DETOURS

De-escalating Empiric Treatment: Opting OUt of Rx for Selected Patients with Suspected Sepsis

Moehring RW, Yarrington MY, Warren BG, Lokhnygina YL, Atkinson E, Bankston A, Coluccio J, David MZ, Davis A, Davis J, Dionne B, Dyer A, Jones T, Klompas M, Kubiak DW, Marsalis J, Omorogbe J, Orajaka P, Parish A, Parker T, Pearson JC, Pearson T, Sarubbi CS, Shaw C, Spivey J, Wolf R, Wrenn RH, Dodds Ashley ES, Anderson DJ, and the CDC Prevention Epicenters Program

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Disclosures

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Clinicaltrials.gov identifier:

NCT03517007

Epicenters Study Sites

- Hospital Univ of Pennsylvania
- Pennsylvania Presbyterian
- Brigham and Women's Hospital
- Duke University Hospital

DASON Partners

- Piedmont Atlanta Hospital
- Piedmont Fayette Hospital
- Piedmont Newnan Hospital
- Iredell Memorial Hospital
- Wilson Medical Center
- Southeastern Regional Medical Center

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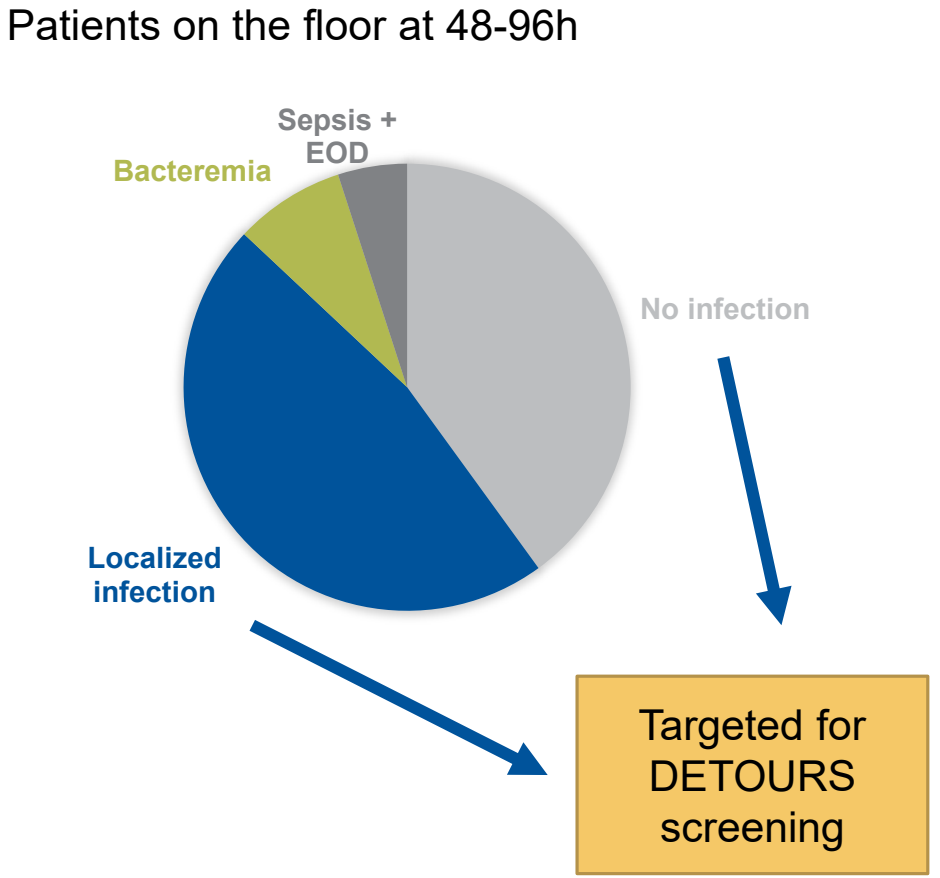
Rationale for the Trial

- Initiation of broad-spectrum antibiotics required in CMS SEP-1 Core Measure.[1] No requirement for de-escalation.
- Surviving Sepsis guidelines[2] recommend a daily review to de-escalate or discontinue antibiotic treatment in appropriate patients
- Overall, antibiotics in septic shock are important, but implementation of SEP-1 could lead to overuse: Timing; misdiagnosis; mandates.
  - Need to find "equilibrium" in sepsis care[3]
- *Aim: Assess effects of an opt-out protocol to decrease unnecessary antibiotics in selected patients with suspected sepsis*

[1]Inpatient Hospital Specifications Manual. Available at: https://www.qualitynet.org/
[2]Levy et al. CCM 2018; 46(6): 997-1000. Rhodes et al. Intensive Care Med 2017; 43 (3):304-77.
[3]Klompas et al. JAMA 2018; 320(14):1433-1434. Rhee et al. CID 2021; 72(4): 541-552.

DETOURS Randomized Controlled Trial

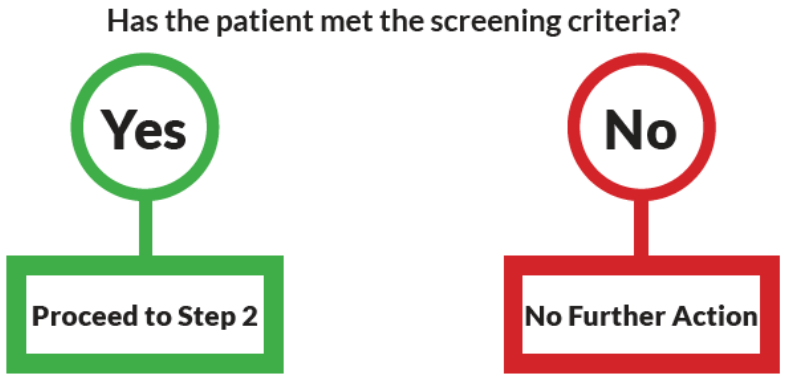
- Study Design: multicenter, patient-level randomized trial
- Study population: adult patients in non-ICU inpatient units with negative initial blood cultures on broad antibiotics at 48-96h + passed DETOURS safety screen
- Study period: 9/2018 through 5/2020
- Intervention: DETOURS opt-out protocol



1 Screening

Goal Identify the pool of patients potentially eligible for the intervention

- Blood cultures negative at 48-96 hours*
  * OK to include CoNS patients without a central line
- Patient on broad-spectrum antibiotics (Rank 2, 3 or 4 on Antibiotic Rank Chart)



