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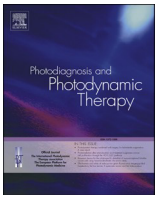

Case Report

Use of photodynamic therapy to combat recurrent pharyngotonsillitis: Three case reports

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ABSTRACT

Background: Pharyngotonsillitis (PT) is an inflammatory and infectious condition affecting the tonsils in the oropharynx, predominantly caused by a variety of viral, fungal, and bacterial pathogens, including *Streptococcus pyogenes*. With the increasing challenge of antibiotic resistance, alternative therapeutic approaches are needed.
Methods: This study explores the effectiveness and safety of Photodynamic Therapy (PDT) as a therapeutic approach for managing acute PT. PDT involves the use of a photosensitizer, light, and molecular oxygen. We utilized a curcumin-based photosensitizer incorporated into a gum formulation, followed by exposure to blue LED irradiation (455 ± 30 nm, intensity of 200 mW for 6 min) with 1 to 2 PDT sessions depending on the clinical case.
Results: The treatment's impact was assessed through systematic monitoring of clinical progression post-treatment, encompassing clinical history, examination, and follow-up. In all three cases examined, PDT was observed to effectively eradicate the infection and prevent its recurrence during the period evaluated.
Conclusion: Photodynamic Therapy, using a curcumin-based photosensitizer and blue LED light, appears to be a promising alternative to traditional antibiotics for the treatment of PT, demonstrating both efficacy in infection eradication and safety in application. Further studies are recommended to substantiate these findings and explore long-term outcomes.

1. Introduction

PT is an inflammatory and infectious condition that involves the tonsils located on the sides of the oropharyx [1]. It is caused by a diverse array of viral, fungal, and bacterial pathogens, with *Streptococcus pyogenes*, holding significant etiological importance in such cases [2]. Oropharyngeal infections represent a significant public health concern, frequently occupying emergency rooms and their complications result in hospitalizations and surgeries [3]. Recurrent pharyngotonsillitis is the repetitive inflammation of the palatine tonsils predominantly, or even exclusively, caused by bacteria [4]. Episodes of tonsillitis are characterized by fever, sore throat, odynophagia, congested tonsils with or without exudate, and cervical lymphadenopathy [4]. Recurrent pharyngotonsillitis can be diagnosed clinically on an anamnestic report [5] and can be considered when more than two distinct episodes of tonsillitis are encountered within a 12-month period [6]. Tonsillectomy is recommended for patients with recurrent tonsillitis who have experienced at least seven attack episodes per year in the preceding one year, five episodes per year in the preceding two years, or three episodes per year in the preceding three years despite adequate antibiotic therapy

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[7].

Recurrent tonsillitis and gross tonsillar hyperplasia are diseases caused by a variety of common upper respiratory tract pathogenic bacterial species [8] and end up leading to the recurrent use of antibiotics and much feared bacterial multiresistance. *Streptococcus pyogenes* is the most common bacterial origin of acute tonsillitis in immunocompetent adults [9].While acute tonsillitis is postulated to only have one etiological factor, recurrent tonsillitis seems to have a multispecies etiology. *S. aureus* seems to have a key role in patients with recurrent tonsillitis caused by biofilm-producing strains [10].

PT is associated with the colonization of multidrug-resistant strains and the formation of bacterial biofilms within inflamed tonsils and their crypts, factors that contribute to the inadequacies of antibiotic treatments [10]. Resistance to antibiotics has become one of the most important public health problems throughout the world nowadays OMS [11]. The antibiotic industry is seen as being unable to develop new molecules that can overcome the appearance of new resistances [12]. In Brazil, unfortunately, the waiting list for surgeries such as tonsillectomy in the public service is very long, which makes this risk of bacterial multidrug resistance even greater. Consequently, the need to establish alternative and effective methodologies to combat these resilient microorganisms in a novel and non-invasive manner has become imperative. One such alternative is PDT [12,13].

