

Genitourinary Infections

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Definitions

- Urinary tract infection
- Asymptomatic bacteriuria
- Symptomatic abacteriuria
- Prostatitis
- Recurrence
 - relapse
 - reinfection

Classification: Anatomic Site

- Lower Tract
 - cystitis
 - urethritis
 - prostatitis
- Upper Tract
 - pyelonephritis

“The term complicated urinary tract infection is a diagnostic conundrum that defies logical review. For 4 decades, we have accepted a broad, imprecise classification of urinary tract infections using the simplistic terms of uncomplicated and complicated without adequately providing scientifically validated, clinically relevant definitions.”

Ronald AR, Harding GKM. 1997. *Infect Dis Clin North America* 11:583-92.

Classification: Uncomplicated / Complicated

Complicated infection characterized by factors predisposing to treatment failure:

1. anatomical/functional abnormalities
2. immunosuppression, diabetes mellitus
3. bacterial resistance
4. compromised delivery of antibiotics
5. male gender?
6. pregnancy?

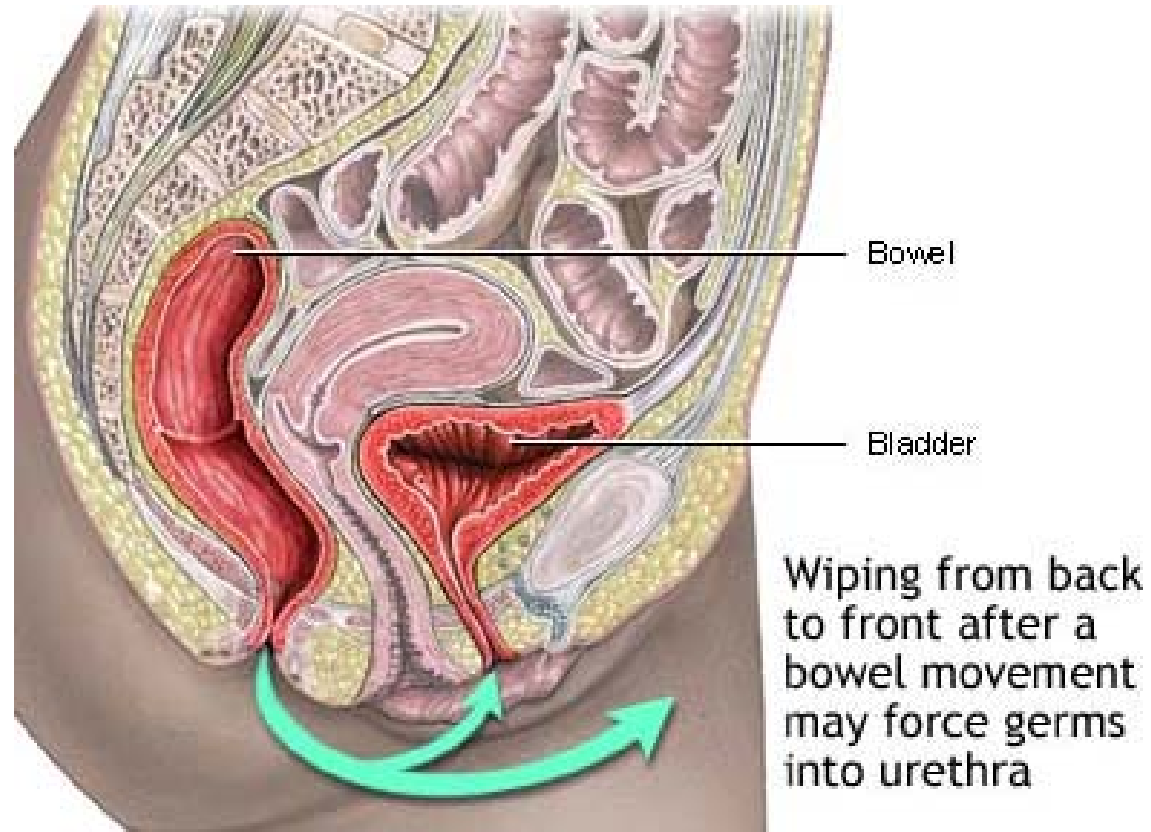
Epidemiology

- One of most common bacterial infections
 - 8 million cases per year, >1 million hospitalizations
 - 40-50% of women will experience a UTI
 - significant economic impact
- Prevalence varies with age and gender
 - sexually active young females are disproportionately affected

