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Article Review

# Effectiveness of metronidazole in the treatment of tumor wound odors

## Efetividade do metronidazol no tratamento de odores em feridas tumorais

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**Objective**: to analyze the evidence of the effectiveness of Metronidazole in the treatment of odors in tumor wounds. **Methods**: this is an integrative review performed at the health databases and the PubMed portal. The studies were evaluated by the Jadad Scale (randomized clinical trials), Downs and Black (quasi-experiment) and the Strengthening the Reporting of Observational studies in Epidemiology (observational). A sample of the ten studies and articles were considered cut-off points that reached 50.0% of the criteria. **Results**: Metronidazole was effective in 95.6% of the cases and the gel preparation at 0.75% was the most used in the studies. **Conclusion**: the evidence indicates that metronidazole is safe and effective in the control of tumor wound odors, but there is no consensus on the most effective forms of presentation and administration routes. Most studies associate the appearance of bad odor with the growth of anaerobic bacteria in the tumor tissue.
**Descriptors:** Wounds and Injuries; Odorants; Metronidazole; Neoplasms.

**Objetivo:** analisar as evidências da efetividade do Metronidazol no tratamento de odores em feridas tumorais. **Métodos:** revisão integrativa realizada nas bases de saúde e no portal PubMed. Os estudos foram avaliados pela Escala de Jadad (ensaios clínicos randomizados), Downs e Black (quase experimentais) e o *Strengthening the Reporting of Observational studies in Epidemiology* (observacionais). Amostra de dez estudos e considerou-se como ponto de corte artigos que atingiram 50,0% dos critérios. **Resultados:** o Metronidazol se mostrou efetivo em 95,6% dos casos e a preparação em gel a 0,75% foi a mais utilizada nos estudos. **Conclusão:** as evidências apontam o metronidazol como seguro e eficaz no controle de odores em feridas tumorais, porém não há consenso sobre as formas de apresentação e vias de administração mais efetivas. A maioria dos estudos associa o surgimento de mau odor com o crescimento de bactérias anaeróbias no tecido tumoral.
**Descritores:** Ferimentos e Lesões; Odorantes; Metronidazol; Neoplasias.

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## Introduction

A tumor neoplastic wound is characterized by the infiltration and proliferation of neoplastic cells in the skin, causing rupture of the tissue integrity[1]. They may have ulcerative or fungal features, causing pain, exudate, secondary infections, bleeding, bad odors, and physical, emotional, social and spiritual frailties[2].

There is no exact estimate for the incidence of tumor wounds but studies indicate that in cancer patients, the prevalence of these wounds is between 5 and 10.0%, with 5.0% referring to primary tumors and 10.0% due to metastases. One of the most impetuous symptoms is bad odor, described by patients as a barrier to approaching people, isolating them from social interaction and generating various emotional problems[3]. Odors in neoplastic wounds are caused by bacterial infections and/or anaerobic fungi, associated with the production of fatty acids by the necrotic tissues present in the wound[4]. Thus, different forms and substances have been used in topical wound therapy for the control or reduction of odor, such as metronidazole.

Metronidazole is a derivative of nitroimidazole with antiprotozoal action. It has bactericidal activity to gram-negative anaerobic bacilli, to all anaerobic cocci and sporulated gram-positive bacilli. For this reason, it is recommended in clinical practice for odor control in wounds and, especially, regarding the treatment of neoplastic wounds[5].

Clinical nursing care for people suffering from tumor wounds should be comprehensive to avoid unnecessary procedures, improving the quality of life of the individual and his/her family[6].

Interest in the topic arose during the multi-professional residency with emphasis in oncology, in which the main author of the study observed the application of metronidazole in several presentations in the topical therapy of tumor wounds to combat the foul odor and positive impact in the psychosocial scope of patients with reduction odor in these lesions.

In this context, the following guiding question emerged: what is the effectiveness of metronidazole in controlling/reducing and/or eliminating odors in adults with stinking tumor wounds? Considering the need for more information about the topic, this study proposes to seek scientific evidence to subsidize clinical nursing care in the topical therapy of a person with fetid tumor wounds. In this way, the objective was to analyze the evidence of the effectiveness of Metronidazole in the treatment of odors in tumor wounds.

