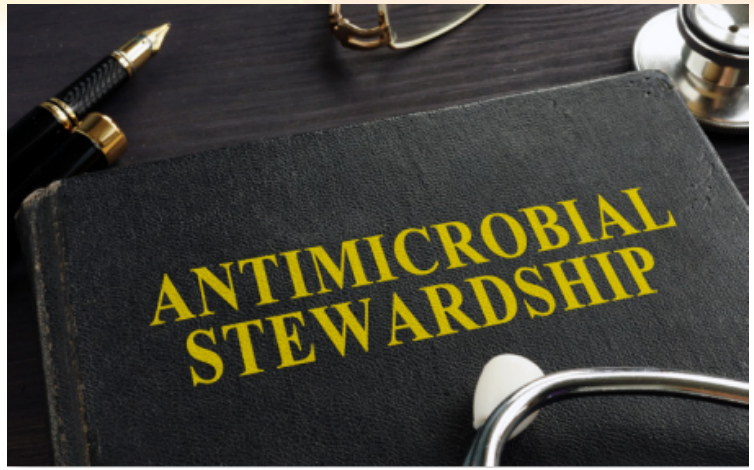
TRANSPLANT
WEBINAR SERIES



Antimicrobial Stewardship: Improving Transplant Outcomes and the Patient Experience

June 4, 2020| 3-4pm ET

Speakers: Stephanie M. Pouch, MD, MS| Miranda SO, BScPhm, Pharm D

The Alliance

CEPTC Information

For more information:

Contact The Alliance at

info@odt-alliance.org

The Alliance

- **1.0 Category CEPTC credits** are being offered for this webinar as well as a Certificate of Attendance
- Participants must fill out the evaluation form within 30 days of the event; the link for the evaluation form will be sent to you via email within the next 48 hours
- You will receive a certificate via email upon completion of the evaluation
- Group Leaders - Please keep track the names of the participants in your group and share the evaluation link with them.

Nursing Contact Hours

- **1.0 Nursing contact hour** is being offered for this webinar.
- Participants desiring nursing contact hours must request their certificate within 30 days.
- We highly encourage you to provide us with your evaluation electronically. Detailed instructions will be in the email which will be sent to you within the next 48 hours
- You will receive a certificate via email upon completion of a certificate request or an evaluation.
- Group leaders, please share the follow-up email.

Certificate of Attendance

- Participants desiring CE's that are not being offered, should complete a certificate of attendance.
- Certificates should be claimed within 30 days of this webinar.
- We highly encourage you to provide us with your feedback electronically. Detailed instructions will be emailed to you within the next 24 hours.
- You will receive a certificate via email upon completion of a certificate request or an evaluation.
- Group leaders, please share the follow-up email.

WEBINAR SPEAKERS

Moderator:

Betty Crandall
Retired Transplant Administrator
2020 Alliance Webinar Faculty Member

Stephanie M. Pouch, MD, MS
Assistant Professor of Medicine,
Division of Infectious Diseases
Emory University School of Medicine

Miranda SO, BScPhm, Pharm D
Pharmacotherapy Specialist,
SHS-UHN ASP Assistant Professor (Status),
Leslie Dan Faculty of Pharmacy
University Health Network and University of Toronto

The Alliance

EMORY UNIVERSITY SCHOOL OF MEDICINE | Department of Medicine

SHS + UHN ASP ANTIMICROBIAL STEWARDSHIP PROGRAM

UNIVERSITY OF TORONTO LESLIE DAN FACULTY OF PHARMACY

Antimicrobial Stewardship: Improving Transplant Outcomes and the Patient Experience

Stephanie M. Pouch, MD, MS

Miranda So, BScPhm, PharmD

Disclosures

- Neither presenter has financial disclosures relevant to this presentation
- This presentation will not include discussion of off-label or investigational use of drugs or devices

Objectives

- Define antimicrobial stewardship and discuss the need for antimicrobial stewardship in solid organ transplant programs
- Describe the infrastructure of solid organ transplant-centered antimicrobial stewardship programs
- Describe components of an effective solid organ transplant-centered antimicrobial stewardship program

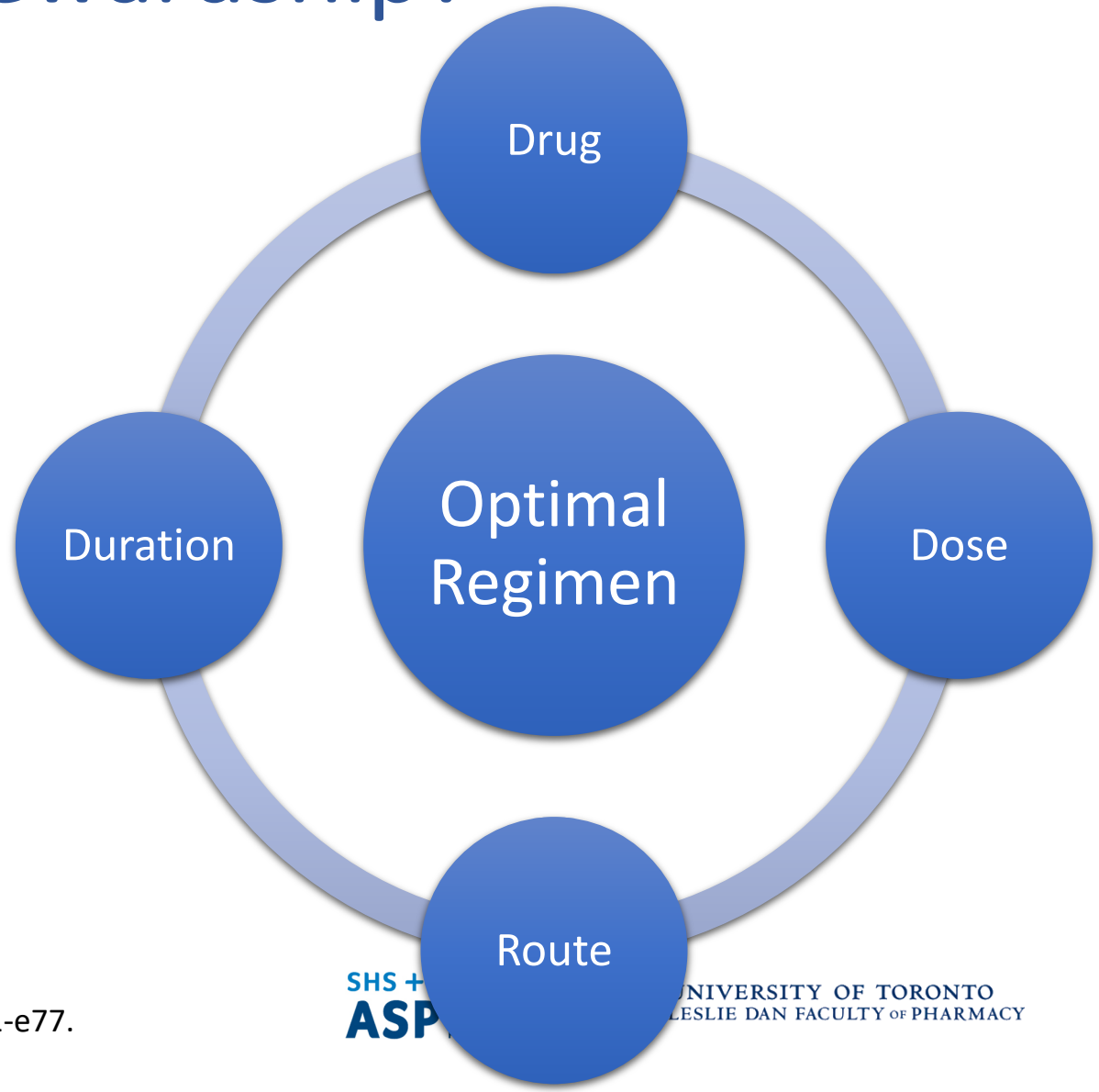
Question

The primary goal of antimicrobial stewardship programs (ASPs) is to:

A. Decrease costs
B. Decrease antimicrobial use
C. Increase antimicrobial appropriateness
D. Improve patient safety and outcomes

What is Antimicrobial Stewardship?

"*Coordinated* interventions designed to *improve* and *measure* the appropriate use of antibiotic agents by promoting the selection of the optimal drug regimen"



Barlam TF et al. Clin Infect Dis 2016; 62(10): e51-e77.

