Original Article

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Invasive *Group B Streptococcal* Infection in Non-Pregnant Adult Patients in A Tertiary Care Centre

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Abstract

Introduction: Group B streptococcus (GBS) is an important cause of illness in newborns, pregnant women as well as in non-pregnant elderly patients particularly those with significant underlying diseases. The study was carried out to determine the clinical spectrum, antibiogram and outcome of *Group B Streptococcus infection* as it can cause invasive infections in non-pregnant adults that can lead to substantial morbidity and mortality in them.

Materials and Methods: A retrospective observational chart based study was conducted in a tertiary care centre for a period of one year (June 2016 to May 2017). Multisite samples like pus, wound swabs, blood, body fluids and urine samples were collected from male and female adult patients (adults were defined as >18 years old) with Group B streptococcus infections. The samples were processed for culture and sensitivity aerobically according to the standard operating guidelines. Statistical analysis of the data was performed using SPSS v.21 by frequency, percentage, Fisher's exact test and a p value less than 0.5 was considered as significant.

Results: In 156 cases of GBS infections among non-pregnant adults, the prevalence was higher in the age group of 50-64 years (37.8%) with female to male ratio of 1.1:1. The most frequent clinical presentations were urinary tract infections (65.4%) with a significant female gender predominance (p value <0.0001). All tested isolates were susceptible to Ampicillin, Cephalosporins, Penicillin and Vancomycin.

Conclusion: Elderly people with underlying diseases are more prone to GBS infections. Therefore, evaluation of risk factors and development of an antibiotic policy is useful for the successful treatment of GBS infections.

Keywords: Noninvasive; Non-Pregnant; *Streptococcus Agalactiae; Group B Streptococcus*.

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Introduction

Group B streptococcus (GBS) is a normal commensal of the gastrointestinal and genitourinary tracts, but it's also an important cause of illness in newborns, pregnant women, and non-pregnant elderly patients particularly those with significant underlying diseases like diabetes, neurological impairment, cirrhosis and increase risk for invasive *Group B Streptococcal* (GBS) disease. Common presentations are skin, soft-tissue, and osteo-articular infections, pneumonia, and urosepsis etc. [1] Though meningitis, *Streptococcal* toxic shock syndrome and endocarditis are less common, its associated with serious morbidity and mortality. The main manifestations of GBS in infancy are bloodstream infections, with or without pneumonia. Incidence

of invasive GBS infections has increased two to four-fold in non-pregnant adults over the last 2 decades, with rates ranging from 4.1 to 7.2 cases per 100,000 non pregnant adults [1]. The severity of GBS infection increases with age; the mean age of non- pregnant adults with invasive GBS disease is about 60 years, and the associated mortality rate is close to 25% [1]. On an average 1(5%) out of every 20 non-pregnant adults with invasive Group B Streptococcal infections die [1]. Between 15% and 35% of pregnant women are asymptomatic carriers of GBS, and in the early 1990's 0.2 to 0.8% of neonates had GBS bacteremia [2]. GBS is regarded as uniformly susceptible to penicillin, but recent reports have highlighted the emergence of strains resistant to erythromycin and clindamycin [3]. The resistant strains raise the importance of the use of erythromycin and clindamycin for the prophylaxis or treatment of GBS infections in patients allergic to beta-lactams [3].

Moreover, increasing antimicrobial resistance has implications for GBS disease treatment and intrapartum prophylaxis among penicillin intolerant patients. This present work deals with the clinical spectrum and antibiogram of *Group B Streptococcus* that can help in better approach towards empirical treatment and outcome of these patients.

Materials and Methods

This retrospective observational chart based study was carried out for a period of one year from June 2016 to May 2017, in the Department of Microbiology, in a tertiary care centre, after ethical clearance. Clinical data, epidemiological and demographic profile of each case including comorbidities and outcomes were abstracted by chart review. Multisite samples like pus, wound swabs, blood, body fluids and urine samples were collected from male and female adult patients (adults were defined as anyone >18 years old) with *Group B streptococcus* infections, which were received in the laboratory from the ailing patient and outpatient facilities, were included in the study. For patients who had more than one GBS culture positive during the study period, only the first episode of GBS infection was analyzed. Vaginal samples, samples from pregnant women and samples from neonates were excluded from this study. The samples were cultured aerobically on 5% Sheep blood agar and MacConkey agar and *Group B Streptococcus* identification was based on the following criteria: a narrow zone of beta-hemolytic colonies on 5% sheep blood agar plate (Fig. 1), Gram-positive cocci in pairs or short chains on Gram's staining, a negative-catalase reaction, positive hippurate hydrolysis test, positive reaction with Christie, Atkins, Munch-Peterson (CAMP) (Fig. 2) and a bacitracin differential disk resistance pattern. Antimicrobial susceptibility testing was done on Mueller Hinton agar supplemented with 5% sheep blood by Kirby-Bauer disc diffusion method according to the updated CLSI guidelines. Statistical analysis of the data was performed using SPSS v. 21 by frequency, percentage and Fisher's exact test.

