



Late Onset Neonatal Sepsis Due to *Hafnia alvei* in Three Neonates at the University of Nigeria Teaching Hospital, Enugu, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Authors UN, KI, IO, CO, IN, HO, GA made significant contributions to the conceptualization of the work, literature search, drafting and approval of the final version for publication. IN also assisted in the blood cultures. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Background: *Hafnia alvei* is a Gram-negative motile bacillus, belonging to the *Enterobacteriaceae* family. It is commonly found in stool of humans and animals and soil. It is very rare in neonates. This organism is resistant to most commonly used antibiotics, and causes nosocomial outbreaks with significant mortality. Therefore, awareness regarding this organism is important to improve outcome.

Presentation of Cases: We report three cases of late onset neonatal sepsis caused by *Hafnia alvei*. Of these, two were preterm while one was term. The term neonate was referred on account of perinatal asphyxia and developed fever, reduced activity, tachycardia, and tachypnoea 5 days into admission. The two preterm neonates were delivered at the index hospital and developed hypothermia, and other symptoms on the 4th day of life. Two sets of blood cultures were done for

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each case after collecting blood from two different sites. Blood culture was done using BACT/ALERT 3D (BioMerieux, Marcy l'Etoile, France) which uses a colorimetric sensor and reflects light to monitor the presence of carbon dioxide produced by micro-organisms. This yielded *Hafnia alvei* in all three samples after 72 hours of incubation. Gram stain done showed presence of Gram negative bacilli and subculture was done on MacConkey and 5% sheep agar incubated at 37 °C for 18-24 hours. Identification of isolates was done with standard biochemical test and confirmed with API 20 E identification system (BioMerieux, Marcy l'Etoile, France). Antibiotic sensitivity was done using the modified Kirby Bauer disc diffusion method (Oxoid, Cambridge, UK). At most five antibiotic discs were used for each isolate and these were incubated at 37°C for 24 hours. Isolates were sensitive to fluoroquinolones, cefepime and meropenem. Patients received intravenous antibiotics for two weeks, phototherapy and exchange blood transfusion. They were subsequently discharged and are currently on follow up.

Discussion and Conclusion: Though rare, three infections with *H. alvei* were reported in this study. The isolates were sensitive to fluoroquinolones, cefepime and meropenem and resistant to amoxicillin/clavulanic acid, piperacillin/tazobactam. The outcomes were improved by a high index of suspicion, early diagnosis, prompt institution of appropriate antibiotics and supportive care.

Keywords: Late onset; neonatal; sepsis; *Hafnia alvei*.

1. INTRODUCTION

Hafnia alvei (*H. alvei*) is currently the only known species of the genus *Hafnia*, which belongs to the *Enterobacteriaceae* family.[1] It is a Gram negative motile bacillus and a facultative aerobe.[2] It is commonly found in stool of humans and animals and soil.[1] *H. alvei* causes a variety of infections, including septicaemia, meningitis, abscesses, pneumonia and gastrointestinal infections in adults, especially the immuno-compromised.[3] However, it is a very rare cause of infection in neonates, compared to adults.[4]

A study by Washington et al [5] on seventeen patients with *Hafnia* infections showed that about half of these infections were transmitted via nosocomial spread from faecal contamination of hospital environment or surfaces. Infections in neonates have also been linked to maternal carriage of *Hafnia alvei* as part of the normal flora of the vagina and GIT.[6] Community-acquired infections have also been reported.[7]

The first *H. alvei* infection in a neonate was reported in 1988 in a 20 day old preterm delivered at 30 weeks, who had sepsis and necrotising enterocolitis (NEC).[8] A search of the available literature revealed that only nineteen cases of *H. alvei* infections have been reported in humans worldwide, and none in Africa.[8,9,10,11,12,13]

We report three cases of late onset neonatal sepsis that were managed in our new born Special Care Unit (NBSCU) within the same period.

2. CASE REPORTS

2.1 Case 1

A term male neonate, weighing 3950 grammes, who was delivered via emergency lower segment Caesarean section at 40 weeks of gestation to a 22 year old primiparous woman on account of uterine rupture and antepartum haemorrhage. Apgar scores were 5 and 6 in the first and fifth minutes of life respectively. Baby was referred to the NBSCU six hours after birth due to poor cry at birth, difficulty in breathing and convulsions which were noticed shortly after birth.

The salient examination findings at presentation are summarised in Table 1. An admitting diagnosis of perinatal asphyxia (hypoxic ischaemic encephalopathy stage 2 according to the Sarnat and Sarnat staging) was made.

