AL-KUFA JOURNAL FOR BIOLOGY
ISSN (Print): 2073-8854 **ISSN (online):** 2311-6544

Original Research Paper

Investigating the Prevalence and Virulence Factors of Oral Candidiasis in Neonates

Sheylan Salah Abdullah[1]

[1]*Department of Medical laboratory Technology, Erbil Technical Health and Medical College, Erbil Polytechnic University, Erbil, Iraq.*

Article history
Received: 11/01/2025
Revised: 07/03/2025
Accepted: 24/03/2025

*Corresponding Author:
Sheylan Salah Abdullah, Department of Medical laboratory Technology, Erbil Technical Health and Medical College, Erbil Polytechnic University, Erbil, Iraq;
Email:
sheylan.salah@epu.edu.iq

Abstract: A thrush is an oral yeast infection caused by the fungal pathogen Candida albicans. Oral thrush predominantly occurs in newborns and is typically not a dangerous problem on its own. Fifty percent of the population harbours candida in their oral cavities. Under typical conditions, Candida albicans is regulated by microorganisms.

Objective: The objective is to ascertain the epidemiological agents of newborn oral candidiasis and to isolate and identify Candida spp. from the oral cavities of infants at Raparin Teaching Hospital in Erbil Province using standard laboratory procedures. Additionally, to identify the virulence factors of Candida spp., including protease and hemolysis, which play a significant role of the pathophysiology of disorders of the mouth.

Patients and methods*:* The study comprised 65 newborns exhibiting oral lesions who were enrolled in the Medical Care and Consulting Clinic of Raparin Teaching Hospitals, as well as the Neonatal Care Unit of Erbil Maternity Teaching Hospital. Samples gathered between February 2024 and April 2024. The control group consisted of 30 ostensibly children in good health who provided mouth swabs for collection. Biochemical assay, culture, and direct inspection were used to identify the isolated yeasts. API – 20 C system and the Vitek II, subsequently assessing protease activity and hemolysis in Candida species obtained from oral lesions.

Results: The results of the present study indicated that over 62.07% of participants were male, and more than half of the instances occurred within the first three months of age. Approximately 59% of cases involve mothers with a low level of education, specifically at the primary level. It has been demonstrated that 46.55% of infants are delivered via cesarean section. About 58.62% of the mothers had a history of birth canal infections. 43.10% of neonatal patients were artificially fed. The fungal isolates in the current study exhibited a range of virulence factors. Hemolysin and protease production were observed in C. albicans at rates of 12 (100%) and 9 (75%), respectively, while C. glabrata exhibited hemolysin production at 1 (50%) and protease production at 1 (50%). Additionally, C. parapsilosis isolates generated both protease and hemolysin. C. krusei produced just hemolysin 1 (100%).

Conclusions: The oral lesions revealed the presence of *Candida albicans* and other yeasts. and additional causes, demonstrating the infection was spread to and from the afflicted children. Proteinase and hemolysin, two crucial virulence factors, are produced by the isolates in *Candida albicans* much more frequently than in other yeasts.

Keywords: Oral infants, Candida species, Virulence factors.

1.Introduction

Oral and pharyngeal candidiasis is commonly referred to as thrush.Thrush is an infection of the oral cavity caused by *Candida albicans.* [1, 2] It was initially delineated by the French doctor Francois Valleix in 1838. [3] The condition is confined to infant, neonates, and individuals undergoing antibiotic or steroid treatment. [4,5]. Candida colonization in infants is a risk factor for the development of candidiasis infection [6, 7]. Neonates affected are generally colonized by *Candida albicans* during their transit through the birth canal. Other transmission sources to newborns encompass colonized breasts (breastfed infants), hands, and/or inadequately sanitized bottle nipples. [4,8, 9].

