

Analysis of Pyelonephritis-Associated Beta Hemolytic Streptococcus in Japan

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Abstract

Pyelonephritis is an inflammation of the kidney tissue, calyces, and renal pelvis. It is commonly caused by bacterial infection that has spread up the urinary tract. Common bacteria are *Escherichia coli* and *Enterococcus faecalis*. Beta hemolytic streptococci also cause pyelonephritis. Beta hemolytic streptococcus such as *Streptococcus agalactiae*, and *S. dysgalactiae subsp. equisimilis*, when grown on blood-agar, produce complete hemolysis around each colony, usually cause severe infections including many cases of cellulitis, pneumonia, meningitis and sepsis. However the analysis of pyelonephritis causing beta hemolytic streptococcus has seldom been investigated. In this study, we tried to clarify the relationship between beta hemolytic streptococcus and pyelonephritis patient in Japan. We investigated beta hemolytic streptococcus isolated from pyelonephritis patient at two tertiary care hospitals in the central region of Japan by analyzing the background and antimicrobial susceptibility of beta hemolytic streptococcus. We recovered total sixteen beta hemolytic streptococcus in nine years. In pyelonephritis patients, beta hemolytic streptococcus was isolated from 9 *S. agalactiae* and 7 *S. dysgalactiae subsp. equisimilis*, respectively. The numbers of streptococci from female patients were more than those from male patients. Bacteria were not isolated from under 30 year patients. All *S. dysgalactiae subsp. equisimilis* were isolated from 60-year-age patients. About one fifth of beta hemolytic streptococcus had erythromycin and minocycline-resistant ability. Four beta hemolytic streptococci that were all *S. agalactiae*, had levofloxacin-resistant ability. Only one *S. agalactiae* had trimethoprim-sulfamethoxazole-resistant ability. Ampicillin was effective against all beta hemolytic streptococci. In our results, beta hemolytic streptococcus caused pyelonephritis in aged people and the quarter of these bacteria had some antibiotics resistance.

Keywords

Beta Hemolytic Streptococcus, Pyelonephritis, *S. agalactiae*, *S. dysgalactiae subsp. equisimilis*, Antimicrobial Susceptibility

1. Introduction

Beta hemolytic streptococci are gram-positive bacteria that are mainly involved in *S. agalactiae*, *S. dysgalactiae subsp. equisimilis*, and *S. pyogenes* [1]. As they exist in the part of the commensal flora such as throat, genital and lower gastrointestinal tracts [2], they also cause most of the acute severe infections including many cases of cellulitis, pneumonia, meningitis and sepsis [3] [4]. Especially, they have been recognized as emerging infection in aged people under medical control (mainly malignancy and diabetes mellitus) [5]. This trend might be explained because of increasing number of patients with chronic medical conditions [6]. The increase of drug resistant rate in beta hemolytic streptococcus has also been reported over the last 20 years [7]. The loss of efficacy of erythromycin and clindamycin expressed the increasing rates of resistance in *S. agalactiae* and *S. dysgalactiae subsp. equisimilis* [3] [4].

Acute pyelonephritis is one of the most common diseases of the kidney. It is a bacterial infection causing inflammation of renal system [8]. Symptoms usually include fever, flank pain, nausea, vomiting, burning on urination, increased frequency, and urgency. The main cause of acute pyelonephritis is *Escherichia coli* and *Enterococcus faecalis* [8] [9]. Acute pyelonephritis in the United States is found at a rate of about 16 cases per 10,000 females and about 4 cases per 10,000 males annually [8] [10]. Young sexually active women are the patients that are most often affected by acute pyelonephritis [8]. Despite pyelonephritis improving in most cases, there is still significant morbidity and mortality that can be associated with severe cases of pyelonephritis [8] [11]. Some case reports about beta-hemolytic streptococcus related pyelonephritis demonstrated that pyelonephritis causes pseudohyperaldosteronism, spinal epidural abscess, hemolytic anemia, and acute nephritis [12] [13] [14] [15]. However, the comparative analysis of pyelonephritis by beta hemolytic streptococci has seldom been performed.

The present study was conducted to find out the recent clinical characteristics of pyelonephritis associated beta hemolytic streptococcus isolated at two tertiary care hospitals in the central of Japan.

