Impact of implementing an automatic 5-day antimicrobial stop order policy on antibiotic utilization

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Disclosure Statement

- Disclosure Statement: These individuals do not have anything to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation
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    - Abdel Bello, PharmD

Presentation Objective

- Recognize the goals of automatic antimicrobial stop order policies

Antibiotic Resistance

- One of the largest threats in healthcare today

- Greater than 23,000 deaths yearly due to antimicrobial resistant infections

- Several strategies exist to combat resistance
  - Antimicrobial cycling
  - Narrow-spectrum antibiotics
  - Combination antibiotic therapy
  - Decreased utilization

Ventola CL. P&T. 2015;40(4):277-83.
CDC and Prevention. (2017).
Kollef MH. Clin Infect Dis. 2006;43 Suppl 2:S82-8.

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Automatic Stop Orders (ASOs)

- Implemented in 71% of university-affiliated institutions
- Function of computerized order-entry systems
- Automatically discontinue drugs that require regular review (e.g., antibiotics)
- Goals of an ASO:
  - Encourage active reassessment
  - Evaluate need for continuation of treatment
  - Minimize antibiotic use

Lesar TS, Briceland LL. Ann Pharmacother. 1996;30(1):31-4.

ASOs in the Literature

	Duration of ASO	Population	Antibiotic outcomes
Murray, et al (2014)	5 days	502 Adults	Duration: 8.3 to 6.8 days (p=<0.0001) Adverse effects: 31% to 19% (p=0.03)
Ross, et al (2016)	48 hours	116,893 Children	No differences in mortality, 30-day readmission, or length of stay
Tolia, et al (2017)	48 hours	674 Neonates	Duration → 6.5 to 4.0 days No mortality differences
Grant, et al (2018)	48 hours	488 Neonates	>48-hrs of antibiotics→ 81% to 27% Lumbar punctures → 35% to 20%

Murray C, et al. J Antimicrob Chemother. 2014;69(2):515-8.
Ross RK, et al. Infect Control Hosp Epidemiol. 2016;37(8):974-8.
Grant CH, et al. Clin Pediatr (Phila). 2018;57(1):76-81.
Tolia VN, et al. Am J Perinatol. 2017;34(2):105-110.

Study Rationale

Lack of clinical data in adult populations

- Therapeutic efficacy of antibiotics within ASOs

Safety concerns

- Inappropriate discontinuation
- Patient harm

Ascension St. Vincent's recently initiated a 5-day automatic antibiotic stop order

Research Setting

- Ascension St. Vincent's
  - Riverside
    - 528-bed non-profit, adult, community, teaching hospital
  - Southside
    - 313-bed non-profit, adult, community hospital
  - Clay County
    - 104-bed non-profit, adult, community hospital

Study Design

- IRB-approved, multi-centered, retrospective, non-inferiority, observational chart review

- Six-month periods were evaluated

Implementation of 5-day ASO: July 2016

Pre-ASO: Dec 2015 to May 2016

Post-ASO: Sept 2016 to Mar 2017
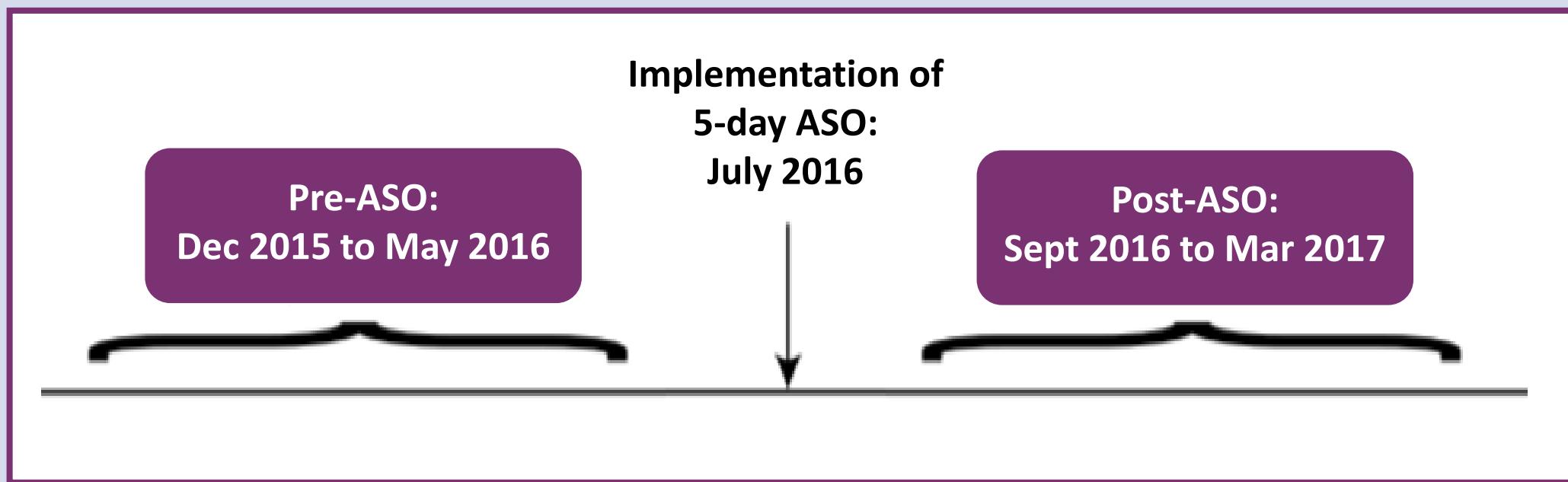
Subject Selection

