

# Trend of Respiratory Tract-Associated *Streptococcus dysgalactiae* Subsp. *Equisimilius* at General Japanese Hospital from 2013 to 2015

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## Abstract

*Streptococcus dysgalactiae* subsp. *equisimilius* are pathogenic bacteria which cause various infectious diseases from acute pharyngitis to streptococcal toxic shock syndrome. Although *Streptococcus dysgalactiae* subsp. *equisimilius* infection has been increasing recently, the recent characteristic investigation of respiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilius* has not been performed in Japan. In this study, we analyzed the relationship between respiratory tract and norespiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilius* by investigating the recent clinical characteristics and antimicrobial susceptible patterns of 98 *Streptococcus dysgalactiae* subsp. *equisimilius* isolated during 2013-2015 in Japan. There was significant difference of gender between respiratory tract and no respiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilius*. No *Streptococcus dysgalactiae* subsp. *equisimilius* from no respiratory tract were found under 18 years-old patients. The prevalence of clindamycin non susceptible *Streptococcus dysgalactiae* subsp. *equisimilius* isolates from respiratory tract was significant greater than those from non-respiratory tract. We also analyzed the relationship between respiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilius* and *Streptococcus pyogenes* in 2014. There was no significant difference of gender between *Streptococcus dysgalactiae* subsp. *equisimilius* and *Streptococcus pyogenes*. The numbers of *Streptococcus pyogenes*-infected patients were significantly greater than those of *Streptococcus dysgalactiae* subsp. *equisimilius*-infected patients in children from 1 to 18 years old. From antimicrobial resistance, we found that the numbers of clarithromycin resistant *Streptococcus pyogenes* were greater than those

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of clarithromycin resistant *Streptococcus dysgalactiae* subsp. *equisimilius* among respiratory tract isolation. Our results suggest that the clinical and antimicrobial susceptible patterns are useful for screening the respiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilius* infection.

## Keywords

*Streptococcus dysgalactiae* subsp. *equisimilius*, Susceptibility, Antimicrobial Resistance, Epidemiology

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## 1. Introduction

Most  $\beta$ -hemolytic streptococcus from human are categorized as *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus dysgalactiae* subsp. *Equisimilis* [1]. In contrast to *Streptococcus pyogenes* and *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis* had been long considered as commensal organisms that have low virulence as opportunistic pathogens [2]. In 1996, *Streptococcus dysgalactiae* subsp. *Equisimilis* was proposed to be a new streptococcal taxon [3]. It has also been reported to cause a wide variety of human infections such as pharyngitis, cellulitis, sepsis, meningitis, endocarditis, and streptococcal toxic shock syndrome (STSS) [4].

*Streptococcus dysgalactiae* subsp. *equisimilis* have many virulence factors shared with *Streptococcus pyogenes*, such as M protein, streptolysin O, streptolysin S, streptokinase, and streptococcal inhibitory of complement lysis [5] [6]. Although *Streptococcus dysgalactiae* subsp. *equisimilis* infection has been increasing recently [7] [8], the recent characteristic investigation of respiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilis* has not been performed in Japan [9] [10]. The present study was conducted to find out the relationship between respiratory tract and no respiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilis* by investigating the recent clinical characteristics and antimicrobial susceptible patterns of *Streptococcus dysgalactiae* subsp. *equisimilis* isolated in Japan.

## 2. Materials and Methods

### 2.1. Strains and Clinical Data Collection

A total of 98 *Streptococcus dysgalactiae* subsp. *equisimilius* from 2013 to 2015 and 161 *Streptococcus pyogenes* from 2014 was obtained at Daido Hospital. Daido Hospital is a 404-bed private general hospital in the central region of Japan. We used medical records appended to clinical species for the analysis of clinical feature at Daido Hospital. 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 or the VITEK2 system (bioMérieux, Durham NC, USA). Our experimental design was approved by the ethics committee at Daido hospital.