Candida albicans commonly and asymptomatically resides in the gastrointestinal tract of numerous children and adults. [3]. Thrush manifests as pale, Sores that feel smooth in the oral cavity and onto the tongue. Below the pale substance, there exists red tissue that is may be to hemorrhage. The lesions may gradually increase in both number and size [4]. There are at least 15 species of Candida yeasts capable of infecting humans. *Candida albicans is the most common* species. *The species C. albicans, C. parapsilosis, C. tropicalis, and C. glabrata* collectively constitute 95% of identified Candida infections. It is commonly referred to as oral thrush when it infects the oral cavity. [10] If untreated, the symptoms will likely endure, resulting in ongoing discomfort in your mouth. In untreated extreme cases, there is a chance of the infection disseminating farther throughout the body, which can be grave [11]. The predominant form of candidiasis affecting this age group is acute pseudomembranous candidiasis [12]. Candidiasis in the oral cavity, pharynx, or esophagus is rare in healthy adult individuals. Individuals at elevated risk for oral and pharyngeal candidiasis include infants, particularly those under one month of age, while healthy adults are infrequently affected [13]. Oral candidiasis's onset occurs due to a disparity between host defenses and fungal virulence factors [14]. The virulence factors of fungi are essential to the development of infection from colonization. The initial phase is epithelial adherence, which entails Interactions between proteins and glycoproteins, The last stage involves fungal proliferation and tissue infestation, predicated on the filamentation abilities of *C. albicans*, together with the release of proteases and phospholipases [15]. Therefore, this study was conducted to determine which types of Candida cause children' mouth infections, and to identify the origins of infection and related risk factors, and assess the ability of *Candida* species isolates to generate protease and hemolysin as virulence determinants.

2.Methodology

Study area

This study was conducted on infants aged 1 month to over 6 months (under 2 years) of both sexes, who attended Raparin Teaching Hospital for Children and Maternity Teaching Hospital in Erbil city, Erbil governorate center. From February, 2024 to March, 2024; after the acquisition of ethical approval from the patients enlisted in the study, the research was approved by the scientific and ethics committee of the College. The demographic information was acquired by a structured questionnaire administered via direct interviews with the mother of the infant.

Sampling Technique

The patients underwent clinical examination, and two sterile swabs were utilized to get samples from the infant's oral cavity to verify the diagnosis. We exclude all the negative cases based on culture. The sample comprised 65 infected newborns and 30 control apparently healthy infant, who were gender and age-matched with the infected cohort. Oral swabs were treated similarly to those of the patients.

Laboratory examinations of samples

The oral cavity swabs were promptly transported to the Microbiology Department laboratory and evaluated using two methods:

Direct Microscopic Examination: A drop was extracted from the swab stick for examination, placed on a clean glass slide, and subsequently analyzed using light microscopy to confirm the presence of budding yeast cells and pseudomycelium. [16].

Indirect examination

Another swab was treated to fungal culture by using Sabouraud dextrose agar augmented with chloramphenicol (Merck, Germany) subsequently incubate at 37 °C for 24 to 48 hours [17]. After that, Individual colonies were isolated and purified from every sample that had previously cultured on SDA for diagnostic testing [18].

Candida Isolate Identification

Morphological Characteristics: The exterior morphology of colonies cultivated on SDA was assessed, noting the colony's color, shape, texture, diameter, height, and odor [19].

Microscopic Characteristics

A sample of the colony was obtained using the inoculation loop and combined with a drop of Lactophenol Blue stain. After that the sample was placed

on a sterile glass slide and subsequently covered with a cover slip. Subsequently, it was examined by using a light microscope to observe yeast cell pseudohyphae and blastoconidia [19]. The API – 20 C system was employed for the Yeast species identification, while the Vitek II system (Durham, USA) served as the automated identification method, utilizing a plate containing 40 distinct tests for carbohydrates and amino acids, incubated at 35°C for a duration 24 - 48 hours.

Estimate the ability of candida species to produce certain virulence factors:

Haemolysin Activity test: The haemolysin activity was assessed using a blood plate assay [20].
Protease Production test: The protease synthesis was assessed in accordance with Aoki [21] using a test medium that included SDA plates containing bovine serum albumin (BSA).

Data analysis
Statistical analysis was conducted using SPSS program. (Statistical Package for Scientists version 20.0, SPSS, Inc., Chicago, IL, USA). The Chi-squared ($\chi 2$) test was employed to determine significant differences in characteristics among patients. Differences with $p < 0.05$ were considered statistically significant.

3. Results and discussion

A total of sixty-five swabs were collected. According to Table (1), those who had positive yeast isolates were (58) from oral thrush.

Table 1: Distribution of Infant Oral Candidiasis based on the gender

	Male		Female		P value
	No.	%	No.	%	
*Positive	36	94.74	22	81.48	
Negative	2	5.26	5	18.52	0.217
Total	*38	58.46	*27	41.54	

58 infants with a clinically confirmed oral yeast infection were included in this study.The male formed 62.07% and the female formed 37.93%, with their ages ranging from1 month to almost 6 months (mean 2.28 ± SE 0.30) months.

