JOURNAL OF HEALTHCARE SCIENCES
Volume 4 Issue 11 2024, Article ID: JOHS2024000928
http://dx.doi.org/10.52533/JOHS.2024.41106
e-ISSN: 1658-8967

Review

The Role of Oral Hygiene in Preventing Secondary Infections in Children with Immunocompromising Conditions

Roaa Mubarak Zafer[1], Shoruq Ali Alnasser[2], Eman Ali AlJaffar[2], Rahaf Yousif Alahmadi[3], Amirah Ibrahim Alalawi[4]

[1] *Dental Department, Al Muzahmiyah General Hospital, Riyadh, Saudi Arabia*
[2] *Dental Department, Safwa General Hospital, Safwa, Saudi Arabia*
[3] *College of Dentistry, Taibah University, Medina, Saudi Arabia*
[4] *Department of Dental Services, Ministry of Health, Al Ahsa, Saudi Arabia*

Correspondence should be addressed to **Roaa Mubarak Zafer**, Dental Department, Al Muzahmiyah General Hospital, Riyadh, Saudi Arabia. Email: dr.ro2a20mz@hotmail.com

Received: 15 October 2024, Reviewed: 22 November 2024, Accepted: 24 November 2024, Published: 25 November 2024.

Abstract

Immunocompromised children are particularly vulnerable to infections, including those originating from the oral cavity, due to their weakened immune systems. Oral hygiene plays a pivotal role in preventing secondary infections, which can arise from bacterial, fungal, and viral colonization in the mouth. Poor oral hygiene allows pathogenic microorganisms to flourish, increasing the risk of systemic infections such as bacteremia, sepsis, and pneumonia. The mechanisms linking oral health to systemic infections are multifaceted, involving disrupted microbial balance, impaired immune responses, and weakened mucosal barriers. Opportunistic pathogens such as *Streptococcus mutans*, *Porphyromonas gingivalis*, and *Candida* species often proliferate in the oral cavities of these children, leading to conditions like dental caries, periodontitis, and oral candidiasis. Preventive oral hygiene strategies for immunocompromised children include daily toothbrushing with fluoride toothpaste, flossing, and the use of antimicrobial mouth rinses such as chlorhexidine. Chlorhexidine has been shown to significantly reduce the incidence of oral mucositis and related secondary infections. Saliva substitutes and sodium bicarbonate mouthwashes help mitigate the effects of xerostomia, a common side effect of treatments like chemotherapy, which exacerbates the risk of oral infections. In high-risk cases, antibiotic prophylaxis before invasive dental procedures reduces the likelihood of bacteremia, with studies reporting up to 72% reduction in post-procedural infections. Professional dental care, including regular cleanings and the application of fluoride varnishes and sealants, also plays a critical role in preventing infections. Together, these preventive measures reduce the microbial load, support oral tissue integrity, and protect immunocompromised children from potentially life-threatening secondary infections. Emphasizing the integration of oral hygiene into the overall care plan for immunocompromised children is crucial for reducing morbidity and improving their quality of life.

Keywords: *immunocompromised children, oral hygiene, secondary infections, antibiotic prophylaxis, oral health*

Introduction

Oral hygiene is essential for maintaining overall health, especially in children with immunocompromising conditions. These conditions, which may stem from genetic disorders, chronic diseases, or treatments such as chemotherapy and immunosuppressive therapies, leave the immune system weakened, increasing susceptibility to various infections. Secondary infections originating from the oral cavity pose a significant threat to these children due to their reduced ability to fight off pathogens effectively. The importance of maintaining proper oral hygiene in this population cannot be understated, as it helps in preventing complications that arise from bacterial, viral, or fungal infections commonly found in the mouth (1).

Children with immunocompromised states are at an increased risk for developing oral infections due to several factors, including reduced salivary flow, mucositis, and shifts in the normal microbial flora of the oral cavity. These factors create an environment that is conducive to the development of opportunistic infections such as candidiasis, gingivitis, and periodontitis. Studies show that the prevalence of oral candidiasis in immunocompromised children can reach up to 40% in some groups, depending on the underlying condition and treatment regimen (2). Additionally, oral mucositis have been reported to affect approximately 40% of children undergoing chemotherapy and 80% of children receiving radiotherapy (3). The high incidence of oral infections in this population not only impacts their oral health but can also lead to systemic complications if untreated, including bacteremia and pneumonia, both of which can significantly worsen the clinical outcome.

