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BEYOND THE LINE: ORAL AGENTS IN THE TREATMENT OF GRAM-POSITIVE BLOOD STREAM INFECTIONS

A presentation for HealthTrust Members

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OBJECTIVES

01

Recognize commonly used oral antibiotic options during the treatment of gram-positive infections along with strengths and/or limitations of their use

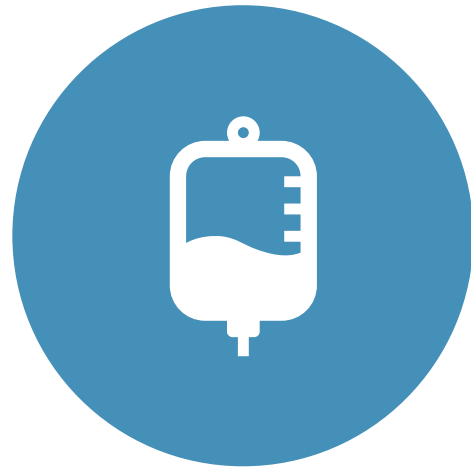
02

Identify patient-specific factors for determining an appropriate candidate for oral antibiotics in the treatment of gram-positive bacteremia

03

Recall evidence-based treatment guidelines utilizing oral antibiotics for the patient with gram-positive bacteremia

WHAT IS BACTEREMIA?



PRESENCE OF BACTERIA
IN THE BLOOD



SOURCE OF INFECTION

COMPLICATED BACTEREMIA

-
- Meningitis
 - Osteomyelitis
 - Septic joint
 - Endocarditis
 - Polymicrobial
 - Lack of source control
 - Persistent bacteremia
 - Catheter-associated bacteremia (without removal or replacement)

HIGH RISK FOR CLINICAL FAILURE

-
- Central venous catheter present at time of bacteremia
 - Prosthetic joint/heart valve
 - Other foreign material
 - History of HIV
 - Bone marrow transplant
 - Intravenous drug use
 - Immunosuppressive medications in the last 21 days

UNCOMPLICATED BACTEREMIA

-
- Exclude endocarditis
 - No implant prosthesis
 - Negative blood cultures at 2-3 days
 - No evidence of metastatic infection
 - Identifiable cause of infection with prompt removal

WHAT IS THE USE OF ORAL AGENTS FOR GRAM-NEGATIVE BACTEREMIA CURRENTLY?

-
- Transition to an oral agent is appropriate after 5-7 days of intravenous antibiotics for uncomplicated bacteremia
 - *E. coli* is the most prevalent gram-negative organism causing bacteremia
 - Fluoroquinolones are the most common oral agent used
 - Evidence suggest 7 days can be an appropriate treatment duration for uncomplicated bacteremia patients

*Staphylococcus
aureus*

*Streptococcus
species*

*Enterococcus
species*

GRAM-POSITIVE BACTERIA

STAPHYLOCOCCUS AUREUS

Common Sources

- Skin and soft tissue
- Intravascular catheters
- Bone and joint infections
- Pneumonia
- Endocarditis

MSSA Agents

- Nafcillin
- Oxacillin
- Cefazolin

MRSA Agents

- Vancomycin
- Daptomycin
- Linezolid

Duration of Treatment

- Uncomplicated: 2 weeks
- Complicated: 4-6 weeks

MSSA: methicillin-susceptible *Staphylococcus aureus*
MRSA: methicillin-resistant *Staphylococcus aureus*

STREPTOCOCCI SPECIES

Streptococci Groups

- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

Common Sources

- Skin and soft tissue
- Urinary tract
- Respiratory tract
- Endocarditis
- Meningitis
- Septic arthritis

Recommended Agents

- Penicillin G
- Nafcillin
- Oxacillin
- Ceftriaxone
- Ampicillin

Treatment Duration

- Uncomplicated: 2 weeks
- Complicated: up to 6 weeks

ENTEROCOCCUS SPECIES

Groups

- *Enterococcus faecalis*
- *Enterococcus faecium*

Common Sources

- Urinary tract
- Gastrointestinal tract
- Intravascular catheters
- Skin and soft tissue
- Meningitis
- Endocarditis

