broome ME. Integrative literature reviews for the development of concepts. In: Rodgers BL, Knafl KA. Revisão sistemática e meta-análise. 2006 [cited 2018 Dez 10]. Available from: www.metodologia.org/meta1.PDF
13. Oslon Curtis A. Using a literature to improve research and practice in Continuing Education for health professionals. J Cont Educ in Heath Prof. 2013;33(1):1-3.
14. Brun CN, Zuge SS. Revisão sistemática da literatura: desenvolvimento e contribuição para uma prática baseada em evidências na enfermagem. In: Lacerda MR, Costenaro RG, editors. Metodologias da pesquisa para a enfermagem e saúde. Porto Alegre: Moriá; 2015. p.77-98.
15. Mourad O, Hossam H, Zbys F, Ahmed E. Rayyan – a web and mobile app for systematic review. Sys Rev. 2016; 5:210.
16. Agency for Healthcare Research and Quality (AHRQ). Quality Improvement and monitoring at your fingertips. Rockville: Agency for Healthcare Research and Quality; 2016.
17. Bogaert HM, Saleta BM, Sanchez MD, Garcia MD. Trophic Leprosy Ulcers: Treatment with Topical and Systemic Phenytoin (PHT). Int J Dermatol. 1990; 29(2):156-7.
18. Kaada B. Emru M. Promoted healing of leprous ulcers by transcutaneous nerve stimulation (TNS). Acunpuncture e eletroc-therapeutics Res Int J. 1988;13(4):165-76.
19. Nagaraju U, Sundar PK, Agarwal P, Raju BP, Kumar M. Autologous Platelet-rich Fibrin Matrix in Non-healing Trophic Ulcers in Patients with Hansen's Disease. J Cutan Aesthet Surg. 2017;10(1):3-7.

20. Mumford JW, Mumford SP. Occlusive hydrocolloid dressings applied to chronic neuropathic ulcers. A study of efficacy in patients at a rural South Indian Hospital. Int J Dermatol. 1988;27(3):190-221.

21. Malhotra YK, Amin SS. Role of topical phenytoin in trophic ulcers of leprosy in India. Int J Lepr. 1991;59(2):337-8.

22. Noe JM, Barber J. Chronic leg ulceration in a patient with leprosy. West J Med. 1974;121(5):430-32.

23. Griffts G. Notes on treatment of ulcers in leprosy patients with Polybactrin. Lep Rev. 1966;37(4):227-9.

24. Hu X, Sun H, Han C, Wang X, Yu W. Topically applied rhGM-CSF for the wound healing: a systematic review. Burns. 2011;37(5):729-41.

25. Quege GE, Bachion MM, Lino Junior RS, Lima AB, Ferreira PS, Santos QR. Pimenta FC. [Comparison of the activity of fatty essential acids and biomembrane in the microbiota of infected chronic wounds]. Rev Eletr Enf. 2008;10(4):890-905. Portuguese.

26. Gomes FG, Frade MA, Foss NT. Úlceras cutâneas na hanseníase: perfil clínico-epidemiológico dos pacientes. An Bras Dermatol. 2007;82(5):433-7.

27. Basso ME, Silva RL. Perfil clínico-epidemiológico de pacientes acometidos pela hanseníase atendidos em uma unidade de referência. Rev Soc Bras Clin Med. 2017;15(1):27-32.

28. Eidt LM. Being leprous: feelings and experiences. Hansen Int. 2004;29(1):21-7.

29. Belo Horizonte (Cidade). Prefeitura Municipal de Belo Horizonte, Secretaria Municipal de Políticas Sociais, Secretaria Municipal de Saúde, Gerência de Assistência – Coordenação de Atenção Básica à Saúde do Adulto e do Idoso. Protocolo de assistência aos portadores de feridas [Internet]. Belo Horizonte; 2006 [citado 2018 Dez 10]. 52 p. Disponível em: http://www.pbh.gov.br/smsa/biblioteca/protocolos/curativos.pdf.

30. Borges EL. Tratamento tópico de úlcera venosa: proposta de uma diretriz baseada em evidências [tese]. Ribeirão Preto (SP): Universidade de São Paulo, Escola de Enfermagem de Ribeirão Preto; 2005.

31. Sehgal VN, Prasad PV, Kaviarasan PK, Rajan D. Trophic skin ulceration in leprosy: evaluation of the efficacy of topical phenytoin sodium zinc oxide paste. Int J Dermatol. 2014;53(7):873-8.

32. Firmino F, Almeida AM, Silva RJ , Alves GS, Granadeiro DS, Penna LH. Scientific production on the applicability of phenytoin in wound healing. Rev Esc Enferm USP. 2014;48(1):162-9.

33. Cândido LC. Livro do feridólogo: tratamento clínico e cirúrgico de feridas cutâneas agudas e crônicas. São Paulo: LC Candido; 2006. 646 p.