Serotypes, Hemolysin Production, and Receptor Recognition of *Escherichia coli* Strains Associated with Neonatal Sepsis and Meningitis

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Sixty-three *Escherichia coli* strains isolated from neonatal sepsis or meningitis were studied and compared with previous data on fecal or urinary pyelonephritis-associated isolates from children. Characteristics significantly associated with neonatal infection were capsular type K1 (54%), O group 18 (27%), rough-type lipopolysaccharide together with K1 capsule (19%), and S fimbriae (29%). Within the neonatal infection group, the K1 capsule and rough lipopolysaccharide were most common among the youngest infants (0 to 21 days old) and in meningitis. Hemolysin production, P fimbriae, and X adhesins (adhesins not identifiable as type 1, P, or S) were significantly more common in the two materials from infections as compared with the fecal isolates. One large clone of 11 strains (O18:K1:H7, with both type 1 and S fimbriae) and three smaller ones (O7:K1:H1 and O6:K2:H1, both with type 1 and P fimbriae and X adhesins; and R:K1:H33 with no adhesins) were identified among the strains from neonatal infections. Only O6:K2:H1 strains were also common among the strains from pyelonephritis.

*Escherichia coli* is the most common cause of neonatal septicemia and meningitis but is rarely seen in similar infections in older children (10). The realization that most of the *E. coli* strains in these neonatal infections had the K1 type capsule was a major breakthrough in our understanding of the pathogenesis of this condition (23). It strongly suggested that, of the variety of *E. coli* strains available to the newborn in the birth canal, only some, namely those with the K1 capsule, were capable of invading its blood and cerebrospinal fluid. The initial observation led to the further recognition that the K1 strains from neonatal infections represented a very limited number of clonal groups (1) as opposed to a variety of K1 strains, e.g., in healthy adult feces, and suggested that these clones must have special, as yet uncharacterized virulence properties for the newborn.

On the other hand, adhesion of the bacteria to host epithelium has been recognized as an important virulence factor in many bacterial infections, including both diarrhea and urinary tract infections (UTI) caused by *E. coli* (7, 25) and genital infections caused by Neisseria gonorrhoeae (27). The adhesion is in most instances mediated by fimbriae which recognize specific receptors on the epithelial cells (12). In some cases, the epithelial receptors for *E. coli* are known at the molecular level. Thus, P fimbriae, a major virulence factor in childhood pyelonephritis (31), recognize the galactosylgalactose (Gal[a1-4]Gal[b1-4]Gal) moiety of the P blood group antigens (9, 13, 16). M fimbriae recognize blood group M-specific determinants of glycoprotein A (29), and S fimbriae bind to sialyl-(a2-3)-galactoside structures on human erythrocytes (13, 21). The two latter types of fimbriae were found on a small number of *E. coli* isolated from childhood UTI, and their clinical significance remained uncertain. All of these fimbriae cause hemagglutination that is not inhibited by mannose and have been described as mannose resistant (MR) in distinction from the "common" type 1 fimbriae. The latter do not seem to be correlated with virulence in human disease (8) and have even been suggested to decrease virulence by enhancing phagocytosis (24).

Hemolysin production is another property of many *E. coli* strains isolated from invasive infections, including pyelonephritis (2, 3). It is believed to be a virulence factor in these cases, and its ability to enhance virulence has been demonstrated in several experimental situations (17, 32). It therefore appeared pertinent to ask whether similar properties, i.e., specific adhesion and hemolysin production, would be factors contributing to the specific pathogenicity of *E. coli* causing septic infections and meningitis in the newborn. We present here an analysis of 63 such strains compared with sets of *E. coli* isolated in the same area from healthy children or from children with pyelonephritis (31).

### MATERIALS AND METHODS

A total of 63 *E. coli* strains were obtained in 1974 through 1977 from a number of diagnostic laboratories in Finland as strains isolated from blood or cerebrospinal fluid of young infants (<6 months of age) with a septic infection. The hospital records of the infants were obtained from the representative hospitals. The strains were stored as stab cultures in nutrient agar at room temperature for 1 to 5 years before this study. Fecal strains from healthy children and urinary tract isolates from children with UTI were isolated in Helsinki in 1977 through 1981 and have been fully described before (28, 31). Serotyping of the strains was performed according to standard methods of the State Serum Institute, Copenhagen, Denmark (19).