Narrow spectrum	Broad spectrum	Extended spectrum, including MDRO and Pseudomonas	Protected
1	2	3	4
1st- and 2nd-generation cephalosporins Amoxicillin TMP/SMX Nafcillin, Oxacillin Metronidazole Doxycycline Nitrofurantoin Penicillin	Ceftriaxone 3rd-generation oral cephalosporins Azithromycin Clarithromycin Amoxicillin/clavulanate Ampicillin/sulbactam Clindamycin	Anti-pseudomonal penicillins Fluoroquinolones Aminoglycosides Vancomycin Cefepime, Ceftazidime Ertapenem Aztreonam	Anti-pseudomonal Carbapenem Colistin Tigecycline Linezolid, Tedizolid Daptomycin Ceftaroline Ceftazidime/avibactam Ceftolozane/tazobactam

Moehring et al. CID 2020 Jul 8. doi: 10.1093/cid/ciaa932

Step 2

Safety Check:

Developed by CDC/Epicenters expert collaborators + site stakeholders[1]

Modified Delphi panel process

Lit Review + Survey + Discussion

[1]Yarrington et al. ASHE 2021 (in press).

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2 Safety Check

Goal: Determine if patient passes the safety check

- Select population considered Low Risk "Rule Outs"
- Identify scenarios where SAFE to stop antibiotics.

Apply the safety check

☐ **Ongoing Signs/Symptoms of Infection**
- ☐ continued fever
- ☐ new chest x -ray infiltrate
- ☐ empyema
- ☐ lung abscess
- ☐ continued significant leukocytosis

☐ **Concerning/Inadequate Microbiological Data**
- ☐ positive blood cultures*

**Note: OK to stop if contaminate and no central line*
- ☐ positive microbiological data
- ☐ no cultures during sepsis work-up
- ☐ antibiotic use prior to blood culture

☐ **High-Risk Comorbidity/Severe Illness**
- ☐ bronchiectasis
- ☐ asplenia/splenectomy
- ☐ cystic fibrosis
- ☐ pregnant
- ☐ recent I&D procedure
- ☐ ongoing respiratory insufficiency
- ☐ immunocompromised
  - ☐ HIV/AIDS with CD4 count <200
  - ☐ taking immunosuppresive agents
  - ☐ agammaglobulinema
  - ☐ bone marrow aplasia
  - ☐ neutropenia
  - ☐ transplant recipient

Patient fails safety check if meets any of the above criteria

Has the patient passed the safety check?

Yes → **Proceed to Step 3**

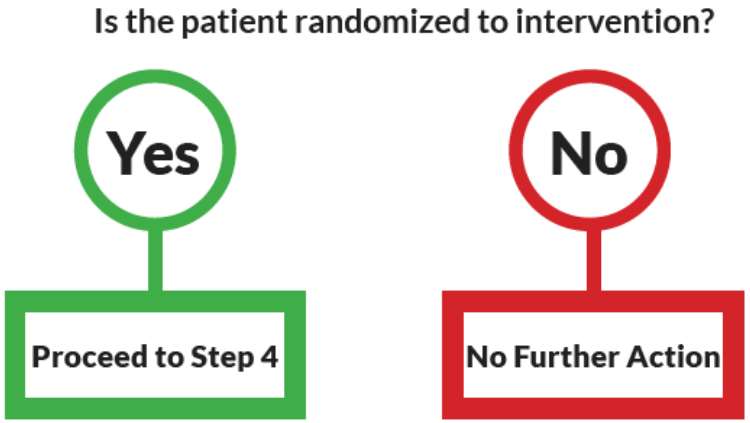
No → **Document Reason for Fail. Then No Further Action Required**

Step 3

3 Randomization

Goal Determine if patient is randomized to intervention or standard of care

Consult Randomization Scheme provided by study team



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Step 4

Verbal Interaction Required

Suggested language provided

“Opt-out” = Antibiotics were continued.

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4 Opt-Out

Goal | Stop the antibiotic therapy unless the treatment team opts out

Interact with the 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.”

Did the treatment team opt-out?

Step 5

Still an opportunity to impact therapy!

Voice rationale, diagnosis, plan

De-escalation (broad to narrow)

Duration

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5 Guided De-Escalation Discussion

Goal Better understand opt-out rationale and identify opportunities for antibiotic optimization

Engage with treatment team and document answers to four 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?"

   - Refer to Local Empiric Guidelines, Antibiogram, patient's culture data, and Antibiotic Rank Chart

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 ?"

   - Refer to Local Duration Guidelines for common syndromes
   - Offer to adjust orders or stop dates to match the voiced de-escalation and duration plan
   - Reassess in 48 hours if other opportunities to de-escalate may be possible

Primary Outcome: Patient-level post-randomization DOT, inpatient and post-discharge

- A third or more antibiotic exposures occur post-discharge[1,2]
- DOT count started the day AFTER enrollment, ends 30 days after enrollment
- Assume post-discharge DOT starts the day AFTER discharge
- If stopped antibiotics on day of enrollment, then DOT=0

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
			DOT=1	2	3
BCx		Enrolled			
Inpatient	Inpatient	Inpatient	Inpatient	Discharged	Post-dc

[1]Dyer AP, et al. ICHE. 2019; 40: 847–854.
[2]Feller et al. Clin Microbiol Infect. 2020; 26(3):327-332.

SA5 Analyses:

- #1: Post-enrollment DOT: Hurdle model regression, treatment as the only covariate
- #2: Probability of a better DOOR/RADAR:[1] intervention vs. control, Wilcoxon rank-sum test

- Secondary (Descriptive): individual components of DOOR; AU Rank (1-4); AU inpatient vs. post-discharge; rationales for Opt-Out
- Subgroup analyses: community vs. academic hospital; medicine vs. med-surgical/surgery

[1]Evans et al. CID 2015 Sep 1;61(5):800-6.

