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Original Article

Prolonged *Streptococcus gallolyticus* subsp. *pasteurianus* gut colonization in healthcare workers and potential transmission role in neonatal sepsis

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Abstract *Background: Streptococcus gallolyticus* subsp. *pasteurianus* (SGSP) is a commensal in the intestinal tract and a potential pathogen of neonatal sepsis. During an 11-month period, four consecutive cases of SGSP sepsis were identified in one postnatal care unit (unit A) without evidence of vertical transmission. Therefore, we initiated this study to investigate the reservoir and mode of transmission of SGSP.
Method: We performed cultures of stool samples from healthcare workers in unit A and unit B (another unit without SGSP sepsis). If SGSP was positive in feces, we performed isolate pulsotyping and genotyping by using pulsed-field gel electrophoresis (PFGE) and analyzing random amplified polymorphic DNA (RAPD) patterns, respectively.
Results: Five staff members in unit A showed positivity for SGSP. All samples from unit B were negative. We identified two major pulsogroups (groups C and D) by PFGE. In group D, the strains isolated from 3 consecutive sepsis patients (P1, P2 and P3) were closely related and clustered together as those from 2 staff members (C1/C2, C6). One staff (staff 4) had a direct contact history with patient (P1) confirmed to have the same clone. The last isolate of the patient in our study (P4) belonged to a distinct clone.

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Conclusion: We found prolonged gut colonization of SGSP in healthcare workers and its epidemiological relatedness to neonatal sepsis. Fecal-oral or contact transmission is a possible route of SGSP infection. Fecal shedding among staff may be associated with neonatal sepsis in healthcare facilities.

Introduction

The *Streptococcus bovis/Streptococcus equinus* complex (SBSEC) is a group of gram-positive, catalase-negative, oxidase-negative streptococci expressing the Lancefield group D antigen. The nomenclature and taxonomy of the *S. bovis* group are complicated and have evolved over time. Based on mannitol fermentation, organisms that could ferment mannitol are classified as biotype I, and the remainder are referred to as biotype II. Among biotypes, biotype II can be further divided into biotypes II/1 and II/2 according to biochemical features and molecular testing. The SBSEC includes four major species: *Streptococcus gallolyticus* subsp. *gallolyticus* (biotype I) (SGSG), *Streptococcus infantarius* subsp. *coli* (biotype II/1), *S. infantarius* subsp. *infantarius* (biotype II/1) and *S. gallolyticus* subsp. *pasteurianus* (biotype II/2) (SGSP).[1–4]

Several human and animal diseases are associated with SBSEC infection, such as endocarditis, bloodstream infection, and colorectal cancer.[3,5] SGSP is a potential pathogen of neonatal infections. In a large retrospective care series in France from 2001 to 2012, *S. bovis* infection accounted for 0.5% of bacterial meningitis in infants. When *S. bovis* subspecies were analyzed, 80% were SGSP.[6] The clinical course, host factors and management of SGSP sepsis are very similar to those of invasive group B streptococci (GBS) disease.[7–9] Although the outcomes are usually favorable, central nervous system complications may occur.[10,11]

In our previous study, we reported 3 consecutive neonatal sepsis cases caused by SGSP from December 2019 to February 2020.[12] Patients were referred from the same postnatal care unit. The molecular typing results indicated that all isolates belonged to a single clone. A possible nosocomial outbreak was suspected. We provided hospital authorities with this information, and infection control measures were strengthened. However, in November 2020, another neonate with SGSP meningitis and bacteremia was transferred from this unit. The origin and transmission route of the SGSP are uncertain. Because SGSP is a commensal inhabiting the human gastrointestinal tract, we hypothesized that there were SGSP carriers in this postnatal care unit causing this epidemiological cluster of neonatal sepsis. Therefore, we initiated this study to investigate the potential reservoir and mode of transmission of SGSP.

