Journal of Infection (2017) 74, S34—S40

BIA
British Infection Association

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The controversial role of breast milk in GBS late-onset disease

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Available online 23 June 2017

KEYWORDS
Streptococcus agalactiae;
Late-onset sepsis;
Infant;
Colonisation;
Antibiotics

Summary Group B streptococcus (GBS) is one of the most common causes of neonatal sepsis and meningitis. Intra-partum antibiotic prophylaxis does not play a significant role in reducing the risk of GBS late-onset disease. One of the proposed mechanisms for GBS late-onset disease is infection through contaminated breast milk. Infants in whom breast milk is thought to be the source for GBS late-onset disease are more heavily colonised and reports suggest they have a higher recurrence rate compared to infants with other potential sources. There is no consensus whether the breast milk of mothers of infants with GBS late-onset disease, especially those with recurrent episodes, should be tested for GBS. In addition, recommendations differ on whether breast-feeding should be interrupted or breast milk pasteurised, or whether the mother and infant should be treated for colonisation. In this review we discuss these different approaches.

Introduction

Group B streptococcus (GBS) is one of the most common causes of neonatal sepsis and meningitis. Over two thirds of infants with GBS infection present with early-onset disease (EOD), occurring within the first week of life with a case-fatality rate from 3 to 10%, while the remainder present with late-onset disease (LOD), occurring between day 7 and day 89 of life with a case-fatality rate from 1 to 6%.[1] Widespread use of intrapartum antibiotic prophylaxis (IAP) has led to a decrease in the incidence of EOD by 80% to approximately 0.25 per 1000 infants, but has not influenced the incidence of LOD, which is currently estimated at 0.28 per 1000 infants.[2,3] EOD, which usually presents as septicaemia, pneumonia, or meningitis, is commonly caused by serotypes Ia, Ib, II, III and V and results from vertical transmission from the mother.[4] LOD also presents as septicaemia and meningitis but, in contrast to EOD, presents in a significant proportion of cases with cellulitis, osteomyelitis, or septic arthritis. LOD is mainly caused by serotype III, Ia and V. LOD

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can either result from late onset presentation after early colonisation or from horizontal acquisition, which can be healthcare-associated or community-acquired (mother and other caregivers, household contacts or other environmental sources, like contaminated pump extraction devices).[5,6]

Maternal genital and lower gastrointestinal tract GBS colonisation is relatively common with rates between 15 and 40%. The risk for an infant to become colonised, when the mother is colonised is 50%.[7] Therefore, in the absence of IAP, approximately 7.5 to 20% of all infants are colonised with GBS. The risk of an infant developing sepsis if colonised is around 1%, but is influenced by inoculum size, duration of exposure and gestational age of the infant. Whilst IAP prevents transmission of GBS from a colonised mother to her baby during delivery, it does not eradicate colonisation in the mother who may therefore subsequently be a source of GBS in LOD.[8] IAP has been shown to delay colonisation (infants are GBS free at discharge, but are colonised later).[8]

Recurrent GBS LOD occurs in 0.5 to 3% of infected infants.[9–11] In recurrent cases, the mean age at the first episode is 10 days and at the second episode is 42 days.[10] The second episode is usually caused by genotypically identical strains.[10,12] Proposed causes for recurrence include a persistent focus, inadequate dose or duration of antibiotic therapy, increased bacterial virulence, reinfection with the same or different strain, persistent infant mucosal or gastrointestinal colonisation or impaired integrity of the mucosal surfaces.[9,13] Risk factors for recurrent GBS LOD are prematurity, and immaturity or defects of the immune system.[13]

Many reports have identified contaminated breast milk, with or without occurrence of mastitis, as the cause of both single and recurrent episodes of GBS LOD. Approximately 0.8 to 3.5% of mothers carry GBS in their breast milk.[14,15] In this review we summarise all published cases of GBS disease resulting from contaminated breast milk and discuss different options for managing cases of recurrent GBS LOD attributed to contaminated breast milk.

