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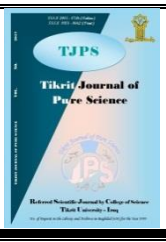

Relationship between interleukin 1beta and virulence factors produced by some bacteria isolated from patients with sinus infections

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ABSTRACT

Background: Sinusitis is an inflammatory process of the mucosa lining the paranasal cavity. Currently, the term rhinosinusitis has been more accepted because rhinitis and sinusitis are continuous diseases. The study aimed to demonstrate the relationship between interleukin beta 1 and virulence factors of the bacteria that cause sinusitis**. Method s**::This study was conducted in Salah al-Din Governorate in the city of Balad in Balad General Hospital and Balad Healthcare Sector in the period from 1/11/2022 to 1/6/2023. From 1-50 years of both gender by taking nasal swabs with a carrier medium and blood samples, where 90 samples were collected from patients.**Results**: the present study showed that Interleukin -beta 1.scored high sensitivity (91% and 83%) and specificity (84% and 60%) with significant differences ($p<0.05$) in screening patients with sinusitis, The positivity of *Escherichia coli* 13.3% ,*Staphylococcus haemolyticus* 11.7%, *Klebsiella pneumonia*, 13.3%,*Yersinia enterocolitica* 8.3%,*Providencia stuartii* 8.3%, *Staphylococeas epidermidi* 18.3%, *Pesedomonas oryzihabitans* 15.0%, *Leuconostoc psedomesenteroides* 16.7%,and *Burkhoderia cepacia* 16.7% respectively .

العلاقة بين الانترلوكين 1 بيتا وعوامل الظراوة التي تنتجها بعض البكتيريا المعزولة من مرضى التهابات الجيوب الأنفية

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الملخص

الخلفية: التهاب الجيوب الأنفية هو عملية التهابية في الغشاء المخاطي المبطن للتجويف المجاور للأنف. حاليًا، أصبح مصطلح التهاب الجيوب الأنفية أكثر قبولًا لأن التهاب الأنف والتهاب الجيوب الأنفية من الأمراض المستمرة. هدفت الدراسة إلى توضيح العلاقة بين الإنترلوكين بيتا 1 وعوامل ضراوة البكتيريا المسببة لالتهاب الجيوب الأنفية. الطرق::أجريت هذه الدراسة في محافظة صلاح الدين في مدينة بلد في مستشفى بلد العام وقطاع الرعاية الصحية في بلد في الفترة من 2022/11/1 إلى 2023/6/1. من 1−50 سنة لكلا الجنسين وذلك بأخذ مسحات أنفية بالوسط

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الحامل وعينات الدم حيث تم جمع 90 عينة من المرضى.النتائج: أظهرت الدراسة الحالية أن إنترلوكين بيتا 1 سجل حساسية عالية (91% و 83%). والنوعية (84% و 60%) مع وجود فروق ذات دلالة إحصائية (P<0.05) في فحص مرضى التهاب الجيوب الأنفية، إيجابية.

Yersinia ,*Staphylococcus haemolyticus* 11.7%,*Klebsiella pneumonia13.3./. Escherichia coli 13*.3./. *18*.3%, *Pesedomonas oryzihabitans enterocolitica* 8.3%,*Providencia stuartii* 8.3%, *Staphylococeas epidermidi* على التوالي. 15.0%, *Leuconostoc psedomesenteroides* 16.7%,and *Burkhoderia cepacia* 16.7%

Introduction

Sinusitis is an inflammatory process of the mucosa lining the paranasal cavity. Currently, the term rhinosinusitis has been more accepted because rhinitis and sinusitis are continuous diseases [1] .In a healthy individual, mucus should be secreted in appropriate quantity and quality from the sinuses, and this mucus should be transported to the nasal cavity at an appropriate speed and completely by ciliary activity. Sinusitis occurs as a result of disruption of mucociliary transport for any reason[2] .Nasal and paranasal sinus disease are highly prevalent diseases and significantly impair the quality of life of patients there are two types of acute sinusitis: viral and bacterial, which are associated with significant acute and chronic morbidity and possible serious complications. When considering the possible diagnosis of acute sinusitis, it is essential to differentiate a simple upper respiratory tract infection or allergic rhinitis from a bacterial sinus infection. Some patients with underlying predisposing disorders have chronic sinus disease that does not appear infectious. Among the bacterial pathogens that cause acute bacterial sinusitis in children and adolescents are Streptococcus pneumoniae 30%; *Haemophilus influenzae* not typeable 20% and Moraxella catarrhalis 20% [3].*Staphylococcus aureus a*nd anaerobic bacteria have a prominent role in the pathogenesis of chronic sinusitis and severe infections. Although anaerobes, other streptococci, and *Staphylococcus aureus* are seldom implicated as causative agents of acute bacterial sinusitis in pediatric patients. Children who suffer from chronic sinus disease often have *H. influenzae*, a- and *b-hemolytic streptococci, M. catarrhalis, S. pneumoniae*, and coagulase-negative *staphylococci* identified as pathogens in their condition [4].

