Infection with Group B Streptococcus (GBS), also known as Streptococcus agalactiae, may cause invasive diseases with high mortality (1). Particularly, GBS serotypes IV and VI have been implicated in invasive diseases and reported to have a high prevalence of macrolide resistance (2,3). Increasing resistance of GBS to quinolones and macrolides has also been reported worldwide (4,5). GBS infection is associated with high mortality in elderly people, pregnant women, neonates, and those with comorbidities (1); however, to our knowledge, no data till date suggests that quinolone and macrolide resistance in GBS infection increases the mortality risk. Quinolones and macrolides constitute approximately 50% or more of all oral antibiotics consumed in Japan (6), and the rate of quinolone and macrolide resistance in GBS isolates has been reported to be as high as 20%–30% (7). Thus, infectious diseases caused by quinolone- and macrolide-resistant GBS may potentially hold some risk of treatment failure. Since GBS serotyping and genome analysis are not routinely performed in the clinical setting, it may be useful to predict the patient outcome based on antibiotic susceptibility. Therefore, in this study, we evaluated whether blood stream infection (BSI) caused by quinolone- or macrolide-resistant GBS is associated with high mortality.

Data regarding patients with bacteremia caused by GBS and antibiotic susceptibility profile of GBS isolates were collected between January 2013 and December 2018 from 7 participating hospitals of Niigata Prefecture, Japan (Kaetsu Hospital, 261 beds; Shinrakuen Hospital, 325 beds; Sado General Hospital, 354 beds; Kashiwazaki General Hospital and Medical Center, 400 beds; Kido Hospital, 312 beds; Niigata City General Hospital, 676 beds; and Agano City Hospital, 250 beds). Duplicate isolates from the same patients in each year were excluded. BSI was defined as GBS infection confirmed by blood culture. The primary outcome was 30-day mortality from any cause. Infections occurring after 48 h or more of hospital admission were defined as hospital-acquired. Quinolone resistance was defined as levofloxacin minimum inhibitory concentration (MIC) >2 mg/L, and macrolide resistance was defined as erythromycin or clarithromycin MIC >0.25 mg/L (8), and both were measured at each hospital. For these definitions, “intermediate” was included in “resistance,” according to the criteria of the Clinical and Laboratory Standards Institute. Chronic kidney disease stages were determined according to the Kidney Disease Outcome Quality Initiative criteria, and the estimated glomerular filtration rate was calculated using the Japanese version of the estimation equations. This study was approved by the Institutional Review Board of each participating hospital and performed in accordance with the ethical guidelines of the Japanese Ministry of Health, Labour, and Welfare.

SUMMARY: The prevalence of quinolone- and macrolide-resistant Group B Streptococcus (GBS) is increasing worldwide, but the relationship between the resistance of GBS to these antibiotics and patient outcome remains unclear. Therefore, we evaluated whether blood stream infection caused by quinolone- or macrolide-resistant GBS is associated with high mortality. Our findings in 77 patients with GBS bacteremia demonstrate that quinolone and macrolide resistance may not be risk factors for 30-day mortality.

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standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Changes in quinolone and macrolide resistance rates in all GBS isolates were analyzed every year. Patient background was then assessed by dividing patients with BSI into 2 groups: with 30-day mortality outcome and without. Finally, multivariable logistic regression analysis was performed to identify the independent risk factors associated with 30-day mortality with odds ratios (ORs) and 95% confidence intervals (CIs). Explanatory variables were selected for quinolone and macrolide resistance, and significant patient characteristics (P ≤0.1) were classified based on 30-day mortality. The primary sites of infection found to have low association with 30-day mortality in this study, such as urinary tract, skin and soft tissue, central nervous system, pulmonary, and pregnancy related infections, were summed as reference infections in the logistic regression analysis because of several explanatory variables. All analyses were performed using R 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria), with P-value <0.05 considered statistically significant.

The isolation rate (number of resistant bacteria/total number of isolates) of quinolone- and macrolide-resistant GBS was 37% (1,210/3,279) and 37% (1,225/3,279), respectively. No isolates were observed for penicillin-, cephalosporin-, or vancomycin-resistant GBS. Changes in the rates of resistance each year are listed in the Tables 1 and 2. Of 77 patients with BSI, 15 (19%) showed a 30-day mortality outcome.