- Inclusion criteria
  - 18 years of age or older
  - Administered antibiotics for at least 48 hours

- Exclusion criteria
  - Vancomycin or aminoglycoside monotherapy
  - Surgical prophylaxis
  - Postpartum
  - Pregnant
  - Incarcerated

Primary Outcome

Clinical cure rates of patients placed on antibiotics before and after initiation of a 5-day ASO policy

- Clinical cure rate:
  - Resolution of signs and symptoms of infection:
    - Temp < 38°C and > 36°C
    - WBC between 4,000 cells/mm^3 and 12,000 cells/mm^3
    - No additional antibacterial or surgical therapy
  - And:
    - No positive repeat cultures
    - No clinical documentation suggesting persistent infection

Secondary Outcomes

Hospital length of stay

Inpatient mortality

30-day readmission

Inappropriate discontinuation of antibiotics

Duration of antibiotics

Data Collection

- Demographics
- Comorbidities
- Length of stay
- Infection type
- Microbiological reports

- Prior 30-day antibiotic use
- Antibiotics prescribed on discharge
- Antibiotic therapy:
  - Drug
  - Route
  - Dose
 - Duration

Statistical Analysis

Power calculation

- Average clinical cure rate of 90%
- One-sided non-inferiority margin of 10%
- Power: 80%
- Alpha: 0.05
- Total of 160 subjects in each group

Inferential statistics

- Continuous: Student's t-test & Mann-Whitney U
- Nominal: Chi-squared & Fisher's exact

Subject Selection

Antibiotic orders screened for eligibility (n=149,577)

Excluded (n=101,910)
- One-time doses (n=33,924)
- Surgical Prophylaxis (n=30,534)
- Vancomycin/Aminoglycosides (n=37,452)

Met initial eligibility (n=47,663)
Antibiotic orders across 18,108 subjects

Pre-ASO (n=8,983)

Randomized

Evaluated in Pre-ASO (n=236)
- Excluded for < 48 hours duration (n=76)

160 included

Post-ASO (n=9,125)

Randomized

Evaluated in Post-ASO (n=280)
- Excluded for < 48 hours duration (n=120)

160 included

Baseline Demographics

Characteristic	Pre-ASO (n=160)	Post-ASO (n=160)	p-value
Age, yr	66 (64-69)	64 (61-67)	0.425
Female, n (%)	93 (58)	74 (46)	0.034
Height, cm	168 (166-170)	170 (168-171)	0.179
Weight, kg	82 (78-85)	83 (79-87)	0.787
Race, n (%)			
White	124 (78)	108 (68)	0.187
African American	33 (21)	44 (28)	
Other	3 (2)	8 (5)	

median (IQR) unless otherwise noted

Baseline Demographics

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Characteristic	Pre-ASO (n=160)	Post-ASO (n=160)	p-value
WBC Count, cells/m^3	14 (13-15)	13 (12-14)	0.650
Positive cultures, n (%)	76 (48)	73 (46)	0.519
Antibiotic use (<30 days), n (%)	27 (17)	43 (27)	0.031
Discharge antibiotics, n (%)	89 (56)	87 (54)	0.822
Comorbidities, n (%)			
COPD	36 (23)	25 (16)	0.154
Renal insufficiency	18 (11)	12 (8)	0.338
Malignancy	22 (14)	9 (6)	0.022
Cirrhosis	3 (2)	1 (1)	0.623
Diabetes mellitus	28 (18)	26 (16)	0.881
Immunocompromised	8 (5)	8 (5)	1