Hemolysin production was determined on sheep blood agar plates inoculated with a heavy streak as a clear zone of lysis around the streak. Type 1 fimbriation was determined.
from bacteria grown in Luria broth tubes without agitation by mannose-sensitive yeast cell agglutination (11). Other adhesins were tested from cultures grown on colonization factor antigen plates (4). P fimbriation was detected by the P-specific particle agglutination test (26) and hemagglutination of human OP, but not of OP erythrocytes (28). All hemagglutinations were performed on glass slides over crushed ice in the presence of 0.1 M methyl-α-D-mannoside (Sigma Chemical Co., St. Louis, Mo.) to measure only MR hemagglutination. S fimbriation was tested by colony blotting with specific anti-S fimbrial antiserum (13) as described previously (30). The adhesion of strains showing MR hemagglutination without having P or S fimbriae was called X (28).

Statistical methods. Significance of differences between patient groups was tested with the χ² test.

RESULTS

Characteristics of the neonatal infections. A total of 63 E. coli strains isolated from the blood or cerebrospinal fluid of infants with a septic infection were studied; 45 of the isolates came from infants younger than 22 days. Among these, meningitis was identified by lumbar puncture in 10 infants with definite symptoms of meningeal involvement but was probably present in a large part of the others as well, although lumbar puncture was not performed (10). In addition, one was diagnosed as having pneumonia. Eighteen of the infants were slightly older (3 weeks to 5 months); among them, meningitis was identified in four, pneumonia was identified in two, and UTI was identified in two. Of the 63 infants, 12 died; 10 of them were younger than 22 days. Eleven of the deaths were associated with bacteria without an identified localization, and only 1 of the 14 infants with recognized meningitis died.

Capsular types. Of the 63 strains, 34 (54%) were of the capsular type K1, which was found in only 22% of E. coli isolates from the feces of healthy children in Finland and in 31% of strains from pyelonephritis (Table 1). When the present isolates were grouped according to age, it was evident that K1 capsule was significantly associated with infections in the youngest infants (67% of the 45 isolates) and found in only 22% of the 18 isolates from the older infants (P < 0.001). It was present in 78% of the strains from meningitis (9 of 10 strains from infants younger than 22 days and 2 of 4 strains from the older ones).

Other K types were much less common in the newborn infections. The most common were K2 and K5, found in four and six strains, respectively; in contrast to K1, they were most frequent in the older infants and in localizations other than meningitis. Thus, four of these eight isolates came from bacteria associated with pneumonia or UTI. Other K serotypes, each found in one or two isolates, were K12, K25, K52, K95, and K96.

O antigens. The most common O serotypes (Table 1) among the isolates were O18 (17 of 63 [27%]), O6 (8 of 63 [13%]), O2 (6 of 63 [10%]), and O7 (5 of 63 [8%]). Of these, O6 was seen more often in the older patients (six of the eight isolates), and O7 was seen more often in the youngest ones (all five isolates), whereas O18 and O2 strains were seen equally in both age groups. A considerable number of the isolates (13 of 63 [21%]) were rough (R), and these were significantly associated with younger patients (11 of 13) and with meningitis (6 of 13). Other O types, each seen among one to three isolates, were O1, O4, O8, O9, O22, O77, O83, O88, and O119. The O-type distribution was thus different from that seen in pyelonephritis or in fecal isolates (Table 1) and strongly suggests the existence of clones with special virulence for the newborn.

Hemolysin. Hemolysin production was recorded in 25% of the isolates (Table 2) and was more common in the older patients (44% of these) than in the younger (18%). None of the 14 meningitis strains produced hemolysin, whereas 4 of the 5 strains from infants with pneumonia or pyelonephritis did so. Compared with these figures, hemolysin production was quite rare (10%) in fecal isolates but common (60%) in strains from pyelonephritis (Table 2).

Adhesins. Type 1 fimbriae were identified in 81% of the isolates and showed no significant difference according to the age or disease of the patients (Table 2). Thus, type 1 fimbriae in this material was not different from that in previously analyzed materials, whereas the frequency of MR adhesins among the strains from newborn infections was higher than among fecal isolates but lower than among
strains from pyelonephritis. The receptor specificity of the MR adhesin in the newborn infections was, moreover, different from that seen in either of the previous materials. Thus, only 38% of the newborn isolates but 76% of the pyelonephritis isolates had P fimbiae, whereas 29% of the newborn isolates but only 4% of 7% of the others had S fimbiae. Among the newborn isolates there was a tendency for the P specificity to be associated with the older infants, especially with localization other than meningitis, and for the S fimbiae to be associated with meningitis. X adhesins were present in 19% of the strains from newborn infections, as compared with 12% among strains from pyelonephritis and 4% in fecal isolates.