Routes of Infection

- Ascending
- Hematogenous
- Lymphatic

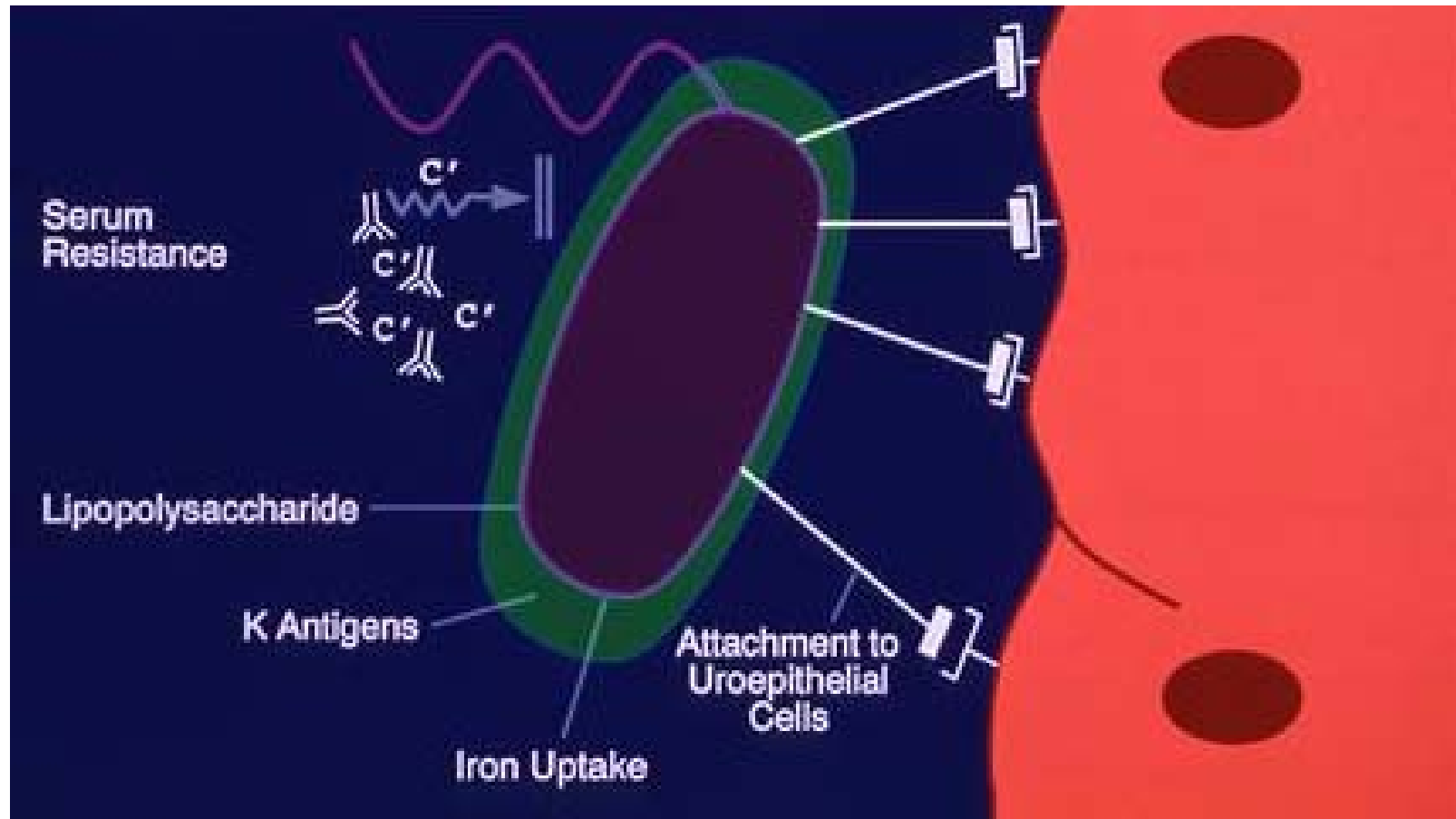
Ascending Route of Infection



Host Defense Factors

- Urine characteristics: pH, organic acids
- Prostatic secretions: antibacterial effect
- Tamm-Horsfall protein
 - glycoprotein with mannose residues
- Bladder antiadherence mechanisms
 - glycosaminoglycan, urinary Ig

Bacterial Virulence Factors



Causative Organisms

Uncomplicated

Escherichia coli

Staphylococcus saprophyticus

Other Gram -

Enterococcus spp.