Benefits of Antimicrobial Stewardship

Minimize Adverse Events

- *C. difficile* infection
- Colonization and infection with multidrug-resistant organisms (MDROs)
- Adverse drug events

Improve antibiotic susceptibilities

Improved Patient Outcomes

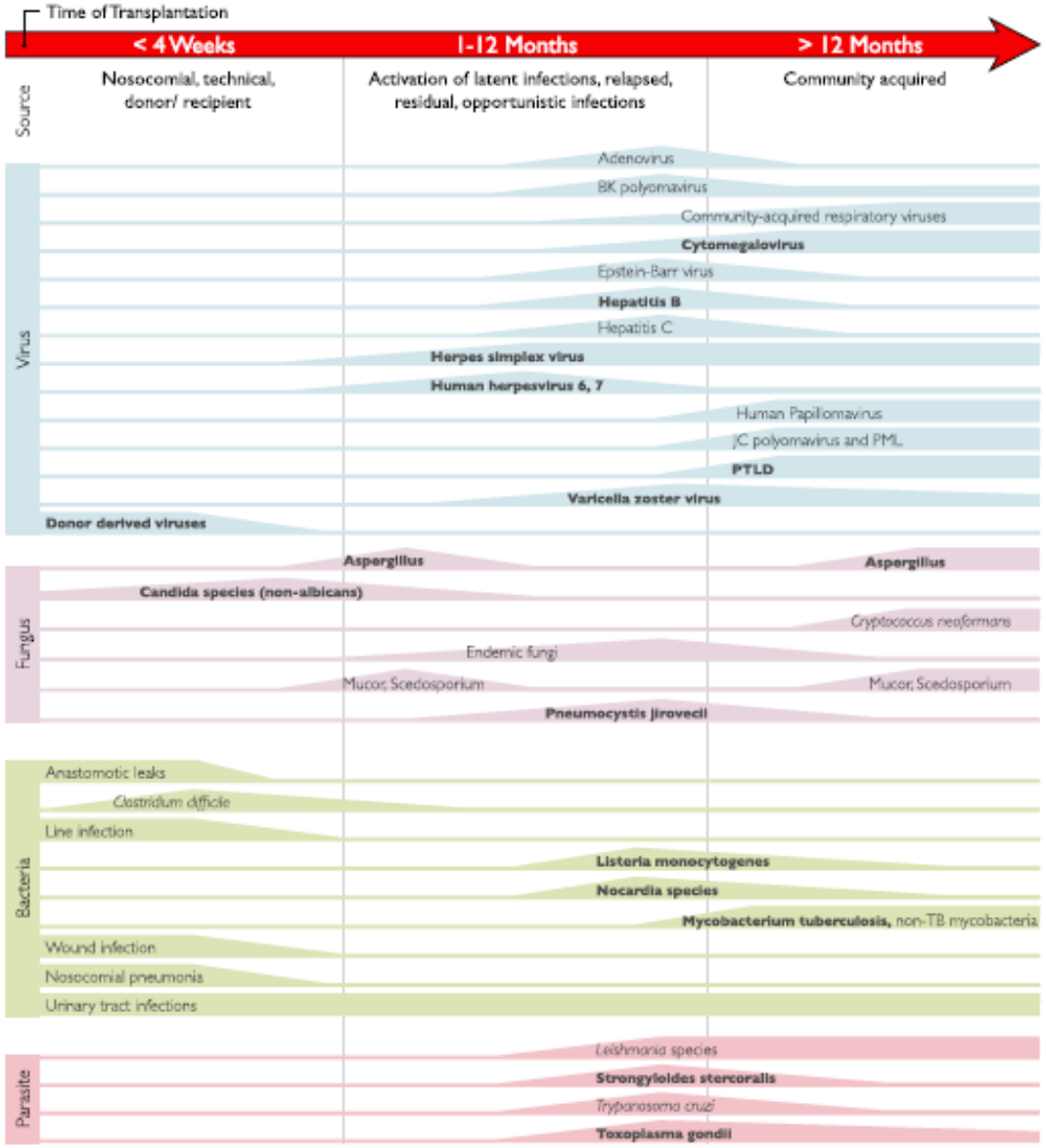
Barlam TF et al. Clin Infect Dis 2016; 62(10): e51-e77.

Need for Antimicrobial Stewardship in Solid Organ Transplantation

Case for Bespoke Solid Organ Transplant (SOT) Stewardship

Risk of infection is

- Dynamic
- Impacted by organ transplanted
  - Liver and lung transplant candidates may be colonized with MDROs prior to transplant



Fishman JA. Am J Transplant 2017; 17: 856-879.
Bert F et al. *Transpl Infect Dis*. 2014;16:84-89.
Hadjiliadis D et al. J Heart Lung Transplant 2007; 26: 834-8.

Antibiotic Use and MDROs

- Antibiotic use drives antimicrobial resistance
- Odds of developing a MDRO in an antibiotic exposed patient is 1.8-5.1 times that of patients not receiving an antibiotic
- Nearly 50% of hospitalized patients and 75% of critically ill patients receive an antibiotic during their hospitalization
  - 50% of these are considered inappropriate

Barnes SL et al. Infect Control Hosp Epidemiol 2017;38(6):663-9

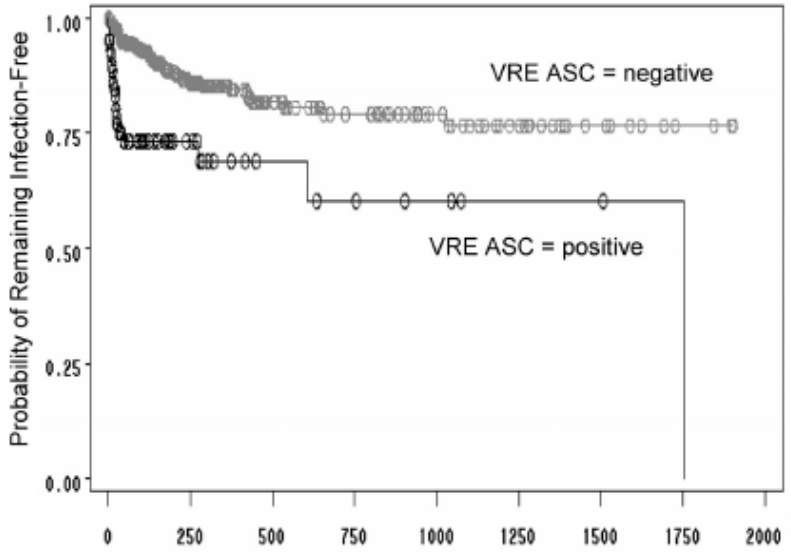
MDROs and SOT

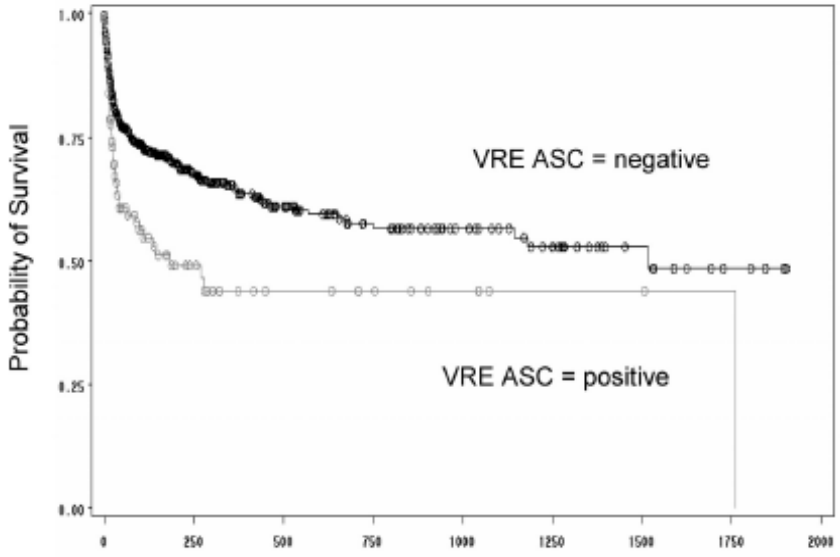
- Major threat to patient and graft survival
- Poor functional status, prolonged hospitalization, and use of broad-spectrum antimicrobials increase risk of MDRO acquisition
  - *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp.
- Management of MDROs in SOT recipients complicated by
  - Drug-drug interactions
  - Limited antimicrobial pipeline

Patel et al. Curr Infect Dis Rep 2013; 15: 504-13.
Cervera et al. Clin Microbiol Infect 2014; 20 (Suppl 7): 49-73.

