Laboratory Diagnosis, Antimicrobial Susceptibility And Genuine Clinical Spectrum of *Streptococcus anginosus* Group; Our Experience At A University Hospital

**Nasser M. Kaplan¹, Yousef S. Khader², Dua’a M. Ghabashineh¹**

**ABSTRACT**

**Background:** *Streptococcus anginosus* group (SAG) may be unrecognized or misidentified in the Clinical Microbiology Laboratory resulting in under-reporting. Consequently, their role as genuine pathogens remains underestimated. **Objectives:** The aim of this study is to suggest a reasonable identification approach that is suitable for laboratories of limited resources, to detect any possible emerging antimicrobial resistance, and to assess the genuine clinical spectrum of infections that are caused solely by SAG. **Methods:** Our research included 190 bacterial isolates from 190 patients. The isolates were examined by colonies’ morphology, odor, hemolytic pattern on 5% sheep Blood agar and Gram staining. Lancefield serogrouping was determined by agglutination test. Antimicrobial susceptibility testing (AST) was performed by disc diffusion method. The isolates were subjected to automated identification and AST by Vitek 2 compact instrument. The collected patients’ data included age, gender, clinical condition and/or site of infection, and probable predisposing factor. **Results:** All isolates produced minute-sized colonies that consistently generated distinct odor. The isolates showed variable hemolytic patterns, and the majority (74.7%) were non-hemolytic. The isolates showed different Lancefield serogroups, and the commonest was group F (54.2%). A total of 188 (98.9%) isolates were identified by Vitek 2 compact instrument at ≥95% confidence. The isolates showed high rates of antimicrobial susceptibility, however the highest rate of antimicrobial resistance was detected to gentamicin (60.5%). A total of 98 (51.6%) strains were isolated from superficial non-invasive skin and soft tissue infections, 67 (35.3%) strains from deep invasive and sterile body fluids’ infections, and 25 (13.1%) strains from upper respiratory tracts’ infections. **Conclusion:** a combination of phenotypic characteristics could still represent a reasonable Laboratory identification battery. There was no significant emerging antimicrobial resistance detected. A broad genuine spectrum of clinical infections that are caused solely by SAG was reported in our institution.

**Keywords:** *Streptococcus anginosus* group, laboratory diagnosis, antimicrobial susceptibility testing, clinical infections

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Infections involving SAG showed co-infection by other pathogens (obligate anaerobic, Gram-negative and Gram-positive bacteria and Candida) and also Mycobacterium tuberculosis. The co-existence with other microbes such as Eikenella corrodens, a Gram negative facultative anaerobic bacillus, has been also suggested as important pathogenetic mechanism.

The most likely predisposing conditions for SAG infections include previous surgery, trauma, diabetes mellitus, immunodeficiency, malignancy, as well as patient's general health condition and hygiene. The pathogenic mechanisms of SAG have been attributed to different virulence factors mainly a polysaccharide capsule, and many extracellular tissue-destroying enzymes such as collagenase, hyaluronidase, gelatinase, deoxyribonuclease, and ribonuclease, as well as massive release of cytokines through T-cell immune response to certain exotoxins (15). The co-existence with other microbes such as Eikenella corrodens, a Gram negative facultative anaerobic bacillus, has been also suggested as important pathogenetic mechanism (16, 17).

2. OBJECTIVE

This study aimed to suggest a reasonable identification approach that is suitable for laboratories of limited resources, to detect any possible emerging antimicrobial resistance, and to assess the genuine clinical spectrum of infections that are caused solely by SAG. We will also discuss the factors that may affect the isolation of SAG in clinical microbiology laboratory (CML).

3. METHODS

Study Design

This prospective observational laboratory-based study was conducted between January 2019 and December 2021 in King Abdullah University Hospital (KAUH); a tertiary care reference teaching hospital affiliated with Jordan University of Science and Technology (JUST), Irbid (32.5568° N, 35.8469° E), Jordan. The hospital is the largest medical center in the north of Jordan serving approximately one million inhabitants. This hospital provides comprehensive multidisciplinary health services with a capacity of eight hundred inpatient beds, as well as outpatient clinics, emergency facilities, and laboratory and radiology diagnostic services.

Procedure and ethical considerations

This study was approved by the Institutional Review Board of Jordan University of Science and Technology (IRB # 13/123/2019). All adult participants and parents of the children were informed about subject of the study. Participation in this study was anonymous and all collected data were treated confidentially.

