The Role of _Citrobacter_ in Clinical Disease of Children: Review

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Various species of _Citrobacter_ may cause infections in neonates and immunocompromised hosts. _Citrobacter koseri_ (formerly _Citrobacter diversus_) is best known as the cause of sepsis and meningitis leading to central nervous system (CNS) abscesses in neonates and young infants. Early onset and late-onset infections occur as for other neonatal bacterial infections. The majority of cases are sporadic, with no clear source of infection. A few have been confirmed to be vertically transmitted, and nosocomial outbreaks have occurred in neonatal care units. The pathophysiology is not well understood, but a surface protein has been identified as a possible virulence factor among strains that cause _citrobacter_ brain abscesses in neonates. Despite improvements in diagnostic imaging techniques, surgery, and antibiotic therapy, approximately one-third of infants with abscesses die, and one-half sustain CNS damage. In this article, the taxonomy, epidemiology, pathogenesis, diagnosis, treatment, and outcome of _citrobacter_ disease in children are reviewed.

Bacteria of the genus _Citrobacter_ are infrequent causes of infections in neonates and in immunocompromised adults or older children [1, 2]. Neonates may acquire the organisms horizontally as nosocomial infections or vertically from the mother at delivery. Frequently the origin of sporadic cases is unknown. In the neonatal period, _Citrobacter koseri_ (formerly _Citrobacter diversus_) is responsible for most infections, while both _C. koseri_ and _Citrobacter freundii_ (along with several other species recently split taxonomically from _C. freundii_) cause disease in immunocompromised individuals.

In the first 2 months of life, _C. koseri_ has a strong predilection for affecting the CNS, causing meningitis and brain abscesses. There are also occasional reports of neonatal sepsis or bacteremia without CNS disease. _Citrobacter_ is an uncommon cause of infections of bones, joints, or soft tissues in early infancy. In contrast, immunocompromised adults or older children rarely develop CNS disease, but a variety of other infections have been reported. For infants with meningitis and CNS abscesses, optimal therapy has not been established, and outcome is generally poor. This review of _Citrobacter_ will examine the organism, epidemiology, infectious processes, diagnosis, and treatment options with regard to children.

Classification and Properties

Organisms of the genus _Citrobacter_ are gram-negative bacilli of the family Enterobacteriaceae, tribe Citrobacterae [1, 2]. The genus was originally in the tribe Salmonelleae but was reclassified as a unique tribe. These bacteria have undergone frequent, sometimes confusing changes in nomenclature that make it difficult to clearly determine whether some reported cases are legitimately attributable to _Citrobacter_ or to particular species within the genus. Serotyping and biotyping schemes have been developed to alleviate some of the confusion [2–8]. This has become more important following reorganization of the genus into 11 species (8 named and 3 as yet unnamed species) [8–10], as shown in table 1.

Organisms of the genus _Citrobacter_ are straight, facultatively anaerobic bacilli, found singly or in pairs, and are typically motile by means of peritrichous flagellae [2]. They catabolize glucose and numerous other carbohydrates by production of acid and gas. They are oxidase-negative, catalase-positive, methyl red–positive, Voges-Proskauer-negative, lysine decarboxylase–negative [1, 2, 8], and usually citrate-positive. A report in 1928 of a new organism, _Bacterium freundii_, was the initial description [11] of the organism reclassified as _Citrobacter_ in 1932 [12]. At that time the genus had seven species, including _C. freundii_ and _Citrobacter diversus_ (later _C. diversus_), which continued to be recognized as valid species over an extended period of time. A number of genus names have been used and discarded for these organisms over 70 years, including _Colobactrum_, _Escherichia_, _Salmonella_, _Arizona_, and others, some of which are no longer valid bacterial genus names (table 1).

At various times the organisms were classified as part of the paracolon group [13–17] and as part of the Ballerup [18], Bethesda [19] and Bethesda-Ballerup groups [20] of bacteria. The paracolon and Bethesda-Ballerup terminology continued to be used at times for many years after they had lost practical utility. Classification problems continued from 1970 to the present [17].

In the 1970s several genus and species designations were proposed, most of which were later discarded. _C. koseri_ was used to describe a collection of strains that was differentiated biochemically from _C. freundii_ [21]. The genus _Levinea_ was proposed in 1971 to include _Levinea malonatica_ and _Levinea_...
amalonatica, differentiated by whether malonic acid was hydrolyzed [22]. C. diversum reemerged as a species in the early 1970s but was changed for grammatical reasons to C. diversus [6].

For a period of time the names C. diversus, C. koseri, and L. malonatica were in use simultaneously. The name C. diversus temporarily replaced the others as the correct name and L. malonatica and C. koseri were eliminated as valid species [23]. From that point until 1990, the genus Citrobacter was recognized to have four species, C. freundii (the type species), C. diversus, C. amalonaticus, and sometimes C. amalonaticus biogroup 1 [24]. In 1990 C. koseri replaced C. diversus, which was eliminated as a valid species. In 1993 C. freundii was found to be a complex of eight species, including Citrobacter youngae, Citrobacter braakii, Citrobacter werkmanii, and Citrobacter sedlakii and the unnamed genomospecies 9, 10, and 11 [9]. The current classification for Citrobacter is shown in table 1.

Epidemiology

Citrobacter species are occasional inhabitants of human and animal intestines and of soil, water, sewage, and food [1, 2]. Two groups are at the highest risk for clinical disease due to these organisms. Neonates occasionally develop sepsis and meningitis and have a propensity for development of CNS abscesses. The second broad group is persons of any age who are debilitated or immunocompromised.

