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14. Effects of an Opt-Out Protocol for Antibiotic De-escalation among Selected Patients with Suspected Sepsis: The DETOURS Trial

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The CDC Prevention Epicenters Program

Session: O-03. Building Your Toolkit for HAI Surveillance and Stewardship

Background. Sepsis guidelines recommend daily review to de-escalate or stop antibiotics in appropriate patients. We conducted a randomized controlled trial (NCT03517007) of an opt-out protocol to decrease unnecessary antibiotics in selected patients with suspected sepsis.

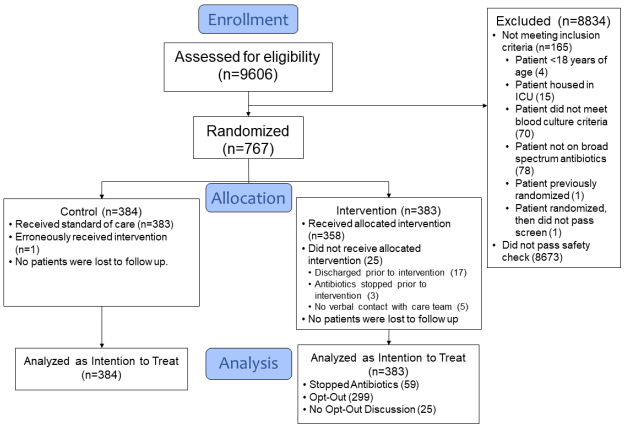
Methods. We evaluated non-ICU adults remaining on broad-spectrum antibiotics with negative blood cultures at 48-96 hours at ten U.S. hospitals during September 2018-May 2020. A 23-item safety check excluded patients with ongoing signs of infection, concerning or inadequate microbiologic data, or high-risk conditions (Figure 1). Eligible patients were randomized to the opt-out protocol vs. usual care. The primary outcome was 30-day post-enrollment antibacterial days of therapy (DOT). Clinicians caring for intervention patients were contacted by a pharmacist or physician to encourage antibiotic discontinuation or de-escalation using opt-out language, discuss rationale for continuing antibiotics, working diagnosis, and de-escalation and duration plans. Hurdle models separately compared the odds of antibiotic continuation and DOT distributions among those who continued antibiotics.

Components of the De-Escalating Empiric Therapy: Opting-OUt of Rx in Selected patients with Suspected Sepsis (DETOURS) Trial Protocol

DETOURS Protocol Component	Criteria or Intervention
1. Screening for suspected sepsis at 48-96 hours after blood culture collection	• Hospitalized adult in non-intensive care unit. • Blood cultures negative (or indicating skin contaminant). • Patient remains on broad-spectrum antibiotics.
2. Safety Check (Must exclude all)	• Ongoing signs or symptom of infection Continued fever, new chest X-ray infiltrate, empyema or lung abscess, continued leukocytosis • Concerning or inadequate microbiologic data Positive blood cultures not indicating contaminant, positive non-blood microbiology, no cultures during sepsis work up, antibiotic use prior to blood culture • High-risk comorbidity or severe illness Bronchiectasis, cystic fibrosis, asplenia, pregnant, recent I&D procedure, ongoing respiratory insufficiency, immunocompromised, osteomyelitis, endocarditis
3. Randomize	1:1 Randomization
4. Opt-Out Discussion	Interact with the treatment team using the following language: "[This patient] passed the safety screen for de-escalation of antibiotics. Antibiotics will be stopped per protocol unless you opt-out."
5. Guided De-escalation Discussion for clinicians who choose to continue antibiotics.	Engage with treatment team and document answers to 4 questions: 1. "Why should antibiotics be continued in this patient?" 2. "What is the patient's infection diagnosis?" 3. "Can you narrow the breadth of antibacterial coverage to the most likely pathogens?" 4. "If the patient remains stable and no new clinical data emerge to suggest a different diagnosis, do you have an empiric de-escalation and/or duration of therapy plan?"