Identification of clones. It soon became apparent that the characteristics described above were not randomly distributed but rather occurred associated with each other in certain patterns. Thus, the K1 capsule was seen together with O18 (11 of 17 strains), O7 (5 of 5 strains), O2 (4 of 6 strains), or R character (12 of 13); K2 was seen with O6 (3 of 8 strains) or O2 (1 of 6 strains); K5 was seen with O18 (3 of 17 strains), O6 (1 of 8 strains), or R (1 of 13 strains). Hemolysin production was seen in some strains of most O groups but was most strongly associated with O6 (five of eight strains), O2 (two of six strains), or O22 (two of three strains). P-specific fimbiae were most often seen in O7:K1 (5 of 5 strains), O6:K2 (3 of 3 strains), and O18:K5 (3 of 3

TABLE 3. Characteristics of certain O and K serotypes and presumptive identification of four clones (in bold face) among the 63 E. coli isolates from neonatal septic infections compared with previous isolates from pyelonephritis or feces of healthy children

<table>
<thead>
<tr>
<th>Samples</th>
<th>All strains</th>
<th>O18ac:K1:H7</th>
<th>Other O18 (not K1)</th>
<th>O7:K1:H1</th>
<th>Other O7</th>
<th>O6:K2:H1</th>
<th>Other O6 (not K1 or 2)</th>
<th>R:K1:H33</th>
<th>Other R:K1</th>
</tr>
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<tbody>
<tr>
<td>All isolates</td>
<td>63</td>
<td>34</td>
<td>29</td>
<td>11</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
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<td>O serotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td>O6 strains</td>
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</tr>
<tr>
<td>O2 strains</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>O7 strains</td>
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<td>0</td>
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<td>15</td>
<td>0</td>
<td>4</td>
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<td>3</td>
<td>2</td>
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<tr>
<td>Type 1 fimbiae</td>
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<td>25</td>
<td>26</td>
<td>11</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>5</td>
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<td>P fimbiae</td>
<td>24</td>
<td>11</td>
<td>13</td>
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<td>7</td>
<td>8</td>
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<tr>
<td>X adhesins</td>
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<td>4</td>
<td>7</td>
<td>0</td>
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<td>Age 0–21 days</td>
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<td>30</td>
<td>15</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>0</td>
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</tr>
<tr>
<td>Age 22 days–5 mo</td>
<td>18</td>
<td>4</td>
<td>14</td>
<td>2</td>
<td>3</td>
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<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other localization</td>
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<td>1</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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<td>Fatal outcome</td>
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<td>5</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>67</td>
<td>21</td>
<td>46</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Fecal isolates</td>
<td>50</td>
<td>11</td>
<td>39</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*ND, Not determined.

a Pneumonia in three strains.

b Ten deaths in 0 to 21-day-old infants (1 of which associated with meningitis): all others without recognized localization.

c Data from references 28 and 31.

TABLE 2. Fimbriae, adhesins, and hemolysin production among the 63 E. coli isolates from neonatal septic infections compared with previous isolates from pyelonephritis or feces of healthy children

<table>
<thead>
<tr>
<th>Clinical sample</th>
<th>All cases</th>
<th>No. of isolates from:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All &lt;6 mo</td>
<td>0–21 days</td>
</tr>
<tr>
<td>All strains</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>Hemolysin</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Type 1 fimbiae</td>
<td>51</td>
<td>35</td>
</tr>
<tr>
<td>P fimbiae</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>S fimbiae</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>X adhesins</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>No adhesins</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

* Meningitis, pneumonia, or UTI in two.

b Data from references 28 and 31.

c One of these strains recognizes the human blood group M-specific glycophorin (29).
strains) but were also found in 13 other strains of varying serotypes. S fimbriae were found in serotypes O18:K1:H7 (8 of 11 strains), other O18 strains (2 of 6 strains), O6 (3 of 8 strains), O2 (2 of 6 strains), O4:H5 (1 of 1 strain), or R:K1 (2 of 12 strains), and X-specific adhesion was found in O6:K2 (3 of 3 strains), O7:K1 (3 of 5 strains), or sporadically in 5 other serotypes.