There have been 11 neonatal cases that can be attributed to mother-to-child transmission of Citrobacter (table 2) [25–35]. Some of these are proven by isolating the organism from mother and child. Other neonates have had symptoms within hours of birth, strongly suggesting vertical transmission. Nine of 11 developed disease, and two were only colonized [25, 29]. The latter are included in the summary of these cases to confirm the growing body of evidence that vertical transmission of Citrobacter occurs. These cases are discussed in more detail below.

In most cases the source of the organism is not known. Clinical and culture data from the mothers are often sketchy or lacking. There are several cases in the literature of newborns becoming infected within the first few days of life. It is a reasonable assumption that these infections may have been vertically acquired, though the confirmatory data are lacking. The presence of symptoms in the mothers of infected infants suggests but does not prove vertical transmission. There have been interesting reports of cases in which only one infant of a twin [27, 36–38] or triplet set [39] was found to be infected. A great deal of information is lacking with regard to the vertical transmission risks of Citrobacter.

Several well-documented nosocomial outbreaks resulting in colonization or disease [25, 29, 31, 36, 37, 39–47] have been described (table 3). These outbreaks have lasted for periods of a few months to several years. The sources of the organisms have most frequently been found to be the gastrointestinal tracts or hands of hospital staff members [25, 29, 37, 39, 41–44], with hospital personnel described as the sources in seven of nine clusters. In contrast, environmental sources were not important reservoirs of the organisms. A nosocomial cluster of C. freundii isolates from a neonatal intensive care unit was traced to contaminated infant formula [46]. On the basis of the available information, person-to-person transmission seems to be much more prevalent than transmission from environmental sources.

Most cases of neonatal citrobacter disease are considered sporadic [48–72] if there is not a clear understanding of how the organism was acquired. These could be vertically acquired from the mother in the perinatal period or horizontally acquired from environmental sources, hospital personnel, or family members.

Citrobacter Disease in Neonates

Age at diagnosis. In 1981, Graham and Band summarized 74 cases of neonatal meningitis due to Citrobacter species [73], including a few previously reported by the Second Neonatal Meningitis Cooperative Study Group [74]. Among the 56 additional cases reviewed for the current article, there were 54 infants with clinical disease. Fifty-one had meningitis, one had bacteremia, and two had sepsis, but it was not clear whether meningitis was also present. Two were only colonized but are included since they are among the small number of reports verifying vertical transmission of Citrobacter.

Onset of symptoms normally occurred between 1 and 42 days of age. Citrobacter infections may occur as early onset or late-onset disease, as has been reported for other neonatal infections, such as those due to group B Streptococcus and Listeria. In the current review, there was found to be a natural breakpoint in the cases at 15 days, and that breakpoint may be arbitrarily used to distinguish early and late-onset cases. In the
Table 2. Factors associated with vertical transmission of *Citrobacter koseri* (*Citrobacter diversus*).

<table>
<thead>
<tr>
<th>Case no. [reference]</th>
<th>Maternal factors</th>
<th>Maternal culture specimen(s)</th>
<th>Neonatal factors: birth weight/ gestational age in w</th>
<th>Onset of symptoms (d)</th>
<th>Positive neonatal culture(s)</th>
<th>Neonatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [25] Hospital nurse</td>
<td>Perineum</td>
<td>NA</td>
<td>NA</td>
<td>Umbilicus</td>
<td>Colonization</td>
<td></td>
</tr>
<tr>
<td>2 [26] Cerclage; ROM, 11 h; asymptomatic fever</td>
<td>Cerclage</td>
<td>1,670 g/34 w</td>
<td>5</td>
<td>Stool (bloody), blood, skin</td>
<td>Sepsis, meningitis</td>
<td></td>
</tr>
<tr>
<td>3 [27] ROM, 18 h; chorioamnionitis; preterm labor/ fever</td>
<td>Placenta</td>
<td>800 g/27 w</td>
<td>1</td>
<td>Blood, endotracheal</td>
<td>Meningitis, sepsis; survived</td>
<td></td>
</tr>
<tr>
<td>4 [28] Cerclage; premature labor; ROM, 36 h</td>
<td>Cervix, placenta</td>
<td>985 g/29 w</td>
<td>1</td>
<td>Blood, skin</td>
<td>Sepsis; died at 2 d</td>
<td></td>
</tr>
<tr>
<td>5 [29] NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Colonization</td>
<td></td>
</tr>
<tr>
<td>6 [30] NA</td>
<td>Vagina</td>
<td>. . .</td>
<td>. . .</td>
<td>CSF</td>
<td>Meningitis</td>
<td></td>
</tr>
<tr>
<td>7 [31] Asymptomatic</td>
<td>Vagina</td>
<td>. . .</td>
<td>. . .</td>
<td>Blood</td>
<td>Bacteremia</td>
<td></td>
</tr>
<tr>
<td>8 [32] Chorioamnionitis</td>
<td>Blood, amniotic fluid</td>
<td>3,800 g/term</td>
<td>1</td>
<td>Blood</td>
<td>Sepsis, meningitis (?)</td>
<td></td>
</tr>
<tr>
<td>9 [33] Chorioamnionitis; bacteremia; ROM, 7 d</td>
<td>Blood, placenta</td>
<td>2,525 g/35 w</td>
<td>1</td>
<td>Blood</td>
<td>Sepsis, meningitis, neurological deficits</td>
<td></td>
</tr>
<tr>
<td>10 [34] Fever; intramniotic infection</td>
<td>Blood (?), vagina (?)</td>
<td>Term</td>
<td>1</td>
<td>Blood (?), CSF (?)</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>11 [35] UTI 2 w before delivery</td>
<td>Not done</td>
<td>890 g/27 w</td>
<td>1</td>
<td>Blood, CSF, tracheal aspirate</td>
<td>Intraventricular hemorrhage/ hydrocephalus</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. NA = not applicable; ROM = rupture of membranes; UTI = urinary tract infection; . . . = not available.

