NOVEL STRATEGIES FOR EVALUATING ANTIBIOTIC USE

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SHEA ANTIMICROBIAL STEWARDSHIP RESEARCH WORKSHOP – NOVEMBER 2016

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Royalties – UpToDate

Slides largely borrowed from Tom Holland and Scott Evans

- Antibacterial Resistance Leadership Group (ARLG)

Outline

Background

- Limitations of traditional approaches

Desirability of Outcome Ranking (DOOR) – a novel paradigm to assess outcomes

- Basics
- Examples
- Build a DOOR!

Future directions

Background

Shorter is Better!

Less is Better!

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Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

Disease	Treatment, Days	
	Short	Long
Community-acquired pneumonia[1-3]	3-5	7-10
Nosocomial pneumonia[6,7]	≤8	10-15
Pyelonephritis[10]	5-7	10-14
Intraabdominal infection[11]	4	10
Acute exacerbation of chronic bronchitis and COPD[12]	≤5	≥7
Acute bacterial sinusitis[13]	5	10
Cellulitis[14]	5-6	10
Chronic osteomyelitis[15]	42	84

Abbreviation: COPD, chronic obstructive pulmonary disease.

The JAMA Network

JAMA Intern Med. 2016;176(9):1254-1255. doi:10.1001/jamainternmed.2016.3646

Example Stewardship Study

- Prospective study evaluating post-prescription review of broad-spectrum antimicrobial agents
  - Five academic centers
- Primary outcome – days of therapy (DOT)/1000 pt-days
  - Intervention period vs. baseline period
- Conclusion – worked in some but not all

TABLE 1. Rate of Study and Total Antimicrobial (ABX) Use and Incidence Rate Ratios (IRR) in Each Study Period

	Hospital A	Hospital B[a]	Hospital C	Hospital D	Hospital E
ABX-days/1,000 patient-days					
Study ABX					
Baseline	419.56	574.37	509.03	615.59	519.85
Intervention	469.62	533.84	497.28	512.62	596.07
Follow-up	446.33	...	476.67	602.72	642.47
Total ABX					
Baseline	395.63	548.02	474.07	522.25	473.46
Intervention	443.30	484.01	460.80	421.42	560.87
Follow-up	397.36	...	425.20	500.57	605.77
IRR (95% CI)					
Study ABX					
Intervention vs baseline	1.12 (1.05–1.19)	0.93 (0.88–0.98)	0.98 (0.91–1.04)	0.83 (0.79–0.88)	1.14 (1.08–1.22)
Intervention vs follow-up	0.95 (0.89–1.01)	...	0.96 (0.90–1.02)	1.18 (1.12–1.24)	1.08 (1.01–1.15)
Total ABX					
Intervention vs baseline	1.12 (1.06–1.18)	0.88 (0.85–0.92)	0.97 (0.92–1.03)	0.81 (0.77–0.84)	1.18 (1.13–1.25)
Intervention vs follow-up	0.90 (0.85–0.95)	...	0.92 (0.87–0.97)	1.19 (1.14–1.24)	1.08 (1.03–1.13)

Cosgrove et al. ICHE 2012; 33: 374-380.

Example – Setup

BASELINE

Design a study to determine the impact of stewardship intervention “X”

Target antibiotics
- Piperacillin-tazobactam
- Carbapenems

Utilization
- 2000 DOT/1000 ptd for 1 year

Average LOS
- 4.5 days

POST-INTERVENTION

Evaluate data from first 6 months after starting the intervention (n=100)

Utilization decreased
- 842 DOT/1000 ptd

LOS decreased
- 3 days

SUCCESS?

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Example - Results

BASELINE

Mortality = 2%

POST-INTERVENTION

Mortality = 35%

Example 2 - Setup

Two important outcomes to consider

- Efficacy (benefit)
- Toxicity

Running a trial comparing 3 stewardship interventions

- Restriction
- Time Out
- Post-Rx review

In this study, outcomes are binary

Example 2 – Analysis of Endpoints

Restriction (n=100)	Time Out (n=100)	Post-Rx Review (n=100)
Benefit: 50%	Benefit: 50%	Benefit: 50%
Toxicity: 20%	Toxicity: 50%	Toxicity: 50%

Which stewardship intervention was the best?

