



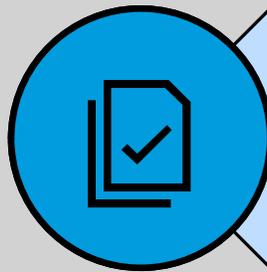
Oral Antibiotics in Infective Endocarditis:

No Longer a Tough Pill to Swallow?

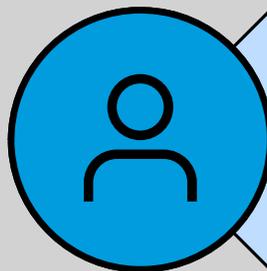
Kyle Wamlsey, Pharm.D.
PGY1 Pharmacy Resident

Pharmacy Grand Rounds
November 10, 2020

Learning Objectives



Discuss current literature surrounding the use of oral antimicrobials in the treatment of IE.



Identify specific patient populations in whom it may be appropriate to consider oral therapy for the treatment of IE.



Outline oral antimicrobial regimens which may be most appropriate for use in the treatment of IE.



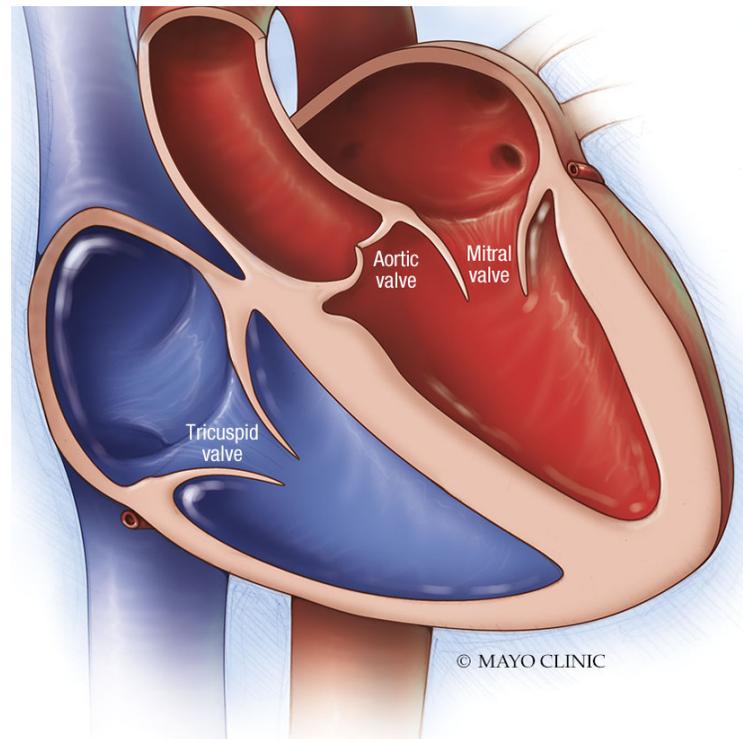
Infective Endocarditis

- Potentially lethal disease dependent on host and pathogenic factors
 - 200,000 cases annually
 - 10-40% mortality rate
- Bloodstream infection that settles in the heart lining, valve, or vessel
- Treatment regimens tailored on three key characteristics
 - Valve type (native or prosthetic)
 - Organism
 - Susceptibility

Risk Factors

Right Side (Tricuspid)

- PWID
- Less Frequent

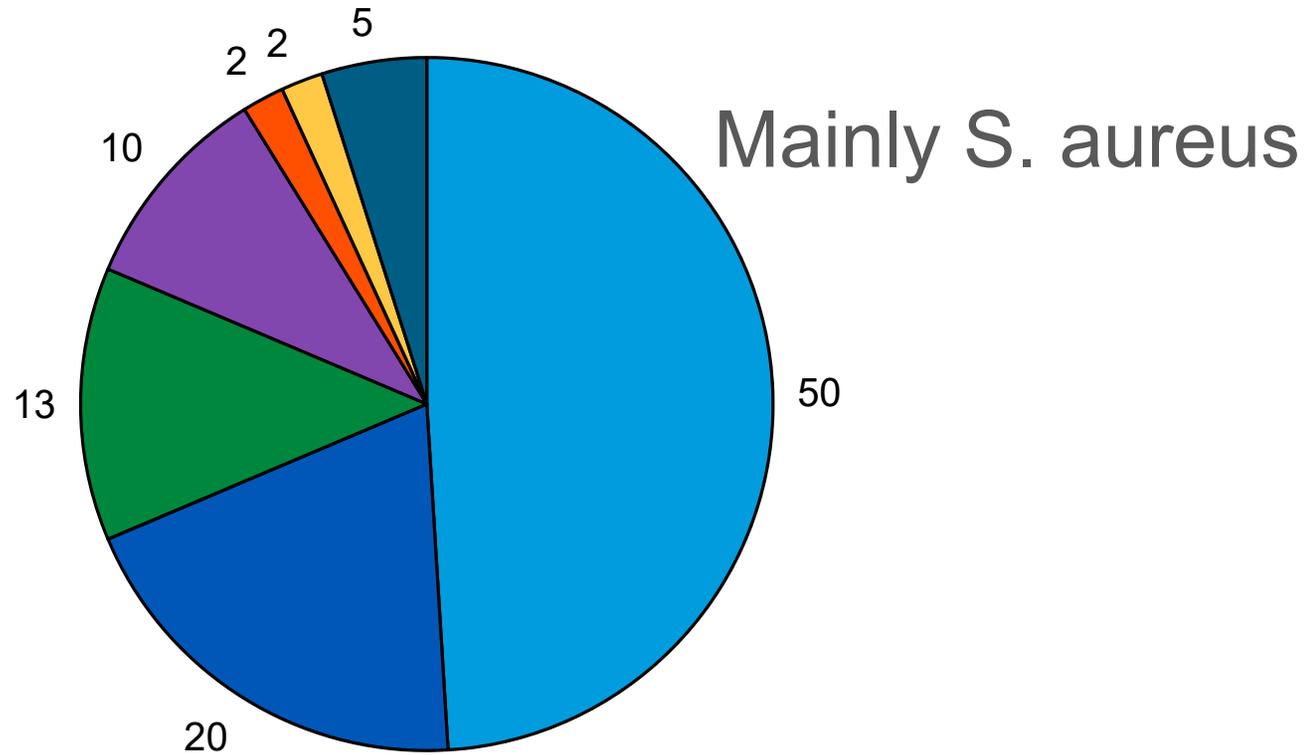


Left Side (Aortic/Mitral)

- Valvular Disease
- More Frequent

PWID= persons who injects drugs

Causative Organisms (%)



