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Streptococcus agalactiae-associated Urinary Tract Infections amongst Male Patients at a Tertiary Care Setting in Southwest India

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ABSTRACT

Introduction: The occurrence of urinary tract infections (UTIs) caused by the group B *Streptococcus* (GBS) in females is well documented. On the contrary, the prevalence amongst males is infrequent, and studies from the Indian subcontinent are limited. This study aimed to determine the occurrence of GBS bacteriuria and its antibiotic susceptibility profile amongst male patients. **Methods:** Clean-catch, midstream, catheterized, or voided urine samples from patients were used for the study. Urinary samples from patients either admitted or attended to a tertiary care center in Southwest India were promptly sent to the laboratory for culture, identification, and antibiotic susceptibility test. **Results:** A total of 16,190 urine specimens were processed during the 1-year study period, of which 45 patients (0.27%), including 30 females (0.19%) and 15 males (0.09%), had GBS bacteriuria. The patients were mainly in the 19-45 years old group (53%). The most typical comorbidity was type 2 diabetes mellitus (42%). The majority of the GBS isolates from male patients (>80%) were susceptible to benzylpenicillin, ceftriaxone, ampicillin, and cotrimoxazole. The isolates showed the least susceptibility to tetracycline (26.1%) **Conclusion:** Though GBS-associated UTI amongst male patients is uncommon, antimicrobial resistance amongst *S. agalactiae* isolates is widespread. Nevertheless, antimicrobial resistance rates differ depending on the geographical areas and study duration. Considering the emergence of drug resistance in GBS, culture and antibiotic susceptibility testing patterns of all the strains of GBS, even in asymptomatic patients with a low count, are recommended.

INTRODUCTION

Streptococcus agalactiae, also known as group B *Streptococcus* (GBS), is the primary cause of sepsis and meningitis in neonates [1]. The GBS infections cause significant mortalities in both neonates and adults. The average case fatality rate in the United States between 2008 and 2016 was 6.5% for invasive GBS infection, highest in elderly patients having comorbid medical conditions [2]. In 2016, the rate in non-pregnant women increased to ~11 cases per 100,000 population [2]. The GBS infection is linked with unfavorable pregnancy outcomes even when the women are asymptomatic [3]. In the United States, antibiotic prophylaxis has decreased GBS-associated neonatal sepsis from 1.8 per 1000 births in the 1990s to 0.23 in 2015 [4]. However, the GBS-associated illness in the developing world is not well defined. In 2017, a meta-analysis in 53 countries showed early- and late-onset GBS disease incidence of 0.41 and 0.26 per 1000 births, respectively [5].

Streptococcus agalactiae is a commensal microorganism of the genitourinary tract and rectum in ~25% of adult females [1]. The urinary tract infections (UTIs) in females by this bacterium are well documented, while the prevalence amongst males is infrequent. A one-year study in a Bulgaria healthcare setting on males and non-pregnant females revealed urinary GBS in 32 patients (59.3%), of which 7 (12.96%) were males [6]. GBS bacteremia has been reported sporadically in adults, with the urinary tract as one of the most common sources of such bacteremia [7]. In a single-center analysis in Birmingham Hospital, University of Alabama, United States, during a routine assessment of UTI in adults, GBS was cultured from 2% of urine samples, most with asymptomatic bacteriuria in adults [8], similar to findings in California, United States (2004) [9, 10].

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In many countries, *S. agalactiae* resistance to erythromycin and clindamycin has increased over the last decade [1]. Nevertheless, such reports from the Indian subcontinent are limited. The alarming rise in resistance to clindamycin and erythromycin among GBS strains is a worrying fact, as this limits antibiotic choice for prophylaxis or treatment of GBS-associated infections.

This study examined the GBS-associated UTI and the antibiotic susceptibility patterns of the associated bacteria amongst male patients in a tertiary care setting.

MATERIAL AND METHODS

Clinical specimens. In a prospective cross-sectional study from September 01, 2017, to August 31, 2018, at Kasturba Hospital, Manipal, southwest coastal Karnataka, India, 16,190 clean-catch, midstream, catheterized, or voided urine samples were collected from patients. The samples belonged to out-patients and those hospitalized in different wards. The Kasturba Medical College and Kasturba Hospital Institutional Ethics Committee approved the study (code No. 251/2019)

Isolation and Identification. The examination of urine specimens included quantitative plating onto blood agar medium alongside a selective and differential agar culture for Gram-negative bacteria to detect the presence of co-infections [11]. All specimens were inoculated into 5% blood sheep agar and differential media (MacConkey Agar) plates and incubated at 37 ºC for 18-24 h. Beta-hemolytic colonies, grown as Gram-positive cocci in chains under microscopy and negative catalase test, were presumptively defined as GBS. Patients with colony count ≥10,000 CFU/ml were further investigated.