Vancomycin-Resistant *Enterococcus* (VRE) in SOT

- High prevalence of VRE in liver transplant recipients
- Colonization associated with infection



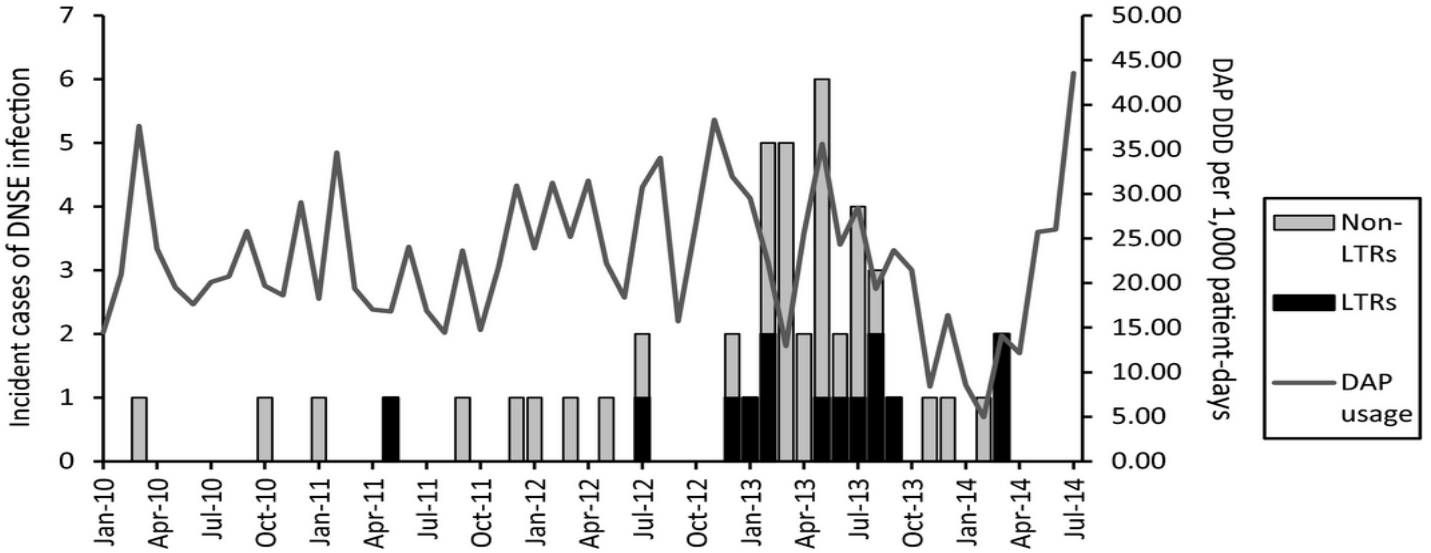


- VRE bacteremia associated with decreased 1-year survival after liver transplant (57.1% vs 75%) and 32% 30-day mortality

Odrobina et al. Abstract 162. ATC 2016.
Russell Am J Transplant 2008; 8: 1737-43.

Daptomycin-Non-Susceptible Enterococci (DNSE) in Liver Transplantation

- Single-center retrospective review of DNSE in liver transplant recipients



- Retrospective multicenter study of bacteremic liver transplant recipients
  - Previous daptomycin use associated with DNSE bacteremia (p=0.04)
  - DNSE bacteremia associated with death-censored allograft failure (p=0.008)

Lewis JD et al. Transpl Infect Dis. 2016; 18: 341-53.
Lee R et al. Am J Transplant 2018; 18 (Suppl 4).

Carbapenem-Resistant *Enterobactieriaceae* (CRE) in SOT

Reference	Geographic Location	Incidence of Post-Transplant CRE Infection	Median Time from Transplant to CRE Infection	Type of Infection[a]	Mortality Rate
Heart Transplants					
20	Brazil	16.7% (2/12)	90 days	Bacteremia: 50% Pneumonia: 50%	50% (30-day)
Lung Transplants					
21b	Pittsburgh	0.4% (2/546)	218 days	Bacteremia: 100%	0% (30-day)
22	Israel	5.9% (8/136)	27 days	Pneumonia: 38% UTI: 25% Bacteremia: 25%	88% (overall)
Liver Transplants					
20	Brazil	12.9% (4/31)	16 days	Bacteremia: 100% Pneumonia: 25%	25% (30-day)
21b	Pittsburgh	1.3% (8/610)	24 days	Bacteremia: 100% Pneumonia: 50%	25% (30-day)
23	New York City	8% (14/175)	12 days	Bacteremia: 86% Peritonitis: 79%	71% (overall)50% (30-day)
31b	Greece	NR (17 cases)	13 days	Bacteremia: 100%	82% (ICU mortality)
24	New York City	6.6% (20/304)	11 days	SSI/intra-abdominal: 65% Bacteremia: 55%	45% (overall)
95	Italy	8.4% (20/237)	42 days	Bacteremia: 90% Pneumonia: 30%	45% (180-day)
Kidney Transplants					
25	Brazil	1.9% (21/1101)	49 days	SSI: 48% Bacteremia: 39%	42% (30-day)
20	Brazil	26.3% (5/19)	17 days	UTI: 60% Bacteremia: 60%	60% (30-day)
26	Argentina	13.3% (6/45)	36 days	UTI: 83% Bacteremia: 17%	33% (overall)
27c	New York City	1.1% (20/1852)	47 days	Bacteriuria: 100%	30% (overall)
28	New York City	2.5% (13/522)	185 days	UTI: 69% Bacteremia: 38%	46% (overall)
30	Italy	NR (8 episodes)	NR	UTI: 100% Bacteremia: 100%	0% (30-day)
Intestinal Transplants					
21b	Pittsburgh	5.4% (6/112)	209 days	Bacteremia: 100%	33% (30-day)

Pouch SM and Satlin MJ. Virulence 2017; 8: 391-402.

Antibiotic Exposure and CRE

TABLE 2 Antibiotic exposure as a risk factor for acquisition of CRE, based on multivariable analysis[c]

Associated risk factor	Frequency	RE	RE range	No. of cases (range)	Study reference(s)
Carbapenem use	25	OR	1.83–29.17	9–100	12, 13, 16, 19, 22, 32, 36–48,[d] 49–53
Carbapenem use	1	HR	2.68	19	22
Cephalosporin use	15	OR	2.24–49.56	15–100	11, 12, 13, 19, 33, 38, 46, 48,[d] 52, 54–57, 58
Quinolone use	9	OR	1.18–28.9	18–88	33, 36, 43, 52, 59–63
Antibiotic exposure (in general)[a,b]	9	OR	1.66–13.37	26–464	41, 43, 61, 64–69
Other β-lactam use	9	OR	1.08–11.71	34–464	49, 52, 57, 60, 65, 70–73
Other[a]	7	OR	1.02–33	25–103	44, 47, 52, 58, 72, 74, 75
Glycopeptide use	5	OR	2.94–43.84	20–203	11, 16, 47, 73, 76
No. of antibiotics administered[a,b]	3	OR	1.6–12.60	59–164	39, 50, 77
Duration of exposure[a,b]	3	OR	1.04–9.8	25–104	74, 78, 79

[a] This category was not included in a random-effects meta-analysis.
[b] Exposure to any antibiotic.
[c] Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; RE, risk estimate; OR, odds ratio; HR, hazard ratio.
[d] This risk factor was identified two times in the study of Orsi et al. (48).

van Loon et al. Antimicrob Agents Chemother 2018; 62(1): e01730-17.

Resistance Not Limited to Bacteria…

Ganciclovir-Resistant Cytomegalovirus Infection in Abdominal Solid Organ Transplant Recipients: Case Series and Review of the Literature

Katherine E. Rolling,[1] Margaret R. Jorgenson,[2,*] Jillian L. Descourouez,[2] Didier A. Mandelbrot,[3] Robert R. Redfield,[4] and Jeannina A. Smith[3]

Emergence of *Aspergillus calidoustus* Infection in the Era of Posttransplantation Azole Prophylaxis

Adrian Egli,[1] Jeff Fuller,[2] Atul Humar,[1] Dale Lien,[3] Justin Weinkauf,[3] Roland Nador,[3] Ali Kapasi,[3] and Deepali Kumar[1,4]

Rolling et al. Pharmacotherapy 2017;37(10):1258–1271.
Egli et al. Transplantation 2012; 94: 403-410.

Resistance Not Limited to Bacteria…

Ganciclovir-Resistant Cytomegalovirus Infection in
Abdo

Katherine E.

FIRST OPINION

Antibiotic resistance: the hidden threat lurking behind Covid-19

By JULIE L. GERBERDING / MARCH 23, 2020

…n in the
Era of Posttransplantation Azole Prophylaxis

Adrian Egli,[1] Jeff Fuller,[2] Atul Humar,[1] Dale Lien,[3] Justin Weinkauf,[3] Roland Nador,[3] Ali Kapasi,[3] and Deepali Kumar[1,4]

Rolling et al. Pharmacotherapy 2017;37(10):1258–1271.
Egli et al. Transplantation 2012; 94: 403-410.