■ Staphylococcus aureus

■ Viridans group Streptococcus (VGS)

■ HACEK

■ Culture Negative

■ Coagulase-negative Staphylococcus (CoNS)

■ Enterococcus

■ Non-HACEK

Diagnosis - Duke Criteria

Pathological Criteria

- Microorganism in a vegetation (culture or histology)
- Pathologic lesions (histology)

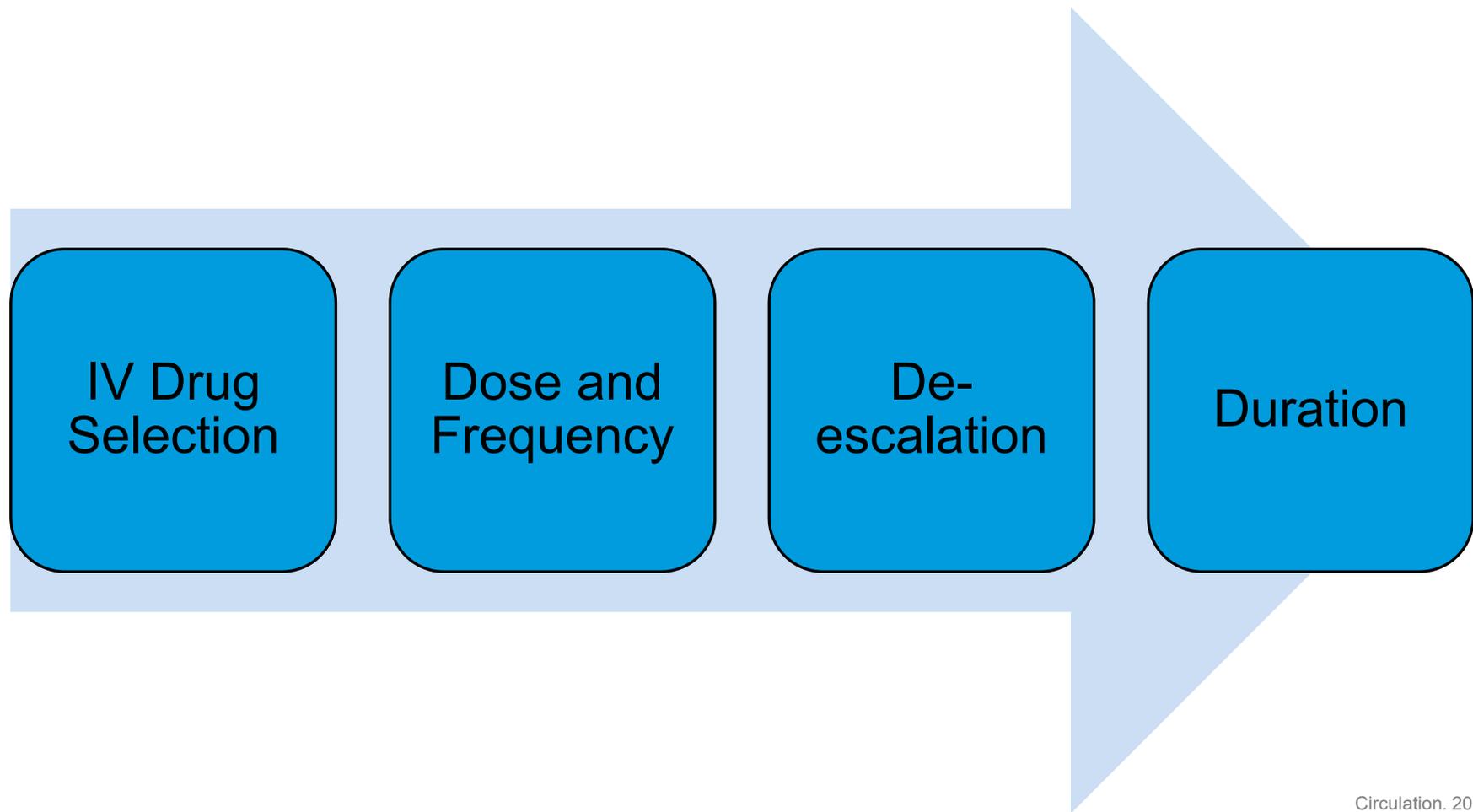
Major Criteria

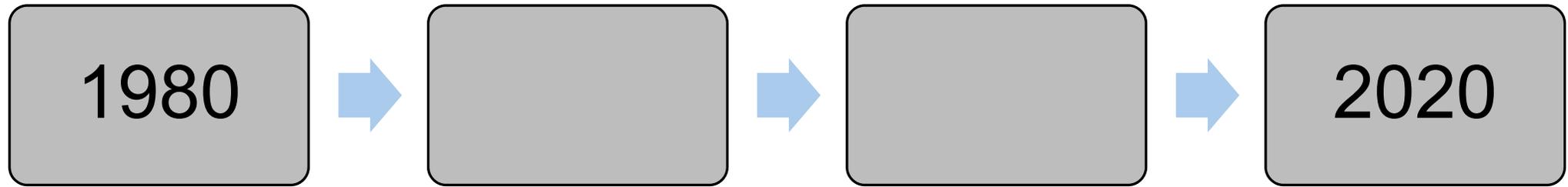
- Positive blood cultures with typical organism
- Positive echocardiogram

