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Capnocytophaga species and preterm birth: case series and review of the literature

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Abstract

Capnocytophaga, a genus of Gram-negative anaerobes that inhabit the oral cavity, has been reported to be an unusual cause of chorioamnionitis and neonatal infection. We report five cases of *Capnocytophaga* spp. infections in preterm infants (one proven infection and four probable infections) and review 14 previously reported cases. We suggest that *Capnocytophaga* sp. may be responsible for some occult causes of chorioamnionitis or preterm birth, and that the prevalence of this infection may be higher than previously reported.

Keywords: *Capnocytophaga* species, chorioamnionitis, neonatal infection, preterm birth
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Introduction

Capnocytophaga, a genus of Gram-negative fastidious anaerobic organisms usually isolated from the oral cavity, is responsible for infections, especially in immunocompromised children [1,2], but also in immunocompetent children after animal bites [3]. It also appears to be a potential risk factor for preterm birth [4–6] and an infrequent cause of chorioamnionitis and neonatal infection.

A review of the microbiology records of neonates hospitalized in a tertiary-care perinatal centre over the last 12 years, with regard to all peripheral or blood cultures positive for *Capnocytophaga* sp, revealed five cases of early-onset sepsis (EOS) due to *Capnocytophaga* spp. (one proven infection and four probable infections). A Medline search of all reported cases of neonatal infection due to *Capnocytophaga* spp. revealed an additional 14 cases.

Infection with *Capnocytophaga* sp. is therefore probably an underestimated aetiology of occult chorioamnionitis and preterm delivery leading to neonatal infection.

Case reports

Case 1

A 790-g male infant was born prematurely at 26 weeks of gestation to a 26-year-old mother, gravida 2, para 2. The pregnancy was uncomplicated until the mother experienced rupture of the membranes at 25 weeks of gestation. Chorioamnionitis was suspected in the presence of elevated C-reactive protein (CRP), at 38 mg/L. The white blood cell (WBC) count was 8600×10^9/L. Urine and vaginal swab cultures were positive for *Klebsiella pneumoniae*. She was treated with cefotaxime and remained afebrile. Prenatal steroids were administered. She progressed into labour despite nifedipine tocolysis. A caesarean section was performed for transverse presentation and fetal tachycardia. Histological examination of the placenta revealed chorioamnionitis. Apgar scores were 3, 9 and 10 at 1, 5 and 10 min, respectively. The infant was treated for respiratory distress syndrome (RDS) by intubation, surfactant administration and assisted ventilation. Intravenous ampicillin, cefotaxime and gentamicin were administered empirically after bacterial sampling, as recommended by French guidelines (http://www.has-sample/portrait/upload/docs/application/pdf/recos-imm-mu-2006/pdf).

The infant exhibited laboratory signs of infection: $37\,700 \times 10^9$ WBCs/L and a CRP level of 4.6 mg/L at birth and 14 mg/L

12 h later. He remained clinically stable after surfactant treatment. At day 3, tracheal aspirate and gastric fluid cultures obtained at birth yielded pure growth of a Gram-negative bacillus identified as *Capnocytophaga sputigena*. Blood culture was negative. The subsequent course was favourable in response to treatment with cefotaxime for 8 days.

Case 2

A 1180-g preterm female infant was delivered at 28 weeks of gestation from a 29-year-old mother, primipara, gravida 2, who had been admitted to the obstetric department for preterm labour. The afebrile mother received tocolysis with salbutamol, ampicillin (2 g/day) and one dose of steroids. *Trichomonas vaginalis* was recovered in vaginal cultures. The CRP level was 85 mg/L and the WBC count was 11 200 $\times$ 10^9/L. Despite the treatment, the patient progressed into labour and delivered vaginally. Amniotic fluid was foul-smelling. Histological examination of the placenta revealed chorioamnionitis. Apgar scores were 7, 5 and 9 at 1, 5 and 10 min, respectively. The infant presented RDS, which was treated by intubation, surfactant administration and assisted ventilation. Intravenous ampicillin, cefotaxime and gentamicin were administered empirically for 72 h. The WBC count was normal, at 8200 $\times$ 10^9/L, and the CRP level was increased to 6 mg/L in the first hour of life. Blood culture and gastric aspirate samples recovered soon after birth revealed the presence of *C. sputigena*, and cefotaxime alone was given for the following 10 days. The infant recovered rapidly from both the infection and RDS.