Immunocompromised = Organ transplant, tuberculosis, HIV, inflammatory bowel diseases, systemic lupus erythematosus

Primary Outcome Results

	Pre-ASO (n=160)	Post-ASO (n=160)	p-value
Clinical cure, n (%)	138 (86.3)	140 (87.5)	0.002 Farrington-Manning method for non-inferiority
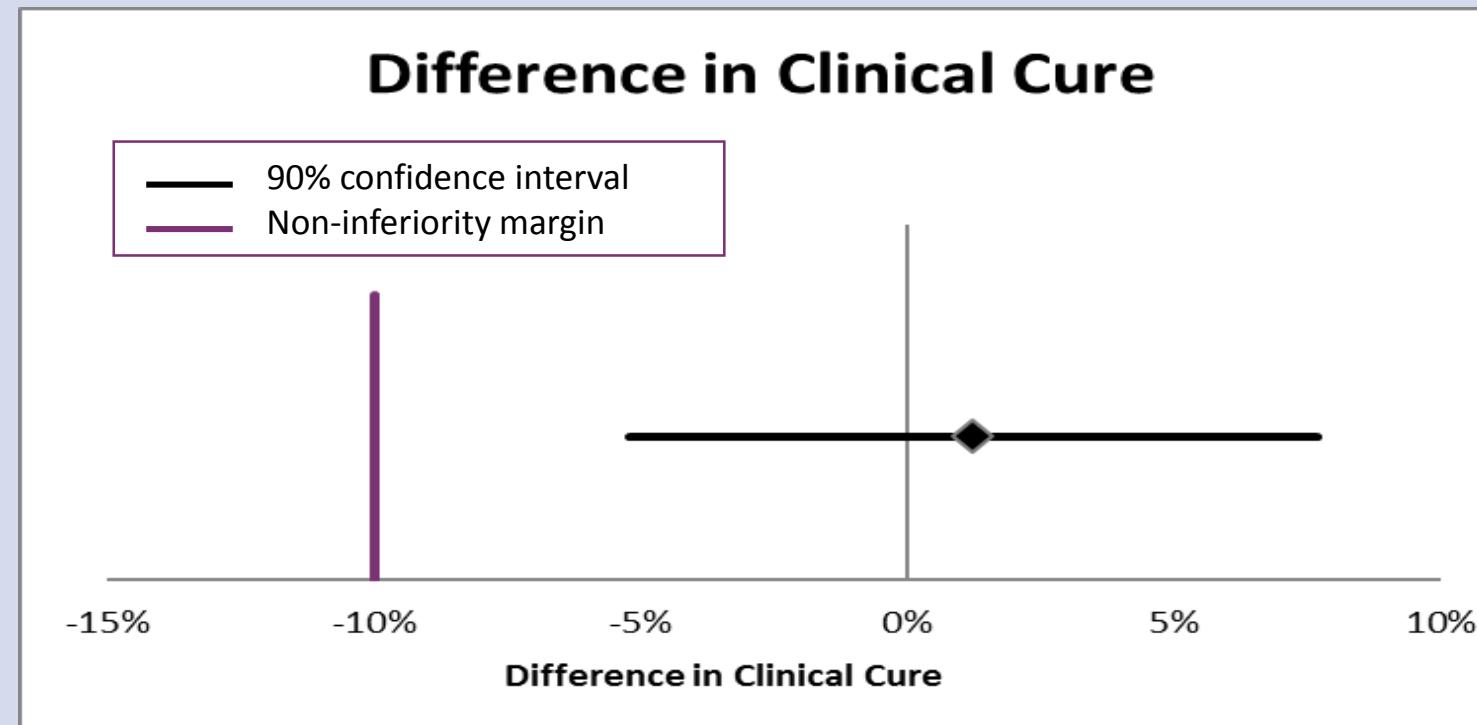
Secondary Outcome Results

| Antibiotic duration days, (IQR)	30-day readmission n, (%)	Length of stay days, (IQR)	Mortality n, (%)
Pre: 5.5 (2.95-6.25)	Pre: 31 (19)	Pre: 10.5 (8.7-12.3)	Pre: 3 (2)
Post: 4.8 (2.97-5.3)	Post: 24 (15)	Post: 9.5 (8.2-10.7)	Post: 6 (4)
p=0.184	p=0.362	p=0.980	p=0.502