Recommended Agents

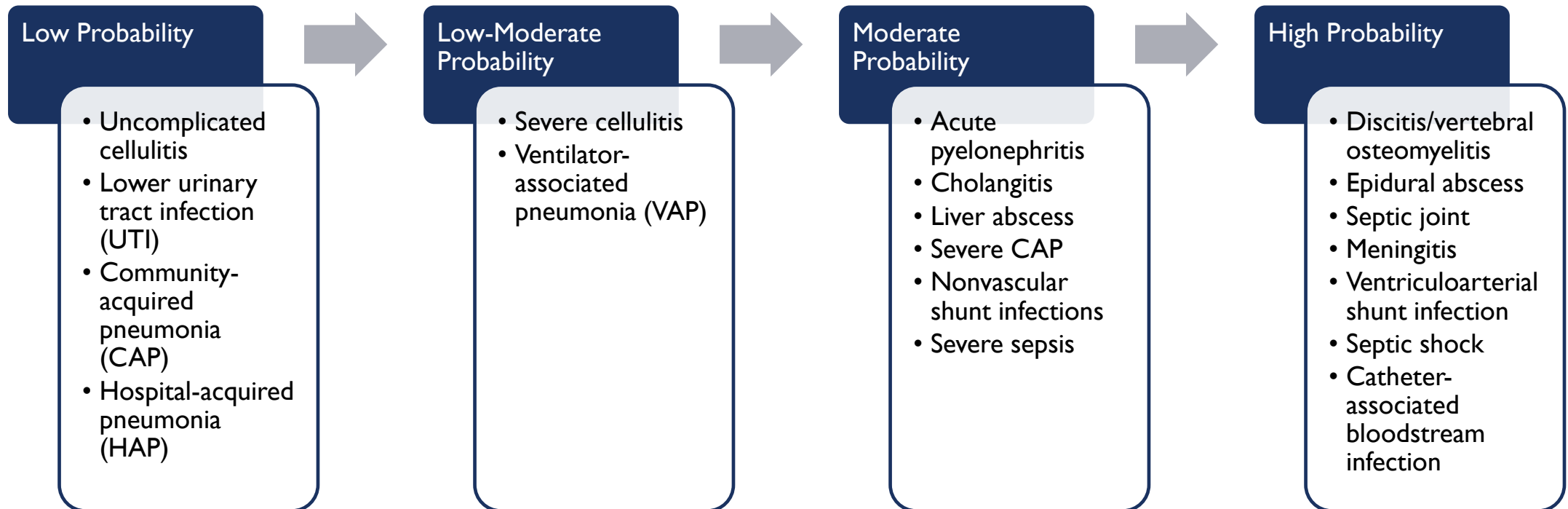
- Penicillin G
- Ampicillin
- Vancomycin
- VRE:
 - Linezolid
 - Daptomycin

Treatment Duration

- Uncomplicated: 5-7 days
- Complicated: up to 6 weeks

VRE: vancomycin-resistant *Enterococcus*

PROBABILITY OF BACTEREMIA FROM COMMON CLINICAL SCENARIOS



ENDOCARDITIS RATES BASED ON ORGANISMS

Staphylococci
species

36% of
cases

Streptococci
species

26% of
cases

Enterococci
species

10% of
cases

CURRENT TREATMENT RECOMMENDATIONS



Tailor therapy to growth from blood cultures and sensitivities



Duration of treatment: 14 days from first negative culture



Intravenous antibiotics are recommended



Emerging evidence of utilizing oral agents, but only for certain patient populations

WHAT IS THE IMPORTANCE OF THIS TOPIC?



BARRIERS TO IV ANTIBIOTICS



EXPANDED PATIENT CARE



STREAMLINED PATIENT CARE



POSITIVE RESULTS ASSOCIATED
WITH ORAL AGENTS USED FOR
GRAM-NEGATIVE BACTEREMIA

WHAT ORAL AGENTS ARE OPTIONS FOR BACTEREMIA TREATMENT?