Complicated

Escherichia coli

Pseudomonas aeruginosa

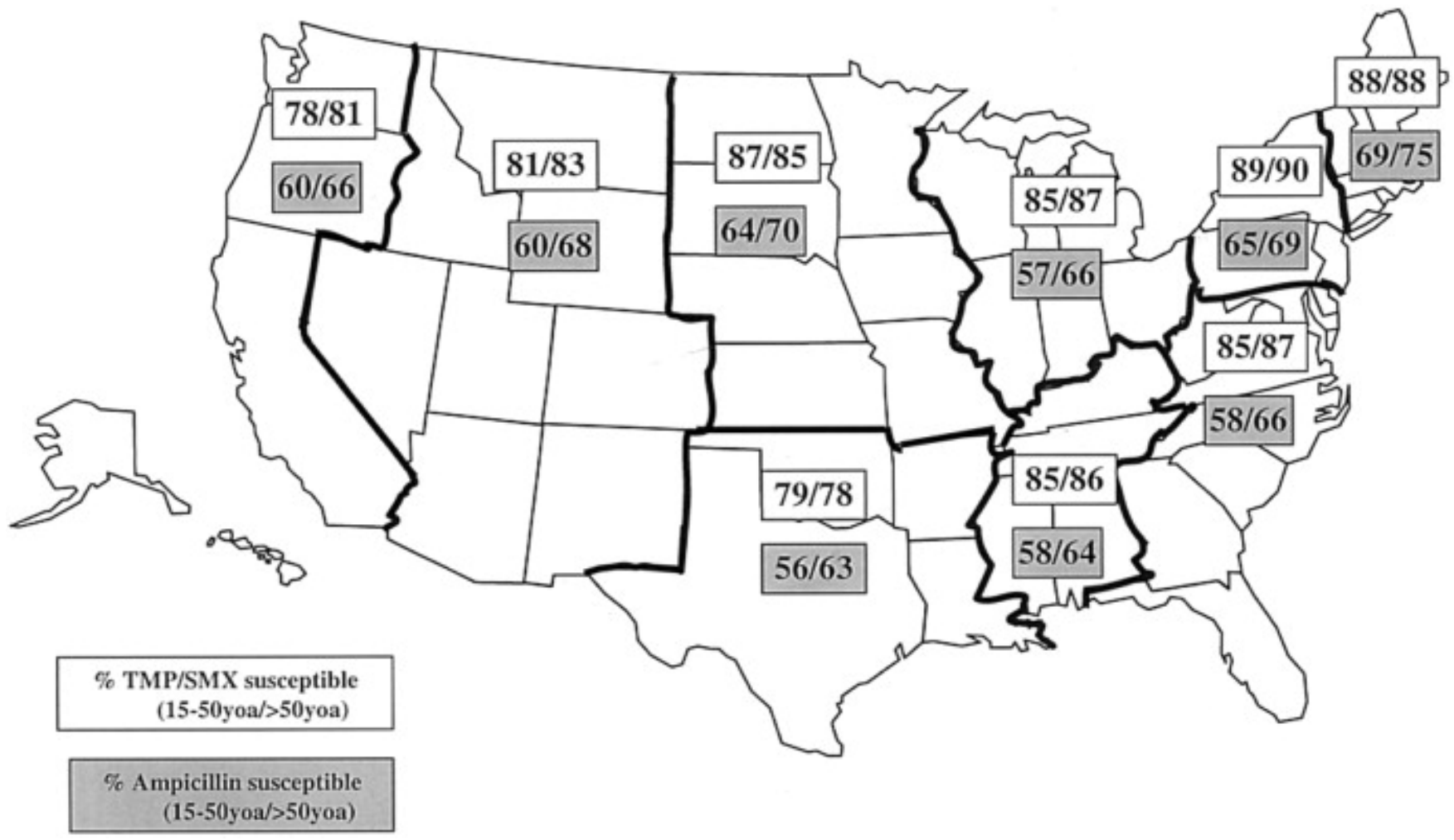
Enterobacteriaceae

Enterococcus spp.

Fungi

Bacterial Resistance in UTI

| Antibiotic | % Resistance | |
|----------------|--------------|------|
| | 1992 | 1996 |
| amoxicillin | 29 | 36 |
| TMP/SMX | 8 | 16 |
| ciprofloxacin | 0.3 | 0.3 |
| nitrofurantoin | 7 | 6 |



Bacterial Resistance in UTI

| Antibiotic | % Resistance | |
|----------------|--------------|---------------|
| | All Isolates | U.S. Isolates |
| ampicillin | 37.7 | 39.3 |
| TMP/SMX | 21.3 | 22.6 |
| ciprofloxacin | 5.5 | 6.8 |
| Levofloxacin | 5.1 | 6.4 |
| nitrofurantoin | 1.1 | 1.4 |

Risk Factors

- Urinary tract abnormalities
 - impaired clearance of organisms
- Female gender
 - urethral length
- Sexual activity (60x ↑ within 48h)
 - introduction of pathogenic bacteria
- Diaphragm/spermicide use (2-3x ↑)
 - alterations in microflora

