A state-wide assessment of the association between epidural analgesia, maternal fever and neonatal antibiotics in Colorado, 2007–2012

Alice White,1 Daniel Olson,2 Kevin Messacar2

ABSTRACT
Objective To determine if an association exists between epidural analgesia, maternal fever and neonatal antibiotic exposure in a state-wide birth cohort.

Design, setting and participants We performed a retrospective cohort study of the population-based Colorado Department of Public Health and Environment birth certificate database. Data included all reported births in the state of Colorado between 2007 and 2012. Live, non-preterm, vaginal, singleton, in-hospital births were included in analysis.

Exposure Maternal epidural analgesia and maternal fever.

Main outcomes measures Neonatal antibiotic treatment for suspected sepsis. A stratified analysis was conducted to evaluate whether epidural use was an effect modifier of the association between maternal fever and neonatal antibiotic treatment.

Results The final cohort included 261 457 births. 2.2% of women who received an epidural had a fever, as compared with 0.4% of women who did not receive an epidural (OR: 5.4; 95% CI 4.9 to 6.0), and neonates born to women who received an epidural had 1.26 times increased odds of antibiotic treatment (95% CI 1.1 to 1.4). Stratification by epidural use did not alter the association between maternal fever and neonatal antibiotic treatment.

Conclusions Colorado providers treat neonates born to mothers with maternal fever without respect to whether the mother had an epidural. Further research into improved criteria for neonatal sepsis evaluation that accounts for the contribution of maternal epidural fever should be developed to decrease unnecessary neonatal antibiotic exposure.

INTRODUCTION
Administration of antibiotics to neonates at increased risk of infection is essential for the prevention of neonatal sepsis. However, unnecessary antibiotic exposure in neonates is associated with significant risks, including invasive procedures, drug toxicity, decreased breastfeeding at discharge and microbiome alterations.1-4 It is crucial to target antibiotics to neonates at high risk for sepsis and also important to minimise antibiotic exposure in neonates who are not at risk.

One of the major criteria for sepsis evaluation is maternal intrapartum fever. However, epidural analgesia can also lead to maternal fever and is not associated with an increased risk of infection in the neonate, thus leading to unnecessary neonatal exposure to antibiotics.5-7 Previous single-centre studies have found conflicting results with regards to the contribution of maternal epidural analgesia to neonatal receipt of antibiotics.8-10

The primary aim of this study was to use a state-wide birth cohort to determine if an association exists between epidural analgesia and neonatal antibiotic exposure. A secondary aim was to determine if neonates born to mothers with fever were differentially treated depending on whether an epidural was used.

METHODS
A retrospective study of the population-based Colorado Department of Public Health and Environment birth certificate database between 2007 and 2012 was conducted. The birth certificate database is a compilation of the Colorado Standard Certificate of Live Birth worksheet (see online supplementary appendix) completed by
was used in 66.3% of births. Characteristics by epidural group
receive care from an MD. Women who gave birth without an
constituted non-human subject research given the de-identi-
Multiple Institutional Review Board determined that this study
Carolina, USA) was used for statistical analysis. The Colorado
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and registered midwife delivery attendant (whose scope of prac-
tice in Colorado does not include epidurals) were excluded.
The primary exposure was maternal epidural analgesia, col-
lected on the birth certificate worksheet as 'epidural or spinal
analgesia during labour' (checkbox for yes). The primary
outcome was neonatal antibiotic treatment for suspected sepsis,
collected on the worksheet as 'antibiotics received by the
newborn for suspected neonatal sepsis' (checkbox for yes). For
the secondary analysis, maternal fever was the exposure, col-
collected as 'clinical chorioamnionitis diagnosed during labour or
maternal temperature ≥38°C (100.4°F)' (checkbox for yes); neo-
natal receipt of antibiotics was the outcome and epidural was
the effect modifier.
We considered confounding factors associated with epidural
use and neonatal antibiotic treatment for sepsis based on previ-
ous literature, clinical practice and univariate results. These
factors included maternal age (categorised as <20 years, 20–
40 years, >40 years), maternal race (white, non-Hispanic; white,
Hispanic; African-American), income (<US$25 000, US
$25 000 to 50 000, >US$50 000), education (less than high
school, high school, college or more), gravida (primigravida,
multigravida), attendant type (medical doctor, doctor of oste-
opathy, certified nurse midwife), maternal antibiotics (any antibio-
tics received during labour, including administration for group B
streptococcus (GBS)), 5 min APGAR score <7, presence of meconi-
om, premature rupture of membranes (PROM), maternal
GBS positivity, gestational age (37–38 weeks, 39–40 weeks,
>40 weeks), smoking status (any reported smoking during preg-
nancy), alcohol consumption (greater than seven drinks per
week at any time during pregnancy), sexually transmitted infec-
tions during pregnancy (gonorrhoea or chlamydia), pre-existing
maternal diabetes and gestational diabetes. Univariate analysis
was conducted to determine differences in maternal demo-
graphic characteristics of the exposure groups (epidural and no
epidural) as well as risk factors for neonatal sepsis treatment.
For the primary analysis, multivariable logistic regression was
performed to determine the association between epidural use
and neonatal antibiotic treatment, adjusting for confounders
and precision variables. For the secondary analysis, the associa-
tion between maternal fever and neonatal antibiotic treatment
was stratified by epidural use. ORs were calculated with a signi-
ficance level of p<0.05. SAS V9.4 (SAS Institute, Cary, North
Carolina, USA) was used for statistical analysis. The Colorado
Multiple Institutional Review Board determined that this study
constituted non-human subject research given the de-identified
nature of aggregate data collected, therefore informed consent
was not required.

