Antibiotics in Out-Patient Setting

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Disclosures

- There are no relevant financial relationships with commercial interests to disclose

Antibiotics in Out-Patient Setting

- Respiratory Tract Infections
- Skin and Soft Tissue Infections
- Urinary Tract Infections
- Gastrointestinal Infections
- Central Nervous System Infections
- Newly Approved Out-Patient Antibiotics

Respiratory Tract Infections

Case History: Pharyngitis

- A 26-year old man is diagnosed with group A streptococcal pharyngitis. What is the likelihood that this organism is resistant to penicillin?

1. 0-5%?
2. 5-10?
3. 20-30%
4. 40-50%

Group A Streptococcal Pharyngitis

- “Penicillin-resistant group A streptococcus has never been documented.”

Shulman ST, et al. Clin Infect Dis 2012;55:1279-82.

Group A Streptococcal Pharyngitis
2012 IDSA Treatment Guidelines for Adults

- Oral: Penicillin V (or Amoxicillin)
  - 250 mg qid x 10d
  - 500 mg bid x 10d
- Parenteral: Benzathine Penicillin G
  - 1.2 x 10^6 units IM x 1
- Penicillin-Allergic Patients
  - Cephalexin
  - Cephadroxil
  - Clindamycin
  - Azithromycin
  - Clarithromycin

Source: Shulman ST, et al. Clin Infect Dis 2012;55:1279-82.

Case History: Bacterial Sinusitis

- A 22-year old woman has 11 days of nasal congestion and 3 days of purulent nasal discharge and facial pain. She is diagnosed with sinusitis.
- What treatment would you recommend?

1. Trimethoprim-Sulfamethoxazole x 7 days
2. Ciprofloxacin x 7 days
3. Amoxicillin-clavulanic acid x 7 days
4. Amoxicillin x 10 days

Acute Bacterial Rhinosinusitis
Most Common Pathogens

- *Streptococcus pneumoniae*
- *Moraxella catarrhalis*
- *Haemophilus influenzae*

Most Common

- *Staphylococcus aureus*
- *Streptococcus pyogenes*

Less Common

Acute Bacterial Rhinosinusitis
2012 IDSA Treatment Guidelines for Adults

- **Preferred Initial Therapy**
  - Amoxicillin-clavulanic acid x 5-7 days
- **Intranasal Corticosteroids**
  - Recommended—primarily if h/o allergic rhinitis
- **Intranasal Saline Irrigation**
  - Recommended—physiologic or hypertonic
- **Decongestants (Topical or Oral) or Antihistamines**
  - NOT recommended

Source: Chow AW, et al. Clin Infect Dis 2012;54:e72-e112.

Case History: CAP

- A healthy 48-year-old man is diagnosed with community-acquired pneumonia. He is stable and you plan to treat him as an out-patient. He has no allergies.

- Which antibiotic is recommended for this infection?

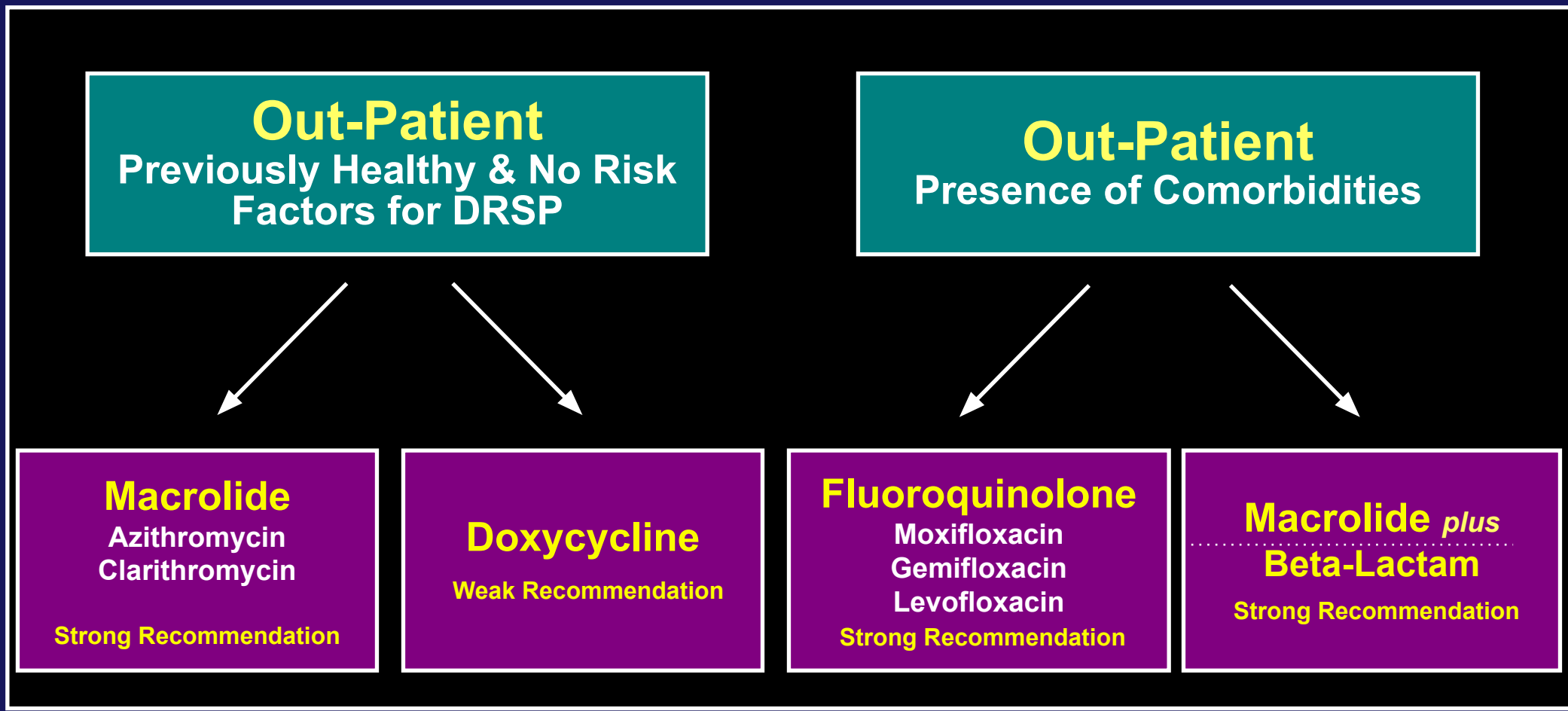
1. Azithromycin
2. Ciprofloxacin
3. Amoxicillin-clavulanic acid
4. Trimethoprim-sulfamethoxazole

Community-Acquired Pneumonia
Most Common Pathogens

- *Streptococcus pneumoniae*
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Haemophilus influenzae*

New CAP Guidelines Projected Fall 2019

Community Acquired Pneumonia
2007 IDSA/ATS Treatment Guidelines for Adults



Source: Mandell LA et al. Clin Infect Dis. 2007;44:S27-42.

Skin and Soft Tissue

Case History

- Which one of the following is true regarding impetigo?

1. Penicillin is the optimal oral therapy
2. Group A Streptococcus alone causes >90% of cases
3. Patients usually have little or no systemic toxicity
4. If localized, Mupirocin is effective therapy

Treatment of Impetigo
2014 IDSA SSTI Guidelines

- **Topical (for limited number of lesions): 7-day Rx**
  - Mupirocin ointment bid x 7d
  - Retapamulin ointment x 7d

- **Oral: 7-day Rx**
  - Dicloxacillin
  - Cephalexin
  - Erythromycin
  - Clindamycin
  - Amoxicillin-CA

Source: Stevens DL, et al. Clin Infect Dis. 2014;59:e10-52.

Skin Lesions: Ecthyma

Treatment of Ecthyma
IDSA 2014 SSTI Guidelines

- **Empiric Therapy**
  - Cephalexin x 7d
  - Dicloxacillin x 7d
- **Suspected or Confirmed MRSA**
  - Doxycycline
  - Clindamycin
  - TMP-SMX

Source: Stevens DL, et al. Clin Infect Dis. 2014;59:e10-52.