C

Example 2 – Analysis of Patients

Restriction (n=100)	Time Out (n=100)	Post-Rx Review (n=100)
Benefit: 50%	Benefit: 50%	Benefit: 50%
Toxicity: 20%	Toxicity: 50%	Toxicity: 50%

Restriction (n=100)

Tox \ Benefit	+	-
+	10	10
-	40	40

Time Out (n=100)

Tox \ Benefit	+	-
+	50	0
-	0	50

Post-Rx Review (n=100)

Tox \ Benefit	+	-
+	0	50
-	50	0

Benefit (without toxicity)	40%	0%	50%

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Could More Antibiotic Use be Good?

Under treatment/no treatment of serious infections

- Sepsis

Better adherence to guidelines

- *S. aureus* bacteremia
- Fungemia

Limitations – Competing Risks

Common endpoints can be distorted and are challenging to interpret

- Days in the hospital
- Days in the ICU
- Days of antibiotic use

Shorter is better…or is it?

Less is better…or is it?

The faster a patient dies, the fewer the days

Interpretation of these endpoints needs clinical context of other outcomes for the same patient

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

Scott R. Evans,[1] Daniel Rubin,[2] Dean Follmann,[3] Gene Pennello,[4] W. Charles Huskins,[5] John H. Powers,[6,7] David Schoenfeld,[8] Christy Chuang-Stein,[9] Sara E. Cosgrove,[10] Vance G. Fowler Jr,[11] Ebbing Lautenbach,[12] and Henry F. Chambers[13]

800 • CID 2015:61 (1 September) • HEALTHCARE EPIDEMIOLOGY

A NOVEL PARADIGM?

DOOR Advantages

Measure to evaluate the global patient outcomes

- More informative and pragmatic benefit:risk evaluation

Patient-level interpretation

Superiority design; avoids NI complexities

Reduction of sample size in some cases

Conceptual Framework

Ask if new strategies are BETTER than standard strategies

- Totality of intervention: benefits, harms, QoL
- Incorporate antibiotic use

Use an ordinal outcome to rank patients

Compare DOOR distributions between strategies

But…

- How to logically put together the important outcomes?
- Weighting outcomes is challenging

Evans et al. CID 2015; 61(5): 800-6.

Step 1: Ordinal Outcome

Number and definition of levels is tailored to clinical disease

- Hierarchical layers are importantly different
  - Within layers are not importantly different
- Top and bottom categories are often obvious
  - Layers between?

Generic Example - 5 Levels
1. Benefit w/o toxicity
2. Benefit w/ toxicity
3. Survive, no benefit w/o toxicity
4. Survive, no benefit w/ toxicity
5. Death

Evans et al. CID 2015; 61(5): 800-6.

Step 2: DOOR

All participants receive a DOOR

Two rules:

- If 2 patients with different clinical outcomes, the patient with the BETTER clinical outcome receives higher rank
- If 2 patients with same clinical outcomes, the patient with the SHORTER duration of antibiotics receives higher rank

Step 3: Evaluate Superiority of DOOR

Compare DOOR distributions between strategies

- Estimate probability (with CI) that a randomly selected patient will have a better DOOR if assigned to a new strategy vs. a control
- >50% implies superiority

Example

DOOR – 3 LAYERS

1. Success without AE
2. Success with AE
3. Failure

Subject	Tx Arm	Clinical Outcome	Days of Abx Use	DOOR	Lower DOOR
A	New	2	5		
B	New	1	3		
C	New	1	4		
D	New	2	4		
E	New	3	3		
F	New	2	3		
G	New	3	5		
H	New	3	4		
I	New	1	7		
J	New	2	8		
K	Control	3	12		
L	Control	2	7		
M	Control	1	9		
N	Control	2	8		
O	Control	3	6		
P	Control	2	11		
Q	Control	1	10		
R	Control	2	9		
S	Control	3	9		
T	Control	2	6		