Risk Factors

- Pregnancy
 - impingement of ureters
- Hospitalization, catheterization
 - introduction of (multiresistant) bacteria
- History of recurrent UTI
 - important factor for antibiotic resistance

Risk Factors: Recurrent UTI

- Sexual activity
 - new sexual partner within 1 year
- Spermicide use
- Maternal history of UTI
- 1st UTI before age 15
- Note that voiding patterns have not been shown to be a risk factor for UTI

Diagnosis

Physical Findings

- Lower tract infections
 - absence of systemic symptoms
- Upper tract infections
 - systemic symptoms
- Elderly patients
 - altered mental status, GI, etc.
- Bacterial prostatitis
 - perineal/sacral pain; prostatic signs

Laboratory Analysis

- Key to diagnosis of UTI
- Appropriate urine collection is essential
- Macroscopic and microscopic evaluation
- Biochemical markers
- Culture & susceptibility?

Urine Specimen Collection

- 3 methods:
 - midstream clean catch
 - catheterization
 - suprapubic bladder aspiration

Urinalysis

- Appearance
- pH
- Specific gravity
- Protein
- Glucose
- Nitrite
- Leukocyte esterase
- WBC
- Casts
- RBC
- Epithelial cells
- Bacteria

Biochemical Markers

Nitrite

- Formed by bacteria that reduce nitrate:
Gram - bacteria
- Normal value: negative

Biochemical Markers

Leukocyte esterase

- Enzyme found in neutrophil granules
- Indicator of pyuria
- Normal value: 0

| Finding | Normal | Lower UTI | Upper UTI |
|------------------|---------------|--------------|--------------|
| appearance | clear | turbid | turbid |
| specific gravity | 1.001 – 1.035 | upper normal | upper normal |
| pH | 4.6 – 8 | 7 – 8 | 7 – 8 |
| WBC | 0 – 5 | > 5 | > 5 |
| nitrite | - | + (Gram -) | + (Gram -) |
| LE | 0 | up to + 5 | up to + 5 |
| epithelial cells | 0 | 0 | 0 |

Criteria for Bacteriuria

| CFU/mL | Patient Type |
|--------|---|
| 10^2 | symptomatic female (coliforms) catheterized patient |
| 10^3 | symptomatic male |
| 10^5 | symptomatic female (noncoliforms) asymptomatic (2 specimens) |

Urine Culture

- Most reliable method of diagnosis
- Allows susceptibility determination
- Not cost-effective in many cases
- Potential candidates:
 - recurrence
 - pyelonephritis
 - pregnancy
 - male gender

Treatment

Goals of Treatment

- Clinical cure
- Successful bacterial eradication
- Relief of symptoms
- Prevention of progression of infection
- Minimize development of resistance

Evaluating Clinical Trials

- 1° outcome: clinical cure
 - remember that many patients will experience cure even without treatment
- 2° outcome: bacterial eradication
 - clinical studies should include this data

Treatment Considerations

- Uncomplicated vs. complicated infection
- Lower tract vs. pyelonephritis
- New infection vs. recurrence
- Previous treatment with antimicrobials
- Regional susceptibility patterns

Antimicrobial Characteristics

- Pharmacokinetic factors
- Extent of glomerular filtration
- Effects on normal bacterial flora
- Susceptibility

Methenamine (Hiprex^R)

- Mandelate or hippuric acid salt of methenamine
- MOA: converted to formaldehyde and organic acid if pH remains < 5.5
- Caution in gout, hepatic or renal disease
- Little evidence to support use

Cystex^R

- Methenamine mandelate 162 mg
- Sodium salicylate 162.5 mg
- “Fast relief of frequent, painful, burning urination”
- \$13.29 for 100 tablets at drugstore.com

Penicillins

- Unacceptable level of resistance with some agents (e.g., *E. coli* – amoxicillin/ampicillin)
- Usually do not fully eradicate *E. coli*
- Extended-spectrum agents useful in hospitalized patients
- Poor pharmacokinetic characteristics

Cephalosporins

- Oral agents: generally more expensive and offer no efficacy advantages
 - cefixime (Suprax^R), cefpodoxime (Vantin^R)
- Parenteral 2nd and 3rd generation agents may have utility in hospitalized patients
 - urosepsis
 - complicated pyelonephritis
 - nosocomial UTI

β -lactams in UTI

- No longer recommended for empiric therapy of UTI
 - poor ability to eradicate vaginal *E. coli*
 - unacceptable rates of resistance
- Utility in select instances
 - pregnancy
 - urosepsis, etc.
 - infection with enterococci (penicillins only)

TMP/SMX (Bactrim^R, Septra^R)