## 2.2. Antimicrobial Susceptibility Analysis

*Streptococcus dysgalactiae* subsp. *equisimilis* and *Streptococcus pyogenes* isolates were examined for 15 antibiotic susceptibilities as follows sulbactam/ampicillin, piperacillin, amoxicillin, cefotiam, flomoxef, ceftazidime, ceftriaxone, vancomycin, fosfomicin, panipenem, meropenem, clarithromycin, clindamycin, minocycline, ciprofloxacin. Minimal inhibitory concentrations (MICs) were determined at clinical laboratory in Daido Hospital using broth micro dilution methodology with the VITEK2 system. Evaluation of susceptibilities was calculated based on Clinical Laboratory Standard Institute (CLSI) break point [11].

## 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 confirmed that all *Streptococcus dysgalactiae* subsp. *equisimilis* and *Streptococcus pyogenes* isolates had beta hemolytic activity in this study. Next, we compared the differences between respiratory tract and no respiratory tract isolates in this study. Respiratory tract isolates were defined as isolation from pharynx, nasal discharge, tonsillar, and sputum. After that, we compared the differences of clinical and bacteriological features between respiratory tract and no respiratory tract isolations in this study. Firstly, we analyzed the relationship between respiratory tract and no respiratory tract related *Streptococcus dysgalactiae* subsp. *equisimilis*. Total ninety-eight were isolated among which 53 were from respiratory tract and 45 were from non-respiratory tract. **Table 1** demonstrated the comparative analysis of *Streptococcus dysgalactiae* subsp. *equisimilis* between respiratory tract and no respiratory tract. Ninety-eight *Streptococcus dysgalactiae* subsp. *equisimilis* were isolated among which 36 were from male and 17 were from female. The numbers of males in respiratory tract disease were significantly greater than those of males in no respiratory tract disease ( $p = 0.04$ ). The age incidences among 0 - 1 and among 1 - 18 years age group were 11 (11.2%) and 17 (17.3%), respectively. These were only isolated from respiratory tract disease. The age incidence among 19 - 64 years age group, 17(17.3%) [respiratory tract-4, no respiratory tract-13], and in over 65-years, it was 53 (54.1%) [respiratory tract-21, no respiratory tract-32]. Furthermore the numbers of aged-patient were significantly increasing gradually both respiratory and no respiratory disease ( $p = 0.04$ ). The results of antimicrobial susceptible patterns of *Streptococcus dysgalactiae* subsp. *equisimilis* isolates against four antibiotics were shown in **Table 1**. Because other antibiotics were the most active antibiotics with 100% susceptible rates against *Streptococcus dysgalactiae* subsp. *equisimilis* and *Streptococcus pyogenes*. Although there were no significant differences of three antimicrobial (clarithromycin, minocycline, ciprofloxacin) susceptibility between respiratory tract and no respiratory tract *Streptococcus dysgalactiae* subsp. *equisimilis*, the prevalence of clindamycin resistant from respiratory

tract was significant greater than that from no respiratory tract ( $p = 0.02$ ). We next analyzed the relationship between respiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilis* and *Streptococcus pyogenes*. Because *Streptococcus pyogenes* are more popular than related *Streptococcus dysgalactiae* subsp. *equisimilis* in terms of respiratory tract pathogen. **Table 2** demonstrated the comparative analysis between *Streptococcus dysgalactiae* subsp. *equisimilis* isolates and *Streptococcus pyogenes* from respiratory tract. There was no significant difference of gender between *Streptococcus dysgalactiae* subsp. *equisimilis* and *Streptococcus pyogenes*. Both bacteria were isolated

**Table 1.** Clinical characteristics between respiratory tract and non-respiratory tract *Streptococcus dysgalactiae* subsp. *equisimilis*.

		Respiratory tract			Norespiratory tract		
		2013 (n = 29)	2014 (n = 14)	2015 (n = 10)	2013 (n = 14)	2014 (n = 21)	2015 (n = 10)
Gender	Male	17	10	9	4	14	3
	Female	12	4	1	10	7	7
Age	0 - 1	7	3	1	0	0	0
	1 - 18	11	2	4	0	0	0
	19 - 64	2	2	0	2	5	6
	65-	9	7	5	12	16	4
No-susceptibility	Clarithromycin	8	6	3	2	6	2
	Clindamycin	8	4	2	1	1	1
	Ciprofloxacin	10	4	1	7	9	1
	Monocycline	3	4	3	1	3	3

**Table 2.** Clinical characteristics between respiratory tract *Streptococcus dysgalactiae* subsp. *equisimilis* and respiratory tract *Streptococcus pyogenes*.