RESULTS
The final cohort included 261 457 births. Epidural analgesia
was used in 66.3% of births. Characteristics by epidural group
are presented in table 1. Mothers who received epidurals were
more likely to be white, high income, college educated and
receive care from an MD. Women who gave birth without an
epidural were more likely to be Hispanic, low income and have
less than a high school education.
A total of 2069 neonates (0.79%) were documented to have
received antibiotics during the study period for suspected sepsis.
Risk factors by treatment status are displayed in table 2. Maternal
fever, maternal antibiotic treatment, APGAR score, GBS, meco-
nium, PROM, prolonged labour and low birth weight were
strongly associated with neonatal antibiotic treatment.
In neonates treated with antibiotics, 72% of mothers received
an epidural, compared with 66% in mothers of neonates who
were not treated with antibiotics (table 2). The odds of treating
a neonate with antibiotics was 30% higher (95% CI 1.1 to 1.4),
if epidural analgesia was given to the mother, after correction
for maternal demographic factors, provider type and neonatal
sepsis risk factors described above.
To test the hypothesis that epidural status was not considered
when evaluating neonatal sepsis, the association between fever
and antibiotic treatment was stratified by epidural use (figure 1).
In women who received an epidural, 2% developed a fever,
compared with 0.4% in the no epidural group (figure 1). The
unadjusted odds of developing fever was 5.4 times higher (95%
 CI 4.9 to 6.0) in women with an epidural than in women
without an epidural (table 1) and the adjusted OR was 5.0
(95% CI 4.5 to 5.6). Overall, neonates born to mothers with
fever had a 14 times increased odds of antibiotic treatment
(95% CI 12.8 to 16.3) (table 2). Of the mothers who had a
fever and epidural, 11% of neonates were treated with antibio-
tics, which was the same proportion of neonates treated with
antibiotics in mothers with fever and no epidural (figure 1).
Conversely, in women with an epidural and no fever, 0.6% of
babies received antibiotics, the same rate as afebrile women
without an epidural. The interaction term (maternal fever ×
epidural status) in the adjusted model was non-significant
(p=0.43).

DISCUSSION
Among a large cohort of mother-neonate pairs across the state
of Colorado over 6 years, epidural analgesia was associated with
a 26% increased odds of neonate exposure to antibiotics.
Although mothers who received an epidural were 5 times more
likely to have fever, the proportion of neonates treated with
antibiotics did not differ by epidural status. This result supports
the hypothesis that epidural analgesia is a risk factor for non-
infectious maternal fevers, but neonates born to mothers with
fever may not be treated differentially by epidural use.
Epidural analgesia is associated with increased rates of mater-
nal intrapartum fever. However, the relationship between epidural
analgesia, maternal fever and neonatal anti-
biotic treatment has been limited to conflicting single-centre
studies at academic, tertiary care institutions. Lieberman et al
found maternal epidural analgesia was associated with a 14-fold
increased rate of maternal fever and a nearly 4-fold increase in
neonate antibiotic treatment in a cohort of 1109 singleton
births at Brigham and Women’s Hospital (Boston, Massachussetts,
USA). Goetzl et al conducted a follow-up study of a similar cohort of
1934 births at the same institution, which demonstrated that in mothers with low grade (<37.5°C) or no fever, epidural analgesia was associated with threefold increased
risk of sepsis evaluation in neonates as well as increased rates of
neonatal antibiotic treatment. In contrast, Kaul et al found no
association (p=0.23) between epidural analgesia and neonate
sepsis evaluation in 1177 primiparous births at Magee-Women’s
Hospital (Pittsburg, Pennsylvania, USA). These discrepancies
likely reflect differences in study design and practice variability