DETOURS Results: Hospital Characteristics

	N hospitals N= 10
Inpatient Bed size, median (range)	297 (154-952)
Medium (150-350)	6
Large (351-500)	1
Very large (>500)	3
Rural	2
Urban	8
State	
Georgia	3
Massachusetts	1
North Carolina	4
Pennsylvania	2
Hospital Type	
Major Academic Medical Center (AMC)	3
Teaching, affiliated with AMC	1
Teaching, not affiliated with AMC	2
Non-teaching	4

Protocol Implementation Strategy

Sites developed written SOP for DETOURS based on:

Research staff resources

BCx Reports/Tools in their system

ASP resources

Communication strategies already in practice

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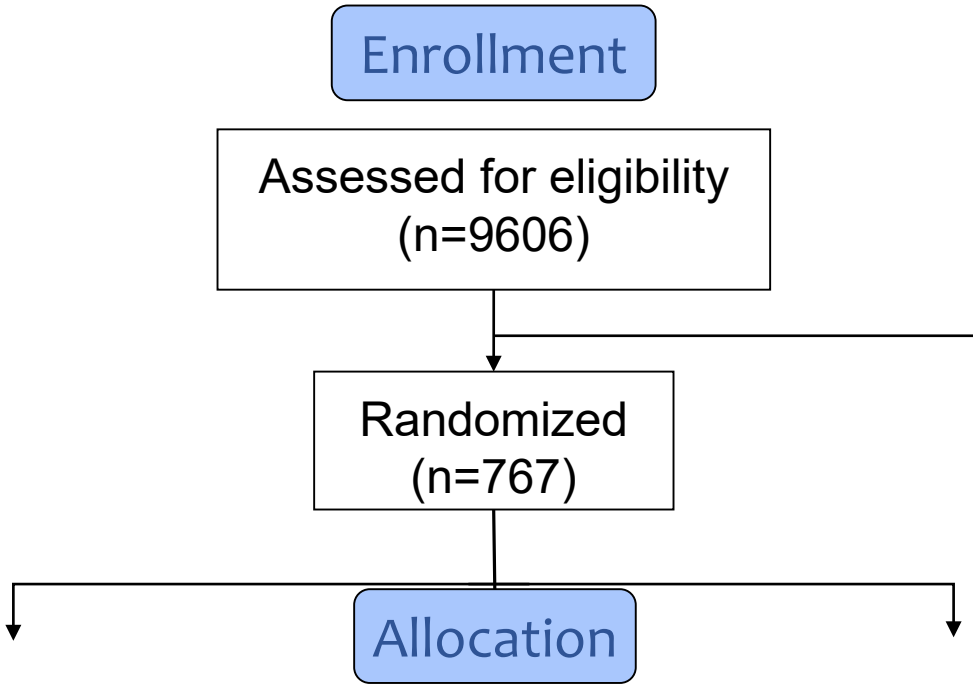
	N hospitals (%) N= 10
Pharmacist(s) performing opt-out discussion	
Clinical pharmacist	4
ID-trained pharmacist	5
Both	1
Study coordinator performed screening	4
ASP MD review of patients after screening	4
Communication method	
Pager/phone	4
Face-to-face discussion	1
Both	5
Focused screening by clinical service line	
Medicine only	2
Medicine and surgery	8


Enrollment
Assessed for eligibility (n=9606)
Randomized (n=767)
Allocation
Excluded (n=8839)
• Not meeting inclusion criteria (n=163)
• Patient <18 years of age (4)
• Patient housed in ICU (15)
• Patient did not meet blood culture criteria (70)
• Patient not on broad spectrum antibiotics (78)
• Did not pass safety check (8673)
• Patient previously randomized (1)
• Patient randomized, then did not pass screen (2)

Safety Screen (Top 10)

Screened patients Safety Check Criteria	Total Screened N=9440
Antibiotics 48 Hours Prior to First Blood Culture	3245 (35)
Positive Bacterial Cultures in Previous 4 Days	2410 (26)
New or Higher than Baseline Oxygen Requirement	1987 (21)
New and Persistent Infiltrate on Chest Imaging in the Last 4 Days	2416 (26)
Fever (>= 38.0°C) in the Last 48 Hours	1716 (18)
White Blood Count (WBC) > 14 in the Last 24 Hours	1479 (16)
Actively Taking Immunosuppressant Medications	1185 (13)
Diagnosis of Bacteremia or Bloodstream Infection During this Admission or from an Outside Hospital Prior to Transfer	1039 (11)
Solid Organ or Bone Marrow Transplant	607 (7)
Incision and Drainage Procedure for Infection in the Last 7 Days	792 (9)

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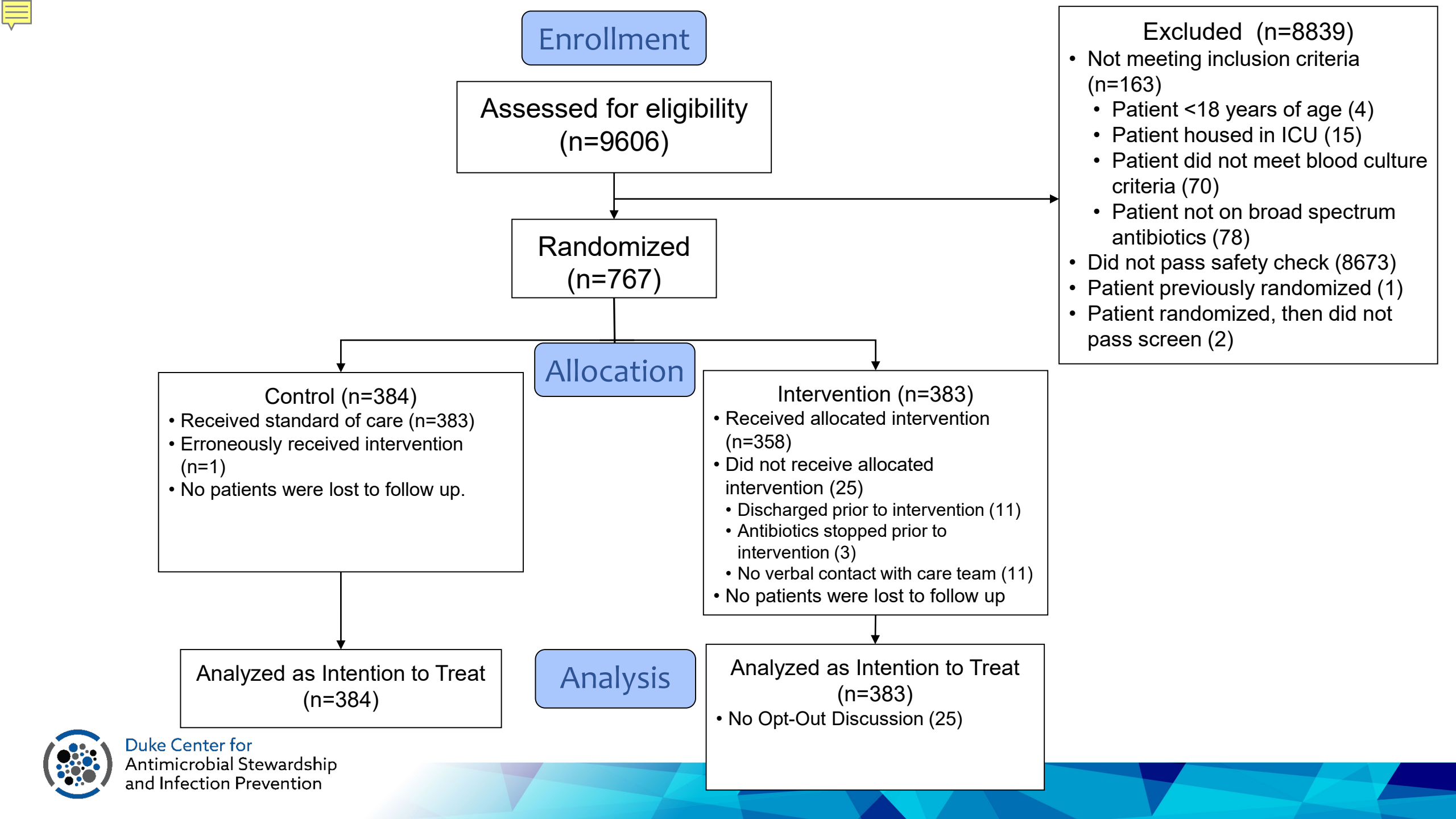