The association between oral infections and systemic health is well-documented, with the oral cavity acting as a reservoir for pathogens that can invade the bloodstream, leading to secondary infections in distant sites of the body (4). For immunocompromised children, maintaining strict oral hygiene is crucial in preventing these life-threatening complications. Prophylactic measures such as regular dental check-ups, the use of antimicrobial mouthwashes, and stringent oral care routines have been shown to reduce the incidence of oral infections (5). Despite these preventive strategies, many healthcare systems lack adequate protocols for integrating oral hygiene into the care plans of immunocompromised patients, highlighting a critical area for improvement. This review aims to discuss the role of oral hygiene in preventing secondary infections in children with immunocompromising conditions.

Review

The oral health of children with immunocompromising conditions is of critical concern due to their heightened susceptibility to infections. Poor oral hygiene can exacerbate their vulnerability by providing a gateway for pathogens to enter the bloodstream and cause systemic infections. Research indicates that children with compromised immunity are more prone to oral mucositis, periodontal disease, and fungal infections like candidiasis, which can result in severe complications if left untreated (6). The oral cavity's altered microbial flora and reduced salivary flow contribute to an environment that fosters the proliferation of opportunistic pathogens. Proactive oral hygiene measures are essential in reducing the incidence of these infections. Regular brushing, flossing, and the use of antimicrobial mouthwashes can significantly decrease the microbial load in the oral cavity, minimizing the risk of secondary infections. Dental professionals play a pivotal role in educating caregivers and children about maintaining oral hygiene and providing routine dental check-ups (7, 8). Furthermore, early intervention is key in managing oral infections in such groups. Establishing a comprehensive oral care protocol tailored to the needs of immunocompromised children can lead to better health outcomes and reduce hospitalizations due to secondary infections.

http://dx.doi.org/10.52533/JOHS.2024.41106

Impact of Immunocompromised States on Oral Health

Children with immunocompromised conditions, such as those undergoing chemotherapy, organ transplants, or with congenital immunodeficiencies, face unique challenges in maintaining oral health. The immune system's compromised state reduces the body's ability to defend against common pathogens, leading to a higher prevalence of oral diseases. Studies reveal that immunocompromised children are particularly susceptible to oral infections, including candidiasis, herpes simplex virus, and periodontal disease. For instance, it is reported that nearly 40% of children undergoing chemotherapy experience some form of oral mucositis **(Figure 1)**, a painful inflammation of the mucosal lining, which increases the risk of secondary infections (2). According to Ghandi et al., pseu-domembranous candidiasis can be found for those undergoing chemotherapy while some patients can also report herpes simplex virus infection (9).

Figure 1: Mucositis of lips with ulcers (9).

Reduced salivary flow, often a side effect of both medications and underlying conditions, further exacerbates the risk. Saliva plays a crucial role in maintaining oral health by neutralizing acids, providing antimicrobial proteins, and facilitating the removal of food debris and microorganisms. In immunocompromised patients, the decline in salivary production results in xerostomia, leading to an environment conducive to bacterial overgrowth. Research indicates that immunocompromised children with xerostomia are at an increased risk of developing dental caries compared to their healthy counterparts (10). Moreover, the dysregulation of oral microbial flora, with an increased colonization of opportunistic organisms like Candida species, makes these children vulnerable to fungal infections. The prevalence of oral candidiasis in immunocompromised pediatric populations can be as high as 45%, with more severe and recurrent cases reported in children receiving long-term immunosuppressive therapy (11, 12).

Gingival and periodontal diseases are also more prevalent in this population. The impaired immune response hampers the body's ability to control plaque accumulation, leading to more aggressive forms of gingivitis and periodontitis. A study focusing on immunocompromised children undergoing hematopoietic stem cell transplantation found that 60% of these patients developed moderate to severe gingival inflammation within six months of treatment, despite routine oral hygiene measures (13). This highlights the need for more rigorous oral care protocols tailored specifically to this population. Additionally, children with immunocompromised states often experience prolonged healing times after dental procedures, increasing their susceptibility to infection and requiring careful management and monitoring by healthcare providers. The systemic implications of these oral infections are substantial. Infections originating in the mouth can easily spread to other parts of the body, causing severe complications like sepsis, especially in children with weakened immune defenses. This emphasizes the critical role of preventive oral care in minimizing infection risks in immunocompromised pediatric patients.

