Microbial infection and its control in cases of symptomatic apical periodontitis: a review

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Summary. Apical periodontitis is an inflammation of dental periapical tissues developed as a response to colonization of microorganisms in root canal system. Etiology of periapical pathology is associated with different species of microorganisms that are not fully defined yet. The changes in the composition of root canal microbiota as well as other factors, such as host resistance to various infections and concomitant viral infection, etc., can influence development of the symptomatic apical periodontitis. Etiology of disease is reviewed in this article.

The purpose of treatment of symptomatic apical periodontitis is to eliminate the infection in root canal system and to obtain relief of symptoms. It can be done by conventional root canal therapy, which can be combined with anti-inflammatory medication. Indications for antibiotic therapy in such cases are limited to particular occasions, which are considered in article. Nevertheless, findings show that usually dentists prescribe antibiotics improperly in clinical practice. It can render drugs ineffective against diseases of dental origin as well as against potentially fatal infectious diseases. Selection of antibiotics for the treatment of root canal infections is reviewed in this article. Importance of antimicrobial susceptibility testing is emphasized.

There is a need for more research on microbial causes and interactions in different forms of apical periodontitis to improve diagnosis and treatment.

Introduction

Apical periodontitis is a defense response of the human organism to the destruction of dental pulp and microbial settlement of root canal system (1). Microorganisms have been implicated in root canal infections since 1890, when Miller first observed microorganisms associated with an inflamed pulp. The necrotic pulp offers a selective habitat for microflora in the root canal. The microbes grow in adhesive biofilms, aggregates, and as planktonic cells suspended in the fluid phase of canal. Studies have shown that cells of microorganisms in biofilm are one thousand times more resistant to biocides than the same microorganisms in planktonic form (2). The survival strategy of most microbes is their ability to form biofilm, which must be considered as one of a virulence factors for disease producing organisms (1).

There is no doubt that microorganisms are the main causative factor of apical periodontitis. Up till now, it is not clear what species are playing the main role in that process (3). It is known that of the more than 500 species of bacteria found in oral infections, only 20–40 of them are more frequently involved in root canal infection, and no one of them was given name of “major” pathogen (4). Even use of advanced molecular techniques did not give answer to this question (5–9). It is possible to list the microorganisms involved in endodontic infections, but role of specific mixtures of species is unclear (4, 10–12).

The aim of this article was to review microbial causes of symptomatic apical periodontitis and to evaluate the data obtained from studies on antimicrobial susceptibility of bacteria isolated from infected root canal.

Microorganisms in case of symptomatic apical periodontitis

Microflora in infected root canals is a mixture of...
bacteria with a predominance of obligate and facultative anaerobes. Anatomical complexity of root canal system such as isthmuses, ramifications, deltas, irregularities, and dentinal tubules creates specific conditions for bacteria to survive and withstand intracanal disinfecting measures and adapt to a new environment and act as a reservoir for future dental and systemic infections (13). Reliability of microbial culturing procedure is associated with numerous factors, including sampling, cultivation, methods for identification, etc. (11).

Two terms are often used when the ability of microorganisms to induce the disease is discussed: pathogenicity and virulence. Pathogenicity is the ability of microorganisms to cause the disease. Virulence denotes the degree of pathogenicity of a microorganism. The sum of virulence factors will determine the pathogenicity of the endodontic microflora. Microbial virulence factors implicated in periapical disease can have a direct or indirect damage to the periapical connective tissues and bone by producing extracellular bacterial enzymes such as proteases, collagenases, etc. (4).

Oral microbiota contains only several pathogenic species, and most of them have low virulence. This is consistent with the slowly progressive nature of most forms of apical periodontitis. In some instances, the presence of more virulent species or strains, or virulent mixed consortium, can predispose to abscess formation in periapical tissues (4).

Reasons why an asymptomatic case with long-standing infection becomes symptomatic are not fully understood. It could be associated with the changes in the composition of microbiota. The composition of the bacterial communities in symptomatic teeth has been shown to be significantly different from that found in asymptomatic teeth (14). Differences are represented by changes of dominating species and higher numbers of species involved in symptomatic cases. Such a shift is probably due to arrival of new pathogenic bacterial cells or rearrangements in the bacterial consortium. A number of studies have shown that there is no key pathogen involved in symptomatic infections, but the occurrence of certain specific bacterial combinations in infected root canals may be a decisive factor in causation of symptoms (5, 7, 15–18).