among paediatricians surrounding sepsis evaluation, which is not standardised. Our large state-wide cohort indicates a significant association between maternal epidural analgesia and neonate antibiotic exposure, as described by Lieberman et al, and suggests non-infectious maternal fever is not differentially evaluated whether epidural analgesia was received or not. An equal proportion of neonates were treated with antibiotics in mothers with a fever in the epidural group as mothers with a fever in the non-epidural group, despite evidence that mothers who receive epidurals are more likely to develop a fever. Ideally, these maternal fevers would be treated differentially in sepsis evaluation; however, the evidence here indicates that they are not. Our findings also indicate practice variability in neonatal sepsis evaluation practices, as reflected in county-level data. The percentage of neonates treated with antibiotics varied by county of residence, and ranged between 0% and 5.9%. Practices vary within an institution, or even by provider, which may partially explain the differing results in previous studies.

The mechanism by which epidural analgesia leads to maternal fever and other physiologic changes is poorly understood, but it does not appear to be due to maternal infection. While some have theorised that epidural analgesia prolongs duration of labour, leading to increased risk of chorioamnionitis, studies using objective evidence of infection by placental culture and PCR have found similar rates of infection between women who receive epidurals and those who do not. The most supported mechanism leading to maternal fever is that epidurals trigger an increased inflammatory state, leading to elevated temperature. Some evidence suggests that a specific subpopulation of women may be more susceptible to maternal fever; one group of women with elevated interleukin-6 levels on hospital admission was 2.3 times more likely to develop fever after receiving epidural analgesia. It is also possible that placental inflammation without infection, or ‘sterile’ chorioamnionitis, is part of the epidural-associated inflammatory response. Roberts et al demonstrated histologic chorioamnionitis in 34% of placentas among a group of low-risk mothers that was strongly associated with fever and epidural analgesia; infection was identified in only 4%, despite the use of both culture and molecular diagnostics.

This study suggests that the decision to start antibiotics in neonates is based on suspicion of chorioamnionitis using maternal fever as a primary marker of infection. In addition, this study demonstrates that while fevers are more common in