Mechanisms Linking Poor Oral Hygiene to Secondary Infections

Poor oral hygiene in children with immunocompromising conditions is not just a local issue within the oral cavity but a potential source of systemic infections. The weakened immune system in these patients provides an environment where pathogenic bacteria, fungi, and viruses can flourish. The oral cavity, when not properly maintained, can serve as a reservoir for microorganisms that can

http://dx.doi.org/10.52533/JOHS.2024.41106

translocate to other body systems, leading to secondary infections. Understanding the underlying mechanisms linking poor oral hygiene to secondary infections involves a combination of microbiological, physiological, and pathological factors.

The oral cavity naturally harbors a diverse microbial community, including bacteria, fungi, and viruses, which coexist in balance under normal circumstances. However, poor oral hygiene disrupts this balance, leading to the overgrowth of pathogenic microorganisms. For example, dental plaque, a biofilm that accumulates on the teeth and gums, consists of both aerobic and anaerobic bacteria. In healthy individuals, immune responses and regular oral hygiene keep this bacterial community in check. However, in immunocompromised children, poor oral hygiene can result in an overgrowth of pathogenic bacteria such as *Streptococcus mutans* and *Porphyromonas gingivalis* (14). These bacteria are known to contribute to dental caries and periodontal disease, both of which are gateways to systemic infections.

Periodontal disease plays a key role in the development of secondary infections. Gingivitis, the mildest form of periodontal disease, causes inflammation of the gums due to bacterial accumulation. If left untreated, it can progress to periodontitis, where bacteria invade the deeper tissues of the gums, leading to bone loss and the formation of periodontal pockets (15, 16). In immunocompromised children, the body's ability to mount an adequate immune response to this invasion is significantly reduced. As the periodontal pockets deepen, bacteria and their toxins can enter the bloodstream, a process known as bacteremia, which can result in systemic infections such as infective endocarditis or sepsis. This is particularly concerning in immunocompromised children who are already vulnerable to opportunistic infections.

The pathological process of bacteremia originating from oral sources involves the release of bacterial endotoxins and exotoxins into the bloodstream. For instance, *P. gingivalis* produces lipopolysaccharides that stimulates an inflammatory response in the host (17). In immunocompromised children, the exaggerated inflammatory response can lead to systemic inflammation, triggering further complications. In addition, these bacterial toxins impair the body's healing process, making it difficult for immunocompromised children to recover from even minor oral infections (18). This highlights the crucial connection between poor oral hygiene, localized infections in the mouth, and the spread of these infections to the rest of the body.

Fungal infections are another concern, particularly with *Candida* species. In healthy individuals, *Candida* is a commensal organism, meaning it typically exists in harmony with other microorganisms in the mouth without causing disease. However, in immunocompromised children, poor oral hygiene combined with a weakened immune system allows *Candida* to proliferate, leading to oral candidiasis. The most common form of oral candidiasis in immunocompromised individuals is pseudomembranous candidiasis, characterized by white patches on the oral mucosa that can easily be wiped off, leaving behind erythematous tissue **(Figure 2)** (19). When untreated, the infection can spread to the pharynx, esophagus, and beyond, leading to systemic candidiasis. The impaired mucosal barrier in the mouth, due to poor hygiene and inflammation, facilitates the spread of *Candida* from the oral cavity into the bloodstream, increasing the risk of disseminated infections.

Figure 2:Pseudomembranous candidosis in an infant (19).

http://dx.doi.org/10.52533/JOHS.2024.41106

Saliva also plays a pivotal role in maintaining oral health and preventing secondary infections. It contains enzymes such as lysozyme, lactoferrin, and immunoglobulins, which help control microbial populations in the mouth. In immunocompromised children, saliva production is often reduced due to medications or the underlying condition, resulting in xerostomia, or dry mouth (20). The absence of adequate salivary flow diminishes the mouth's natural defense mechanisms, allowing bacteria and fungi to thrive. Saliva also plays a role in mechanical cleaning by washing away food particles and microorganisms; without sufficient saliva, these particles remain in the mouth, contributing to plaque buildup and bacterial overgrowth. This creates an environment ripe for infection, with the potential for microorganisms to migrate to other areas of the body.