MRSA SSTI

2010 IDSA Practice Guidelines
Therapy for CA-MRSA Skin & Soft Tissue Infection

- Simple Abscess or Boil
  - Incision and Drainage
- Complicated Abscess
  - Incision and drainage + antimicrobial therapy

Source: Liu C, et al. Clin Infect Dis. 2011:52:1-38.

2010 IDSA Practice Guidelines
Therapy for CA-MRSA Skin & Soft Tissue Infection

- Complicated Abscess
  - Severe or extensive disease or rapid progression of cellulitis
  - Signs and symptoms of systemic illness
  - Associated comorbidities or immunosuppression
  - Extremes of age
  - Abscess in area difficult to drain (eg, face, hand, genitalia)
  - Associated septic phlebitis
  - Lack of response to incision and drainage alone

Source: Liu C, et al. Clin Infect Dis. 2011:52:1-38.

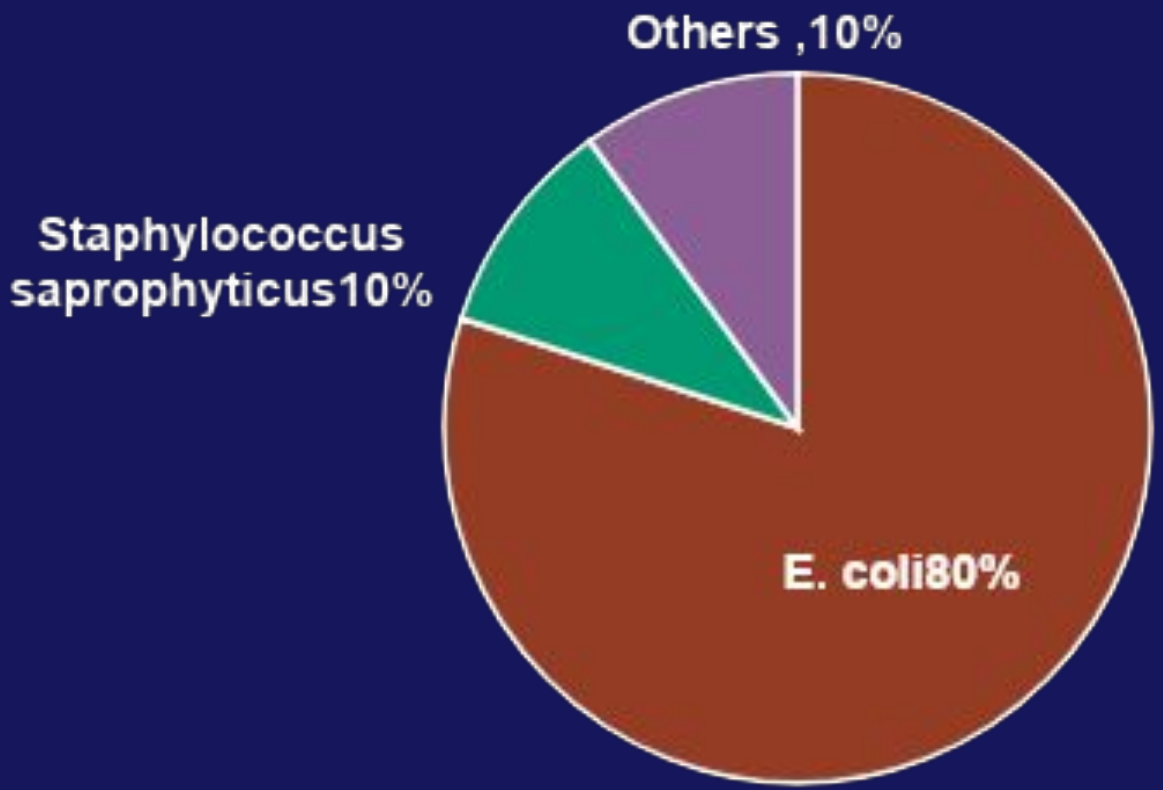
2010 IDSA Practice Guidelines
Therapy for CA-MRSA Skin & Soft Tissue Infection

- **Empiric Therapy for Out-Patient Management**
  - TMP-SMX: 1-2 DS tabs PO BID
  - Clindamycin: 300-450 mg PO TID
  - Doxycycline: 100 mg PO BID
  - Minocycline: 200 mg x1, then 100 mg PO BID
  - Linezolid: 600 mg PO BID
- **If Also Covering for Group A Streptococcus**
  - TMP-SMX + Amoxicillin: 500 mg PO TID
  - Clindamycin
  - Doxycycline/Minocycline + Amoxicillin: 500 mg PO TID
  - Linezolid

Source: Liu C, et al. Clin Infect Dis. 2011:52:1-38.