40 early onset cases for which data were reported, the mean age was 7.1 days (range, 1–15 days) at diagnosis; in the nine late-onset cases, the mean age was 32.9 days at diagnosis (range, 15 days to 6 weeks). The mean age at diagnosis was 11.8 days for all cases combined. This compares to a previous review [73] in which the children ranged in age from 1 day to 8 weeks at diagnosis, with a mean of 7.4 days.

Of the 11 documented cases of vertical transmission (table 2), 9 were infections and 2 were only colonizations [25–35]. Of the nine infected children, all had the organism isolated from the blood. Five had culture-confirmed meningitis or probable meningitis, diagnosed on the basis of abnormal CSF cellularity and chemistry results [26, 27, 31, 33, 35], and another infant was treated for “presumed” or possible meningitis [32]. In some cases in which no organism was isolated from CSF, the patients were apparently unstable infants for whom antibiotic therapy had been initiated prior to lumbar puncture. One infant had bacteremia [31], and another died of sepsis on the second day of life (there was no mention of meningitis in the report) [28]. For one infant, “pancultures” were performed, although it was not clearly indicated that these included CSF culture [34]. Of the 9 infected children, 6 (5 with meningitis) developed disease on the first day of life, 1 developed disease on day 5, and 2 had an undocumented onset of disease.

It is likely that in some cases considered to be sporadic, the *citrobacter* disease was acquired vertically. Likewise, nosocomial transmission may be responsible for some sporadic cases, though confirmatory data are lacking. Almost one-third of sporadic cases were of late onset, typically occurring at ~4–5 weeks. Most early onset cases occur between 5 and 12 days of age (mean, 7.1 days). Cases of vertically acquired disease, a subset of the early onset cases, tend to occur earlier, usually on the first day of life (as in the few proven cases).

**Gestational age and conditions.** Prematurity (gestation of <37 weeks) was common (71.4%) in cases of proven vertically acquired *citrobacter* infections. Those infants had a mean gestational age of 32.6 weeks (range, 27–40 weeks). In contrast, 27.3% of infants described as having been infected as part of nosocomial outbreaks were premature, and 25.9% of sporadically infected children were premature. The infants with disease diagnosed as part of nosocomial outbreaks had a mean gestational age of 39.2 weeks, and those infected sporadically had a mean age of 37.7 weeks. Among all infants, 34.1% were premature and the mean gestational age was 37.5 weeks. This finding is comparable to that of a previous review [73], in which it was indicated that 23 (36.5%) of 63 infants were premature or weighed <2,440 g at delivery, with a mean gestational age of 37.7 weeks.

Data regarding maternal conditions were sparse, but the mothers in the two cases of vertical transmission had cerclages, possibly serving as the site of initial infections. Several had chorioamnionitis or endometritis, and four had positive blood
Table 3. Data concerning outbreaks of *Citrobacter koseri* (*C. diversus*) infection in neonatal intensive care units.

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>No. of neonates infected/colonized</th>
<th>Infection(s)</th>
<th>Site and/or % of neonatal colonization</th>
<th>No. of staff members colonized or environmental source</th>
<th>Duration of outbreak</th>
</tr>
</thead>
<tbody>
<tr>
<td>[40]</td>
<td>4/2</td>
<td>Meningitis</td>
<td>NA</td>
<td>None</td>
<td>6 mo</td>
</tr>
<tr>
<td>[37]</td>
<td>4/3</td>
<td>Meningitis</td>
<td>Feces, umbilicus</td>
<td>1 (feces)</td>
<td>8 mo</td>
</tr>
<tr>
<td>[36]</td>
<td>3/65</td>
<td>Meningitis</td>
<td>Intestine, umbilicus</td>
<td>None</td>
<td>6 mo</td>
</tr>
<tr>
<td>[41, 42]</td>
<td>2/9</td>
<td>Meningitis/sepsis</td>
<td>Umbilicus</td>
<td>1 Nurse (hands)</td>
<td>3 mo</td>
</tr>
<tr>
<td>[41, 43]</td>
<td>5/140</td>
<td>5/5, Meningitis; 4/5, brain abscess, meningitis</td>
<td>Feces (includes 2 with meningitis); 79% initially colonized</td>
<td>6 Nurses</td>
<td>2 y</td>
</tr>
<tr>
<td>[31]</td>
<td>13</td>
<td>Sepsis, meningitis, UTI, skin, soft tissue</td>
<td>. . .</td>
<td>. . .</td>
<td>4 y</td>
</tr>
<tr>
<td>[25]</td>
<td>2/14</td>
<td>Meningitis/sepsis</td>
<td>Cluster 1: 11/40 (27.5%), feces, umbilicus; cluster 2: 3, nasopharynx/umbilicus</td>
<td>Cluster 1: 2 nurses (hands, ×2; rectum, ×1); cluster 2: 1 pregnant nurse</td>
<td>3 mo</td>
</tr>
<tr>
<td>[29, 44]</td>
<td>6*</td>
<td>Meningitis; 2, brain abscess</td>
<td>23, rectum; 14, skin</td>
<td>6 Nurses, 1 physician (hands, ×6; rectum, ×2)</td>
<td>2 y</td>
</tr>
<tr>
<td>[39]</td>
<td>13³</td>
<td>Sepsis</td>
<td>23.4%</td>
<td>1 Nurse (hands)</td>
<td>3.5 y</td>
</tr>
<tr>
<td>[46]</td>
<td>38</td>
<td><em>C. freundii</em> infection</td>
<td>NA</td>
<td>Infant formula</td>
<td>. . .</td>
</tr>
<tr>
<td>[47]</td>
<td>14</td>
<td>14, Sepsis; 3, meningitis; 2, septic arthritis</td>
<td>Umbilicus, eye, urine, skin pustules</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

**NOTE.** NA = not applicable; UTI = urinary tract infection; . . . = not available.

* At four hospitals.
³ Twelve of the 13 were premature.