Association Between *C. difficile* and Graft Loss

	Mortality analysis		Graft loss analysis	
	Univariate HR [95% CI] *P*-value	Multivariable HR [95% CI] *P*-value	Univariate HR [95% CI] *P*-value	Multivariable HR [95% CI] *P*-value
Clostridium infection (CDI)	2.31 [1.33, 3.99] 0.003	1.63 [0.94, 2.83] 0.085	3.72 [1.92, 7.20] <0.001	2.24 [1.15, 4.37] 0.02
Surgical complications			11.99 [7.71, 18.64] <0.001	7.22 [4.53, 11.50] <0.001
Medical problems			3.54 [2.01, 6.23] <0.001	2.35 [1.33, 4.15] 0.003
Rejection			10.58 [6.67, 16.77] <0.001	7.56 [4.70, 12.18] <0.001

Cusini A et al. Am J Transplant 2018 Jul;18(7):1745-1754.

C. difficile Associated with Worse Outcomes in SOT Recipients

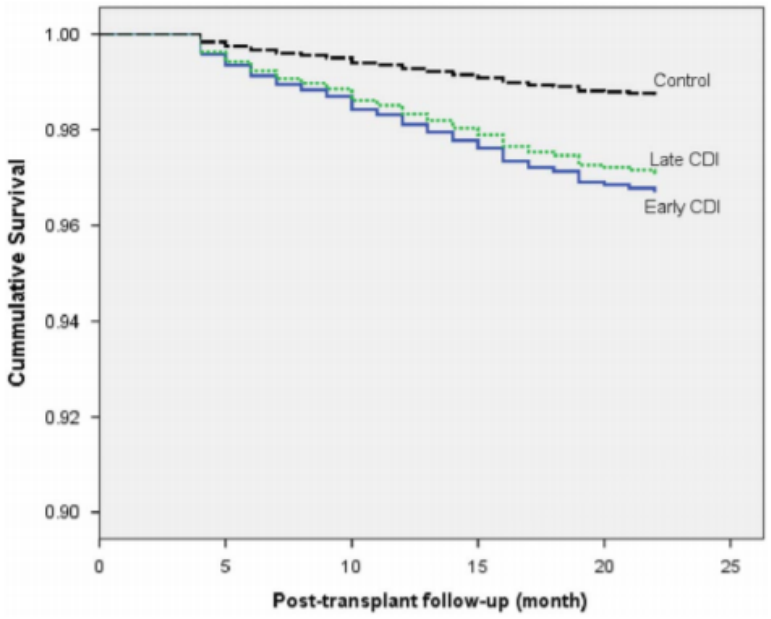


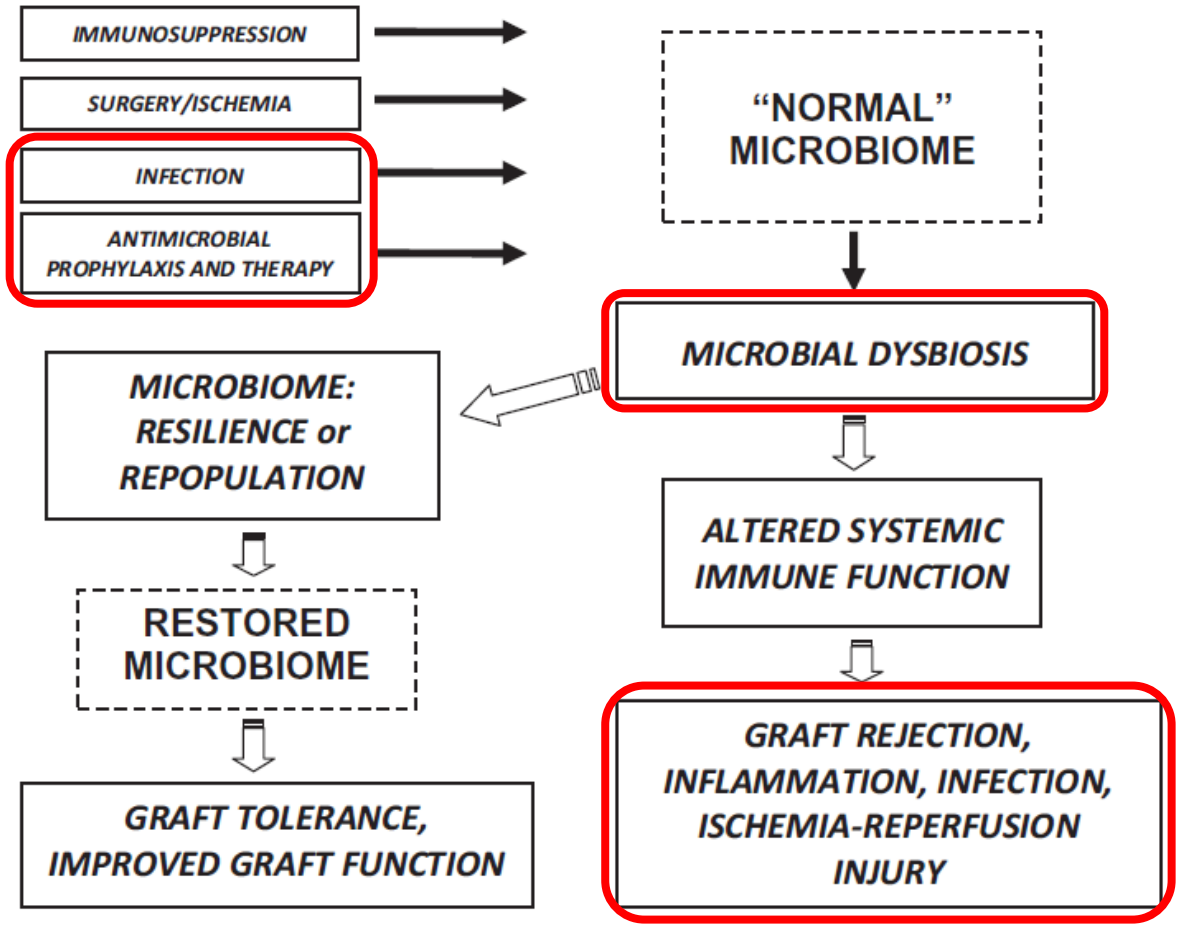
FIGURE 3. Survival curves of solid organ transplant recipients surviving posttransplant >90 days in early *Clostridium difficile* infection (CDI), late CDI, and control group by Cox regression.

TABLE 4. Impact of *Clostridium difficile* infection (CDI) on Mortality and Transplant Organ Complication-Related Hospitalization (TOH) in Solid Organ Transplant (SOT) Recipients Surviving >90 Days Posttransplant

	Risk for Death[a]		Risk for TOH[b]	
Characteristic	HR (95% CI)	*P* Value	OR (95% CI)	*P* Value
CDI occurrence	Reference: No CDI		Reference: No CDI	
Early CDI	2.64 (1.22–5.71)	.014	2.24 (1.46–3.45)	<.001
Late CDI	2.33 (1.02–5.33)	.045	4.17 (2.71–6.42)	<.001

Luo R et al. Infect Control Hosp Epidemiol 2018 May;39(5):563-570.

Role of Antimicrobials in Dysbiosis



Fishman JA. Am J Transplant 2017; 17: 856-879.

American Journal of Transplantation 2013; 13: 2499
Wiley Periodicals Inc.

doi: 10.1111/ajt.12364

Letter to the Editor

Call for Antimicrobial Stewardship in Solid Organ Transplantation

- Stewardship decreases the inappropriate use of antimicrobials and limits the emergence of multidrug resistance

- While transplant recipients have likely derived some down-stream effect of ASP on a hospital-wide basis, stewardship had not been systematically studied in this population

Aitken et al. Am J Transplant 2013;13: 2499.

Infrastructure of Antimicrobial Stewardship Program in Solid Organ Transplant Patients

What can we “borrow” and what can we “steal”?

Accrediting Organizations

The Joint Commission approved antimicrobial stewardship as a new standard in 2017 for hospitals, with the 2020 updates expanded to ambulatory care settings

R³ Report | Requirement, Rationale, Reference

Standard MM.09.01.03: Antimicrobial stewardship is identified as an organizational priority.