-
- Amoxicillin
 - Amoxicillin-clavulanate
 - Cefdinir
 - Cefadroxil
 - Cefuroxime
 - Cefpodoxime
 - Cephalexin
 - Clindamycin
 - Levofloxacin
 - Linezolid
 - Sulfamethoxazole-trimethoprim
 - Penicillin VK

WHAT ORAL AGENTS ARE OPTIONS FOR BACTEREMIA TREATMENT?

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- Amoxicillin
 - Amoxicillin-clavulanate
 - Cefdinir
 - Cefadroxil
 - Cefuroxime
 - Cefpodoxime
 - Cephalexin
 - Clindamycin
 - Levofloxacin
 - Linezolid
 - Sulfamethoxazole-trimethoprim
 - Penicillin VK

ORAL AGENTS

Agent	Coverage	Renal Dose Adjustments	Bactericidal or Bacteriostatic	Special Considerations
Amoxicillin	Enterococcus species MSSA Streptococcus species	Yes, CrCl < 30 mL/min	Bactericidal	Penicillin allergies
Amoxicillin-clavulanate	Enterococcus species MSSA Streptococcus species	Yes, CrCl < 30 mL/min	Bactericidal	Penicillin allergies Diarrhea
Cephalexin	MSSA Streptococcus species	Yes, CrCl < 30 mL/min	Bactericidal	
Sulfamethoxazole-trimethoprim	MSSA MRSA Streptococcus species	Yes, CrCl < 30 mL/min	Bactericidal	Sulfa allergies Drink plenty of fluids Thrombocytopenia

ORAL AGENTS, *CONTINUED*

Agent	Coverage	Renal Dose Adjustments	Bactericidal or Bacteriostatic	Special Considerations
Levofloxacin	Enterococcus species MSSA Streptococcus species	Yes, CrCl < 50 mL/min	Bactericidal	QTc prolongation
Linezolid	Enterococcus species VRE MSSA MRSA Streptococcus species	No	Bacteriostatic	Thrombocytopenia Pancytopenia Serotonin syndrome
Clindamycin	MSSA MRSA Streptococcus species	No	Bacteriostatic	<i>C. difficile</i> infection

KNOWLEDGE CHECK #1

Which of the following antibiotics would not be considered for use in gram-positive bacteremia?

- A. Sulfamethoxazole-trimethoprim
- B. Linezolid
- C. Vancomycin PO
- D. Levofloxacin

KNOWLEDGE CHECK #1: CORRECT RESPONSE

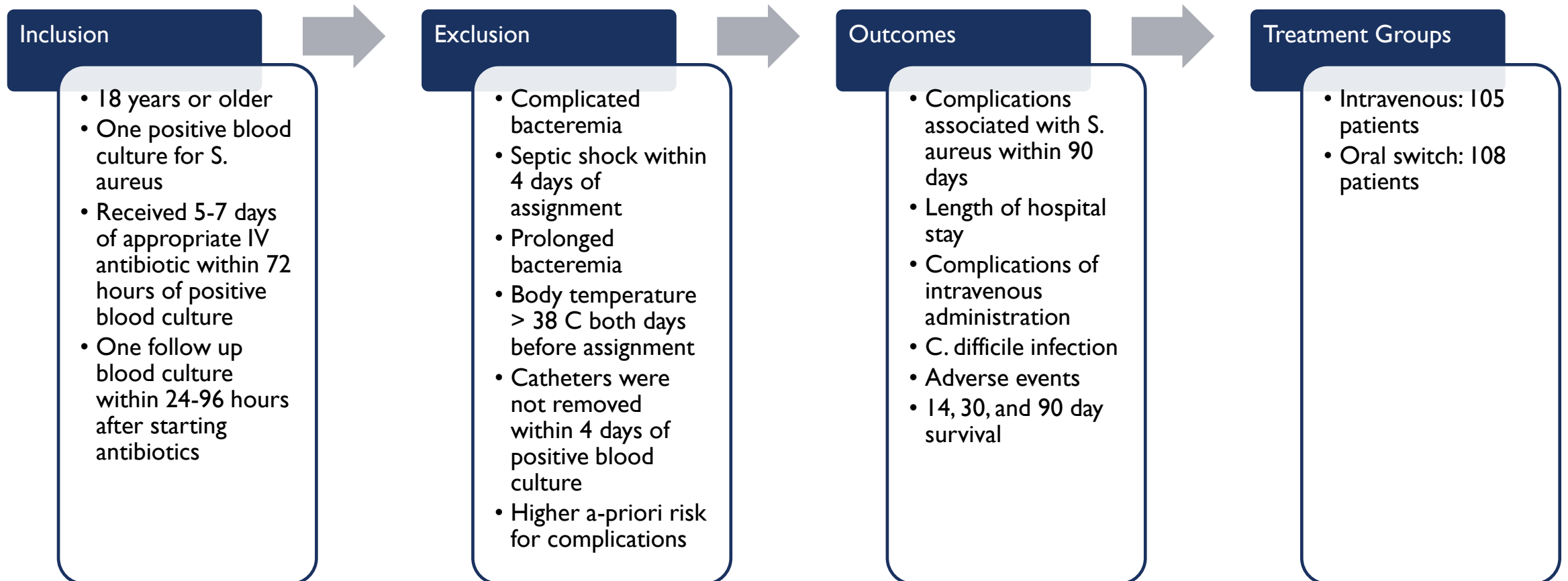
Which of the following antibiotics would not be considered for use in gram-positive bacteremia?