Cultures. Rupture of membranes occurred between 11 hours and 7 days prior to delivery (six women). A few of the reports of sporadic and nosocomial cases also included information about maternal conditions (premature rupture of membranes, maternal infections, etc.) that might support the possibility of vertical acquisition. In many cases such data were not reported and confirmatory laboratory studies were inadequate to verify the means of acquisition.

Meningitis and CNS abscesses. In a prior review of 74 cases of citrobacter meningitis, *C. koseri* (*C. diversus* in that article) was overwhelmingly (in 68 cases) the most frequent causative species; another 5 cases reportedly were caused by *C. freundii* and 1 by an unidentified species [73]. The current article includes an additional 54 cases of neonatal disease caused by *Citrobacter* [25–46, 48–72]. Of those 54 who were infected, 51 had meningitis, and of the other 3, 1 had bacteremia and 2 had sepsis, with no clear evidence of meningitis. The latter three were included only to document the growing evidence of vertical transmission.

The 51 children with documented meningitis included 33 sporadic cases, 6 vertically transmitted cases, and 12 nosocomial cases (proven or presumed). Most have been reported since 1981, though a few were gleaned from older literature not previously reviewed. In 39 of 51 cases, *C. koseri* (*C. diversus*) was the causative organism. In addition, *L. malanotica*, a species since subsumed by *C. koseri*, accounted for five cases.

Hence, 44 of 51 meningitis cases (86.3%) were caused by *C. koseri* by any of its current or former names. Two were caused by *C. freundii* and one by *C. sedlakii* (reclassified from *C. freundii*), accounting for 5.9%. In four older cases, *Paracolon* was identified as the causative agent (7.8%). These cases were included because of their characteristics, which were similar to those of other cases involving neonates.

The role of *C. freundii* in neonatal disease is limited. Some cases were reported decades ago, when classification of the species was less certain, and in several articles mention is made of the difficulty with biochemical studies and microbiological identification. These need to be interpreted with caution. When reviewed in 1981 [73], *C. freundii* was reportedly responsible for 6.8% of the neonatal cases, and the current review verifies this low prevalence.

The cases attributable to *Paracolon* species and other older designations should also be interpreted with caution. They were often reported at a time when the tools available for differentiating the genera and species were not well developed. There are other reports dating back to the 1920s of cases caused by organisms that might have been *Citrobacter* species. The few more recent cases included here were similar to other cases of citrobacter disease in terms of age at onset of symptoms and pathology, and they were included for completeness.

The cases of bacteremia and sepsis due to vertical transmission that were included in this series (table 2) were caused by
C. koseri

Citrobacter species (not further clarified) and *Citrobacter* on autopsy suggested but did not prove that abscesses had once been present. How often bacteremia or sepsis occurs without meningitis or how often meningitis occurs without abscesses. Such cases may be reported less often. Only eight cases were clearly without abscesses, and for another eight this information was not given. Hence, 35 (81.4%) of 43 patients for whom the information is known had proven or probable CNS abscesses, with 68.6% of all patients having had proven abscesses. Overall, between the previous [73] and current reviews, approximately four of every five children with citrobacter meningitis had abscesses, hemorrhagic necrosis, or (occasionally) ventriculitis without true abscess formation. Abscesses within the spinal cord as well as the brain have been described [70].

It is interesting that none of the children with proven vertically transmitted disease developed abscesses. Possible explanations include the early use of antibiotics; absence of some necessary virulence factor, which might cause abscess formation; and the acute nature of disease onset. Additional characterization of cases of vertical transmission and very early acute onset meningitis is needed to show whether the absence of abscess formation may be typical for this subpopulation of neonates.

Among 12 neonates with nosocomially acquired disease, 7 had known or probable CNS abscesses, with inadequate information given for 5. Twenty-seven of 33 patients with sporadic disease had abscesses, 1 had a possible abscess, and 2 had an unknown status. Only three cases were clearly documented not to have abscesses. Information is more often complete in the sporadic cases than in other categories, possibly because the focus of those reports is often some aspect of diagnosis, pathology, or treatment of the abscess.

Occasionally *Citrobacter* is found as part of a mixed culture in cases of CNS abscess. It has been found in association with *Bacteroides* [58] and *Enterobacter cloacae* [66]. A child with maxillary sinusitis, described above [60], had *Citrobacter* isolated from the nasopharyngeal mass and alveolar ridge, the site of purulent osteomyelitis, and *Staphylococcus aureus* from an oral lesion. The resulting CNS abscess, of which a specimen was cultured after initiation of antibiotic treatment, was sterile. *Citrobacter* was the more likely cause because of proximity of the osteomyelitis and CNS abscess. In one case, *C. diversus* grew in a culture of CSF, while *Escherichia coli* grew in a blood culture [72].