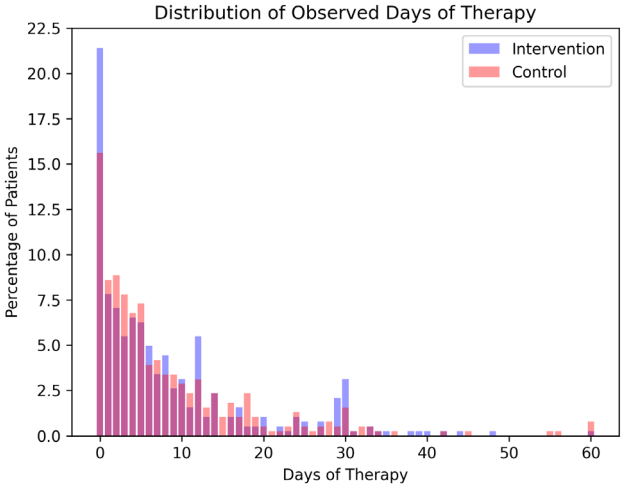
Results. Among 9606 screened, 767 (8%) were enrolled (Figure 2). Common reasons for exclusion were antibiotics given prior to blood culture (35%), positive culture from non-blood sites (26%), and increased oxygen requirement (21%). Intervention patients had 32% lower odds of antibiotic continuation (79% vs. 84%, OR 0.68, 95% confidence interval [0.47, 0.98]). DOT distributions among those who continued antibiotics were similar (ratio of means 1.06 [0.88-1.26], Figure 3). Fewer intervention patients were exposed to extended-spectrum agents (38% vs. 44%). Common reasons for continuing antibiotics were treatment of localized infection (76%) and belief that stopping antibiotics was not safe (31%). Safety outcomes such as mortality, readmission, sepsis relapse, *C. difficile*, and length of stay did not differ.

DETOURS Trial Flow Diagram



Flow of participants through the DETOURS Trial.

Observed Days of Antibiotic Therapy Among Intervention and Control Subjects in the DETOURS Trial



Post-enrollment days of antibiotic therapy among 767 DETOURS Trial participants in 10 US acute care hospitals within 30 days after enrollment. Dark pink color indicates percent overlap between intervention (purple) and control (light pink) groups.

Conclusion. In this patient-level randomized trial of a stewardship intervention, the opt-out de-escalation protocol targeting selected patients with suspected sepsis resulted in more antibiotic discontinuations but did not affect safety events.

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15. Real-World Changes in *Clostridioides difficile* infection (CDI) Treatment Utilization and Clinical Outcomes Associated with Updated 2017 IDSA Guidelines among Medicare Beneficiaries in the U.S.

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Session: O-04. Challenges in *C. difficile*

Background. The 2017 IDSA CDI guideline update phased out metronidazole (MTZ) and recommended vancomycin (VAN) or fidaxomicin (FDX) for first-line use. This study examined changes in CDI antibiotic use and clinical outcomes among Medicare beneficiaries with CDI pre- vs. post- the guideline update.

Methods. This retrospective claims analysis used 2016-2018 national Medicare claims data. The two study samples included continuously eligible fee-for-service Medicare beneficiaries aged ≥66 years with a new CDI diagnosis followed by an antibiotic fill in the pre-period (04/01/2017-09/30/2017) and post-period (04/01/2018-09/30/2018), respectively. Outcomes included type of CDI antibiotic received; sustained response and CDI recurrence. Multivariable regressions compared pre- vs. post-period outcomes while controlling for sociodemographic and clinical factors.

Results. The pre-period (N=7,389) and post-period (N=7,746) samples had similar characteristics (59% > 75 years, 32% male). Post-guideline update, absolute rates of MTZ use declined 27.7% (relative change [RC] -34.1%, p< 0.001) and VAN use increased 26.9% (RC +150.2%, p< 0.001) (Figure 1). While FDX use increased 0.8% (RC +87.8%, p< 0.001), overall use remained low (1.63%). Surprisingly, clinical outcomes did not improve between the pre- and post-period (Table 1). Even after adjustment, overall sustained response rates decreased (Odds Ratio [OR]: 0.93, p=0.0197) and overall CDI recurrence rates increased (OR: 1.13, p=0.0018) slightly in the post- vs. pre-period. Additional analyses by type of antibiotic showed that VAN (55.0% and 35.1%) was similar in outcomes to MTZ (54.2% and 33.0%), whereas FDX (71.4% and 20.9%) had higher sustained response and lower CDI recurrence rates, respectively (Figure 2).

Figure 1. First-line use of CDI treatments, pre- vs. post- the guideline update, among Medicare beneficiaries with CDI

