



Original Article

Variations in antibiotic susceptibility of group B *Streptococcus* in Japanese women: A long-term population-based cohort studyYousuke Gomi ^a, Liangcheng Wang ^{a, b, *, 1}, Hisashi Matsushima ^c, Ayaka Kawabe ^a, Atsuko Kikugawa ^a, Akiyoshi Takagi ^a, Kenichi Kuromaki ^a^a Department of Obstetrics and Gynecology, Warabi City Hospital, Saitama, Japan^b Department of Obstetrics and Gynecology, Saitama Medical Center, Jichi Medical University, Japan^c Department of Clinical Laboratory Center, Warabi City Hospital, Saitama, Japan

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ABSTRACT

Objective: To investigate the long-term antibiotic susceptibility of group B *Streptococcus* (GBS) present in the vagina.**Materials and methods:** A population-based retrospective cohort study was performed. A total of 19,899 women who underwent vaginal swab examination between 2005 and 2017 was enrolled. Specimens were cultured on modified Drigalski agar, blood agar, and chocolate agar media. Antibiotic susceptibilities of GBS were assessed using eight antibiotics, namely penicillin-G (PC-G), cefotiam (CTM), cefditoren (CDTR), ceftriaxone (CTRX), meropenem (MEPM), chloramphenicol (CP), levofloxacin (LVFX), and azithromycin (AZM), by the broth microdilution method when GBS was positive in the culture. The main outcome was antibiotic sensitivity based on the culture results.**Results:** GBS was 100% susceptible to PC-G, CTM, CTRX, CDTR, and MEPM. However, the susceptibility trend showed a considerable decrease for CP (99%–81%), LVFX (91%–70%), and AZM (87%–57%).**Conclusions:** Our study demonstrated a significant decrease in the antibiotic sensitivity of GBS in Japan in the past 13 years. Based on these results, current policies on antibiotic resistance of GBS in maternal and neonatal care may need to be reassessed.© 2019 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Group B *Streptococcus* (GBS; *Streptococcus agalactiae*) is a major causative organism of meningitis, pneumonia, and septicemia in neonates. GBS-associated neonatal sepsis was first described in 1964 [1]. In 1971, GBS was recognized as normal flora in the maternal birth canal that could infect neonates [2]. Since 1996, the US guidelines for prevention of early-onset group B streptococcal disease have recommended that vaginal and rectal swab examinations should be performed for all pregnant women at 35–37 weeks of gestation, and the perinatal management should be based on the bacterial examination results [3,4]. Early onset GBS infection in neonates is currently rarely observed in developed countries

because routine prenatal screening for GBS and prophylactic antibiotic administration during labor are standard procedure.

However, recently, a new concern has been raised that such universal prenatal screening may increase the risk of unfavorable perinatal outcomes, such as anaphylaxis and nosocomial infections, caused by long-term use of prophylactic antibiotics in the labor and neonatal period, and lead to an increase in antibiotic-resistant organisms owing to unnecessary antibiotic administration to large populations. Therefore, in 2017, the National Institute for Health and Care Excellence (NICE) guidelines in the UK documented that routine prenatal screening of GBS should not be introduced into practice in the UK [5,6]. The evidence to support the NICE guidelines of abandoning GBS screening for low-risk pregnant women was that in the UK, clindamycin and erythromycin (EM) resistance rates increased from 8% to 18% and 15%–23%, respectively, between 2010 and 2014 [7].

Despite similar short-term studies on antibiotic susceptibility of GBS being reported [8], long-term research on antibiotic susceptibility of GBS is required to determine whether the present policy on

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GBS screening requires any alteration. If a trend of decrease in antibiotic sensitivity of GBS is found during an observed long-term period, the evidence of risk of occurrence of multiple drug-resistant GBS in near future is established, strongly supporting that current policies on antibiotic resistance of GBS in maternal and neonatal care require urgent reassessment, as recommended by the NICE guidelines. Thus, this study aimed to investigate the antibiotic susceptibility of GBS by analysis of swab examination results accumulated at our hospital for the past 13 years.

Materials and methods

This study was approved by the Ethics Review Board of the Warabi City Hospital, Saitama, Japan. Informed consent from patients was waived because of the retrospective nature of this study. We retrieved data from vaginal bacterial reports from 2005 to 2017, calculated the prevalence rate of GBS, and evaluated the drug susceptibility of GBS during the study period.