Case 3

A 1170-g preterm male infant was born at 29 weeks of gestation to a 29-year-old primigravida mother admitted to the obstetric department at 29 weeks of gestation for preterm labour with a temperature of 38.3°C, a WBC count of 21 000 $\times$ 10^9 cells/L, and a CRP level of 83 mg/L. Cultures of vaginal samples yielded *Escherichia coli*. Treatment with ampicillin was started, and one dose of corticosteroids was administered on the day before delivery. The patient progressed into labour despite nifedipine tocolysis, and delivered vaginally. The amniotic fluid was clear. Histological examination of the placenta demonstrated chorioamnionitis. Apgar scores were 5, 7 and 8 at 1, 5 and 10 min, respectively. The baby was hypotonic and in respiratory failure, and was immediately treated with ampicillin (100 mg/kg per day), cefotaxime (100 mg/kg per day) and gentamicin (2.5 mg/kg per day). The infant was treated for RDS by surfactant administration and assisted ventilation. The WBC count was 2100 $\times$ 10^9/L, and the CRP level was 12 mg/L at birth and 46 mg/L on the first day of life. Cultures of gastric fluid and tracheal aspirate revealed a *Capnocytophaga* sp. after 3 days. A blood culture was sterile. He was treated with ampicillin and gentamicin for the first 2 days, and then with ampicillin alone for 8 days, with a favourable outcome.

Case 4

An 800-g preterm female infant was born at 25 weeks of gestation to a 34-year-old mother, primipara, gravida 3, who presented in labour with intact membranes at 25 weeks of gestation and was afebrile. Vaginal culture on admission was sterile. The WBC count was 22 800 $\times$ 10^9/L, and the CRP level was 28 mg/L. She received one injection of prenatal steroids and ampicillin. Labour progressed rapidly, despite tocolysis with nifedipine and then atosiban, and she delivered vaginally. Apgar scores were 4 and 8 at 1 and 5 min, respectively. Histological examination of the placenta revealed chorioamnionitis. The infant was intubated and received surfactant under mechanical ventilation. Initial laboratory investigations revealed a WBC count of 4900 $\times$ 10^9/L, and a CRP level of 8.4 mg/L. These parameters increased to peak values of 75 900 $\times$ 10^9/L and 17 mg/L, respectively. Empirical therapy with ampicillin, cefotaxime and gentamicin (2.5 mg/kg per day) was started. A *Capnocytophaga* sp. was isolated from cultures of gastric fluid, meconium and tracheal aspirate on day 2. Blood culture remained sterile. The infant was treated with ampicillin for 8 days, and recovered from her infection with a favourable respiratory outcome.

Case 5

An 855-g preterm female infant was born at 25 weeks of gestation to a 33-year-old mother, primipara, gravida 4. Pregnancy was complicated by preterm labour with rupture of the membranes at 25 weeks of gestation. The mother was afebrile, with a WBC count of 16 300 $\times$ 10^9/L and a CRP level of 78 mg/L. Vaginal cultures were positive for *Capnocytophaga* sp. The mother was treated with ampicillin. She progressed into labour despite nicardipine tocolysis, and delivered vaginally. The infant was treated for RDS by intubation, surfactant administration and assisted ventilation. Intravenous ampicillin, cefotaxime and gentamicin were administered empirically, after bacterial sampling. The CRP level was slightly increased, at 5.2 mg/L at birth and 6.5 mg/L on the first day of life, with a WBC count of 23 900 $\times$ 10^9/L. Cultures of tracheal aspirate and gastric fluid yielded *Capnocytophaga* spp. Blood culture was negative. A favourable outcome was observed in response to treatment with ampicillin for 1 week.

Bacteriological data

Gastric aspirate, meconium and tracheal aspirate samples, collected soon after birth, were cultured in all cases of this

series. After 3 days of incubation on sheep blood agar (bioMérieux, Marcy l'étoile, France) under anaerobic conditions, and on chocolate agar (bioMérieux) under 10% CO_2, some colonies exhibited typical gliding mobility. The bacteria were fusiform, Gram-negative and non-spore-forming rods. On the basis of CO_2 requirements, cellular morphology, and negative catalase and oxidase reactions, the organisms were suspected of belonging to a *Capnocytophaga* sp. The genus was identified at 99% similarity with the bioMérieux VITEK anaerobe identification system (bioMérieux). Identification was confirmed by 16S rRNA gene sequencing. Blood cultures were performed in a BACTEC 9000 (BD, Becton Dickinson Diagnostic Systems, NJ, USA). All *C. sputigena* strains were susceptible to penicillins, cephalosporins, macrolides, clindamycin and tetracycline, and were not β-lactamase producers.