- Minimal effect on vaginal flora
- Achieves high urinary concentrations
- 3-day regimen associated with ~ 94% rate of bacteriologic cure
 - not increased with longer duration

TMP/SMX (Bactrim^R, Septra^R)

- Low incidence of adverse effects
- Caution in pregnancy
- Sulfa allergy can limit use
- Inexpensive
- Resistance rates increasing – use is now limited

Trimethoprim

- Efficacy similar to that of TMP/SMX
- Useful in patients with sulfa allergy

Fluoroquinolones

- Excellent pharmacokinetic characteristics
 - good oral absorption, high urinary concentrations
- 3-day regimen associated with ~ 92% rate of bacteriologic cure
 - not increased with longer duration
- Resistance is currently rare, but increasing

Fluoroquinolones

- Low incidence of adverse effects
 - avoid in pregnancy
 - avoid in children?
- Moderate cost

Nitrofurantoin (Macrobid^R)

- Minimal resistance despite many years of use
- Usually does not eradicate *E. coli*
- Do not use if Cl_{Cr} is < 40 mL/min
- Generally low incidence adverse effects, but rare severe pulmonary reactions

Nitrofurantoin (Macrobid[®])

- Moderate cost
- Few controlled trials available
- Suitable for 7-day regimens only

Short-Course Nitrofurantoin

| Outcome | Patients, # / Total # (%) | |
|--------------------------|---------------------------|----------------|
| | TMP/SMX | Nitrofurantoin |
| Primary outcome | | |
| overall clinical cure | 117/148 (79) | 134/160 (84) |
| Secondary outcomes | | |
| early clinical cure | 133/148 (90) | 144/160 (90) |
| early microbiologic cure | 131/144 (91) | 141/154 (92) |

Fosfomycin (Monurol[®])

- Only FDA-approved single-dose agent
- Lack of comparative trial data
- Less effective than 7-10 day regimens of FQ or TMP/SMX
- Potential psychological impact on patient (compliance)
- Adverse effects minimal
- Expensive

Dosing: Acute Cystitis

| Antibiotic | Dose | Duration |
|----------------|------------|----------|
| TMP/SMX | 1 DS BID | 3 days |
| TMP | 100 mg BID | 3 days |
| nitrofurantoin | 100 mg BID | 7 days |
| ciprofloxacin | 250 mg BID | 3 days |
| levofloxacin | 250 mg QD | 3 days |
| fosfomicin | 3 gm | 1 dose |

Treatment by Disease State

Acute Uncomplicated Cystitis

- Direct initial therapy against *E. coli*
- Careful history-taking important
- Cost-effective approach to management
 - urinalysis
 - initiate empiric therapy
 - no culture performed in most cases

Acute Uncomplicated Cystitis

- Consider regional TMP/SMX resistance:
 - if < 10-20%, use TMP/SMX for 3 days
 - if > 10-20%, use FQ x 3 days
- Agents lacking substantial evidence:
 - penicillins
 - cephalosporins
 - fosfomycin

Short-Course Therapy

3-day course is standard of care

- Advantages vs. longer duration:
 - improved tolerance and compliance
 - diminished bacterial resistance, cost
 - equivalent efficacy

Single-Dose Therapy

- Associated with higher relapse rates
- New data may support single-dose FQ
 - ciprofloxacin: 1 trial
 - gatifloxacin: 1 trial

Symptomatic Abacteriuria

Definition: symptoms of UTI, no bacteria isolated

- General principle: treat symptoms
- Short-course or single-dose therapy
 - TMP/SMX or FQ x 3 days
 - single-dose regimens not preferred
- Consider *Chlamydia trachomatis* if recent sexual activity or treatment failure

Asymptomatic Bacteriuria

Definition: bacteriuria without UTI symptoms

- Management depends on risk group
- Comorbidities dictate whether treatment is necessary to prevent sequelae

Asymptomatic Bacteriuria

Patient Type

Treatment?

children

treat to prevent renal damage

nonpregnant females

do not treat

pregnant females

treat to prevent effects on fetus

s/p renal transplant

treat to prevent rejection

diabetics

evidence supporting treatment is unclear

elderly

obtain 2 cultures before treating

Pregnancy and UTI

- Untreated asymptomatic bacteriuria may lead to significant effects on fetal development
- Drugs of choice:
 - sulfonamides (except 3rd trimester and possibly 1st trimester)
 - amoxicillin, amoxicillin/clavulanate
 - nitrofurantoin
- Avoid FQ
- Duration: 7 days

Acute Pyelonephritis

- Aggressive management vs. outpatient therapy
- Pretreatment culture and susceptibility
- TMP/SMX and FQ are drugs of choice
- Broad spectrum of coverage in seriously ill patients (treat as urosepsis)
- Duration: 14 days usually sufficient, but shorter durations now more common

