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Original Article

Variation in erythromycin and clindamycin resistance patterns between New Zealand and Australian group B streptococcus isolates

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Background: Intrapartum chemoprophylaxis for group B streptococcus (GBS) carriers reduces the risk of early-onset neonatal GBS infection. For women with β-lactam allergy, either erythromycin or clindamycin are administered. Recent reports worldwide suggest that GBS resistance to these antibiotics is increasing.
Aims: To compare erythromycin and clindamycin resistance phenotypes in invasive neonatal GBS isolates across New Zealand and Australia over the past two decades and to determine whether regional variation in resistance patterns exist.
Method: Invasive neonatal GBS isolates were collected from laboratories across New Zealand (n = 107) and Australia (n = 74) over two time periods (1992–1994 and 2002–2004 in New Zealand; 1982–2001 and 2002–2006 in Australia) and subjected to standard antibiotic susceptibility testing. A nested sub-study in New Zealand examined antibiotic susceptibilities of 112 maternal colonising GBS isolates during 2003–2004.
Results: Erythromycin resistance among invasive neonatal GBS isolates increased across both countries over the past decade, with similar rates of resistance in New Zealand (9%) and Australia (6%) in recent years. New Zealand erythromycin-resistant GBS isolates commonly displayed cross-resistance to clindamycin. Also, there were significantly higher rates of isolated clindamycin resistance in GBS isolates from New Zealand than Australia (P = 0.034). Maternal GBS isolates from New Zealand showed similar resistance patterns to neonatal isolates.
Conclusion: Erythromycin and clindamycin resistance among invasive neonatal GBS isolates has emerged in both New Zealand and Australia over the past decade and is consistent with global trends in GBS resistance patterns. Although regional variations exist, these findings should be considered when implementing intrapartum GBS prevention strategies.

Key words: antimicrobial resistance, clindamycin, erythromycin, Group B streptococcus.

Introduction

Group B β-haemolytic streptococcus (GBS) infection is an important cause of early-onset neonatal morbidity and mortality. GBS commonly colonises the female genital tract (10–40% of pregnant women), which is the usual source of early-onset neonatal infection.[1] The introduction of risk-based or universal screening and intrapartum chemoprophylaxis for pregnant women with known or suspected GBS colonisation has led to a remarkable reduction in rates of early-onset GBS infection among neonates over the past two decades.[2–4]

The usual recommendation for preventing intrapartum GBS transmission from colonised mothers to their newborn babies is to administer intravenous penicillin 4-hourly for the duration of labour.[5] Almost all GBS isolates are susceptible to penicillin, and there have been only a few reported instances of reduced penicillin susceptibility worldwide.[6,7] Approximately 10% of pregnant women will, however, report a β-lactam antibiotic allergy.[8] Current Australian guidelines recommend erythromycin or clindamycin as second-line prophylactic agents for women with β-lactam allergy.[9,10] In contrast, in New Zealand these antibiotics are only recommended if the susceptibilities of the colonising GBS isolates are known: otherwise, vancomycin is the drug of choice for women deemed to be at high risk of anaphylaxis from penicillin or cephalosporins and where GBS either demonstrates macrolide resistance or when antibiotic susceptibility is unknown.[10]

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Recent reports from around the world have, however, raised concern about rising rates of erythromycin (3–54%) and clindamycin (1–43%) resistance in GBS,[11,12] which may in part be associated with the introduction of intrapartum antibiotic prophylaxis.[13] A recent case report of clindamycin-resistant early-onset neonatal GBS disease in a baby whose mother received intrapartum clindamycin highlights the potential risk antibiotic resistance poses for GBS prevention programmes.[14]

Depending on the mechanism of resistance, erythromycin-resistant GBS may also be resistant to clindamycin. In general, resistance to macrolides, such as erythromycin, in GBS is conferred either by methylases encoded by *erm* genes (giving rise to the MLS_B phenotype, with cross-resistance to lincosamides such as clindamycin and lincomycin) or by membrane-bound pumps encoded by *mef* genes that cause efflux of macrolide antibiotics (giving rise to the M phenotype, with isolated macrolide resistance).[15] Among GBS with the MLS_B phenotype, clindamycin resistance may be either inducible or constitutive. Mechanisms of resistance vary regionally, and testing for inducible clindamycin resistance in penicillin-allergic patients is now recommended.[16] A further phenotype involving low-level clindamycin resistance alone in GBS isolates has been reported previously in New Zealand (LSA phenotype), although the underlying mechanism and genetic determinants remain to be established.[17,18]

To date, apart from one small cross-sectional study from New Zealand,[19] there are no published data on resistance rates among invasive neonatal GBS isolates in New Zealand and Australia, to help determine if either erythromycin or clindamycin resistance rates are increasing in this region. The objective of this study was to compare erythromycin and clindamycin resistance phenotypes in invasive neonatal GBS isolates across both countries. We sought to determine if resistance has increased over the past decade and if regional variation in resistance patterns exists between the two countries. This will enable an assessment of whether Australian and New Zealand guidelines for intrapartum prophylaxis among penicillin-allergic women remain current and appropriate.