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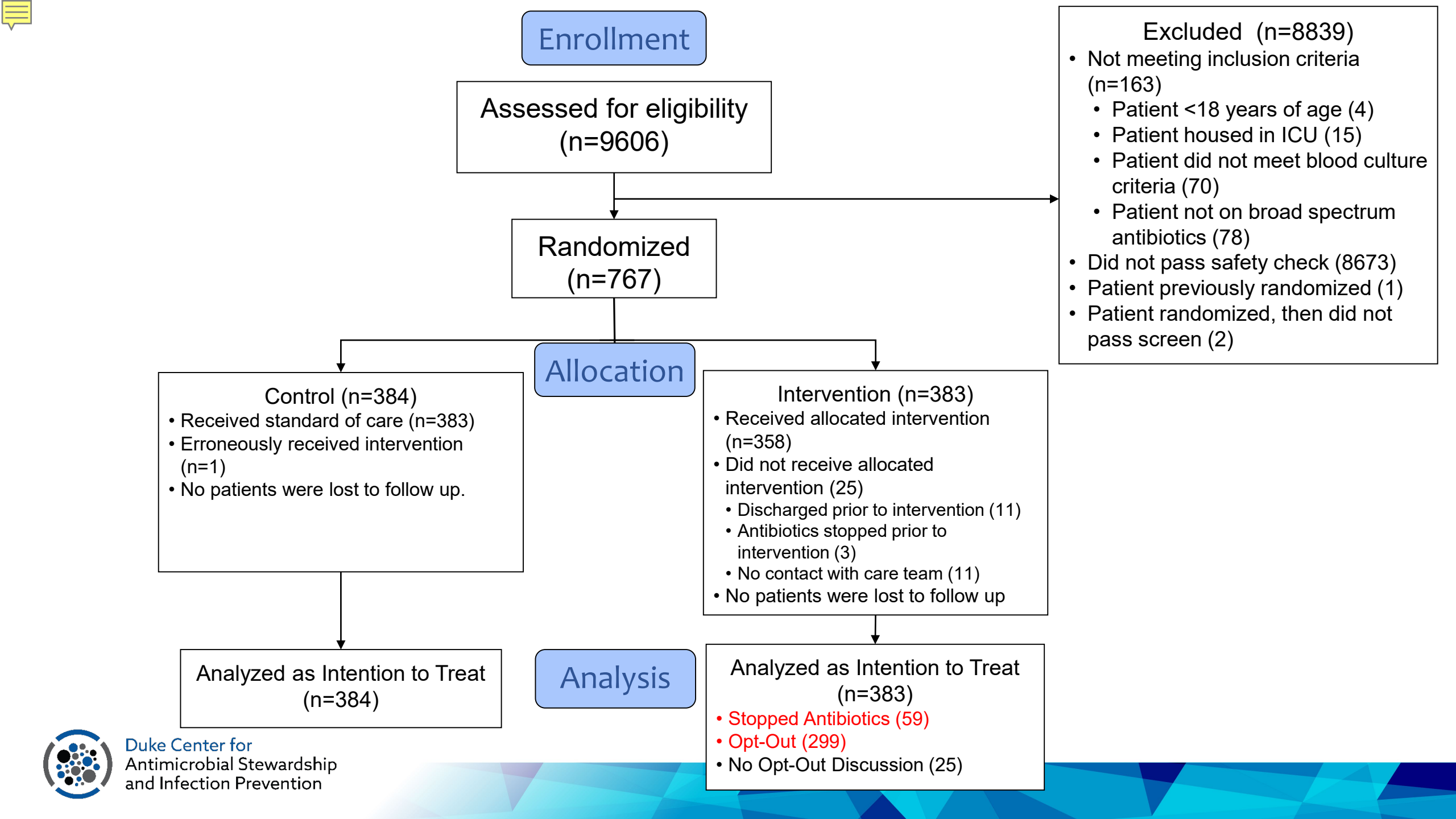
Results: Descriptive

	Control (N=384)	Intervention (N=383)	Total (N=767)
Age	63.6 (17.2)	60.6 (18.0)	62.1 (17.7)
Female	173 (45)	189 (49)	362 (47)
Race			
White	195 (51)	187 (49)	382 (50)
Black/AfAm	139 (36)	149 (39)	288 (38)
Native Amer	25 (7)	18 (5)	43 (6)
Asian	3 (1)	5 (1)	8 (1)
Hispanic	2 (1)	0 (0)	2 (1)
Other/Unk	19 (5)	22 (6)	41 (2)
Pre-enroll LOS Median (IQR)	3 (3-4)	3 (3-4)	3 (3-4)
Elixhauser Median (IQR)	11 (4-20)	11 (5-19)	11 (5-20)
Academic Hospital	205 (53)	204 (53)	409
Recent surgery	28 (7)	36 (9)	64 (8)
Recent admit	113 (29)	123 (32)	236 (31)