It is likely that there is a selection bias in reporting cases of citrobacter abscesses. The most interesting cases, such as those in which abscesses occurred or for which evaluation of imaging methods is the thrust of the article, are probably reported in preference to those with meningitis or sepsis alone. It is not clear from the available literature how often citrobacter bacteremia or sepsis occurs without meningitis or how often meningitis occurs without abscesses. Such cases may be reported less frequently, since they might be considered less noteworthy.

### Table 4. CNS abscesses in children with citrobacter meningitis.

<table>
<thead>
<tr>
<th>Means of acquisition</th>
<th>With abscess</th>
<th>Without abscess</th>
<th>With unknown abscess status</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical</td>
<td>0</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
<td>6</td>
</tr>
<tr>
<td>Nosocomial</td>
<td>7 (58.3)</td>
<td>0</td>
<td>5 (41.7)</td>
<td>12</td>
</tr>
<tr>
<td>Sporadic*</td>
<td>28 (84.8)</td>
<td>3 (9.1)</td>
<td>2 (6.1)</td>
<td>33</td>
</tr>
<tr>
<td>All [25–46, 48–73]</td>
<td>35 (68.6)</td>
<td>8 (15.7)</td>
<td>8 (15.7)</td>
<td>51</td>
</tr>
</tbody>
</table>

* Includes 19 (79.2%) of 24 early onset sporadic cases and 9 (100%) of 9 late-onset sporadic cases.

*Citrobacter* species (not further clarified) and *C. diversus* (*C. koseri*). Among these, together with the 74 cases previously reviewed [73], *C. koseri* (by current or former designations) accounted for 89.6% of neonatal meningitis cases, *C. freundii* (by any of its designations) accounted for only 6.4%, and miscellaneous *Citrobacter* species accounted for 4.0%.

Twenty-four of the 51 patients with meningitis described here also had *Citrobacter* isolated from blood cultures. Six were reported to be blood culture-negative, and for 21 this information was not available. Therefore, in 80% of cases for which the results are known, blood cultures were positive. Even if it is assumed for those cases in which no information is given that blood cultures were negative, the minimum figure of 47% positivity is still higher than the 35% (17 of 48) previously reported [73]. The reasons for the differences between the two series are not clear. Combining data yields a total of 125 meningitis cases, among which 41 patients had positive blood cultures, 37 were culture-negative, and 47 were of unknown status. Hence, 52.6% (41) of the 78 infants with citrobacter meningitis whose culture results are known had positive blood cultures. Presumably, blood cultures are negative because they are performed incorrectly, outside of the bacteremic period, or (in some cases) after the neonates have been given antibiotics.

One child was reported to have maxillary osteomyelitis, which led to meningitis by direct extension [60], while another had a lumbosacral defect allowing direct access of the organisms to the CSF [54]. Most cases of citrobacter meningitis are assumed to be hematogenously spread [75], as is true for most other types of meningitis.

Graham and Band [73] noted that in 41 (77%) of 53 meningitis cases for which information was adequate, CNS abscesses occurred, and in 2 more ventriculitis occurred. Among the 51 cases of meningitis described in the current article, information regarding abscess formation was adequate in 43 cases (table 4). Thirty-two patients had abscesses, including two described as having hemorrhagic necrosis and three described as having necrosis that might be considered to be descriptively equivalent to an abscess, on the spectrum of disease. Two others had suspected (probable) abscesses, and one had ventriculitis.

In a few cases, the presence of porencephalic cysts found on autopsy suggested but did not prove that abscesses had once been present. Only eight cases were clearly without abscesses, and for another eight this information was not given. Hence, 35 (81.4%) of 43 patients for whom the information is known had proven or probable CNS abscesses, with 68.6% of all patients having had proven abscesses. Overall, between the previous [73] and current reviews, approximately four of every five children with citrobacter meningitis had abscesses, hemorrhagic necrosis, or (occasionally) ventriculitis without true abscess formation. Abscesses within the spinal cord as well as the brain have been described [70].

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Among 12 neonates with nosocomially acquired disease, 7 had known or probable CNS abscesses, with inadequate information given for 5. Twenty-seven of 33 patients with sporadic disease had abscesses, 1 had a possible abscess, and 2 had an unknown status. Only three cases were clearly documented not to have abscesses. Information is more often complete in the sporadic cases than in other categories, possibly because the focus of those reports is often some aspect of diagnosis, pathology, or treatment of the abscess.

Occasionally *Citrobacter* is found as part of a mixed culture in cases of CNS abscess. It has been found in association with *Bacteroides* [58] and *Enterobacter cloacae* [66]. A child with maxillary sinusitis, described above [60], had *Citrobacter* isolated from the nasopharyngeal mass and alveolar ridge, the site of purulent osteomyelitis, and *Staphylococcus aureus* from an oral lesion. The resulting CNS abscess, of which a specimen was cultured after initiation of antibiotic treatment, was sterile. *Citrobacter* was the more likely cause because of proximity of the osteomyelitis and CNS abscess. In one case, *C. diversus* grew in a culture of CSF, while *Escherichia coli* grew in a blood culture [72].

It is likely that there is a selection bias in reporting cases of citrobacter abscesses. The most interesting cases, such as those in which abscesses occurred or for which evaluation of imaging methods is the thrust of the article, are probably reported in preference to those with meningitis or sepsis alone. It is not clear from the available literature how often citrobacter bacteremia or sepsis occurs without meningitis or how often meningitis occurs without abscesses. Such cases may be reported less frequently, since they might be considered less noteworthy.