Methods

Study population

As part of a national laboratory surveillance programme, invasive (blood and cerebrospinal fluid) neonatal GBS isolates were prospectively referred to a central reference laboratory from 16 centres across New Zealand over two time periods separated by a decade, 1992–1994 and 2002–2004. In addition, a sample of maternal colonising GBS isolates was compiled from the first 5–10 consecutive GBS isolates identified each calendar month between December 2003 and December 2004 inclusive from antenatal genital swabs submitted to a regional public hospital laboratory for routine testing. At the time this study was conducted, the laboratory provided microbiological services to antenatal clinics in both hospital and community settings.

Similarly, invasive neonatal GBS isolates were collected from across Australia as part of a nationwide survey conducted by the Australasian Group for Antimicrobial Resistance (AGAR), which included all states and territories, except for Tasmania and the Northern Territory. Isolates were collected predominantly from large tertiary hospitals in urban areas. Stored neonatal invasive GBS isolates collected between 1982 and 2001 were obtained, as well as prospectively collected invasive neonatal GBS isolates from 2002 to 2006.

As the study examined stored isolates collected as part of public health surveillance programmes for infectious diseases and recorded results of extended GBS antimicrobial susceptibility testing, the study was deemed to be low-risk observational research and audit not requiring full review by an Ethics Committee.

Confirmation of GBS identification and susceptibility testing

All GBS isolates had their identification confirmed by standardised methods at the central reference laboratory in New Zealand and Australia, including a CAMP test to confirm identification.[20]

All confirmed GBS isolates were tested for susceptibility to penicillin, erythromycin and clindamycin by disc diffusion according to the methods and interpretive standards of the Clinical and Laboratory Standards Institute (CLSI)[21]. Erythromycin-resistant, clindamycin-susceptible isolates were tested for inducible clindamycin resistance by the D-zone test.[21] In Australia, the D-zone test was performed with a 25-mm edge-to-edge spacing between erythromycin and clindamycin discs; in New Zealand, the CLSI recommended spacing of 12 mm was used.

The penicillin minimum inhibitory concentration (MIC) of all isolates was determined by Etest (AB Biodisk, Solna, Sweden) and interpreted according to CLSI guidelines. In addition, all erythromycin-resistant and/or clindamycin-resistant isolates had erythromycin and clindamycin MICs determined by Etest.

Statistical analysis

The Pearson's chi-square and Fisher's exact tests were used to assess the nonparametric data. The test of significance was two-tailed, and $P < 0.05$ was considered significant. The test was performed with the SPSS software Version 12 (SPSS, Chicago, IL, USA) program.

Results

New Zealand

A total of 24 invasive neonatal GBS isolates were collected from 1992 to 1994 in New Zealand. Among these stored isolates, 19 were viable and underwent susceptibility testing; all were fully susceptible to penicillin, erythromycin and clindamycin.

Over the period 2002–2004, there were 92 invasive neonatal GBS isolates collected and stored, of which 88 were able to be re-cultured and have susceptibility testing performed. All isolates were penicillin susceptible. A total of 14 isolates (16%; 95% confidence interval (CI) 9, 25) were erythromycin and/or clindamycin resistant. Overall, 8/88 (9%; 95% CI 4, 17) were erythromycin resistant and 13/88 (15%; 95% CI 8, 24) were clindamycin resistant. Among the eight erythromycin-resistant isolates, five had the constitutive and two the inducible MLS_B phenotype, while another exhibited the M phenotype. Six (7%; 95% CI 2.5, 14) isolates were erythromycin susceptible, but clindamycin resistant (LSA phenotype). These isolates had clindamycin MICs of 1–4 mg/L.

Similar results were obtained among the 112 maternal colonising GBS isolates collected over the period 2003–2004. While all tested colonising GBS isolates were susceptible to penicillin, 16 (14%; 95% CI 8, 22) were erythromycin resistant and/or clindamycin resistant. Of the four erythromycin-resistant isolates (3.6%; 95% CI 1, 9), two had the constitutive and two the inducible MLS_B phenotype. A further 12 isolates (11%; 95% CI 6, 18) were erythromycin susceptible, but clindamycin resistant (LSA phenotype). These isolates had clindamycin MICs of 1–4 mg/L.

Australia

In Australia, 27 invasive neonatal GBS isolates were collected for the period 1982–2001 and another 47 invasive neonatal isolates were available from 2002 to 2006.