For species identification, all the GBS strains were subjected to matrix-assisted laser desorption/ionization-time of flight (MALDI-ToF) based automated bacterial identification system (bioMerieux, France) which identified all the strains as *Streptococcus agalactiae*. All *S. agalactiae* isolates were checked for susceptibility against benzylpenicillin (0.06, 0.12, 0.5, 2 µg/ml), ampicillin (1, 2, 4, 16 µg/ml), cotrimoxazole (8/152, 16/304, 64/1216 µg/ml), tetracycline (0.12, 0.5, 1, 4 µg/ml), ceftriaxone (0.12, 0.25, 1, 4 µg/ml), levofloxacin (1, 2, 4, 16 µg/ml), clindamycin (0.12, 0.25, 0.5 µg/ml), and erythromycin (0.12, 0.25, 1, 4 µg/ml) by an automated turbidimetric system (Vitek 2, bioMerieux, France). Susceptibility cards were inoculated and interpreted according to the manufacturer's instructions [12].

The GBS frequency in urine samples was monitored for one year, along with the antibiotic susceptibility patterns of each isolate. In cases, *S. agalactiae* grew in urine cultures, medical records of the male patients were reviewed for blood culture reports, comorbidities, and demographic data. Urinary tract infection diagnosis was provisionally made by *S. agalactiae* growth alongside at least one symptom, including fever (>38ºC), painful urination (dysuria), flank pain, increased urinary frequency or urgency, and lumber tenderness. Pure growths of GBS with colony count of ≥10,000 CFU/ml, both in symptomatic and asymptomatic cases, were considered positive samples. A positive urinary leukocyte esterase and pyuria presence were also considered for the diagnosis in cases where these tests were performed.

Statistical analysis. Statistical analysis to determine the antibiotic susceptibility patterns of urinary GBS isolates obtained from male study subjects was performed using SPSS Ver. 16.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Of 16,190 urine specimens processed during the study period, 45 (0.27%), including 30 from females (0.19%) and 15 from males (0.09%) had a significant GBS bacteriuria. Of these 45 patients, 30 (67%) were in-patients and 15 (33%) were out-patients. The most common comorbidity amongst the patients was diabetes mellitus (n=19, 42%). None of the patients had a positive *S. agalactiae* blood culture. Following antibiotic treatment, all patients became *S. agalactiae* negative for urine culture.

The male patients' age ranged from 6 to 86 years old, with a mean of 59.87 ± 19.61 years. The majority of the male patients were in the age groups > 65 years (Fig. 1.).

The female patients' age ranged from 19 to 69 years old, with a mean of 37.67 ± 15.2 years; the majority were between 19 and 45 years (Fig. 2.).

Antibiotic susceptibility testing. Majority of the GBS isolates (>80%) exhibited susceptibility patterns to benzylpenicillin (n=15, 100%), ceftriaxone (n=15, 100%), ampicillin (n=15, 100%), clindamycin (n=13, 86%), and cotrimoxazole (n=14, 93%), followed by erythromycin (n=11, 73.3%). Only 26.7% (n=4) of the isolates showed susceptibility to tetracycline.

DISCUSSION

Unlike in females, GBS-associated urinary tract infections (UTIs) in males are not well documented and rarely attributed to GBS [13]. In this study, 0.09% of cultures from male patients became positive for GBS. A study in Malmo, Sweden, from 1982 to 1984 at a general hospital on males and non-pregnant females ≥15 years of age identified GBS in 1% of 24,000 urine cultures (in quantities ≥ 10^5 CFU/ml), and further 0.9% harbored GBS in quantities ≥ 10^4 CFU/ml but < 10^5 CFU/ml [14]. A study conducted by Sewaify M et al. (2016) showed that GBS was the responsible pathogen in around 6% of the UTI cases in diabetic male and female patients [15].