Example

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Subject	Tx Arm	Clinical Outcome	Days of Abx Use	DOOR	Lower DOOR
B	New	1	3		
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I	New	1	7		
M	Control	1	9		
Q	Control	1	10		
A	New	2	5		
D	New	2	4		
F	New	2	3		
J	New	2	8		
L	Control	2	7		
N	Control	2	8		
P	Control	2	11		
R	Control	2	9		
T	Control	2	6		
E	New	3	3		
G	New	3	5		
H	New	3	4		
K	Control	3	12		
O	Control	3	6		
S	Control	3	9		

Example

DOOR – 3 LAYERS

1. Success without AE
2. Success with AE
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Subject	Tx Arm	Clinical Outcome	Days of Abx Use	DOOR	Lower DOOR
B	New	1	3		
C	New	1	4		
I	New	1	7		
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D	New	2	4		
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T	Control	2	6		
L	Control	2	7		
J	New	2	8		
N	Control	2	8		
R	Control	2	9		
P	Control	2	11		
E	New	3	3		
H	New	3	4		
G	New	3	5		
O	Control	3	6		
S	Control	3	9		
K	Control	3	12		

Example

DOOR – 3 LAYERS

1. Success without AE
2. Success with AE
3. Failure

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Subject	Tx Arm	Clinical Outcome	Days of Abx Use	DOOR	Lower DOOR
B	New	1	3	1	
C	New	1	4	2	
I	New	1	7	3	
M	Control	1	9	4	
Q	Control	1	10	5	
F	New	2	3	6	
D	New	2	4	7	
A	New	2	5	8	
T	Control	2	6	9	
L	Control	2	7	10	
J	New	2	8	11.5	
N	Control	2	8	11.5	
R	Control	2	9	13	
P	Control	2	11	14	
E	New	3	3	15	
H	New	3	4	16	
G	New	3	5	17	
O	Control	3	6	18	
S	Control	3	9	19	
K	Control	3	12	20	

Example

DOOR – 3 LAYERS

1. Success without AE
2. Success with AE
3. Failure

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Subject	Tx Arm	Clinical Outcome	Days of Abx Use	DOOR	Lower DOOR
A	New	2	5	8	8
B	New	1	3	1	10
C	New	1	4	2	10
D	New	2	4	7	8
E	New	3	3	15	3
F	New	2	3	6	8
G	New	3	5	17	3
H	New	3	4	16	3
I	New	1	7	3	10
J	New	2	8	11.5	5.5
K	Control	3	12	20	**SUM=68.5**
L	Control	2	7	10	
M	Control	1	9	4	
N	Control	2	8	11.5	
O	Control	3	6	18	
P	Control	2	11	14	
Q	Control	1	10	5	
R	Control	2	9	13	
S	Control	3	9	19	
T	Control	2	6	9	

Example

No. of control participants with a lower DOOR = 68.5

Probability of a better DOOR for a randomly selected participant from the new strategy

- Number of new strategy participants with higher door divided by number of pairwise comparisons
- 68.5/100 pair-wise comparisons = 68.5%

BUILD A DOOR

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Build a DOOR

Compare two scenarios and select the one with the better global outcome

Consider five items:

1. Cure vs. Failure
   - Cure – global resolution of infection
   - Failure – lack of cure
2. Infectious complication – development of resistance AFTER intervention or recurrent/persistent infection
3. Ongoing symptoms
4. Adverse Events (AE) – temporally associated with the use of antibiotics but no judgement about causality
5. Survival

Patient #1

75 y/o man admitted from nursing home for pneumonia.

Patient #1 – 75 y/o with pneumonia

Scenario A – transitioned from IV to PO antibiotics and has prompt recovery. Returns to NH after 4 day hospitalization on supplemental oxygen.