Bacterial strains

Different clinical samples were properly and aseptically collected, subjected to direct Gram staining and inoculated onto 5% sheep Blood agar, Chocolate agar, and MacConkey agar plates (Oxoid, Basingstoke, UK). The inoculated plates were incubated for 24–48 hours at 37°C in humid aerobic atmosphere enriched with 5% carbon dioxide.

Only pure suspected bacterial cultures were consecutively selected, enrolled in the study and immediately examined by colonies’ morphology, odor, hemolytic pattern on 5% sheep Blood agar, and Gram staining.

Serotyping

Lancefield serologic grouping was determined by direct detection of the antigenic carbohydrate present in the cell wall of intact bacteria using rapid qualitative latex serological agglutination slide test (Streptex, Remel, Kent, UK) according to the manufacturer’s instructions. Serotype-specific anti-sera for groups A, B, C, D, F and G were used. Agglutination that occurred within 60 seconds was interpreted as a positive reaction and indicated the presence of particular homologous antigens.

Automated identification

The pure isolates were subjected to automated confirmatory identification using Gram-positive bacteria identification (GPI) cards of Vittek 2 Compact instrument (bioMérieux, Marcy l’Etoile, France) according to the manufacturer’s instructions.

Antimicrobial susceptibility testing (AST)

Bacterial isolates were subjected to manual AST by disc diffusion method. Bacterial colonies from overnight (18–24 hours) culture were suspended in a 0.45% sterile normal saline solution. The bacterial cell suspension was adjusted to the turbidity of a 0.5 McFarland standard that was equivalent to 10⁶ colony-forming units per milliliter. The adjusted cell suspension was uniformly spread in three different directions onto the entire surface of 4-mm depth plate of Muller-Hinton agar (Oxoid) with 5% sheep blood. A total of 20 antimicrobial agents were used. Approximately, 6–7 antimicrobial discs (Oxoid) were gently applied per plate. The plates were then incubated for 18–24 hours. During the incubation, the antimicrobial agents diffused around the disc and inhibited the growth of bacteria generating a clear (zone of inhibition). The diameter of inhibition zone was measured by a caliper or a ruler with a handle. The interpretation of the results as susceptible (S), intermediate (I), or resistant (R) was determined according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI, 2019). Streptococcus pneumoniae (ATCC 49619) was used as a quality control strain.

The pure isolates were also subjected to automated AST using Gram-positive bacteria susceptibility (GPS) cards of Vitek 2 Compact instrument (bioMérieux) according to the manufacturer’s instructions.

Patients

SAG strains were isolated from different patients in a non-duplicate manner with only one single isolate collected from the same anatomic site of each patient. The patients were located in the different wards and outpatient clinics of KAUH including the emergency room. The patients’ data were recorded and included age, gen-
Laboratory Diagnosis, Antimicrobial Susceptibility And Genuine Clinical Spectrum of Streptococcus anginosus Group

4. RESULTS

A total of 190 SAG isolates were examined in this study. The phenotypic characteristics of these isolates were shown in (Table 1). On both 5% sheep Blood and Chocolate agar plates, all the isolates (n = 190, 100%) produced minute-sized colonies ≤0.5 mm in diameter that consistently generated distinct caramel-like odors. There were no bacterial growths on MacConkey agar plates that selectively isolate Gram-negative bacilli and inhibit the growth of Gram positive organisms.

The colonies showed variable hemolytic patterns on 5% sheep Blood agar. A total of 142 (74.7%) isolates were non-hemolytic, 41 (21.6%) isolates alpha-hemolytic, and 7 (3.7%) isolates beta-hemolytic.

The colonies showed variable Lancefield serological grouping reactions. A majority of the isolates (n = 103, 54.2%) were Lancefield group F. A total of 75, (39.5%) isolates exhibited insufficient or no agglutination and were therefore serologically nontypable. A total of 8 (4.2%) isolates were group C and 4 (2.1%) isolates group G. None of the isolates showed positive agglutination with Lancefield groups A, B or D.

A total of 188 (98.9%) isolates were identified by using Gram-positive bacteria identification (GPI) cards of the automated Vitek 2 Compact instrument at ≥95% confidence whereas 1 (0.53%) strain was incorrectly identified and 1 (0.53%) strain remained unidentified.

The antimicrobial susceptibility profile of Streptococcus anginosus group isolates was shown in (Table 2). All the 190 (100%) isolates were consistently susceptible to benzyl penicillin (penicillin G), ampicillin, amoxicillin/ clavulanic acid, cefotaxime, ceftriaxone, vancomycin and teicoplanin. High rates of antimicrobial susceptibility were also detected to the other antimicrobial agents. However, the highest rate of antimicrobial resistance was detected to gentamicin (60.5%), followed by tetracycline (5.8%).

