Antibiotic Spectrum Index and Risk of *Clostridioides difficile* Infection

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INTRODUCTION

- Antibiotic therapy is a risk factor for *Clostridioides difficile* infection (CDI), and magnitude of risk likely varies by spectrum of antibiotic activity and duration of therapy
- Traditional measures of antibiotic use, such as days of therapy (DOT), fail to capture complete information about intensity of antibiotic therapy
- The antibiotic spectrum index (ASI) quantifies spectrum of antibiotic therapy using a simple score that weights the spectrum of activity of an agent based upon the number of common pathogens for which the agent provides coverage[1]
- ASI could provide a more accurate quantification of risk of CDI attributable to antibiotics and thus support decision-making around antibiotic prescribing and stewardship initiatives

OBJECTIVE

- Quantify the risk of healthcare-associated CDI (HA-CDI) attributable to antibiotic therapy using the Antibiotic Spectrum Index (ASI)

METHODS

- Retrospective cohort study at Oregon Health & Science University (OHSU) of adult inpatient encounters from January 2018-February 2020 with length of stay ≥ 4 days
- Exclusion criteria:
  - CDI diagnosis within first 3 days of encounter
  - CDI in previous 8 weeks or recurrent CDI ICD-10 code (A04.71)
- Outcome: Incident, hospital-associated CDI (HA-CDI) defined as:
  - Anti-CDI antibiotic therapy (metronidazole, oral vancomycin, or fidaxomicin) initiated on hospital day 4 or later **AND**
  - ICD-10-CM code (A04.72) for non-recurrent CDI present **OR**
  - Positive *C. difficile* test (PCR, stool toxin) collected on hospital day 4 or later
- Primary Exposure: Aggregate, patient-level ASI per antibiotic day; sum of ASI scores for each individual systemic antibiotic (ABX) agent across all days and divided by number of antibiotic days (Figure 1)
- Time at-risk: duration of encounter or until HA-CDI diagnosis
- Colonization pressure: Number of CDI or *C. difficile* colonized patients present in the same hospital location on the same day / time at-risk
- Statistical Analysis
  - Generalized estimating equations (GEE) approach to build a marginal model with robust covariance estimation to generate adjusted relative risks
  - Stepwise model selection procedure (significance level entry = 0.15)
- Adjusted absolute risk differences generated using SAS Margins Macro[2]
  - Number needed to harm (NNH) calculated
  - Estimated HA-CDI cases prevented calculated using hypothetical reductions our institution's actual short course therapy (≤ 3 days) divided by NNH

Figure 2. Estimated HA-CDI cases prevented after hypothetical reductions in short-course antibiotic therapy