The most frequent serotypes (by O, K, and H typing) were O18ac:K1:H7 (n = 11), O7:K1:H1 (n = 4), O6:K2:H1 (n = 3), and R:K1:H33 (n = 3), which together accounted for 33% of all strains and for 56% of the K1 isolates (of the remaining 16 K1 strains, 9 were R but of a number of different H types). These serotypes are analyzed in detail in Table 3 and compared with related serotypes with the same O or K type.

The most common serotype was O18ac:K1:H7, found in 11 infants. None of the 11 strains produced hemolysin, whereas all had type 1 fimbriae. Eight of them had S fimbriae, but no other MR adhesins were found among the 11 strains. Strains of this serotype showed no special features with respect to the age of the patient, localization, or fatality rate of the infection in the newborn material. However, when compared with the previous materials, the difference is large. This serotype caused 17% of the newborn infections but was found only once among 50 fecal isolates and not at all among the 67 strains from pyelonephritis. None of the remaining six O18 strains had a K1 capsule or S fimbriae. Three of the six had a K5 capsule and P fimbriae, and two of them produced hemolysin. P-fimbriated O18:K5 occur quite frequently in pyelonephritis (31).

The second most common serotype was O7:K1:H1, which was found four times among the newborn infection strains but never among the 117 strains from pyelonephritis or feces. These four strains did not produce hemolysin and had both type 1 and P-specific fimbriae; three of the four also had X adhesins. All four strains came from very young infants without recognized localization of the infection; furthermore, three of these infections were fatal. The fifth O7 strain was a P- and type 1-fimbriated O7:K1:H- strain; two similar strains were found in pyelonephritis, but none was found in feces.

Three strains were of serotype O6:K2:H1 and were characterized by the production of hemolysin and the presence of three hemagglutination specificities: type 1 and P fimbriae and X adhesins. All of them came from the slightly older infants and from bacteremia associated with pneumonia (one case) or UTI (two cases). The behavior and properties of these strains are very similar to those of a pyelonephritis-associated O6:K2:H1 clone previously identified among older children (31); however, the newborn strains differ from that clone by having X adhesins in addition to their P specificity. Other O6 strains were also found in the material but differed from the O6:K2:H1 strains in several respects.

Strains of serotype R:K1:H33 were also encountered in three infants. They differed from most other strains studied by lacking both hemolysin and all recognizable adhesins. The latter property was not obviously caused by their R cell surface, because only one of nine other R:K1 (not H33) strains lacked adhesins, whereas type 1 as well as P and S fimbriae or X adhesins were found among the other eight strains. However, all R:K1 strains were significantly associated with meningitis; 6 of the 14 meningitis strains and 6 of the 49 other strains were R:K1.

**DISCUSSION**

**Possible virulence-associated factors.** In accordance with previous work (23), we found the K1 capsular antigen to be strongly associated with *E. coli* strains from neonatal infections. This association was strongest for strains from recognized meningitis and infections that occurred in the first 3 weeks of life rather than in the following few months. In fact, in this later period, K1 was not more prevalent than it is in pyelonephritis or feces of older children (31). Meningitis was recognized in 14 of the 63 infants but was probably present in several others in whom lumbar puncture was not performed. Because of this uncertainty (due to diagnostic difficulties in septic infections in the neonatal period [10]), it is not possible to decide which is more characteristic the K1-dependent specific virulence, the age or the meningeval localization, and it is possible that it really is a combination of the two. An association with meningitis is suggested by the isolation from the neonatal brain of a glycopeptid with long (a2-8)-linked polysialosyl stretches, showing immunological cross-reaction with the K1 antigen which is an (a2-8)-linked sialic acid polymer (5, 6). The cross-reacting material disappears from the tissues very rapidly within the first weeks of life (6), the same time period when susceptibility to K1 meningitis disappears.

A number of adhesions were demonstrated in the neonatal *E. coli* strains. The frequency of the mannose-binding type 1 fimbriae (81%) among these strains was not significantly different from their frequency among fecal isolates from older children. This fact is not surprising, since these fimbriae have so far not been found to be associated with any particular human infection. By contrast, the galactosyl-(a1-4)-galactoside-recognizing P fimbriae were more frequent (38%) in the neonatal strains than in fecal strains. In particular, they were present in four of the five strains from bacteremia associated with pyelonephritis or pneumonia, strongly suggesting that they play a part in aiding the attachment of the bacteria to the epithelium in these locations.