Acute bacterial rhinosinusitis (ABRS) is a rare complication of viral infections of the upper respiratory tract that can cause mucosal damage and bacterial superinfection. Damage or interruption of mucociliary function is probably one of the main causes of bacterial infection. Bacterial and fungal infections are usually accompanied by viral infections, as seen in the common cold.The symptoms of rhinitis and sinusitis are similar and are usually present in a patient with sinusitis. For this reason, the "Task Force of the Rhinology and Paranasal Sinus Committee" decided to use the term "rhinosinusitis (RS)" instead of "sinusitis" in 1997 [5]. The three main symptoms in RS are nasal congestion, nasal or postnasal inflammatory discharge, and facial pain. Other symptoms and signs include facial pressure, decreased sense of smell, and fever. RS basically consists of three stages according to the duration of at least two of these symptoms. These; acute stage, subacute stage and chronic stage[6] the pathogenesis of sinusitis is multifactorial and involves a complex interaction between host defence mechanisms and pathogen virulence. To understand the pathological events that result in clinical sinusitis, it is necessary to review the physiology of the paranasal sinuses. The pseudostratified columnar ciliated epithelium that lines the nasal and paranasal sinuses plays a crucial role in maintaining sinus health.

The Objectives of study:

The objectives of the present study involved

1. Isolation and identification of bacterial pathogen2.
2. Detection of biofilm production and some virulence factors

3.Evaluation of immunological indicators in sera of patients and healthy subjects

Material and Methods

1. Sterilization :

Every single prepared culture medium and other solution used in this investigation was sterilized in an autoclave for 15 minutes at 121°C and 15 pounds/inches of pressure. Glassware was sterilized in an electric oven at 180 ° C for two hours while the solutions impacted by high temperature were sterilized using Millipore filters with a diameter of 0.22 Micrometer [7].

2. Preparation of culture media:All these media were prepared according to Manufacture Company, sterilized by autoclaving at 121 0C for 15 minutes, and then dispensed into sterile Petri dishes or tubes as required and stored at 4 0C until use [8].

3. Egg -yolk -agar:Prepare the medium by adding 15 ml of fresh egg white to 85 ml of the sterilized and cooled nutritious agar medium to a temperature of 45-50, then pour the medium into dishes and leave to cool Transport media.

4. The carrier media ;was used, which is swabs placed in a tube that works to preserve bacteria and transfer them only to the laboratory without helping them to grow.

Detection some virulence factors

Detection of hemolysin production

This test was conducted for the purpose of knowing the ability of bacteria to produce the hemolytic enzyme using blood agar. The isolates were inoculated by streaking on plate of blood agar and incubated at 37 °C for 48 hours, after incubation, the

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hemolytic activity was observed and the kind of haemolysin (alpha , beta , gam[9].

Detection protease enzymes

Skim milk agar On this medium, many species can flourish. The generation of the proteases that break down casein into soluble peptides is detected using this media. There is a clear zone as a result. The cell can then take up soluble peptides. The milk's white tint is a result of casein. The white agar becomes transparent and colorless after being broken down by exoenzymes. On this agar, bacterial colours are clearly visible. [10].

Detection Lecithinase production

The egg yolk medium that was previously prepared was used, and then the pure colonies were planted on the medium by the planning method, and the dishes were incubated at a temperature of 37 °C for a period of 24-48 hours. Clear areas around the growing colonies are evidence of the ability of the bacteria to produce the enzyme lecithinase.