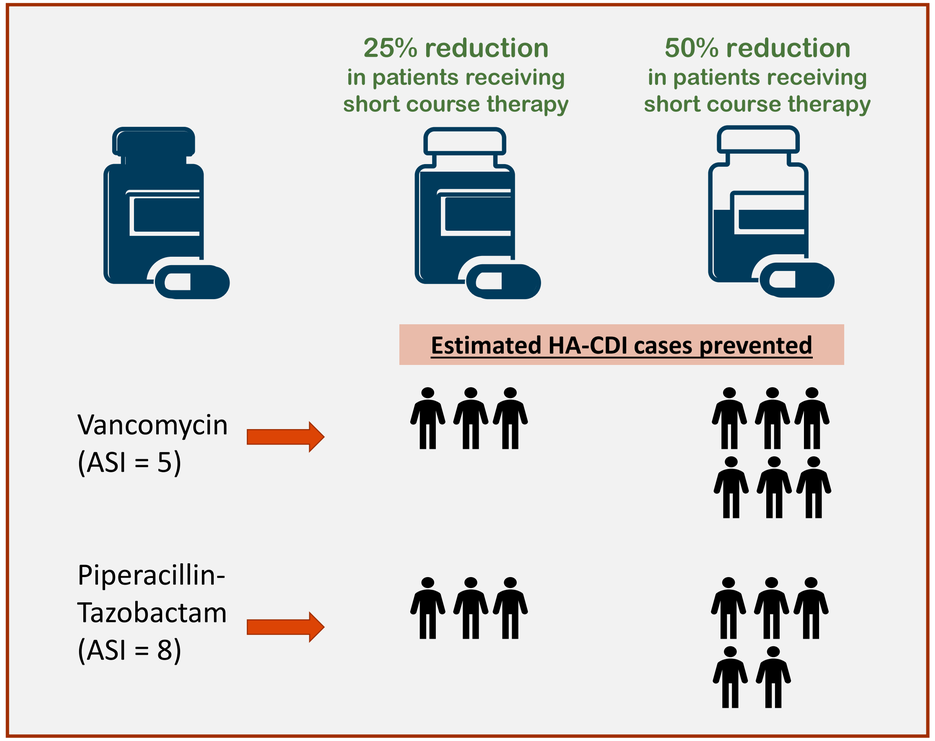

Figure 1. ASI calculations for example patients

Example patient #1	Example patient #2
10-day LOS	11-day LOS
8 days of **cefazolin** (ASI 3) – Day 3-10	2 days of **cefoxitin** (ASI 5) – Day 1-2
5 days of **vancomycin** (ASI 5) – Day 1/5	2 days of **ertapenem** (ASI 9) – Day 1-2
10 antibiotic days	2 antibiotic days
49 total ASI	28 total ASI
4.9 ASI per antibiotic day	**14.0 ASI per antibiotic day**

Table 1. Adjusted relative risks for HA-CDI

	Relative Risk (95% CI)
ASI per antibiotic day (per 1-point increase)	1.09 (1.06, 1.12)
Time at-risk (per day)	1.011 (1.004, 1.020)
Elixhauser comorb. (per 1-point increase)	1.05 (1.02, 1.08)
PPI/H2RA	3.08 (1.76, 5.41)
NG tube placement	2.30 (1.56, 3.41)
Colonization pressure (per case-day/day at-risk)	2.00 (1.83, 2.18)

RESULTS

- Cohort includes 37,631 inpatient encounters representing 27,771 distinct patients
- We identified 145 HA-CDI cases, representing a cumulative incidence of 0.39% or incidence rate of 4.4 per 10,000 patient-days
- 68 percent of our patient population received at least one antibiotic
- Patients had median length of stay of 6 days, a median of 2 days of antibiotic therapy, and a mean of 4.4 ASI per antibiotic day
- Each additional unit of ASI per antibiotic day is associated with 1.09 times greater risk of HA-CDI (Table 1)
  - After adjusting for time at-risk, Elixhauser comorbidity index, PPI/H2RA receipt, nasogastric tube placement, and colonization pressure
- For vancomycin, we calculated a NNH of 801, meaning treating 801 patients with a short course of vancomycin would cause one additional HA-CDI case
  - For piperacillin-tazobactam, we calculated a NNH of 433

CONCLUSIONS

- The Antibiotic Spectrum Index was strongly associated with HA-CDI and potentially provides information beyond measures like DOT
- Our results illustrate utility of the ASI and attributable risk as tools for estimating CDI reduction following stewardship interventions
- ASI could also be useful tool for quantifying individual patient risk of CDI according to the specific antibiotic therapy received
- While NNH values were relatively large, reduction is HA-CDI is still meaningful given the extremely high frequency of antibiotic therapy among hospitalized patients
- Striving for reductions in average ASI represent a valuable antibiotic stewardship target
- Strengths
  - Comprehensive, longitudinal dataset
  - Absolute risk measures are often more clinically applicable than relative measures
- Limitations
  - The CDI burden at our institution is relatively low compared to the nation
  - Antibiotics with the same ASI could confer very different CDI-specific risks depending on mechanism of activity

REFERENCES

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FOR MORE INFORMATION

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