Acute Pyelonephritis

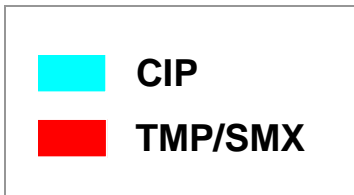
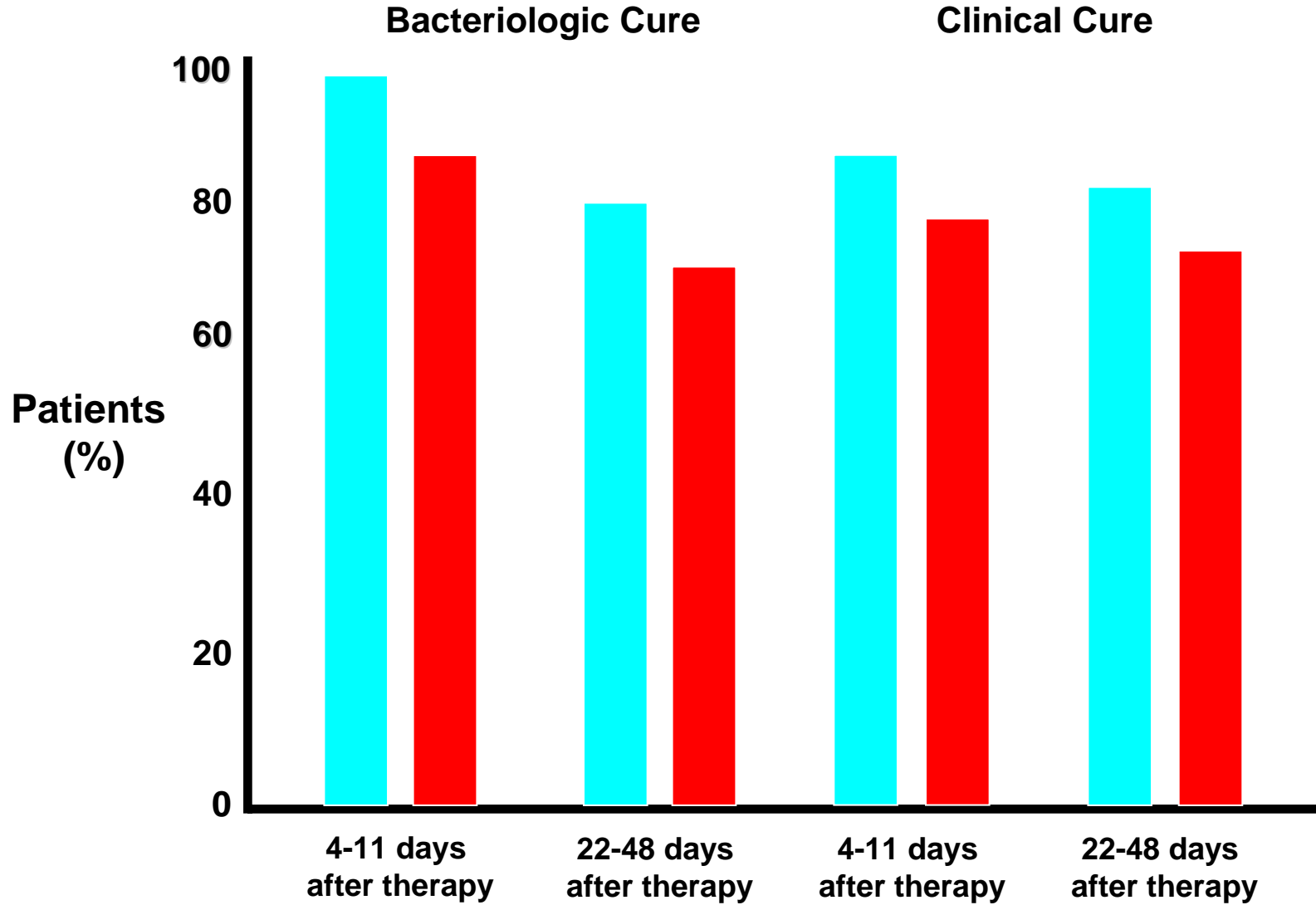
- Patients should be stabilized within 12-24h
- Reduction in urinary bacterial counts should occur within 48h
 - if no response, re-evaluate antibiotic choice
- If patient afebrile for 24h, IV → PO switch
- Post-treatment culture: 2 weeks after antibiotic course is completed