PDT involves the oxidation of microorganisms. This intricate process is driven by a photochemical effect, resulting in the reduction of pathogenic agents, their proliferation, and invasiveness. Consequently, it fosters the patient's recuperation devoid of any lingering effects and with an enhanced quality of life [14]. The utilization of visible light, in conjunction with a photosensitizer and molecular oxygen, induce the generation of cytotoxic species [13] Photosensitizer are molecules designed to interface with light, thereby generating highly reactive oxygen species, notably oxygen itself. The choice of photosensitizer is contingent upon the intended application site, as each one exhibits specificity towards distinct wavelengths. Commonly used photosensitizers includes porphyrins, chlorins, phthalocyanines, and curcumin [15]. In our line of research, the use of curcumin as a photosensitizer was standardized due to its potential in previous studies carried out in vitro. Curcumin is a natural dye used in food that presents bactericidal propertie [16].

Among the emerging alternatives, PDT has garnered attention as a prospective remedy for recurrent PT [16]. In this study, PDT has been examined as a supplementary approach aimed at providing both preventive and therapeutic interventions for PT. The central objective of this investigation revolved around assessing the viability of PDT as a potential remedy to counteract antibiotic treatment failures in managing oropharyngeal infections. The objective of this article is to demonstrate the early results of applying PDT as the only treatment in three cases of patients who were undergoing recurrent use of antibiotics due to PT.

2. Material and methods

This research endeavor scrutinized the efficacy of PDT in PT treatment. Volunteers willing to partake in the study had to satisfy specific inclusion criteria. Eligible participants must be 18 years of age or older and have a medical history including recurrent use of antibiotics prescribed by doctors for PT. The patient needs to have an adequate mouth opening and cooperate during the application. Patients with pregnant women, patients with oral diseases and those taking antibiotics are excluded from the research. Following the fulfillment of all requisites, the patient was expected to provide informed consent by signing a Free and Informed Consent Form CAAE: 61,720,922.0000.8148. The procedural details and research objectives were elucidated to the patient, and any inquiries were addressed. Upon the patient's agreement to participate, completion of a pre-assessment form was obligatory.