One inappropriate discontinuation in the post-ASO group
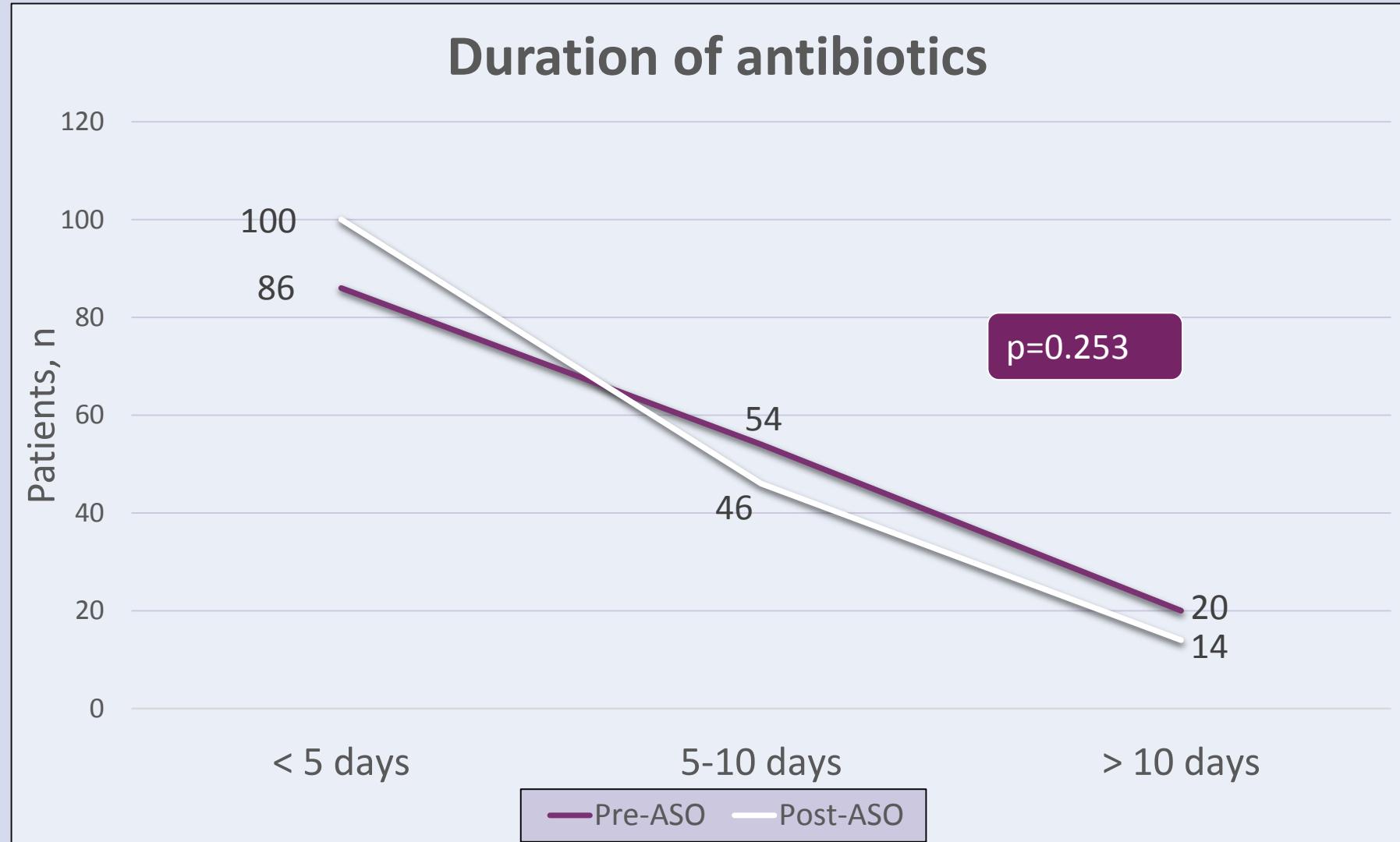
Subgroup Analysis