Short-Course Therapy

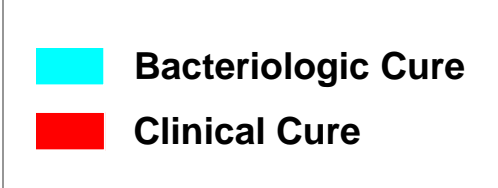
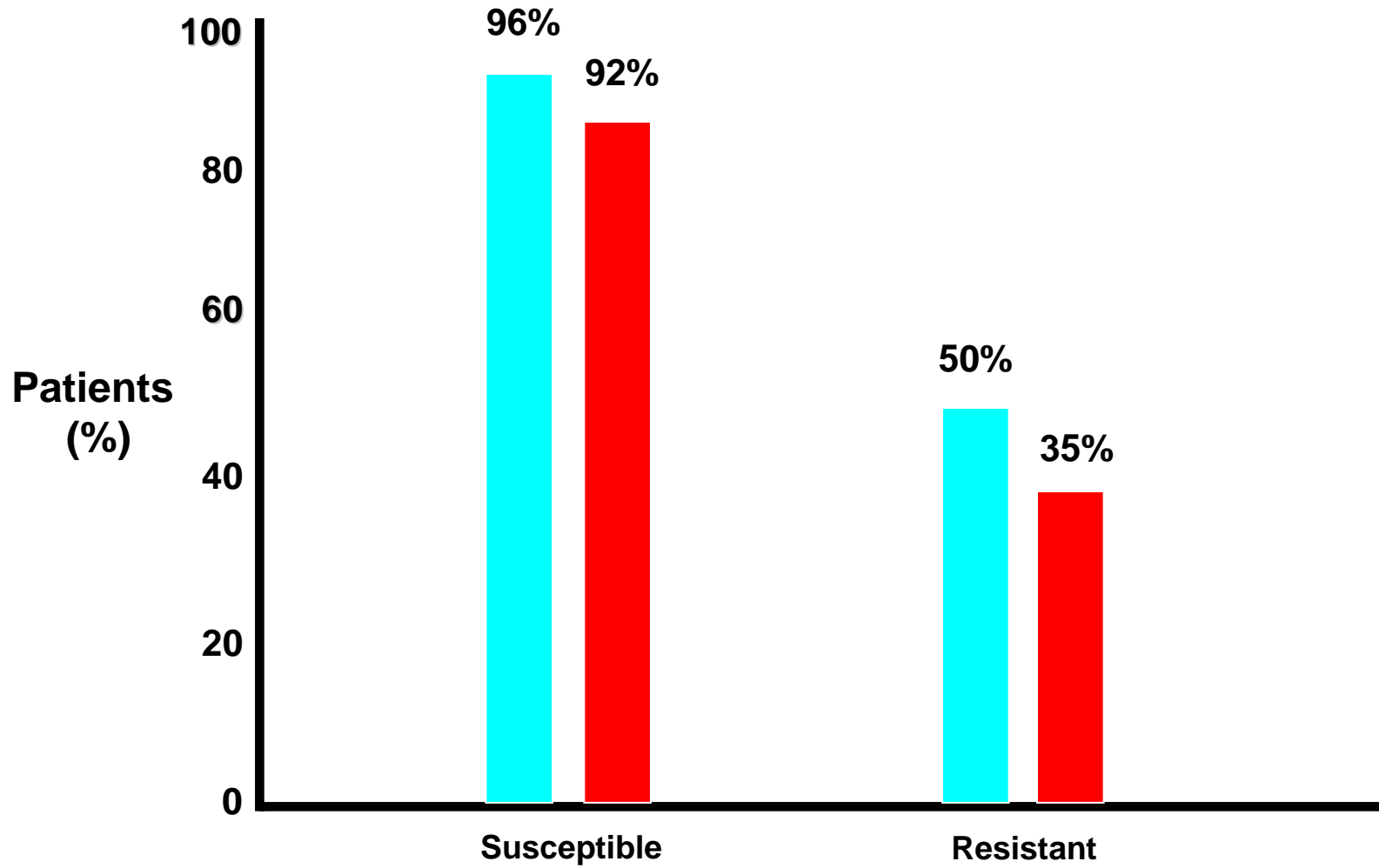
- Randomized, double-blind trial
- 255 premenopausal women analyzed
- Outcomes @ 4-11 and 22-48 days after end of therapy:
 - bacteriologic cure
 - clinical cure

Short-Course Therapy

- Regimens:
 - ciprofloxacin 500 mg BID PO x 7 days
 - TMP/SMX DS BID PO x 14 days
- With or without:
 - ciprofloxacin 400 mg IV x1
 - ceftriaxone 1 gm IV x1



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



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

UTI in Males

- Pretreatment culture
- Consider possibility of prostatic source
- Short-course therapy not recommended
 - usual initial therapy 10-14 days
- TMP/SMX and FQ are good options
- Avoid nitrofurantoin
- Post-treatment culture is important

Prostatitis

- Inflammation of prostate gland and surrounding tissues
- Rare in males < 30 y.o.
- Presentation:
 - ABP: acute illness
 - CBP: more indolent symptoms
(back pain, dysuria, perineal pressure, etc.)