Urinary Tract Infections

Uncomplicated Cystitis in Women

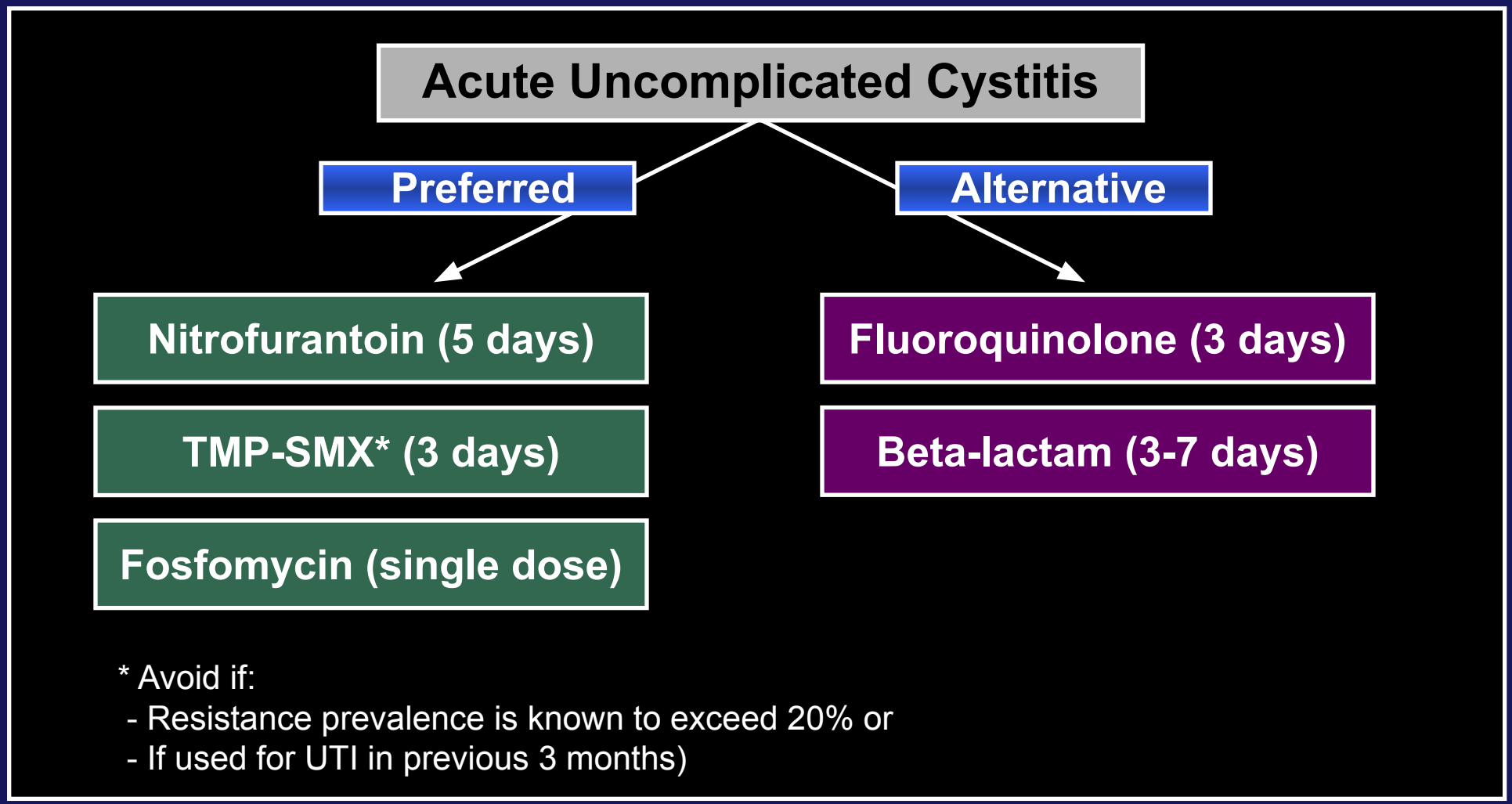


Case History: UTI

- A 31-year-old woman with no major medical problems is seen in the clinic with urinary urgency, frequency, and dysuria. A urine dipstick is positive for leukocyte esterase. She has had one UTI about 3 years ago and is not pregnant? She has no allergies. Assume resistance to TMP-SMX in the community is <15%.
- **Which ONE of the following is considered a preferred therapy according the 2011 IDSA Guidelines?**

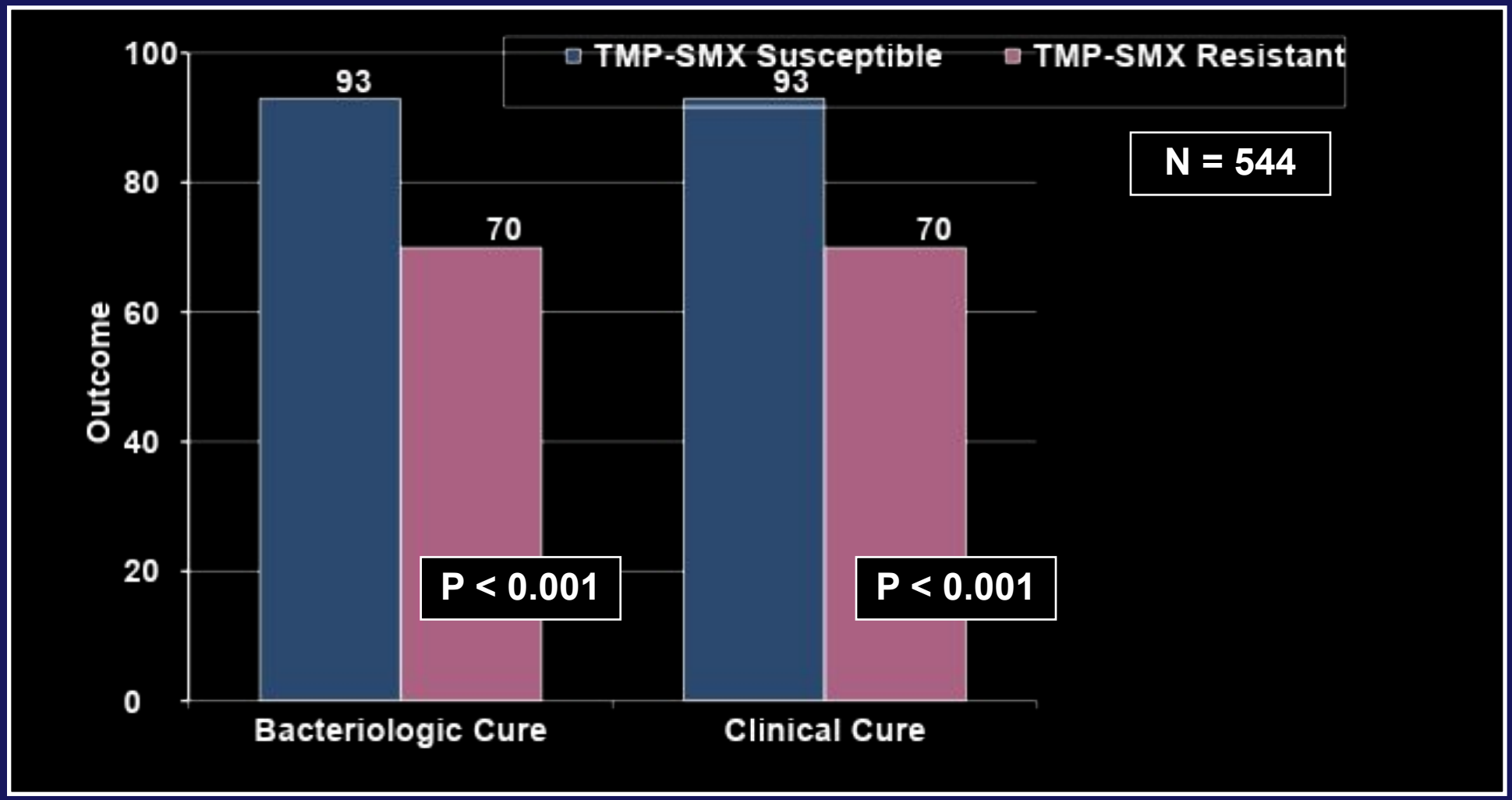
1. TMP-SMX single dose
2. Levofloxacin x single dose therapy
3. Nitrofurantoin x 5d

UTI Therapy (Uncomplicated Cystitis)
2011 IDSA Guidelines



From: Gupta K, et al. Clin Infect Dis 2011:52:e103-e120.

Uncomplicated UTIs in Young Women
Response Related to TMP-SMX Resistance



From: Raz R, et al. Clin Infect Dis 2002;34:1165-9.

Out-Patient Treatment of Pyelonephritis
2011 IDSA Guidelines

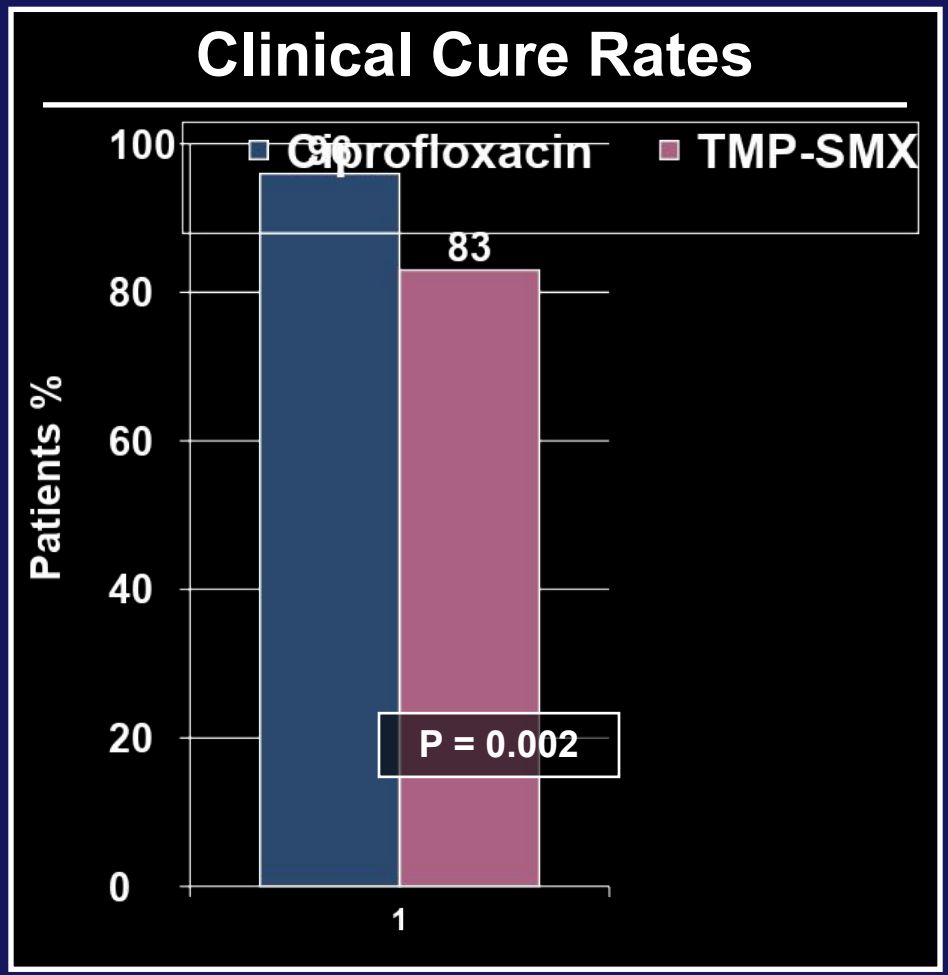
- Obtain Urine Cultures
- Therapy
  - Ciprofloxacin: 500 mg BID x 7 days
  - Levofloxacin 750 mg QD x 5 days
  - TMP-SMX x 14 days IF organism known susceptible
- Consider One Initial IV Dose
  - Ceftriaxone
  - Fluoroquinolone