Scenario B – develops *C. difficile* after receiving FQ and admitted to the ICU. Develops acute renal failure and gets prolonged course of IV antibiotics. Discharged to rehabilitation center on oxygen following 18 day hospitalization and now requires assistance with ADLs.

Patient #1 – 75 y/o with pneumonia

	Scenario A	Scenario B
Cure?	Yes	Yes
Post-randomization infectious complications?	**No**	***C. difficile***
Ongoing symptoms?	Yes	Yes
AE Grade 4+?	**No**	**Yes**
Alive?	Yes	Yes

Better global patient outcome?

Scenario A – short hospitalization, oxygen

Scenario B – *C. difficile*, renal failure, assistance with ADLs

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Patient #2

57 y/o female admitted for travel-associated pulmonary embolism, treated with heparin bridged to warfarin.

During admission, develops sepsis from line-associated MRSA BSI.

Patient #2 – 57 y/o with MRSA BSI

Scenario A – during treatment, she develops acute renal failure thought to be due to contrast nephropathy from the chest CT. She develops hyperkalemia and is *en route* to the ICU for urgent dialysis, however develops VT, suffers cardiac arrest and dies.

Scenario B – one week into treatment, the patient develops back pain and lumbar osteomyelitis is found on CT. She develops acute renal failure attributed to antibiotics, requires temporary dialysis, and is changed to another antibiotic.

Patient #2 – 57 y/o with MRSA BSI

	Scenario A	Scenario B
Cure?	No	No
Post-randomization infectious complications?	No	Vertebral osteo
Ongoing symptoms?	N/A	No
AE Grade 4+?	Yes	Yes
Alive?	No	Yes

Better global patient outcome?

Scenario A – renal failure, death

Scenario B – vertebral osteo, renal failure, alive

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Patient #3

53 y/o female admitted for elective hysterectomy.

During admission, develops *C. difficile* following receipt of ertapenem for antimicrobial prophylaxis prior to HYST.

Patient #3 – 53 y/o with CDI

Scenario A – during treatment, develops toxic megacolon and requires colectomy. Recovers but continues to have loose stools and persistent abdominal discomfort.

Scenario B – recovers well from *C. difficile* but develops acute renal failure after receiving IV contrast for an abdominal CT scan. Discharged on hemodialysis; nephrologists doubt will regain renal function.

Patient #3 – 53 y/o with CDI

	Scenario A	Scenario B
Cure?	Yes	Yes
Post-randomization infectious complications?	**Colectomy**	**No**
Ongoing symptoms?	**Yes**	**No**
AE Grade 4+?	**No**	**Yes**
Alive?	Yes	Yes

Better global patient outcome?

Scenario A – colectomy, persistent abdominal symptoms

Scenario B – hemodialysis

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Clinician Survey to Develop BAC-DOOR