Materials and methods

Study population and design

After identifying the outbreak, the postnatal care unit was informed, and an investigation was requested. The SGSP outbreak occurred in unit A with 23 healthcare workers between December 2019 and November 2020. We conducted environmental sampling in unit A, which included water used for preparing infant formula, faucets for bathing, sinks in the operation room, and drinking fountains. Additionally, we selected another unit (Unit B), with 47 healthcare workers, from the same healthcare system. Unit B had the same protocols for medical care as unit A. No SGSP-infected cases had been reported previously. Due to the urgent need for tracing the source of infection and the minimal risk to participants, informed consent was waived. We collected fecal samples from healthcare workers in both units for bacterial culture. After obtaining informed consent under ethical approval by the Institutional Review Board (IRB) of National Taiwan University Hospital (202106040RINA), we gathered epidemiological and contact information from each participant in the postnatal unit.

Microbiological identification

We collected fecal samples by using flocked swabs. The swabs were transported with 2 mL of Cary—Blair medium in plastic, screw cap tubes (Copan Diagnostics Inc., Murrieta, California, USA). The stool cultures were processed at our microbiology laboratory by inoculating the sample onto a 5% sheep blood agar plate (BAP) and subcultured on phenylethyl alcohol agar (PEA) for the isolation of gram-positive bacteria (Becton, Dickinson Microbiology Systems). Gram-positive bacteria were identified to the species level using a Bruker Biotyper matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) system (Bruker Daltonik GmbH, Bremen, Germany). Subspecies identification was confirmed by both sequencing of the *sod*A gene and performing PCR restriction fragment length polymorphism (PCR-RFLP) assays of the *groESL* gene with the restriction enzyme *Acl*I (New England BioLabs), as described in previous studies.[13,14] The sequences were aligned using the Basic Local Alignment Search Tool (BLAST) against reference sequence databases from GenBank.

Molecular typing of the isolates

We performed genotyping for the isolates by using arbitrarily primed PCR to analyze random amplified polymorphic DNA (RAPD) patterns and by pulsotyping to identify pulsotypes generated from pulsed-field gel electrophoresis (PFGE). Arbitrarily primed PCR was performed using two random oligonucleotide primers: M13 (5′-GAGGGTGGCGGTTCT-3′) and OPM6 (5′CTGGGCAACT-3′) (Operon Technologies, Inc., Alameda, CA, USA), as described in a previous study.[15] In the PFGE experiments, we used the restriction enzyme *Sma*I to

digest the DNA and then separated the fragments in a CHEF-DRIII unit (Bio-Rad Laboratories, Hercules, CA, USA) at 6 V for 20 h.[16] Restriction fragment migration profiles were analyzed by using the BioNumerics program (Applied Maths, Kortrijk, Belgium). Isolates were further classified into clusters when a maximum of three bands differed in the restriction pattern (>80% similarity). When the number and positions of bands in the restriction pattern were the same, isolates were considered to be of the same pulsotype (100% similarity).

Intervention

For healthcare workers with positive SGSP results, we prescribed the probiotic Infloran® (*Bifidobacterium bifidum*-ATCC15696 and *Lactobacillus acidophilus*-NCIMB701748) three times daily. Stool samples were collected after 14 days of probiotic use.

Results

Microbial identification

There were 15 healthcare workers in postnatal care unit A and 9 staff in unit B who participated in our study. We identified 44 isolates from 24 samples. There were 4 main genera: *Enterococcus*, *Lactococcus*, *Streptococcus*, and *Staphylococcus*. Among the 4 genera, *Enterococcus* was predominant, with *Enterococcus faecalis* being the most common species. *Streptococcus* was the second most common genus. SGSP were recovered from 5 stool samples in unit A. In staff from unit B, no SGSP was isolated. There were also no bacteria identified in the 4 environmental samples. Therefore, no decolonization intervention was performed. The details of the bacteria identified in feces are presented in Table 1.

Table 1 Bacteria identified in stool samples from healthcare workers in two postnatal care units.