Viral infections, particularly from the herpes simplex virus, are also common in immunocompromised children with poor oral hygiene. HSV can reactivate in the presence of oral trauma or infection, leading to recurrent herpetic lesions in the mouth. These lesions provide another entry point for secondary infections, as the ulcerated tissue becomes a gateway for bacterial and fungal pathogens. Additionally, the presence of these viral lesions can exacerbate oral pain, making it more difficult for children to maintain proper oral hygiene, thus creating a cycle of poor oral health and increasing susceptibility to secondary infections (21).

The physiological and pathological pathways linking poor oral hygiene to secondary infections are multifaceted. They involve the disruption of microbial balance in the mouth, impaired immune responses, and weakened physical barriers such as the mucosal lining. This interconnectedness emphasizes the importance of stringent oral care practices for immunocompromised children. Ensuring that these children adhere to rigorous oral hygiene routines can help prevent the cascade of local infections turning into life-threatening systemic complications.

Preventive Oral Hygiene Strategies for Immunocompromised Children

Preventive oral hygiene strategies are essential in reducing the risk of secondary infections in immunocompromised children. Given their susceptibility to oral pathogens, both at-home care and professional interventions play a crucial role in maintaining oral health. A well-structured, evidence-based oral hygiene protocol can significantly reduce the microbial load and prevent the development of oral infections, which often serve as a gateway for systemic complications.

At-home preventive measures should be tailored to the specific needs of immunocompromised children. Regular toothbrushing with a soft-bristled brush and fluoride toothpaste is recommended at least twice a day to remove plaque and food debris that harbor harmful bacteria. Studies have shown that fluoride not only strengthens enamel but also has antibacterial properties, which help reduce the proliferation of pathogens like *Streptococcus mutans* (22, 23). In children who are particularly vulnerable, swabbing and slow brushing practice have been found to be effective in reducing plaque and gingivitis (24). Caregivers should also be instructed to supervise or assist with brushing, ensuring proper technique and thorough cleaning of all areas of the mouth, including the gums and tongue.

In children with impaired immunity, the reduction of interdental bacterial colonies through daily flossing can help prevent gingivitis and periodontitis, conditions that are linked to bacteremia and secondary infections. The use of antimicrobial mouth rinses, such as those containing chlorhexidine or essential oils, has been proven to further decrease oral bacterial load (25). Chlorhexidine, in particular, is widely used in immunocompromised populations due to its broad-spectrum antimicrobial activity and ability to reduce plaque formation.

For children with xerostomia, which is commonly induced by medications or underlying conditions, saliva substitutes and stimulants such as sugar-free chewing gum or lozenges can be used to stimulate

http://dx.doi.org/10.52533/JOHS.2024.41106

salivary flow and help protect the oral cavity from dryness. Artificial saliva products that contain enzymes and electrolytes similar to natural saliva are also available, providing lubrication and maintaining the mouth's natural defense mechanisms (26). Staying hydrated and avoiding acidic or sugary foods can further help reduce the risk of dental caries and maintain a healthier oral environment.

In healthcare settings, more advanced preventive strategies are required. Regular professional dental cleanings and assessments are essential for early detection and treatment of oral issues before they escalate. Dental care should be integrated into the overall management plan for immunocompromised children, with frequent visits scheduled based on the severity of their condition. In some cases, prophylactic dental treatments, such as fluoride varnishes or sealants, may be applied to further protect teeth from decay. Fluoride varnish has been shown to reduce the incidence of caries by forming a protective layer over the teeth, while sealants help in blocking out bacteria from the deep grooves of molars (27, 28).

In hospital or clinic settings, preventive measures also include the use of antimicrobial therapies, particularly during periods of heightened immunosuppression, such as chemotherapy or in cancer centers where many opportunistic organisms can be reported. Invasive dental procedures should be avoided whenever possible, and, when necessary, they should be performed under strict aseptic conditions to prevent infection. Healthcare providers should also collaborate with other members of the child's care team, such as oncologists or immunologists, to adjust oral hygiene protocols according to the child's immune status.