Clinical cure rates between groups

Pre-ASO, Post-ASO

	Pre-ASO	Post-ASO	p-value
CAP	95%	91%	
Abdominal	96%	87%	
HCAP	77%	71%	
SSTI	76%	100%	p=0.057
UTI	86%	95%	
Sepsis	72%	80%	
Other	100%	80%	p=0.476
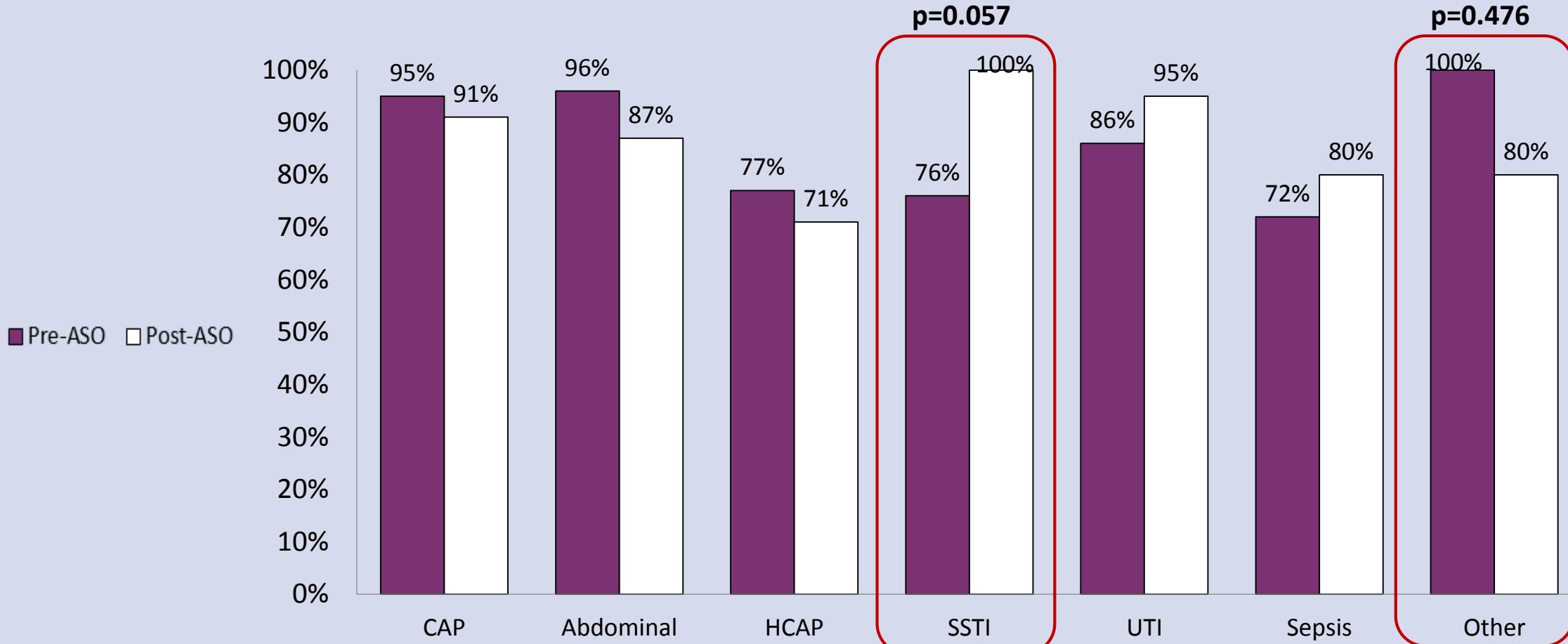
CAP = Community acquired pneumonia; HCAP = Healthcare-acquired pneumonia; SSTI = Skin and soft tissue infection; UTI = Urinary tract infection; Other = Sinusitis, meningitis, COPD exacerbation, bacteremia, fungal

Discussion

- Met non-inferiority for clinical cure

- Numerical decrease in antibiotic duration

- No difference between subgroups in regards to clinical cure

- Inappropriate discontinuation did not affect clinical outcome
  - Order was restarted within 24 hours following stop time

Study Limitations

- Retrospective cohort study
    - Relied on nursing documentation of antibiotics
    - Heterogeneity between groups
        - Female sex/prior antibiotic use/malignancy
- Seasonal differences between groups
    - December-May (Pre-ASO) vs September-March (Post-ASO)
- Other antibiotic stewardship initiatives during study period

Conclusion

- First study to demonstrate antibiotic efficacy in conjunction with ASO policies
  - Supports clinical safety of antibiotic stop orders
  - Minimal risk of premature antibiotic discontinuation
- ASOs offer potential for reduced antibiotic exposure and costs

Assessment Question

Which of the following is NOT a goal of an automatic stop order policy?

A. Encourage active reassessment of the patient on a daily basis

B. Evaluate the need for continuation of treatment

C. Minimize antibiotic use

D. Improve rates of clinical cure

Acknowledgements

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