Fig. 1: *Group B Streptococcus* showing beta hemolysis on Sheep Blood Agar

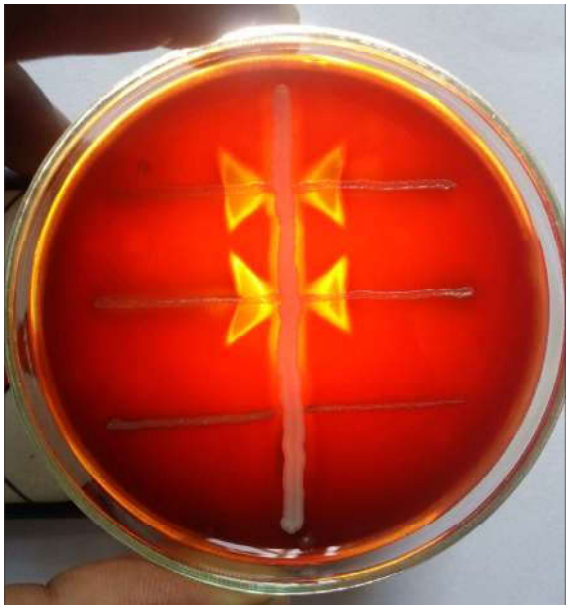


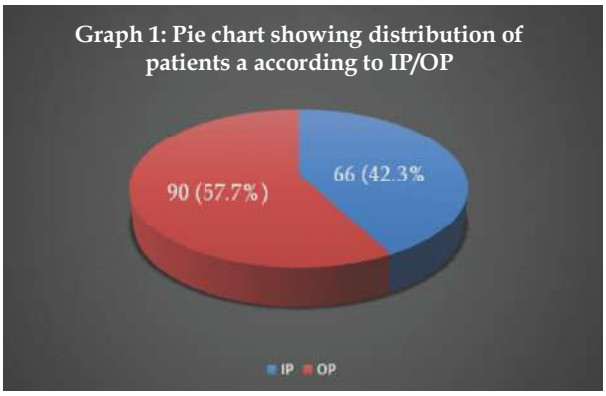
Fig. 2: *Group B Streptococcus* showing positive CAMP test on Sheep Blood Agar

Results

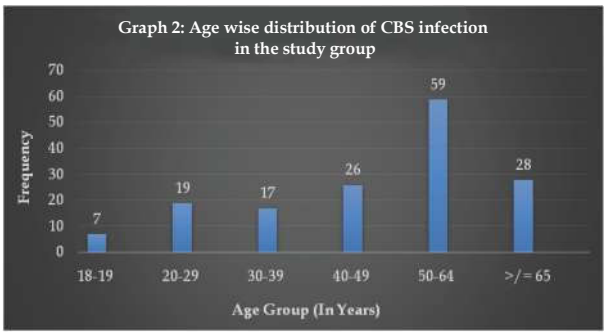
There were 156 cases of GBS disease among non-pregnant adults. Most of the cases in our study were outdoor cases ie. 57.7% from clinics and hospitals around Mangalore (Graph 1). Of these, 83 (53.2%) of the non-pregnant cases occurred in women and 73 (46.8%) cases in men. The prevalence of GBS was higher in the age group of 50-64 years (37.8%), followed by ≥ 65 years (17.9%) with female and male ratio of 1.1:1 (Graph 2). A review of the clinical records of the 156 adult cases revealed that the most frequent clinical presentations was urinary tract infections (65.4%) followed by wound and soft-tissue infections (32.7%) (Table 1). Out of 156 GBS cases, polymicrobial infections occurred in 10 (6.4%) cases of GBS i.e 6 urinary tract infections and 4 soft tissue infections. The most common additional pathogens were *Staphylococcus aureus, Coagulase-negative Staphylococcus and Escherichia coli*. Among 66 (42.3%) admitted patients 58 (87.9%) of the non pregnant patients had > 1 underlying medical conditions or predisposing factors. These were diabetes, surgical intervention, cancer and hospitalization in decreasing order of frequency (Table 2). Among the 17 (29.3%) non pregnant cases associated with nosocomial transmission, 11 (64.7%) patients had undergone surgery before developing the GBS infection and the other 6 (35.3%) cases had been hospitalized for more than 48 hours before the first positive culture. In the current study 2 cases had diabetes mellitus with hypothyroidism and baker's cyst.