- A. Sulfamethoxazole-trimethoprim
- B. Linezolid
- C. **Vancomycin PO**
- D. Levofloxacin



WHAT DOES THE LITERATURE SAY?

Efficacy & Safety of an Early Switch in Low-Risk *Staphylococcus* Bloodstream Infection (SABATO)



Efficacy & Safety of an Early Switch in Low-Risk *Staphylococcus* Bloodstream Infection (SABATO), *continued*

IV Agents

- Cefazolin
- Flucloxacillin
- Cloxacillin
- Vancomycin
- Daptomycin

Oral Agents

- Sulfamethoxazole-trimethoprim
- Clindamycin
- Linezolid

Efficacy & Safety of an Early Switch in Low-Risk *Staphylococcus* Bloodstream Infection (SABATO), *continued*

Complications related to *S. aureus* bacteremia

- IV Group: 12%
- PO Group: 13%
- P-Value: 0.013

Length of Stay

- IV Group: 16 days
- PO Group: 12 days
- P-value: 0.043

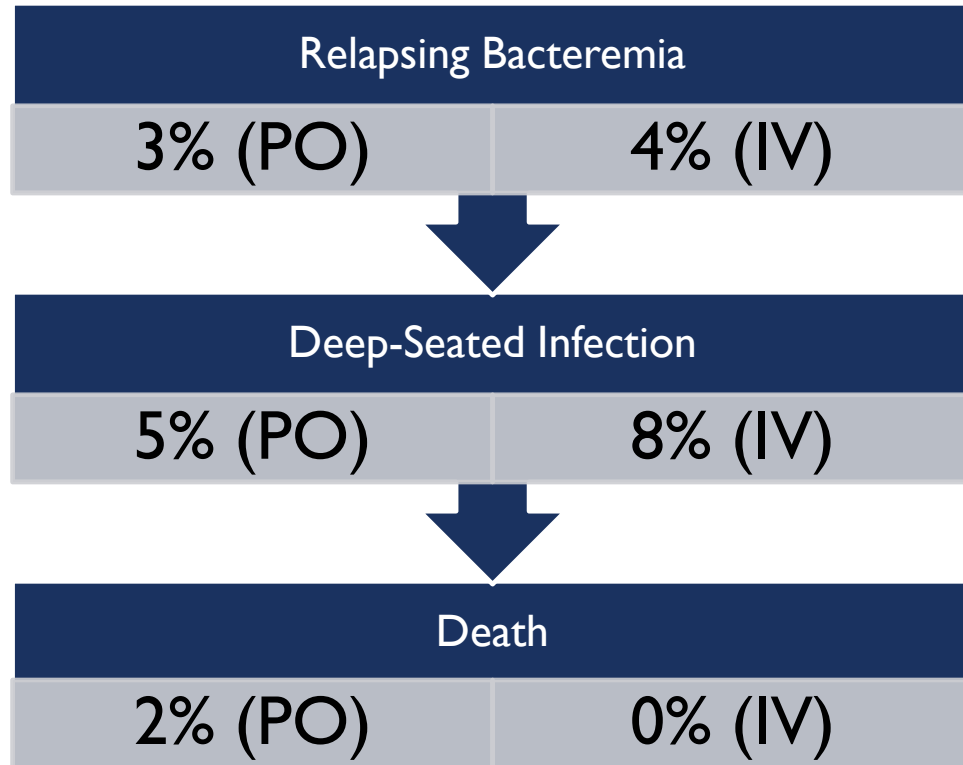