The distribution of SAG isolates according to the age and gender of patients as well as the spectrum of clinical infections and/or sites of isolation was shown in (Table 3). The SAG strains were isolated from 190 different patients. The median age of the patients was 42.5 years. A total of 122 (64.2%) patients were males. SAG strains were predominantly isolated from 109 (57.4%) adult males.

Regarding the anatomical sites of infection and isolation of SAG, a total of 98 (51.6%) strains were isolated from superficial non-invasive skin and soft tissue infections, 67 (35.3%) strains from deep invasive and sterile body fluids’ infections, and 25 (13.1%) strains from upper respiratory tracts’ infections. Infected pilonidal sinus was the commonest superficial infection (n = 52; 27.4%). There was also a high rate of bacteremia and isolation of SAG from blood samples (n = 31; 16.3%).

The predisposing factors for SAG infections were shown in (Table 4). Diabetes mellitus (n = 93; 49%) was the commonest factor, followed by surgical interventions (n = 40; 21%) and malignancy (n = 36; 19%). However, twenty-one (11%) patients did not show any explicit predisposing factors.
In CML, the difficulties that may be encountered in isolation, recognition and identification of SAG isolates may be attributed to different factors. In this study, SAG strains were entirely isolated from collected exudates, aspirates or fluid samples, and blood rather from swabs. The collection of clinical specimens using swabs is usually inferior to the collection of purulent discharges. The swabs typically carry small insufficient quantities of the required representative samples. The material of the swabs may not only satisfactorily support but rather inhibit the growth of SAG. The delay in transport of swab specimens to CML may also result in dryness that may be lethal to SAG. It is fundamentally necessary to process the clinical specimens promptly as many streptococcal species lose viability fairly quickly. Additionally, the overgrowth of mixed bacterial coliforms or environmental fungal contaminants may mask the growth of the easily missed minute-sized colonies of SAG. Although direct microscopic identification of streptococci is most helpful in clinical specimens from sterile body sites, interpretation of Gram stain results from nonsterile body sites is difficult due to the residential microflora, which frequently includes streptococci. However, showing Gram positive cocci in chains of various lengths in direct Gram staining of clinical specimens is definitely important as it provides a valuable preliminary result and stimulates vigilant inspection of culture plates for the easily missed minute-sized colonies of SAG.

5. DISCUSSION

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Most CMLs rely on rapid diagnostic kits (1), automated identification systems (18, 19), or non-sequence-based identification methods, such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (20) for identification of SAG. However, conventional streptococcal identification system is well established and still of value especially in the routine setting of CMLs of limited resources (2).
fication (GPI) cards of the automated Vitek 2 Compact instrument revealed a high identification rate (n = 188, 98.94%) at ≥95% confidence.

Although agar cultures of SAG are associated with characteristic odor resembling caramel or butterscotch, often attributed to the production of a diacetyl metabolite (21), this was not considered a sufficiently sensitive screening test (22). Additionally, opening agar plates and intentional smelling of microbiological growth in CML is highly discouraged and hazardous due to bio-safety concerns of accidental infections. However in this study, the distinct caramel odor was a consistent feature in all SAG clinical isolates (n = 190: 100%).

In this study, it was noted that primary culture growth of SAG was sometimes poor with undetected odor and unclear hemolytic pattern. Therefore, subculture on Blood and Chocolate agar plates and incubation for 24 hours usually revealed the typical minute-sized colonies, the distinct smell and the hemolytic pattern.

Species differentiation of SAG using conventional methods continues to be difficult, time-consuming, and usually unsatisfactory (20, 23). However the modern molecular methods including polymerase chain reaction (PCR) (24, 25) and restriction fragment length polymorphism (RFLP) (26) have been used to identify SAG species and proved to be rapid and reliable. SAG includes three distinct species: S. anginosus, S. constellatus, and S. intermedius (27). These species appear at different isolation rates and are associated with specific isolation sites. They also have different clinical significance and are not equally associated with abscess formation (28). S. intermedius is the least commonly isolated species and it appears to be the most pathogenic and the most often identified in abscesses of the brain or liver (29). Furthermore a number of subspecies have also been recognized based primarily on molecular testing (30), however the clinical relevance of these subspecies remains to be determined. Although identification of SAG to the species level may be of prognostic importance (31), there is practically little clinical need to distinguish between the three species as infections usually require immediate surgical intervention for drainage and debridement of abscesses and timely initiation of appropriate antimicrobial therapy that should be administered until the complete resolution of clinical signs and radiologic features (30, 28).