### Table 1 Maternal demographic characteristics by whether an epidural was used during labour, Colorado, 2007–2012

<table>
<thead>
<tr>
<th></th>
<th>Epidural</th>
<th></th>
<th>No epidural</th>
<th></th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Per cent</td>
<td>n</td>
<td>Per cent</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>173 324</td>
<td>66.3</td>
<td>88 133</td>
<td>33.7</td>
<td></td>
</tr>
<tr>
<td>Maternal fever</td>
<td>3782</td>
<td>2.2</td>
<td>362</td>
<td>0.4</td>
<td>5.4 (4.9 to 6.0)</td>
</tr>
<tr>
<td>Maternal antibiotics</td>
<td>24 606</td>
<td>14.2</td>
<td>7726</td>
<td>8.8</td>
<td>1.7 (1.7 to 1.8)</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>17 154</td>
<td>9.9</td>
<td>8396</td>
<td>9.5</td>
<td>1.0 (1.0 to 1.1)</td>
</tr>
<tr>
<td>20–40 years</td>
<td>153 841</td>
<td>88.8</td>
<td>78 383</td>
<td>88.9</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;40 years</td>
<td>2329</td>
<td>1.3</td>
<td>1354</td>
<td>1.5</td>
<td>0.9 (0.8 to 0.9)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>108 774</td>
<td>63.6</td>
<td>45 574</td>
<td>51.7</td>
<td>Reference</td>
</tr>
<tr>
<td>Hispanic</td>
<td>40 649</td>
<td>23.8</td>
<td>30 456</td>
<td>34.6</td>
<td>0.6 (0.6 to 0.6)</td>
</tr>
<tr>
<td>African-American</td>
<td>8573</td>
<td>5.0</td>
<td>3961</td>
<td>4.5</td>
<td>0.9 (0.9 to 0.9)</td>
</tr>
<tr>
<td>Other*</td>
<td>11 784</td>
<td>6.8</td>
<td>6380</td>
<td>7.2</td>
<td>0.8 (0.8 to 0.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>3544</td>
<td>2.1</td>
<td>1762</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;US$25 000</td>
<td>56 545</td>
<td>32.6</td>
<td>36 435</td>
<td>41.3</td>
<td>Reference</td>
</tr>
<tr>
<td>US$25 000–US$50 000</td>
<td>29 382</td>
<td>17.0</td>
<td>15 833</td>
<td>18.0</td>
<td>1.2 (1.2 to 1.2)</td>
</tr>
<tr>
<td>&gt;US$50 000</td>
<td>64 497</td>
<td>37.2</td>
<td>24 951</td>
<td>28.3</td>
<td>1.7 (1.6 to 1.7)</td>
</tr>
<tr>
<td>Missing</td>
<td>22 900</td>
<td>13.2</td>
<td>10 914</td>
<td>12.4</td>
<td>1.4 (1.3 to 1.4)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;High school</td>
<td>28 040</td>
<td>16.2</td>
<td>23 422</td>
<td>26.6</td>
<td>0.5 (0.5 to 0.5)</td>
</tr>
<tr>
<td>High school</td>
<td>36 411</td>
<td>21.0</td>
<td>18 692</td>
<td>21.2</td>
<td>0.8 (0.8 to 0.8)</td>
</tr>
<tr>
<td>College or more</td>
<td>108 869</td>
<td>62.8</td>
<td>46 816</td>
<td>52.2</td>
<td>Reference</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>0.0</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gravida</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prima</td>
<td>79 732</td>
<td>46.0</td>
<td>31 271</td>
<td>35.5</td>
<td>1.6 (1.5 to 1.6)</td>
</tr>
<tr>
<td>Multi</td>
<td>93 592</td>
<td>54.0</td>
<td>56 862</td>
<td>64.5</td>
<td>Reference</td>
</tr>
<tr>
<td>Attendant type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>144 715</td>
<td>83.5</td>
<td>66 200</td>
<td>75.1</td>
<td>Reference</td>
</tr>
<tr>
<td>DO</td>
<td>5594</td>
<td>3.2</td>
<td>3006</td>
<td>3.4</td>
<td>0.9 (0.8 to 0.9)</td>
</tr>
<tr>
<td>CNM</td>
<td>23 014</td>
<td>13.3</td>
<td>18 927</td>
<td>21.5</td>
<td>0.6 (0.5 to 0.6)</td>
</tr>
<tr>
<td>PROM</td>
<td>4302</td>
<td>2.5</td>
<td>1171</td>
<td>1.3</td>
<td>1.9 (1.8 to 2.0)</td>
</tr>
<tr>
<td>Prolonged labour (≥20 hours)</td>
<td>2735</td>
<td>1.6</td>
<td>687</td>
<td>0.78</td>
<td>2.0 (1.9 to 2.2)</td>
</tr>
</tbody>
</table>

*Including Asian, American Indian, Alaskan Native.

PROM, premature rupture of membranes.
Table 2  Neonatal sepsis risk factors by treatment of the neonate with antibiotics for suspected sepsis, Colorado, 2007–2012