He was resuscitated, and commenced on bubble continuous positive airway pressure (CPAP), anti-convulsants and dextrose containing intravenous fluids (two-thirds of the maintenance fluid). Full blood count, transfontanelle ultrasound and serum electrolyte, urea and creatinine results were essentially normal. Seizures resolved on the 3rd day of life, feeds were commenced, he was weaned off CPAP, and remained stable.

The examination findings on the 6th day of life are summarised in Table 2 while the repeat haematological parameters are summarised in Table 3. Blood culture done using BACT/ALERT 3D (BioMerieux, Marcy l'Etoile, France) yielded

Hafnia alvei after 72 hours of incubation. The isolate was sensitive to ciprofloxacin, levofloxacin and cefepime, but resistant to amoxicillin/clavulanic acid, piperacillin/ tazobactam.

He was managed with a 14-day course of intravenous ciprofloxacin in addition to a single volume exchange blood transfusion. Fever resolved by the third day of antibiotic therapy.

2.2 Case 2

Preterm male neonate, first of a set of quadruplets, delivered by emergency lower segment Caesarean section to a primiparous 26 year old female on account of preterm premature rupture of membranes (6 hours prior to delivery) at a gestational age of 30 weeks. Apgar scores were 8 and 9 in the first and fifth minutes of life respectively, and he weighed 1280 grammes. Liquor was colourless and not foul smelling.

The salient clinical findings at presentation are summarised in Table 1. Admitting diagnosis of very preterm, very low birth weight (appropriate for gestational age) at risk for sepsis and respiratory distress syndrome was made.

He was commenced on bubble CPAP, caffeine citrate, prophylactic antibiotic (ceftazidime), dextrose containing intravenous fluid and incubator nursing. Full blood count parameters were within normal range. Respiratory distress resolved on the second day of life and he was weaned off bubble CPAP, and commenced on trophic feeds (breast milk).

He remained stable until the 4th day of life, when he developed temperature instability, jaundice and hypoglycaemia. The examination findings are summarised in Table 2. Results of repeat full blood count and serum bilirubin are shown in Table 3. Blood culture yielded *Hafnia alvei* after 72 hours of incubation, sensitive to meropenem and ciprofloxacin, but resistant to amoxicillin/clavulanic acid, piperacillin /tazobactam.

He received a double volume exchange blood transfusion, phototherapy, and a two-week course of intravenous meropenem. Fever and jaundice resolved 3 days into therapy.

2.3 Case 3

Preterm male neonate, second of a set of quadruplets, delivered via emergency lower segment Caesarean section to a primiparous 26

year old female on account of preterm premature rupture of membranes (6 hours prior to delivery) at a gestational age of 30 weeks. Apgar scores were 8 and 9 in the first and fifth minutes of life respectively, and he weighed 1050 grammes. Liquor was colourless and not foul smelling.

A summary of the salient examination findings is seen in Table 1. Admitting diagnosis of very preterm, very low birth weight (appropriate for gestational age) at risk for sepsis and respiratory distress syndrome was made.

He was commenced on bubble CPAP, caffeine citrate, prophylactic antibiotic (ceftazidime), dextrose containing intravenous fluid and incubator nursing. Full blood count parameters were within normal range. Respiratory distress resolved on the second day of life and he was weaned off bubble CPAP, and commenced on trophic feeds (breast milk).

On the 4th day of life, he developed hypothermia, jaundice and hypoglycaemia. Repeat full blood count and serum bilirubin results are summarised in Table 3. Blood culture yielded *Hafnia alvei* after 72 hours of incubation, sensitive to meropenem and ciprofloxacin, resistant to amoxicillin/clavulanic acid, piperacillin /tazobactam.

He received a double volume exchange blood transfusion, phototherapy and a two-week course of intravenous meropenem. Fever and jaundice resolved by the 4th day of therapy.

All cases have been discharged, and are currently on follow up.

3. DISCUSSION

Hafnia alvei was initially thought to be a commensal of the gut, and rarely pathogenic, but a recent study suggests that is a significant cause of opportunistic infections in immunocompromised and debilitated individuals.[3] In 1954, Möller first described this genus and suggested the name *Hafnia alvei*. [2] The genus name *Hafnia* is the historical name (Havn) for the city of Copenhagen, Denmark and the species name *alvei* (derived from Latin) means "of a beehive".[1,3]

Nineteen cases of neonatal sepsis caused by *H. alvei* have been reported so far, of which fifteen were among preterm neonates (79%), with a mortality rate of 16% (3 deaths), and all but one