Identified bacteria	Unit A	Unit B
Sample numbers	15	9
Enterococcus spp.	16	9
Enterococcus avium	1	0
Enterococcus casseliflavus	3	1
Enterococcus faecalis	9	4
Enterococcus faecium	1	3
Enterococcus gallinarum	1	1
Enterococcus mundtii	1	0
Lactococcus spp.	2	3
Lactococcus garvieae	2	2
Lactococcus lactis	0	1
Streptococcus spp.	7	3
Streptococcus agalactiae	2	2
Streptococcus gallolyticus	5	0
Streptococcus vestibularis	0	1
Staphylococcus spp.	2	0
Staphylococcus epidermidis	1	0
Staphylococcus hominis	1	0
Others	0	1
Weissella confusa	0	1

Molecular typing

Four patients with SGSP bacteremia/meningitis were labeled P1 to P4, respectively. Four SGSP isolates recovered from four patients with bacteremia treated at our hospital between 2018 and 2020 were labeled P5 to P8 and were considered the control group. In 5 staff in obstetric clinic A, we recovered 7 colonies from fecal samples that were finally identified as SGSP (numbered C1—C7; C1/C2 were recovered from the same staff, and C3/C4 were isolated from another staff). The isolates were further typed by arbitrarily primed PCR and PFGE.

RAPD patterns and PFGE

In Fig. 1, the 15 SGSP strains were analyzed by the RAPD procedure using primers M13 and OPM6. In primer M13, the 3 patients (P1, P2, and P3) and 2 staff (C1/C2, and C6) shared similar RAPD patterns. In primer OPM6, the 5 strains with similar patterns originated from 3 neonatal sepsis patients (P1, P2, and P3) and 1 staff member (C1/C2). Excluding the 4 control isolates, the RAPD analysis revealed that strains collected from 4 different patients exhibited 2 different genotypes. P1, P2, and P3 could be easily discernible from P4.

To better discriminate the isolated strains, PFGE was performed based on the digestion of DNA with the restriction enzyme *Sma*I. Fig. 2 shows the PFGE dendrogram. There were two main pulsotype groups (C and D). The dendrogram indicated that the strains isolated from P1, P2 and P3 were closely related and clustered together in group D as those isolated from 2 staff members (C1/C2, C6). In group C, we identified 3 indistinguishable clones in 2 staff members (C3/C4, C5) and one closely related strain in staff member 5 (C7). The last neonatal sepsis case in our study (P4) belonged to a distinct clone.

Epidemiological link and clinical characteristics

In Table 2 and Table 3, we summarize the molecular typing results and epidemiological links of the 11 isolates from 5 staff and 4 neonates with invasive disease. From December 2019 to February 2020, the 3 consecutive cases (P1, P2, and P3) developing early-onset invasive disease belonged to the same clone (group D). They were all delivered via cesarean section. More than one year after the first case identification, we started to collect fecal samples. Two identical strains were still isolated from 2 staff members (staff 1 and 4). In the PFGE dendrogram, there was another circulating cluster (group C) among the staff (staff 2, 3, and 5). The pulsotype of PFGE in group C was unique, which revealed no molecular epidemiological link with sepsis cases. Among the 5 staff with SGSP-positive fecal samples, one (staff 4) had a direct contact history with patients with the same confirmed clone. After taking probiotics for 14 days, only one staff member remained positive for SGSP. There were no SGSP sepsis cases found in the postnatal care unit up to manuscript submission.