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Antibiotics</th>
<th>No antibiotics</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2069 0.79</td>
<td>259 390 99.2</td>
<td>1.3 (1.2 to 1.4)</td>
<td>1.3 (1.1 to 1.4)*</td>
</tr>
<tr>
<td>Epidural</td>
<td>1486 71.8</td>
<td>171 838 66.2</td>
<td>19.6 (17.6 to 21.9)</td>
<td>14.4 (12.8 to 16.3)*</td>
</tr>
<tr>
<td>Maternal fever</td>
<td>456 22.0</td>
<td>3688 1.4</td>
<td>5.4 (4.9 to 5.9)</td>
<td>5.0 (4.5 to 5.6)</td>
</tr>
<tr>
<td>Maternal antibiotics</td>
<td>880 42.5</td>
<td>31 452 12.1</td>
<td>1.3 (1.2 to 1.4)</td>
<td>1.3 (1.1 to 1.4)*</td>
</tr>
<tr>
<td>5 min APGAR &lt;7</td>
<td>268 13.0</td>
<td>4843 1.9</td>
<td>7.8 (6.9 to 8.9)</td>
<td>Reference</td>
</tr>
<tr>
<td>5 min APGAR ≥7</td>
<td>1800 87.0</td>
<td>254 269 98.1</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Group B streptococcus positive</td>
<td>617 29.8</td>
<td>36 287 14.0</td>
<td>2.6 (2.4 to 2.9)</td>
<td>Reference</td>
</tr>
<tr>
<td>Meconium present</td>
<td>300 14.5</td>
<td>13 628 5.3</td>
<td>3.1 (2.7 to 3.5)</td>
<td>Reference</td>
</tr>
<tr>
<td>PROM</td>
<td>142 6.9</td>
<td>5331 2.1</td>
<td>3.5 (3.0 to 4.2)</td>
<td>Reference</td>
</tr>
<tr>
<td>Prolonged labour (≥20 hours)</td>
<td>71 3.4</td>
<td>3351 1.3</td>
<td>2.7 (2.1 to 3.5)</td>
<td>Reference</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td>1.3 (1.2 to 1.5)</td>
<td>Reference</td>
</tr>
<tr>
<td>37–38 weeks</td>
<td></td>
<td></td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>39–40 weeks</td>
<td></td>
<td></td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;40 weeks</td>
<td></td>
<td></td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td>1.2 (1.1 to 1.3)</td>
<td>Reference</td>
</tr>
<tr>
<td>VLBW (&lt;1500 g)</td>
<td>3 0.1</td>
<td>31 0.01</td>
<td>12.4 (3.8 to 40.5)</td>
<td>Reference</td>
</tr>
<tr>
<td>LBW (1500–2500 g)</td>
<td>92 4.4</td>
<td>7504 2.9</td>
<td>1.6 (1.3 to 1.9)</td>
<td>Reference</td>
</tr>
<tr>
<td>AGA (&gt;2500 g)</td>
<td>1974 95.4</td>
<td>251 855 97.1</td>
<td>1.3 (1.2 to 1.5)</td>
<td>Reference</td>
</tr>
<tr>
<td>Sexually transmitted infection</td>
<td></td>
<td></td>
<td>1.8 (1.4 to 2.2)</td>
<td>Reference</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Any during pregnancy</td>
<td>202 9.8</td>
<td>20 989 8.1</td>
<td>1.2 (1.1 to 1.4)</td>
<td>Reference</td>
</tr>
<tr>
<td>None</td>
<td>1851 89.5</td>
<td>237 701 91.6</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Missing</td>
<td>16 0.8</td>
<td>700 0.3</td>
<td>1.2 (1.1 to 1.4)</td>
<td>Reference</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;7 drinks/week at any time during pregnancy</td>
<td>3 0.1</td>
<td>131 0.1</td>
<td>2.9 (0.9 to 9.1)</td>
<td>Reference</td>
</tr>
<tr>
<td>≤7 drinks/week</td>
<td>2044 98.8</td>
<td>258 309 99.6</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Missing</td>
<td>22 1.1</td>
<td>1078 0.3</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>1.5 (1.2 to 1.8)</td>
<td>Reference</td>
</tr>
<tr>
<td>Male</td>
<td>1091 52.7</td>
<td>130 972 50.5</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Female</td>
<td>978 47.3</td>
<td>128 417 49.5</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Prepregnancy diabetes</td>
<td>26 1.3</td>
<td>918 0.4</td>
<td>3.6 (2.4 to 5.3)</td>
<td>Reference</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>92 4.4</td>
<td>8008 3.1</td>
<td>1.5 (1.2 to 1.8)</td>
<td>Reference</td>
</tr>
<tr>
<td>Geography</td>
<td></td>
<td></td>
<td>0.85 (0.77 to 0.94)</td>
<td>Reference</td>
</tr>
<tr>
<td>Urban</td>
<td>1502 72.6</td>
<td>196 674 75.8</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Rural</td>
<td>542 26.2</td>
<td>60 616 23.4</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

*Adjusted for maternal age, race, education, gestational diabetes, smoking, alcohol, sexually transmitted infection, primagravida, premature rupture of membranes, estimated gestation, group B streptococcus, birth weight, meconium, 5 min APGAR score, prolonged labour and attendant type.