Minor Criteria

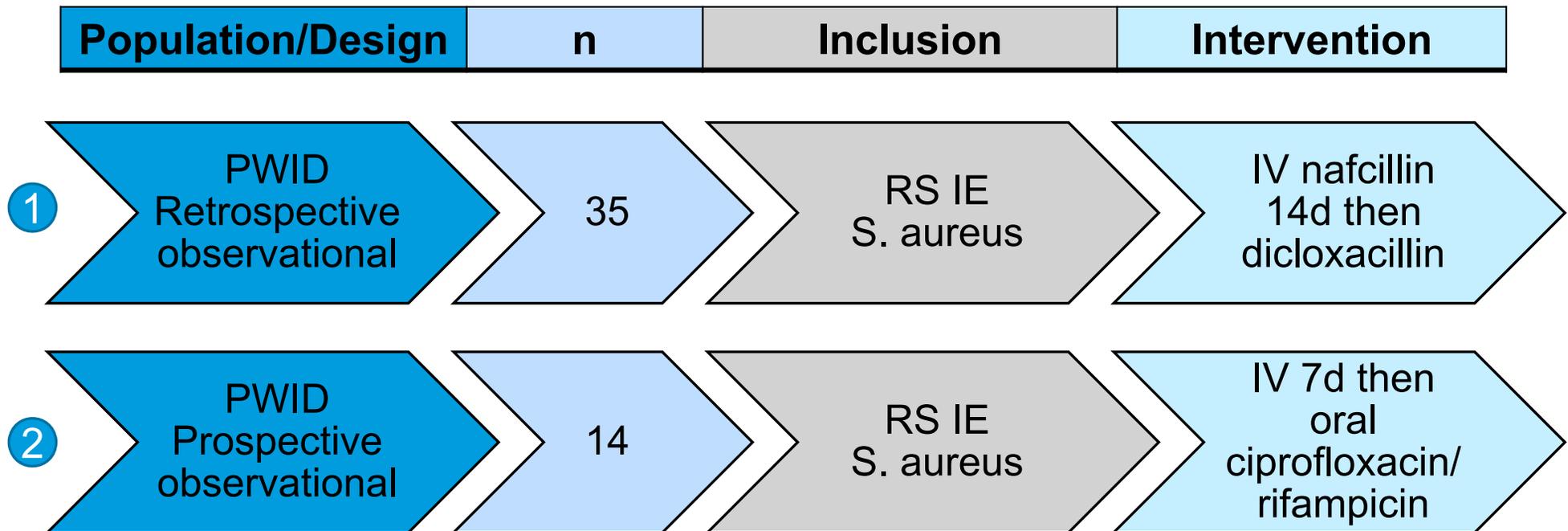
- Predisposing heart condition or PWID
- Fever $>38^{\circ}\text{C}$
- Vascular phenomena (emboli, intracranial hemorrhage)
- Immunologic phenomena (Osler node, Roth spots)
- Microbiologic evidence (alternative organism)

Treatment





Early Studies



- 1) Parker R, et al. Ann Intern Med. 1980; 93(6):832-4
2) Dworkin R, et al. The Lancet. 1989; 2(8671):1071-3

PWID= persons who inject drugs
RS IE = right-sided infective endocarditis

Early Studies

Key Exclusion

Metrics

Outcomes

1 None discussed

-Close follow-up
-Negative blood cultures

100% cured

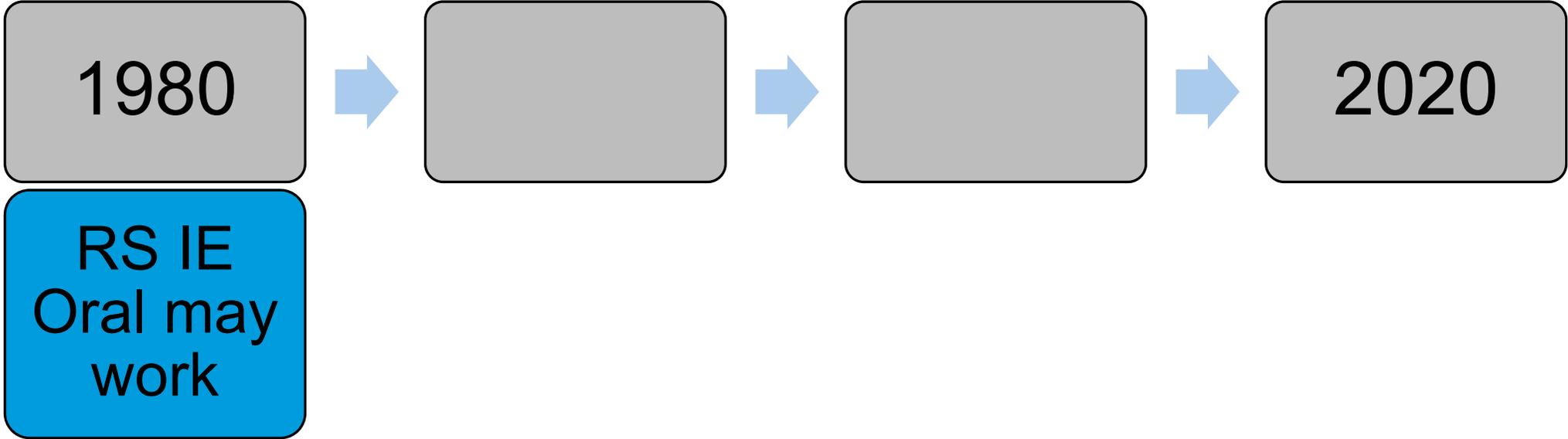
2 MIC >1 ug/mL
for either drug
Prosthetic valves