An HIV positive case was reported in our study. All tested isolates were susceptible to ampicillin, cephalosporins, penicillin and vancomycin. Resistance to erythromycin and clindamycin were common being 52 (33.3%) and 31 (19.9%) respectively. The prevalence of levofloxacin resistance was low 2 (1.3%). None of the Group B Streptococcus isolates showed resistance to ciprofloxacin. (Table 3)

Out of 156 non pregnant adult patients 7 (4.5%) died while hospitalized and 3 (42.8%) deaths were attributed to GBS infection. The deaths included 2 men (an 80 years old who died of acute kidney injury and sepsis, and a 58-years old with dilated cardiomyopathy who presented with abdominal cellulitis and died of sepsis). A 64-year-old woman died of corpulmonale, multi organ dysfunction syndrome and sepsis. The mean interval between positive culture and death was 4 days. 35 (53%) of the 66 hospitalized patients (in patients) were still hospitalized 10 days after their diagnosis with GBS disease. The 90 outpatients were treated on an outdoor basis and showed significant recovery on follow up without any complications.



Graph 1: Pie chart showing distribution of patients according to Inpatient & Outpatient data



Graph 2: Age wise distribution of GBS infection in the study group

Table 1: Clinical spectrum of GBS in the study group

Clinical presentation	Male (%)	Female (%)	Total (%)	p value
Urinary tract infection	34(33.33%)	68 (66.67%)	102 (65.4%)	p = 0.000, <0.0001 (Fisher's exact test)
Bone & Soft tissue infections	31(75.60%)	10 (24.40%)	41(26.3%)	
Wound infection	6(60%)	4 (40%)	10 (6.4%)	
Primary bacteremia	2 (66.67%)	1 (33.33%)	3 (1.9%)	
Total	73 (46.79%)	83 (53.20%)	156 (100%)	

*p value <0.05 is significant

Table 2: Underlying conditions of non pregnant adult patients with GBS infection.

Co-morbidity	Male (%)	Female (%)	Total (%)
Diabetes mellitus	16 (57.14%)	12 (42.86%)	28 (42.4%)
Surgery	7 (63.64%)	4 (36.36%)	11 (16.7%)
Carcinoma	7 (70%)	3 (30%)	10 (15.2%)
Hospitalized for ≥48 hours before first positive culture report	4 (66.67%)	2 (33.33%)	6 (3.8%)
Renal disease	3 (50%)	3 (50%)	6 (3.8%)
Cardiac disease	1 (25%)	3 (75%)	4 (2.6%)
Multi organ dysfunction syndrome	3 (100%)	-	3 (1.9%)
Liver disease	1 (50%)	1 (50%)	2 (1.3%)
Vascular disease	1 (50%)	1 (50%)	2 (1.3%)
Previous trauma to the infected site	-	1 (100%)	1 (0.6%)
HIV positive case	1 (50%)	-	1 (0.6%)
Unknown / not specified	7 (58.33%)	5 (41.67%)	12 (7.7%)

Table 3: Susceptibility and resistance pattern (in percentage) of various antibiotics

Antibiotics	Sensitive (%)	Resistant (%)
Penicillin	100	-
Ampicillin	100	-
Cefazolin	100	-
Ceftriaxone	100	-
Ciprofloxacin	100	-
Levofloxacin	98.7	1.3
Erythromycin	66.7	33.3
Clindamycin	80.1	19.9
Vancomycin	100	-
Linezolid	100`	-

Discussion

Group B Streptococcus (GBS) also known as *Streptococcus agalactiae,* belongs to Group B of the Rebecca Lancefield classification of *Streptococci*. It is a Gram-positive cocci which is beta-haemolytic on blood agar, catalase negative and a facultative anaerobe. GBS was considered to be a veterinary pathogen as it caused bovine mastitis in dairy cows [4]. Its surrounded by a polysaccharide capsule and further subclassified into 10 serotypes (Ia, Ib, II–IX). Various virulence factors play role in the pathogenesis of GBS infection, but the most important are the capsular polysaccharide which is rich in sialic acid, and a pore-forming toxin, β-hemolysin. Capsular polysaccharide helps GBS to evade host defense mechanisms by interfering with phagocytosis [5,6].

GBS is best known to cause postpartum infection and neonatal sepsis, but it has become an emerging cause of invasive infection in non-pregnant adults also. This multisite population based analysis reveals that all age groups are subjected to GBS infection. GBS is more common to cause bimodal age distribution affecting young and middle aged healthy women secondary to obstetrical manipulation and also elderly persons with pre-existing illness [4].

