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Original Article

Antimicrobial effects of N-acetylcysteine against bacterial strains associated with odontogenic infections

Efeito antimicrobiano da N-acetilcisteína contra espécies bacterianas associadas a infecções odontogênicas

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Abstract

Bacterial infections of the oral cavity result from factors such as inadequate biofilm control and host immune status. Odontogenic infections involve a complex polymicrobial community, comprising aerobic and anaerobic species, and have become increasingly challenging to manage due to the global increase in antimicrobial resistance. In this context, alternatives to conventional antibiotics are needed. N-acetylcysteine (NAC), a compound with antioxidant and mucolytic properties, has also been shown to have antimicrobial and antibiofilm activity, representing a promising candidate for dental applications. This study evaluated the antimicrobial activity of NAC by determining the minimum inhibitory and bactericidal concentrations against bacterial species associated with odontogenic infections. NAC showed inhibitory activity against all tested bacteria, including clinically relevant and highly resistant isolates. Although higher concentrations were required for some species, this finding is consistent with the physicochemical mode of action of NAC and its proposed use as a topical agent in dentistry. Overall, the results support the potential of NAC as an alternative or adjuvant antimicrobial strategy in the management of odontogenic infections, especially in the face of the growing challenge posed by antimicrobial resistance.

Keywords: bacteria, antimicrobials, bacterial resistance, infections.

Resumo

As infecções bacterianas da cavidade oral decorrem de fatores como o controle inadequado do biofilme e o estado imunológico do hospedeiro. As infecções odontogênicas envolvem comunidades polimicrobianas complexas, compostas por espécies aeróbias e anaeróbias, e têm se tornado progressivamente mais difíceis de tratar em decorrência do aumento global da resistência aos antimicrobianos. Nesse contexto, alternativas aos antibióticos convencionais são necessárias. A N-acetilcisteína (NAC), um composto com propriedades antioxidantes e mucolíticas, também tem demonstrado atividade antimicrobiana e antibiofilme, representando um candidato promissor para aplicações odontológicas. Este estudo avaliou a atividade antimicrobiana da NAC por meio da determinação das concentrações inibitória e bactericida mínimas contra espécies bacterianas associadas a infecções odontogênicas. A NAC apresentou atividade inibitória contra todas as bactérias testadas, incluindo isolados clinicamente relevantes e altamente resistentes. Embora concentrações mais elevadas tenham sido necessárias para algumas espécies, esse resultado é consistente com o modo de ação físico-químico da NAC e com sua proposta de uso como agente tópico em odontologia. De modo geral, os resultados sustentam o potencial da NAC como uma estratégia antimicrobiana alternativa ou adjuvante no manejo das infecções odontogênicas, especialmente diante do crescente desafio imposto pela resistência antimicrobiana.

Palavras-chave: bactérias, antimicrobianos, resistência bacteriana, infecções.

1. Introduction

Bacterial infections of the oral cavity are increasing globally and are usually caused by opportunistic bacteria present in the oral microbiota. These infections can be attributed to several factors, such as host immunological status, immunosuppression, mechanical trauma, nutritional deficiencies, and unsatisfactory biofilm mechanical control (Gondivkar et al., 2018).

Microbial resistance to antibiotics has become a serious public health problem worldwide and has been classified as a global threat by the World Health Organization (WHO, 2020;

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Ajulo and Awosile, 2024). It is estimated that over 700 species colonize the oral cavity (López-Píriz et al., 2007), forming a highly diverse and spatially structured microbiome whose dysbiosis has been strongly associated with the development of oral and systemic diseases (Baker et al., 2024). According to Villarmet et al. (2007), odontogenic infections are caused by a diverse microbiota, including aerobic and anaerobic bacteria, of which aerobic Gram-positive bacteria such as *Streptococcus* and *Staphylococcus* are prominent. However, many Gram-negative opportunistic bacteria, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Porphyromonas gingivalis*, *Fusobacterium* spp., and *Prevotella intermedia*, may be associated with these infections (Sousa et al., 2003; López-Píriz et al., 2007; Villarmet et al., 2007; Siqueira Junior and Rôças, 2013).