-Close follow-up
-Negative blood cultures x2

100% cured

1. Parker R, et al. Ann Intern Med. 1980; 93(6):832-4
2. Dworkin R, et al. The Lancet. 1989; 2(8671):1071-3

MIC= minimum inhibitory concentration



RS = Right Sided
IE=Infective Endocarditis

Heldman, A

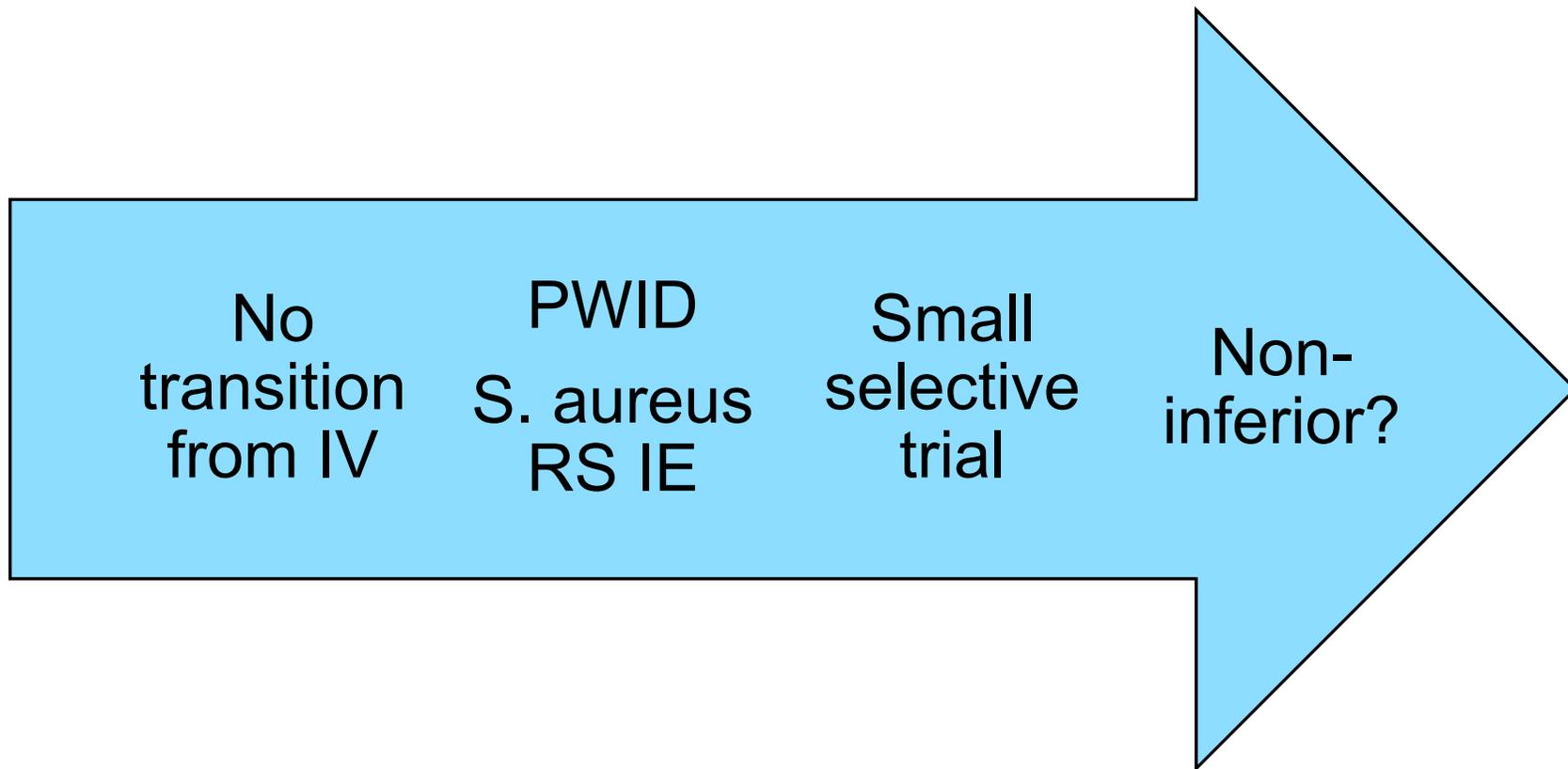
Prospective, randomized, non-blinded trial (n=44)

Population: RS S. aureus IE in PWID patients randomized on admission

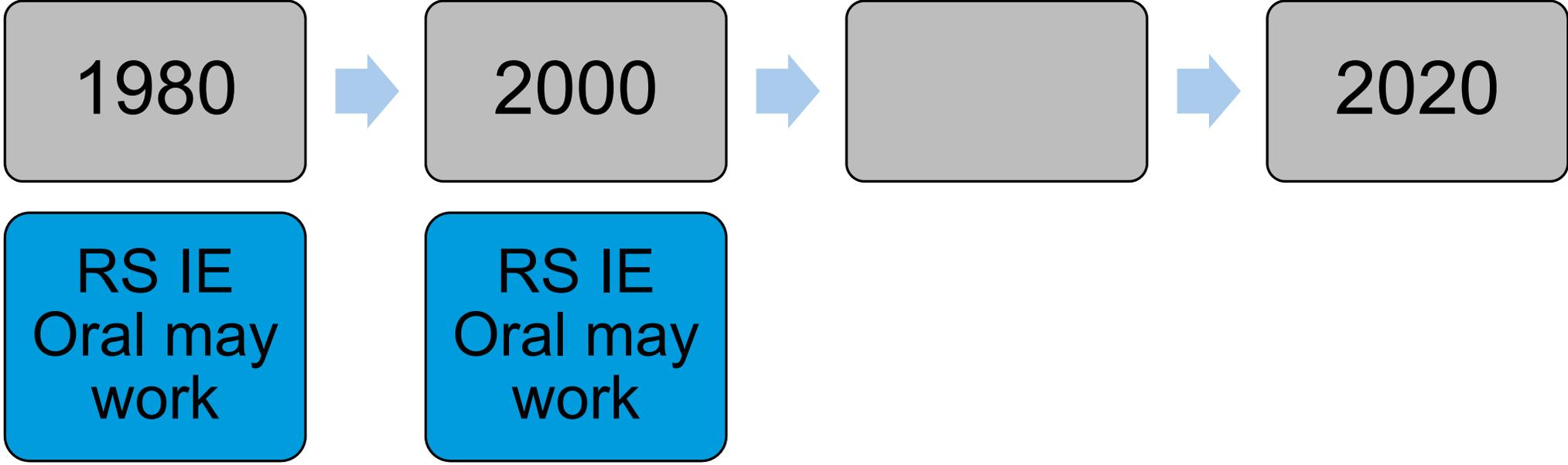
Ciprofloxacin 750mg BID plus rifampin 300mg BID 28 days after transition	Vs.	Oxacillin 2g q4h or Vancomycin 1g q12h (Plus gentamicin 2mg/kg for first 5 days) 28 days after transition
95% negative cultures (18/19)	Results	88% negative cultures (22/25)
Hepatotoxicity: 1 patient	Safety	Hepatotoxicity 13 patients Nephrotoxicity: 10 patients

RS = Right Sided
IE=Infective Endocarditis
PWID= persons who inject drugs

Key Takeaways



RS = Right Sided
IE=Infective Endocarditis
PWID= persons who inject drugs



RS = Right Sided
IE=Infective Endocarditis

Assessment Question #1

Prior to 2000, which of the following unique patient characteristics were present in these studies?

- A. Left-sided IE; PWID
- B. Left-sided IE; non-PWID
- C. Right-sided IE; PWID
- D. Right-sided IE; non-PWID