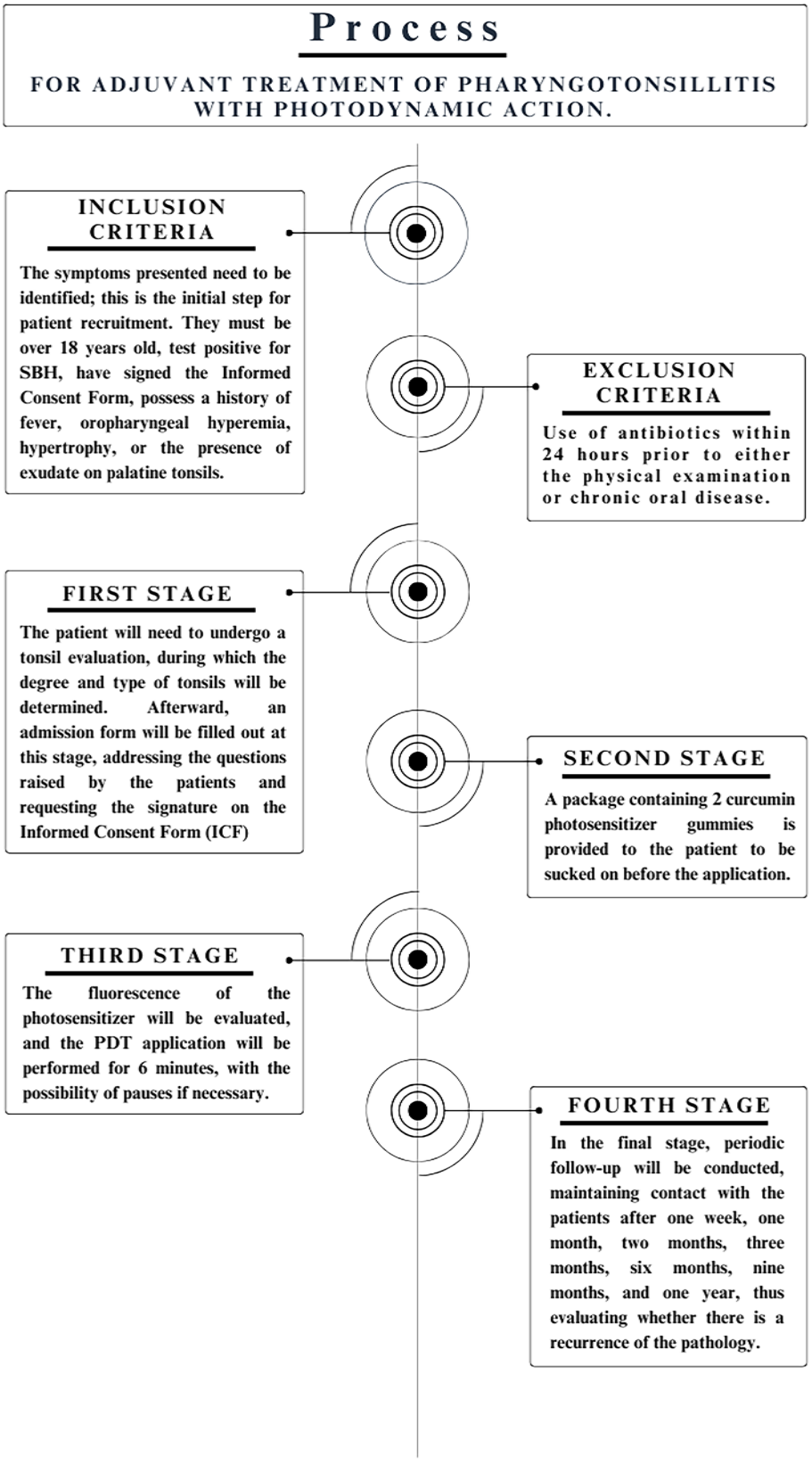
Following the pre-assessment, an otorhinolaryngologist conducted a screening process to ascertain whether the patient met the research's inclusion criteria. Patients whose condition is not suggestive of recurrent PT and who have other pathologies that could justify the symptom of recurrent odynophagia are also excluded from the study.

Patients meeting the project requirements received a package containing two pieces of curcumin gum for consumption, facilitating curcumin distribution throughout the oral cavity [17]. The PDT procedure involved illuminating the oropharynx for 6 min. Patients are followed for a year, with periodic reassessments and whether there are recurrences of infections.

In this specific article, we selected patients with symptoms suggestive of bacterial resistance because they were frequently using antibiotics and maintained symptoms of odynophagia after attacks.

The parameters of the light source used included a power of 200 mW, with a wavelength of 455 $\pm$ 30 nm, and an irradiation time of 6 min per session. The concentration of curcumin, used as a photosensitizer, was 0.75 mg/mL. This was incorporated into a gum formulation, facilitating uniform distribution of the agent in the patients oral cavity.

During treatment, patients consumed the curcumin-containing gum within minutes, preparing the oral cavity for the subsequent lighting procedure. After administration of the gum, illumination was performed using the previously defined power and wavelength configuration. Depending on the clinical response and severity of each patient's case, more than one treatment session was applied. This approach allowed for more effective control of the infection and greater adaptation of treatment to individual needs, aiming for maximum effectiveness in eradicating the symptoms of recurrent PT.



The image illustrates an explanatory diagram about the stages and processes of inclusion and exclusion of cases reports.