Review of the literature

All cases of perinatal infection or colonization with *Capnocytophaga* spp., published in English and found on Medline, were included [7–20]. Data concerning 19 mothers and 20 newborns with possible or confirmed neonatal *Capnocytophaga* sp. infection are summarized in Table 1 (maternal data) and Table 2 (neonatal data). *Capnocytophaga* infection or colonization is mainly associated with preterm labour (18 of 19 cases), but clinical chorioamnionitis, according to the accepted clinical and laboratory criteria [21], was present in less than one-third of the cases, with intact membranes (four of six) or preterm premature rupture of membranes (two of six). Histological examination of the membranes and placentas showed signs of chorioamnionitis in 12 cases, associated with clinical chorioamnionitis in five cases. Nineteen of the 20 infants were preterm, and 16 of them were born before 30 weeks of gestation. The clinical manifestations of *Capnocytophaga* sp. infection are variable. According to the criteria of sepsis of the international sepsis forum 2004 [22], five infants presented proven EOS, five presented probable EOS, and two were not infected. No conclusions could be drawn in the other cases, owing to insufficient data. Only one case of septic shock and one death have been reported, but no information on outcome was provided for five infants. A favourable outcome was reported for the majority of cases.

Discussion

This series of five cases and a review of 14 published cases of chorioamnionitis and neonatal infections caused by *Capnocytophaga* spp., an unusual, non-genital tract organism, indicate that *Capnocytophaga* spp. can be responsible for early preterm labour and delivery, but not for severe neonatal infection.

Occult or clinical chorioamnionitis may be responsible for the majority of preterm deliveries [23]. Organisms not commonly found in the genital tract, such as members of the *Capnocytophaga* genus inhabiting the oral cavity, may be found in amniotic fluid in the context of preterm labour and chorioamnionitis. These organisms may reach the uterus via orogenital contact. Orogenital contact has been described as a cause of chorioamnionitis in several case reports, with isolation of *Capnocytophaga* sp from a partner with periodontal disease, and a temporal relationship between orogenital contact and onset of clinical infection [16–18].

TABLE 1. *Capnocytophaga* species and preterm birth: maternal clinical data

Case	References	Preterm labour	PPROM	Clinical chorioamnionitis	Leukocytosis ($\times 10^9$/L)	Fetal tachycardia	Delivery	Pathological findings	Site of isolation
1	Present	Yes	Yes	No	8600	Yes	CS	Chorioamnionitis	NR
2	Present	Yes	No	No	11 200	No	VD	Chorioamnionitis	NR
3	Present	Yes	No	Yes	21 000	No	VD	Chorioamnionitis	NR
4	Present	Yes	No	No	22 800	No	VD	Chorioamnionitis	NR
5	Present	Yes	Yes	No	16 300	Yes	VD	NR	NR
6	[20]	Yes	No	No	NR	NR	VD	NR	NR
7	[19]	Yes	No	No	15 000	No	VD	Chorioamnionitis	Placenta, cervix
8	[18]	Yes	Yes	No	12 500	NR	VD	Chorioamnionitis	Placenta
9	[17]	Yes	No	Yes	16 600	No	CS	Chorioamnionitis	Amniotic fluid
10	[16]	Yes	No	Yes	NR	Yes	VD	NR	Amniotic fluid, placenta
11	[15]	Yes	No	Yes	9790	NR	CS	Chorioamnionitis	Amniotic fluid, cervix
12	[14]	Yes	Yes	Yes	Yes	NR	CS	Chorioamnionitis	Endometrium
13	[13]	Yes	No	No	NR	NR	VD	NR	Amniotic fluid
14	[12]	Yes	No	No	NR	NR	VD	NR	Amniotic fluid, placenta
15	[11]	Yes	Yes	Yes	NR	NR	CS	Chorioamnionitis	Endometrium
16	[10]	No	No	No	NR	NR	CS	Chorioamnionitis	NR
17	[9]	Yes	No	No	NR	No	VD	Chorioamnionitis	Endometrium
18	[8]	Yes	Yes	No	NR	No	CS	NR	Endometrium
19	[7]	Yes	No	No	20 600	No	VD	NR	Amniotic fluid

CS, caesarean section; NR, not reported; PPROM, preterm premature rupture of membranes; VD, vaginal delivery.

TABLE 2. ***Capnocytophaga*** **species and preterm birth: neonatal clinical data**