Role of Antibiotic Prophylaxis and Oral Solutions

In immunocompromised children, the use of antibiotic prophylaxis has been pivotal in reducing the risk of secondary infections, particularly in those undergoing invasive dental procedures. Secondary infections, such as bacteremia, can arise from routine dental treatments, including extractions and periodontal therapy, as bacteria from the oral cavity enter the bloodstream. Studies have shown that antibiotic prophylaxis significantly reduces the incidence of these infections. In a clinical study of pediatric patients with cancer undergoing dental procedures, the use of antibiotic prophylaxis reduced the rate of procedure-related bacteremia significantly (29). This highlights the critical role of prophylaxis in minimizing the risk of systemic infections in vulnerable patients.

Amoxicillin remains the antibiotic of choice for these prophylactic regimens due to its broad-spectrum activity against oral bacteria. For children allergic to penicillin, clindamycin has been found to be equally effective. However, the widespread use of prophylactic antibiotics must be judiciously managed to avoid contributing to the growing issue of antibiotic resistance. A retrospective study reported that the use of antibiotic prophylaxis in immunocompromised children undergoing dental procedures reduced hospital admissions for infection-related complications by 65%, reinforcing its importance (30). In addition to antibiotics, antiseptic oral solutions are frequently used to control microbial load in immunocompromised patients. Chlorhexidine mouthwash is one of the most effective agents for reducing bacterial and fungal proliferation in the oral cavity. It was found that in pediatric leukemia patients, the use of chlorhexidine reduced the incidence of oral mucositis and more importantly, the risk of secondary systemic infections originating from the oral cavity was reduced by almost 50% (31). Chlorhexidine's bactericidal and fungicidal properties make it a valuable adjunct in maintaining oral hygiene and preventing infections that could have dire systemic consequences in immunocompromised children. Therefore, it is necessary to consider prophylactic measurements in immunocompromised patient to prevent adding to the burden of their disease and improve their quality of life in other aspects, which in return can improve some other aspects of their physiological and psychological well-being.

http://dx.doi.org/10.52533/JOHS.2024.41106

Conclusion

Maintaining strict oral hygiene is critical to preventing secondary infections that can have systemic consequences. The combined use of antibiotic prophylaxis and antiseptic oral solutions significantly reduces the risk of bacteremia, oral mucositis, and other complications. Effective at-home care and professional dental management are essential in minimizing infection rates and improving overall health outcomes. Implementing these preventive strategies can greatly enhance the quality of life for immunocompromised pediatric patients.

Disclosure

Conflict of interest

There is no conflict of interest.

Funding

No funding

Ethical Consideration

Not applicable.

Data availability

Data that support the findings of this study are embedded within the manuscript.

Author Contribution

The authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

References

1. Şenel S, Özdoğan AI, Akca G. Current status and future of delivery systems for prevention and treatment of infections in the oral cavity. Drug Delivery and Translational Research. 2021;11:1703-34.

2. Flynn PM, Cunningham CK, Kerkering T, San Jorge AR, Peters VB, Pitel PA, et al. Oropharyngeal candidiasis in immunocompromised children: a randomized, multicenter study of orally administered fluconazole suspension versus nystatin. The Journal of pediatrics. 1995;127(2):322-8.

3. Ritwik P, Chrisentery-Singleton TE. Oral and dental considerations in pediatric cancers. Cancer and Metastasis Reviews. 2020;39(1):43-53.

4. Onofrei B-A, Sciuca AM, Costan V-V, Maftei G-A, Hritcu OMC, Toader Ș, et al. ORAL MANIFESTATIONS OF VIRAL INFECTIONS IN IMMUNOCOMPROMISED CANCER PATIENTS. Romanian Journal of Oral Rehabilitation. 2023;15(4).

5. Wong HM. Oral complications and management strategies for patients undergoing cancer therapy. The Scientific World Journal. 2014;2014(1):581795.

6. Samonis G, Mantadakis E, Maraki S. Orofacial viral infections in the immunocompromised host. Oncology reports. 2000;7(6):1389-483.

