Original Article

Estimation of Calprotectin Saliva Levels in Patients with Bacterial Tonsillitis

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Abstract

Background: Tonsillitis is a common respiratory tract disease that affects both adults and children, most cases of tonsillitis occur due to infection by viruses, bacteria, allergies, and respiratory problem. The appearance of the tonsillar exudates on the surface of tonsil's can distinguish the early stage of bacterial type from viral infection. A cytosolic antibacterial protein called calprotectin, which is mostly generated from neutrophils, is now frequently employed in this capacity. The content of calprotectin in different body fluids varies according to how much inflammation there is. **Materials and Methods:** A 120 clinical specimens from patients hospitalized in Kirkuk hospitals and 18 control were taken including throat swabs and saliva collection. Culture and biochemical tests used for bacterial isolation and identification then confirmed by Vitek 2 system. The calprotectin is diagnosed by Elisa. **Results:** The current study showed that the incidence of tonsil infections is caused by gram-positive bacteria. *Staphylococcus aureus* was the most abundant species with (24) isolates with a percentage of (58.5%), and *Staphylococcus hemolyticus* had six isolates (14.6%) and *Streptococcus parasanguinis* with a number of (4) isolates (9.7%), the less abundant isolate were *Streptococcus pyogenes* (1) isolate (2.4%) also *Staphylococcus epidermidis* with (1) isolate (2.4%). The younger age group (4–10 years) was the most frequent in infection. Antibiotic sensitivity test was carried out for all bacterial isolates, *Staphylococcus* spp. showed high resistance to cefotoxin (≥85%), benzylpenicillin (100%), ampicillin-sulbactam (≥85%), oxacillin (≥85%), ceftriaxone (≥85%), and erythromycin (≥62%), while *Staphylococcus* spp. showed highly sensitive to linezolid (100%), teicoplanin (100%), vancomycin (100%), and rifampicin (100%). *S. pyogenes* and *Streptococcus sanguinis* showed high sensitivity to all antibiotics (100%). Calprotectin was high (38.02 ± 5.04) in acute infection of tonsils. **Conclusion:** Gram-positive bacteria were only the bacterial isolates from tonsillitis patients, calprotectin level were high in acute tonsillitis.

Keywords: Calprotectin, saliva, *Staphylococcus*, *Streptococcus*, tonsillitis

Introduction

Tonsillitis is a common respiratory tract disease that affects both adults and children, and most cases of tonsillitis occur due to infection by viruses, bacteria, allergies, and respiratory problems.[1] It is the interaction of lymphatic tissue in the tonsils with the factors causing inflammation such as bacteria and as a result of this interaction symptoms are characterized by enlargement of the tonsils, high temperature, congestion and weakness in the performance.[2] Tonsillitis is generally the result of an infection, which may be viral or bacterial. Viral etiologies are the most common, the appearance of the tonsillar exudates on the surface of tonsil's can distinguish the early stage of bacterial type from viral,[3] bacterial infections are typically due to group A beta-hemolytic Streptococcus (GABHS),[4] *Staphylococcus aureus*,[5] *Streptococcus pneumoniae*,[6] and *Haemophilus influenza*,[7] CoNS,[8] *Streptococcus* spp.[9] Bacterial tonsillitis can result from both aerobic and anaerobic pathogens.[10] Tonsillitis occurs when the trapped organisms penetrate the mucosal barrier and attach themselves to the epithelial cells, leading to cytokine production and complement

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activation. These events induce an inflammatory reaction in the tonsillar mucosa.[11] A cytosolic antibacterial protein called calprotectin (CP), which is mostly generated from neutrophils, is now frequently employed in this capacity. The content of calprotectin in different body fluids varies according to how much inflammation there is.[12] A calcium-binding hetero-complex protein consisting of two heavy and one light chain, and composed of two monomers in mammals (e.g., humans and mice): S100A8 and S100A9. It is derived predominantly from neutrophils and has direct antimicrobial effects and a role within the innate immune response. CP is also constitutively expressed by monocytes, dendritic cells, activated macrophages, oral keratinocytes and squamous mucosal epithelium. Moreover, expression can be induced specifically during inflammation.[13,14] Bacteria are killed when this protein competes with them for zinc. It provides other contributions to anti-microbial activity as well. Additionally, this protein has a wide range of potential clinical uses, as seen by the higher serum levels under various immunological and immunopathological circumstances. Bacterial infections cause a sharp rise in serum calprotectin levels.[15] Calprotectin is a biomarker of neutrophilic inflammation, and may be a useful marker of bacterial throat infections. Some throat infections are caused by streptococcal infections in particular group A streptococci [GAS], Streptococcal pharyngitis can, in some cases, be complicated by acute rheumatic fever, acute glomerulonephritis, and invasive disease leading to septicemia. However, these complications are rare, and many thousands of patients with tonsillitis would have to be treated with antibiotics to prevent these complications.[16]