## Methods

This is an integrative review with the following steps: (1) elaboration of the research question; (2) search in the literature; (3) selection of articles; (4) extraction of the data; (5) methodological quality assessment; (6) synthesis of the data; (7) evaluation of the quality of the evidence; and (8) writing and publishing the results[7].

The PICOS strategy was carried out to formulate the research question, consisting of the identification of the P=participant, I=intervention, C=control, O=outcome and S=type of study. The following question was sought to answer: what is the effectiveness of metronidazole in controlling/reducing and/or eliminating odors in people with stinking tumor wounds over 18 years old? Thus, for this study, we have: P: People with stinking tumor wounds older than 18 years old; I: Application of Metronidazole (tablet, cream or liquid); C: No comparison; O: Control/Reduction and/or odor elimination; S: Experimental Studies (clinical trial and quasi-experiment) or Observational Studies (case report, case series, case-control, cohort and transverse). The search key was: Malignant Wound OR Fungating Wound OR Neoplasic Wound AND Metronidazole OR Metronidazol AND Malodorous OR Deodorization OR Odor OR Odour OR Odorants. Also, the connection between the Medical Subject Heading (MeSH) and/or the keywords and Boolean operator "AND" and "OR" was used. Keywords and descriptors in English were

chosen because of the greater possibility of capturing studies from other countries.

The search occurred in July 2017 in the databases: *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS); *Bases de Dados de Enfermagem* (BDENF); *Índice Bibliográfico Español in Ciencias de la Salud* (IBECS); National Library of Medicine and National Institutes of Health (PUBMED) and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The choice was motivated by such sources to have national and international impact publications, breadth of the search spectrum and diversity of indexed journals.

The inclusion criteria were randomized clinical trials, quasi-experiment studies, and observational studies available in full, of people with fetid tumor wounds> 18 years old treated with metronidazole to control, reduce and/or eliminate bad odor. The studies with dubious design were excluded.

The selection process of the studies was conducted through the checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA)[8]. It should be emphasized that the entire process of searching, selecting and cataloging the publications was carried out by two independent researchers, in which the potential primary studies were identified. In this process, the studies went through three filters for selection and evaluation. The first filter was the selection of the relevant publications, where the inclusion and exclusion criteria were applied; the second filter was the selection of publications based on quality criteria; and the third filter was the selection of relevant data.

The Jadad Scale was used to evaluate the quality of the randomized clinical trials, which consists of three items[9] directly related to the reduction of research bias (randomization, blinding and destination of all participants), adding up to 5 points. Studies in which the score totals below 3 points were excluded because they were classified as poor quality.

Accuracy was achieved using the established quality measurement checklist for quasi-experiment studies[10]. The questionnaire contains 27 "yes" or "no" or "unable to determine" questions divided into five sections, totaling 1: Quality of the study (10 items) - overall quality of the study; 2: External validity (3 items) - ability to generalize the results of the study; 3: Bias study (7 items) - to assess bias in intervention and outcome measure(s); 4: Confusion and selection bias (6 items) - to determine the sampling bias or group assignment; and 5: Power of the study (1 items) - to determine if the findings are due to chance. The cutoff used to consider the good quality study should be greater than 50.0% of the maximum score.

The checklist Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) was used to evaluate the observational studies (case report, case series and cohort), in which each item received a score of 0 and 1 (0 - not reported and 1 - reported)[11]. A cutoff item was considered when reaching 50.0% of the criteria. At this stage, two independent researchers evaluated the studies selected in the first filter. After the evaluation, consensus was achieved. Divergent data were solved based on the elements of the protocol, which promoted greater accuracy and avoided biases.

After applying the first filter (selection of relevant publications), until July 2017, 2078 potentially relevant references were identified. There were 1948 articles identified and removed from the application of filters of the own bases and the triage of evaluation of the title and abstract to discard irrelevant articles. The 130 selected publications were submitted by a screening of inclusion criteria for the types of selected studies, with 117 publications eliminated. At the end of the screening, 13 selected articles were obtained, but three were repeated, so ten studies for the application of the quality tests remained (Figure 1).