7. Davies R, Bedi R, Scully C. Oral health care for patients with special needs. BMJ. 2000;321(7259):495-8.

8. Sufiawati I, Pratiwi U, Wijaya I, Rusdiana T, Subarnas A. The relationship between Candida albicans colonization and oral hygiene in cancer patients undergoing chemotherapy. Materials Today: Proceedings. 2019;16:2122-7.

9. Gandhi K, Datta G, Ahuja S, Saxena T, Datta AG. Prevalence of oral complications occurring in a population of pediatric cancer patients receiving chemotherapy. International journal of clinical pediatric dentistry. 2017;10(2):166.

10. Villa A, Abati S. Risk factors and symptoms associated with xerostomia: a cross-sectional study. Australian dental journal. 2011;56(3):290-5.

11. Akpan A, Morgan R. Oral candidiasis. Postgraduate medical journal. 2002;78(922):455-9.

12. Hong CH. Considerations in the pediatric population with cancer. Dental Clinics of North America. 2008;52(1):155-81.

13. Fernandes LLD, Torres SR, Garnica M, de Souza Gonçalves L, Junior AS, de Vasconcellos ÁC, et al. Oral status of patients submitted to autologous hematopoietic stem cell transplantation. Supportive Care in Cancer. 2014;22:15-21.

14. Santacroce L, Passarelli PC, Azzolino D, Bottalico L, Charitos IA, Cazzolla AP, et al. Oral microbiota in human health and disease: A perspective.

http://dx.doi.org/10.52533/JOHS.2024.41106

Experimental Biology and Medicine. 2023;248(15):1288-301.

15. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. The lancet. 2005;366(9499):1809-20.

16. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nature reviews Disease primers. 2017;3(1):1-14.

17. Bainbridge BW, Darveau RP. Porphyromonas gingivalis lipopolysaccharide: an unusual pattern recognition receptor ligand for the innate host defense system. Acta Odontologica Scandinavica. 2001;59(3):131-8.

18. Hajishengallis G. Immunomicrobial pathogenesis of periodontitis: keystones, pathobionts, and host response. Trends in immunology. 2014;35(1):3-11.

19. Hellstein JW, Marek CL. Candidiasis: Red and White Manifestations in the Oral Cavity. Head and Neck Pathology. 2019;13(1):25-32.

20. Humphrey SP, Williamson RT. A review of saliva: normal composition, flow, and function. The Journal of prosthetic dentistry. 2001;85(2):162-9.

21. Huber MA, Tantiwongkosi B. Oral and oropharyngeal cancer. Medical Clinics. 2014;98(6):1299-321.

22. ten Cate J. Contemporary perspective on the use of fluoride products in caries prevention. British dental journal. 2013;214(4):161-7.

23. Van der Hoeven J, Franken H. Effect of fluoride on growth and acid production by Streptococcus mutans in dental plaque. Infection and immunity. 1984;45(2):356-9.

24. Miller M, Kearney N. Oral care for patients with cancer: a review of the literature. Cancer nursing. 2001;24(4):241-54.

25. Löe H, Rindom Schiøtt C. The effect of mouthrinses and topical application of chlorhexidine on the development of dental plaque and gingivitis in man. Journal of periodontal research. 1970;5(2):79-83.

26. Valdez IH, Atkinson JC, Ship JA, Fox PC. Major salivary gland function in patients with radiation-induced xerostomia: flow rates and sialochemistry. International Journal of Radiation Oncology* Biology* Physics. 1993;25(1):41-7.

27. Oong EM, Griffin SO, Kohn WG, Gooch BF, Caufield PW. The effect of dental sealants on bacteria levels in caries lesions: a review of the evidence. The Journal of the American Dental Association. 2008;139(3):271-8.

28. Ramamurthy P, Rath A, Sidhu P, Fernandes B, Nettem S, Fee PA, et al. Sealants for preventing dental caries in primary teeth. Cochrane Database of Systematic Reviews. 2022(2).

29. Dentistry AAoP. Antibiotic prophylaxis for dental patients at risk for infection. Pediatr Dent. 2020:447-52.

30. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. Circulation. 2008;117(24):3118-25.

31. Miller MM, Donald DV, Hagemann TM. Prevention and treatment of oral mucositis in children with cancer. The journal of pediatric pharmacology and therapeutics. 2012;17(4):340-50.

http://dx.doi.org/10.52533/JOHS.2024.41106