Materials and Methods

Study population

A 120 clinical samples include 120 throat swap and 60 saliva samples were collected from tonsillitis patients in Kirkuk General Hospital and Al Children hospital in Kirkuk city and 18 control of both gender and different age groups (4–55 years) at period from November 27, 2022 to February 30, 2023.

Sample collection

Patients were classified into three groups (acute, chronic, and recurrent) according to the type of tonsillitis (by information taken from the patients and by diagnosis of specialist). Sterile cotton swab was used for throat swab and sterile container for saliva collection, and then the swabs were cultured on blood and MacConkey agar by striking method and incubated in 37°C for 24–48 h, whereas the saliva was centrifuged for 10 min and supernatant were separated and kept in Eppendorf tube in freezer until it diagnosed by Elisa (SUNLONG kit) for detecting of Calprotectin levels.

Microbiological analysis was done, and the organisms were identified by direct gram staining, culture methods on blood agar, Macconkey agar, chocolate agar medium, mannitol salt agar at 37ºC for 24–48 h. Different biochemical tests such as catalase test, coagulase, and bacitracin sensitivity test were performed for the identification of the various bacterial pathogens after their isolation, and the conformation and antibiotic sensitivity test is done by using VITEK 2 COMPACT system.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 48205 (including the number and the date in November 1, 2022) to get this approval.

Results

Isolation and identification of bacteria

The process of identifying these isolates involved the use of culture, microscopic examination, biochemical assays, and confirmation by VITEK2 COMPACT system. Gram stain experiments revealed a gram-positive bacteria that appear on blood agar with beta hemolysis surrounded the colonies.

About 41 (37%) of the samples showed positive bacterial growth, whereas 69 (62%) showed no growth [Figure 1], which might be attributed to antibiotic treatment or presence of other types of causative agents, such as viruses which may need specialized diagnostic tests.

The catalase test was preformed to differentiate *Staphylococcus* spp. which were catalase positive from *Streptococcus* spp. which were catalase negative, the positive result indicate that they can produce catalase enzyme and are able to convert H_2O_2 to water and oxygen.

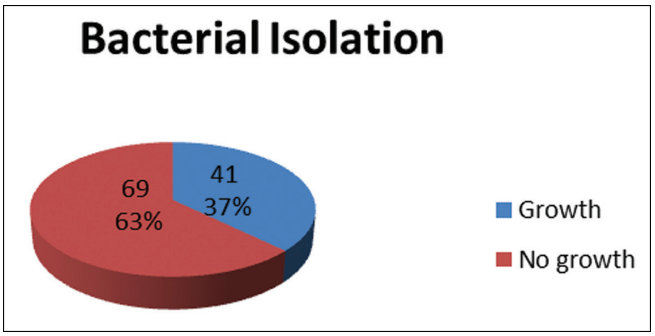

Figure 1: Bacterial growth proportion in clinical samples

About 33 isolates were identified as suspected *Staphylococcus* spp. depending on coagulase slide method test in which they grouped into coagulase negative (9 isolates) and coagulase positive *S. aureus* (24 isolates).

All isolates were subjected to the VITEK-2 system in Al-Balsam hospital for confirmation of the identification of the bacterial isolates.

Results of present study showed there is significant differences ($P < 0.05$) between Patients with bacterial isolates, *Staphylococcus* spp. *Streptococcus* spp. with age groups <10 years scored highest percentage in patients with bacterial isolates (43.90%) [*Staphylococcus* spp. (34.14%) and *Streptococcus* spp. (9%)], compared to 31–40 years that scored lowest percentage (2.4%) in above groups (2% for *Staph*. spp. and 0% for *Strep*. spp.).