At our hospital, vaginal swabs of non-pregnant women with suspected vaginitis, pregnant women in the first trimester, and women with preterm membrane rupture were obtained. Swabs were obtained from both the vagina and rectum of pregnant women at 34–36 weeks of gestation. All specimens were cultured on modified Drigalski agar, blood agar, and chocolate agar media at 35 °C for 48 h. Susceptibilities of GBS to eight antibiotics, namely penicillin-G (PC-G), cefotiam (CTM), cefditoren (CDTR), ceftriaxone (CTRX), meropenem (MEPM), chloramphenicol (CP), levofloxacin (LVFX), and azithromycin (AZM), were routinely investigated for all cases, regardless of pregnancy, when GBS culture was positive. The broth microdilution method was used for testing antibiotic susceptibility according to the Clinical and Laboratory Standard Institute (CLSI) guidelines [9]. In this study, antibiotic susceptibility was defined as the percentage of sensitive organisms in the total population.

Results

We retrieved 28,906 medical records accumulated during the study period. After excluding multiple records from the same individuals annually, 19,899 records were obtained. The prevalence of vaginal GBS colonization was 11.6% (2307/19,899) in Japanese women (Table 1). Antibiotic susceptibilities of GBS to PC-G, CTM, CTRX, CDTR, and MEPM were 100%. However, during the past 13 years, the susceptibility trend considerably decreased from 99% to

81% for CP, 91%–70% for LVFX, and 87%–57% for AZM (Table 1) (Fig. 1).

Discussion

In this study, we assessed the long-term antibiotic susceptibility of vaginal GBS in pregnant and non-pregnant Japanese women and found that the susceptibility to some antibiotics decreased over time, causing a potential public health issue in maternal and neonatal care.

Several studies have demonstrated that antibiotic-resistant GBS may result from long-term exposure of antibiotics in hospitals [10,11]. Despite 100% sensitivity to PC-G, our study indicates that vaginal GBS isolates resistant to CP, LVFX, and AZM have increased considerably during the 13-year study period. In Japan, the clinical use of quinolones started in the 1980s and was found to be very effective for treating streptococcal or chlamydial infections. However, in the mid-1990s, quinolone-resistant *Streptococcus pneumoniae* and *Streptococcus pyogenes* were subsequently reported. Kawamura et al. first reported quinolone-resistant GBS in 2003 [12]. Consistent with our results, the sensitivity rate for quinolone

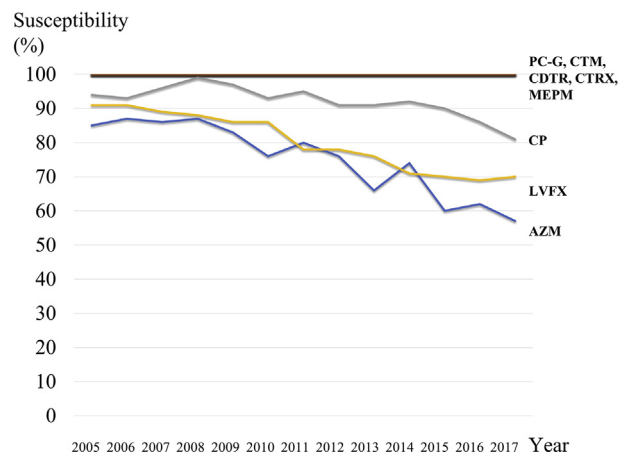


Fig. 1. Variations in antibiotic susceptibility of group B *Streptococcus* (GBS). Antibiotic susceptibility of GBS to PC-G, CTM, CTRX, CDTR, and MEPM is 100%, but significantly decreases from 99% to 81% for CP, 91%–70% for LVFX, and 87%–57% for AZM during the study period. AZM, azithromycin; CDTR, cefditoren; CP, chloramphenicol; CTM, cefotiam; CTRX, ceftriaxone; GBS, group B *Streptococcus*; LVFX, levofloxacin; MEPM, meropenem; PC-G, penicillin-G.

Table 1
Prevalence rate and antibiotic susceptibilities of GBS during 2005–2017.