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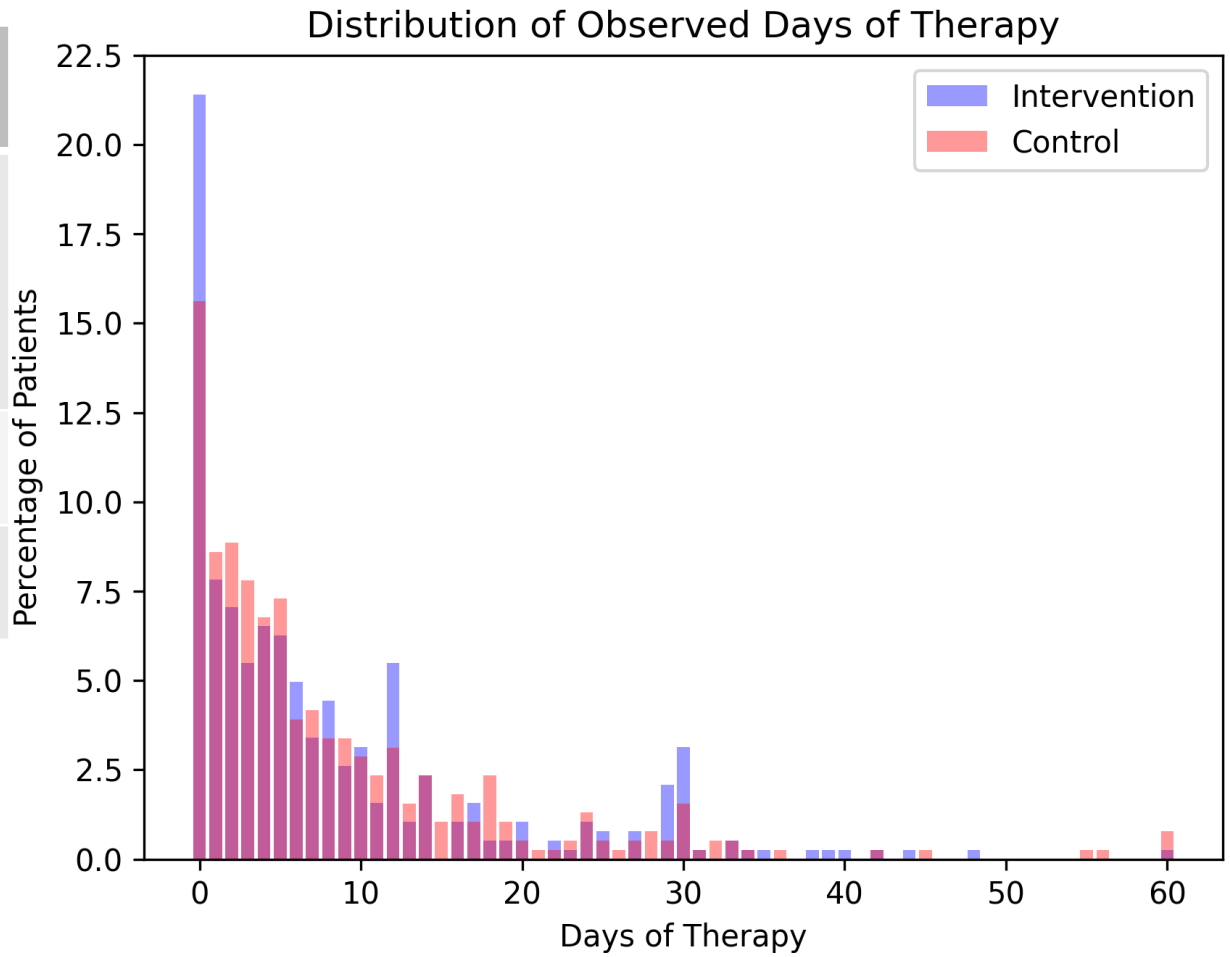
Post-enrollment Days of Therapy (Primary Outcome)

	Control (N=384)	Intervention (N=383)
Mean (STD) Median Q1, Q3 Range	8.3 (10.2) 5.0 2.0, 11.5 (0.0-60.0)	8.2 (9.9) 5.0 1.0, 12.0 (0.0-60.0)
Zero DOT	60 (15.6%)	82 (21.4%)
Non-zero DOT	324 (84.4%)	301 (78.6%)



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Hurdle Models: Primary Outcome

	Odds of Non-Zero DOT OR (95% CI)	P-value	Truncated Negative Binomial for Non-Zero DOT Ratio of Means (95% CI)	P-value
Post-randomization DOT (Primary Outcome)	0.68 (0.47, 0.98)	0.04	1.06 (0.88, 1.26)	0.55

- Odds of continuing antibiotics in the intervention group were 32% smaller, compared to the control group.
- Among those who did receive antibiotics after enrollment, DOT distributions were not statistically different.

AU by Spectrum Rank[1]

Narrow spectrum	Broad spectrum	Extended spectrum, including MDRO and Pseudomonas	Protected
1	2	3	4
1st- and 2nd-generation cephalosporins Amoxicillin TMP/SMX Nafcillin, Oxacillin Metronidazole Doxycycline Nitrofurantoin Penicillin	Ceftriaxone 3rd-generation oral cephalosporins Azithromycin Clarithromycin Amoxicillin/clavulanate Ampicillin/sulbactam Clindamycin	Anti-pseudomonal penicillins Fluoroquinolones Aminoglycosides Vancomycin Cefepime, Ceftazidime Ertapenem Aztreonam	Anti-pseudomonal Carbapenem Colistin Tigecycline Linezolid, Tedizolid Daptomycin Ceftaroline Ceftazidime/avibactam Ceftolozane/tazobactam

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	Control, N=384		Intervention, N=383	
	N patients (%)	Sum DOT (% of total DOT)	N patients (%)	Sum DOT (% of total DOT)
Rank 1	123 (32)	942 (29)	112 (29)	932 (30)
Rank 2	162 (42)	1001 (31)	174 (45)	1071 (34)
Rank 3	167 (44)	1147 (36)	138 (36)	1053 (34)
Rank 4	16 (4)	113 (4)	13 (3)	66 (2)
Rank 3-4	169 (44)	1260 (39)	144 (38)	1119 (36)
Total non-zero	324 (84)	3203	301 (79)	3122

Intervention:

Lower number of patients exposed to Rank 3-4 agents.
Lower number of Rank 3-4 DOT.
57% De-escalation by day 5 (vs. 53% Control)[1]

[1]Moehring et al. CID 2020 Jul 8;ciaa932. doi: 10.1093/cid/ciaa932

Summary: AU

- The intervention worked. Odds of continued antibiotics were a third lower.
- Among those who did continue antibiotics, DOT distributions were not different.
- Observations:
  - Antibiotic Stops were more common among Rank 3 agents and Inpatient DOT.
  - Durations appeared more standardized among intervention patients.
  - Comparing across patients, the Intervention group had a lower number of patients exposed to Rank 3-4 agents, a lower number of Rank 3-4 DOT, a lower number of post-discharge days.