The increasing prevalence of antimicrobial resistance has stimulated the search for alternative antimicrobial strategies capable of controlling pathogenic bacteria. In this context, recent investigations have highlighted the potential of non-conventional antimicrobial approaches, including nano-structured antibacterial materials and bioactive compounds, which have demonstrated significant activity against oral pathogens and biofilm-associated microorganisms. These strategies have been proposed as promising adjuncts or alternatives to traditional antibiotics, particularly in dentistry, where biofilm-mediated infections are frequent and difficult to eradicate (Budi et al., 2024; Al-Awsi et al., 2024).

In theory, any bacteria that reach the root canal system (RCS) can potentially cause an endodontic infection (Huang et al., 2009; Cabral et al., 2017). Recent reviews have emphasized that endodontic infections are polymicrobial, biofilm-mediated, and often persistent, which makes their eradication particularly challenging and highlights the need for effective antimicrobial strategies beyond conventional approaches (Siqueira Junior and Rôças, 2022). RCS-isolated bacteria from patients with pain are usually strictly anaerobic, including *Fusobacterium nucleatum*, *Treponema* spp., *P. intermedia/nigrescens, Shuttleworthia satelles*, *and Dialister* spp., or facultative, such as *Streptococcus constellatus*, *Streptococcus mitis*, *and Eubacterium lentum* (Sousa et al., 2003; Jacinto et al., 2003; Siqueira Junior and Rôças, 2013). Although the RCS represents a key model for studying odontogenic infections due to its complex anatomy and biofilm persistence, similar microbial and therapeutic challenges are also observed in other oral infections such as periodontitis, dental caries, and pericoronitis.

In general, in clinical practice, when an infection is detected, dentists do not know exactly which microorganisms are responsible for it. To determine the causative agent, it is necessary to isolate and identify it; however, this procedure is not routine. As a rule, the treatment is decided empirically based on epidemiological data, considering the microorganisms that usually cause that type of infection (Vallano and Izarra, 2006).

N-Acetylcysteine (NAC), an antioxidant and mucolytic compound, is a derivative of the amino acid cysteine and exhibits antimicrobial properties, including activity against bacterial biofilms. This compound is already used in various medical treatments such as chronic bronchitis, acetaminophen overdose, and chemotherapy-induced toxicity. It should also be stressed that NAC has been described as very effective against Gram-positive and Gram-negative bacteria due to its properties (Dinicola et al., 2014). Although there are already some studies involving NAC in the dental field, in-depth research is needed (Samuni et al., 2013; Miles et al., 2016; Calzetta et al., 2018).

Biotransformation of NAC is known to produce several metabolites, including cysteine and disulfide groups. Subsequently, glutathione (GSH) and other metabolites are produced due to the metabolism of the cysteine metabolites previously formed (Ershad et al., 2025). SH is an antioxidant compound that comprises three amino acids (l-glutamate, l-cysteine, and l-glycine), and although molecular details of the antibacterial mechanism of action are unclear, exogenous GSH is often associated with antibacterial activity, as reported by Alharbe et al. (2017). Nonetheless, the antimicrobial activity of NAC could also be, among other mechanisms, due to the reaction of the -SH group with the disulfide bonds present in bacterial proteins. This reaction results in the bacterial protein bridges, which are essential for bacterial growth and survival, being ruptured (Sevier and Kaiser, 2002).

Therefore, new agents with antimicrobial activity that could be used as root canal irrigants and dressings are clinically essential. Hence, this study aimed to investigate the antimicrobial effect of NAC against bacteria responsible for the most common odontogenic infections, such as periodontitis, abscess, dental caries, endodontic infections, and pericoronitis.

2. Materials and Methods

2.1. Chemicals

The product tested was a solution of NAC 200 mg/mL provided by Farmácia Universitária Cidinha Bonini. The control product was a commercial solution of chlorhexidine digluconate 2% (Rioquímica S.A.). Resazurin solution 0.02% was prepared from commercial resazurin (Alamar Tecno-Cientifica Ltda).

