Current Trends in Antimicrobial Resistance and Need for Antimicrobial Stewardship Among Urologists

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Objectives:
• Describe the origin of antibiotic resistance
• Discuss the current state of antimicrobial resistance and the need for antimicrobial stewardship
• Explain the new challenges that face urologists in the era of multidrug-resistant E. coli
Current Trends in Antimicrobial Resistance and the Need for Antimicrobial Stewardship

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Disclosures

• Research support from:
  – Pfizer Independent Grants for Learning and Change
  – The Joint Commission
Objectives

• Describe why antibiotic resistance is inevitable

• Understand the current state of antimicrobial resistance

• Identify challenges that face urologists in the era of multidrug-resistant *E. coli*
Where do antibiotics come from?

- Synthesized by molds or bacteria (why?)
  - The soil is a very complex milieu!
  - Inhibit growth of competitors – Intermicrobial communication
  - Triggers specific transcriptional changes (dose dependent)
Antibiotics in early life alter the murine colonic microbiome and adiposity

• Mice were given sub-therapeutic doses of abx
  – increased adiposity and hormone levels related to metabolism
  – changes in copies of key genes involved in metabolism
  – alterations in the regulation of hepatic metabolism of lipids and cholesterol
Survival

Harbor Resistance
Elements!!!
Antibiotic resistance is ancient

Vanessa M. D’Costa¹,²*, Christine E. King³,⁴*, Lindsay Kalan¹,², Mariya Morar¹,², Wilso W. L. Sung⁴, Carsten Schwarz³, Duane Froese⁵, Grant Zazula⁶, Fabrice Calmels⁵, Regis Debruyne⁷, G. Brian Golding⁴, Hendrik N. Poinar¹,³,⁴ & Gerard D. Wright¹,²
VanA is OLD – 30K years old
We will never win…

Antibiotic deployment

Antibiotic resistance observed
Antibiotic use drives resistance!

50%

Unnecessary
Antibiotics are unique

Use in one patient can compromise efficacy in another.
• The public will demand [the drug and]...then will begin an era... of abuses....In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with penicillin-resistant organism.

"We must recognize that the misuse of antibiotics affects the cost of medical care and the ecology of the bacterial flora. These are matters of concern to all physicians because the practice of one affects all."
“Virtually all reports agree that careful, discriminating use of antimicrobial agents remains the keystone for minimizing this problem (antimicrobial resistance). This need must be communicated more effectively to prescribers.”
In its recent annual report on global risks, the World Economic Forum (WEF) concluded that “arguably the greatest risk . . . to human health comes in the form of antibiotic-resistant bacteria. We live in a bacterial world where we will never be able to stay ahead of the mutation curve. A test of our resilience is how far behind the curve we allow ourselves to fall.”

1
Total Number of New Antibacterial Agents

- 1983-1987
- 1988-1992
- 1993-1997
- 1998-2002
- 2003-2007
- 2008-2012

ANTIBIOTIC DEVELOPMENT IS DWINDLING

Source: The Epidemic of Antibiotic-Resistant Infections, CID 2008:46 (15 January)
ANTIBIOTIC RESISTANCE THREATS
in the United States, 2013
**Urgent Threats**
- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

**Serious Threats**
- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella Typhi*
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

**Concerning Threats**
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A Streptococcus
- Clindamycin-resistant Group B Streptococcus
# Impact of Antibiotic Resistance

<table>
<thead>
<tr>
<th>Organism</th>
<th>Increased risk of death (OR)</th>
<th>Attributable LOS (days)</th>
<th>Attributable cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA bacteremia</td>
<td>1.9</td>
<td>2.2</td>
<td>$6,916</td>
</tr>
<tr>
<td>MRSA surgical infection</td>
<td>3.4</td>
<td>2.6</td>
<td>$13,901</td>
</tr>
<tr>
<td>VRE infection</td>
<td>2.1</td>
<td>6.2</td>
<td>$12,766</td>
</tr>
<tr>
<td>Resistant Pseudomonas infection</td>
<td>3.0</td>
<td>5.7</td>
<td>$11,981</td>
</tr>
<tr>
<td>Resistant <em>Enterobacter</em> infection</td>
<td>5.0</td>
<td>9</td>
<td>$29,379</td>
</tr>
</tbody>
</table>

Total cost of antimicrobial resistance is estimated to be **30 billion dollars annually**

CRE = KPC = NDM1
Mortality rate ≈ 50%
*Klebsiella pneumoniae*

Guidance for Control of Carbapenem-resistant Enterobacteriaceae – 2012 CRE Toolkit, CDC.
Antibiotic Resistance Threats in the U.S., 2013. CDC
"Nightmare Bacteria" Threat

States with one type of drug-resistant infection, carbapenem-resistant Enterobacteriaceae (CRE), in 2001 and 2013.

2013 CRE Reported to CDC
Notes from the Field


On August 16, 2012, the Colorado Department of Public Health and Environment was notified of two patients at an acute-care hospital in Denver with carbapenem-resistant Enterobacteriaceae (CRE), specifically *Klebsiella pneumoniae* (CRKP), isolated from respiratory specimens during July-August. Both isolates produced New Delhi metallo-beta-lactamase (NDM). A review of microbiology records identified involved in some transmission routes. How NDM-producing CRE was introduced to the facility is unclear.