Pyelonephritis: Ciprofloxacin vs TMP-SMX

Study Design

- Methods
  - N = 255 women
  - Acute pyelonephritis
- Regimens
  - *Ciprofloxacin: 500 mg bid x 7d
  - ^TMP/SMX: 160/800 bid x 14d

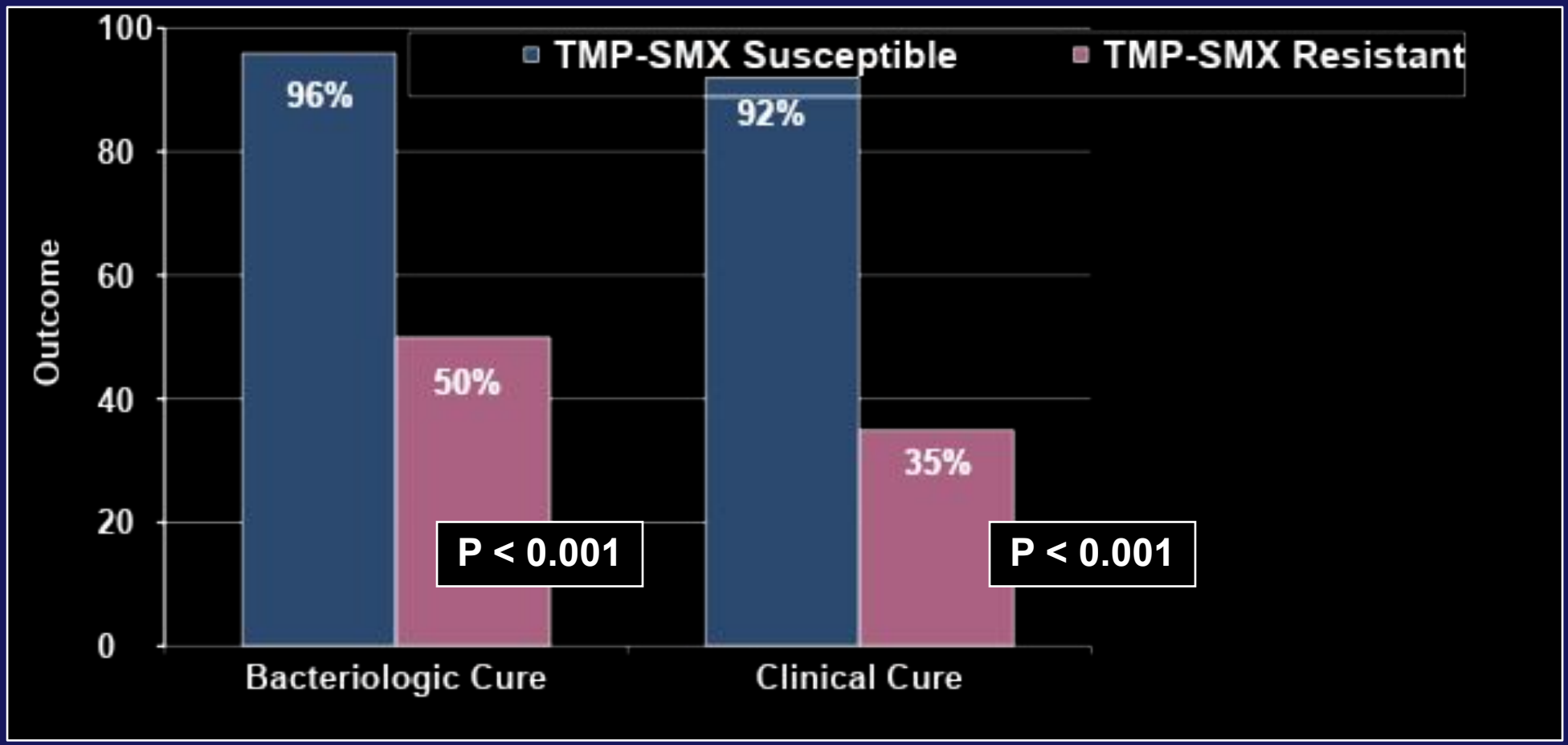
*** +/- 1 dose IV Ciprofloxacin**
^ +/- 1 dose IV Ceftriaxone



From: Talan D, et al. JAMA 2000;283:1583-90.