2.2. Bacterial strains and culture conditions

In this work, the antimicrobial effect of NAC was compared with that of chlorhexidine digluconate 2% (Rioquímica S.A.). Eight bacterial strains were obtained from the American Type Culture Collection (ATCC): *Enterococcus faecalis* ATCC 4083, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *Porphyromonas gingivalis* ATCC BAA308/W83, *Prevotella intermedia* ATCC 25621, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 25923, *and Streptococcus mutans* ATCC 25175. A strain of *Klebsiella variicola* (Kv18L), isolated from a patient attending the Dental Clinic of Universidade de Ribeirão Preto, and a pandrug-resistant (PDR) *Klebsiella pneumoniae* strain (Kp177), defined as resistant to all antimicrobial classes tested and obtained from a patient with a hospital-acquired infection, were also included in this study (Nakamura-Silva et al., 2021; Cerdeira et al., 2021).

All bacterial strains were stored at −80ºC. *P. gingivalis* and *P. intermedia* were initially reactivated in brain heart infusion (BHI) broth (Oxoid, Basingstoke, UK) containing 5% defibrinated horse blood supplemented with 5 µg/mL of hemin (Sigma) and 1 µg/mL of menadione (Alamar Tecno-Cientifica Ltda.), incubating them for 24 h at 37ºC and 10% CO_2. The remaining strains were reactivated in BHI broth, incubating for 24 h at 37ºC and aerobiosis. After reactivation in liquid medium, all strains were cultivated under the same conditions but using solid culture media.

2.3. Evaluation of minimum inhibitory concentration (MIC)

MICs of the products were determined following the antimicrobial activity protocol using microdilution in a 96-well plate according to Clinical Laboratory Standards Institute M07-A9, 9th edition (CLSI, 2012). This method was adapted using 0.02% resazurin (7-hydroxy-3H-phenoxazine-3-one-10-oxide) as a bacterial growth marker according to Pitondo-Silva et al. (2016), with a final bacterial inoculum concentration of 1×10^6 CFU/mL. NAC solution concentration in the serial dilution was in the range of 0.1953–100 mg/mL.

The 96-well plate was incubated at 37ºC for 18 h, and two visual readings were obtained. In the first one, the culture turbidity was evaluated. Subsequently, 30 µL of resazurin was added to all wells, except those with *E. faecalis* ATCC 4083, to which 20 µL was added, and finally, the plate was reincubated for 2 h. Then, a second reading was taken using resazurin as a bacterial growth marker. Resazurin is a nonfluorescent compound that presents an intense blue color; however, upon entering the cells, it is reduced to resofurin, a pink and fluorescent compound, which indicates their viability (Rampersad, 2012). If the original blue color is maintained, it means an absence of reduction of resazurin by the cellular dehydrogenases, possibly signifying a compromise of the cellular metabolism. Thus, resazurin can be applied as a bacterial growth marker, owing to the visually perceived color change (Pitondo-Silva et al., 2016).

2.4. Evaluation of minimum bactericidal concentration (MBC)

The minimum bactericidal concentration was obtained considering the readings from the MIC. For each bacterial strain, all wells with no visible bacterial growth were selected, and 10 µL was taken from each, which was then transferred to Petri dishes containing the culture medium. Mueller–Hinton agar was used as the culture medium for aerobic bacteria, while supplemented tryptic soy broth was used for all anaerobic bacteria. The plates were incubated for another 18 h under appropriate oxygen conditions, followed by a visual reading. MBC value was the lowest solution concentration at which there was no bacterial growth in the region close to the inoculation point.

3. Results and Discussion

The results obtained demonstrated that the NAC solution exhibited considerable antimicrobial activity against all the bacterial strains tested. The MIC and MBC values for each microorganism are presented in Table 1. The positive control, 2% chlorhexidine digluconate, showed complete inhibitory effects on all strains, as expected. The *in vitro* assays confirmed that NAC was capable of inhibiting and eliminating a range of bacterial species relevant to endodontic and periodontal infections, with MIC values ranging from 1.562 mg/mL to 6.25 mg/mL. Overall, Gram-negative and Gram-positive strains displayed variable susceptibility, with *P. aeruginosa* showing the lowest MIC and MBC values (1.562 mg/mL), whereas *Klebsiella* clinical isolates and *P. gingivalis* required concentrations of 6.25 mg/mL for both bacteriostatic and bactericidal effects.