IE = Infective endocarditis
PWID = persons who inject drugs

2015 IDSA Guidelines

Staphylococcus update

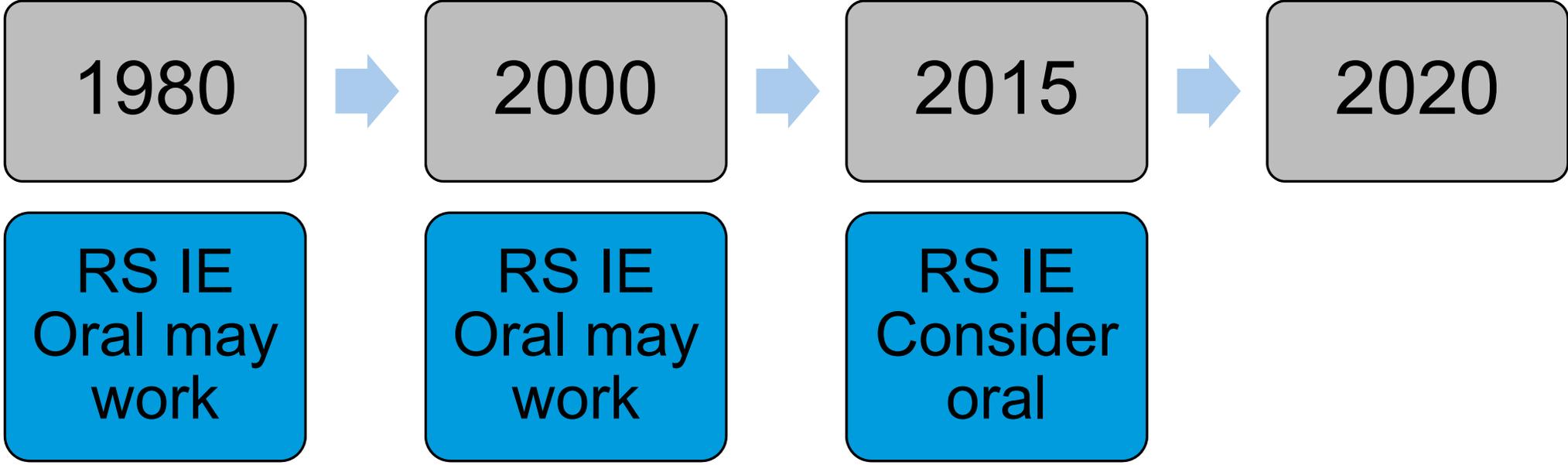
- First guideline recommendation for consideration in:
 - PWID
 - Uncomplicated right-sided IE
 - MSSA-only
 - Leaving against medical advice



PWID = persons who inject drugs

IE = Infective endocarditis

MSSA = methicillin-sensitive staphylococcus aureus



RS = Right Sided
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Tissot-Dupont, H

Prospective, single-center, before-and-after interventional trial

Population:

n=341

Referred patients

2001-2011

2012-2016

Varied baseline characteristics

<15% PWID

Inclusion:

Left-sided IE

S. Aureus

(~13% MRSA)

Native and prosthetic valves

Endpoints:

Hospital mortality,

30-day mortality

90-day mortality,

Cause of death within 30-90 days

IE=Infective Endocarditis

PWID = persons who inject drugs

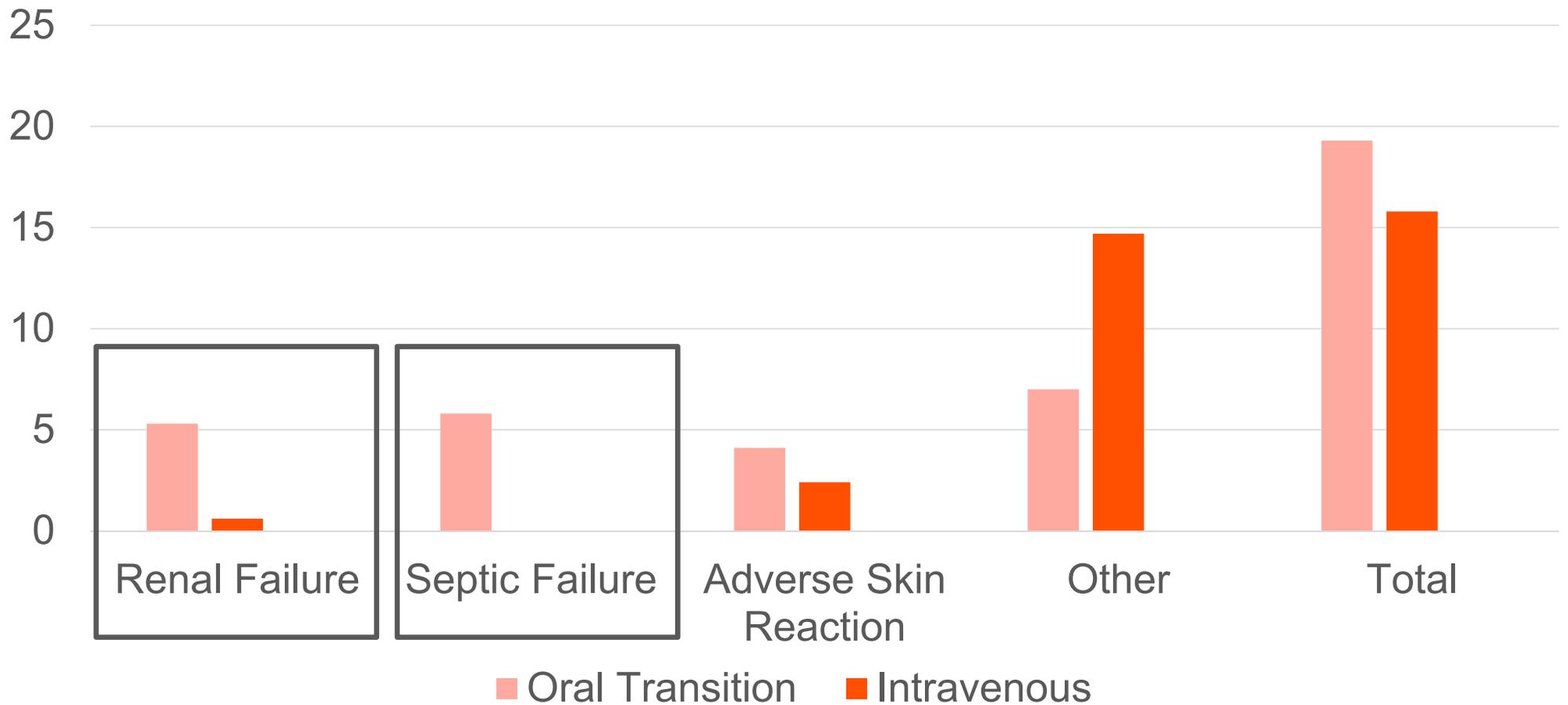
MRSA = methicillin-resistant staphylococcus aureus