Acute Bacterial Prostatitis

- *E. coli* is predominate organism (75%)
- Therapy:
 - oral TMP/SMX, FQ
 - duration: 4 weeks

Chronic Bacterial Prostatitis

- *E. coli* is predominate organism (75%)
- Therapy:
 - therapeutic prostatic concentrations required
 - oral FQ > TMP (no SMX)
 - duration: 4-6 weeks
 - chronic suppressive therapy may be required

Catheterized Patients

- Acquisition rate is 5% per day
- 40% of nosocomial infections
- Most common source of Gram - bacteremia in hospitalized patients
- Diagnosis: >100 CFU/mL bacteria
- Prevention:
 - careful catheter management
 - avoid prophylactic antibiotics

Catheterized Patients: Therapy

- Asymptomatic bacteriuria
 - avoid antimicrobials; catheter removal sufficient
- Symptomatic
 - treat as a complicated UTI?
 - optimal duration unknown; 10-14 days?
 - oral FQ suitable

Recurrence

Recurrent UTI

- Recurrent UTI is a symptomatic UTI that follows clinical resolution of an earlier UTI, generally, but not necessarily, after antibiotic treatment
- Most occur within 3 months of original UTI
- Important to differentiate reinfection vs relapse
 - may affect choice of ABX

Reinfection vs Relapse

- Reinfection
 - caused by different organism than that causing original infection
 - time frame for occurrence generally >2 weeks
- Relapse
 - caused by persistent focus of infection
 - persistence of original pathogen within 2 weeks of original infection

Recurrent Infections

- 80-90% of cases constitute reinfection
- Management depends on # episodes per year, predisposing factors, patient preference
- Treatment options:
 - postcoital therapy
 - continual prophylaxis
 - self-administered therapy

Recurrent Infections: Therapy

- Reinfection
 - treat with short-course therapy if infrequent
 - prophylaxis: continuous, post-coital
 - topical estrogen?
 - *Lactobacillus*?
- Relapse
 - prolonged treatment duration
 - urologic evaluation if infection persists

Continuous Prophylaxis

- Advocated for:
≥ 2 UTI in 6 months, or ≥ 3 UTI in 12 months
- Patient preference most important
- Generally shown to ↓ recurrences by 95%
- Most common duration: 6 months
- Concurrently modify other risk factors
(spermicide use, etc.)

Post-Coital Prophylaxis

- May be preferable to continuous prophylaxis (patient preference)
- Ideal if recurrence is temporally related to sexual intercourse

Self-Treatment

- 3-day regimens most common (TMP/SMX)
- Patient reliability important

Dosing: Continuous Prophylaxis

| Antibiotic | Dose | Duration |
|----------------|---------------|----------|
| TMP/SMX | ½ SS qHS | 6 months |
| TMP/SMX | ½ SS TIW | 6 months |
| TMP | 100 mg qHS | 6 months |
| nitrofurantoin | 50-100 mg qHS | 6 months |
| norfloxacin | 200 mg qHS | 6 months |

Dosing: Postcoital Regimens

| Antibiotic | Dose | Duration |
|----------------|-----------|----------|
| TMP/SMX | ½ or 1 SS | 1 dose |
| nitrofurantoin | 50-100 mg | 1 dose |
| ciprofloxacin | 250 mg | 1 dose |
| levofloxacin | 250 mg | 1 dose |

Prevention

Topical Estrogen

- Topical intravaginal estriol cream
- Normalizes vaginal flora, supports vaginal growth of *Lactobacillus* spp.
- Appears to reduce the risk of recurrence

Lactobacillus

- Acts through competitive exclusion of usual uropathogens
- Possible mechanisms of action:
 - steric hindrance
 - blockage of potential attachment sites
 - production of hydrogen peroxide
 - production of lactic acid

Cranberry Juice

- Formerly thought to work through urinary acidification
- New evidence suggests an antiadherence mechanism
 - proanthocyanidins
- Conclusive proof of efficacy is lacking
- Effect may depend on type/brand
- Dose: 200-750 mL QD?

Adjunctive Measures

- Hydration
- Urinary acidification (vitamin C)
 - little evidence to support use
- Phenazopyridine (Pyridium^R)
 - OTC analgesic