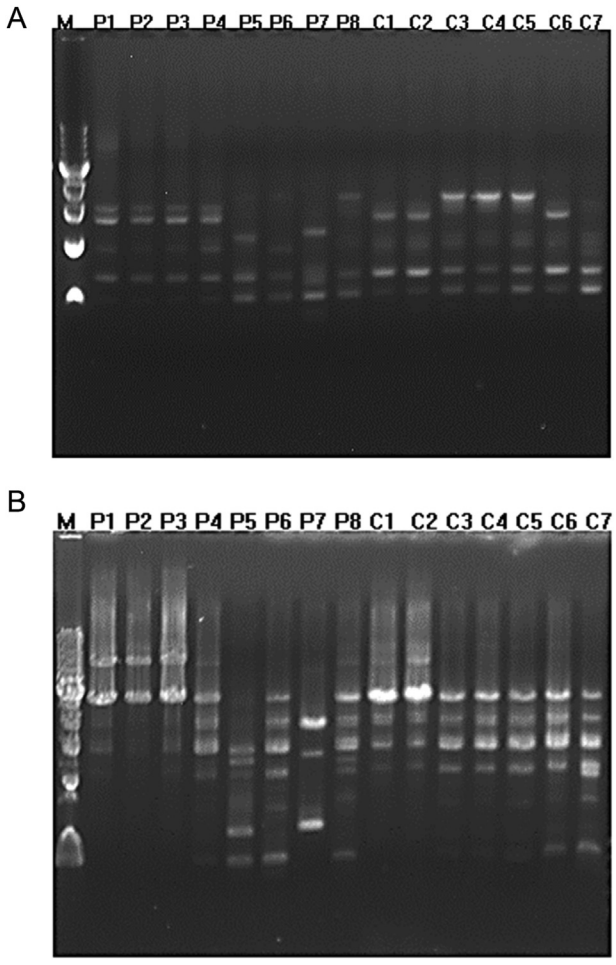

Figure 1. Random amplified polymorphic DNA (RAPD) patterns generated by arbitrarily primed PCR with two random primers, M13 (panel A) and OPM6 (panel B). Lane M, molecular size marker. Lanes P1 to P4, four *Streptococcus gallolyticus* subsp. *pasteurianus* (SGSP) isolates recovered from the four neonates with bacteremia/meningitis. Lanes P5 to P8, four SGSP isolates (control isolates) recovered from four patients with bacteremia treated at our hospital between 2018 and 2020. Lanes C1 to C7, 7 SGSP isolates recovered from 5 staff in postnatal care unit A. C1/C2 were recovered from the same staff, and C3/C4 were isolated from another staff.

Discussion

In our study, we identified evidence of contact or fecal-oral transmission of SGSP in a postnatal care unit. In unit B (control group), no SGSP was isolated from staff fecal samples. However, in the clinic with the SGSP cluster, the strains causing early-onset neonatal sepsis were identical to some SGSP clones in staff fecal samples in a one-year interval. The turnover time of neonates in the obstetric clinic was rapid. In contrast, the intervals between the SGSP-infected or colonized cases in our study were long. Therefore, contamination of breast milk, soap, antiseptic solution, or environmental surfaces is unlikely. The environmental sample cultures were negative, as expected. We then hypothesized that the microorganisms may have been transmitted from asymptomatic carriers in the workplace.

SGSP infections share some similar features with GBS infections.[17] Both early-onset and late-onset disease can occur. Lu et al. reported that one pregnant woman with intrauterine SGSP infection presented with bacteremia.[18] Three patients developed sepsis-like symptoms within 7 days in our series. Microorganisms residing in the external genitalia or gastrointestinal tract with ascending infections could be an explanation for early-onset disease. We did not collect any maternal specimens (including placental tissues, amniotic fluid, vaginal discharge, or stool specimens) due to the time lag. The possibility of maternal vertical transmission could not be completely excluded. However, PFGE is a reliable technique for bacterial typing and determining genetic relatedness. Additionally, 3 out of 4 patients with early-onset disease in our study were born via cesarean section without evidence of maternal infection. Horizontal transmission of SGSP during exposure to environmental organisms was more likely.

Our study provided some new evidence of fecal-oral SGSP transmission in neonates. A previous study reported a cluster of late-onset bacteremia caused by SGSP in 5 preterm neonates during a 2-month period.[19] Epidemiologically related strains were identified via PFGE. However, in the absence of evidence of environmental contamination, transient hand carriage by healthcare workers was suspected without further investigation. In our surveillance, we identified asymptomatic carriers among staff and clonal relatedness to pathogenic strains. The possible route of entry in neonates is mucosal colonization with subsequent invasive disease. Members of the SBSEC are frequently isolated from human and animal intestinal tracts.[4] In early life, prenatal microbial exposure and maternal-fetal immune interactions play major roles in the development of the neonatal gut microbiota.[20] However, postnatal direct and frequent contact with cohabitants may significantly affect the composition of microbial communities.[21,22] For the SGSP closely related subspecies SGSG, transmission resulting in human gut colonization may occur after frequent contact with feces.[23] Therefore, we proposed that intestinal tract colonization develops after contact with an SGSP carrier. Due to the immature mucosal barrier, bacterial translocation and bacteremia may occur in neonates. Interestingly, it was estimated that there were at least three SGSP strains circulating during a one-year period. Two strains were related to invasive disease in our patients. Differences in invasiveness among the strains might be a possible explanation. One hypervirulent strain of SGSP (AL101002) has been isolated in China, which resulted in meningitis, septicemia, and death in ducklings.[24] However, virulence factors and highly virulent strains of SGSP have not been investigated in humans. Additionally, the zoonotic potential was not fully understood. Other factors, such as the time from colonization to infection, the inoculum amount, host immunity, and interactions with other colonized flora, may also need to be taken into consideration.