30-day Safety Outcomes:

	Control (N=384)	Intervention (N=383)	Total (N=767)
Readmission	57 (14.8%)	61 (15.9%)	118 (15.4%)
Relapse of Suspected Sepsis	30 (7.8%)	30 (7.8%)	60 (7.8%)
C. difficile infection	7 (1.8%)	4 (1.0%)	11 (1.4%)
DVT	6 (1.6%)	1 (0.3%)	7 (0.9%)
ICU admission	33 (8.6%)	26 (6.8%)	59 (7.7%)
Hemodialysis	8 (2.1%)	1 (0.3%)	9 (1.2%)
Death	16 (4.2%)	10 (2.6%)	26 (3.4%)
Sum of Safety Events	157 (41%)	133 (35%)	290 (38%)
PICC Line	11 (2.9%)	11 (2.9%)	22 (2.9%)
Post-randomization LOS Median (IQR)	2 (1, 6)	2 (1, 6)	2 (1, 6)
Re-initiation of inpatient antibiotic therapy after >48 hours of no antibiotics within 30-days post-randomization, N (%)	16 (4.2%)	16 (4.2%)	32 (4.2%)

Desirability of Outcome Ranking (DOOR), Response Adjusted for Duration of Antibiotic Risk (RADAR)

DOOR	N (%)	Control	Intervention	Total
1	Alive	289 (75.3%)	301 (78.6%)	590 (76.9%)
2	Readmission, relapse of suspected sepsis, *C. difficile* infection, OR deep venous thrombosis	33 (8.6%)	31 (8.1%)	64 (8.3%)
3	≥2 of items in DOOR=2 above	18 (4.7%)	16 (4.2%)	34 (4.4%)
4	Subsequent ICU Admission OR hemodialysis	25 (6.5%)	25 (6.5%)	50 (6.5%)
5	Subsequent ICU Admission AND hemodialysis	3 (0.8%)	0 (0.0%)	3 (0.4%)
6	Death	16 (4.2%)	10 (2.6%)	26 (3.4%)

Probability of a better DOOR/RADAR (95% CI) = 0.52 (0.48-0.56), p=0.245

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Among Intervention group: Stop vs. Opt-Out

	Stop Antibiotics (N=59)	Opt-Out (N=299)	Total (N=358)*
Clinician Type			
Physician	46 (79)	204 (70)	250 (71)
Trainee physician (fellow, resident or intern)	5 (9)	66 (23)	71 (20)
Nurse practitioner	5 (9)	14 (5)	19 (5)
Physician's assistant	2 (3)	9 (3)	11 (3)
Clinician's rationale for continuing antibiotics (multiple response question)			
Treatment of localized infection		227 (76)	
Believe that stopping antibiotics is unsafe, NOS		93 (31)	
Pending clinical data		61 (20)	
Clinical uncertainty		36 (12)	
Inadequate initial culture or diagnostic work up		35 (12)	
Defer antibiotic decision-making to consultant		30 (10)	
Perceived administrative need for antibiotics		23 (8)	
Other		2 (<1)	

*No opt-out discussion in 25 patients analyzed as ITT.

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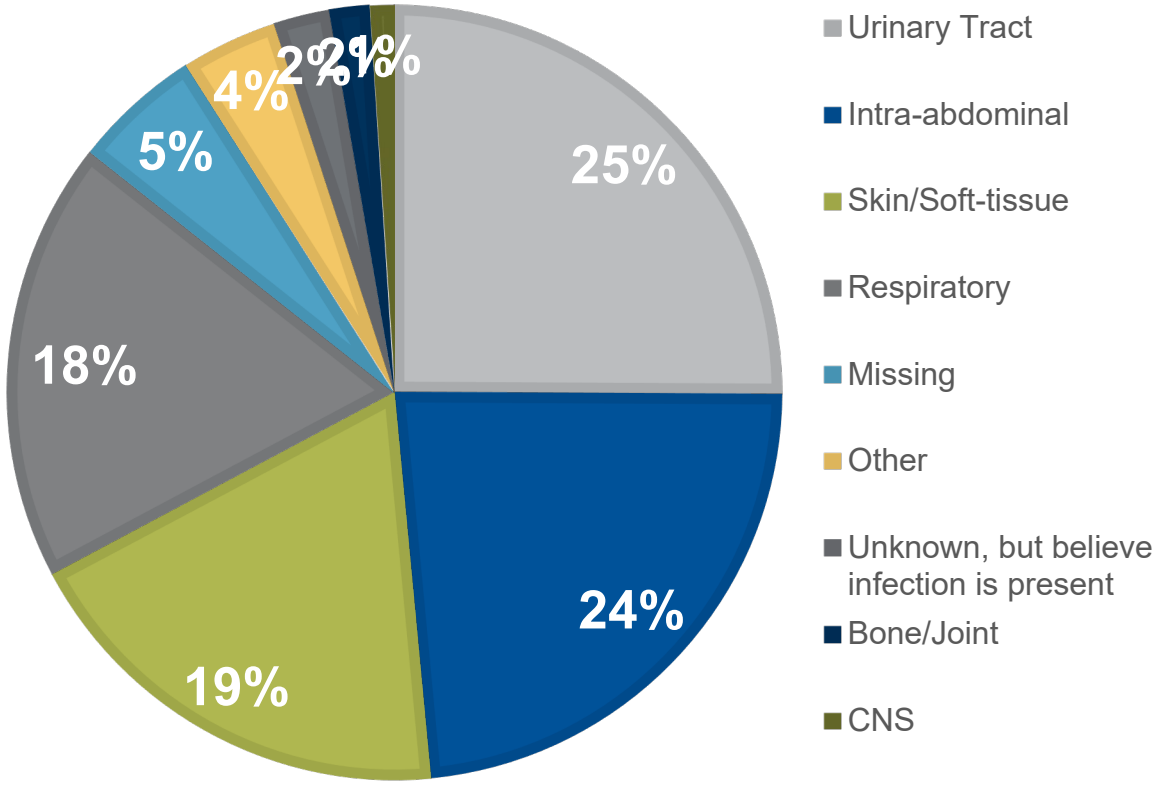
Among Opt-Out Events: Indication