The frequency of S fimbriae among the strains studied was 29%, compared with only 7% in strains from pyelonephritis and 4% in fecal strains; their association with meningitis is notable (36%). The low frequency of S fimbriae among the strains isolated from pyelonephritis might reflect the presence in urine of inhibitory factors, such as glycoproteins or sialyl oligosaccharides, in which the sialyl-(a2-3) linkage is very common (20). On the other hand, it is known that sialyl-(a2-3)-galactoside structures occur in many human tissues, including brain tissues (14, 15), and could thus act as receptors to S fimbriae. However, neither the specific receptor molecules nor their tissue localization have been identified, and the pathogenic role of S fimbriae, if any, remains to be established.

A fourth (X) type of hemagglutination, for which no specific receptor has so far been recognized and which can therefore contain several different recognition systems, was present in 19% of the neonatal strains, compared with 12% in strains from pyelonephritis and 4% in fecal isolates. X adhesion was most common (33%) among isolates from the older (3 weeks to 5 months) infants and usually occurred together with P fimbriae.

Hemolysin production did not seem to be a virulence factor in neonatal septic infections. In fact, none of the 14 strains from proven meningitis produced hemolysin. By contrast, 44% of the strains from infections in the 3-week- to 5-month-old infants produced hemolysin, bringing them close to strains from pyelonephritis, of which 60% were hemolytic. Four of the five strains from infants with pyelonephritis or pneumonia in this study were hemolytic as well.

**Neonatal infection clones.** Two main clones previously
identified as associated with neonatal meningitis and septiciemia (1) were present in this material also, and in fact accounted for nearly one-fourth of the 45 strains from the youngest infants. The O18ac:K1:H7 clone (11 strains) was characterized by S fimbriae demonstrated in 8 of the 11 strains. Because the hemagglutination caused by S-fimbriated bacteria is in many cases weak, we used colony blotting with specific antisera (13, 30) to screen for the presence of S fimbriae. It remains to be shown whether the apparent lack of S fimbriae in one of the strains is due to variable expression, perhaps based on phase variation, which has been demonstrated for type 1 S, and P fimbriae (18, 18a:22). Our view of all 11 O18ac:K1:H7 strains as one clone (as well as of the other proposed clones) is supported by their homogeneity, with respect to all other markers tested here, and also by identical outer membrane protein profiles and similar isoenzyme patterns within each clone (unpublished data). We suggest that both the K1 capsule and S fimbriae are factors contributing to the pathogenic properties of this clone.

The second clone O7:K1:H1 (four strains) also produced no hemolysin but had P fimbriae, and three of the four strains could be shown to produce X adhesins as well. As with S fimbriae, the hemagglutination caused by X adhesins is often weak and may be overlooked; the synthesis of X adhesin can also be expected to be variable. Again, the clone was homogeneous for all other markers tested. The fifth O7:K1 strain among the newborn isolates and the two O7:K1 strains from pylonephritis differed from this clone by being nonflagellated and lacking X adhesins.

The third K1 clone, R:K1:H33, consisted of three strains differing from most other strains studied (including other R:K1 strains) by the total lack of any demonstrable adhesins, including type 1 fimbriae present on 81% of all strains. Finally, the fourth clone, O6:K2:K1, did not have the K1 capsule. Instead, all three strains produced hemolysin, P fimbriae, and X adhesins. It resembled the O6:K2:H1 clone previously identified as pylonephritis-associated (31) in all properties except X adhesin production.

All of these clones were extremely infrequent among E. coli strains from other sources, indicating that they indeed had some properties that made them specially capable of causing invasive infections in the newborn. It should be pointed out that simple localized outbreaks could not have led to the erroneous recognition of these strains as neonatal infection clones, because representatives of each clone were isolated several months apart and in different parts of the country.

Whereas the O18:K1:H7 and the R:K1:H33 clones corresponded, in the spectrum of the infections caused, to the general pattern of the K1 strains from neonatal infections, the two other clones appeared to have a characteristic pathogenic potential of their own. Thus, the P-fimbriated O7:K1:H1 strains caused a nonlocalized (four of four strains), often fatal (three of four strains) infection in the youngest infants (four of four strains), whereas the O6:K2:H1 strains, which were also P-fimbriated and in addition produced X adhesin and hemolysin, caused localized nonmeningal infections in the slightly older infants. In the latter case, the P fimbriae could certainly contribute to the localization of the infection, and the absence of K1 fits with their preference for the older infants. The high pathogenicity of the O7:K1:H1 clone, shown by the extremely high case fatality and perhaps also by the lack of localization, is striking; its cause, however, remains unknown, and the possible role of its adhesins remains undetermined.

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LITERATURE CITED