Other infections. The occurrence of citrobacter sepsis without meningitis in neonates has been described often in reports of case series [39, 45, 47, 76–78], but it occurs less often or is reported less often than when meningitis and abscesses are present. How often bacteremia or sepsis occurs without menin-
Pathophysiology

The confirmation that *Citrobacter* can be transmitted vertically is important to an understanding of neonatal disease. Nosocomial outbreaks are largely due to gastrointestinal and hand carriage by hospital personnel. Vertical or nosocomial transmission may account for some sporadic cases, and transmission from carriers such as family members and other contacts accounts for others. Presumably the organisms then colonize the oral cavity, lower gastrointestinal tract, or respiratory tract, followed by penetration that results in bacteremia. It is not always possible to confirm bacteremia, but it is the presumed intervening step leading to meningitis [75].

The particular propensity of *Citrobacter*, especially *C. koseri*, for the meninges is not well understood. Specific outer-membrane proteins may provide the organism with tropism for nervous tissues and associated meningitis and abscesses [30, 75, 92–94]. Li and co-workers found that 79% of strains of *C. diversus* (*C. koseri*) from CSF had a unique 32-kD outer-membrane protein, which was found in only 9% of non-CSF isolates [93]. This suggests a role as a neurovirulence factor for this protein, though the mechanism remains unclear. One intriguing finding from that study was that a strain of *C. diversus* (*C. koseri*) having the 32-kD outer-membrane protein was less likely to cause bacteremia, meningitis, or death in infant rats infected by intraperitoneal or intranasal inoculation than was a strain that lacked this protein [75]. However, the strain with the 32-kD protein, when it did cause disease, was more likely to cause CNS abscesses or ventriculitis.

Rat pups older than 5 days did not develop disease, even with large inocula of bacteria, while significant rates of infection occurred with 2-day-old pups [75]. This suggests that some physiological change in the animals occurs that provides protection from these organisms. It is not known what occurs to allow this apparent protection, but something similar may occur in humans, since they rarely develop *citrobacter* CNS disease beyond the first month of life. The establishment of abscesses in rat pups did not relate to mortality, which was actually higher in animals without abscesses. It was suggested by the authors that low virulence allowed a more indolent course and establishment of abscesses, compared to the highly neurovirulent strains causing meningitis and death quickly [75].

It is uncertain how these findings in rat pups relate to human disease. It is intriguing that none of the few confirmed vertically infected human infants with disease of very early onset developed abscesses [26–28, 30–35], possibly because illness occurs rapidly rather than by the indolent course necessary to cause abscesses, as suggested by the experiments described above. The infants in those reports typically became ill on the first day of life. A critical virulence factor may be needed for abscess formation, or perhaps the rapid use of antibiotics in these typically premature, high-risk infants aborts abscess formation. Late-onset infections typically occur around 3–6 weeks of age, and in all of the cases that have been reported the infants had CNS abscesses. Sometimes the disease has an indolent course in which *Citrobacter* may be isolated from CSF early on only to have the development or identification of abscesses occur days or weeks later [61, 69].

It was shown in the rat pup model that meningeal infiltration by bacteria occurred early after bacteremia, followed by massive dilation of ventricles, ependymal cell loss, and disruption of ventricular walls [75]. At least some abscesses begin as vasculitis of small blood vessels, which explains the propensity for establishment of abscesses in perivascular locations. Parenchymal abscesses occurred late [75] and may not develop fibrous capsules [70]. While *Citrobacter* is widely noted to cause CNS abscesses in infants, it appears that some may not be classic abscesses with a defined capsule. Hemorrhagic necrosis and liquefaction may occur, rather than an abscess with capsule formation [57]. This has been noted in infants with lesions caused by a variety of gram-negative organisms, including *Pseudomonas*, an organism possibly synonymous with *Citrobacter* [95]. Hemorrhagic necrosis and classic abscesses may represent different points on a spectrum [57, 70] that includes meningitis and ventriculitis as well [54, 65, 81]. The mechanisms that favor one over another are not known but may be related to the outer-membrane proteins described [30, 75, 92–94], the rate of progression of disease, or some as yet unclear determinant. In one case, *citrobacter* ventriculitis recurred three times in 4 years, without ever resulting in abscess formation [65].

The special propensity of *C. koseri* for the CNS of the neonate and the production of resulting abscesses, in comparison to the propensities of *C. freundii* or other *Citrobacter* species, also has not been explained. It is not likely that the recently introduced changes in nomenclature will resolve the issue, since most of the new species were split away from *C. freundii,*
a species that has not been shown to be particularly prone to cause neonatal disease.

**Diagnosis**

Classic signs and symptoms of sepsis and meningitis that occur in other neonatal infections apply to citrobacter disease as well. These include temperature instability, irritability, decreased oral intake, seizures, jaundice, vomiting, lethargy, hypotonia, abnormal sighing respirations, seizures, and a bulging fontanelle. Infants with such signs and symptoms should have a complete evaluation, including blood culture, urine culture, lumbar puncture for CSF chemistries, cytology, gram staining, and culture.

Since ~80% of infants with citrobacter meningitis will develop abscesses, imaging studies of the brain should be performed once the diagnosis of citrobacter infection is established. A variety of imaging methods have been used. CT scanning [25, 35, 38, 39, 42–44, 50–67, 70] and ultrasonography [26, 38, 53] are the methods of choice. In some of the earlier articles, ventriculography [37, 48, 69], nuclear scans [69, 96], and angiography [67] were used. Suspected abscesses have sometimes been found only at autopsy [43, 48, 57]. Recent literature shows that CT scans are the most common diagnostic method used to detect CNS abscesses, but sonography and CT have been reported to be comparable in diagnosing CNS abscesses [38]. While CT may be optimal [61], sonography may be more feasible and available for unstable neonates who are unable to be transported for CT. Serial examinations should be performed since abscesses may not be present initially and in some cases may be apparent only near or after the conclusion of therapy [52, 53, 61, 69].