2. Materials and Methods

2.1. Strains and Clinical Data Collection

Bacteria were obtained from aseptically specimens at Japanese Red Cross Nagoya Daiichi Hospital and Japanese Red Cross Nagoya Daini Hospital from 2010 to 2018. Japanese Red Cross Nagoya Daiichi Hospital and Japanese Red Cross

Nagoya Daini Hospital are 852-bed and 812-bed tertiary care hospitals in the central region of Japan, respectively. We used medical records appended to clinical species for the analysis of clinical feature at two tertiary care hospitals. Pyelonephritis was diagnosed by medical doctor such as urologist. It was also involved in bacterial isolation from both blood and urine. We considered several isolates from the same region of the same patient as one isolate per one patient for the analysis in this study. All streptococcus isolates were identified by standard conventional biochemical methods and confirmed by 16S ribosomal DNA sequence analysis as described elsewhere [3] [4] [16]. Our experimental design was approved by the ethics committee at both hospitals.

2.2. Antimicrobial Susceptibility Analysis

Beta hemolytic Streptococcus isolates were examined for typical five antibiotic susceptibilities as ampicillin, erythromycin, minocycline, levofloxacin, and trimethoprim-sulfamethoxazole. Minimal inhibitory concentrations (MICs) were determined by E-test. Evaluation of susceptibilities was calculated based on Clinical Laboratory Standard Institute (CLSI) breakpoint [17].

2.3. Statistical Analysis of the Data

We conducted the statistical analysis with the chi-squared test or Fisher's exact test when appropriate. Differences were considered significant when p was <0.05 .

3. Results

First of all, we evaluated the relationship between pyelonephritis patients' features and beta hemolytic Streptococcus. A total of 16 beta hemolytic Streptococcus (9 *S. agalactiae* and 7 *S. dysgalactiae* subsp. *equisimilis*) were isolated. No *S. pyogenes* was found in this study. Three pyelonephritis associated beta hemolytic Streptococcus in 2011, 2013, and 2017 were isolated (Figure 1). But No beta hemolytic Streptococcus in 2013 were isolated. We did not found any significant differences of periods between *S. agalactiae* and *S. dysgalactiae*. Figure 2 showed that the number of female patients was larger than that of male patients, there was no significant differences between genders ($p = 0.6567$). We did not also found any significant differences between *S. agalactiae* and *S. dysgalactiae* subsp. *equisimilis*. The age range was categorized every 10 years ages in Figure 3. We did not find any patients under 30 year's age (Figure 3). The numbers of over 60 - 69 and 80 - 89 year's patients were largest in this study. Only *S. dysgalactiae* subsp. *equisimilis* were isolated from 60 - 69 and 80 - year's patients. *S. agalactiae* were isolated at a relatively low age. There were no significant differences between ages ($p = 0.3572$). Finally, we analyzed the antimicrobial susceptibility of beta hemolytic Streptococcus (Figure 4). Ampicillin was susceptible against all beta hemolytic Streptococcus. In our study, total erythromycin and minocycline-resistant rate of beta hemolytic Streptococcus were about 19% and 25%, respec-

tively. Same one *S. dysgalactiae subsp. equisimilis* had both erythromycin and minocycline-resistant ability. Total levofloxacin-resistant rate of beta hemolytic Streptococcus were 25%. All levofloxacin resistant beta hemolytic Streptococcus were *S. agalactiae*. Total trimethoprim-sulfamethoxazole resistant rate of beta hemolytic Streptococcus was about 6.3%. At least one *S. agalactiae* isolates had no susceptible activity against trimethoprim-sulfamethoxazole in this study.