Several species of bacteria are found more frequently in symptomatic infections of root canals, with a predominance of obligate anaerobes, especially black-pigmented bacteria (Porphyromonas, Prevotella), Peptostreptococcus, and Fusobacterium (12, 15–19). Black-pigmented bacteria were shown by several authors to be present in 50–59% of necrotic root canals or symptomatic teeth (12, 19). Siqueira et al. found Porphyromonas endodontalis in 70%, Porphyromonas gingivalis in 40%, and Prevotella intermedia in 10% of samples from symptomatic teeth. P. gingivalis was always found to be associated with P. endodontalis in abscessed teeth (19). Jacinto et al. isolated Fusobacterium necrophorum, Fusobacterium nucleatum, Peptostreptococcus micros, and Peptostreptococcus prevotii from symptomatic teeth together with black-pigmented bacteria in their study (12). Later the same authors detected Porphyromonas gingivalis as the most frequently found bacteria in symptomatic cases (17). Pinheiro et al. revealed polymicrobial infection in canals of symptomatic root-filled teeth and Peptostreptococcus as the most frequently isolated genera, which was associated with clinical symptoms (16). Nevertheless, black-pigmented bacteria and other dominant species of microorganisms in symptomatic cases are always associated with other gram-positive and facultative microorganisms, especially streptococci, confirming the synergetic relationships among the bacteria (15). Kuriyama et al. observed most often gram-positive cocci together with gram-negative anaerobic rods in dentoalveolar infections (20). The results of study by Khmaleelakul et al. confirm the existence of mixed infection. Prevotella and Peptostreptococcus species were frequently found to dominate in the mixture in cases of symptomatic apical periodontitis in their study (18).

Studies, where molecular methods for the detection of bacterial cells were used, showed involvement of other bacterial species in symptomatic cases of apical periodontitis. High prevalence of Treponema denticola and Treponema socranskii in cases of symptomatic apical periodontitis was found using the single polymerase chain reaction (PCR) method for identification of microorganisms (7, 8). Foschi et al. revealed an association between the presence of Treponema denticola and the symptomatic root canal disease, with apical bone resorption. T. denticola was detected in 56% of symptomatic teeth using the PCR assay (8). Therefore, Treponema species were also suggested to be the members of the microbiota associated with symptomatic apical periodontitis and able to interact with other species in the consortium.

One of the recent studies, undertaken to investigate uncultivated phylotypes, revealed that novel phylo-
types and newly named species could take part in the microbiota associated with symptomatic root canal infections. The most prevalent novel species/phylotypes Dialister invisus, Olsenella uli, Granulicatella adiacens, and Synergistes clones were detected using molecular genetic method (5).

It is interesting that geographic location can have an influence for the composition of microflora in symptomatic cases as well. A few recent studies compared the bacterial community profiles of the microbiota associated with symptomatic apical periodontitis in patients from different geographical locations. Machado de Oliveira et al. analyzed samples taken from teeth of patients in Brazil and the United States of America (6). Siqueira et al. compared endodontic pathogens in samples from patients in Brazil and South Korea (21). The results of these studies showed that the prevalence of some species in infections of endodontic origin might significantly differ from one geographic location to another (6, 9, 21).

Symptomatic apical periodontitis can occur as a result of primary as well as secondary infection in root canals. Secondary infection is understood as microbial community that remains in the root canal system after primary endodontic treatment and can lead to formation of asymptomatic apical periodontitis. Studies have clearly revealed the differences between microflora in primary and secondary cases of asymptomatic apical periodontitis, but there are no findings in literature to demonstrate differences of microflora in teeth with symptomatic apical periodontitis in cases of primary and secondary infection.