There is no sexual predilection of *Group B Streptococcal* infection among non-pregnant adults, [4] but in our study the prevalence of GBS was slightly higher in females (53.2%) with a male to female ratio 1.1:1 which corresponds with an active surveillance study by Tyrrell G J et al. [7] Previous studies by Lee N Y et al. [8] and Tazi A et al. [9] demonstrated high male preponderance of invasive GBS infections in adults.

In the current study the incidence was higher in older patients of (50-64) years age group followed by ≥ 65 years which are similar to previous reports [9,10]. GBS disease among non-pregnant adults are not well understood as it is said that underlying comorbidities resulting in defective phagocytic function and altered integrity of anatomical barriers with age promote GBS invasion [11]. In support of the previous findings [2], diabetes mellitus (42.4%) had a higher prevalence followed by surgical procedures (16.7%) and carcinoma (15.2%) in the present study.

Many studies have described GBS as a causative agent of skin and soft tissue infections, respiratory infections, sepsis, meningitis, endophthalmitis and urinary tract infections especially in women [2,10,11]. In the current study the most common presenting symptom was urinary tract infection (65.4%) followed by skin and soft tissue infection (32.7%) and bacteremia (1.9%) without any focus which is in agreement with previous reports [12]. Urinary tract infection was more common in female 68 (66.67%) whereas skin and soft tissue infection was more common in male patients 31 (75.60%) in our study which was found to be highly significant statistically (p value <0.0001). As GBS can colonize

in women urethra the prevalence of UTI was higher in women 66.7% (68/102) compared to men 33.3% (34/102) in the current study. Study of invasive GBS in non-pregnant adults by Tazi A et al., out of total 401 patients revealed most GBS strains were primarily isolated from cases of bacteremia without any focus (43.4%) followed by bone and joint infections (18.7%), skin and soft tissue infections (12%), endocarditis (10.5%), meningitis (5.2%), respiratory tract infections (4%), peritonitis (3.2%) and urinary tract infections (3%) [9].

In our study we did not report any GBS causing meningitis, pneumonia, endocarditis or endophthalmitis cases. In adults though GBS causes low bacteremia without any focus or obvious source but sustained bacteremia may result from infected central venous catheter or endocarditis [4]. Skin and soft tissue infections by *Streptococci agalactiae* may result in fatal prognosis ranging from mild cutaneous ulcers, cellulitis to osteomyelitis and limb amputation which lead to substantial mortality and morbidity in non-pregnant adults [8]. In our study the most common bone and joint infection was osteomyelitis followed by osteoarthritis and knee effusion.

Group B Streptococci causes significant mortality in both neonates and adults but mortality rate is higher in elderly patients with comorbid medical conditions [4]. In the current study the overall mortality rate was 4.5% (7/156) where 3 (42.8%) deaths were attributed to GBS infection. The deaths included 2 men (an 80 years old who died of acute kidney injury and sepsis, and a 58-years old with dilated cardiomyopathy who presented with abdominal cellulitis and died of sepsis) and a 64 years old woman who died of corpulmonale, multi organ dysfunction syndrome and sepsis. The mean interval between positive culture and death was 4 days.

Penicillin is the drug of choice for both prophylaxis and treatment of GBS infections and so far, no resistance has been reported [13]. However, macrolides are the second-line agents and recommended for patients with penicillin allergy [14]. In the current study antimicrobial susceptibility of all 156 isolates showed susceptibility to ampicillin, cephalosporins, penicillin, and vancomycin (all being 100% susceptibility) despite increasing antibiotic use which is consistent with other published reports [7,9,15,16].

Correlating with previous studies, [9,16] resistance to erythromycin and clindamycin were common being 52 (33.3%) and 31 (19.9%) in our study. Matsubara K and Yamamoto G reported 2% and 3% erythromycin and clindamycin resistance, respectively in their study of invasive *Group B streptococcal* infections [15]. In a study of prevalence of macrolide resistance in invasive and noninvasive *Group B Streptococcus* isolates, erythromycin resistance was present in 8% of strains, with 4.5% resistance to clindamycin [14]. The most common macrolide resistance mechanisms in *Streptococci* are ribosomal modification by a methylase encoded by an *erm* [17] gene and drug efflux by a membrane-bound protein encoded by a *mef* gene [18]. The prevalence of levofloxacin resistance was low 2 (1.3%) and none of the *Group B Streptococcus* isolates showed resistance to ciprofloxacin and levofloxacin in our study. Further serotyping of GBS isolates and determination of the MIC (Minimum Inhibitory Concentration) value of antimicrobial agents could have helped to target a specific vaccine candidate.

Conclusion

The increasing rates of GBS infections needs an evaluation of risk factors and development of an antibiotic policy to successfully treat GBS infections and minimize its life threatening complications and emergence of resistant strains.

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