Detection of lipase production

The egg yolk medium that was previously prepared was used, and then the pure colonies were planted on the medium by the planning method, and the dishes were incubated at a temperature of 37 °C for a period of 24-48 hours. Presence of halos surrounding colonies is positive for their ability to digest the lipids and thus indicates presence of lipase

Biofilm formation assay

Microtitre culture plate method (MTP) (quantitative assay):

Quantitative determination of biofilm formation was determined by a colorimetric microtiter plate assay[11]. A. All isolates were grown at 37°C in brain heart infusion broth for 24h. Thereafter, 100 µl of bacterial growth were transferred into a tube of 2 ml of normal saline, and then the turbidity was adjusted to McFarland 0.5.B. A volume of 180 µl of brain heart infusion broth contained 1% glucose were added to sterile flat-bottomed 96-well polystyrene microtiter plates (C. A) volume of 20 µl of bacterial suspension (from normal saline) was added to three wells of sterile flat-bottomed 96-well polystyrene microtiter plates. A total of six wells with bacteria-free brain heart infusion broth were considered as a negative control.D. The plates were covered with their lids and incubated under aerobic conditions at 37°C for 24h without shaking. After incubation, all plates were gently washed thrice with PBS and dried.E: For the fixation of the biofilms, 150 µl of methanol was added to each well for 15 min at room temperature, washed and air-dried.f. The plates were stained with 250 µl of 1% crystal violet solution for 15 min at room temperature. Further, wells were washed and dried at 37°C for approximately 15 min to ensure they were completely dryG. The dye was resolubilized with 200 µl of 95% ethanol for 30 min.H. The optical density (OD) of each well was determined at 630 nm using a microtiter plate reader. The cut-off OD (ODc) was set at three standard deviations above the mean OD of the negative control. All isolates were categorized into four categories based on their ODc values: weak biofilm makers, medium biofilm producers, and strong biofilm producers Biofilm and none [12].

Determination of human interleukin 1 beta by ELISA

This kit is designed for the purpose of conducting an enzyme-linked immunosorbent test (ELISA).
Interleukin levels were determined according to the company BTLAB and its origin is China [13].

Statistical analysis

The normalcy of the levels of all indicators was first assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. All parameters were fitted for both tests, and no significant difference was seen. Therefore, the results are shown as Mean ± SD, and the significance of the difference between means was evaluated using the Student's t-test. The other characteristics were provided as frequencies expressed as percentages, and statistical significance of differences between frequencies was evaluated using the Pearson-Chi-square test. The Receiver Operating Characteristic (ROC) curve was used to ascertain the sensitivity and specificity of various criteria in the screening of individuals with rheumatoid arthritis. The statistical software SPSS version 25.0 and GraphPad Prism v.6 were used to conduct the analyses.

Results and Discussion

Results of present study showed the IL-1 b A scored high sensitivity (91% and 83%) and specificity (84% and 60%) with significant different ($p<0.05$) in screening patients with sinusitis,

Table 1: sensitivity and specificity of interleukin 1b

Variables	AUC	SEM	P value	cut off	Sensitivity %	Specificity %
IL-1 b	0.918	0.030	P<0.001***	>341	91	84

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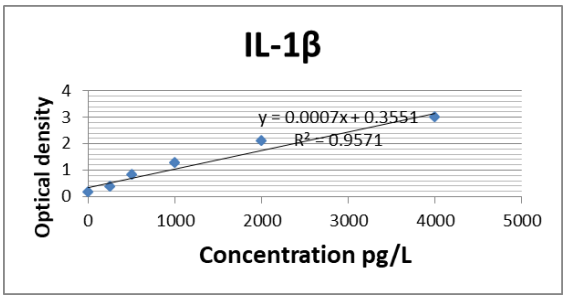

Fig. 1: Standard curve of IL-1B

Results of present study showed there is significant different ($p<0.05$) between positivity of isolated in patients with sinusitis. The positivity of *E.coli, Staphylococcus haemolyticus, Klebsiella pneumonia, Yersinia enterocolitica, Providencia stuartii, Staphylococeas epidermidis, Pesedomonas oryzihabitans, Leuconostoc psedomesenteroides,* and *Burkhoderia cepacia* were as following1-13.3% 2-11.7% 3-13.3%4- 8.3%,.5-8.3%6-18.3.%7-15.0%, 8-16.7% ، 9-16.7% espectively (table 2).