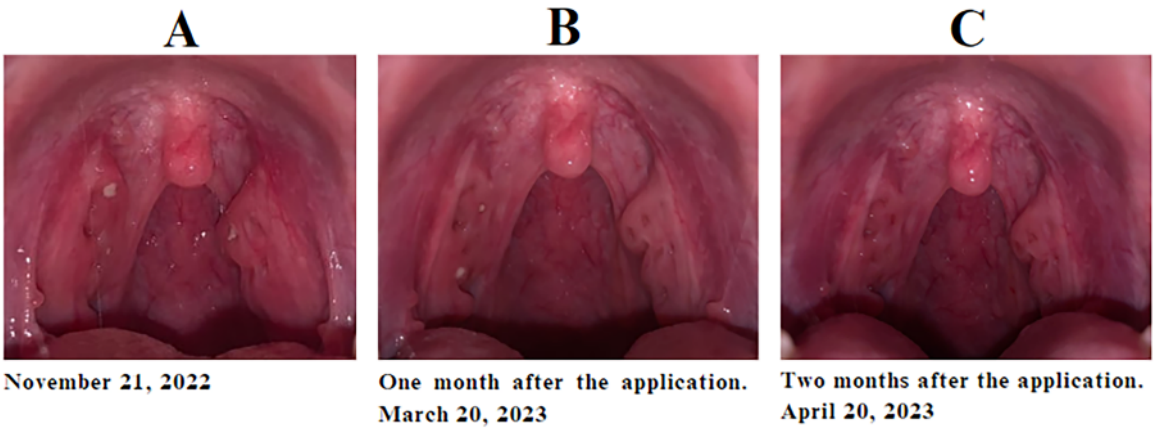


Fig. 1. Pacient M.D.
Caption: The image illustrates the remarkable positive evolution identified in the patient's tonsillar crypts, showing her progress in reducing the caseuns and edema.

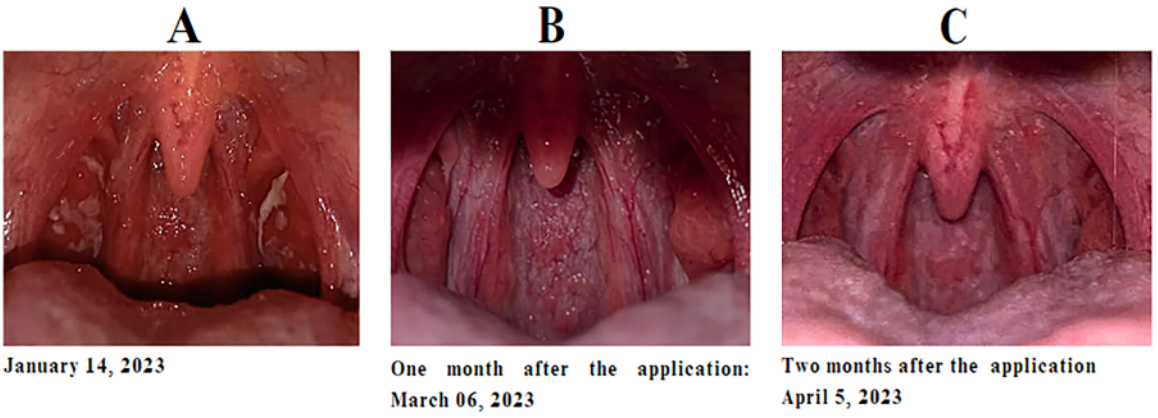


Fig. 2. Pacient L.V.
Caption: The image illustrates the remarkable positive evolution identified in the tonsillar crypts of the patient, presenting her progress in the reduction of edema, hyperemia, and exudate.

3. Results

Case Report 1: M.D. a 22-year-old woman has had a history of recurrent PT since childhood and caseous tonsillitis and denied having other comorbidities. She reported having an average of five infections per year that only improved after using antibiotics. The last antibiotic had been benzathine penicillin 60 days prior to the date of application. On the day of the consultation, she reported persistent discomfort in her throat due to the presence of caseuns. On physical examination it was possible to observe grade 2 palatine tonsils, hyperemic, encrypted and with caseuns. After eleven months of application, the patient evolved without new PT and has not used antibiotics since then. During clinical examination, it was also possible to observe the disappearance of the caseuns and the reduction in the size of the tonsils.