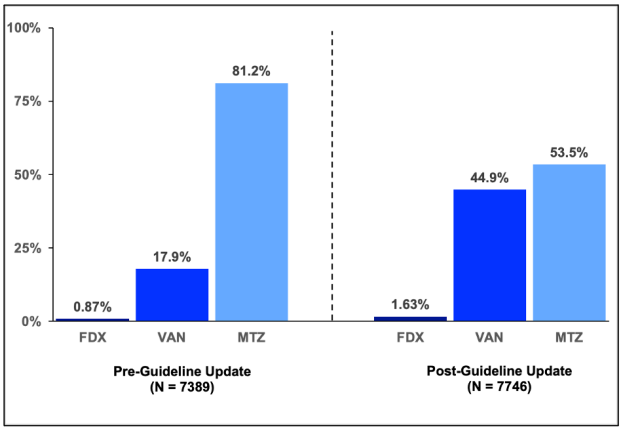
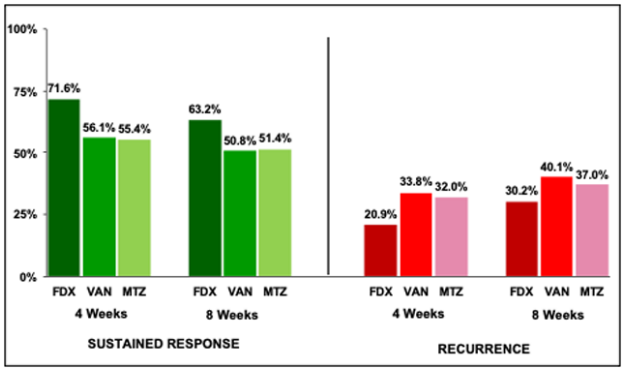


Table 1. Clinical outcomes, pre- vs. post- the guideline update, among Medicare beneficiaries with CDI

	Pre-Guideline Update		Post-Guideline Update		p-value
	N	%	N	%	
Clinical outcomes	**7389**	**100.0%**	**7746**	**100.0%**	**N/A**
Sustained response (4 weeks) (%)	4205	56.9%	4247	54.8%	0.01
Sustained response (8 weeks) (%)	3907	52.9%	3861	49.8%	0.0002
All patients with a clinical resolution	6097	100.0%	6415	100.0%	
CDI recurrence (4 weeks) (%)	1892	31.0%	2168	33.8%	0.001
CDI recurrence (8 weeks) (%)	2190	35.9%	2554	39.8%	<.0001

Figure 2. Clinical outcomes* by type of index CDI treatment among Medicare beneficiaries with CDI



Note. Pooled rates among patients on each index CDI treatment across the pre- and post-index periods.

Conclusion. The 2017 IDSA guideline update was associated with a substantial increase in VAN use and decrease in MTZ use. FDX use rates remained low (< 2%). Overall CDI outcomes did not improve post guideline update despite the shift to guideline-indicated VAN. This may be because VAN was not associated with meaningfully improved outcomes relative to MTZ. However, improved outcomes seen with FDX relative to VAN and MTZ suggest potential benefits from its greater use in Medicare patients.

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16. Attributable Mortality, Healthcare Costs and Out-of-Pocket Costs of *Clostridioides difficile* Infection in US Medicare Advantage Enrollees

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Session: O-04. Challenges in C. difficile

Background. US attributable CDI mortality and cost data are primarily from Medicare fee-for-service populations. Little is known about Medicare Advantage Enrollees (MAEs), who comprise about 39% of the Medicare population.

Methods. Using 2017–2019 Optum's de-identified Clinformatics® Data Mart database, this retrospective cohort study identified first *C difficile* infection (CDI) episodes occurring in 2018 among eligible MAEs ≥66 y of age who were continuously enrolled for 12 mo before CDI diagnosis (baseline period). CDI was defined via ICD10 diagnosis codes or evidence of toxin testing with CDI antibiotic treatment. To assess all-cause mortality and CDI-associated healthcare and patient out-of-pocket (OOP) costs, CDI+ cases were matched 1:1 to CDI– controls using propensity scores (PS) and were followed through the earliest of death, disenrollment or end of the 12 mo followup. Additionally, outcome analyses were stratified by infection acquisition and hospitalization status.

Results. Among 3,450,354 eligible MAEs, 15,195 (0.4%) had a CDI episode in 2018. Using PS generated from >60 variables collected in the baseline period, 14,928 CDI+ cases were matched to CDI– controls.

Over 12 mo of follow-up, the difference in 1-y attributable mortality was 7.9% in the CDI+ (26.3%) vs CDI– (18.4%) cohort (**Figure 1**). CDI-attributable mortality was higher among hospitalized CDI+ cases (18.4% for healthcare associated [HA]; 13.1% for community associated [CA]) vs nonhospitalized CDI+ cases (HA, 4.5%; CA, 1.0%).

Similarly, healthcare costs were higher for CDI+ vs CDI– patients, with excess mean total cost of $13,363 at the 2-mo follow-up (**Figure 2**). Total excess mean healthcare costs were greater among hospitalized CDI+ patients (HA, $28,139; CA, $28,136)