C. difficile infection

- 2% in both groups

Adverse Events

- IV Group: 41%
- 26% serious
- PO Group: 49%
- 34% serious

Efficacy & Safety of an Early Switch in Low-Risk *Staphylococcus* Bloodstream Infection (SABATO), *continued*



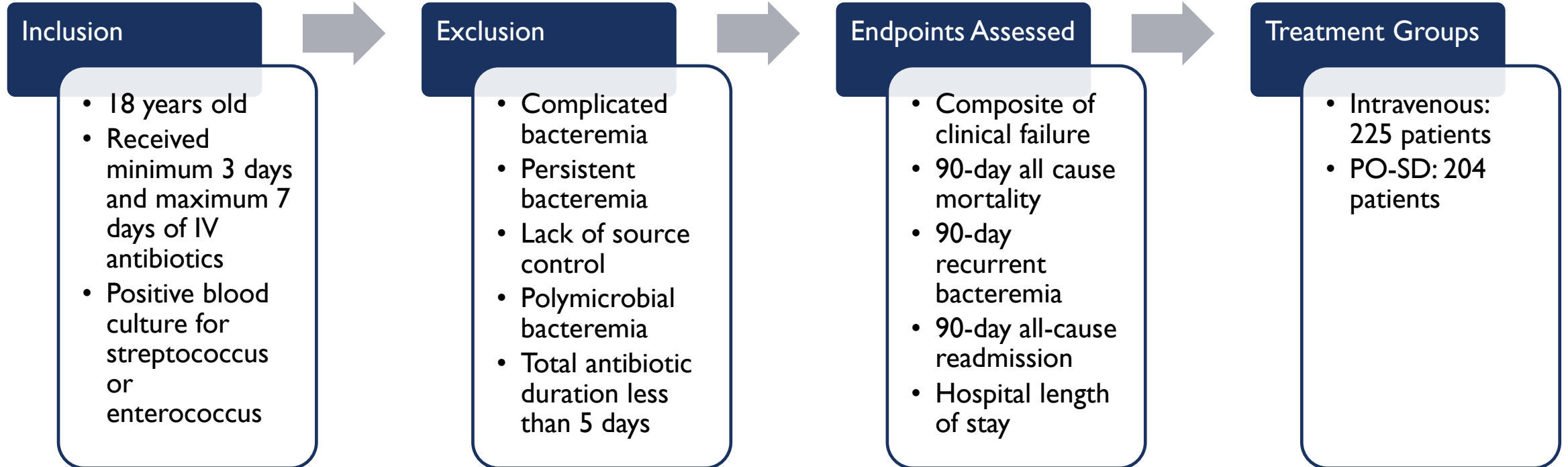
PO Group Safety

- Drug related – 3%
- Infections – 22%
- Respiratory related – 4%
- Cardiac related – 9%
- General disorders – 10%

IV Group Safety

- Drug Related – 0%
- Infections – 17%
- Respiratory related – 10%
- Cardiac related – 5%
- General disorders – 4%

Comparison of Intravenous with Step-Down to Oral Antibiotic Treatment Course for *Streptococcus* & *Enterococcus* Bloodstream Infections



Comparison of Intravenous with Step-Down to Oral Antibiotic Treatment Course for *Streptococcus* & *Enterococcus* Bloodstream Infections, *cont.*