Requirement	EP 1: The organization identifies an individual(s) responsible for developing, implementing, and monitoring activities to promote appropriate antimicrobial medication prescribing practices.
Rationale	Antimicrobial resistance is growing, so improving the use of antimicrobial medications across the care continuum is a patient safety priority. Identifying an individual(s) to be accountable for an organization's antimicrobial stewardship activities increases the likelihood of success by establishing clear lines of accountability. Identifying an individual(s) for this role also demonstrates an organizational commitment to improving the use of antimicrobial medications. Antimicrobial stewardship activities may be the individual(s) primary job responsibility or may be in addition to other duties.

Centers for Medicare and Medicaid Services

Omnibus Burden Reduction (Conditions of Participation) Final Rule CMS-3346-F

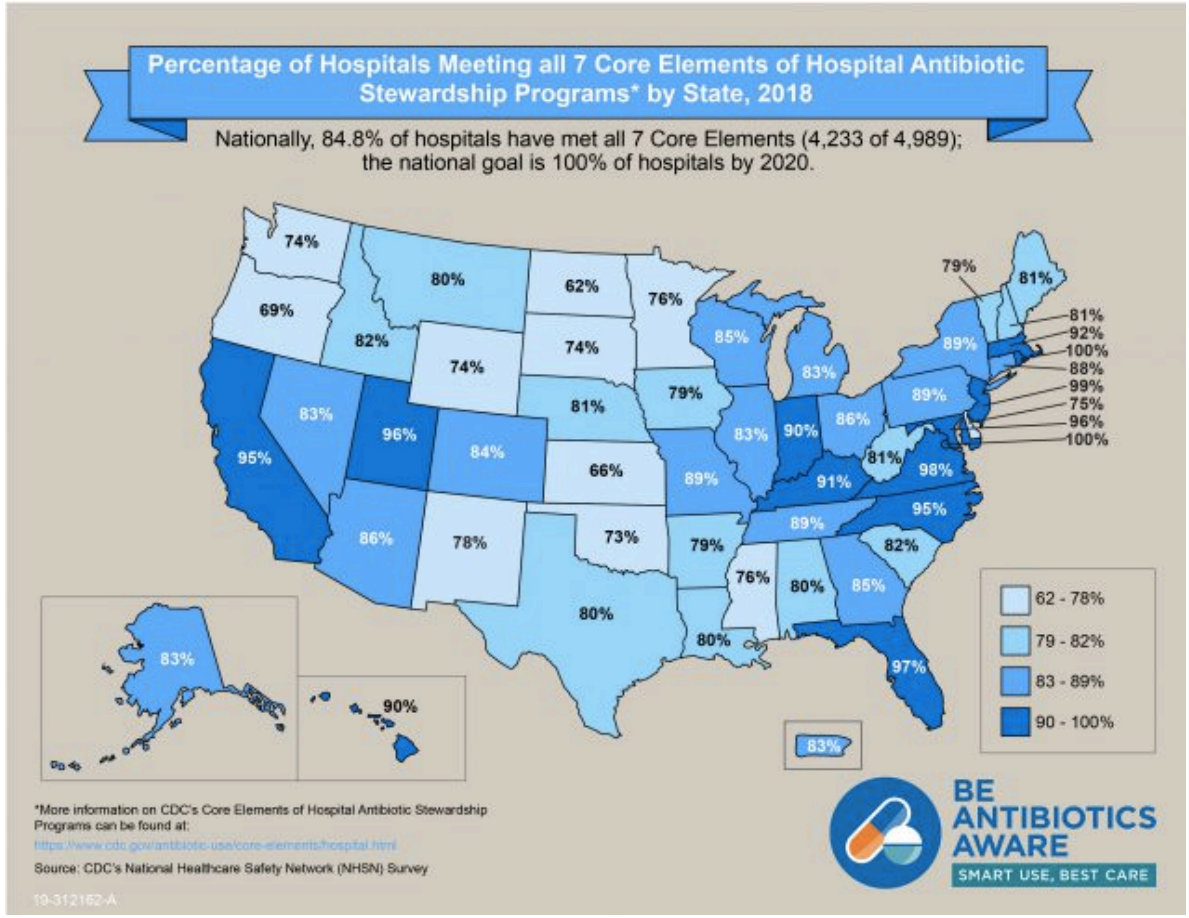
Sep 26, 2019 | Initiatives, Legislation, Physicians

- Requiring hospitals to establish and maintain antibiotic stewardship programs to help reduce inappropriate antibiotic use and antimicrobial resistance. By requiring that hospitals have antibiotic stewardship programs that are not only active and hospital-wide, but also demonstrate adherence to nationally recognized guidelines for the optimization of antibiotic use through stewardship, the changes are aimed at effectively reducing the development and transmission of HAIs and antibiotic-resistant organisms that ultimately will greatly improve the care and safety of patients while adding cost benefits for hospitals;

- Adding flexibility to the hospital CoPs by specifying that a unified and integrated infection prevention and control program may also include a unified and integrated antibiotic stewardship program for a multi-hospital system;

Centers for Disease Control Core Elements for Antimicrobial Stewardship Programs (2019)

1. Hospital leadership commitment
2. Accountability
3. Pharmacy expertise & leadership
4. Action, implementation of intervention (best practices)
5. Tracking
6. Reporting
7. Education

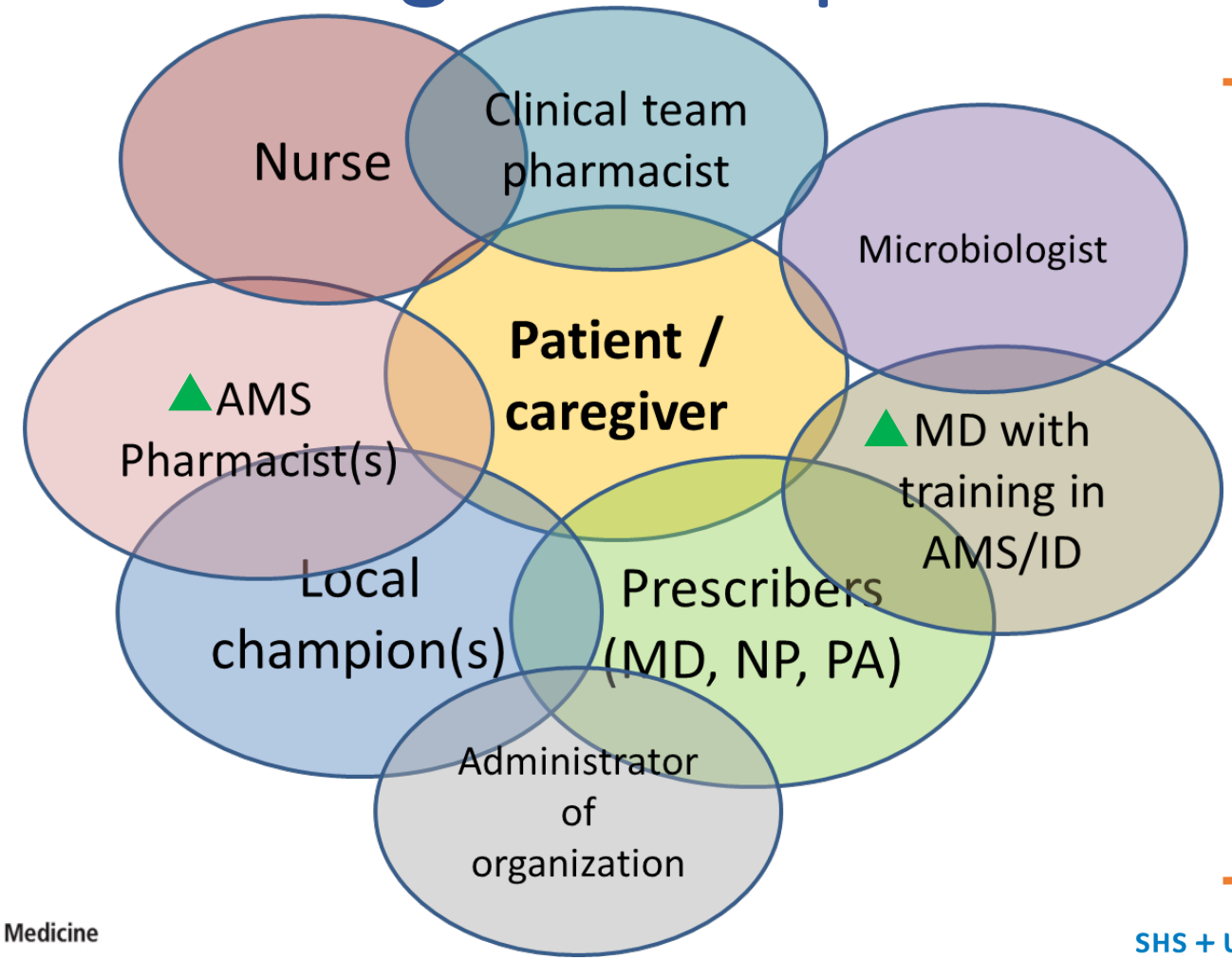


CDC Core Elements: The “Who”

1. Hospital leadership – resource allocation and support
2. Accountability
   - Reporting structure to hospital administration, and identify person(s) responsible for the antimicrobial stewardship program
   - Membership of the team
   - Key stakeholders
3. Pharmacy expertise and co-leadership – antibiotic use

So…what existing elements can we borrow or steal for solid organ transplant recipients?