In contrast, results of the study showed no significant difference ($P > 0.05$) between patients with bacterial isolates, *Staphylococcus* spp. *Streptococcus* spp. and genders [Table 1].

The results showed there are significant differences ($P < 0.001$) among percentages of bacterial isolates in patients with tonsillitis, *S. aureus* scored highest percentage (59%), followed by *Staphylococcus hemolyticus* (15%), and *Streptococcus parasanguinis* (10%) compared to *Staphylococcus epidermidis*, *S. pyogenes*, and *Streptococcus salivarius* that scored lowest percentage (2.4%) [Table 2].

Antibiotic susceptibility testing (AST)

All isolates were tested for antibiotic susceptibility by VITEK-2 system in Al-Balsam hospital in Erbil city.

Antibiotic susceptibility for *Staphylococcus* spp.

The *S. aureus* showed (100%) resistance to benzylpenicillin, (84%) to oxacillin, ampicillin-sulbactam, cefoxitin and ceftriaxone. Also scored resistance to erythromycin (62%). Clindamycin and tetracycline (30%). The bacteria showed high sensitiveness (100%) to rifampicin, linezolid, vancomycin, teicoplanin and tigecycline, also showed sensitivity to gentamycin (92%), ciprofloxacin (85%), levofloxacin, moxifloxacin (85%) for both and fusidic acid (96%) [Figure 2].

The *Staph. epidermidis* and *Staph. hominis* scored (100%) resistance to benzylpenicillin, oxacillin, ampicillin-sulbactam, cefoxitin, ceftriaxone, clindamycin, erythromycin, tetracycline, and fusidic acid whereas they showed high sensitivity (100%) to gentamycin, ciprofloxacin, rifampicin, trimethoprim, levofloxacin, moxifloxacin, linezolid, vancomycin, teicoplanin, and tigecycline.

The *S. hemolyticus* showed (100%) resistance to benzylpenicillin, oxacillin, ampicillin-sulbactam, cefoxitin and ceftriaxone, erythromycin, tetracycline and tigecycline. Fusidic acid (60%), gentamycin, and

Table 1: Distribution of bacterial isolates according to age and gender of tonsillitis patients

		Patients with bacterial isolates ($n = 41$)		*Staphylococcus* spp. ($n = 33$)		*Streptococcus* spp. (n = 8)	
		n	%	*n*	%	*n*	%
Age groups	<10	18	43.90%	14	34.14%	4	9%
	20–11	8	19.51%	7	17.07%	1	2%
	21–30	7	17.07%	5	12.19%	2	4%
	31–40	1	2.44%	1	2%	0	0%
	>40	7	17.07%	6	14.63%	1	2%
P value		<0.001***		<0.001***		<0.05*	
Gender	Males	23	56.09%	18	43.90%	5	12.19%
	Females	18	43.90%	15	36.58%	3	7%
P value		>0.05		>0.05		>0.05	

Table 2: Frequency and percentage of bacterial species isolated from patients with tonsillitis

Isolated bacteria	No. of isolate	Percentage	*P* value
Staphylococcus aureus	24	58.5%	$P < 0.001$***
Staphylococcus hemolyticus	6	14.6%	
Staphylococcus hominis	2	4.8%	
Staphylococcus epidermidis	1	2.4%	
Streptococcus parasanguinis	4	9.7%	
Streptococcus sanguinis	2	4.8%	
Streptococcus pyogenes	1	2.4%	
Streptococcus salivarius	1	2.4%	
Total	41	100%	