Table 1. Changes in rates of quinolone-resistant GBS for all isolates at each hospital

| Year | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|------|------|------|------|------|------|------|
| Hospital A | 79/158 (50) | 80/152 (53) | 67/114 (59) | 66/126 (52) | 50/108 (46) | 59/99 (60) |
| Hospital B | 17/25 (68) | 13/33 (39) | 18/30 (60) | 22/45 (49) | 11/26 (42) | 21/36 (58) |
| Hospital C | 10/22 (45) | 8/17 (47) | 6/15 (40) | 11/19 (58) | 12/18 (67) | 15/29 (52) |
| Hospital D | No data | No data | 7/15 (47) | 19/33 (58) | 7/12 (58) | 8/28 (29) |
| Hospital E | 52/205 (25) | 55/186 (30) | 51/173 (29) | 59/206 (43/150 (29)) | 45/170 (29) |
| Hospital F | 23/72 (32) | 31/94 (33) | 27/111 (24) | 41/110 (37) | 16/55 (29) | 17/66 (26) |
| Hospital G | 10/22 (45) | 8/17 (47) | 6/15 (40) | 11/19 (58) | 12/18 (67) | 15/29 (52) |
| Total | 216/601 (36) | 200/546 (37) | 181/530 (34) | 243/603 (40) | 174/480 (36) | 196/519 (38) |

Values are shown as quinolone-resistant isolates and total number of GBS isolates, and each value in parenthesis is shown as the rate (%).

GBS, Group B Streptococcus.

Table 2. Changes in rates of macrolide-resistant GBS for all isolates at each hospital

| Year | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|------|------|------|------|------|------|------|
| Hospital A | 66/158 (42) | 62/152 (41) | 54/114 (47) | 57/126 (45) | 51/206 (44/108 (41)) | 62/99 (63) |
| Hospital B | 11/25 (44) | 13/33 (39) | 8/30 (27) | 14/111 (29) | 25/64 (15) | 17/66 (26) |
| Hospital C | 2/22 (9) | 7/17 (41) | 8/15 (42) | 8/19 (42) | 16/55 (29) | 15/29 (52) |
| Hospital D | No data | No data | 3/15 (20) | 5/33 (15) | 3/12 (25) | 1/28 (4) |
| Hospital E | No data | 112/186 (60) | 46/173 (27) | 59/206 (29) | 19/111 (32) | 63/170 (37) |
| Hospital F | 18/72 (25) | 25/94 (27) | 20/111 (26) | 29/110 (17) | 19/111 (17) | 25/91 (27) |
| Hospital G | 16/119 (13) | 36/64 (27) | 57/111 (18) | 9/64 (26) | 19/55 (17) | 13/66 (20) |
| Total | 318/601 (37) | 255/546 (34) | 156/530 (40) | 180/603 (36) | 143/480 (35) | 173/519 (33) |

Values are shown as macrolide-resistant isolates and total number of GBS isolates, and each value in parenthesis is shown as the rate (%).

GBS, Group B Streptococcus.
Clinical characteristics according to 30-day mortality are shown in Table 3: 30 patients (39%) presented quinolone-resistant GBS isolates, 19 (25%) presented macrolide-resistant GBS isolates, and 12 (16%) showed both quinolone- and macrolide-resistant GBS isolates. All patients received antibiotic therapy, and no significant differences were observed in the clinical characteristics between those with and without the 30-day mortality outcome. However, the following clinical characteristics tended to be more frequent in the 30-day mortality group: quick sequential organ failure assessment score ≥2, underlying cancer, and primary site of infection (cardiovascular, intra-abdominal, or unknown). The results of the multivariable logistic regression analysis of the factors associated with 30-day mortality are shown in Table 4. Cardiovascular infections (OR 27.10, 95% CI 1.99–367.00) and unknown infections (OR 28.60, 95% CI 3.06–267.00) were found to be significantly associated with 30-day mortality.

To our knowledge, this is the first study evaluating the impact of quinolone and macrolide resistance in GBS on the 30-day mortality outcome in patients. Our findings indicate that neither quinolone nor macrolide resistance is a major risk factor for predicting mortality in patients with GBS BSI. We also found that 95% of patients in our study population received appropriate empirical antibiotic treatment, such as penicillin or cephalosporin, and that only a few invasive GBS isolates were included among the macrolide-resistant isolates.

### Table 3. Clinical characteristics of patients with GBS bloodstream infection

| Death within 30 days | No (n = 62) | Yes (n = 15) | P* |
|----------------------|-------------|-------------|----|
| Age, years, median (range) | 76 (0–94) | 77 (49–91) | 0.58 |
| 0–17, n (%) | 7 (11) | 0 (0) | |
| 18–59, n (%) | 10 (16) | 2 (13) | |
| 60–79, n (%) | 19 (31) | 7 (47) | 0.55 |
| >80, n (%) | 26 (42) | 6 (40) | |
| Male, n (%) | 29 (47) | 9 (60) | 0.40 |
| Body weight, kg, median (range) | 48 (3–96) | 53 (39–67) | 0.30 |
| Quinolone resistance, n (%) | 23 (37) | 7 (50) | 0.38 |
| Macrolide resistance, n (%) | 16 (30) | 3 (25) | 1.00 |
| qSOFA score ≥ 2, n (%) | 12 (19) | 6 (40) | 0.10 |
| CKD stage, n (%) | | | |
| 1–2 | 38 (61) | 6 (40) | 0.16 |
| 3–5 | 24 (39) | 9 (60) | |
| Primary site of infection, n (%) | | | |
| Urinary | 17 (27) | 2 (13) | |
| Skin and soft tissue | 14 (23) | 1 (7) | |
| Cardiovascular | 3 (5) | 3 (20) | |
| Central nervous system | 4 (7) | 0 (0) | 0.10 |
| Pulmonary | 10 (16) | 2 (13) | |
| Intra-abdominal | 4 (7) | 3 (20) | |
| Pregnancy-related | 3 (5) | 0 (0) | |
| Unknown | 7 (11) | 4 (27) | |
| Received appropriate empirical therapy, n (%) | 59 (95) | 14 (100) | 1.00 |
| Hospital-acquired infection1, n (%) | 8 (13) | 3 (20) | 0.44 |
| Underlying disease, n (%) | | | |
| Cardiovascular disease | 21 (34) | 4 (27) | 0.76 |
| Neurological disease | 18 (29) | 3 (20) | 0.75 |
| Diabetes mellitus | 11 (18) | 1 (7) | 0.44 |
| Solid cancer | 12 (19) | 6 (40) | 0.10 |
| Renal disease | 9 (15) | 2 (13) | 1.00 |
| Pulmonary disease | 8 (13) | 2 (13) | 1.00 |
| Liver disease | 4 (7) | 2 (13) | 0.33 |
| Hematologic malignancy | 1 (2) | 1 (7) | 0.35 |