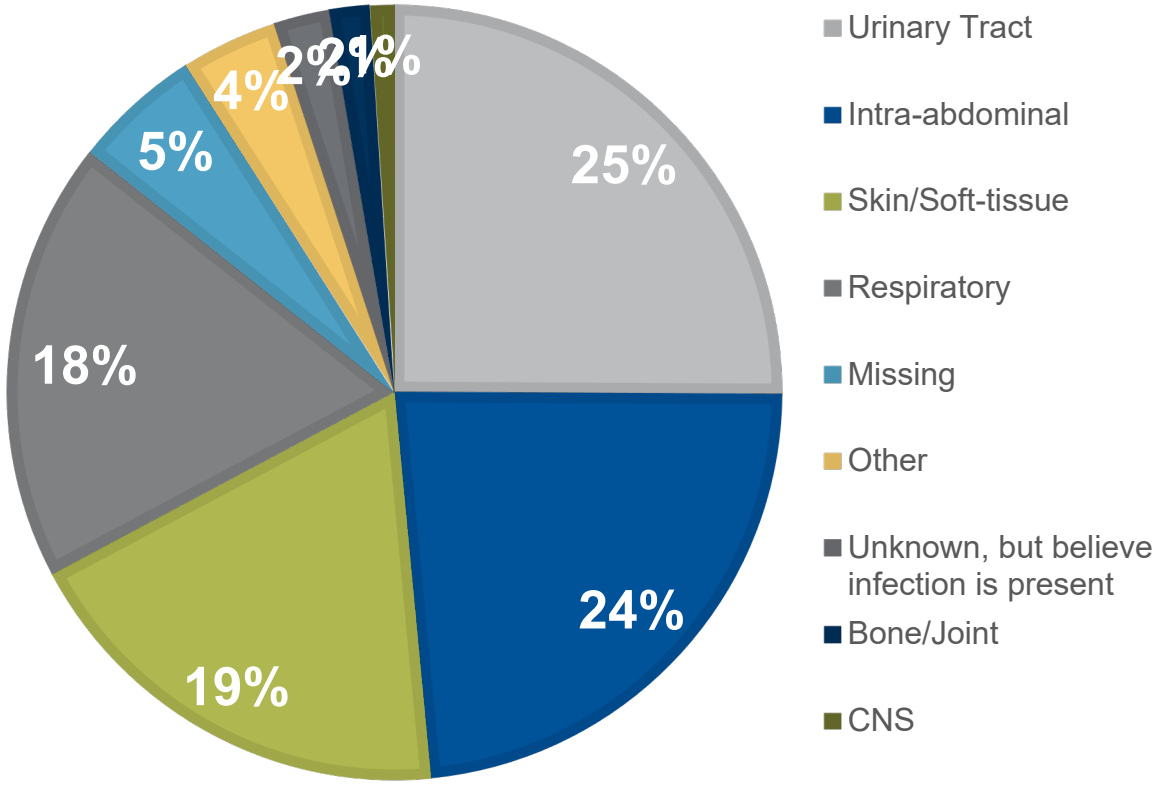
Urinary Tract Infection

Intra-abdominal Infection

Skin/Soft-tissue Infection

Respiratory Tract Infection

Among Opt-Out Events: Indication



Urinary Tract Infection

Intra-abdominal Infection

Skin/Soft-tissue Infection

Respiratory Tract Infection

Respiratory	55
Pneumonia – CAP	29 (53)
Bronchitis/COPD Exacerbation	18 (33)
Pneumonia- HCAP/HAP	6 (11)
URI/ENT	1 (2)
Missing	1

Trial Limitations

10 sites with varied resources, protocol implementation strategies

Selected population for low-risk suspected sepsis events

- Avoided direct measurement of “appropriateness”
- Safety check criteria not perfect

Screening processes required high levels of personnel effort for chart review

Not blinded to intervention

Summary

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De-escalating **E**mpiric **T**reatment: **O**pting O**U**t of **R**x for **S**elected Patients with Suspected Sepsis

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First patient-level RCT evaluating a stewardship intervention.

Done in diverse, multicenter hospital settings.

Safety check screening resulted in narrow patient selection.

Intervention resulted in more antibiotic stops, by about a third.

Tended toward more narrow agents and standard durations, but DOT distributions were similar.

Opt-out Intervention was safe.

Opt-out rationales revealed known challenges in sepsis care: diagnostic uncertainty, risk assessments

Thank you!

Epicenters Study Sites
- Penn (Michael David)
- Penn Presbyterian
- Brigham and Women's (Mike Klompas)
- Duke U (Mike Yarrington)

DASON Study Sites
- Piedmont Atlanta
- Piedmont Fayette
- Piedmont Newnan
- Iredell Memorial
- Wilson Medical Center
- Southeastern Regional Medical Center

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Harvard: Mike Klompas, Chanu Rhee

UPenn: Michael David, Keith Hamilton, Mark Mikkelesen, Craig Umscheid, Bill Schweickert