PROM, premature rupture of membranes.

Figure 1  Stratified analysis of neonate antibiotic treatment between epidural groups with and without fever. *Live, non-preterm (37 weeks or greater gestational age), vaginal, singleton, in-hospital births. Births with precipitous onset of labour (<3 hours), maternal transfer and registered midwives were excluded.

Colorado Births, 2007-2012*

Epidural 173,324 (66%)
No epidural 88,133 (34%)

Maternal fever 3,782 (2%)
No fever 169,542 (98%)

Maternal fever 362 (0.4%)
No fever 87,771 (99%)

Neonate antibiotics 417 (11%)
Neonate antibiotics 1,069 (0.6%)

Neonate antibiotics 39 (11%)
Neonate antibiotics 544 (0.6%)

*Live, non-preterm (37 weeks or greater gestational age), vaginal, singleton, in-hospital births. Births with precipitous onset of labor (less than 3 hours), maternal transfer, and registered midwives were excluded.
women receiving epidurals, this association may not be taken into consideration when choosing to start antibiotics in neonates. While maternal fever in women with epidural analgesia has been associated with a number of neonatal outcomes considered risk factors for neonatal sepsis, including hypotonia, assisted ventilation, low APGAR score and early onset seizures, we are not aware of any published studies demonstrating an increase in documented sepsis in neonates born to mothers with epidurals.13–16

Regardless of the mechanisms leading to initiation of antibiotics in mothers or neonates, there is an increasing recognition of the risks of exposing neonates to antibiotics, both directly to the infant and indirectly through maternal antibiotic exposure. In the short term, neonates are exposed to drug toxicity, invasive procedures such as lumbar punctures and intravenous catheters and other risks associated with hospitalisation. In the long term, antibiotic exposure is associated with necrotising enterocolitis and altered gut microbiome.6–8 Evidence suggests an association exists between altered neonatal gut microbiome and risks of chronic, particularly atopic, disease.17–20

This study has inherent strengths and limitations. The large, state-wide study population reflects clinical practice across multiple centres and time compared with previous studies conducted at single academic centres. In addition, we were able to control for most major confounding variables associated with epidural use and neonatal sepsis. However, data collection was limited to that available on the birth certificate registry. Primary outcome data on the worksheet was collected using single ‘check if present’ boxes, which cannot differentiate negative versus missing data. Therefore, our incidence data were likely underestimated due to underreporting, particularly the low incidence of neonate antibiotic exposure for suspected sepsis and the low incidence of chorioamnionitis during labour or maternal fever, which were substantially lower than estimates described in the literature at academic institutions.21–23 Underreporting of maternal fever may have occurred if providers were more likely to check the box only for suspected clinical infection rather than any infectious or non-infectious fever. A validation study comparing the birth certificate registry with hospital records would be helpful in determining the magnitude of underreporting. However, this was not possible in this study given the de-identified nature of the dataset. Maternal fever and chorioamnionitis were listed as a single variable and there were no data available on documented neonatal sepsis, so care must be taken in the interpretation of these results. We were unable to measure duration of labour, which is one explanation for how epidural could increase the risk of neonatal sepsis. However, we were able to adjust for PROM, which should correlate with prolonged labour.

In conclusion, our data demonstrate that epidural analgesia is associated with an increased risk of maternal fever and neonatal exposure to antibiotics across a large population. The common clinical practice of using maternal fever as a primary marker of maternal chorioamnionitis and driver for administration of antibiotics to neonates should be re-examined. Standardised criteria for neonatal sepsis evaluation are needed to decrease exposure to antibiotics of neonates who are at low risk for infection. One such effort at standardisation is the online Kaiser Permanente infection probability calculator, which allows users to input evidence-based maternal and infant risk factors to calculate risk of sepsis per 1000 births.24–26 Further research that incorporates maternal epidural status could improve standardised neonatal sepsis evaluation and decrease unnecessary neonatal antibiotic exposure.

Contributors All authors contributed substantially to the study, developed the study concept and design, contributed to the data interpretation and drafted and revised the manuscript. KM conceived the study. AW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AW is the guarantor of this study.

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