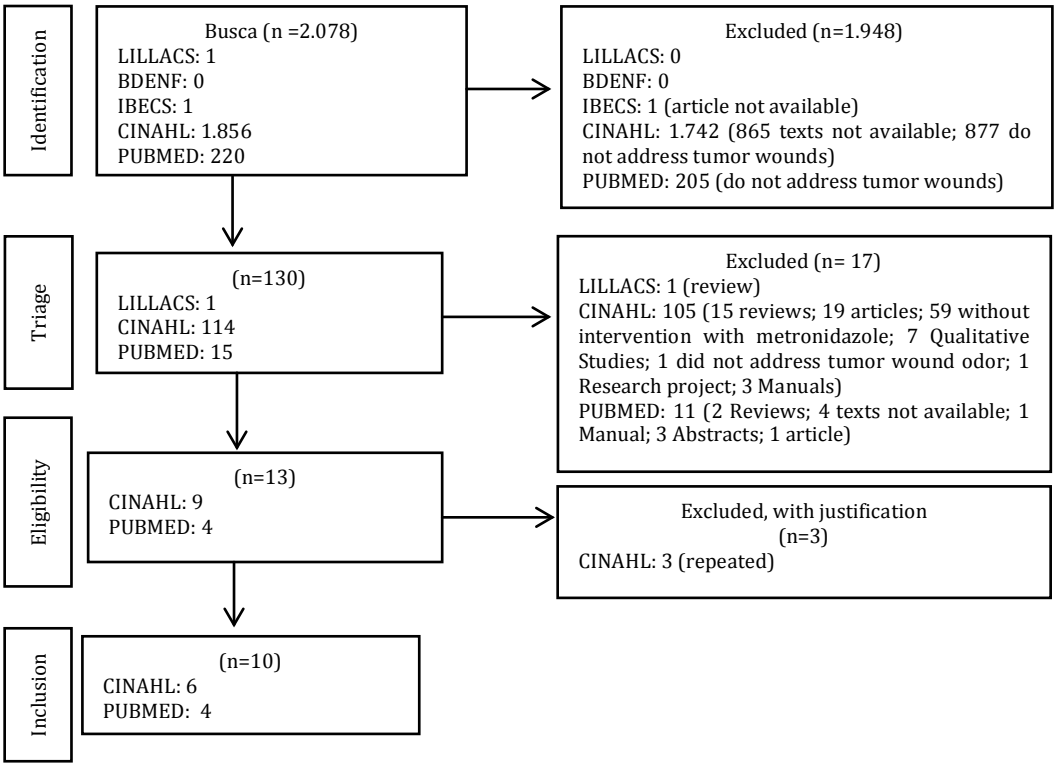


**Figure 1** – Selection of the publications flowchart for the integrative review, based on the PRISMA mode

## Results

Figure 2 shows the categorization of the findings on the type of study, the method (sample, tumor type, metronidazole presentation, duration of treatment), the main conclusions of the authors, the level of evidence and the instrument used to evaluate the quality.

Among the articles analyzed, eight studies were observational (80.0%) (12-19), of which six were case reports (60.0%)[12-15,18-19], one study was case series (10.0%)[17] and one was a cohort study (10.0%)[20]; two are experimental studies (20.0%) [4,15]; a quasi-experiment (10.0%)[15]; and a randomized controlled trial (10.0%)[4]. The predominance of North American studies is observed, with four studies (40.0%)[14-17], followed by two Brazilian studies (20.0%)[12-13], two Japanese studies (20.0% )[4,17], one Canadian (10.0%)[18] and one British (10.0%)[19].

The studies showed seven different pharma ceutical forms of metronidazole: vaginal cream[12], injectable[13], powder[18], tablets[19], 1% saline solution[14], 0.75% gel[4,16,20] and 0.80% gel[17]. The most used form of administration was the topical route in eight studies (80.0%)[4,12,14-19] and two studies used the systemic route (20.0%)[13,20]. The gel preparation at 0.75% was the most used and evidenced in three studies (30.0%)[4,16,20].