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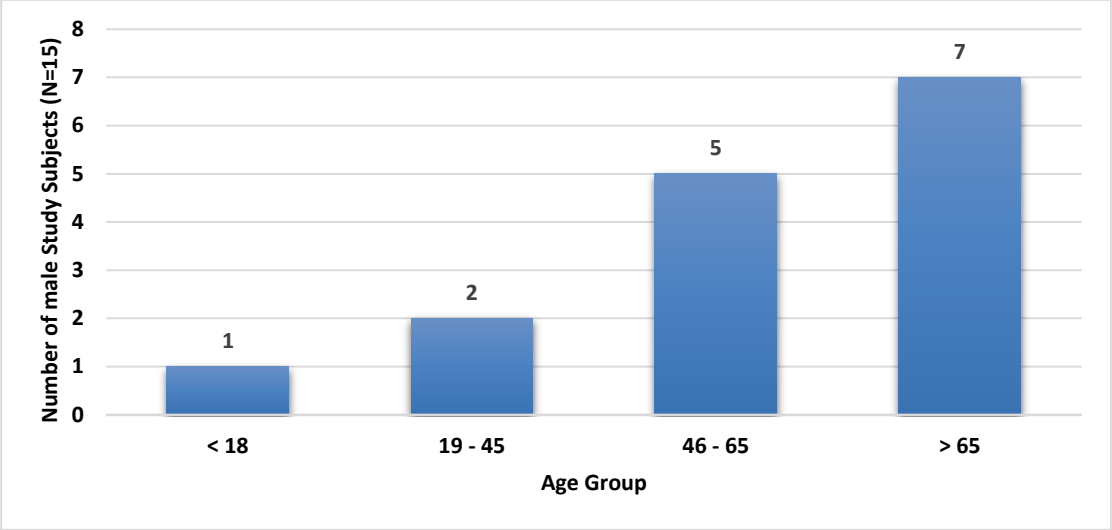

Fig. 1. Number of male patients in different age groups (N=15)

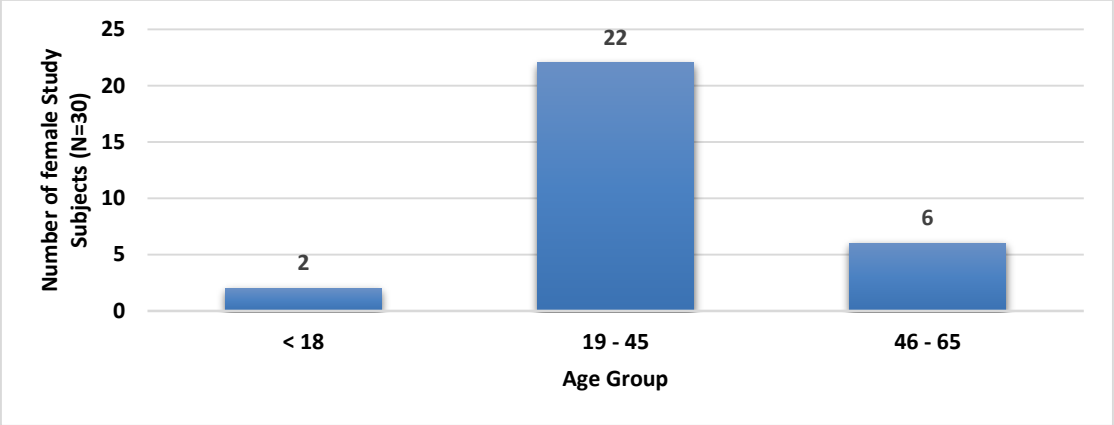

Fig. 2. Number of female patients in different age groups (N=30)