*Mann-Whitney U test or Fisher’s exact test.

1: Infections occurring 48 h or more after hospital admission.

GBS, Group B Streptococcus; qSOFA, quick sequential organ failure assessment; CKD, chronic kidney disease.
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Table 4. Factors associated with 30-day mortality in patients with GBS bloodstream infection

|                          | Odds ratio | 95% CI  | P*     |
|--------------------------|------------|---------|--------|
| No macrolide resistance  | 1.00 (Reference) |         |        |
| Macrolide resistance     | 3.16       | 0.43–23.30 | 0.26   |
| No quinolone resistance  | 1.00 (Reference) |         |        |
| Quinolone resistance     | 0.63       | 0.11–3.62 | 0.61   |
| qSOFA score < 2          | 1.00 (Reference) |         |        |
| qSOFA score ≥ 2          | 5.64       | 0.72–44.30 | 0.10   |
| Underlying disease (non-cancer) | 1.00 (Reference) |         |        |
| Underlying disease (cancer) | 4.95       | 0.78–31.50 | 0.09   |
| Reference infections 1)  | 1.00 (Reference) |         |        |
| Cardiovascular infections| 27.10      | 1.99–367.00 | 0.01   |
| Intra-abdominal infections| 8.86       | 0.79–99.10 | 0.08   |
| Unknown infections        | 28.60      | 3.06–267.00 < 0.01 |

*Logistic regression analysis.

1) Reference infections included infections for which the primary site was the urinary tract, skin and soft tissue, central nervous system, pulmonary, or pregnancy-related.

GBS, Group B *Streptococcus*; qSOFA, quick sequential organ failure assessment.

GBS isolates. Cardiovascular and unknown infections have been reported to be associated with 30-day mortality (1), as seen in this study. Thus, when patients with GBS infection receive appropriate antibiotic therapy, quinolone and macrolide resistance might not affect the outcome.

Although no previous study has investigated the association between patient outcome and quinolone or macrolide resistance in GBS infection, some reports have suggested a link between patient outcome and infectious disease with macrolide-resistant *S. pneumoniae* (9,10). Moreover, quinolone resistance is an independent factor associated with 30-day mortality in infectious diseases caused by *S. pneumoniae* (11). Thus, if patients receive inappropriate antibiotic therapy, they may have a poor outcome. It should be noted that a high isolation rate of quinolone- and macrolide-resistant GBS could indicate a potential risk of antibiotic therapy failure.

In this study, approximately 30%–40% of quinolone- and macrolide-resistant GBS strains were isolated between 2013 and 2018. Although this result was higher than the 20% proportion found in a previous study in Japan from 2010 to 2013 (12), similar results were obtained in France and the United States (4,13). In contrast, a lower rate of approximately 3%–6% quinolone resistance was reported in Italy and Taiwan (5,14). The high rate of quinolone resistance in our study probably reflects the high consumption of quinolones in Japan (6). Indeed, a similar finding of approximately 40% of quinolone resistance was reported in a study conducted in Japan from 2010 to 2013 (12).

This study had some limitations. First, GBS serotyping and genome sequencing were not evaluated because these tests are not routinely conducted in the Japanese clinical setting, except for pregnant women and neonates. Second, we did not collect data regarding the number of patients with both quinolone and macrolide resistance, except for blood cultures, and thus the percentage of strains resistant to both antibiotics was not clear. Third, our findings cannot be readily generalized because of the small sample size.

In conclusion, our results suggest that quinolone- and macrolide-resistant GBS have a limited effect on 30-day mortality in patients with BSI, even in those with high rates of resistance to these antibiotics. However, it is important that caution be exercised when using quinolones and macrolides to treat GBS infection in patients with penicillin allergy. Thus, quinolones and macrolides should be the major targets of antimicrobial stewardship interventions in Japan.

**Conflict of interest** None to declare.

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