Table (2) indicates that the majority of cases occurred in the first three months of life (53.45%), followed by those in the age group more than six months (24.14%). It has been disclosed that about 62.07% of case related to the male gender.

Age in months	Gender		Total
	Male	Female	
< 1-3	18	13	*31 (53.45%)
4-6	11	2	13 (22.41%)
More than 6	7	7	*14 (24.14%)
Total	*36 (62.07%)	22 (37.93%)	58 (100%)

Chi- square is 7.6613. Significant at P< .05

Table 2: Distribution of newborn oral candidiasis cases by gender and age group

The highest infection rate was observed in infants aged (< 1-3) months, followed by those older than six months. The control group comprised 30 healthy infants, with a gender distribution of 46.67% male and female 53.33%, an age of (mean 2.68 ± SE 0.45) months, matched to the patients as shown in Table 3. Table (4) indicates that over 89.66% of cases involved a history of drug intake.

Age in months	Gender					
	Patients			Control		
	Total	Male	Female	Total	Male	Female
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
< 1-3	31 (53.45)	18 (50)	13 (59.09)	15 (50)	8 (57.14)	7 (43.75)
4-6	13 (22.41)	11 (30.56)	2 (9.10)	10 (33.33)	4 (28.57)	4 (25)
More than 6	14 (24.14)	7 (19.44)	7 (31.81)	5 (16.67)	2 (14.29)	5 (31.25)
Total	58 (100)	36 (62.07)	22 (37.93)	30 (100)	14 (46.67)	16(53.33)

Table 3: The infected infant's and the control group's ages and genders

Drug intake	Gender		Total
	Male	Female	
Yes	31	21	*52 (89.66)
No	5	1	6 (10.34)
Total	36	22	58 (100%)

Chi- square is 2.6448. Significant at P< .05

Table (4) Distribution of incidences of infant oral candidiasis based on medication history and gender

Table (5) indicates that over 58.62% of cases with a history of maternal birth canal candidiasis infection and more than 80.65% of infants delivered vaginally were affected. as illustrated in Table (6) as regard to the distribution of cases according to type of delivery of infant, it has been demonstrated that (46.55%) of instances involved deliveries via caesarian section. Figure (1).

Birth canal infection	Gender		Total
	Male	Female	
Yes	19 (52.77%)	15 (68.18)	*34 (58.62%)
No	17	7	24 (41.38%)
Total	36	22	58 (100%)

Chi- square is 3.7817. Significant at P< .05

Table (5) Distribution cases of infant oral candidiasis based on the history of presence of birth canal infections and gender

Birth canal infection	Type o f delivery		Total
	Vaginal	Caesarian	
Yes	*25 (80.65%)	9 (33.33%)	34 (58.62%)
No	6 (19.35%)	18 (66.67)	24 (41.38%)
Total	*31 (53.45%)	27 (46.55%)	58 (100%)

Chi- square is 25. 7676. Significant at P< .05

Table (6)
Distribution of instances of newborn oral candidiasis baed on the history of birth canal infection and delivery method.

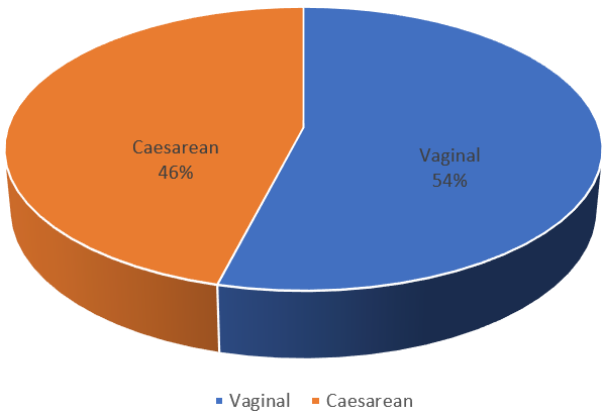

Fig 1. Distribution of incidences of infant oral candidiasis based on delivery method

The distribution of cases by feeding type indicates that (43%) of cases involved artificial feeding, whereas (29%) involved mixed feeding. Figure 2 and Table 7 indicate that the majority of instances were among individuals with artificial feeding (43.10%). And Figure (3) indicates that 59% of mothers were illiterate, whereas 39% possessed a primary education.