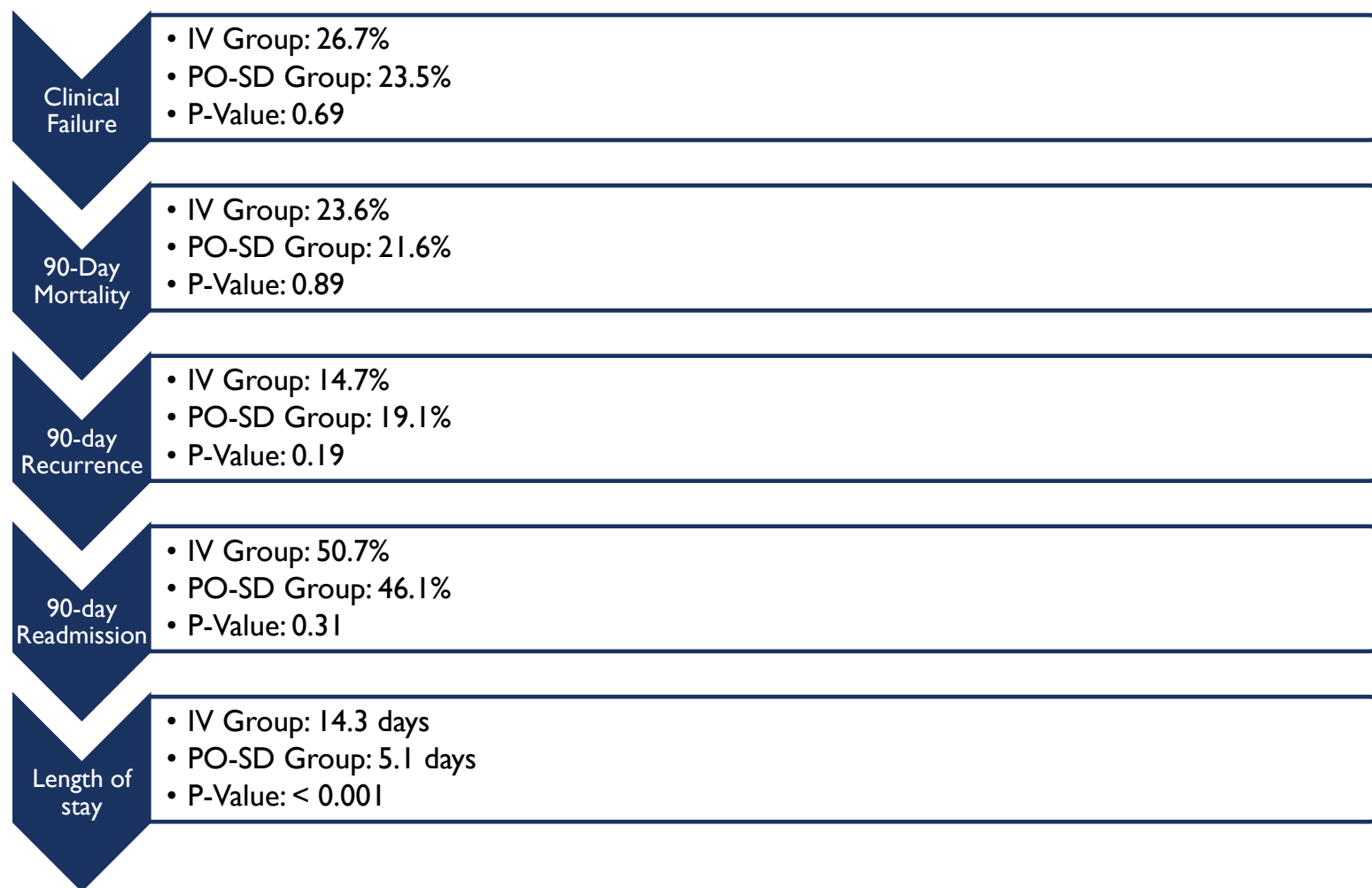
IV Agents

- Ceftriaxone
- Ampicillin
- Piperacillin-tazobactam
- Vancomycin
- Penicillin G
- Cefazolin