**Treatment**

Neonatal citrobacter infections of the CNS have been treated by a variety of methods, the results of which have been generally disappointing. Antibiotics remain the mainstay of therapy, though adjunctive surgical drainage has also been widely but not universally applied in such cases. No standard therapeutic regimen has been established as superior. Antibiotics and surgery are usually used in combination.

As for any organisms causing serious disease, antibiotic susceptibility should guide the final choice of antibiotics. *C. diversus* and *C. freundii* are virtually always resistant to ampicillin [3, 5, 25, 26, 28, 35–37, 40, 42–45, 52, 53, 55, 56, 58–61, 63, 66, 69, 82, 88, 94, 97–105], though occasionally they are intermediate in susceptibility [33, 64]. Susceptibility to aminoglycosides is variable. *C. koseri* is typically susceptible to gentamicin [3, 5, 26, 33, 34, 42–44, 49, 52, 56, 58, 60–64, 66, 67, 69, 74, 82, 88, 99–103, 105, 106] and to other aminoglycosides [3, 26, 33, 34, 37, 40, 44, 49, 52, 53, 60, 63, 66–69, 88, 94, 99–103, 105, 106].

Third-generation cephalosporins are more active against *C. koseri* than are first- or second-generation cephalosporins [99, 104]. *C. koseri* is generally more susceptible to cephalosporins than is *C. freundii* [98, 99, 104]. A number of authors have noted the susceptibilities to third-generation cephalosporins, and they have increasingly been used as the first-line treatment. Development of resistance to cephalosporins by induction of β-lactams has been reported [98, 104].

Other therapeutic agents can be considered for *C. koseri* infections. Susceptibility to chloramphenicol is good, and this drug has been used extensively to treat CNS abscesses caused by *Citrobacter* [3, 35, 37, 40, 42, 44, 49–54, 58, 60, 61, 63, 67–69, 82, 88, 93, 100–103, 105, 106]. *C. koseri* is typically susceptible to imipenem/cilastatin [33, 63, 64, 98, 99], which has been successfully used [65]. Trimethoprim susceptibilities are good [3, 5, 26, 33, 35, 54, 60, 63, 66, 67, 88, 102, 105], and trimethoprim-sulfamethoxazole has also been used successfully to eradicate disease [54].

Multidrug therapy, often with a penicillin or cephalosporin antibiotic plus an aminoglycoside, has been the most common approach. Moxalactam has been used in the past, alone or in combination with other antibiotics [25, 35, 39, 44, 52, 55, 56, 61, 107]. There are numerous reports of cases treated with chloramphenicol, alone or in combination with other antibiotics [37, 40, 42, 44, 49–54, 63]. This is sometimes added only after the identification of CNS abscesses, presumably because of its effective penetration of CNS tissue [108]. Instillation of antibiotics into abscesses or intrathecal has been tried [37, 40, 44, 50, 54, 61, 63, 67, 69, 74, 109], though the data do not convincingly show that this approach significantly improves outcome. Intrathecal antibiotic therapy does not improve mortality or morbidity rates for neonates with meningitis [74, 109]. Mortality is actually higher for infants receiving intrathecal gentamicin plus intravenous antibiotics than for those receiving intravenous antibiotics alone [109]. Intra-abscess instillation of antibiotics does not offer much advantage over intravenous therapy alone.

There is no compelling evidence that favors one antibiotic or combination over another. Once antibiotic susceptibility patterns are known, the choice of antibiotics can be tailored for the particular situation. A third-generation cephalosporin and an aminoglycoside are commonly used in combination against other gram-negative organisms causing meningitis in neonates [110], and this combination is usually preferred in cases of citrobacter disease of the CNS as well [94, 110]. Aminoglycosides have poor penetration and activity in the acidic environment of abscesses. Whether aminoglycoside treatment should be continued for a longer period in cases of CNS abscesses is arguable, but many of the reported infants have received extended two-drug therapy.

Successful management of neonatal citrobacter CNS abscesses with antibiotics alone has been reported [52, 56]. More often a combination of antibiotic therapy and surgical aspiration or drainage of abscesses is used. Surgical treatment has in-
cluded single [42, 44, 58] and repeated aspirations [37, 38, 48, 50, 61, 63] or open drainage [38, 42–44, 48, 51, 53, 58, 60, 64, 67]. When multiple abscesses are present, aspiration may not be feasible. Likewise, when abscesses are in accessible, or in cases when they are small and nonprogressive, conservative management can be considered. Sometimes aspiration will confirm the etiologic agent when the CSF is apparently sterile, as is often the case when antibiotics are given prior to lumbar puncture.

Like other aspects of therapy, there is no agreement on the optimal duration. For patients with meningitis alone, regimens as short as 14 days have been used [33]. Infants with CNS abscesses usually have been treated for 3–8 weeks and most commonly for 4–6 weeks. The risk of mortality is so high and the risk of significant neurological damage among survivors is so common that aggressive, prolonged therapy is in order. Immediate use of broad-spectrum therapy, later adjusted on the basis of Citrobacter susceptibility, is needed. Early imaging, whether by CT or ultrasonography, is needed to assess the need for surgical intervention. Imaging should be repeated even after antibiotic therapy has been completed, as there are reports of abscesses being identified weeks after the initiation of antibiotic therapy [50, 52, 53].