43 ID physicians (ARLG members)

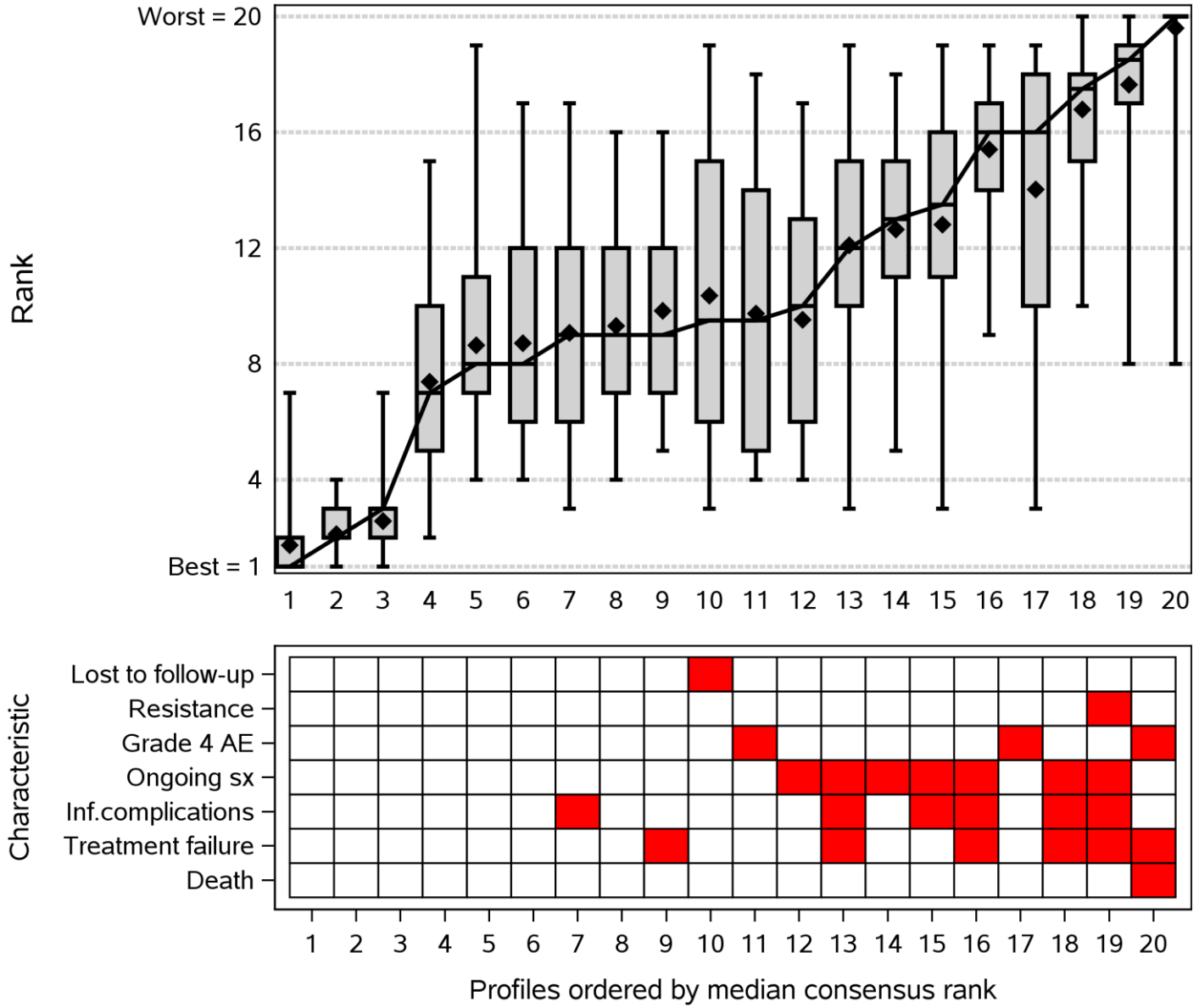
- 72% adult ID, 28% peds ID

20 adult SA-BSI profiles

- Represent the range of experiences and outcomes encountered in clinical practice
- Profiles included information about efficacy, AEs, treatment adjustments during a theoretical trial comparing 2 treatment strategies