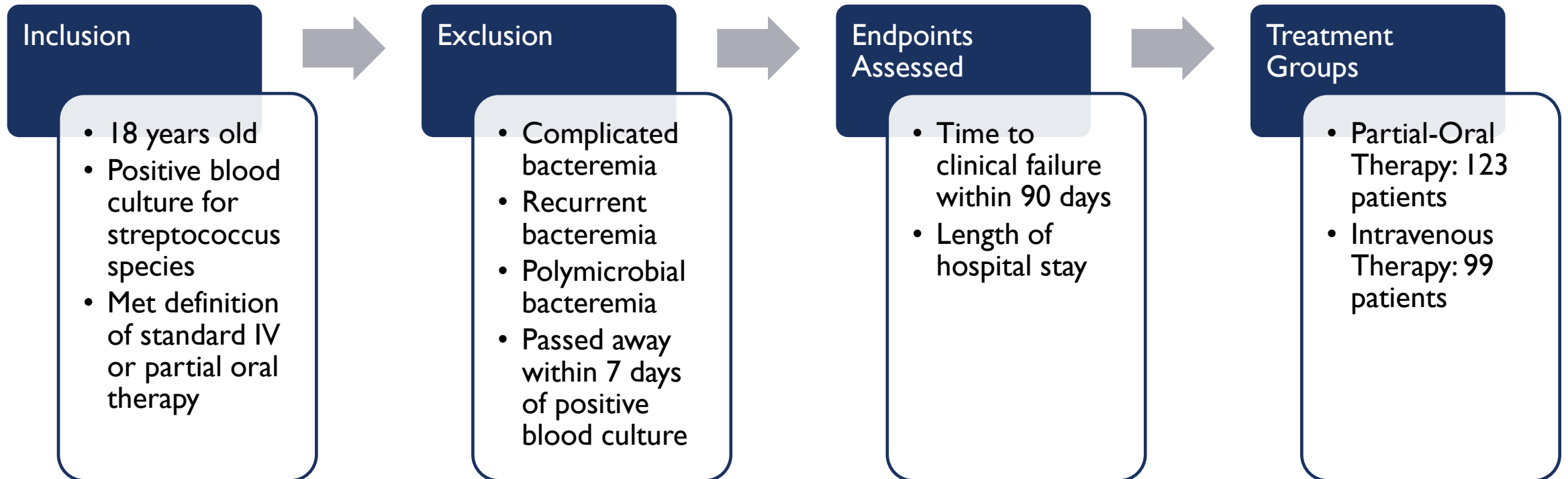
Oral Agents

- High-dose amoxicillin
- Amoxicillin-clavulanate
- Low-dose amoxicillin
- Linezolid
- Levofloxacin
- Cephalexin

Comparison of Intravenous with Step-Down to Oral Antibiotic Treatment Course for *Streptococcus* & *Enterococcus* Bloodstream Infections, *cont.*



Intravenous vs. Partial Oral Antibiotic Therapy in the Treatment of Uncomplicated Bloodstream Infection Due to *Streptococcus* species



Intravenous vs. Partial Oral Antibiotic Therapy in the Treatment of Uncomplicated Bloodstream Infection Due to *Streptococcus* species

Sources

- Skin and soft tissue
- Respiratory tract
- Unknown

Oral Agents Utilized

- Beta-lactams
- Fluoroquinolones
- Clindamycin
- Sulfamethoxazole-trimethoprim
- Linezolid

Organisms

- Beta-hemolytic streptococcus
- *Streptococcus pneumoniae*
- Viridans group streptococcus

Clinical Outcomes

- Treatment failure: 12% vs 4.4% (IV vs PO), P-value = 0.25

Intravenous vs. Partial Oral Antibiotic Therapy in the Treatment of Uncomplicated Bloodstream Infection Due to *Streptococcus* species

Age (per decade)