Case	References	Gestation (weeks)	Birthweight (g)	Clinical signs	WBC count ($\times 10^9$/mm^3)	Maximal CRP level (mg/L)	Site of isolation (fluid)	Treatment	EOS	Outcome
1	Present	26	790	Respiratory failure	37 700	14	Trachea, gastric	Cefotaxime	Probable	Alive
2	Present	28	1180	Respiratory failure	8200	6	Gastric, blood	Cefotaxime	Proven	Alive
3	Present	29	1170	Respiratory failure, hypotonia	2100	46	Trachea gastric	Ampicillin	Probable[a]	Alive
4	Present	25	800	Respiratory failure	75 900	17	Trachea, gastric	Ampicillin	Probable	Alive
5	Present	25	855	Respiratory failure	23 900	6.5	Trachea, gastric	Ampicillin	Probable	Alive
6	[20]	28	1325	Cystic lung disease	4100	23	Blood	Cefotaxime	Proven	Alive
7	[19]	29	1220	Respiratory failure, hypotonia	25 000	121	None	Ampicillin	Probable	Alive
8	[18]	22	493	Low Apgar score	NR	NR	NR	NR	NR	NR
9	[17]	25	890	Respiratory failure	NR	NR	None	NR	No	Alive
10	[16]	24	660	Respiratory failure	NR	NR	NR	NR	NR	Dead
11	[15]	33	NR	Respiratory failure, hypotonia	7700	NR	None	Ampicillin	NR	Alive
12	[14]	25	760	Respiratory failure hypotension, DIC	78 000	44	Gastric, blood	Ampicillin	Proven	Alive
13	[13]	30	1380	Respiratory failure, bradycardia	NR	NR	Gastric	Ampicillin	NR	NR
14	[13]	29	1360	Respiratory failure	NR	NR	Gastric	Ampicillin	NR	NR
15	[12]	26	910	Respiratory failure	13 000	NR	Gastric	Ampicillin	NR	Alive
16	[11]	28	1000	Respiratory failure	NR	NR	NR	Ampicillin	NR	NR
17	[10]	39	3820	NR	NR	NR	NR	NR	No	NR
18	[9]	29	1530	NR	NR	NR	Trachea, blood	Ampicillin	Proven[a]	Alive
19	[8]	33	1800	Respiratory failure, cardiac dysfunction	3000	NR	Trachea, blood	Ampicillin	Proven	Alive
20	[7]	32	1820	NR	NR	NR	Gastric	NR	NR	Alive

CRP, C-reactive protein; DIC, disseminated intravascular coagulopathy; EOS, early-onset sepsis; NR, not reported; WBC, white blood cell.
[a]Probable or proven according to the consensus criteria of sepsis of the international sepsis forum 2004.

Chorioamnionitis may also be due to haematogenous spread of bacteria from the bloodstream to the uterus across the placenta. Preterm labour can also be secondary to systemic inflammation triggered by oral organisms [24], and several papers have emphasized the importance of periodontal infection as a trigger for preterm labour [25,26].

Capnocytophaga is a fastidious, fusiform, non-spore-forming, gliding, Gram-negative bacillus, usually isolated from the oral cavity and rarely found in the genital tract. Previously known as CDC biogroup DF-1 and *Bacteroides ochraceus*, this genus was discovered in 1979 and includes three species: *Capnocytophaga ochracea*, *C. sputigena* and *Capnocytophaga gingivalis* [27]. Identification and sequencing of 16S rRNA genes in culture-negative amniotic fluid from women in premature labour may have helped to reveal the bacterial origin of preterm labour, as bacterial organisms such as capnocytophagae can be identified by this molecular approach [28]. As these techniques are not performed routinely, most cases of preterm labour caused by *Capnocytophaga* spp. are probably not identified.

In the cases reported here, as in previous cases, infection was rarely proven, but probable. The favourable neonatal course in most cases indicates that neonatal *Capnocytophaga* infections are not severe. The prognosis therefore appears to be related more to early preterm birth than to neonatal infection.

Capnocytophaga isolates are usually sensitive to ampicillin or cephalosporins, the antibiotics mainly used to treat suspected neonatal infections. In our five cases of EOS, *Capnocytophaga* was susceptible to penicillins, ampicillin and cephalosporins, and was resistant to gentamicin, as previously reported [19].

This case series has a number of limitations. We report only one case of proven *Capnocytophaga* infection and four probable infections. However, these four probable cases were defined according to the criteria of sepsis of the international sepsis forum 2004 [22], and all infants presented markers of inflammation. Similarly, the organism was not found in placental, endometrial or amniotic fluid cultures, but cultures of these samples are not performed routinely in our department. Although histological examination of the membranes and placenta demonstrated signs of chorioamnionitis in four patients, failure to isolate the organism from maternal samples is obviously a weakness of our series, as compared with the cases reported in the literature, in which *Capnocytophaga* was usually isolated from endometrial, amniotic fluid or placenta samples.

This highlights the difficulties of isolating this organism and the importance of tracking *Capnocytophaga* in these maternal samples.

In conclusion, the incidence of perinatal infections caused by *Capnocytophaga* spp. is probably underestimated, and these organisms may be responsible for occult chorioamnionitis and preterm birth. Clinicians must be aware of the role of this organism as a possible cause of premature labour and EOS in neonates. Owing to the difficulties of isolation, the

prevalence of this organism may be higher than previously suggested, and there is a need for the application of molecular methods of identification. Further studies are needed to elucidate a possible relationship between periodontal disease and preterm birth.

Transparency Declaration

The authors have no financial disclosure or conflict of interest.

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