Intervention

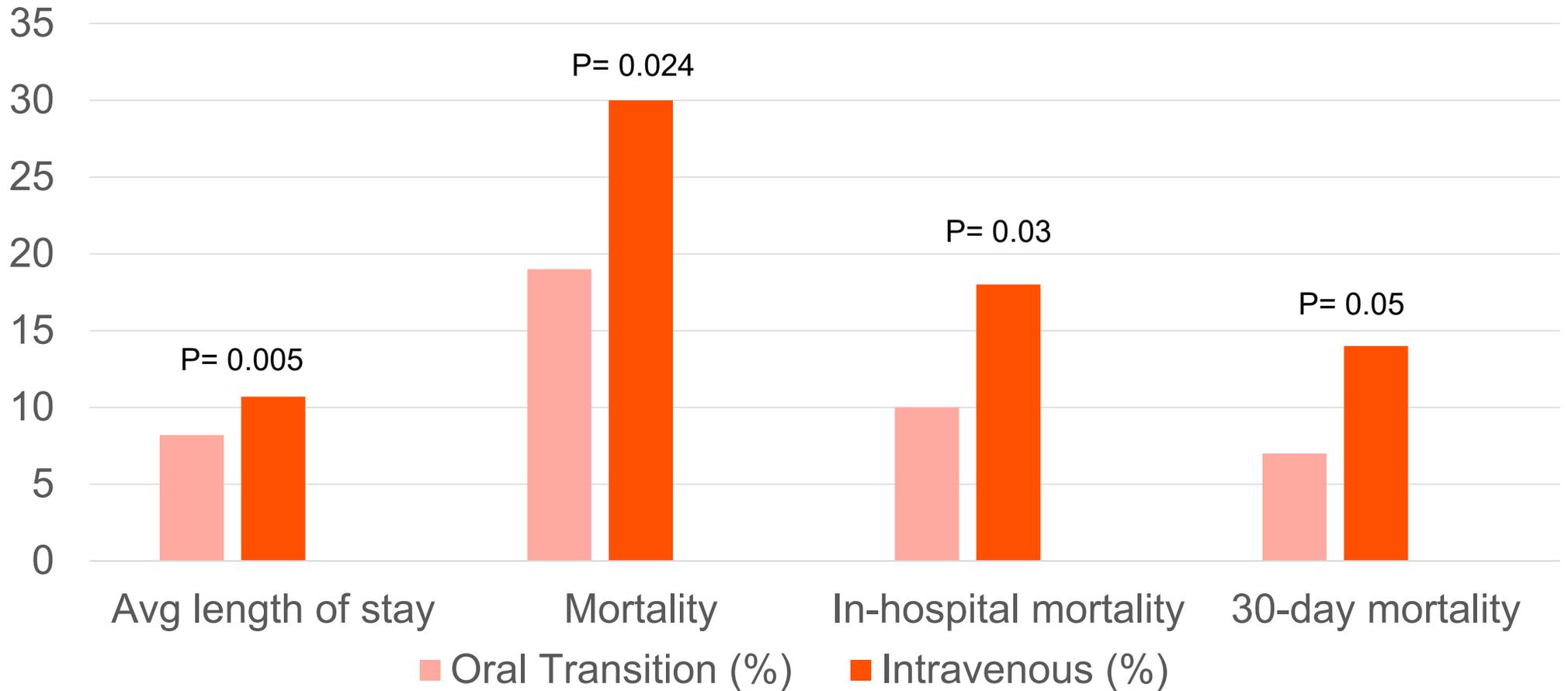
From 2001 to 2011	From 2012 to 2016
<p>70% Oxacillin for 6 weeks</p> <p>30% Vancomycin 30 mg/kg/day with gentamycin 3 mg/kg for the first 5 days</p>	<p>40% High dose IV SMX-TMP with IV clindamycin</p> <p>60% Standard of Care</p> <p>Day 7 -transitioned oral SMX/TMP (gentamycin and rifampicin added if cardiac abscess or persistent bacteremia)</p>

SMX-TMP = sulfamethoxazole-trimethoprim

Therapy Interruptions



Oral Had Improved Mortality



Int J Antimicrob Agents. 2019;54(2):143-148.

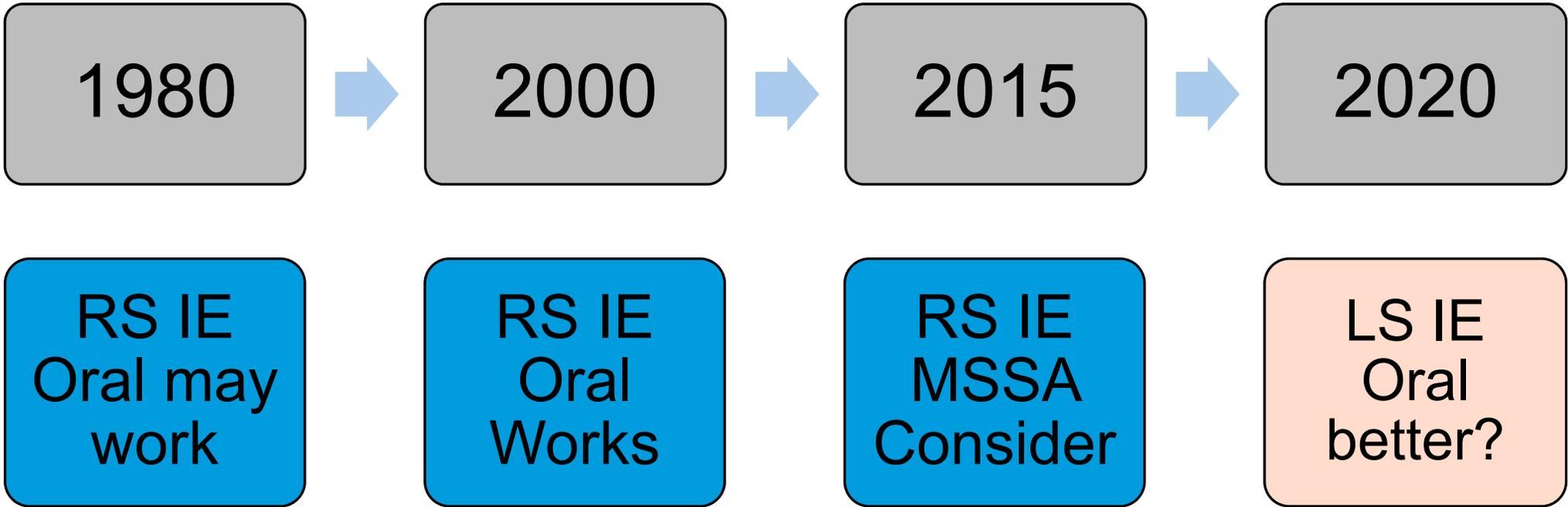
Key Takeaways

● Unequal patient populations

● Varying time periods

● Drug protocol deviation

● Hard to apply results



RS = Right Sided
LS = Left Sided
IE=Infective Endocarditis

POET Trial

Randomized, multicenter, open-label non-inferiority trial

Population:

n=400
Left-sided IE
Native + prosthetic
valves
<2% PWID
Mixed organisms
(No MRSA)