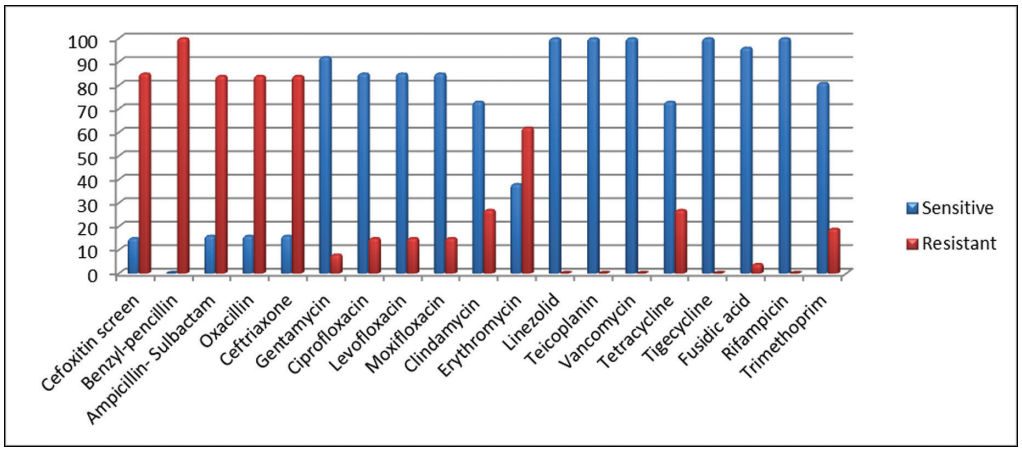

Figure 2: Frequency of antibiotic susceptibility of *S. aureus* between clinical samples

ciprofloxacin (40%). Also showed highest sensitivity (100%) to rifampicin, linezolid, vancomycin, clindamycin, moxifloxacin, teicoplanin, and (85%) to levofloxacin.

Antibiotic susceptibility for *Streptococcus* spp.

Results of present study showed the *S. pyogenes* and *S. parasanguinis* is scored highest sensitivity (100%) to antibiotic. *S. salivarius* is scored resistance (100%) to erythromycin and tetracycline and demonstrated that other antibiotics were more sensitive (100%) to it.

S. sanguinis scored highest resistance (100%) to erythromycin, clindamycin, and tetracycline, also showed (50%) resistance to benzylpenicillin, ampicillin, cefotaxime, and ceftriaxone, whereas it showed highest sensitiveness (100%) to others antibiotics (levofloxacin, moxifloxacin, chloramphenicol, tigecycline, vancomycin, and linezolid).

Calprotectin level in tonsillitis

Calprotectin scored at *Staphylococcus* spp. (20.07 ± 10.02) and in *Streptococcus* spp. (11.28 ± 9.47) which showed significant differences ($P = 0.033$) [Figure 3].

The result of presented study showed significant increase in saliva calprotectin levels at acute infection (38.02 ± 5.04 pg/mL) and recurrent (29.29 ± 3.6 pg/mL) than in chronic infection (18.94 ± 2.47 pg/mL) compared to control group (18.49 ± 2.73 pg/mL) in the view of mean of ($P = 0.054$) as showed in Figure 4.

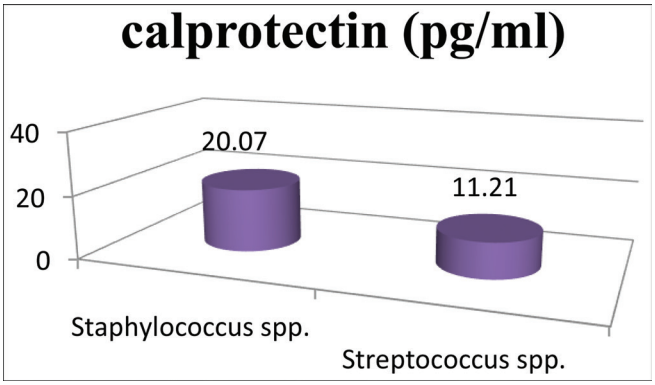

Figure 3: Saliva levels of calprotectin in *Staphylococcus* spp. compared with *Streptococcus* spp. infection

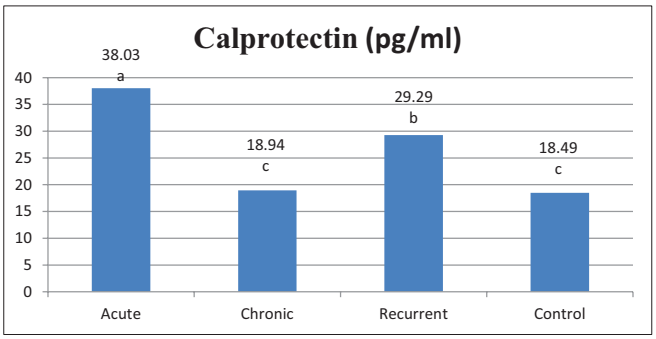

Figure 4: Mean saliva levels of calprotectin in tonsillitis patients and control groups. *The similar letters mean that there are no significant differences groups and the different letter mean that there are significant differences between them, at a potential level $P < 0.05$