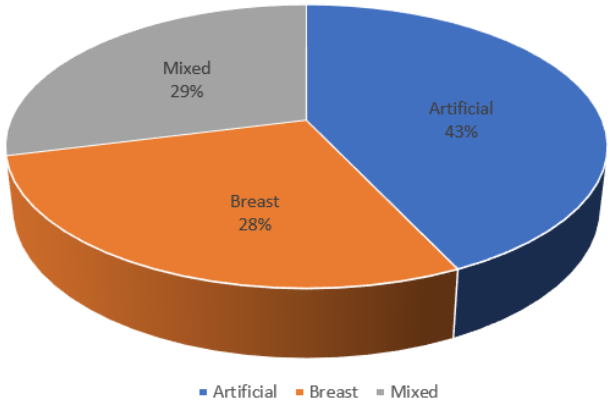

Fig 2. Distribution of instances of infant oral candidiasis according on the kind of infant feeding

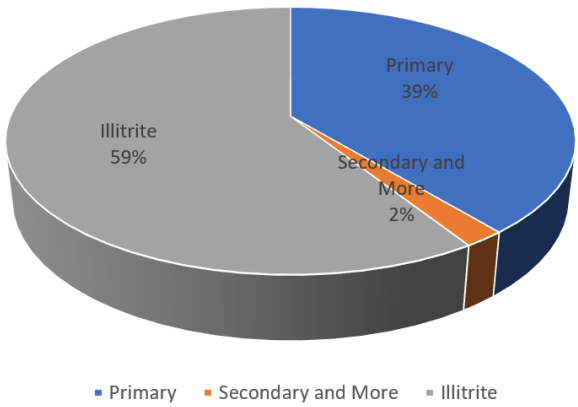

Fig 3. Educational level of infant mothers

Infant feeding	Infected Infant	
	No.	%
Breast	16	27.59
Artificial	25	*43.10
Mixed	17	29.31
Total	58	100

Table 7:
The relationship between feeding methods and mouth inf ections

The isolated type of yeasts between individuals from the control group and oral lesions are displayed within the table (8). *C. albicans* is the predominant isolate found in both the control and patient population (86.46%; 68.75%respectively). The isolates of non-*Candida albicans* (NCAS) from both of them (patients and control groups) were as follows: *Candida. tropicalis* (5.21%; 18.78%), *C. parapsilosis* (5.21%; 6.25%), and *Candida glabrata* (2.08%; 6.25%) respectively. While *Candida krusei* was isolated from one sample that also included *C. parapsilosis.*

Table (8) Candida species isolated from patients and control group

Candida spp.	**Number of species**	
	Patients	**Control**
Candida albicans	83 (86.46%)	11 (68.75%)
Candida tropicalis	5 (5.21%)	3 (18.78%)
Candida parapsilosis	5 (5.21%)	1 (6.25%)
Candida glabrata	2 (2.08%)	1 (6.25%)
Candida krusei	1 (1.04%)	0(0.00)
Total	96 (100%)	16 (100%)

This study, investigation identified extracellular protease production in 9 (75%) of the tested *C. albicans*, 3 (60%) of *Candida parapsilosis*, and 2 (40%) of *Candida tropicalis*, however *C. krusei* exhibited no protease production, as illustrated in Table (9) and Figure (4). Our results demonstrated that 12 (100%) of *C. albicans*, 4 (80%) of *C. tropicalis*, 3 (60%) of *C. parapsilosis*, and 1 (50%) of *C. glabrata* isolates were able to production of hemolysin, as illustrated in Table (9) and Figure (5).

Table (9) Virulence factor production percentage of Candida species isolated from oral lesions

Candida spp.	**Isolates no.**	**Virulence factors**			
		Protease		Hemolysis	
		No.	%	No.	%
Candida albicans	12	9	75	12	100
Candida tropicalis	5	2	40	4	80
Candida parapsilosis	5	3	60	3	60
Candida glabrata	2	1	50	1	50
Candida krusei	1	0	0	1	100