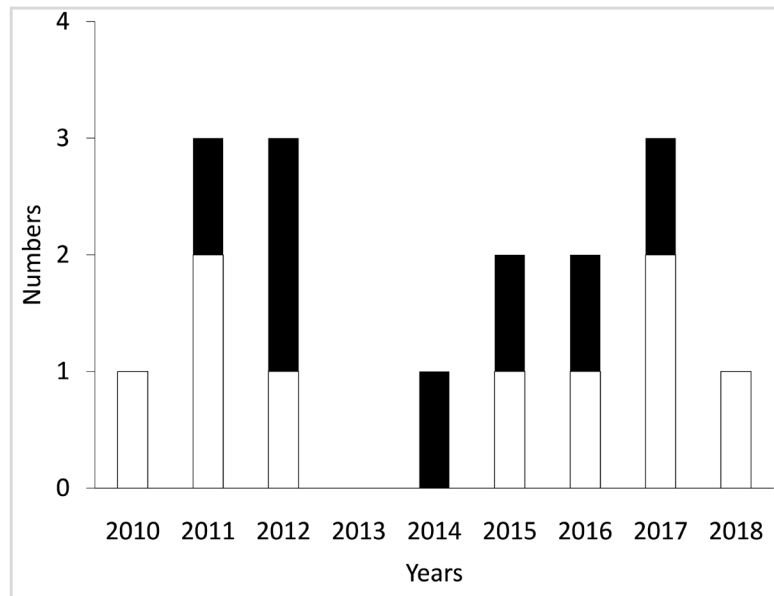


Figure 1. Period distribution of beta hemolytic Streptococcus isolates. White box; *S. agalactiae*. Black box; *S. dysgalactiae subsp. equisimilis*.

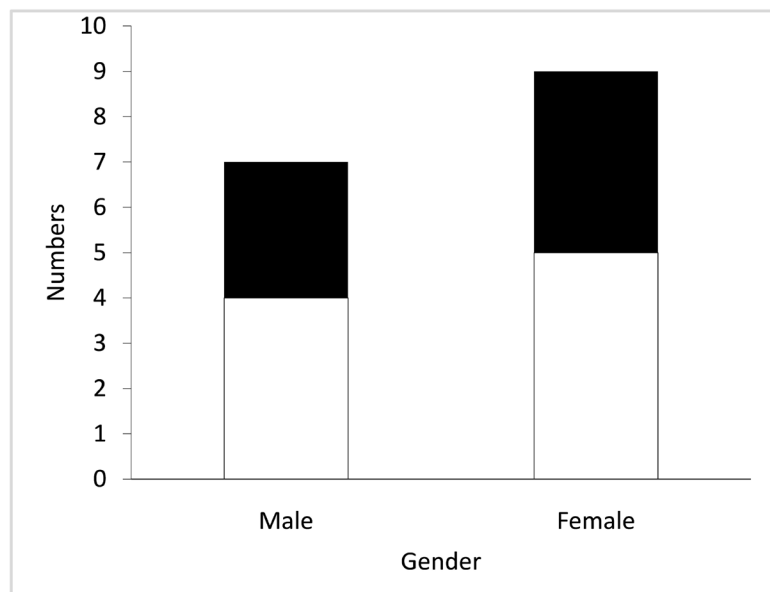


Figure 2. Gender distribution of beta hemolytic Streptococcus isolates. White box; *S. agalactiae*. Black box; *S. dysgalactiae subsp. equisimilis*.

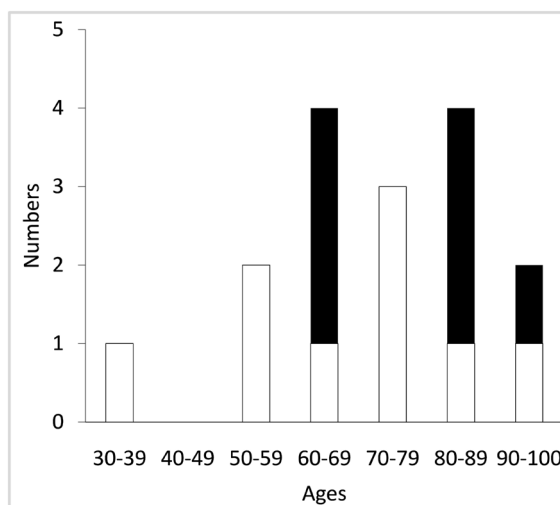


Figure 3. Age distribution of beta hemolytic streptococcus isolates. White box; *S. agalactiae*. Black box; *S. dysgalactiae subsp. equisimilis*.