The physical examination revealed swollen tonsils, noticeable redness, and the presence of exudate as shown in Fig. 1A. One month

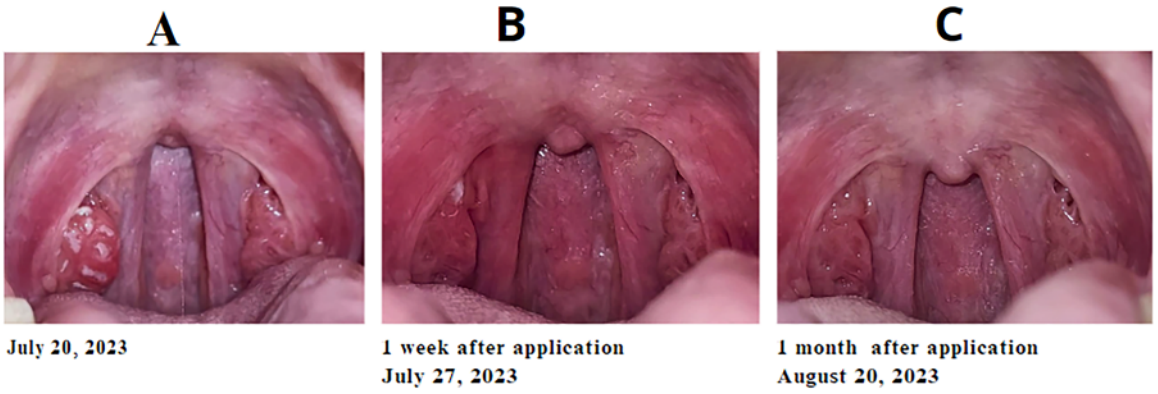


Fig. 3. Paciente L.A.
Caption: The image illustrates the remarkable and positive progression of a patient's case who was facing an infection. With just a single 6-minute application, the potential of PDT for tonsillar decontamination becomes evident.

after the application, a significant reduction in hyperemia and the overall size of the tonsils was observed. Throughout the monitoring period, the patient did not report any pain or discomfort related to the tonsils (Fig. 1B). At the eleven-month mark post-treatment, the patient continued to remain free from both visible and symptomatic infections. Additionally, the disappearance of caseum, indicative of a positive clinical outcome from the PDT treatment, has been observed as illustrated in Fig. 1C.

Case Report 2: A 31-year-old woman, L.V has been grappling with recurrent sore throats since her childhood, necessitating frequent employment antibiotics. She had already undergone preventive drug treatments without improvement, such as the use of bacterial lysate and was already considering tonsillectomy as a therapeutic option. She reported having an average of four infections per year with the last antibiotic being three weeks prior to application. On the day of the consultation, the patient was stressed because she was suffering from odynophagia again and had finished taking antibiotics due to a tonsillitis attack three weeks before, where she had been evaluated and medicated by an otorhinolaryngologist. She was also already suffering from side effects from the frequent use of antibiotics such as vaginal candidiasis and allergic reactions on her facial area. Upon physical examination, the patient presented grade 1 palatine tonsils, hyperemia and covered with exudate. After twelve months of application, the patient's symptoms improved, without new attacks of PT and without the use of antibiotics since then. During the clinical examination, it was possible to observe the disappearance of the exudate in the tonsils and a reduction in their size.

Patient L.V., during an ongoing infection presented with hyperemic tonsils displaying the presence of exudate during the clinical evaluation (as illustrated in Fig. 2A). During the administration of PDT, the patient reported feeling a slight burning sensation in the illuminated area, but did not report significant pain. Following the application of PDT, the patient reported observing an improvement in the pain. A minimum exsudate is visible on the tonsils, with mild hyperemia noted (as seen in Fig. 2B). In the subsequent month, the patient expressed concerns about throat irritation, prompting a second PDT session. Notably, a reduction in tonsil size was observed, accompanied by a decrease hyperemia and the disappearance of exudate in the tonsillar crypts (as illustrated in Fig. 2C). The patient no longer reported subsequent infections, irritations, or inflammations. Additionally, the patient highlighted an improvement in their overall quality of life.