Table 1. Salient examination findings of the cases at presentation

Parameter	Case 1	Case 2	Case 3
Temperature (°C)	36	36.7	35.7
Heart rate (b/min)	128	148	168
Respiratory rate (b/min)	36	53	64
Central nervous system	Unconscious (GCS 8/15), poor spontaneous activity, normotensive anterior fontanelle, hypotonia, depressed primitive reflexes.	Conscious, fair spontaneous activity, fair cry on stimulation, hypotonia	Conscious, fair spontaneous activity, fair cry on stimulation, hypotonia
Respiratory system	Shallow respiration, no adventitia on auscultation	Mild respiratory distress (flaring of the alar nasii), no adventitia on auscultation	Mild respiratory distress (flaring of the alar nasii), no adventitia on auscultation

GCS: Glasgow coma score

Table 2. Clinical parameters of the cases at time of infection

Parameter	Case 1 (6 th day of life)	Case 2 (4 th day of life)	Case 3 (4 th day of life)
Temperature (°C)	39.2	35.6	35.8/38
Heart rate (b/min)	176	185	180
Respiratory rate (b/min)	66	76	72
Systemic examination findings	Reduced spontaneous activity, no other abnormality	Jaundice, pallor, reduced spontaneous activity, no other abnormality	Jaundice, reduced spontaneous activity, no other abnormality

Table 3. Laboratory parameters of the cases

Parameter	Case 1	Case 2	Case 3
White blood cell count (/mm ³)	20,300	25,600	30,690
Neutrophil (%)	84	76	75
Haemoglobin level (g/dl)	12.6	9.6	12.8
Platelet count (/mm ³)	164,000	86,000	286,000
Serum bilirubin (mg/dl)	-	Total bilirubin: 11.03, Direct bilirubin: 1.8	Total bilirubin: 14.65, Direct bilirubin: 1.2

case presented with late onset sepsis.[8,9,10,11,12,13] In 1988, *H. alvei* infection was first reported in neonates in a 20 day old preterm (30 weeks) baby with sepsis and NEC.[8] Later in 2004, a nosocomial outbreak of *H. alvei* sepsis was reported in 4 preterm babies (24-31 weeks) by Pérez A *et al* [11] in Spain.

Of the three cases presented in this report, two were preterm, with maternal history of preterm premature rupture of membranes, which is a risk factor for neonatal sepsis.[14]The first case was resuscitated as a result of birth asphyxia, and sepsis has also been reported following instrumentation during resuscitation.[11]

All cases had late onset neonatal sepsis, and had been on admission in the NBSCU since the day of birth, suggesting a source of infection other than their mothers. Cultures from the mother of the last two cases presented yielded no bacterial growth. In addition, the organism was not cultured from the other remaining siblings. *Hafnia alvei* is commonly found in the gut of immuno-competent adults, and could cause nosocomial outbreaks following poor hygiene in nursery staff.[3,5] Transmission via the maternal vagina has also been reported, [6] but this was not the case in the present report.

Extra-intestinal manifestations were seen in the cases reported in this study. *H. alvei* causes a variety of infections, including septicaemia, meningitis, abscesses, pneumonia and gastro-intestinal infections.[3] Ginsberg and Goldsmith [8] and Basani and Aepala [9] documented *H. alvei* neonatal sepsis manifesting with symptoms of necrotising enterocolitis.

The cases presented exhibited similar sensitivity pattern, sensitive to quinolones, cephalosporins and carbapenems. Basani and Aepala [9] in India, also reported intermediate sensitivity to moxifloxacin, meropenem and imipinem. Infections with this organism are usually susceptible to second and third generation cephalosporins and quinolones.[3]

The antibiotic resistance patterns of the cases presented were similar, with resistance to amoxicillin/clavulanic acid, cefepime and piperacillin/tazobactam. Basani and Aepala[9] also noted resistance to aminoglycosides, extended spectrum penicillins and cephalosporins.

Risk factors for *H. alvei* infection include prolonged hospital stay, antibiotic therapy longer than 14 days, mechanical ventilation and presence of central venous, endotracheal or umbilical catheters.[11-13] These risk factors were absent in the cases presented.

4. CONCLUSION

Though still uncommon in NICUs, three infections with *H. alvei* were reported in this study. The isolates were sensitive to fluoroquinolones, cefepime and meropenem and resistant to amoxicillin/clavulanic acid, piperacillin/tazobactam. The outcomes were improved by a high index of suspicion, early diagnosis, prompt institution of appropriate antibiotics and supportive care.

CONSENT

All authors declare that written informed consent was obtained from the parents of the subjects for publication of this case report. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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