It has been suggested that some specific microorganisms, especially gram-negative anaerobic bacteria, could be closely associated with the etiology of symptomatic apical periodontitis. Nevertheless, several studies have revealed that certain species commonly associated with symptoms may also be frequently found in asymptomatic cases (3, 22–24). Rocas et al. have reported the occurrence of the same Treponema species in root canal infections, but associated with asymptomatic periodontitis. T. denticola was detected in 77.3% of the asymptomatic cases and T. socranskii in 40.9% in their study (25). Peptostreptococcus micros and Fusobacterium necrophorum were found together with Enterococcus faecalis in asymptomatic cases with previous root canal treatment (15). Baumgartner et al. did not show a significant relationship for the presence of black-pigmented bacteria with clinical signs and symptoms in their study (22). Although Jung et al. detected significant relationships in the combination of Bacteroides forsythus/Porphyromonas gingivalis and Treponema sp./P. gingivalis among the analyzed bacteria in root canal infection, but they did not find a significant association between any bacteria and any symptoms (23).

Therefore, it could be that factors other than the presence of a given putative pathogenic species can influence the development of the symptoms (26–30). These factors include the presence of not equally virulent clonal types of the same species, microbial synergism or antagonism in mixed root canal bacterial community, which can also influence virulence, number of microbial cells, which is probably higher in symptomatic cases, host resistance to various infections, concomitant herpesvirus infection, etc (28, 29, 31). It is suggested that cytomegalovirus (HCMV) or Ebstein-Barr virus (EBV) infections are also involved in the pathogenesis of periapical symptomatic lesions. Herpes viruses may produce periapical pathosis as a direct result of viral infection and replication or as a consequence of virally induced impairment of the host defense and subsequent increased virulence of resident bacterial pathogens (29).

**Do we need antibiotics for treatment of symptomatic apical periodontitis?**

The most important decision-making problem in antibiotic therapy is to ascertain indications and group of antibiotics for a particular situation.

During acute phases of apical periodontitis, the infection may develop to produce an accumulation of pus and formation of an abscess. From this point, the inflammation may become chronic or exacerbation can occur with the formation of a clinical abscess. This leads to an increase in tissue pressure by pus formation, bone resorption, and the pus outbreak through the bone underneath the periosteum into the tissue spaces. The exact location of the accumulation of the pus and exudate is dependent on the anatomical location of the root apex. Most commonly, the drainage occurs to the oral vestibule (32).

The aim of treatment of symptomatic apical periodontitis is to control the spread of the infection, by eliminating the irritant that causes the symptoms, and to obtain relief of symptoms. The main etiological factor of apical periodontitis is microorganisms that inhabited the root canal system. The only predictable treatment in such cases is chemomechanical instrumentation and disinfection of the root canal space followed by obturation and high-quality coronal seal. Although it is evident that an absolutely microorganisms-

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free canal system cannot be achieved by any of the contemporary root canal treatment procedures, it has been shown that periapical tissue heals after conventional root canal therapy in a large number of cases (2). Such therapy can be combined with anti-inflammatory medication in cases of symptomatic apical periodontitis. In most cases, such method of treatment is sufficient for the management of the clinical situation. There are no strict indications for the antibiotic therapy during treatment of symptomatic apical periodontitis in healthy patients with localized swelling (11, 32, 33).

Discussion about the use of antibiotic therapy during treatment of symptomatic apical periodontitis still exists. The question, which has not been answered yet, is important to all practitioners, “Can the usage of antibiotics give better effect for relief of clinical symptoms than conventional root canal treatment alone?”

A few studies, focused on changes of clinical symptoms during treatment, were consistent in showing that patients with pulp necrosis and localized symptoms of acute apical periodontitis had a significant improvement in their condition following conventional cleaning and shaping of the root canal system and that the use of antibiotic did not affect the results (34, 35). These findings confirm that symptomatic apical periodontitis in a healthy patient displaying a localized swelling and without systemic involvement is not an indication for systemic antibiotic therapy. In such cases, incision, drainage, and root canal treatment can effectively control and suspend the outbreak of radicular infection (4).

However, it is known that antibiotics can help to impede the spread of infection and the development of secondary infections in medically compromised patients.

There are particular occasions in which antibiotics are indicated in the treatment of symptomatic apical periodontitis:

- Apical abscess associated with systemic involvement, including fever, malaise, and lymphadenopathy;
- Spreading infections resulting in progressive diffuse swelling and/or trismus;
- Apical abscess (even with localized swelling) in medically compromised patients who are at increased risk of a secondary infection at a distant site following bacteremia;
- Some cases with persistent exudation not resolved after revision of intracanal procedures.