▲With specialized knowledge in transplant infectious diseases



Key Stakeholders:
Transplant Surgeons & Physicians

Transplant program directors

So, et al. ATC 2019. Submitted manuscript

CDC Core Elements: The "What" and the "How"

4. Implementation of ASP Interventions
    - Audit-feedback
    - Restriction on prescribing
    - Guidelines
    - Dose optimization, IV→PO
    - Duration
    - Tailoring of antibiotics
    - De-label "penicillin allergy"

5. Tracking* – how much, how well

6. Reporting* – "sharing is caring"

7. Education

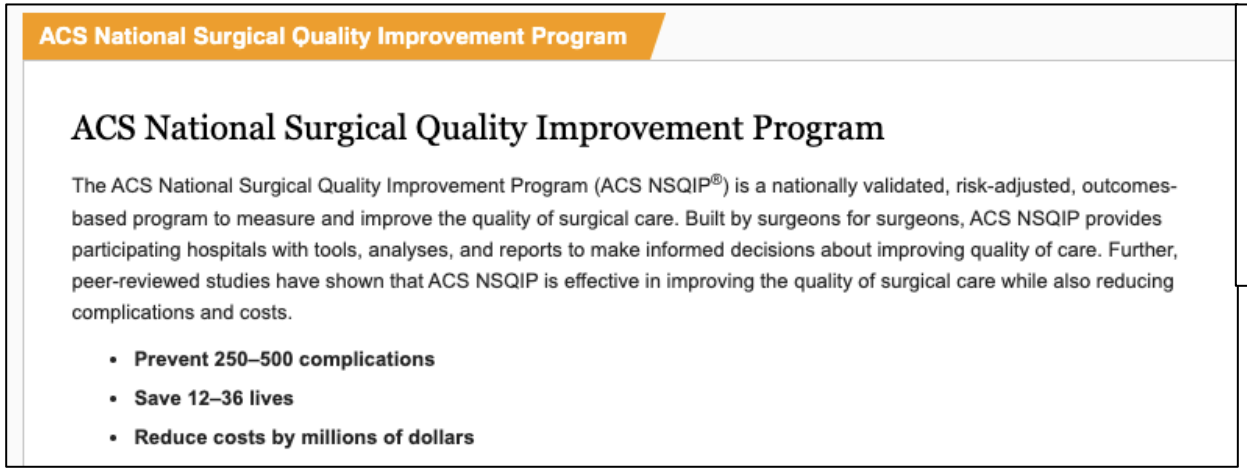
*Quality improvement framework

CDC National Healthcare Safety Network (NHSN)

- Antimicrobial use (AMU) / antimicrobial resistance (AMR) modules
- Standardized to patient volume (patient-days) for internal comparison and external benchmarking with peer hospitals
  - Standardized antimicrobial administration ratio (SAAR) for specific antibiotics
  - Organism- and antibiotic-specific resistance rate
- Applicable to solid organ transplant patients
- Patient safety metrics on healthcare-associated infections

Surgical site infections and complications

NSQIP Program



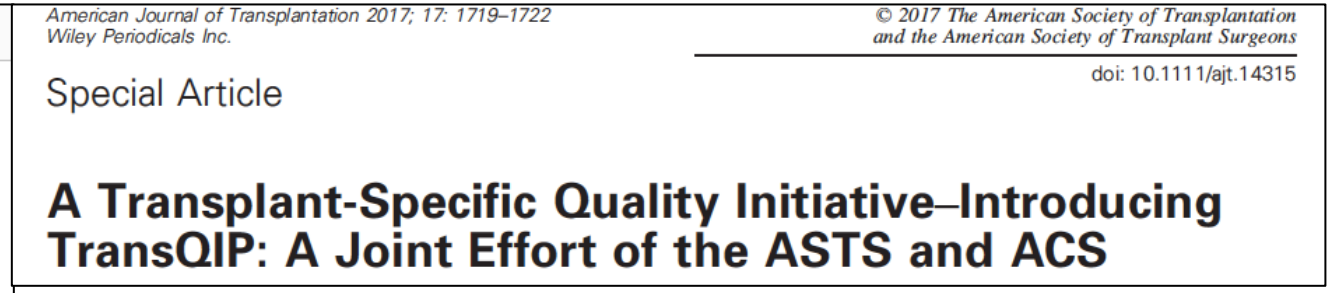
ACS National Surgical Quality Improvement Program

ACS National Surgical Quality Improvement Program

The ACS National Surgical Quality Improvement Program (ACS NSQIP®) is a nationally validated, risk-adjusted, outcomes-based program to measure and improve the quality of surgical care. Built by surgeons for surgeons, ACS NSQIP provides participating hospitals with tools, analyses, and reports to make informed decisions about improving quality of care. Further, peer-reviewed studies have shown that ACS NSQIP is effective in improving the quality of surgical care while also reducing complications and costs.

- **Prevent 250–500 complications**
- **Save 12–36 lives**
- **Reduce costs by millions of dollars**

TransQIP Program



American Journal of Transplantation 2017; 17: 1719–1722
Wiley Periodicals Inc.

doi: 10.1111/ajt.14315

Special Article

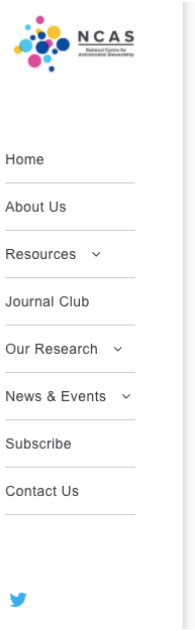
A Transplant-Specific Quality Initiative–Introducing TransQIP: A Joint Effort of the ASTS and ACS

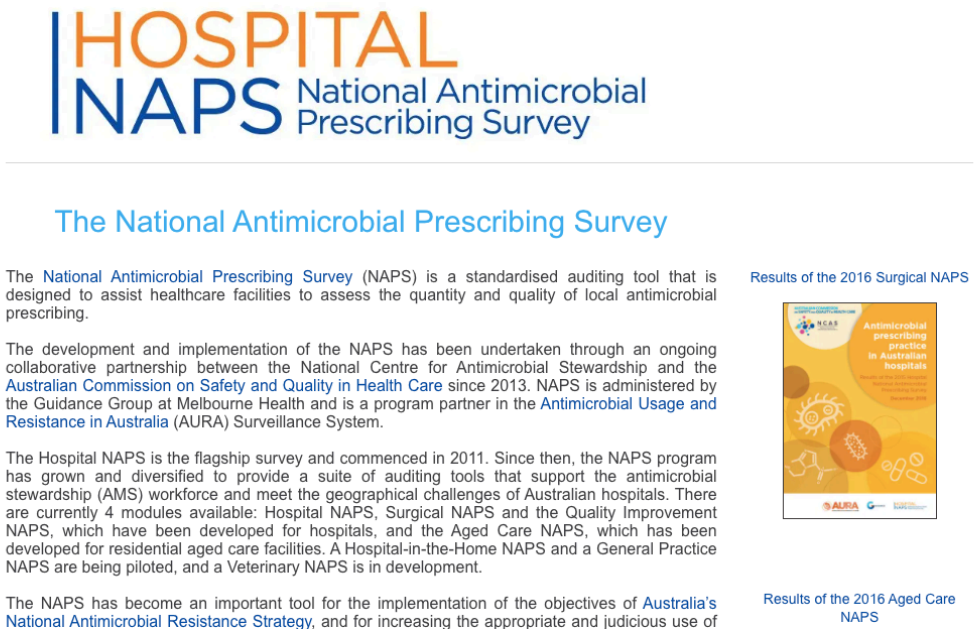
Includes transplant-related, healthcare-associated infections – quantity and quality (appropriateness) of antibiotic use

Parekh et al., Am J Transplant 2017;17:1719-22.