Discussion

Acute, recurrent, and chronic tonsillitis was clinically diagnosed and identified throughout the patient's medical history, clinical symptoms, and laboratory tests for diagnosis the isolates of *Staphylococcus* spp. and *Streptococcus* spp. The isolates of *S. aureus* were found to be 24 isolates (59%) while *S. pyogenes* was 1 isolate only (2.4%). This result agreed with Kostic *et al.*[17] who showed high prevalence of *S. aureus* (44%) and *S. pyogenes* in patients (4%) with tonsillitis, and these results matched with present results that showed *S. aureus* (58.5%) and *S. pyogenes* (2.4%). The presence of *S. aureus* in tonsil infections and its persistence in tonsillar tissue even after the inflammatory process may be related to its ability to form biofilm. The

presence of the biofilm can explain therapeutic failures and, therefore, recurrence of the infection, and represent an important element of chronicity, even in the absence of acute inflammatory process.[18]

Radi *et al*.[19] showed patients with tonsillitis have bacterial species, (47.61%) *S. aureus* and *S. parasanguinis* (8.33%), and these results were nearly matching to present results, where it found the *S. aureus* and *S. parasanguinis* scored (58.5%) and (9.7%) in those patients.

Present results showed 2.4% of *S. pyogenes* in patients with tonsillitis, and these results did not match with results Radi *et al.*[19] that showed 30.8% of *S. pyogenes* in patients with tonsillitis. Another study by Ughasoro *et al.*[20] showed the *S. pyogenes* and *S. aureus* scored (15.32%) and (16.2%) in patients with tonsillitis, and these results different to present results that showed the *S. aureus* and *S. pyogenes* scored (58.5%) and (2.4%) in those patients.

The type of sample (sputum, saliva, etc.) used has a major impact on the recovery of *S. pyogenes*. *S. pharyngitis* has been identified as the patient's condition.[21] Authors in Jordan suggested that sputum was more effective at detecting *S. pyogenes* than throat swabs were. *S. pyogenes* diseases vary by location, as seen by the high incidence of this organism among patients with respiratory tract infections.[19]

Results of current study showed the *Staphylococcus* spp. and *Streptococcus* spp. scored highest percentage in tonsillitis patients less than 10 years due to weak immune system in children as well as to close contact among kids in school that increase probability exposure to infection.

Abraham *et al.*,[22] showed the prevalence of tonsillitis was found to be higher in men than women with no significant difference ($P > 0.05$), and these results matched with an earlier conducted study that showed high prevalence of tonsillitis in men than women. A recent study showed chronic tonsillitis was found to be higher among the male gender residing in the urban area.[23] Men frequently stay outdoors and are exposed to infecting microorganisms and have more direct contact with diseased people, as well as the possibility of having allergies attributed to exposure to urban pollution. All these factors could likely be the reason for the male preponderance with chronic tonsillitis.

In contrast to present study, Alasil *et al.*[24] showed high prevalence of tonsillitis in women than men. These differences could be attributed by differences in immune status, environmental factors, and study population.

Finally, present findings showed no impacts of gender on bacterial infection in patients with tonsillitis.

Antibiotic susceptibility testing (AST)

The study found that *S. aureus* had a 24.6% resistance rate to ciprofloxacin, and these results are concerning because they are almost identical to a recent study that found that *S. aureus* had a 15.4% resistance rate to ciprofloxacin.[18] This drug has been reported to be effective against several pathogenic agents of tonsillitis, including *S. aureus*, and increased resistance leaves few therapeutic options to treat this condition.[25]

Previous results showed the Levofloxacin is active against *S. aureus* (sensitivity 75%) in patients with tonsillitis, and these results matched with present study that showed the Levofloxacin scored sensitivity 85% against *S. aureus*.[26]

Study results showed the all *Staphylococcus* species are sensitive Trimethoprim, and these results compatible to results Cavalcanti *et al*.[18]

Katkowska *et al*.[26] showed the Gentamycin is best antibiotic toward *Staphylococcus* spp., where this antibiotic scored sensitivity of 77% against this bacterial species. Their results matched with our results.