Pyelonephritis: Ciprofloxacin vs TMP-SMX

Response Related to TMP-SMX Resistance

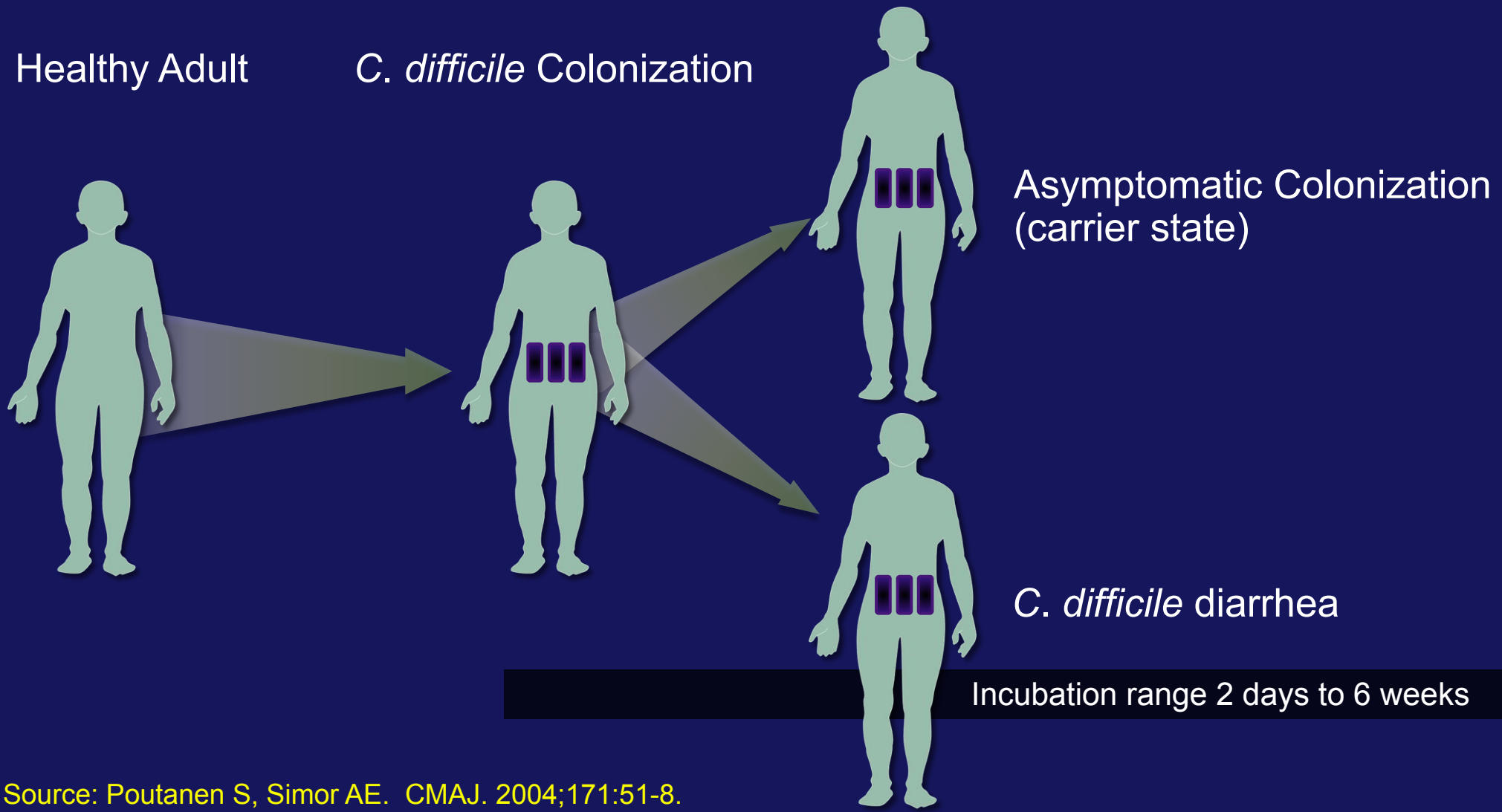


From: Talan D et al. JAMA 2000;283:1583-90.

Gastrointestinal Infections

Clostridium *difficile*-Associated Diarrhea

Pathogeneis



Source: Poutanen S, Simor AE. CMAJ. 2004;171:51-8.

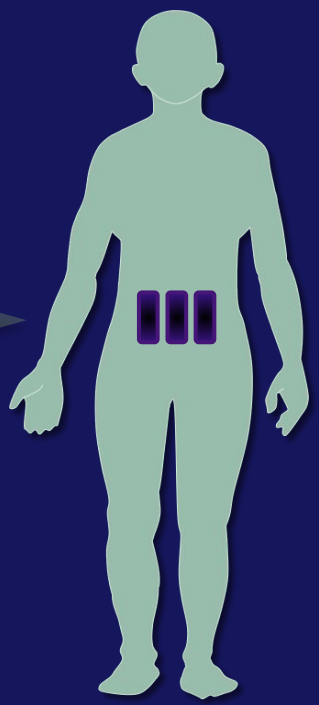
Clostridium difficile-Associated Diarrhea
Pathogeneis

Healthy Adult

Risk Factors

- Antibiotics
- Prolonged hospital stay
- Age > 65
- Severe Illness
- GI Surgery
- Nasogastric tube
- Antacids
- Stool softeners

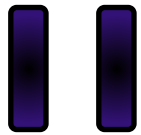
C. difficile Colonization



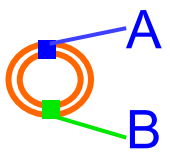
Clostridium difficile Associated Diarrhea
Diagnostic Tests

- Stool culture for *C. difficile*
  - Most sensitive, but labor intensive and slow
  - High false-positive rate (culture nontoxigenic strains)

- Antigen Detection
  - Detects presence of *C. difficile* (not toxin)

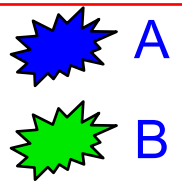


- Toxin Genes: Molecular Tests (PCR)
  - Rapid detection of genes encoding Toxins
  - High sensitivity and specificity



- Toxin Detection: Tissue culture cytotoxic assay
  - "Gold Standard" but high cost and takes >48h

- Toxin Detection: Enzyme immunoassay
  - Detects toxins A and B



Case History: Hospitalized Patient with Diarrhea

- A 41-year-old man is treated for a tooth abscess with Clindamycin and 4 days after finishing the course of antibiotics he develops cramping and watery diarrhea. The patient's vital signs are normal; Serum Cr = 1.1, and WBC = 10,600. The *C. difficile* PCR toxin is positive. This is the first episode of *C. difficile* infection in this patient).

- What do you recommend for treatment in this patient based on 2017 IDSA/SHEA guidelines for adults?

1. Oral Metronidazole
2. Oral Vancomycin

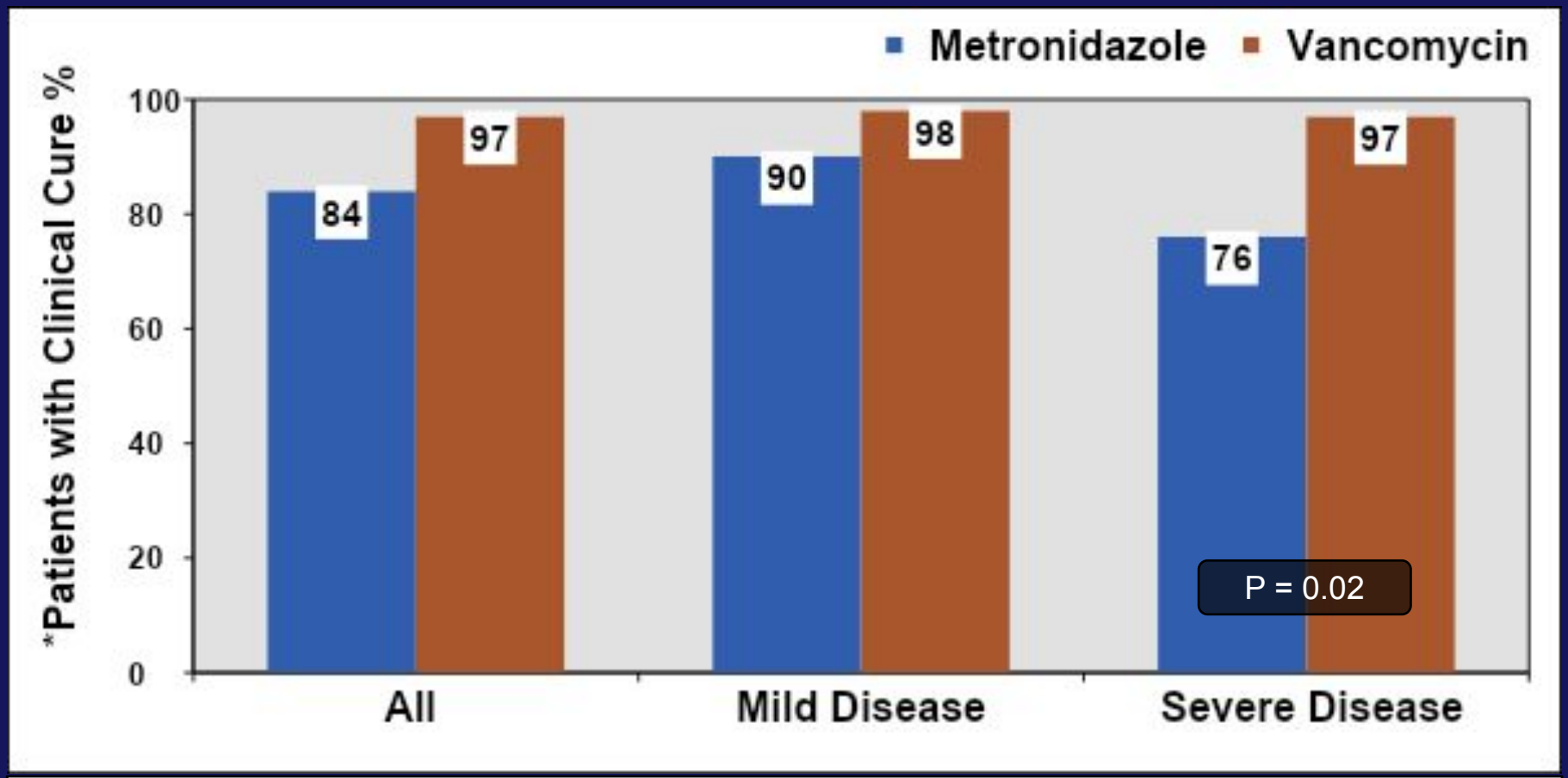
Clostridium difficile

2017 SHEA and IDSA Clinical Practice Guidelines

Severity of Disease	Recommended Therapy: 1st Episode for Adults
Mild-moderate WBC ≤15,000 AND Creatinine <1.5x baseline	**Preferred** **Vancomycin:** 125 mg 4 times daily x 10 days *or* **Fidaxomicin:** 200 mg twice daily x 10 days
	Alternative **Metronidazole**: 500 mg PO 3 times daily x 10 days

Source: McDonald LC, et al. Clin Infect Dis. 2018;66:e1-e48.