Australia's National Centre for Antimicrobial Stewardship National Antimicrobial Prescribing Survey

- Web-based tool
  - Adaptable to transplant patients
  - Patient's clinical data and antibiotic prescription data for real-time adjudication of appropriateness against guidelines (local or published), or antimicrobial stewardship principles
  - Can be specific to unit (e.g. transplant units), patient group (e.g. liver recipient), prescriber group, or hospital-wide





https://www.ncas-australia.org/naps

Phoompoung et al. Manuscript in preparation.
James R et al. J Antimicrob Chemother 2015

Best Practices for the Implementation of Antimicrobial Stewardship in Solid Organ Transplant Programs

Challenges in Implementing ASPs for SOT Recipients

- Diagnostic uncertainty
- Atypical presentations
- Colonization with MDROs
- Difficulties in obtaining source control
- Perception of severity of infection
- Lack of guidelines delineating optimal length of therapy

Abbo et al. Infect Dis Clini N Amer 2014; 28: 263-79.
So et al. Clin Transplant 2016; 30: 659-668.
Seo et al. Infect Control Hosp Epidemiol 2016; 37: 1195-1200.

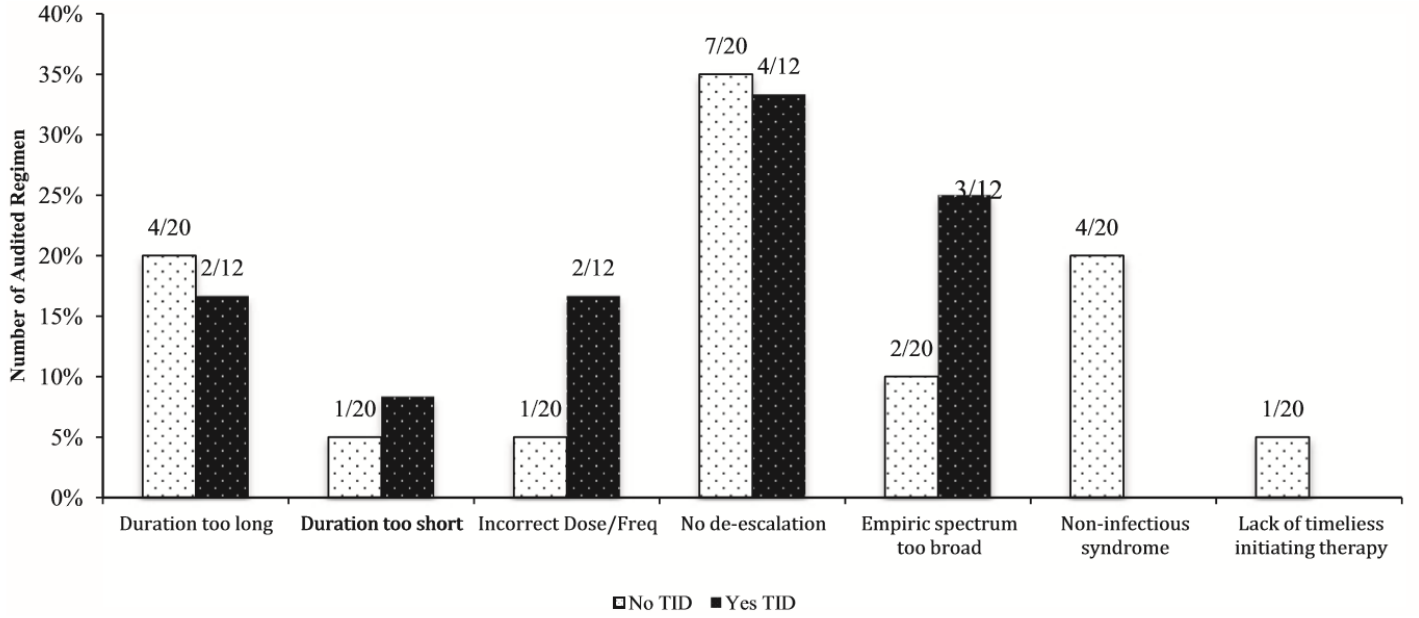
Perceptions of Stewardship by Transplant Clinicians

- 308 respondents (33% ID physicians, 27% transplant physicians)
- 66% of respondents felt the main goal of an antimicrobial stewardship program (ASP) is to increase the appropriateness of antimicrobials
- >40% of respondents noted that their patients had experienced antibiotic-resistant infections
- 90% of ID clinicians and 75% of non-ID clinicians considered ASPs to have made a positive impact on the quality of patient care
- 92% of non-ID respondents would be more likely to follow ASP recommendations if transplant ID was part of the team

So et al. Am J Transplant 2019;19 (Suppl 3).
Submitted manuscript

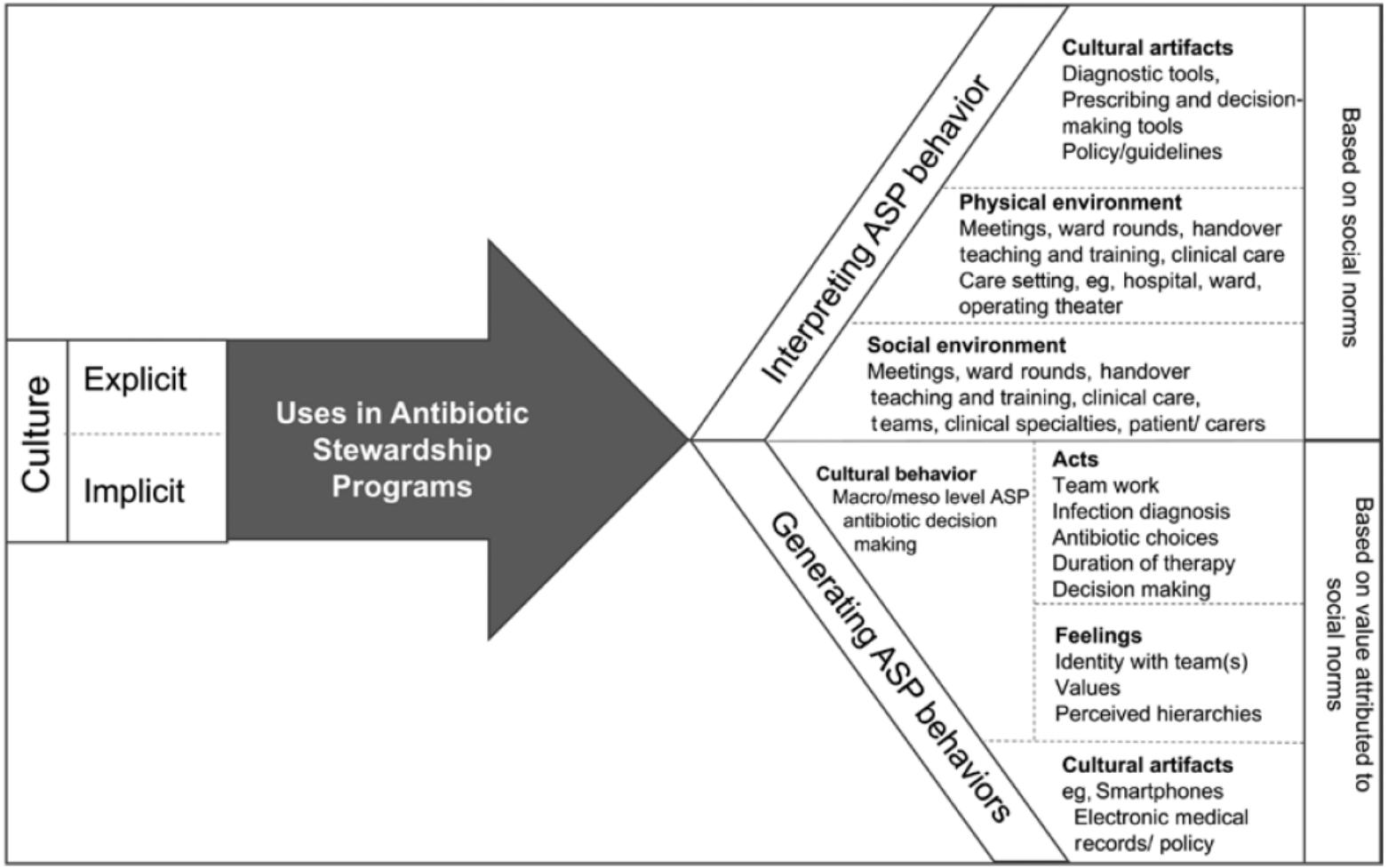
Opportunities for Stewardship in SOT

- Transplant ID (TID) was consulted on 54% of prescriptions
- TID consult was associated with a higher percentage of stewardship-concordant prescriptions (78.5% vs. 59.6%, p = 0.03)
- Discordance related to non-adherence to recommendations



So et al. Clin Transplant 2016; 30: 659-668.

Culture Impacts Prescribing Patterns



Charani E et al. Clin Infect Dis 2019 Jun 18;69(1):12-20.