Case Report 3: L.A., a 24-year-old woman, reports having started to experience recurrent tonsillitis after entering adulthood, needing to resort to antibiotics 5 a 6 times per year. She denied having other comorbidities. She was already in the public service queue waiting for her turn to undergo tonsillectomy surgery. The last antibiotic was azithromycin, which she had taken four weeks before the application. On the day of the consultation, she was already starting to experience odynophagia again and was beginning to present plaques on her right tonsil. Upon physical examination, it was possible to observe an inflammatory process starting in the right tonsil, which was very hyperemic and with a lot of exudate. One week after application, the plaques disappeared and after six months of follow-up, a reduction in the size of the tonsils and their crypts was observed, as well as a reduction in it.

Patient L.A., while experiencing an incipient infection. With the aim of avoiding the administration of antibiotics, PDT was applied, allowing the assessment of its effectiveness. Initially, the patient presented a significant amount of exudate in the right tonsil, along with visible hyperemia as shown in Fig. 3A. Throughout the follow-up of the case, a considerable reduction in exudate and hyperemia has been observed, as illustrated in Fig. 3B. In the following month, the patient reported the absence of pain, which can be observed in the provided image, demonstrating a significant improvement in the clinical condition. In this image (Fig. 3C), the disappearance of exudate, hyperemia and size reduction in the tonsils is evident.

4. Discussion

These three cases in particular were decided to be published separately so that it was possible to provide more details about each one and how the use of PDT enabled a favorable outcome in patients who were unable to overcome the recurrent use of antibiotics and their side effects, as well as the low quality of life caused by frequent sore throat. In two cases, the patients were waiting for tonsillectomy surgery through the public system, with no date set for it to take place. With the covid-19 pandemic in 2020 and the suspension of elective surgeries by public hospitals, which lasted for a long period, an alternative to the surgical procedure became even more necessary and urgent.

In the treatment of recurrent PT, PDT has demonstrated efficacy in destroying bacterial biofilms and reducing bacterial load in the tonsils, as observed in the three clinical cases reported. In case 1, the application of PDT resulted in complete resolution of symptoms and no recurrence of infections, highlighting the effectiveness of PDT in eradicating both active infections and preventing future recurrences by disintegrating the biofilm [18]. Curcumin is absorbed by bacterial cells present in tonsil biofilms and when exposed to light at 450 nm is activated, leading to the transfer of energy to the molecular oxygen present in the tissue, forming reactive oxygen species (ROS) [19]. In case 2, the patient showed significant improvement after the application of PDT, with a reduction in inflammation and pain symptoms. This shows the anti-inflammatory action of ROS, in addition to their bactericidal properties, including free radicals such as singlet oxygen [20]. These radicals are highly reactive and have the ability to quickly damage bacterial cells by inducing the oxidation of vital cellular components such as microbial membranes and proteins [21]. In case 3, the intervention was successful in eliminating the visible presence of infection and reducing discomfort, showing the effectiveness of PDT in acute conditions, even in the presence of resistant biofilms. The elimination of pathogenic bacteria through treatment can reduce the production of toxins and inflammatory enzymes, leading to a reduction in inflammation and consequently pain [22].

It can be observed that PDT was very well tolerated in all applications, with practically no adverse effects. As previously stated, curcumin assumes a pivotal role in the mechanism of PDT owing to its proficiency in absorbing blue light and engendering ROS. Its mode of action is ascribed to the hindrance of bacterial proliferation by suppressing protein kinases [16]. Furthermore, numerous approaches exist for the effective and secure utilization of the photosensitizer, with considerations linked to variables such as the method of administration, whether topical, intravenous, transdermal, subcutaneous, or through the respiratory tract [16].

Antibiotics are compounds with the capability to eradicate or hinder the proliferation of bacteria. However, their repeated use can engender the emergence of antibiotic resistance. The consequences of antibiotic resistance are difficult to forecast, but it is estimated that in 2050 it will be the cause of death of around ten million people and assume an enormous economic cost. In light of this, the cases under consideration hold substantial significance in assessing the efficacy of PDT as an alternative to antibiotics. Notably, in the selected cases, the patients were increasingly using antibiotics and maintaining persistent symptoms of odynophagia between attacks and with persistent exudate after treatment on physical examination. In these cases of bacterial resistance, PDT has played a fundamental role in addressing this challenge. In light of this, it is possible to deduce that PDT had two mechanisms of action: bactericidal and anti-inflammatory. Probably the most important action of PDT in resolving PT is its ability to eliminate the presence of biofilm on the palatine tonsils.