Our study demonstrated the association between asymptomatic SGSP fecal colonization and invasive disease. There is existing evidence that enteric bacteria can cause late-onset bloodstream infections.[25,26] In animal models,

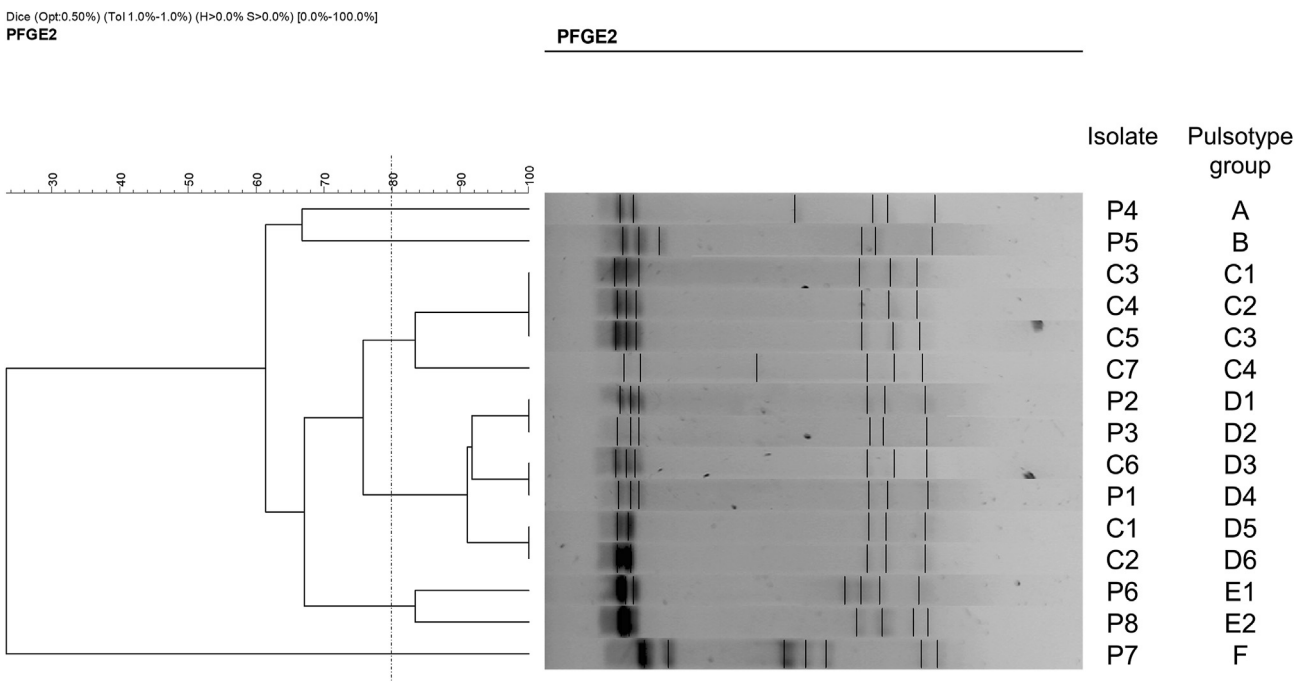

Figure 2. Pulsed-field gel electrophoresis (PFGE) profiles of *Sma*I-digested DNA of *Streptococcus gallolyticus* subsp. *pasteurianus* isolates. Band comparison was performed using the Dice coefficient with 0.5% optimization (Opt) and 1.0% position tolerance (Tol). H, minimum height; S, minimum surface.