Clostridium difficile : Metronidazole vs Vancomycin
Results



*Cure = resolution of diarrhea by day 6 of treatment and negative *C. difficile* toxin A at days 6 and 10

Source: Zar FA, et al. Clin Infect Dis. 2007;45:302-7.

Clostridium difficile

2017 SHEA and IDSA Clinical Practice Guidelines

Severity of Disease	Recommended Therapy: 1st Episode for Adults
Severe WBC >15,000 *or* Creatinine ≥1.5x baseline	**Preferred** **Vancomycin:** 125 mg 4 times daily x 10 days *or* **Fidaxomicin:** 200 mg twice daily x 10 days

Source: McDonald LC, et al. Clin Infect Dis. 2018;66:e1-e48.

Clostridium difficile

2017 SHEA and IDSA Clinical Practice Guidelines

Severity of Disease	Recommended Therapy: 1st Episode for Adults
Fulminant Hypotension *or* Shock *or* Ileus *or* Megacolon	**Preferred** **Vancomycin:** 500 mg 4 times daily by mouth or nasogastric tube (consider rectal instillation with ileus) *plus* **Metronidazole:** 500 mg every 8 hours IV daily

Source: McDonald LC, et al. Clin Infect Dis. 2018;66:e1-e48.

Central Nervous System Infections

Case History: Meningitis

- A 57-year-old woman is seen in the ER with headache and fever and confusion. Emergent CT is normal and LP shows 8,600 WBCs (85% polys) and low glucose.

  For empiric IV antibiotics, you would recommend:

  1. Ceftriaxone
  2. Ceftriaxone + Ampicillin
  3. Ceftriaxone + Vancomycin
  4. Ceftriaxone + Vancomycin + Ampicillin

Empiric Therapy for Bacterial Meningitis
2004 IDSA Treatment Guidelines for Adults

Age 18-50

Ceftriaxone[#]
+
Vancomycin^
+
Dexamethasone

Age > 50

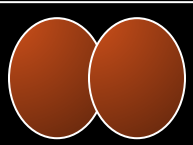
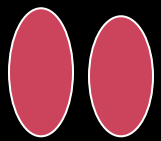
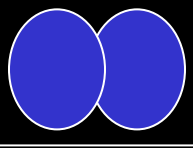
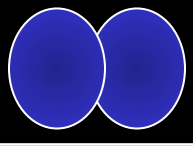
Ceftriaxone[#]
+
Vancomycin^
+
Ampicillin
+
Dexamethasone

[#]Cefotaxime can be substituted for Ceftriaxone

^ Vancomycin trough should be maintained at 15-20 ug/ml

Source: Tunkel AR, et al. Clin Infect Dis. 2004:39:1267-84.

Therapy for Bacterial Meningitis in Adults

Ceftriaxone		***Neisseria meningitidis***
		***Haemophilus influenzae***
		***Streptococcus pneumoniae***
Vancomcycin		***Drug-Resistant Streptococcus pneumoniae***
Ampicillin		***Listeria monocytogenes***

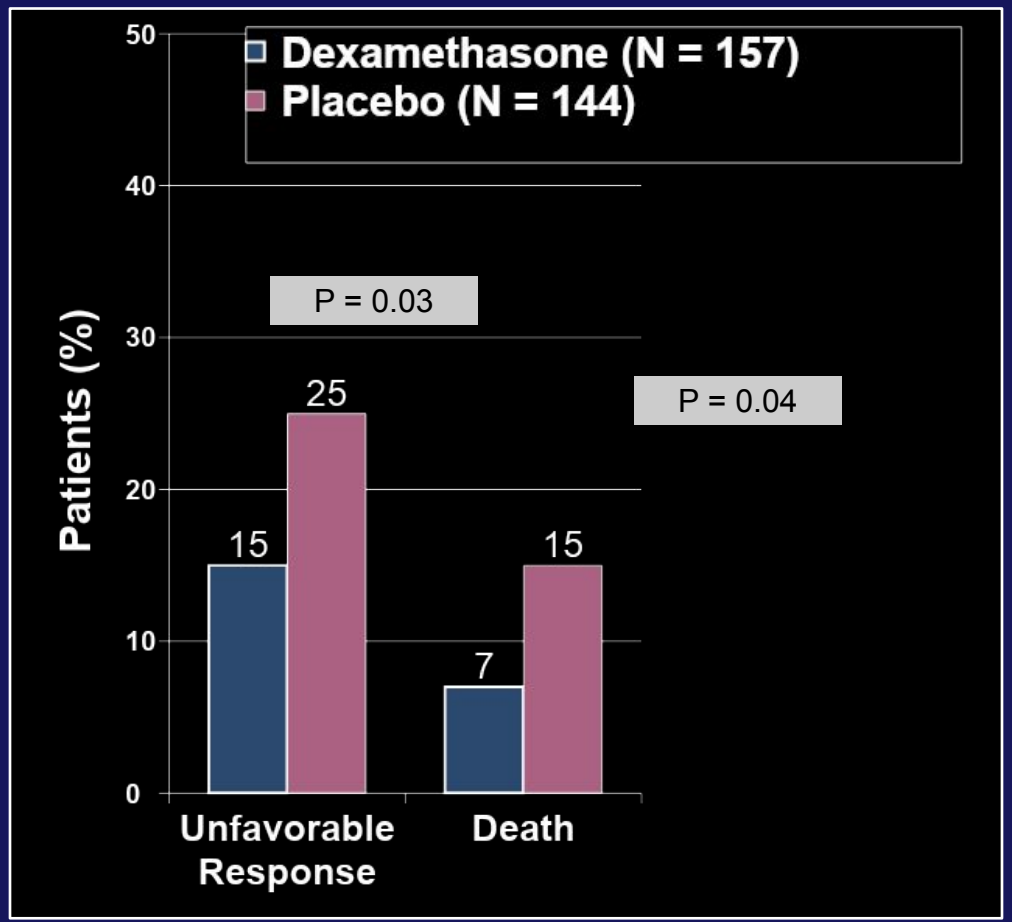
Dexamethasone in Adults with Bacterial Meningitis

Study Design

- Methods
  - N = 301 adults
  - Acute bacterial meningitis
  - Randomized, double-blind
- Regimens
  - Dexamethasone*
  - Placebo

*10 mg 15-20 minutes before (or with) first dose of antibiotics, then q 6h x 4 days