Inclusion:

Clinically improving
Normal GI uptake

Exclusion:

Predetermined low
compliance

Endpoints:

Composite
all-cause mortality,
unplanned cardiac
surgery, clinically
evident embolism,
relapse of
bacteremia

IE=Infective Endocarditis

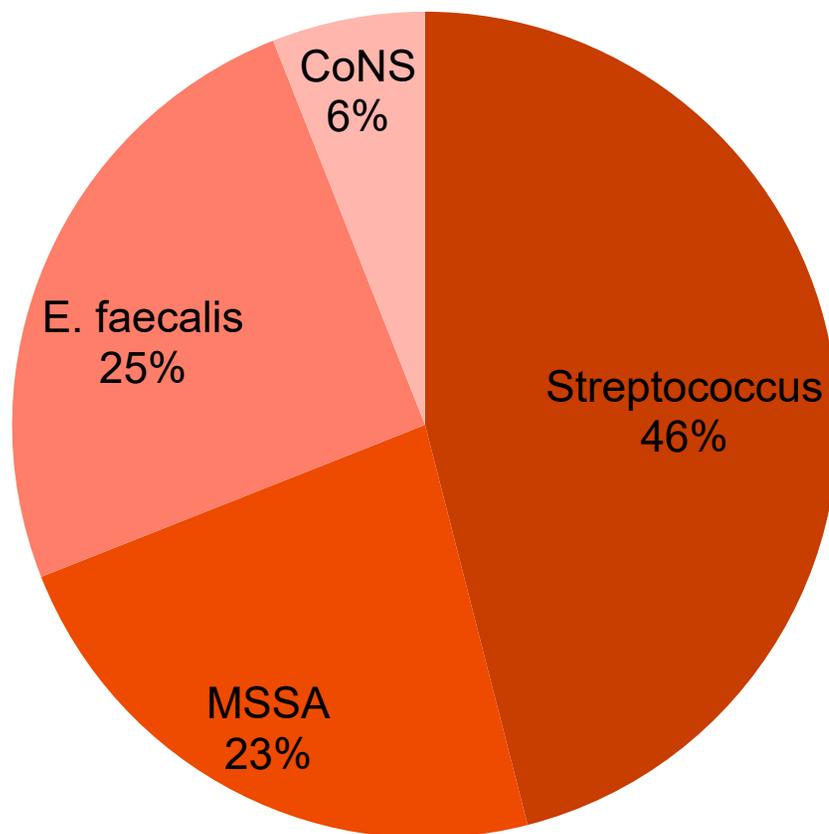
PWID = persons who inject drugs

MRSA = methicillin-resistant staphylococcus aureus

N Engl J Med. 2019;380(5):415-424.

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Mostly Streptococcus (%)



CoNS = coagulase negative staphylococcus
MSSA = methicillin-sensitive S. aureus

Dicloxacillin + rifampicin*

- MSSA

Amoxicillin + rifampicin*

- CoNS, *E. faecalis*, *Strep* sp. PCN MIC < 1 mg/L

Linezolid + rifampicin*

- CoNS, *E. faecalis*, MSSA, *Strep* sp. PCN MIC < 1 mg/L

Moxifloxacin + rifampicin or clindamycin

- *Strep* sp. PCN MIC > 1 mg/L

CoNS = coagulase negative staphylococcus
MSSA = methicillin-sensitive *S. aureus*
MIC = minimum inhibitory concentration
PCN = penicillin

* Or fusidic acid

Oral Non-Inferior

Component	IV Treatment (n= 199)	Oral Treatment (n= 201)	Difference in percent (95% CI)
Composite	9%	12.1%	3.1% (-3.4 to 9.6)
All-cause mortality	13 (6.5)	7 (3.5)	3.0 (-1.4 to 7.7)
Unplanned cardiac surgery	6 (3.0)	6 (3.0)	0 (-3.3 to 3.4)
Embolic event	3 (1.5)	3 (1.5)	0 (-2.4 to 2.4)
Relapse	5 (2.5)	5 (2.5)	0 (-3.1 to 3.1)

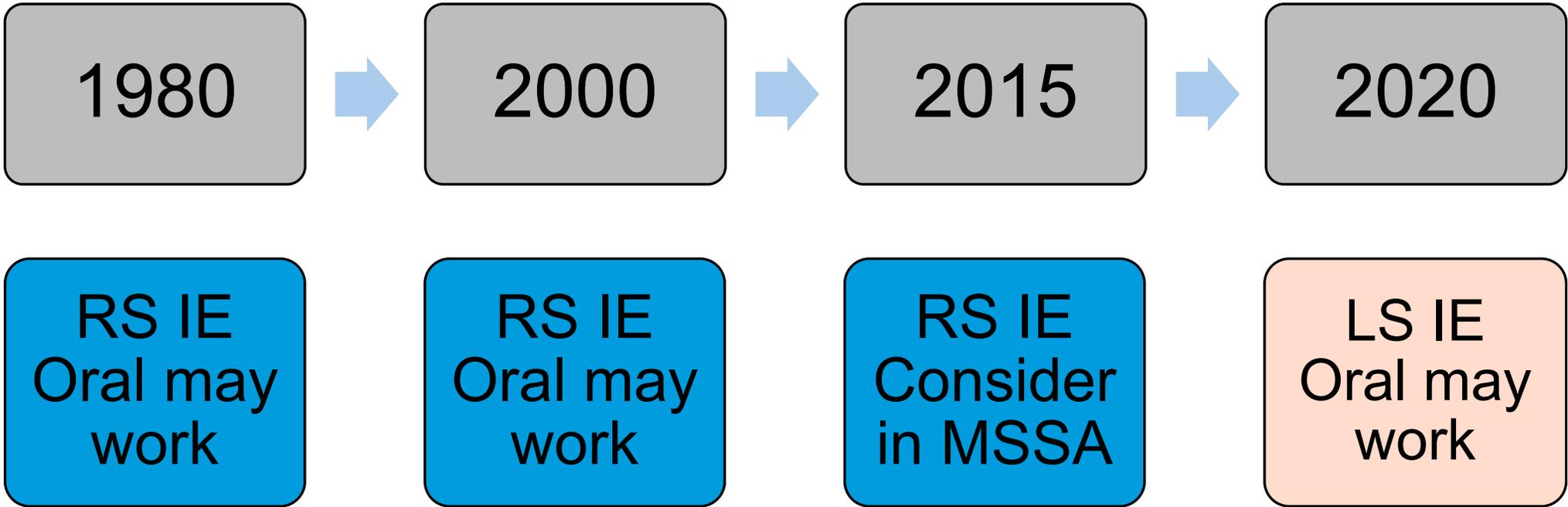
Key Takeaways

- Pre-published trial design
- Only improving clinical picture
- ~25% of patients with *S. aureus*, no MRSA
- Multiple combination regimens

Assessment Question #2

What key patient characteristics differed between studies before and after 2000?