Recommended duration of treatment for uncomplicated neonatal meningitis caused by gram-negative bacteria, including Citrobacter, varies somewhat by author. Two similar approaches to treatment that have been recommended include a minimum of 21 days [110, 111] or 14 days after sterilization of CSF, for a minimum of 21 days [112, 113]. A repeated lumbar puncture should be considered 24–72 hours after initiation of therapy for neonatal meningitis [111, 113]. The failure to achieve sterilization of CSF or the continuation of symptoms is reason to reevaluate antibiotics and to perform imaging studies to assess for possible abscess, ventriculitis, or empyema.

For abscesses, a strong consideration should be given to surgical aspiration or open drainage and antibiotic treatment for 4–6 weeks [94]. All children should have close posttreatment follow-up, with consideration given to repeated imaging studies to ensure that abscesses have resolved or have not formed. Some infants will require ventriculoperitoneal shunting for hydrocephalus. All children should have long-term follow-up, as the majority will have some type of neurological deficit (see below) requiring further medical intervention and educational assistance.

Outcome

In one report, 22 (34.3%) of 64 infants with citrobacter meningitis died [73]. Thirteen (27.7%) of 47 infants with meningitis evaluated for the current review and for whom data were available also died. Hence, ~30% of infants with citrobacter meningitis die of the disease and its complications. Many other infants have significant damage to the CNS, including profound retardation, hemiparesis, seizures, and other disorders. In one report, 31 (48.4%) of 64 infants with citrobacter meningitis were retarded [73]. Of the 47 additional children reported here and for whom information was available, 20 (42.6%) had some type of developmental delay, physical impairment, or both. Three were reported to be developmentally normal but had ventriculoperitoneal shunts placed because of acquired hydrocephalus.

In one study of gram-negative meningitis [114] that included nine children, some of whom were apparently included in a previous review [73], all survived. Seven of the nine had complications, including abscesses in four. Four of five for whom follow-up was adequate had sequelae. Those nine children included some who had apparently been part of the Neonatal Meningitis Cooperative Study and had received intrathecal antibiotics [107, 109].

Among the 35 children reviewed in the current article who had abscesses, 11 (31.4%) died. Thirteen (37.1%) had neurological deficits, and two were apparently neurologically intact except that ventriculoperitoneal shunts were required. For two the outcome was unknown, and 7 (20%) of 35 were apparently normal. All of the seven children who were reported not to have abscesses survived, though three had CNS damage, presumably from the meningitis. Of the five infants for whom information is available in the study described above [114], four had sequelae, though none died.

Specific data about developmental delays are often lacking, and long-term follow-up data are generally unavailable. One letter described the very favorable outcome for two infants with citrobacter abscesses, 13 years after they were treated with antibiotics alone [115]. One required placement of a ventriculoperitoneal shunt, but both were apparently cognitively and functionally normal.

Overall, ~30% of children with citrobacter meningitis die, and one-half sustain some type of damage to the CNS. Developmentally and structurally intact survivors are in a minority, at the rate of 9 (19.6%) of 46 reviewed for this article and 11 (17.2%) of 64 previously reported [73]. Whether any children with mild delays had significant improvement or resolution of delays with time is not known. Optimal therapy is not known but would include early and prolonged use of appropriate antibiotics and surgical intervention in most cases. Whether prevention of vertical transmission is possible or feasible is not known, since it has been described infrequently. Nosocomial transmission is at least theoretically preventable, primarily by proper handwashing. When outbreaks occur, consideration should be given to performing cultures of hand and stool specimens in order to identify carriers.

Summary

Citrobacter infections are uncommon among neonates but are associated with a high risk of meningitis and CNS abscesses. Other than bacteremia or sepsis, infections outside of the CNS are uncommon. The origin of the bacteria is unknown.
in many cases, but some cases have been documented to be vertically transmitted from mother to child, and others have been shown to occur as nosocomial infections. The latter occur when hospital personnel carry the organisms on their hands, with gastrointestinal tract carriage having been demonstrated in some cases.

C. koseri is responsible for the majority of cases of neonatal disease. The propensity of the organism to affect this population and especially to cause CNS disease in neonates, while sparing older infants and children, is largely unexplained. Abscess formation may be related to the presence of a specific 32-kD outer-membrane protein. Abscesses have not been confirmed in a small number of cases attributable to vertical transmission. This may support a theory that abscess formation is more likely to occur in indolent disease than in rapidly progressive disease.

The complex of signs and symptoms of citrobacter disease in neonates is similar to what is seen in other neonatal infections. Diagnostic studies should include lumbar puncture, and if citrobacter meningitis is confirmed, imaging is necessary, preferably by CT or ultrasonography. Treatment with two antibiotics, including a third-generation cephalosporin and an aminoglycoside, is preferred. These should be given for a minimum of 2 weeks for sepsis alone, a minimum of 3 weeks for uncomplicated meningitis (or 2 weeks after a repeated CSF culture is negative, for a minimum of 3 weeks), and 4–6 weeks when an abscess is present. Surgical drainage should be strongly considered, though successful management of citrobacter abscesses has been reported with antibiotic treatment alone.

The overall outcome for children with citrobacter disease of the CNS remains poor, regardless of treatment. Approximately one-third will die, and one-half will survive with CNS sequelae, ranging from mild to severe. A great deal of information about epidemiology, pathogenesis, diagnosis, and treatment will need to be elucidated if outcomes are to be affected.

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