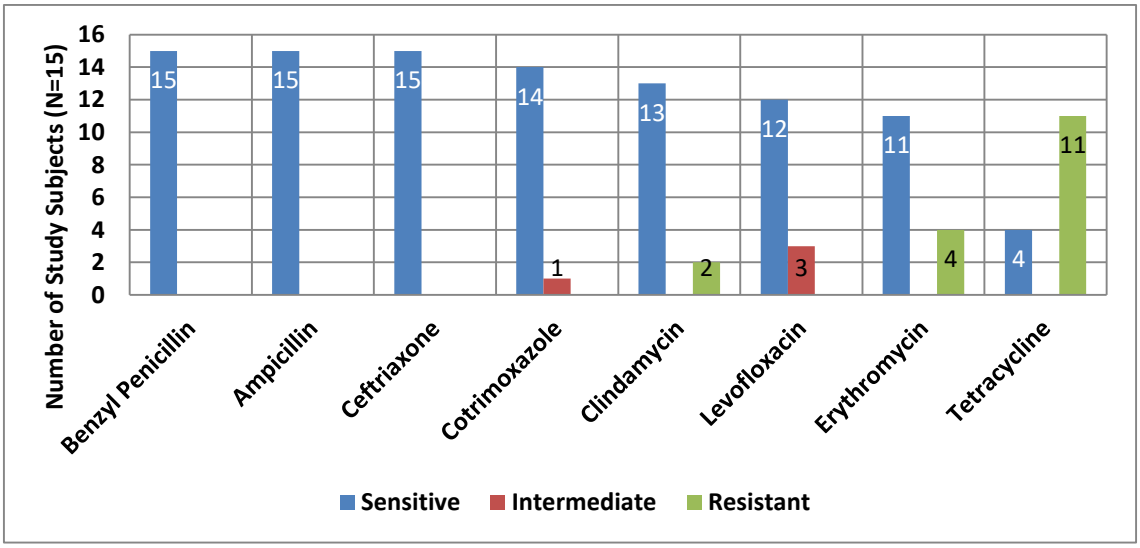

Fig. 3. Antibiotic susceptibility patterns of urinary GBS isolates obtained from male subjects (N=15)

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GBS occurs mainly in adults with significant underlying medical conditions [16]. One of the most critical underlying diseases for developing GBS infections is diabetes mellitus [16, 17], and the increased frequency of UTIs in diabetic patients may be primarily due to glycosuria, neutrophil dysfunction, or increased adherence of the bacteria to uroepithelial cells [18].

In a cohort study on Denmark's general population, UTI rates were higher (adjusted hazard ratio=3.03; 95 % CI, 2.04–4.49) in diabetic patients than non-diabetic individuals [19]. Likewise, in Germany, diabetic women had higher recurring UTI rates than non-diabetic women (P<0.001) [19]. Our findings were similar as approximately half of the subjects, i.e., men, in our study were diabetic.

In the current clinical study, all 15 urinary *S. agalactiae* isolates obtained from male patients with signs and symptoms suggestive of UTI were subjected to antibiotic susceptibility testing using the antimicrobials known to control *S. agalactiae* infections. The results revealed that almost all isolated uropathogenic *S. agalactiae* isolates were sensitive to penicillin, consistent with many other reports worldwide [6]. GBS is sensitive to many antibiotics, mostly beta-lactams. Hence, penicillin or ampicillin is extensively used to treat GBS infections [20]. A high percentage of tetracycline-resistant GBS isolates was detected in our study, similar to reports from other countries [21, 22, 23]. Studies from Iran have also shown high susceptibility rates among *S. agalatiae* isolates to ampicillin and benzylpenicillin. A study in 2012 in Ardabil, Iran, exhibited susceptibility of all GBS isolates to ampicillin and benzylpenicillin [24]. However, on the contrary, another study reported high resistance rates (89.4%) to penicillin in uropathogenic *S. agalatiae* isolates [25]. Furthermore, in another study by Sewaify *et al.* (2016), of the 13 urinary *S. agalatiae* isolates, 2 (15%) were resistant to clindamycin and erythromycin; two isolates showed resistance to ciprofloxacin and trimethoprim-sulfamethoxazole [15].

Antimicrobial resistance amongst *S. agalactiae* isolates is widespread globally; yet, antimicrobial resistance rates differ depending on the geographical areas and study duration [1]. The antibiotic susceptibility patterns of *S. agalactiae* against lincosamides and macrolides must be investigated since identifying erythromycin-sensitive phenotypes can be beneficial in selecting an appropriate substitute treatment for penicillin-allergic patients [1].

The mechanism of pathogenesis in GBS-associated UTI is not well defined. Moreover, its association with male patients in causing UTI is uncommon [1]. We suggest an appropriate antibiotic therapy even in asymptomatic male patients. Considering the emergence of drug resistance in GBS, culture and antibiotic susceptibility testing patterns for all the GBS isolates, even in asymptomatic patients with a low bacterial colony count (< 10^5 CFU/ml) in urine culture, are recommended.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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