Respondents instructed to rank the profiles based on global patient outcome

BAC-DOOR



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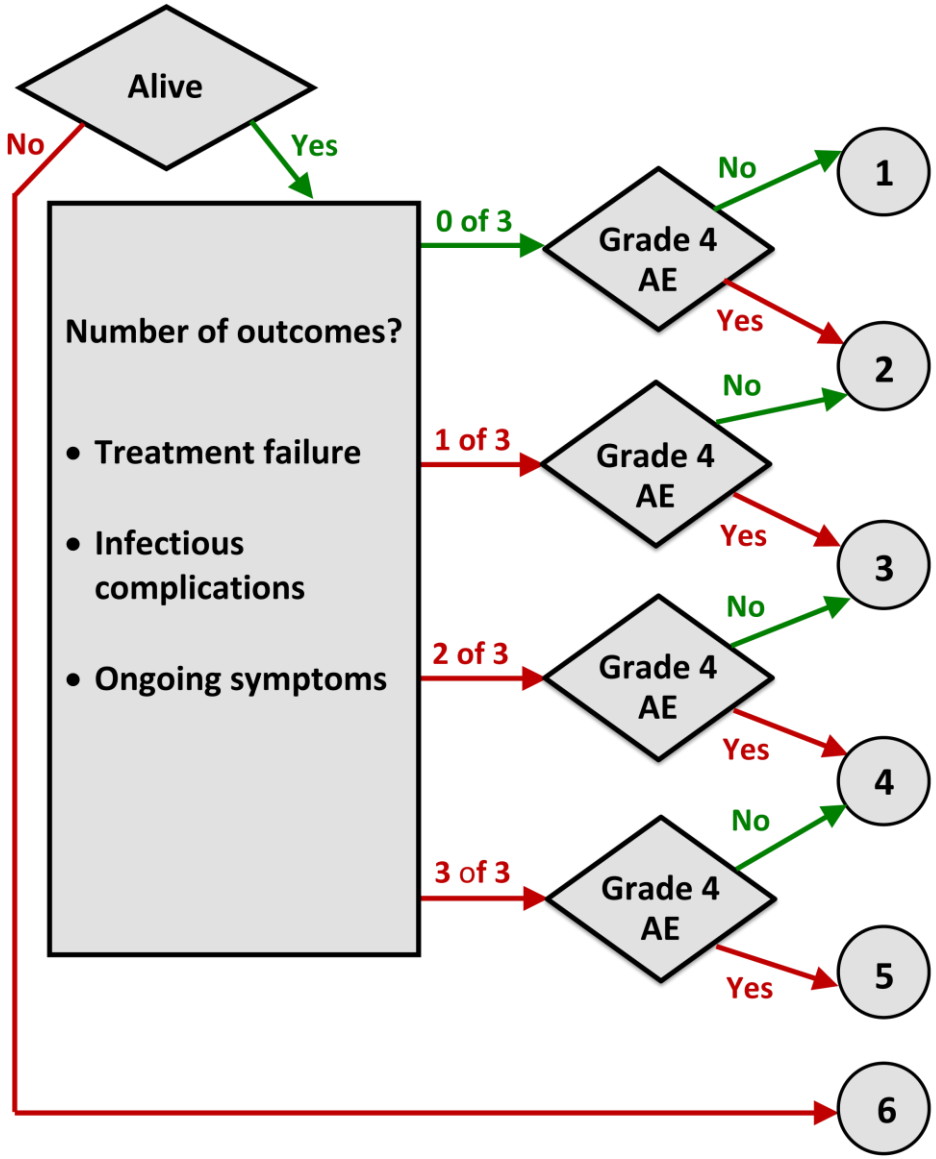
Updated BAC-DOOR algorithm



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DOOR Challenges

Cultural change

Construction of ordinal outcome is novel

Composite endpoint complexities

- Potentially too much influence given to certain components

Focus on randomization at patient-level

Solutions?

- Composite endpoint fundamentals
- Sensitivity analyses that reduce or eliminate influence of particular components deemed of lower importance
- Co-primary endpoints

What's Next?

RADAR/DOOR approach being used in upcoming trial on abx use in pediatric patients with CAP

- SCOUT-CAP

First attempts at using in unit-level interventions

Ongoing work to refine, improve, and provide additional alternative approaches

- Partial Credit
- BED-FRAME
  - Diagnostic tools; prevalence
- COMPASS (Comparing personalized antibiotic stewardship strategies)

Take Home Points

Key message: you need to measure more than antimicrobial use in your antimicrobial stewardship research

Novel strategies have been developed and are being further refined

- Focus first on composite patient outcome
- THEN, focus on antibiotic use (as a tie breaker)

Best news of all – great deal of work being done in the area

- Stay tuned for future updates

QUESTIONS?

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