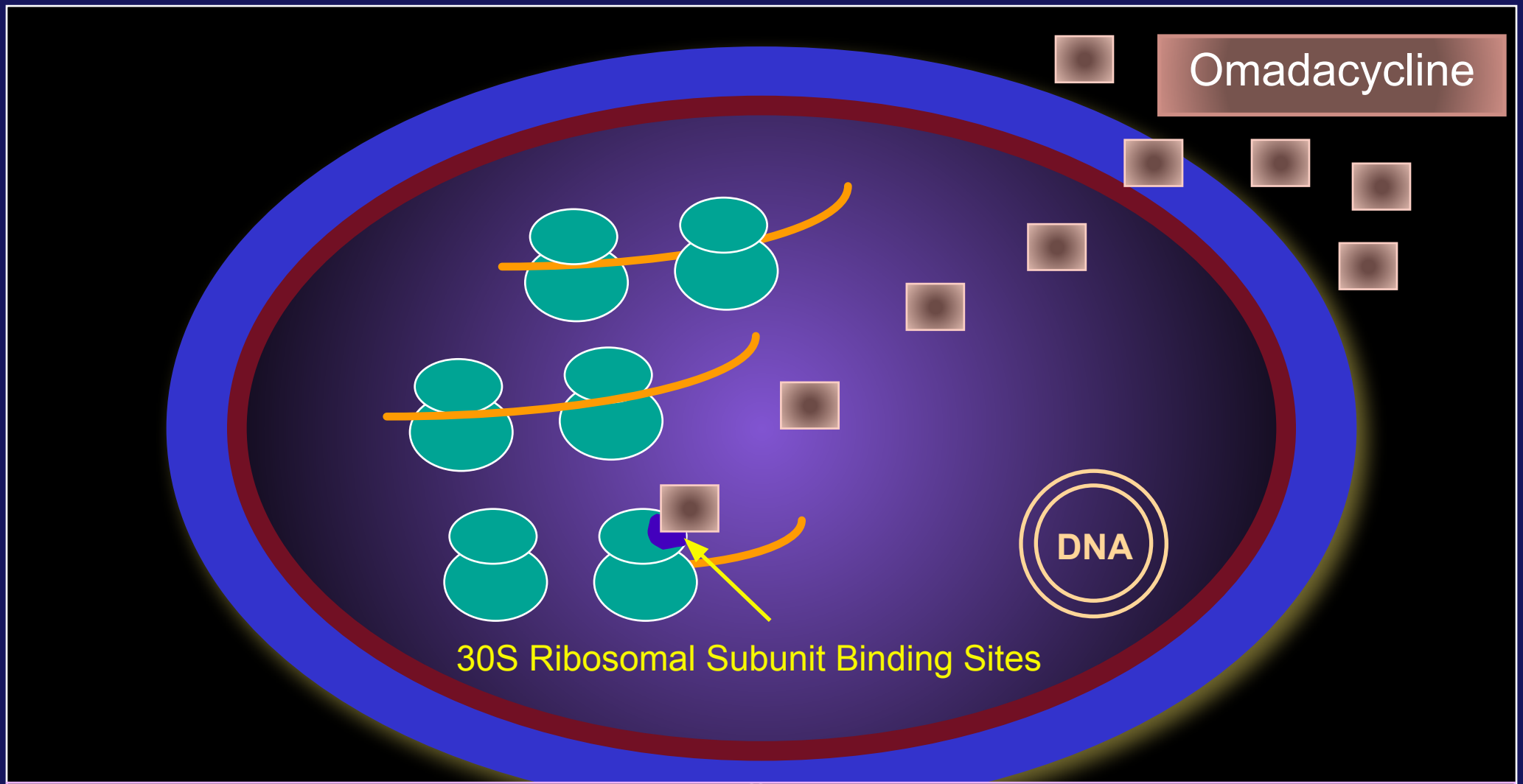
Outcome



Source: de Gans J, et al. N Engl J Med. 2002; 347:1549-56.

Newer Out-Patient Antimicrobials

Omadacycline: Mechanism of Action

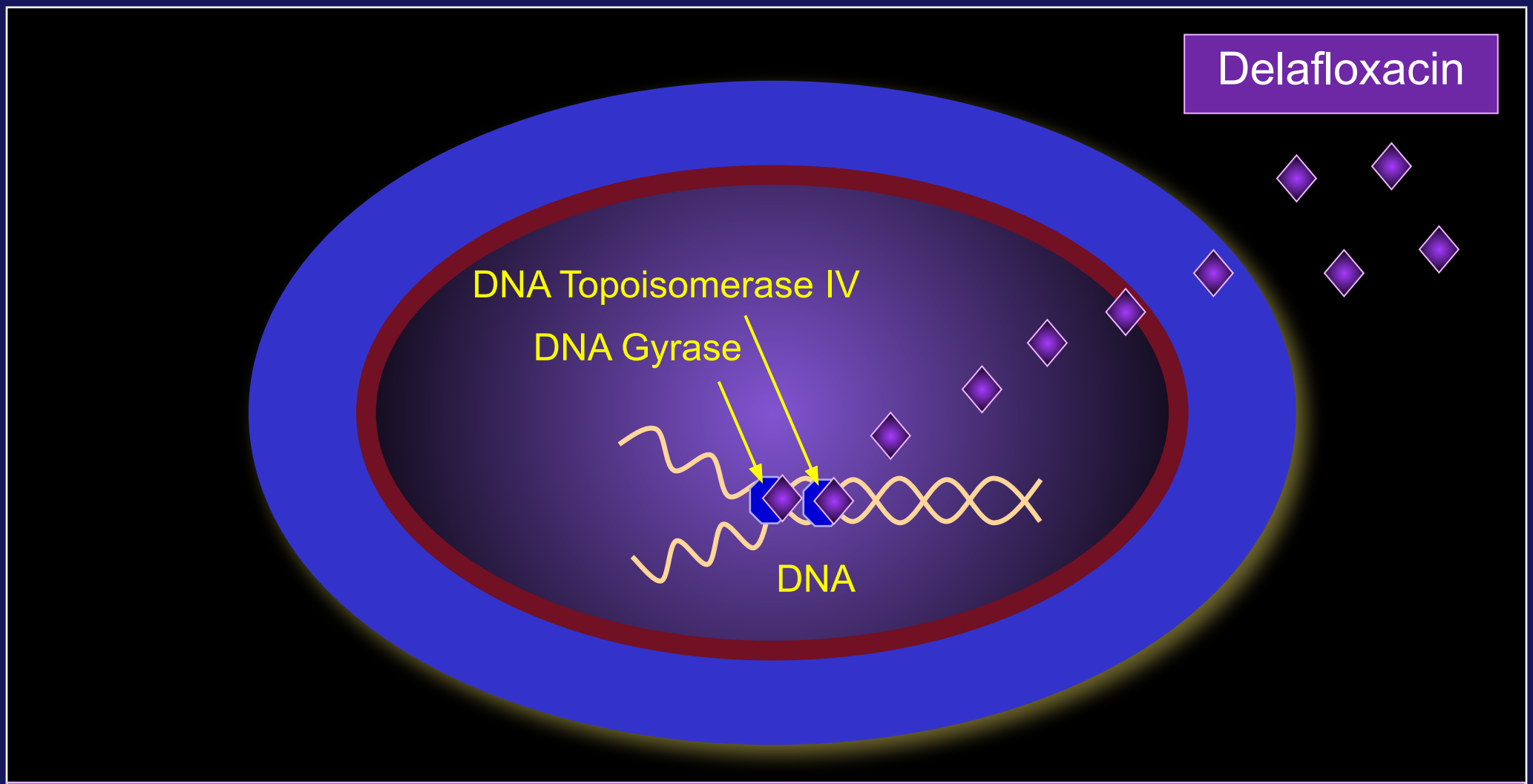


Active in vitro against tetracycline resistance efflux pumps (tetK and tet L) and ribosomal protection proteins (tet M)

Omadacycline

- FDA Approval October 2, 2018
- Antimicrobial Class
  - Aminomethycycline (within tetracycline class)
- Indications
  - Community acquired bacterial pneumonia (CABP)
  - Acute bacterial SSTI, including MRSA (ABSSTI)
- Dosing or Oral Therapy (Duration 7-14 days)
  - CABP: 200 mg IV d1, then 300 mg PO QD
  - ABSSTI: 450 mg PO days 1 and 2, then 300 mg PO QD
- Adverse Effects
  - Tooth discoloration (<8 years; last half of pregnancy)

Delafloxacin: Mechanism of Action



Equally potent against DNA gyrase and DNA topoisomerase IV enzymes

Delafloxacin

- Class: FDA Approval: June 19, 2017 for acute bacterial SSTI
- Dose:
  - Oral: 450 mg every 12 hours with or without food
  - Intravenous: 300 mg every 12 hours
- Activity:
  - Key gram-positives: MSSA, MRSA, *S. pyogenes*, *E. faecalis*
  - Key gram-negatives: *E. coli*, *E. cloacae*, *P. aeruginosa*
- Adverse Effects
  - Tendonitis and tendon rupture
  - Peripheral neuropathy
  - CNS: neuropsychiatric and exacerbate myasthenia gravis