Over the period 1983–2001, all stored invasive neonatal GBS isolates were fully susceptible to penicillin, erythromycin and clindamycin. Meanwhile in 2002–2006, although all GBS isolates remained penicillin susceptible, 4 of 47 (9%; 95% CI 2, 20) displayed erythromycin or clindamycin resistance. Overall, 3 of 47 (6%; 95% CI 1, 18) invasive neonatal GBS isolates were erythromycin resistant only and one of 47 (2%; 95% CI 0, 11) was clindamycin resistant (LSA phenotype). No isolate was resistant to both erythromycin and clindamycin. Overall, significantly higher rates of clindamycin resistance were observed in New Zealand than Australian invasive neonatal GBS isolates (13/88 vs 1/47; $P = 0.034$)

Discussion

Comparative resistance rates

Until recently there was no evidence of macrolide (i.e. erythromycin) or lincosamide (i.e. clindamycin) resistance among invasive neonatal GBS isolates in either New Zealand or Australia. However, this has changed within the last decade in Australia and since the late 1990s in New Zealand.[18,19] In the present study, we observed similar rates of erythromycin resistance for invasive neonatal GBS isolates in both Australia and New Zealand. In contrast, significantly higher rates of isolated clindamycin resistance (LSA phenotype) were observed in GBS isolates from New Zealand than in GBS isolates from Australia. The pattern of erythromycin and clindamycin resistance in New Zealand neonatal GBS isolates was also similar to that found among GBS isolates colonising the genital tracts of New Zealand women late in pregnancy.

Most erythromycin-resistant GBS isolates from New Zealand displayed the MLS_B phenotype. This differed from Australian GBS isolates, which in this study did not demonstrate any cross-resistance with clindamycin. It should be emphasised however that the small number of resistant Australian isolates makes it difficult to draw conclusions about resistance phenotypes. In addition, it is possible that some inducible cross-resistance in the Australian isolates was missed, as the disc spacing for the erythromycin and clindamycin discs in the D-zone test was wider than that recommended in the CLSI guidelines. Interestingly, a recently published study of invasive GBS isolates from Sydney reported no increase in inducible clindamycin resistance detection rates by the D-zone test when erythromycin and clindamycin discs were either 22–25 or 15 mm apart.[22] Importantly, this particular study and another involving invasive GBS strains from Australian patients of all ages did find the MLS_B phenotype in some isolates.[22,23] This suggests that in both countries, care should be taken to recommend testing for inducible clindamycin cross-resistance among erythromycin-resistant strains, through the routine use of the D-zone test, and is consistent with the current advice in the latest guidelines published by the Centers for Disease Control and Prevention in the United States,[13] while reaffirming the local evidence-base for the New Zealand consensus guidelines on GBS prevention in newborn babies.[10]

Rates of GBS erythromycin resistance in both New Zealand and Australia remain relatively low in comparison with recent data from other regions, such as South East Asia[12,24] or the United States.[11] However, there is no guarantee that this will continue indefinitely. For this reason, it is advisable that all maternal colonising GBS isolates should have routine erythromycin and clindamycin susceptibility testing performed, to ensure that β-lactam allergic mothers receive appropriate and effective intrapartum chemoprophylaxis.

While it is possible that widespread antibiotic prophylaxis may be contributing to the development of macrolide and lincosamide resistance in GBS, it is also important to emphasise the benefits of intrapartum antibiotic prophylaxis that in both New Zealand and Australia, as well as other countries have resulted in a significant reduction in neonatal morbidity and mortality from early onset GBS sepsis.[3,13] Consequently, until alternative methods become available, such as for example a safe and effective licensed GBS vaccine,[25] it is important that clinicians continue to follow current GBS prevention guidelines.

Limitations of the study

While these comparative data provide useful information to guide New Zealand and Australian intrapartum GBS

prevention guidelines, they do have some important limitations. Firstly, the two sets of isolates were collected independently over slightly different periods in New Zealand and Australia and processed in different laboratories, which could introduce some selection bias. Furthermore, neonatal isolates were obtained by passive-laboratory surveillance whereby diagnostic microbiology laboratories in both countries were asked to submit GBS isolates from blood or cerebrospinal fluid; the results may therefore not adequately represent the true geographical spread of GBS phenotypes in Australia and New Zealand. Additionally, the maternal GBS isolates were provided by a single diagnostic microbiology laboratory in a New Zealand public hospital and these isolates may not necessarily be representative of all maternal strains. However, the pattern of resistance detected in these maternal GBS strains is similar to that observed previously in isolates obtained from hospitals and community antenatal clinics elsewhere in New Zealand.[26] Finally, the numbers of isolates tested were comparatively small leading to relatively broad confidence intervals around each of the proportional estimates for antibiotic resistance.

Conclusion

This comparative study demonstrates the emergence of erythromycin and clindamycin resistance among invasive neonatal GBS isolates across both New Zealand and Australia. It also reaffirms the presence of resistance to these antibiotics in GBS strains colonising the genital tracts of pregnant New Zealand women. These observations are consistent with a globally recognised increase in erythromycin and clindamycin resistance in GBS isolates, although there remains significant regional variation in resistance patterns. Importantly, New Zealand GBS isolates differed from Australian isolates in that, although based upon small numbers, they more commonly demonstrated the MLS_B phenotype and had significantly higher rates of isolated clindamycin resistance (LSA phenotype). As clindamycin has been recommended as the antibiotic of choice in penicillin-allergic women at high risk of anaphylaxis,[13] these changes in antibiotic resistance patterns should be reflected in intrapartum GBS prevention policies in both countries and alternative strategies provided. Moreover, it is recommended that laboratories test for macrolide and lincosamide susceptibility in such settings.

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