PDT has emerged as an emerging therapy with the potential to solve a major problem related to bacterial multiresistance to antibiotics. Additional studies are being carried out to better demonstrate the effectiveness of the therapy, such as: longer follow-up time to assess how long the patient remains infection-free and the use of technology in

acute tonsillitis, thus eliminating the need for antibiotics during infection.

PDT presents itself as a promising alternative to conventional treatments for recurrent PT, such as the use of antibiotics and tonsillectomy. Comparison between these methods can be structured around key criteria such as effectiveness, cost-benefit, side effects and patient satisfaction. The effectiveness of PDT has been documented in the treatment of various bacterial infections and inflammatory conditions [23]. Specifically for PT, PDT can significantly reduce bacterial load [24] and to desestructure of biofilm [25] in tonsils without contributing to the development of antibiotic resistance [26].

The PDT itself, once established, tends to have a low variable cost [27]. Furthermore, reducing the need for antibiotics and preventing surgery can result in considerable savings in the long term. The indirect costs of antibiotic in PT due to growing resistance and failed treatments can be significant [28]. Tonsillectomy has a high direct cost due to the need for a surgical environment and anesthesia, in addition to the costs associated with recovery time and potential complications [29].

PDT generally has few side effects; the most common are mild and localized, such as irritation in the treated area [30]. Moreover, there are no reports of long-term side effects described in this cases report. Regarding patient satisfaction, PDT had high patient satisfaction due to its non-invasive nature and effective symptom relief. Patient satisfaction with antibiotics may decrease with frequent use, especially due to side effects or when treatment fails due to resistance [31]. In tonsillectomy, despite postoperative discomfort, risks of bleeding, infections, and significant postoperative pain, patients report a significant improvement in quality of life when other treatments have failed [32]. Therefore, while conventional treatments such as antibiotics and tonsillectomy have their established places in the management of recurrent PT, PDT offers an alternative with the potential for sustainable efficacy, fewer side effects and good acceptance by patients. The choice between these options must consider the patient's individual profile, the severity of the symptoms and the history of previous treatments.

5. Conclusions

Through this study it is possible to conclude that PDT is a therapy with promising results. More studies are being carried out with the aim of proving the effectiveness of this treatment on a large scale, as well as elucidating how long the patient benefits from the technique after a single application. It has been shown to be a potential therapeutic weapon in combating bacterial PT and antibiotic resistance. It is also worth highlighting that it is a simple, quick and easily accessible therapy, making it suitable for outpatient use. PTD has demonstrated its ability as an effective, non-invasive strategy that contributes to improving patient quality of life, particularly evident in recurrence scenarios subsequent to unsuccessful conventional antibiotic interventions. PDT has the potential to be an invaluable tool in combating oropharyngeal infections by eliminating the microbial load, thus improving symptom manifestations and subsequently decreasing the need for antibiotics in cases of recurrence. Consequently, PDT has the potential to become a laudable therapeutic approach, offering a solution to the challenge of antibiotic resistance in treating infections. Its potential lies in its ability to effectively address a broad spectrum of microbial loads within the tonsils, which may not respond optimally to antibiotics.

To validate and expand the promising results of the current study on PDT in the management of recurrent PT, the authors plan to conduct a prospective randomized study directly comparing PDT with current standard treatment (use of antibiotics). This prospective study would not only confirm the efficacy and safety of PDT as an alternative to conventional treatment, and also provide first level evidence, potentially inducing a significant change in global clinical practices for the treatment of PT. Such a change could positively impact antimicrobial resistance, reducing dependence on antibiotics and offering a more sustainable therapeutic option with fewer side effects for patients.

CRediT authorship contribution statement

Laíza Mohana Pinheiro Duarte: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Isabella Dotta Damha Santiago:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Kate Cristina Blanco:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Vanderlei Salvador Bagnato:** Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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