It is important to emphasize that antibiotics are considered an adjunct chemotherapy to aid the host defenses in the elimination of microorganisms overwhelming the host. Antibiotic therapy alone in cases of symptomatic apical periodontitis is not effective. Therefore, antibiotics cannot be considered a substitute for root canal cleaning, disinfection and drainage of soft and hard tissues.

Clinician must make a distinction between localized and spreading infections. The dental practitioner must investigate if the patient’s medical history includes conditions or diseases known to reduce the host defense mechanisms or expose the patient to higher systemic risks.

There are two forms of symptomatic periradicular infection: acute apical periodontitis and periapical abscess. Both forms of symptomatic periodontitis can be characterized as inflammation in the periradicular tissues associated with pain and swelling. Degree of swelling depends on how deep infection has penetrated through the bone. Primary stages of disease are concomitant with pain and infiltration of soft tissues or localized swelling. Such form can be defined as localized infection and must be treated by elimination of bacteria from root canal system or by incision for drainage if endodontic treatment is impossible in a particular clinical case. Whereas spreading infections are associated with diffuse swelling, fever, malaise, trismus, and submandibular lymphadenopathy. Such more serious cases usually require extensive surgical drainage and must be supported by treatment with systemic antibiotics. Nevertheless, the main etiologic factor of disease must be eliminated by extraction of causative tooth or by root canal treatment after relief of symptoms.

Recommendations for the use of antibiotics in cases of particular forms of symptomatic apical periodontitis are shown in Table (11, 33).

**Antibiotics for treatment of root canal infections**

Although the vast majority of infections of endodontic origin and most cases of symptomatic apical periodontitis are treated without the need of antibiotics, these drugs are used in clinical practice more often than necessary. Data from few surveys showed that most dentists prescribed antibiotics for patients incorrectly, using them with no indications in cases such as necrotic pulp and periradicular pain. Moreover, such trend did not change with each year (33). Physicians often prescribe antibiotics that kill a wide variety of bacteria whereas a more specific
antibiotic, with selected antibacterial activity could be prescribed for treatment of infections of endodontic origin. The prescription dosage and treatment duration is often a matter of incorrect choice as well. Improper prescribing of antibiotic therapy is due to many factors such as patients, which insist on antibiotics, physicians not having enough time to explain why antibiotics are not necessary and finding the decision to prescribe them being simpler, or physicians being mistaken in recognition of a serious bacterial infection. It is important to amplify that prescription of antibiotic therapy certainly depends on medical knowledge of practicing dentists. Inaccurate use of antibiotics may predispose secondary infections and super infections and can render drugs ineffective against potentially fatal medical infectious diseases (4).

The main goal of antimicrobial therapy is to support the host to overcome the infection. Nevertheless, antibiotics also have adverse side effects such as hypersensitivity reactions to β-lactam antibiotics, toxicity and interactions with other drugs, pseudomembranous colitis, which occurs due to disturbance of balance of normal microflora. Therefore, the risk-benefit ratio should be always weighted before the prescription of antibiotics. One more serious problem related with antibiotic use is antimicrobial resistance. It became worldwide public health problem during last years.

Overuse and misuse of antibiotics have been considered as the major cause responsible for the emergence of multidrug-resistant strains. Therefore, diseases that were effectively treated in the past with a given antibiotic may now require the use of another drug, usually more expensive and potentially more toxic, to achieve effective antimicrobial treatment.

Although antibiotics are rarely required for treatment of root canal infections, the microbial sensitivity test can be considered as an important auxiliary resource in cases resistant to endodontic therapy (36). The determination of in vitro antimicrobial susceptibility can be important in certain situations, for example, to monitor patterns of susceptibility and resistance in the population and to aid in the selection of an appropriate antibiotic when indicated in root canal treatment. Usually it is required in cases when a significant infection appears to be resistant to the antibiotics prescribed on an empirical basis, in patients who are significantly immunocompromised, or in infections that are considered very serious in nature (11).

Susceptibility testing may be done by the diffusion test or the dilution test. Diffusion test shows sensitivity of the tested organism to some antibiotics as indicated by zones of inhibition of bacterial growth around the disks. Dilution test is the minimal inhibitory concentration (MIC) test, which determines the lowest concentration of the antibiotic that will inhibit visible growth in vitro (37).