For *E. coli* ATCC 25922, *S. aureus* ATCC 25923, *K. pneumoniae* ATCC 700603, *E. faecalis* ATCC 4083, and *S. mutans* ATCC 25175, the MIC was 3.125 mg/mL and the MBC was 6.25 mg/mL, except for *E. coli*, which required 12.5 mg/mL to achieve bactericidal activity. These findings confirm the broad-spectrum potential of NAC but also emphasize that its effectiveness is species dependent,

Table 1. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of N-acetylcysteine (NAC) solution against the tested bacterial species.

NAC 200 mg/mL Solution		
Species tested	**MIC (mg/mL)**	**MBC (mg/mL)**
Escherichia coli ATCC 25922	3.125	12.5
Pseudomonas aeruginosa ATCC 27853	1.562	1.562
Staphylococcus aureus ATCC 25923	3.125	6.25
Klebsiella pneumoniae ATCC 700603	3.125	6.25
Enterococcus faecalis ATCC 4083	3.125	6.25
Streptococcus mutans ATCC 25175	3.125	6.25
Klebsiella pneumoniae PDR (clinical)	6.25	6.25
Klebsiella variicola (clinical)	6.25	6.25
Porphyromonas gingivalis ATCC BAA308/W83	6.25	6.25
Prevotella intermedia ATCC 25611	6.25	12.5

highlighting the importance of strain-specific assessment when considering its application as an adjunctive antimicrobial agent in dental practice.

Of the analyzed strains, *P. aeruginosa* ATCC 27853 was most susceptible to NAC, requiring the lowest concentrations for bacterial inhibition and eradication (1.562 mg/mL). This finding is particularly important as *P. aeruginosa* is a well-known opportunistic pathogen frequently associated with odontogenic and hospital-acquired infections, including root canal infections and biofilm-related diseases (Lister et al., 2009; Percival et al., 2015). Given the increasing resistance of *P. aeruginosa* to conventional antibiotics, alternative agents such as NAC offer promising therapeutic options in clinical practice (Tacconelli et al., 2018).

In contrast, *P. intermedia*, one of the main anaerobic pathogens implicated in endodontic infections (Siqueira Junior and Rôças, 2013; Sousa et al., 2003; Jacinto et al., 2003) required the highest NAC concentration among the tested strains (MIC 6.25 mg/mL and MBC 12.5 mg/mL). Despite this observation, these values remain relatively low within the tested concentration range (0.19531–100 mg/mL), confirming NAC's effectiveness even against more resistant species. *P. intermedia* is a strict anaerobic Gram-negative bacterium strongly associated with aggressive and chronic periodontal diseases as well as endodontic, peri-implant, and other oral infections. Its virulence and biofilm-forming ability make treatment challenging, often requiring combined mechanical and pharmacological strategies. Furthermore, its resistance to antibiotics such as amoxicillin, amoxicillin/clavulanic acid, tetracycline, clindamycin, and metronidazole has been described (Castillo et al., 2022). The formation of biofilms, especially in polymicrobial communities, further complicates elimination with mechanical debridement or antimicrobials alone (Sousa et al., 2003; Jacinto et al., 2003; Siqueira Junior and Rôças, 2013).

Moon et al. (2015) demonstrated in their study that NAC can effectively inhibit planktonic growth and biofilm formation of *P. intermedia*; however, it has limited ability to disrupt pre-established biofilms. Furthermore, the researchers observed that NAC may reduce the effectiveness of certain antibiotics, such as ampicillin and tetracycline, when targeting mature biofilms. These findings suggest the value of NAC as a preventive antibiofilm agent rather than a strategy for eradicating mature biofilms, reinforcing the need for further research on its interactions with conventional antibiotics and its role in the management of oral infections.