The study showed the *S. pyogenes* was susceptible to ceftriaxone 95.7%; azithromycin 93.6%; doxycline 91.5%; clindamycin 87.2%; ampicillin 80.9%; and erythromycin 74.5%. Above results were matched with our results that showed high sensitivity of *S. pyogenes* towards these antibiotics.[27] Another study showed the antimicrobial susceptibility testing revealed that the highest sensitivity rate of the group A Streptococci was to azithromycin (80.3%) followed by penicillin G (77.5%) and ceftriaxone (74.7%).[28]

Authors showed the most isolated of *S. pyogenes* that isolate from patients with tonsillitis were highly sensitive to antibiotics such as clindamycin, rifampin, and azithromycin, whereas those are moderately sensitive to penicillin-G cefotaxime, ceftriaxone, and trimethoprim, and resistant to ampicillin and cloxacillin.[29]

A recent study showed imipenem and levofloxacin had the highest sensitivity (95% and 77%) across all the *Streptococcus* isolates. Ceftriaxone, azithromycin, and amoxicillin/clavulanic acid had sensitivity of 68.1%, 57.4%, and 42.6% respectively. The least sensitive antibiotics was ampicillin 17%.[20] Above results were nearly to our study results.

Fahad,[30] showed the *Streptococcus* isolates were highly sensitive to chloramphenicol (95.9%) in tonsillitis patients, and their outcome agreed with present study (100%).

Tadesse *et al.*,[31] showed the penicillin, vancomycin, chloramphenicol, clindamycin, and ceftriaxone were effective against 100%, 95.7%, 95.7%, 91%, and 87% of *S. pyogenes*, respectively. These results matched with our study that showed penicillin, vancomycin, chloramphenicol, clindamycin, and ceftriaxone were effective against *S. pyogenes*.

Spiekermann *et al*.[32] in their study showed increase levels of S100A8/A9 in serum and saliva of patients with

recurrent acute tonsillitis (RAT) compared to healthy controls.

Schofield *et al*.[33] showed increased levels of calprotectin in tonsillitis patients that infected with Streptococcus species than controls, and these results matched with present results. Calprotectin is released upon activation and turnover of neutrophils and is recognized as an important marker for neutrophil mediated inflammation. Bacterial and viral infections cause an acute phase response which will counterattack the infection and reduce the damage.[34] Calprotectin can be measured from throat swab samples and levels are consistent with the hypothesis that streptococcal infection leads to higher throat calprotectin levels.[33]

Jonsson *et al*.[35] showed plasma calprotectin appears to be a useful early marker of bacterial infections in critically ill patients, with better predictive characteristics than WBCs and procalcitonin (PCT).

Havelka *et al.*[36] showed the calprotectin was significantly increased in patients with bacterial infections; bacterial pneumonia, mycoplasma pneumonia and streptococcal tonsillitis compared with viral infections. Additionally, authors showed the rapid determination of calprotectin may improve the management of respiratory tract infections and allow more precise diagnosis and selective use of antibiotics.

Recent study of Lamot *et al*.,[37] showed the serum calprotectin could have substantial added value in the management of a child with fever and positive urinalysis and is a promising biomarker in distinction between bacterial urinary tract infection and viral respiratory causes of febrile illness in children under the age of 3 years.

Conclusion

Gram-positive bacteria were only the bacterial isolates from tonsillitis patients. All *Staphylococcus* spp. isolates showed high resistant to benzyl-penicillin, ampicillin-sulbactam, oxacillin, ceftriaxone, and erythromycin. All *Staphylococcus* bacterial isolates except *S. aureus* were resistant to tetracycline and fusidic acid, and *S. aureus* was the most prevalent bacteria among tonsillitis patients. Also calprotectin level was high in acute tonsillitis.

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Conflicts of interest

There are no conflicts of interest.

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