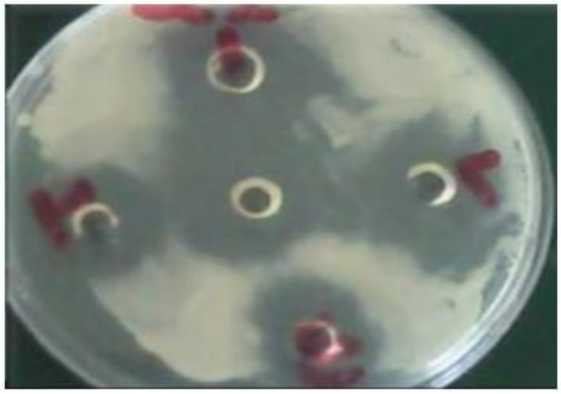

Fig. 4: Hemolytic activity of four Candida albicans strains

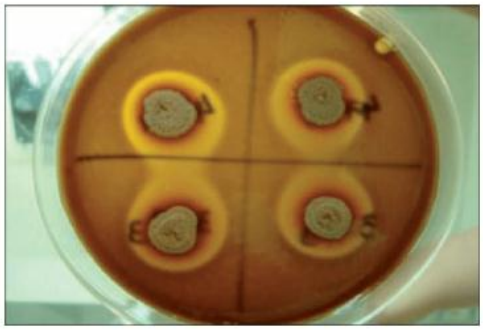

Fig. 5: Protease activity for C.alicans

Fungal infections continue to pose a significant global health issue, impacting individuals of all ages, especially children. Consequently, numerous research has been undertaken regarding several epidemiological, economic management and this infection's therapeutic aspects [22]. *Candida sp.* is common and usually found on the skin and mucous membranes, 5-7% of infants under one month old are thought to get oral thrush. Thrush is a mycotic infection caused by any of the form of *Candida spp*., usually referred to as a candidiasis. Oral thrush is a superficial infection of mucous membrane that is often accompanied by white adhering patches of pseudomycelium. It can cause either acute or chronic oral lesions, sores, fissures, and ulcers [23]. Generally, the oral microbiota and body physiological defenses help to Control these microorganisms. However, when the body's immune defenses are compromised (due to factors like HIV, malignancy, radiation and chemotherapy, immunosuppression, or the use of broad-spectrum antibiotics), colonization of this organism occurs [24]. It has been recorded that the majority of patients were male (62.07%), with analogous findings reported in other studies [25,26], while other studies

indicated no gender disparity in affection [27]. Research conducted by Seebacher et al. indicated that female patients experienced a lower incidence of fungal infections compared to male patients [28]. Conversely, numerous investigations have demonstrated a greater prevalence of superficial and cutaneous fungal infections in men than in women [29]. The lesions' clinical manifestation in the patients under study displayed strong or moderate white spots. The highest infection rate seen during the research occurred in infants within the first months of life, accounting for (53.45%). This is confirmed by prior studies indicating that oral candidiasis is more commonly observed in babies [30] which attributing this influence to their undeveloped immune systems [27]. According to Nneka and Ebele (2005) demonstrated that younger newborns had a higher prevalence of oral candidiasis than older infants, with a significant difference observed between the two groups [23]. The study indicated that over (89.66%) of newborns had a positive history of antibiotic use. Antibiotics administered to infants are a risk factor for the development of the disease. Antibiotics influence bacterial development, resulting in the proliferation of yeasts. [31, 32, 33]. About a history of yeast-related birth canal infections in mothers. A higher percentage of mothers (58.62%) had a positive history. The results of the present investigation indicated (53.45%) infant deliveries were conducted via normal vaginal delivery, and among this group, (80.65%) of the women had a history of birth canal infection. These findings agree with studies that demonstrated the association between birth canal infections and the incidence of baby oral thrush. [31, 32, 33]. A higher percentage (43.10%) was observed in artificially fed infants compared to those that were mixed or breastfed (29.31% and 27.59%, respectively), corroborating recent studies indicating Infants who are bottle-fed have a higher prevalence of oral thrush than those who are breastfed. [34, 35]. Other study indicated oral candidiasis did not develop more readily when breastfed or bottle fed. [36]. Identical Candida species were isolated from the oral lesion. and the aforementioned objects suggests the infection was spread among the children. Various research has examined the origins of diseases. The risk factor that makes nursing women more susceptible to nipple candidiasis have been investigated by numerous researchers, However, there is evidence linking breast candidiasis in moms to mouth thrush in newborns [37, 38]. newborns can transmit the diseases to their mothers throughout the breastfeeding process, and the disease may subsequently circulate between the maternal breast and the infant's mouth [39]. Furthermore, a pacifier utilization can serve as a vector for inoculation as well as reinfection if, after being diagnosed with moniliasis, it is not sufficiently cleaned [40]. Candida albicans was predominant isolated from the study's Candida species and was present in both the control and the Patient groups at rates of (86.46%) and (68.75%), respectively. Additional NCAC species isolated included *C. tropicalis* (5.21%; 18.78%), *C. parapsilosis* (5.21%; 6.25%), and *C. glabrata* (2.08%; 6.25%) from both infected infants and the control, whereas a single isolate of *Candida krusei* (1.04%) was obtained only from the patient group. Human opportunistic fungal infections are most frequently caused by *Candida* species, with *Candida albicans* being the most common pathogen causing systemic and mucosal infections. [41]. According to Castilho and Rocha (2009) [42], in 60% to 80% of instances, Candida albicans is the most often isolated species from the oral cavity in both healthy and ill individuals. Additional, species such as C. parapsilosis, C. krusei, C. glabrata, and C. tropicalis have been identified as the cause of oral infections. [43, 44]. The clinical importance of NCAC has grown increasingly significant, particularly in high-risk patients [44]. As it is widely recognized fungi can induce disease and surpass host defensive mechanisms due to the presence of many genes and proteins linked to pathogenicity, referred to as virulence factors [45]. Extracellularly released Microbial pathogen enzymes have garnered significant interest because of their probable pathogenesis roles and as prospective future targets for antibacterial treatment treatments [46]. In (2002) Kantarcioglu and Yucel, indicated the predominant enzymes that catalyze hydrolyzsis produced by *Candida sp.* are phospholipase and proteinase, that are crucial in pathogenesis [47]. Within the current investigation, and from the mouth lesions, the isolates which created proteinase enzymes with varying scores were *C. albicans*, *C. tropicalis*, *C. parapsilosis*, and *C. glabrata*, but *C. krusei* didn't create this enzyme. The findings of the current study align with De Bernardis [48], who documented elevated in vitro protease activity in all Strains of *C. parapsilosis* isolated from patients.