It is known that antibiotic testing is a slow process. Therefore, treatment is frequently started on empirically selected antibiotics. Just in exceptionally difficult cases, when empirical antibiotic therapy is not effective, testing of microbial sensitivity is required (18, 33). It is evident that empirical therapy may be used for diseases with known microbial causes. This is especially applicable to infections of endodontic origin, because culture-dependent antimicrobial tests can take too long to provide results about susceptibility of root canal anaerobic bacteria to antibiotics (7–14).

### Microbial infection and its control in cases of symptomatic apical periodontitis

| Clinical symptoms                                      | Recommendations for treatment                                                                 |
|--------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Acute apical periodontitis (tooth pain, especially on  | Conventional root canal treatment                                                          |
| biting or percussion, no swelling or localized swelling)| Antibiotics are not recommended                                                         |
| Periapical abscess (tooth pain, localized swelling,    | Conventional root canal treatment                                                          |
| no systemic signs such as fever, malaise)              | Antibiotics are not recommended.                                                            |
| (tooth pain, diffuse swelling, can be systemic         | Consider antibiotics if the patient is medically compromised.                               |
| involvement such as fever, malaise, lymphadenopathy)   | Antibiotics are recommended to supplement local treatment (conventional root canal treatment or incision) |

| Table. Recommendations for the use of antibiotics in conjunction with root canal treatment in particular forms of symptomatic apical periodontitis |
|---------------------------------------------------------------------------------------------|
| Clinical symptoms                                      | Recommendations for treatment                                                                 |
| Acute apical periodontitis (tooth pain, especially on biting or percussion, no swelling or localized swelling) | Conventional root canal treatment |
| Antibiotics are not recommended | |
| Periapical abscess (tooth pain, localized swelling, no systemic signs such as fever, malaise) | Conventional root canal treatment |
| Antibiotics are not recommended. Consider antibiotics if the patient is medically compromised. | |
| (tooth pain, diffuse swelling, can be systemic involvement such as fever, malaise, lymphadenopathy) | Antibiotics are recommended to supplement local treatment (conventional root canal treatment or incision) |
days). Therefore, it is preferable to consider an antimicrobial agent, the action spectrum of which includes the most commonly detected bacteria. Although it is known that etiology of apical periodontitis is polymicrobial, possible changes of the microbial root canal ecosystem in symptomatic situations, if compared with asymptomatic primary or secondary cases, may influence the choice of the antibiotics in particular clinical situations (38).

Whenever possible, narrow-spectrum antibiotics should be prescribed because broad-spectrum antibiotics produce more alterations in normal microflora, resulting in more side effects. In addition, broad-spectrum antibiotics select the resistant organisms (11). The risk/benefit ratio should be always weighted before the prescription of antibiotics.

There are very few studies that analyzed antimicrobial susceptibility of microorganisms isolated from root canals in cases of symptomatic or asymptomatic endodontic infections. It has been shown that most of the root canal microbiota are susceptible to penicillins (12, 18, 20, 39–41). This makes them the drugs of the first choice to be used in infections of endodontic origin. Baumgartner et al. found the following percentages of susceptibility for the 98 microbial species studied: penicillin V, 83/98 (85%); amoxicillin, 89/98 (91%); amoxicillin + clavulanic acid, 98/98 (100%); clindamycin, 94/98 (96%); and metronidazole, 44/98 (45%) (39). Bacterial resistance to metronidazole was the highest; however, if used in combination with penicillin V or with amoxicillin, susceptibility of root canal bacteria increased to 93% and 99%, respectively (39). Jacinto et al. showed that amoxicillin, amoxicillin + clavulanate, and cephaclor were effective against five species of anaerobic bacteria most commonly found in the root canals of symptomatic teeth in their study (12). Kuriyama et al. also confirmed that penicillin is effective against most major pathogens in odontogenic infections although it can be affected by β-lactamase-producing Prevotella found in their studies. They detected that cefmetazole, clindamycin, and minocycline may be effective against most pathogens, including penicillin-unsusceptible bacteria (20, 40, 41).