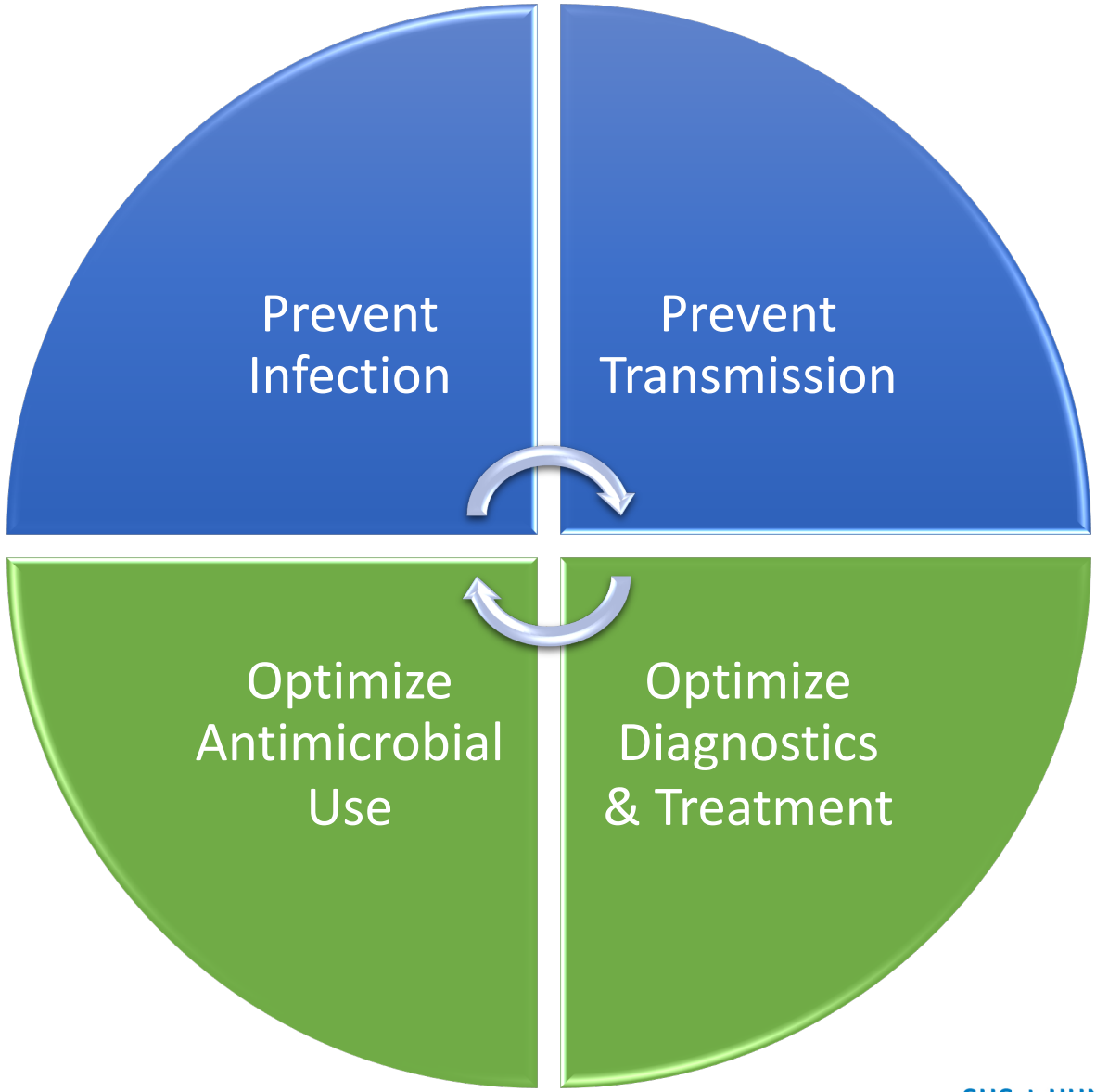
Team-Based Approach Starts with a Handshake

“Handshake Stewardship”

- In-person rounding with pharmacist/physician members of the ASP team
- Associated with reductions in antibiotic use
- Additional benefits
  - Better understanding of the culture of antibiotic prescribing
  - Reinforces shared goal of positive patient outcomes and team-based approach to patient care

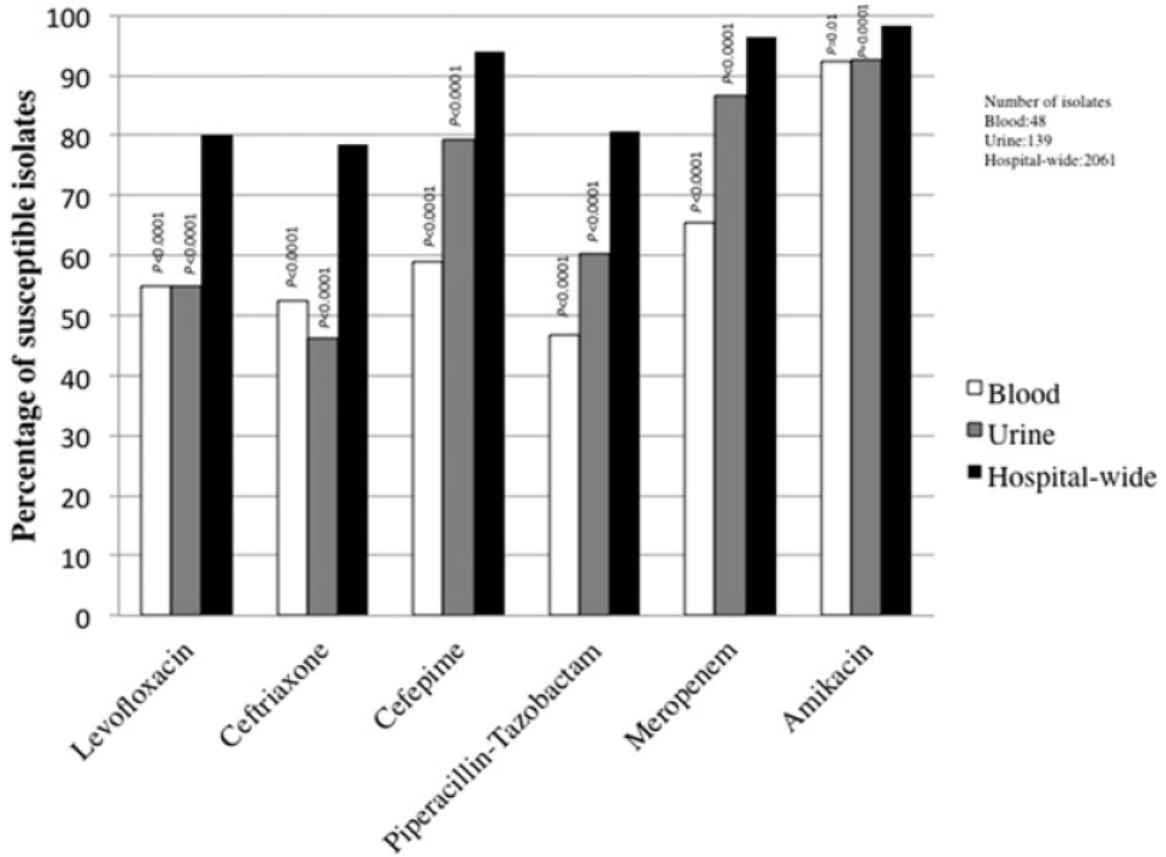
Hurst AL et al. Pediatr Infect Dis J 2016 Oct; 35(10):1104-10.
Messacar K et al. Clin Infect Dis 2017 May 15; 64(10):1449-1452.

Infection Prevention & Control



Antimicrobial Stewardship

Reducing Time to Effective Antibiotic Therapy: Engagement with Microbiology



- Rapid diagnostics
  - Multiplex PCR panels detecting organisms from blood, gastrointestinal, and respiratory specimens may provide organism identification and genotypic resistance information
  - Multiplex panels and other rapid diagnostics may have a role in transplant stewardship
  - Additional study is warranted

Rosa et al. Diagn Microbiol Infect Dis 2016; 86: 460-3
Hand et al. Curr Opinion Organ Transplant; 2019 Aug;24(4):497-503.

What Would You Be Asking the C-Suite to Support an ASP for Transplant Patients?

- Understand what is already available at your center/institution, what resources can be leveraged
- Support your “ask” with transplant-specific data
- “What’s in it for them, the C-Suite?” (How to make them look good)
  - Positive impact on clinical outcome, quality of care
  - Optimization of resources: fiscal, personnel
  - Metrics: cost, length of stay, readmission, complications
  - Justify the incremental investment for transplant population