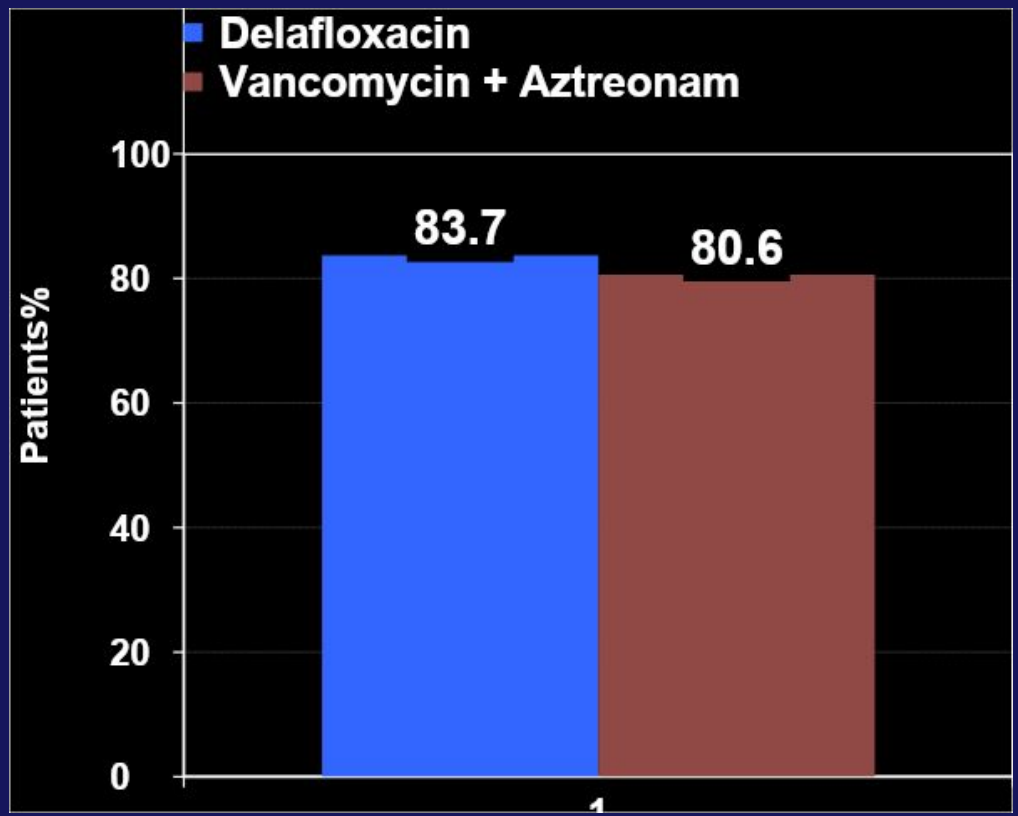
Delafloxacin vs. Vancomcyin + Aztreonam for SSTI

Study Design

- Methods (N = 850)
  - Randomized, phase 3, double blind
  - Adults with SSTI/wound infection
- Regimens
  - Delafloxacin: 300 mg IV q12h x 3d, then 450 mg PO twice daily
  - Vancomycin + Aztreonam

Source: O'Riordan W. Clin Infect Dis. 2018;67:657-66.

Clinical Success*

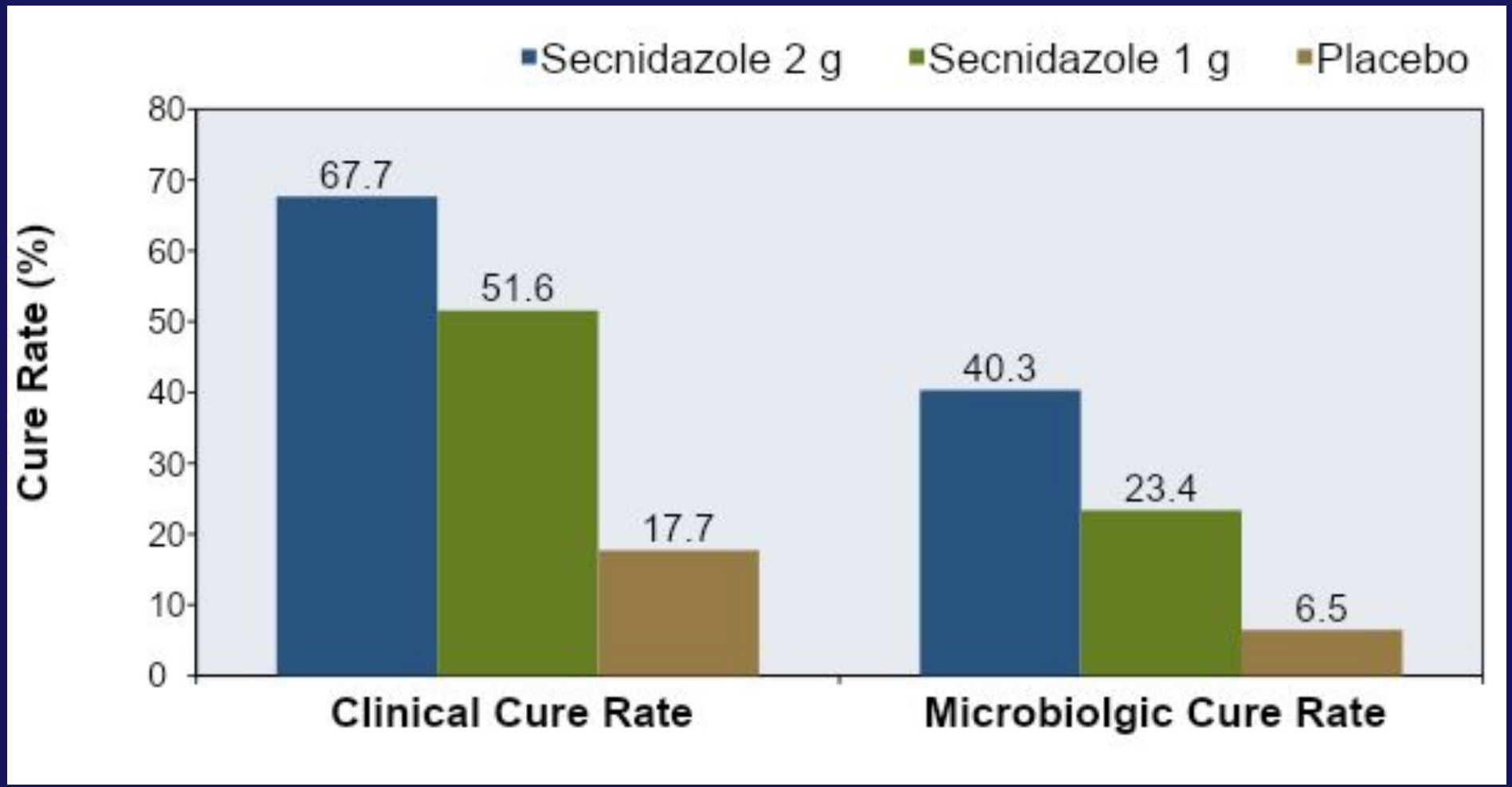


*Complete or near resolution of signs and symptoms with no further antibacterial needed.

Secnidazole

- FDA approval: September 15, 2017
- Indication: bacterial vaginosis
- Dosing: 2-g packet dose (take 1 packet)
- Formulation: packet with oral granules
  - Sprinkle on applesauce, yogurt or pudding
  - Ingest without chewing granules

Treatment of Bacterial Vaginosis with Secnidazole



Source: Hillier S, et al. Obstet Gynecol. 2017;130:379-86.

Thank you!