Table 2 Characteristics of 4 *Streptococcus gallolyticus* subsp. *pasteurianus* (SGSP) neonatal sepsis cases and cluster analysis results.

Patient No	Sex	Admission day	Gestational age	Birth body weight	Onset day	Maternal GBS status/ Treatment	Mode of delivery	Identified source	Pulsotype group
1	Female	Dec 6, 2019	35 + 1/7 (Twin B)	2580 gm	3 days	(−)/(−)	CS	Blood	D
2	Female	Feb 13, 2020	37 + 3/7 (Twin B)	1861 gm	3 days	(+)/(−)	CS	CSF Blood	D
3	Male	Feb 15, 2020	37 + 3/7 (Twin A)	2112 gm	5 days	(+)/(−)	CS	CSF	D
4	Female	Nov 4, 2020	38 + 1/7	2800 gm	12 days	(−)/(−)	CS	CSF Blood	A

Abbreviations: CS, cesarean section; CSF, cerebrospinal fluid; GBS, group B Streptococcus.

Table 3 Epidemiological links of healthcare workers with fecal samples positive for *Streptococcus gallolyticus* subsp. *pasteurianus* (SGSP) and fecal colonization after intervention.

Staff	Sex	Isolate ID in PFGE	Date of SGSP isolation	Pulsotype group	Contact with infected neonate	Stool culture after taking probiotic for 2 weeks
1	Female	C1/C2	Dec 29, 2020	D	No	Positive for SGSP
2	Female	C3/C4	Jan 7, 2021	C	No	Negative for SGSP
3	Female	C5	Jan 7, 2021	C	Patient 1, 3	Negative for SGSP
4	Female	C6	Jan 7, 2021	D	Patient 1, 4	Negative for SGSP
5	Female	C7	Jan 7, 2021	C	No	Negative for SGSP

Abbreviations: PFGE, pulsed-field gel electrophoresis; SGSP, *S. gallolyticus* subsp. *pasteurianu*.

dysbiosis of the neonatal intestinal microbiome is one of the causes of late-onset sepsis.[27] Commensals in the gastrointestinal tract that undergo intermittent shedding in asymptomatic carriers are a potential threat to susceptible hosts. In a previous study, surrounding asymptomatic SGSP carrier density correlated with the rate of bacteremia, which supports our findings.[28] Although implementation of infection control measures, such as hand hygiene, could reduce contact transmission from asymptomatic carriers to neonates, they are somehow passive. In healthcare facilities with active outbreaks and known carriers, prompt interventions are necessary. We achieved decolonization in 4 out of 5 staff members by using probiotics. Probiotics may restore the physiological balance of the intestinal microbiota and modulate immunologic status.[29] A recent open-label clinical trial also showed the effect of carbapenemase-producing *Enterobacterales* modulation after Infloran® use.[30] Although optimizing strains or duration to achieve digestive decontamination is uncertain, probiotics might be a cost-effective solution.

Our study has some limitations. First, there was a one-year interval between index case identification and surveillance initiation. We could not collect maternal samples or patient fecal samples for further identification to clarify other possible transmission routes and causal relationships. No solid evidence of direct spread from staff to neonates. However, the long carriage duration also implies the possibility of infection in the subsequent period. Second, we did not collect feces from all healthcare workers; therefore, epidemiological tracing was not comprehensive. Third, we could not determine the time of acquired mutations among strains by PFGE or RAPD pattern analysis. Virulence factors and genetic evolution could not be assessed in our study. Gut microbiota profiling through a metataxonomic approach or whole-genome sequencing may provide further insight into disease transmission and control.

In this study, we demonstrated that fecal-oral or contract transmission was the possible cause of SGSP infection in a neonatal sepsis cluster. An identical clone of SGSP colonized healthcare workers' intestinal tracts. Prolonged fecal shedding may be associated with neonatal gut colonization. Bacterial translocation from the intestinal tract thereby leads to further invasive disease.

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