Additionally, Kanatrcioglu and Yucel [47] shown in vitro protease synthesis in most clinical isolates of *C. albicans*, *C. parapsilosis*, and *C. tropicalis*, whereas *C. glabrata*, *C. guillermondii*, and *C. krusei* exhibited no protease activity. Yamamoto (1992) [49] found that most isolates of *C. tropicalis* and *C. parapsilosis* exhibited proteolytic activity, however none of the examined *C. glabrata* strains produced the enzyme. In our analysis, all *C. albicans* isolates exhibited hemolytic activity, with the majority demonstrating mild hemolytic activity. Numerous prior studies have demonstrated similar outcomes. These results align with Ramesh *et al.* [50], who evaluated the hemolytic efficacy of 50 strains of *Candida* obtained from HIV patients and 10 strains of Candida from immunocompetent individuals. Each strains exhibited

hemolysis; however, the Activity of hemolysis was significantly elevated in *C. albicans* strains obtained from patients of HIV in contrast to those sourced from immunocompetent individual. Rossoni et al. [51] observed that C. albicans (100%) produced hemolysins, while C. glabrata and C. krusei each exhibited hemolysin production in all cases, and 40% of C. parapsilosis isolates produced hemolysins. Luo et al. (2001) [52] noted that Candida species can produce one or more forms of hemolysins in vitro, with variations in production across different species. These discrepancies may be attributed to environmental conditions, the source of the isolate, and the detection method employed in identifying the enzyme.

Conclusion

The study concludes that *C. albicans* is the predominant species in oral Candida infections, and most Candida species isolates had the capacity to produce substantial amounts of protease and hemolysin. Infant thrush is prevalent throughout the first three months of life and occurs more frequently in children with specific risk factors, such as maternal breast and birth canal infections. Ultimately, we determined that children who utilized drug intake had (soothers) a higher incidence of infections compared to those who do not use them. Consequently, it is advisable to do additional confirmatory tests to ascertain the genotypic origin by Multilocus Sequence Typing (MLST) or other contemporary techniques.

Acknowledgements

The author expresses gratitude to all support personnel and participating patients in this study.

Funding Information

Self-funded for the author

Author's Contributions

Author listed has made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Ethics

The protocol of the study was approved by the ethical committee in Erbil Technical Health and Medical College - Erbil Polytechnic University. Verbal and written consent was obtained from all participants included in the study.

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