Then, the tablets were presented in two studies (20.0%)[15,19], and the tablet was administered in two forms: by oral administration (systemic use)[19] and macerated tablets being administered directly into the lesion (topical)[15]. One study used the vaginal cream directly on a lesion located on the face and obtained a satisfactory result[12]. The 1% saline solution was administered orally to make the preparation mouthwash since the tumor lesion was in the oral cavity[14].

| Type of study/Sample/Neoplasia/Local/Presentation of Metronidazole/Duration of treatment/Outcome/Instruments: Scales[9-10]/ STROBE[11] |
|---|
| Case report. Sample: 1 patient. Neoplasia: Basal Cell Carcinoma Terebrante. Location: Face. Presentation: Vaginal Cream. Duration: not reported. Outcome: Reduction of odor level[12] was observed. Instrument[11]: 54.0%. |
| Case report. Sample: 1 patient. Neoplasia: Invasive Ductal Carcinoma Grade II. Location: Mama left. Presentation: Intravenous. Duration: not reported. Outcome: Reduction of odor from Grade III to Grade I[13]. Instrument[11]: 59.0%. |
| Case report. Sample: 1 patient. Neoplasia: Squamous cell carcinoma. Location: Left oral cavity. Presentation: Saline solution with 1% Metronidazole. Duration: 7 days. Outcome: Drastic reduction of odor level, pointing to the solution of Metronidazole as an effective option for the treatment of symptoms of oral carcinoma[14]. Instrument[11]: 50.0%. |
| Case report. Sample: 1 patient. Neoplasia: not reported. Location: Right breast. Presentation: Topical application in lesion bed of 250 and 500 mg macerated tablets. Duration: not reported. Outcome: Patient observed reduction of odor level, which increased the quality of life, providing the return of social activities[15]. Instrument[10]: 50.0%. |
| Quase experiment. Sample: 20 patients. Neoplasia: 13 breast neoplasms, 1 oral carcinoma, 1 basal cell carcinoma, 1 prostate carcinoma, 1 Marjolin, 1 Sarcoma, 1 tongue carcinoma, 1 metastatic carcinoma. Location: breast, oral cavity, tongue, prostate, lower limbs. Presentation: Metronidazole gel 0.75% at the lesion site. Duration: 14 days. Outcome: 64.0% of patients rated the odor of their lesions as moderate or extremely aggressive prior to treatment. On the 14$^{th}$ day the percentage was 4.0%. Metronidazole was effective in the treatment of bad odor in neoplastic lesions[20]. Instrument[10]: 55.0%. |
| Cohort. Sample: 13 patients. Neoplasia: Squamous cell carcinoma (11); Adenocarcinoma (1); Small cell carcinoma (1). Location: Cervix (10); Vulva (3). Presentation: Metronidazole gel 0.75% at the lesion site. Duration: 7 days. Outcome: 11 of the 13 study patients reported odor reduction in 1 or 2 post-treatment graduations[16]. Instrument[11]: 68.0%. |
| Case Series. Sample: 5 patients. Neoplasia: not reported. Location: Mama. Presentation: Metronidazole Gel 0.8% at the wound place. Duration: Continuous. Outcome: The odor disappeared in 4 patients on average 4 days after starting treatment[17]. Instrument[11]: 63.0%. |
| Case report. Sample: 1 patient. Neoplasia: Squamous Cell Carcinoma. Location: Abdomen. Presentation: Metronidazole powder applied directly to the bed of the wound. Duration: not reported. Outcome: The odor was eliminated most of the time[18]. Instrument[11]: 50.0%. |
| Instrumento[9]: 3. Controlled and Randomized Clinical Trial. Sample: 21 patients. Neoplasia: Mammary Neoplasia Stage IV (16); Stage III (5). Location: Injury in Mamas. Presentation: Metronidazole Gel 0.75%. Duration: 14 days. Outcome: The researchers evaluated the improvement in bad odor in 95.2% (20/21) of the patients[4]. Instrument[9]: 3. |
| Case report. Sample: 1 patient. Neoplasia: Moderately differentiated squamous cell carcinoma. Location: Anus. Presentation: Metronidazole via oral 400mg 3x daily from day 1 to day 10 and 200mg 2x daily. Duration: continuous treatment. Outcome: Odor control was achieved by treatment with metronidazole[19]. Instrument[11]: 59.0%. |

**Figure 2** – Characterization of the studies based on the article code, type of study, sample, neoplasia, local, presentation of metronidazole, duration of treatment, outcome and quality assessment instrument

## Discussion

The heterogeneity between the studies is highlighted as a limitation, regarding the target audience and different modes of application of the intervention, which enable to compare their results.