The pandrug-resistant (PDR) *K. pneumoniae* strain, isolated from a hospital-acquired infection, also showed susceptibility to NAC (6.25 mg/mL for both MIC and MBC). This strain required twice the concentration for inhibition compared with the *K. pneumoniae* ATCC 700603 reference strain. This finding is clinically relevant given the increasing prevalence of highly resistant *K. pneumoniae* strains in healthcare settings (Pitout et al., 2015; Cerdeira et al., 2021). Infections caused by such strains are particularly difficult to manage due to resistance to last-line antibiotics, including carbapenems and colistin (Wang et al., 2023). Notably, the *K. pneumoniae* isolate evaluated in this study is resistant to 42 antibiotics covering all therapeutic classes (Cerdeira et al., 2021). The observed susceptibility to NAC underscores its potential role as an adjunct or alternative agent for combating infections caused by highly resistant bacteria.

The same NAC concentration (6.25 mg/mL for both MIC and MBC) showed antimicrobial activity against *K. variicola*, an emerging human pathogen. Although this isolate had been previously identified and reported (Nakamura-Silva et al., 2021), the present study represents the first evaluation of its susceptibility to NAC. Given the increasing clinical relevance of *K. variicola* and the challenges associated with its accurate identification, these findings provide novel insights into alternative antimicrobial approaches targeting this species.

Several studies have demonstrated that NAC exhibits promising antimicrobial and antibiofilm properties against a broad range of bacteria, including both Gram-negative and Gram-positive pathogens linked to endodontic and periodontal infections (Aslam and Darouiche, 2011; Moon et al., 2015; Rasmussen et al., 2016). Its antimicrobial effect is largely attributed to its ability to break disulfide bonds within the extracellular matrix, destabilizing biofilms and preventing bacterial adhesion (Ghatole et al., 2022).

Importantly, NAC is not a conventional antibiotic and exerts its antimicrobial activity through physicochemical mechanisms rather than specific molecular targets. Consequently, higher MIC and MBC values compared to classical systemic antibiotics are expected and should not be interpreted as reduced efficacy. In clinical dentistry, NAC may be safely applied at high local concentrations as a topical agent, irrigant, or intracanal dressing, with low cytotoxicity and a well-established safety profile, making direct comparisons with systemically administered antibiotics inappropriate. Moreover, NAC has shown potential in reducing mortality in cases of septic shock caused by carbapenem-resistant *K. pneumoniae* and *Acinetobacter baumannii* when used in combination with specific antibiotics (Oliva et al., 2021). These findings, together with the present study, reinforce the viability of NAC as an alternative or adjunctive agent in combating diverse bacterial infections. Given its antioxidant, anti-inflammatory, and antimicrobial properties, NAC is a promising option to complement conventional treatments for odontogenic infections. Its ability to inhibit and eradicate pathogenic bacteria at relatively low concentrations highlights its potential contribution to mitigating the global challenge of antimicrobial resistance (AMR), which is one of the greatest public health threats worldwide (Ajulo and Awosile, 2024).

A limitation of this study is that antimicrobial activity was assessed using planktonic cells. It is well established that biofilm-associated bacteria may require higher concentrations for effective eradication. Therefore, future studies should investigate the activity of NAC against mature biofilms to better reflect clinical conditions.

4. Conclusion

This study demonstrates that N-acetylcysteine (NAC) represents a promising alternative or adjunctive

antimicrobial agent for the management of odontogenic infections. Rather than acting as a conventional antibiotic, NAC exerts its effects through physicochemical mechanisms that impair bacterial adhesion and biofilm stability, which is particularly relevant in the context of persistent oral infections. Its favorable safety profile and low cytotoxicity support its potential application at high local concentrations in dentistry, such as in topical formulations, irrigants, or intracanal dressings. In light of the growing global challenge of antimicrobial resistance, NAC emerges as a versatile and clinically relevant strategy that may complement existing therapeutic approaches in oral healthcare.

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Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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