Since the use of antibiotics is restricted to severe infections or to prophylaxis, it seems prudent to use amoxicillin, semi-synthetic penicillin with broad-spectrum antimicrobial activity. In even more serious cases, including life-threatening conditions, an association of amoxicillin with metronidazole may be required to achieve optimum antimicrobial effects as a result of the extended spectrum of action to include penicillin-resistant strains. In patients allergic to penicillins or in cases refractory to amoxicillin therapy, clindamycin is indicated. Clindamycin has a strong antimicrobial activity against oral anaerobes (20, 42).

It is evident that microbial resistance rates are not equally distributed around the world. In addition, in Europe, there are great differences among countries in antimicrobial drug resistance among human pathogens and great differences in the use of systemic antibiotics as well. The use of antimicrobial drugs was described to be much higher in some Mediterranean countries in comparison to central and northern countries (43). Consequently, antimicrobial drug resistance in southern European countries is significantly higher than it is in other countries of the European community. Van Winkelhoff et al. described differences in susceptibility profiles of periodontal pathogens isolated from patients in Spain and the Netherlands (44, 45). Information from such studies indicates that it may not be possible to develop uniform protocols for usage of antibiotics in the treatment of oral infections in the European countries. Results may also differ in the same geographical place after some time.

Conclusions

Specific mixtures of the bacterial species as well as other factors responsible for the pathogenesis of symptomatic apical periodontitis are impossible to define. Further studies focused on differences in composition of root canal microorganisms associated with different clinical conditions might be useful to collect more information about this issue.

It is evident that microbial resistance is becoming a worldwide medical, economic, and public health problem. The misuse of broad-spectrum antibiotics in the treatment of local infections such as apical periodontitis may enhance the development of bacterial resistance to a number of antimicrobial agents and, consequently, may diminish therapeutic potential as well as cause health problems in the treatment of serious infectious diseases.

It is limited extent of studies, which have been investigated the antibiotic resistance in root canal microflora. The increasing resistance of anaerobic bacteria to some widely used antibiotics for treatment and prophylaxis of infections ensures the need of monitoring susceptibility patterns periodically by using susceptibility tests. Studies of microbial resistance to antibiotics are needed, and the data from such studies should be considered for application in clinical practice.
Mikrobinė infekcija ir jos kontrolė esant simptominiam viršūniniam periodontitui

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Raktažodžiai: infekcija, antibiotikai, viršūninis periodontitas.

Santrauka. Viršūninis periodontitas – danties šaknies periapikalinių audinių uždegimas, pasireiškiantis kaip atsakas į danties pulpos pažeidimą ir mikroorganizmų patekimą į danties šaknies kanalų sistemą. Periapikalinių patologijos etiologija siejama su skirtingomis mikroorganizmų rūšimis, kurios dar nepakankamai išitirtos. Simptominiam viršūniniam periodontitui įtakos gali turėti danties šaknies kanalo mikrofloras pokyčiai, organizmo imuninis atsakas, virusinė infekcija ir kiti veiksniai. Straipsnyje apžvelgiama ligos etiologija.

Simptominio viršūninio periodontito gydymo tikslas – infekcijos pašalinimas iš danties šaknies kanalų sistemos bei klinikinių simptomų sumažinimas. Šiam tikslui reikalingos įprastos danties šaknies kanalų gydymas, kartu skiriant nesteroidinių priešuždegiminių vaistų. Indikacijos, sisteminiam antibiotikų vartojimui simptominio viršūninio periodontito atveju, yra ribotos ir susijusios tik su konkrečiais atvejais, kurie yra apžvelgiami straipsnyje. Deja, tyrimai rodo, kad odontologai antibiotikus dažnai skiria netinkamai. Tai gali lemti ne tik šių vaistų veiksmingumo sumažėjimą sergant odontogeninės kilmės ligomis, bet gali sukelti problemų gydant sudėtingas bendražys infekcines ligas. Straipsnyje apžvelgiami studijos, susijusios su antibiotiko parinkimu gydant danties šaknies kanalų infekciją bei pabrėžiama tyrimų svarba, nustatant mikroorganizmų jautrumą antibiotikams.

Reikalinių moksliniai tyrinėjimai, nagrinėjantys mikroorganizmų tarpusavio sąveiką, jų įtaką skirtingų viršūninio periodontito formų pasireiškimui, siekiant tobulinti šios ligos diagnostiką ir gydymą.

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