According to the analysis of the quality of the studies found, there is a large number of articles with low scientific evidence, according to the international evaluation scales, due to lack of control group, blinding and/or randomization. There is little scientific production in this area, evidenced by the scarcity of controlled and randomized clinical trials to more accurately assess the effectiveness of metronidazole in controlling/reducing odor of tumor wounds.

In the analyzed publications, it was observed that metronidazole is available in vaginal cream (8% - 400mg/5g and 10% - 500mg/5g), oral suspension (40mg/ml), tablets (250mg or 400mg) or parenteral solution (0.5%)[2]. No studies have been found on which route of administration is most effective, which allows researchers to evaluate the most appropriate option for the patient. One study considered improper use of the topical route because of the large amount of exudate present in the lesion, which could reduce the tissue absorption efficiency[19]. However, one clinical trial[4] evaluated the bioavailability of 0.75% metronidazole gel and concluded that the systemic exposure level of ≤ 30g daily did not exceed the exposure level of 250mg metronidazole taken orally in a single dose.

For the cases of topical route, all the studies mentioned the necessity to carry out the previous cleaning of the lesion with jet saline for the removal of exudate and of necrotic tissue that can be removed mechanically and then proceed with the topical application of the metronidazole[4,12,14-19]. No study reported the storage conditions of metronidazole and only one study[20] analyzed the tubes used to detect contamination.

Regarding the duration of treatment, no reports were found in four studies (40.0%)[12-13,15,18], two studies (20.0%)[14,16] underwent treatment for seven days, two other studies (20.0%)[4,20] underwent treatment for 14 days and finally, two studies (20.0%)[17,19] performed the treatment continuously. One study[17] followed the application of metronidazole gel 0.8% for 131 days in one patient and no side effects were reported. No side effects were observed in any of the studies due to continued use.

Regarding the method for measuring odor and ascertaining the effect of the use of metronidazole, five studies (50.0%) did not present scales for odor level, they only showed reports of improvements by the patient and the team that followed the study and/or patient[12,14-15,18-19]; four studies (40.0%) performed the odor level measurement using scales of their own, with different graduation levels[4,15-17]; and only one study (10.0%) used references from the literature to use an odor scale[13].

A study held in 2000 considered patient reporting of odor evolution and assessment using a scale., Six (46.0%) of the 13 patients surveyed reported continuing odor on the lesions, but when they were asked to evaluate the odor level through the scale, 11 patients (85.0%) reported improvement in one or two grades on a scale of four graduations[16].

Also, in six studies (60.0%), only the patients' reports were evaluated[12-15,18-19] and the other studies had an evaluation of the degree of odor performed by the patient and more than one evaluator that varied between the researchers and the patient care team[4,15-17].

All studies report that metronidazole is an effective tool in controlling and/or eliminating odor in neoplastic wounds at different presentations and concentrations. The average rate of success in odor treatment in all of the elective studies is 95.6%, achieved by the ratio of total treatment successes obtained in the studies with the total samples from all studies. Three studies[4,15,17] associate the appearance of bad odor with the growth of anaerobic bacteria sensitive to the use of metronidazole. However, in a study[16] performed with patients with tumors in the reproductive tract, the association between anaerobic bacteria

and bad odor is inconclusive.

The most indicated duration of treatment was not found, but in two studies[4,15] in which the treatment was performed for 14 days, a significant improvement of the odor reduction rates was observed when compared to the 7th day of follow-up. However, there are reports of odor return when treatment is discontinued[19] and no studies have followed patients at intervals longer than 14 days.

Concerning the safety of medication use, only three reports of adverse events were directly associated with the use of metronidazole[4,15]. There was also loss of follow-up and exclusion of study participants, but none of these cases was directly related to the side effects of metronidazole.

This study may contribute to clinical nursing care for patients suffering from bad odor in tumor wounds and instigate nurses to carry out intervention studies with a higher level of evidence.

## Conclusion

The evidence points to metronidazole as safe and effective in the control of tumor wound odors, but there is no consensus on the most effective forms of presentation and routes of administration. Most studies associate the appearance of bad odor with the growth of anaerobic bacteria in the tumor tissue.

## Collaborations

Barreto AM and Marques ADB contributed in the conception and design, analysis, interpretation of data, article writing, critical review of the intellectual content and final approval of the version to be published. Cestari VRF, Cavalcante RC and Moreira TMM contributed with the relevant critical revision of the intellectual content and final approval of the version to be published.

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