Does giving antibiotics increase the risk of Hemolytic Uremic Syndrome?

Wong CS et al. The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. N Engl J Med 2000; 342:1930-6.

Take Home Message: Children with *E.coli* O157:H7 infections who receive antibiotics have a greater risk of developing hemolytic uremic syndrome than do children who do not receive antibiotics.

Highlights: There has been concern that antibiotics may increase the risk of hemolytic uremic syndrome (HUS) in patients with *E.coli* O157:H7 infections, but the data has been conflicting. Wong et al. conducted this prospective cohort study[i] over two years looking at whether antibiotic treatment alters the risk of HUS. They followed 71 patients with confirmed *E.coli* O157:H7 infections. Antibiotics were administered at the discretion of the primary providers. 9 of the 71 patients received antibiotics. Ultimately, 10 patients (14%) developed HUS: 56% of those who had received antibiotics and 8% of those who had not received antibiotics.

To adjust for severity of illness as a possible confounder (i.e., patients with severe illness, who may develop HUS regardless, may be more likely to receive antibiotics), a logistic regression was performed which adjusted for initial white blood cell count as well as the day of illness on which the stool culture was sent –surrogates of severe illness. This multivariate analysis showed that children who received antibiotics, even after adjusting for these factors, still had a higher risk of HUS than did those who had not received antibiotics, with an adjusted relative risk of 17.3 (though with a wide 95% confidence interval of 2.2 to 137). The authors concluded that the association between antibiotics and HUS in patients with *E.coli* O157:H7 is strong so to avoid giving antibiotics to children who may be infected with this bacteria.

In 2012, this same group, also led by Wong, published the completion of the cohort study, adding on 7 more years of data to provide stronger data.[ii] Now with 259 subjects, 25 of whom received antibiotics, the rate of HUS remained 14% (36% in the antibiotic group vs. 12% in the no antibiotic group). With their larger sample size, they found antibiotics were still associated with the development of HUS, with an adjusted odds ratio of 3.62 (with a tighter 95% confidence interval of 1.2-10.6). Though there is still much to be elucidated about the connection between antibiotics and HUS, now most recommendations, including the CDC's[iii], include avoiding antibiotics for suspected enterohemorrhagic *e.coli* infections this infection has been ruled out.

The Nitty-Gritty:

- **Design:**
    - Observational, prospective, cohort study
    - N= 71
        - Antibiotics group (n=9)
        - No antibiotics group (n=62)
    - Setting: Washington, Oregon, Idaho, and Wyoming
    - Enrollment: 1997-1999
    - Primary outcome: development of hemolytic-uremic syndrome (HUS), defined as:
        - 1) hemolytic anemia (hematocrit <30% with evidence of destruction of erythrocytes on a peripheral blood smear),

- § 2) thrombocytopenia (platelet count < 150,000/mm3), and
- § 3) renal insufficiency (serum creatinine concentration that exceeded upper limit of normal range for age)

- **Population:**
  - **Inclusion Criteria:**
    - § Children < 10 years of age
    - § Laboratory identified *E.coli* O157:H7 infection
    - § Stool culture obtained within the first seven days after onset of illness
  - **Baseline Characteristics –** from the no antibiotics group; there were no significant differences between the two groups; plus-minus values are means +-SD
    - § Female sex: 47%
    - § Age: 4.1 +- 2.6 years
    - § Race: 87% white
    - § Bloody diarrhea: 92%
    - § Vomiting: 54%
    - § Fever: 38%

- § Initial white cell count: 11.6+-4.2 x 103/mm3
- § Initial serum urea nitrogen: 10.2+-6.1 mg/dl
- § Initial serum creatinine: 0.4 +-0.1 mg/dl
- § Stool culture obtained on: 3.3+-1.4 day of illness
- § Initial white cell count obtained on: 4.7+-2.0 day of illness
- § Stool culture positive for *E.coli* O157:H7 on: 5.3+-1.6 day of illness

- **Intervention**:
  - o Children with laboratory determined *E.coli* O157:H7 infections identified
  - o Medications were administered at the discretion of each child's primary care, inpatient, or emergency department physician
  - o Daily blood counts and renal function tests were drawn until the development of hemolytic uremic syndrome or until the diarrhea had resolved and hemolytic uremic syndrome clearly did not develop

- **Outcomes:**
  - o **Primary outcome: Development of hemolytic uremic syndrome**
    - § 14% of all patients (10/71)

§ *Frequency of development of HUS according to treatment with antibiotics:* Antibiotics vs. no antibiotics: 56% (5/9) vs. 8% (5/62) (P<0.001)

§ *Frequency of development of HUS according to potential confounding characteristics (surrogates of severity of illness):*

- WBC count: 3200-8700 vs. 8800-11,800 vs. 11,900-14,200 vs. 14,300-24,600/mm3: 0% vs. 6% vs. 17% vs. 35% (P=0.005)

- Day stool culture obtained: days 1-2 vs. day 3 vs. day 4-7 of illness: 33% vs. 9% vs. 0% (P=0.01)

- Day initial white cell count obtained: days 1-3 vs. days 4-5 vs. days 6-10 of illness: 28% vs. 12% vs. 0% (P=0.009)

o **Logistic-Regression Analysis**

§ Adjusted relative risk of HUS (adjusted for initial WBC count and day on which initial stool culture was obtained)

- Antibiotics given within first 7 days after onset of illness: 17.3 (95% CI, 2.2 to 137; P=0.007)

- Antibiotics given within first 3 days after onset of illness: 32.3 (95% CI, 1.4 to 737; P=0.03)

- **Criticisms**

o Strains other than *E.coli* O157:H7 were not included[iv]

- Severity of illness is not actually a confounder, as it is probably a marker for an intermediate factor in the causal pathway[v]

- Relative risk could have been directly calculated instead of estimating with odds ratio which may have overestimated the risk

[i] Wong CS et al. The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. N Engl J Med 2000; 342:1930-6.

[ii] Wong CS et al. Risk factors for the hemolytic uremic syndrome in children infection with *Escherichia coli* O157:H7: a multivariable analysis. Clin Infect Dis. 2012; 55:33-41.

[iii] http://www.cdc.gov/ecoli/clinicians.html

[iv] Aragon T et al. The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. N Engl J Med 2000; 343: 1271-2.

[v] O'Ryan M and Prado V. The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. N Engl J Med 2000; 343: 1271.