Case reports

There are 59 case reports of infants with GBS LOD associated with contaminated breast milk.[1,5,13,16–41] Twenty-nine (49%) infants were term and 30 (51%) preterm babies. Eighteen infants (31%) were a twin or triplet[1,16,21,23,26,31,38,40,42] and, with the exception of 2 cases,[1,16] all siblings were affected. Of the 36 infants with documented delivery mode, 21 (58%) were born by caesarean delivery (time of membrane rupture rarely specified) and 15 (42%) vaginally. The site of infection was reported in 50 infants: blood in 41 infants (82%), cerebrospinal fluid 19 (38%), urine 5 (10%) and osteoarticular 1 (2%). Forty infants (68%) had 1 episode, 15 (25%) had 2 episodes and 4 (7%) had 3 episodes of GBS LOD. Mastitis was reported in 24 mothers (41%). Results from prenatal recto-vaginal swabs were available in 22 mothers and were positive in 9 (41%). GBS strains were identified in 30 infant-mother pairs and in all cases, the strain isolated from the infant was identical to that found in the mother's breast milk.[5,13,19,21,23,24,26,34–38,40] GBS serotype III was the most frequently isolated strain, identified in 22 of the 30 infant-mother pairs (74%), Ia identified in 2 infants and Ib and IV each in 1 infant. A DNA-profile of the isolated strains was done in 25 infant-mother pairs and all of them had identical profiles. In 4 infant-mother pairs the strain was not specified but they had an identical DNA profile. The hypervirulent clone ST-17 serotype 3 GBS, which expresses the adherence protein *Hygo*, required for translocation through the intestinal barrier,[43] and which also has a tropism for meninges, was isolated in 5 infants.[29,40] Three of these infants had recurrent infections.[29,40]

In the 31 cases that provided this information, breast-feeding was temporarily or permanently ceased in 25 infants (81%) and continued in the remainder. Milk was pasteurised in 1 case.[23,34] Seventeen mothers (29%) were treated with antibiotics either for mastitis or colonisation (amoxicillin/ampicillin 12,[18,21–24,28,31,34–37] cephalexin 1,[1] cloxacillin plus cephalexin 1,[32] dicloxicillin 1,[16] oxacillin 1,[27] rifampicin 1[13]). Eight (47%) of the 17 mothers were thought to be successfully decolonised after antibiotic treatment, shown by negative breast milk cultures,[13,22,31,35,36] breast milk PCR[28] and/or negative culture from a vaginal-rectal swab.[13,18,32] In 3 of the 17 mothers (18%) eradication was not successful,[1,21,34] and in 6 mothers (35%) no retesting was done.[16,23,24,27,37]

Of 7 cases involving twins or triplets in which more than one infant was affected by GBS LOD, 3 mothers were treated with antibiotics,[21,23,31] 3 mothers ceased breast-feeding[26,40,42] and for 1 mother, no information about the management was reported.[38]

Three infants (5%) were treated with rifampicin with the aim of eradicating colonisation.[13,21,34] One of these was given rifampicin for a duration of 6 days while on treatment[34] and the other 2 were given rifampicin for a duration of 4 days[21] and 7 days respectively,[13] starting after treatment for the GBS had been completed. While eradication was successful in 2 of these 3 cases,[13,34] 1 had a recurrent episode of GBS LOD 2 days after stopping rifampicin.[21]

There are 8 reports in the literature describing infants with 3 episodes of GBS septicaemia with or without meningitis.[13,34,39,44–47] In 3 infants, breast milk was suspected to be the cause of recurrence.[13,34,39] In the remaining infants, recurrence was attributed variously to prematurity,[46,47] persistent mucosal colonisation,[44] persistent infective focus,[45,47] short duration of treatment,[45] and hypogammaglobulinemia.[48]

Mechanisms of contamination of breast milk

Breast milk plays an important role in protecting infants against infections and GBS-specific immunoglobulin G, found in breast milk protects infants from GBS disease.[49,50] On rare occasions, however, breast milk can also be a source of infection. In cattle, GBS is a major cause of epidemic mastitis, leading to decreased milk production, the reason for this bacterium being named *Streptococcus agalactiae*.[51] In contrast, in humans, GBS is not a common cause of mastitis.

One possible mechanism by which breast milk becomes contaminated by GBS is through retrograde transmission from the infant: the infant becomes GBS colonised during delivery or after birth and persistent oral mucosal colonisation leads to contamination of maternal mammary ducts, facilitated through negative pressure created during sucking (Figure 1).[1,18,19,22,27,32] GBS can then multiply in the mammary ducts and hence, bacterial concentration