Residence at skilled nursing facility

Diabetes

Cancer

End-stage renal disease

Recent hospitalization

Respiratory source infection

LITERATURE SUMMARY – INCLUSION CRITERIA

18 years or
older

Uncomplicated
bacteremia

Received IV
antibiotic for
certain duration

Positive blood
cultures

LITERATURE SUMMARY – DURATION OF THERAPIES

Staphylococcus aureus	Streptococcus species	Enterococcus species
IV Antibiotics: 5-7 days Total Duration: 14 days	IV Antibiotics: 3-6 days, median 4 days Total Duration: 14 days	IV Antibiotics: 3-9 days Total Duration: 13-14 days

Durations are from the first negative culture

LITERATURE SUMMARY – ORAL AGENTS UTILIZED

Beta-lactams

- Amoxicillin
- Amoxicillin-clavulanate
- Cephalexin
- Sulfamethoxazole-trimethoprim

Fluoroquinolones

- Levofloxacin

Others

- Linezolid
- Clindamycin

LITERATURE SUMMARY - RESULTS

-
- No difference in outcomes
 - Oral agents were not associated with increased clinical failure, 90-day recurrence, 90-day mortality, or 90-day readmissions
 - Transitioning to oral agents was associated with decreased lengths of hospital stays

CONCLUSIONS FROM LITERATURE

Uncomplicated bacteremia can be appropriate to transition to oral agent

Account for limitations in studies

Higher clinical failure in IV groups

PATIENT FACTORS TO CONSIDER

-
- Allergies
 - Renal function
 - Culture sensitivities/susceptibilities
 - Past medical history
 - Complicated versus uncomplicated

KNOWLEDGE CHECK #2

Which patient would be an appropriate candidate to receive an oral agent for treatment of gram-positive bacteremia?

- A. Uncomplicated bacteremia
- B. Received 7 days of IV treatment
- C. Infective endocarditis
- D. MRSA infection
- E. A & B

KNOWLEDGE CHECK #2: CORRECT RESPONSE

Which patient would be an appropriate candidate to receive an oral agent for treatment of gram-positive bacteremia?

- A. Uncomplicated bacteremia
- B. Received 7 days of IV treatment
- C. Infective endocarditis
- D. MRSA infection
- E. **A & B**

KNOWLEDGE CHECK #3

A 58 year-old is admitted with a positive blood culture for *Staphylococcus aureus*. He has been receiving intravenous vancomycin for 7 days and has had a negative blood culture for the last 2 days. What would be an appropriate evidence-based regimen to facilitate an optimal outcome for this patient's gram-positive bacteremia?

Sensitivities are below

Oxacillin	S
Ceftriaxone	S
Cefazolin	S
Sulfamethoxazole-trimethoprim	S
Daptomycin	S
Vancomycin	S

- A. Continue vancomycin for another 12 days (total 14 days of treatment after first negative culture)
- B. Change to daptomycin with a duration of 14 days (total 16 days of treatment after first negative culture)
- C. Change to sulfamethoxazole-trimethoprim DS (2 tabs BID) for 12 days (total 14 days of treatment after first negative culture)
- D. Discontinue antibiotics as they are no longer indicated

KNOWLEDGE CHECK #3: CORRECT RESPONSE

A 58 year-old is admitted with a positive blood culture for *Staphylococcus aureus*. He has been receiving intravenous vancomycin for 7 days and has had a negative blood culture for the last 2 days. What would be an appropriate evidence-based regimen to facilitate an optimal outcome for this patient's gram-positive bacteremia?

Sensitivities are below

Oxacillin	S
Ceftriaxone	S
Cefazolin	S
Sulfamethoxazole-trimethoprim	S
Daptomycin	S
Vancomycin	S

- A. Continue vancomycin for another 12 days (total 14 days of treatment after first negative culture)
- B. Change to daptomycin with a duration of 14 days (total 16 days of treatment after first negative culture)
- C. Change to sulfamethoxazole-trimethoprim DS (2 tabs BID) for 12 days (total 14 days of treatment after first negative culture)**
- D. Discontinue antibiotics as they are no longer indicated

OVERALL CONCLUSION

-
- Who is considered an appropriate candidate for an oral agent?
 - When is it appropriate to transition to an oral agent?
 - What factors should be considered when choosing an oral agent?
 - Research is evolving

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THANK YOU

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