Table 2 frequency and percentage of microbial isolates in patients with sinusitis

		Count	Percent	p value
E.*coli*	Negative	52	86.7%	p<0.001***
	Positive	8	13.3%	
Staphylococcus haemolyticus	Negative	53	88.3%	p<0.001***
	Positive	7	11.7%	
Klebsiella pneumonia	Negative	52	86.7%	p<0.001***
	Positive	8	13.3%	
Yersinia enterocolitica	Negative	55	91.7%	p<0.001***
	Positive	5	8.3%	
Providencia stuartii	Negative	55	91.7%	p<0.001***
	Positive	5	8.3%	
Staphylococeas epidermidis	Negative	49	81.7%	p<0.001***
	Positive	11	18.3%	
Pesedomonas oryzihabitans	Negative	51	85.0%	p<0.001***
	Positive	9	15.0%	
Leuconostoc psedomesenteroides	Negative	50	83.3%	p<0.001***
	Positive	10	16.7%	
Burkhoderia cepacia	Negative	50	83.3%	p<0.001***
	Positive	10	16.7%	

It is believed that bacterial infection plays a significant factor in the pathophysiology of CRS. As a result, CRS is frequently treated with empirical antibiotic treatment in outpatient settings. Inappropriate antibiotic medication can exacerbate the development of antibiotic resistance and result in side effects from antibiotic usage as a result of treatment failure [14]. Therefore, in order to enable culture-guided antibiotic therapy and perhaps enhance treatment results, it is desirable to collect a culture reflective of the patient's sinus microbiological profile. To acquire a sinus culture, maxillary sinus puncture is frequently utilized. Nevertheless, both technological issues and patient pain place limitations on this operation. It is crucial to identify a substitute culture technique that faithfully captures the sinus bacterial composition. Ethmoid cultures are more challenging to obtain and almost always need intraoperative collection. Nonetheless, the middle meatus is simple to reach in an outpatient context, and as it serves as the anterior ethmoid, frontal, and maxillary sinuses' sinus outflow region, it ought to represent the microbial makeup of those sinuses. Several investigations have demonstrated that endoscopically obtained middle meatus cultures properly represent the bacteriology of the maxillary sinus [15]. Subsequent research reveals a strong association between ethmoid sinus bacteriology and middle meatus in CRS9 patients. Our data indicates that there is no discernible change in the microbiological profile between endoscopic samples obtained from the middle meatus and the ethmoid sinus, which is consistent with prior investigations.

According to a recent research, MRSA (32.6%) was the most often isolated bacteria, followed by coagulase-negative staphylococci (19.6%) and s*taph. aureus* (10.7%). In contrast, the majority of studies state that coagulase-negative *staphylococci* and Staph. aureus are the most frequently identified bacteria in sinus cultures11,12. This could point to a recent rise in antibiotic-resistant organisms, such MRSA, at our facility as a result of improper antibiotic use [16]

A prior research revealed an increase in the frequency of patients with methicillin-sensitive S. aureus (MSSA) I sinusitis. Most oral and parenteral antibiotics were not effective against any of the isolates from our investigation. The number of Gram-negative rods, primarily Pseudomonas aeruginosa and Klebsiella spp., has also increased, according to the authors [12]. As a result, antibiotic prescriptions should be streamlined to reduce the likelihood of an increasing trend in antibiotic resistance.

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revealed [17]. Although Escherichia coli infections are less prevalent in healthy individuals, they are more common in those with impaired immune systems, such as those with uncontrolled diabetes. These findings align with the current investigation, which found that patients with sinusitis had a low incidence of Escherichia coli (13.3%).

In low-income nations, Klebsiella pneumoniae, a bacterium that typically colonizes the gastrointestinal system, is a major cause of community-acquired pneumonia (CAP) and is occasionally discovered in the nasopharynx. These bacteria are often benign and asymptomatic when carried by the nasopharynx. A research [16] found that 8.3% of individuals with sinusitis had Klebsiella pneumoniae, and these findings were almost identical to the current study's findings of 13.3% of patients with sinusitis.