		<i>Streptococcus pyogenes</i> (%)	<i>Streptococcus dysgalactiae</i> subsp. <i>equisimilis</i> (%)
Gender	Male	66.2	71.4
	Female	33.8	28.6
Age	0 - 1	4.4	21.4
	1 - 18	89.7	14.3
	19 - 64	3.7	14.3
	65-	2.2	50
No-susceptibility	Clarithromycin	66.9	42.9
	Clindamycin	27.9	28.6
	Ciprofloxacin	33.8	28.6
	Mnocyline	18.4	28.6

from more male than female. The numbers of *Streptococcus pyogenes*-infected patients were significantly greater than those of *Streptococcus dysgalactiae* subsp. *equisimilis*-infected patients in children from 1 to 18 years old ( $p < 0.01$ ). Clarithromycin was less antimicrobial effective in respiratory tract disease than in no respiratory tract disease significantly ( $p < 0.01$ ). Because the numbers of *Streptococcus pyogenes* were also significantly greater than those of *Streptococcus dysgalactiae* subsp. *equisimilis* according to clarithromycin-resistance. However, the numbers of *Streptococcus dysgalactiae* subsp. *equisimilis* tended to be greater than those of *Streptococcus pyogenes* according to minocycline-resistance. There were no significant differences of other three antibiotics between respiratory tract and no respiratory tract isolation.

#### 4. Discussion

In this study, we described the characteristics of respiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilis* isolates at general hospital in the central of Japan from 2013 to 2015. We found the numbers of bacteria from respiratory tract were about 1.2 times as same as those from no respiratory tract. In the analysis of gender, we did not find any significant differences of gender in our previous report [8]. However, the numbers of *Streptococcus dysgalactiae* subsp. *equisimilis* isolated from male were greater than those from female in current study. We also clarified *Streptococcus dysgalactiae* subsp. *equisimilis* with age distribution. The previous our study showed that the numbers of *Streptococcus dysgalactiae* subsp. *equisimilis* isolated from children (1 to 10 year-old) and elder people (over 65 year-old) were most popular. However, the numbers of no respiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilis* isolated from elder people (over 65 year-old) were most popular [8]. In the analysis of antimicrobial susceptibility, previous our study demonstrated that the prevalence of clarithromycin resistant, clindamycin resistant, minocycline-resistant, and ciprofloxacin-resistant *Streptococcus dysgalactiae* subsp. *equisimilis* were 37%, 23%, 25%, and 55%, respectively. In our current study, we showed that the prevalence of clarithromycin resistant, clindamycin resistant, minocycline resistant, and ciprofloxacin resistant *Streptococcus dysgalactiae* subsp. *equisimilis* were 28%, 17%, 17%, and 33%, respectively. From those results, we suggested that the four antimicrobial resistant rate of *Streptococcus dysgalactiae* subsp. *equisimilis* were gradually decreasing. As macrolide is popular for treatment of respiratory infection disease in Japan [6] [9], the macrolide-resistant rate of *Streptococcus pyogenes* were increasing gradually [10]. Although both *Streptococcus pyogenes* and *Streptococcus dysgalactiae* subsp. *equisimilis* have beta-hemolytic activity, there were differences of the trend of antimicrobial susceptibility between *Streptococcus dysgalactiae* subsp. *equisimilis* and *Streptococcus pyogenes*. Further investigation about this point will be needed. Furthermore, we did not find any penicillin and cephalosporin-resistant *Streptococcus dysgalactiae* subsp. *equisimilis* in both our previous and current studies [8]. However, four incidents of penicillin-resistant *Streptococcus dysgalactiae* subsp. *equisimilis* isolated from blood cultures of three patients were reported in Denmark [12]. Thus, we need further antimicrobial surveil-

lance to prevent the spread of penicillin-resistant *Streptococcus dysgalactiae* subsp. *equisimilis*. Our results suggest that the clinical and antimicrobial susceptible pattern are useful for screening the respiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilis* infection. Further continuous epidemiological analysis is needed for the clarification of several problems about respiratory tract associated *Streptococcus dysgalactiae* subsp. *equisimilis*.

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