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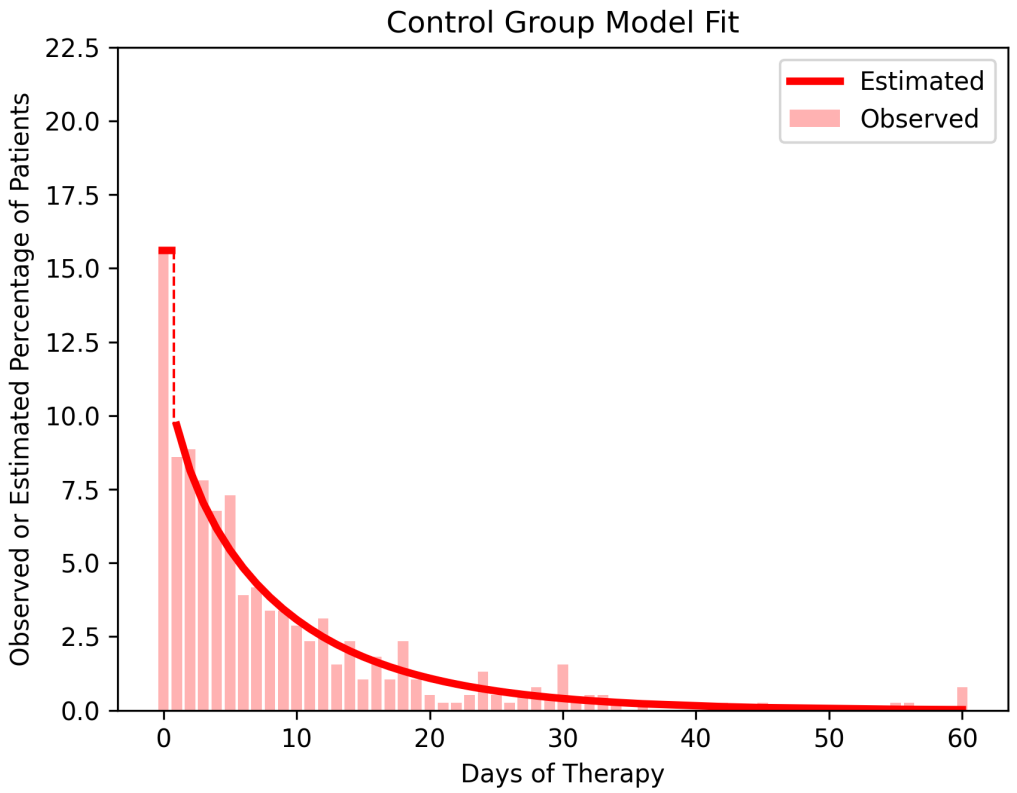
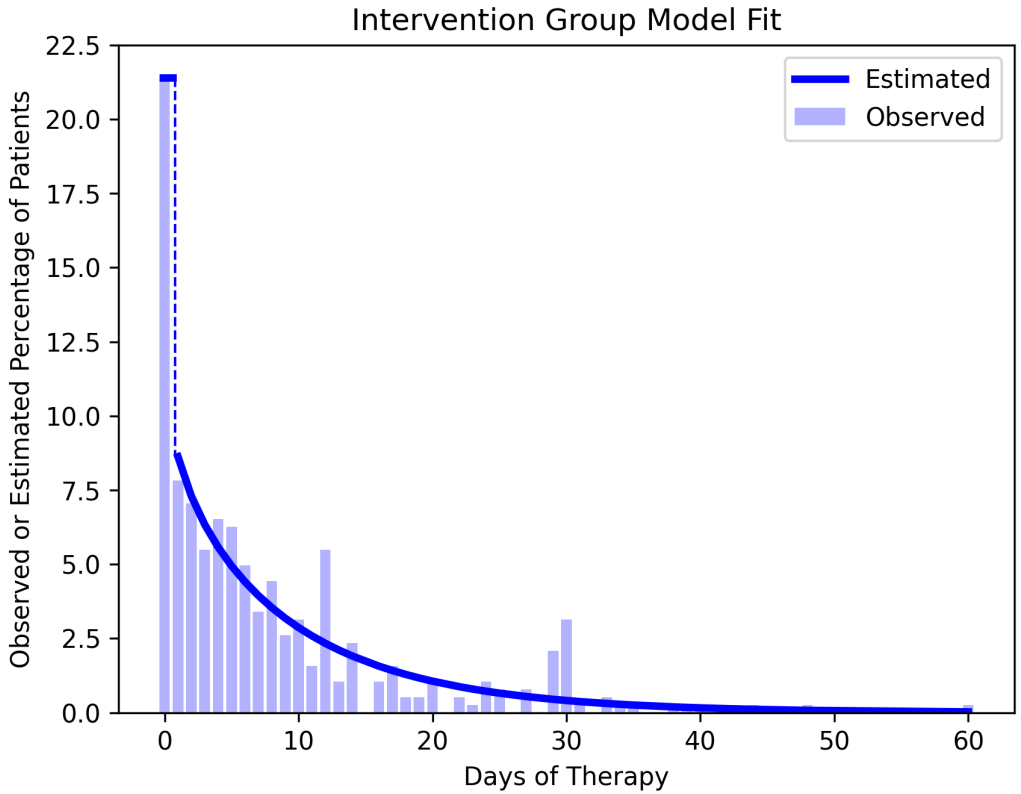
EXTRA SLIDES

Model Fit: Primary Outcome





Descriptive

*Assigned at the end of admission.

	Control (N=384)	Intervention (N=383)	Total (N=767)
Unit type at enroll			
Medical	223 (58)	217 (57)	440 (58)
Med/Surg	57 (15)	51 (13)	108 (14)
Surgical	76 (20)	84 (22)	160 (21)
Tele	12 (3)	15 (3)	27 (3)
Other	14 (4)	15 (5)	29 (4)
ICD-10 Infxn Dx*			
None	106 (28)	94 (25)	200 (26)
>1 Infection	103 (27)	102 (27)	205 (27)
Bloodstream/Septicemia	27 (7)	16 (4)	43 (6)
UTI	51 (13)	54 (14)	105 (14)
Skin and soft tissue	42 (11)	43 (11)	85 (11)
Intra-abdominal	19 (5)	36 (9)	55 (7)
Pneumonia	20 (5)	19 (5)	39 (5)
ENT	8 (2)	13 (3)	21 (3)
GI tract	3 (<1)	3 (<1)	6 (<1)
CNS	3 (<1)	0 (0)	3 (<1)
Bone and Joint	1 (<1)	2 (<1)	3 (<1)
GU/STI	1 (<1)	1 (<1)	2 (<1)

Goebel et al. Clin Micro Rev 2021. https://doi.org/10.1128/CMR.00003-20

Context/Implications

Inpatient AS = time/effort, expertise, and relationships

One-time interventions produce varied, and somewhat small effects on DOT

- DETOURS: “sped up” decisions to stop

One-time review + feedback vs. follow-up, multiple points of contact, persuasive communication, coaching

Diagnosis continues to be the hardest “D” in sepsis and suspected sepsis

Diagnosis	Make and document the right diagnosis
Drug	Use the right empiric antibiotic
Dose	Use the right dose of antibiotic based on site of infection and renal or hepatic dysfunction
Duration	Use antibiotics for the recommended duration
De-escalation	De-escalate therapy based on susceptibilities and when urine cultures are negative