Year	Total swabs	Individual	GBS isolates	GBS culture-positive rate (%)	Antibiotic susceptibilities							
					PC-G	CTM	CTRX	CDTR	MEPM	CP	LVFX	AZM
2005	1532	1093	107	13.4	100	100	100	100	100	94	91	85
2006	1714	1149	151	13.1	100	100	100	100	100	93	91	87
2007	1777	1244	140	11.3	100	100	100	100	100	96	89	86
2008	2032	1378	125	9.1	100	100	100	100	100	99	88	87
2009	2548	1697	216	12.7	100	100	100	100	100	97	86	83
2010	2528	1752	202	11.5	100	100	100	100	100	93	86	76
2011	2579	1777	244	13.7	100	100	100	100	100	95	78	80
2012	2459	1707	188	11.0	100	100	100	100	100	91	78	76
2013	2189	1494	161	10.8	100	100	100	100	100	91	76	66
2014	2307	1531	197	12.9	100	100	100	100	100	92	71	74
2015	2337	1651	166	10.1	100	100	100	100	100	90	70	60
2016	2547	1744	195	11.2	100	100	100	100	100	86	69	62
2017	2357	1682	215	12.8	100	100	100	100	100	81	70	57
Total	28,906	19,899	2307	11.6								

AZM, azithromycin; CDTR, cefditoren; CP, chloramphenicol; CTM, cefotiam; CTRX, ceftriaxone; GBS, group B *Streptococcus*; LVFX, levofloxacin; MEPM, meropenem; PC-G, penicillin-G.

rapidly decreased in 15 years. Similarly, the rate of macrolide-resistant GBS that was resistant to EM and AZM also increased worldwide [7,13–15]. However, there is no report on CP-resistant GBS in the literature. Thus, CP resistance may be caused by the very frequent use of vaginal CP in obstetrics and gynecology departments for treating bacterial vaginitis, thereby threatening preterm labor caused by bacterial vaginosis in Japan.

Prenatal prophylactic administration of penicillin is performed worldwide since 1996 as it was recommended by the Centers for Disease Control to prevent early onset neonatal GBS infections. In Japan, according to the obstetrics guidelines [16], maternal penicillin/ampicillin administration during labor is recommended as the first-choice treatment for preventing neonatal GBS infection. However, in 2008, Kimura et al. reported that GBS with reduced penicillin susceptibility (PRGBS) was identified in Japan [17]. The isolation rate of PRGBS reportedly increased from 2002 to 2012 [18]. Although there are no reports of neonatal infections caused by PRGBS to date, whether PRGBS or other antibiotic-resistant GBS will continue to increase in future is a concern if the current universal perinatal policy remains immovable. Since obvious trends in the increase in antibiotic-resistant GBS and PRGBS cases are being reported, the possibility of multiple drug-resistant GBS infections, which cannot be treated by any antibiotics, could emerge in the very near future if further preventive action is not taken.

Currently, determining the best policy for an obstetrician to prevent GBS infection in neonates is important and raises questions on the way forward. Virranniemi et al. reported that GBS could be detected with the highest sensitivity and specificity by culture within 7 days prior to labor [19]. Therefore, culture obtained much closer to the delivery may aid in preventing unnecessary use of antibiotics. Real-time polymerase chain (rt-PCR) is another option to detect GBS in emergency [20]. However, the use of rt-PCR entails a high cost per screening. If the prophylactic antibiotic administration needs to be suspended in low-risk pregnant women during labor onset, as recommended by NICE, a strict alternative management policy, including indication of antibiotics administration on rupture of membrane or prolonged labor to prevent unexpected intrauterine infection, is required without question. To prevent a national-wide increase in the incidence of antibiotic-resistant GBS, the indication of antibiotics, such as AZM and vaginal CP administration, should be more strictly restricted. To prevent iatrogenic infection during obstetrics and gynecological examination, careful vaginal ultrasound probe cleaning after each use should be considered [21]. To detect and evaluate the rate of PRGBS, PRGBS-sensitive agar, such as ceftibuten-containing agar, may be reliable to detect GBS in the future [22]. Continuous further studies and discussion are required to resolve these disputes.

This study has some limitations. All swabs in the present retrospective study were obtained from pregnant women routinely and most non-pregnant women with clinical suspicion of bacterial vaginitis. Therefore, all age ranges were included. However, demographic information of pregnant/non-pregnant women was not available because pregnancy status of swab records was not retrievable. The prevalence of GBS in the present study may be different to the prevalence obtained from a normal distribution-based population, especially in reproductive-aged women. However, since there is no study that indicates a different prevalence rate of antibiotic-resistant GBS between pregnant women and non-pregnant women, we believe that the results of our study can be an appropriate reference for perinatal GBS policy.

Conclusion

Our study demonstrated a considerable decrease in antibiotic susceptibility of GBS in Japan during the past 13 years. The current

universal perinatal GBS policy may require reassessment in the near future, and a national-wide, and even worldwide, discussion on the issue is urgently necessary.

Conflicts of interests

The authors have no conflicts of interest relevant to this article.

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