There is a current under-diagnosis of infections caused by SAG. This is mainly attributed to the limited awareness by healthcare providers. Consequently, the clinical significance of SAG has not been appropriately appreciated. This research reported a genuine spectrum of clinical infections that were caused solely by SAG. These infections were diagnosed and confirmed as “proven bacterial diseases” because SAG was the only and pure isolated pathogen recovered by culturing of clinical specimens that were collected by sterile procedures from clinically abnormal sites consistent with infectious disease processes. SAG in mixed bacterial growths were not included in this study because of the difficulty to differentiate between the pathogenic role of SAG in poly-

microbial synergistic coinfections or the mere existence as part of normal flora of human body sites. This cautious investigative approach might have resulted in an element of underreporting.

In this study, SAG infection prevalence was higher in adult males (57.4%). This is in concordance with the findings of other recent studies (14, 32).

The anatomical sites of SAG infections in adults and children were reported in other recent studies. In Saudi Arabia, 105 adults with culture-positive SAG infections were identified. The infection frequencies were skin and soft tissue infections (55%), intra-abdominal infections (24%), bacteremia (14%), genitourinary infections (8.5%), and pleuropulmonary infections (5%) [32]. In Australia, 200 children with culture-positive SAG infections were identified. The most common sites were intra-abdominal infections (39%), soft tissues’ infections (36%) and head and neck infections (21%) (33).

In cases of bacteremia due to SAG, high level of suspicion should be maintained and the presence of underlying distant suppurrative foci of infection, including brain, liver and intra-abdominal abscesses, and empyema, should be promptly investigated (34). Also odontogenic infection cannot be ruled out in bacteremia with mixed growth of SAG and other oral anaerobes especially in patients with poor dental hygiene. Despite of the high rate of bacteremia and isolation of SAG from blood samples (n= 31; 46.3%) in this study, further investigations to detect the primary focus of infection was not among the aims of this research.

Although ninety-three (49%) patients with SAG infections had diabetes mellitus in this study, twenty-one (11%) patients did not show any explicit predisposing factors. However, another recent study reported an expanded list of underlying conditions associated with SAG infections. In China, 463 patients with culture-positive SAG infections were identified. Approximately 45.4% had underlying risk factors, which were mostly malignant tumors and diabetes (14).

Most CMLs do not routinely perform AST for SAG as the in-vitro activity of antimicrobial agents does not necessarly imply in-vivo effectiveness. SAG infections continue to respond well to penicillin G and cephalosporins (35). Of the clinically available cephalosporins, ceftiraxone is the preferred antimicrobial agent due to excellent potency and spectrum and tissue penetration with once-daily dosing. Vancomycin is an appropriate alternative agent for patients with beta-lactam allergies. In this study, the highest rate of antimicrobial resistance was detected to gentamicin (60.5%); a broad spectrum aminoglycoside that inhibits intracellular bacterial protein synthesis and is most effective against aerobic Gram-negative rods. Most strains of SAG are relatively resistant to aminoglycosides (30). This is mainly attributed to the thick peptidoglycan layer and impermeability of the bacterial cell wall. However, the use of aminoglycosides and beta-lactam agents in combination is a reasonable practice for treatment of endocarditis due to SAG because of the expected synergy.
Although there was no detection of significant emerging antimicrobial resistance in SAG isolates in this study, different antimicrobial susceptibility profiles were reported elsewhere (36). Although SAG members are susceptible to fluoroquinolones in vitro, these agents are not appropriate for treatment of clinical SAG infections as resistance tends to develop easily (37, 38). Additionally, macrolide resistance has emerged in members of SAG (39). Sulfonamides also have no clinical activity against SAG isolates (40). If mixed infection is suspected or confirmed by Gram stain and culture results, other microorganisms such as anaerobes should be treated by adding metronidazole or clindamycin.

6. CONCLUSION

An active coordinated communication system should be continuously maintained between the laboratory and the wards to ensure early laboratory diagnosis and favorable therapeutic outcomes. The microbiologists should have a high index of suspicion for enhanced laboratory presumptive recognition. A practical conventional identification approach is still of value especially in the routine setting of laboratories of limited resources. The clinicians should appreciate the genuine pathogenic role of SAG for proper management of the clinical infections regardless of species and subspecies of SAG. Further studies are recommended to increase the knowledge of SAG susceptibility profile to antimicrobials in other health centers.

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