- A. “Side” for endocarditis
- B. Illicit IV drug use
- C. Antibiotic regimens
- D. All of the above



RS = Right Sided
LS = Left Sided
IE=Infective Endocarditis

Summary

Study (n)	Population	Intervention	Outcome	Results
Parker, R.H. (35)	RS IE PWID	Dicloxacillin	Cure rate	100% cure rate
Dworkin, R.J. (14)	RS IE PWID	Ciprofloxacin + rifampicin	Cure rate	100% cure rate
Heldman, A. (44)	RS IE PWID	Ciprofloxacin + rifampicin	Cure rate	95% cure rate
Tissot-Dupont, H. (341)	LS IE <15% PWID	Sulfamethoxazole/ trimethoprim	Mortality	Oral arm had lower mortality and decreased hospital stay
POET Trial (401)	LS IE <2% PWID	Variable	Composite*	Oral non- inferior

RS = Right Sided
 LS = Left Sided
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 PWID = Persons who inject drugs

*Composite all-cause mortality, unplanned cardiac surgery, clinically evident embolism, relapse of bacteremia

Assessment Question #3

Free Text Response:

Name a patient characteristic you feel is important to consider prior to contemplating oral antibiotics for continued treatment of infective endocarditis.

Summary

Older Data	Newer Data
PWID	Low-PWID
Native valves	Mixed valves
Mainly observational	Randomized
Small populations	Larger populations
Dicloxacillin/rifampicin Ciprofloxacin/rifampicin	Dicloxacillin/rifampicin Linezolid/rifampicin SMX/TMP
Feasibility	Non-inferiority

Conclusion

Ideal patient

- PWID leaving AMA
- Native Valve
- Rapid clinical improvement

Ideal organism

- Cultured and susceptible
- Highly susceptible MIC

Ideal drug combo

- Combination therapy
- High oral bioavailability (Ciprofloxacin, linezolid, rifampin, SMZ/TMX, doxycycline)
- Safe for long-term use

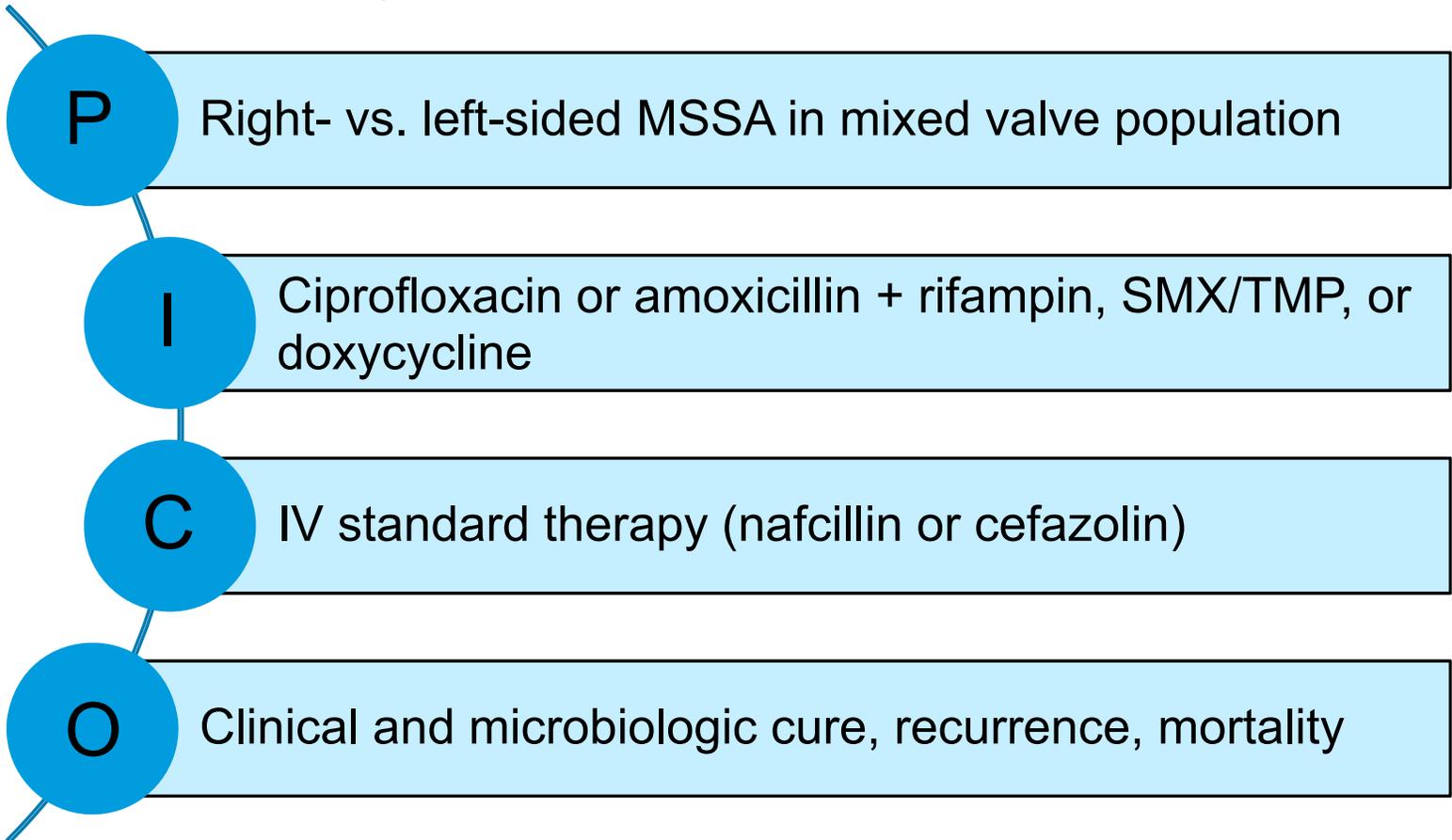
PWID= person who injects drugs

AMA= against medical advice

MIC = minimum inhibitory concentration

SMZ/TMX = sulfamethoxazole-trimethoprim

My Ideal Study



QUESTIONS & ANSWERS