Results of present study showed there is significant different ($p<0.05$) and positivity of *E coli*, where it found the level of interleukin was low in patients with E. coli infection (68.41±33.02) than patients without E. coli. IL-1 b was low in patients with E.coli (941.36±230.78), and Staphylococeas epidermidis (1162.25±651.89) compared to patients without E. coli with significant different ($p<0.05$). in contrast, the levels of IL-1 b was high in patients with Yersinia enterocolitica (1789.66±762.32) and Leuconostic (2152.88±725.31) compared to patients without these isolates with significant different ($p<0.05$) was low in patients with Staphylococeas epidermidis (170.42±68.66) compared to patients without this isolates with significant different ($p<0.05$) (table 4).

Table 3: comparative microbial isolates with interleukins, IL-1b,.

		IL-1 b	
		Mean	
E.*coli*	1542.08	817.00	negative
	941.36	230.78	positive
P value		p<0.05*	
Staphylococcus haemolyticus	1479.45	788.31	negative
	1329.78	862.54	positive
P value		p>0.05	
Klebsiella pneumonia	1432.36	760.29	negative
	1654.57	1006.71	positive
P value		p>0.05	
Yersinia enterocolitica	1432.20	793.57	negative
	1789.66	762.32	positive
P value		p<0.05*	
Providencia stuartii	1472.85	809.94	negative
	1342.47	594.73	positive
P value		p>0.05	
Staphylococeas *epidermidis*	1529.27	809.54	negative
	1162.25	651.89	positive
P value		p<0.05*	
Pesedomonas oryzihabitans	1484.20	814.71	negative
	1336.12	667.24	positive
P value		p>0.05	
Leuconostic	1323.81	734.76	negative
	2152.88	725.31	positive
P value		p<0.05*	

Prior research indicates that the microenvironment has a significant impact on the functional activities of innate lymphoid cells (ILCs). Tissue-resident innate lymphoid cells (ILCs) possess plasticity that enables them to adjust to dynamic environments and potentially modify their migration characteristics. Therefore, the transdifferentiation of innate lymphoid cells (ILCs) will aid in the elimination of invasive infections that need distinct immune responses or pathogens that inhabit various niches during their life cycle. Innate lymphoid cells (ILCs) may thus go through cell-reprogramming once the disease resolves in order to prevent further mucosal damage, repair the mucosal tissue, and reestablish a positive interaction with commensal bacteria[18].

T-cells and B-cells, monocytes, fibroblasts, keratinocytes, endothelial cells, mesangial cells, adipocytes, and some tumor cells are among the cell types that generate IL-6. The primary extrinsic source of aggressiveness in CRSwNP, such as bacteria, fungus, and lipopolysaccharides—the primary component of Gram-negative bacteria's outer surface membrane—may account for the rise in IL-6 production in NPs.Increased fibroblast activity reliant on a persistent, chronic local inflammation that may have been sparked by an infection might potentially account for the up-regulation of IL-6 [19].

Results of present study showed the all microbial isolates in patients with sinusitis produce moderate

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biofilm, in exception the Leuconostoc psedomesenteroides that produce strong biofilm.

Tablbiofilm e 4 intensity of microbial isolates.

Isolates	Biofilm intensity
E.coli	Moderate
Staphylococcus haemolyticus	Moderate
Klebsiella pneumonia	Moderate
Yersinia enterocolitica	Moderate
Providencia stuartii	Moderate
Staphylococeas epidermidis	Moderate
Pesedomonas oryzihabitans	Moderate
Leuconostoc psedomesenteroides	Strong
Burkhoderia cepacia	Moderate

The ability of biofilm formation plays an essential role in the virulence of bacterial species protecting the organism against host immune response and action of antibiotics. In the biofilm form, these organisms are notorious to cause persistent or recurrent infections particularly through indwelling devices. Formation of biofilms within sinuses is postulated to cause repeated infections, persistent mucosal inflammation leading to chronicity of the disease. The hardy nature of biofilms makes their eradication near impossible and their symbiotic existence leads to the development of multi drug resistance [20].

A better understanding of biofilm function and their contribution to the chronic rhinosinusitis (CRS) disease process will be pivotal to the development of novel treatments that may augment and, potentially, redefine the chronic rhinosinusitis (CRS) treatment paradigm) [21].

Conclusions

The results showed that the IL-1 bcored high sensitivity (91% and 83%) and specificity (84% and 60%) lsoainfection with Yersinia enterocolitica and Leuconostica psedomesenteroide is associated with elevated levels of IL-1b in patients with sinusitis.

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