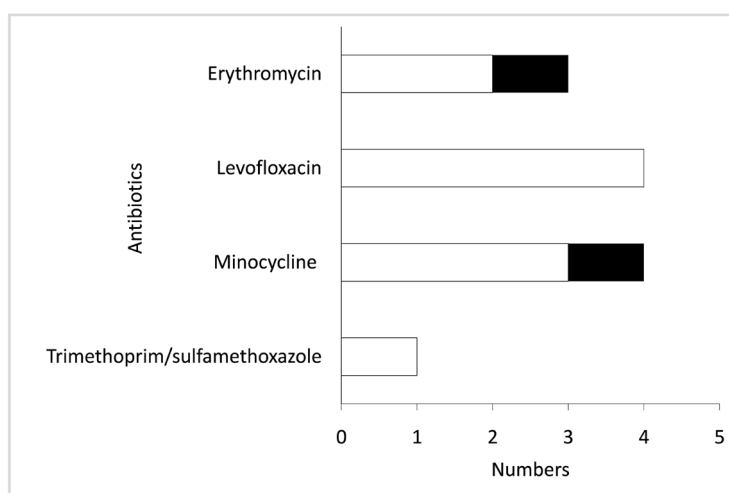


Figure 4. Antimicrobial resistance of beta hemolytic streptococcus isolates. White box; *S. agalactiae*. Black box; *S. dysgalactiae subsp. equisimilis*.

4. Discussion

In this study, we described the clinical characteristics and antimicrobial susceptibility patterns of pyelonephritis-associated beta hemolytic *Streptococcus* isolated from two tertiary care hospitals in the central of Japan among recent 9 years. Although we have little interest of pyelonephritis as compared with other *Streptococcal* disease before, this study may imply that beta hemolytic *Streptococcus* will be important pathogen about pyelonephritis. With respect to gender group, the numbers of isolation in female patients were more than those in male patients. This result is almost consistent with previous report [6]. Next, we clarified *Streptococcus* with age distribution. Although *S. agalactiae* usually causes pyelonephritis in pregnant female, our result showed no pregnant female was involved. As *S. agalactiae* is also popular in neonatal infection, no children oc-

curred pyelonephritis in our study. Our study demonstrated that beta hemolytic Streptococcus frequently caused pyelonephritis in older people. As we have recognized beta hemolytic Streptococcus as serious infectious disease for female and neonate, we may also reevaluate beta hemolytic Streptococcus as pyelonephritis for aged-people. With respect to antimicrobial susceptibility, we did not find any ampicillin non-susceptible beta hemolytic Streptococcus in this study. Indeed, penicillin resistant *S. agalactiae* and *S. dysgalactiae subsp. equisimilis* have not been isolated from invasive disease in Japan before [8] [9]. *S. agalactiae* from female patients with pyelonephritis were resistant to erythromycin and clindamycin [18]. Previous report showed that the macrolide non-susceptible rates of streptococcus was about 30% [3] [4]. The total erythromycin-resistant rate of beta hemolytic Streptococcus was about 19% in our study. Previous report demonstrated that the tetracycline resistant rates of beta hemolytic Streptococcus were about 44% [3] [4]. Our study revealed that minocycline resistant rates of beta hemolytic Streptococcus were 25%. We assumed that antimicrobial resistant rate of erythromycin and minocycline seemed to be slightly lower. Levofloxacin resistant rates of *S. agalactiae* were about 40% in former study [3] [4] [14] [19]. As our study revealed that levofloxacin resistant rates of beta hemolytic Streptococcus were 25%, levofloxacin resistant rates of *S. agalactiae* were about 44%. No *S. dysgalactiae subsp. equisimilis* had levofloxacin resistant ability in this study. As trimethoprim-sulfamethoxazole resistant rate of beta hemolytic Streptococcus was about 6%, trimethoprim-sulfamethoxazole resistant rate of *S. agalactiae* was about 11% in our study. As fluoroquinolone and co-trimoxazole has been widely used genitourinary disease, digestive disease and respiratory disease [20], careful treatment selection is necessary because levofloxacin and trimethoprim-sulfamethoxazole may be not effective for *S. agalactiae* caused pyelonephritis. Although *S. dysgalactiae subsp. equisimilis* are susceptible of levofloxacin, we assume that the change of fluoroquinolone resistance among beta hemolytic Streptococcus spread worldwide gradually. There are some limitation in this study. As we did not perform genetic analysis of bacteria such as emm typing, we did not clarify the relationship between bacterial virulent genes and clinical features. Although there are few results with significant differences in this study, this seems to be problematic in the small number of samples investigated. From these views, we considered the further necessity of the analysis of beta hemolytic Streptococcus strains from pyelonephritis.

5. Conclusion

In summary, we clarified the characteristics of pyelonephritis-associated beta hemolytic streptococcus in two tertiary care hospitals in the central of Japan. Although several antibiotics such as penicillin are effective against beta hemolytic streptococcus, incidence of invasive Streptococcus infection such as pyelonephritis is not significant decreasing. The results from our study suggest the need for further epidemiological surveillance of antibiotic resistant pathogen.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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