NDM, a carbapenemase enzyme first described in 2009 in a patient who had received medical care in India (1), has since been detected and reported worldwide (2). In the United States, before this outbreak, only 16 isolates in clusters with two or fewer cases had been identified since 2009; 14 isolates were from patients who had received medical care in endemic (South Asian) regions. The cases described here represent the largest U.S. outbreak of NDM-producing CRE to date, highlighting the risk for spread of these organisms among persons receiving healthcare.

...ations with carbapenem-resistant *Enterobacteriaceae* were increasing among patients in medical facilities in northeastern Illinois. *Klebsiella pneumoniae* carbapenemase (KPC) is responsible for much of the increase in the incidence of New Delhi metallo-β-lactamase (NDM-1) in Illinois.

50% of patients exposed were colonized!
• ESBL Positive organisms – *E. coli*!!!!
• Urine is a very common source
• Treatment – IV antibiotics (carbapenem)
Prospective, observational study of patients with community acquired E. coli infection in the United States

New York City
Pittsburgh
Detroit
San Antonio
Iowa City
Results

• 3.9% (1.8 – 6.7%) of E. coli were ESBL positive
  – 15% of E. coli bacteremia isolates ESBL+ at IMC

• 36% were community associated, almost all were due to urinary tract infections

• No Risk Factors Present!!!!

Marya D. Zilberberg, MD, MPH; Andrew F. Shorr, MD, MPH

- From 2000 – 2009, total number of hospitalizations with a UTI diagnosis increased 50%
CRE and ESBL

- Incidence is on the rise
- All require IV antibiotics
- High morbidity and mortality
- Prior antibiotics are a major risk factor

What about more common resistance patterns?
Fluoroquinolone Resistant *E. coli*

- Why a rise in FQ Res *E. coli*?

- How does this impact your practice and what do I do about it?
  - Specifically…TRUS biopsy
Calculations of nationally representative estimates:

- 985 Million ambulatory visits / year
- 101 Million visits – Antibiotics prescribed (10%)
Acute sinusitis is diagnosed in over 3 million visits annually among adults and children in the United States. Of these, more than 80% result in an antibiotic prescription; however, many of these prescriptions are often limited to empirical treatment of sinusitis; current treatment guidelines do not recommend the use of fluoroquinolones as first-line therapy for upper respiratory infection, urinary tract infection, skin/soft tissue infection, or acute maxillary sinusitis. The most common antibiotic prescribed was macrolides (29%), followed by fluoroquinolones (19%), amoxicillin (17%), and amoxicillin/clavulanate (16%).
E. coli resistance on the rise


Majdi N. Al-Hasan¹,²*, Brian D. Lahr³, Jeanette E. Eckel-Passow³ and Larry M. Baddour²

Population based study of *E. coli* bacteremia (80% GU)
Global Rise in Resistance

*E. coli* isolates in Belgium

![Graph showing the rise in resistance of *E. coli* isolates in Belgium over years. The graph displays the percentage of non-susceptible isolates for different antibiotics.]
### Fluoroquinolone Prophylaxis for Urology Procedures

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Easy of oral and IV use</td>
<td>• High collateral damage</td>
</tr>
<tr>
<td>• Good safety profile</td>
<td>• Widespread use outside of urology</td>
</tr>
<tr>
<td>• Excellent bioavailability</td>
<td>• Resistance!!!</td>
</tr>
<tr>
<td>• Excellent prostate tissue levels</td>
<td>– Transrectal US guided biopsy</td>
</tr>
<tr>
<td>• Active against gut microbiota</td>
<td></td>
</tr>
<tr>
<td>• Low cost</td>
<td></td>
</tr>
</tbody>
</table>
### Table 3a. Recommended antimicrobial prophylaxis for urologic procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Organisms</th>
<th>Prophylaxis Indicated</th>
<th>Antimicrobial(s) of Choice</th>
<th>Alternative Antimicrobial(s)</th>
<th>Duration of Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Tract Instrumentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Removal of external urinary catheter</td>
<td>GU tract†</td>
<td>If risk factors‡,§</td>
<td>Fluoroquinolone†, TMP-SMX‡</td>
<td>Aminoglycoside (Aztreonam†) ± Ampicillin†, 1st/2nd gen. Cephalosporin†, Amoxicillin/Clavulanate†</td>
<td>≤24 hours†</td>
</tr>
<tr>
<td>Cystography, urodynamic study, or simple cystourethroscopy</td>
<td>GU tract</td>
<td>If risk factors§</td>
<td>Fluoroquinolone, TMP-SMX</td>
<td>Aminoglycoside (Aztreonam†) ± Ampicillin</td>
<td>≤24 hours</td>
</tr>
<tr>
<td>Cystourethroscopy with manipulation §§</td>
<td>GU tract</td>
<td>All</td>
<td>Fluoroquinolone, TMP-SMX</td>
<td>Aminoglycoside (Aztreonam†) ± Ampicillin</td>
<td>≤24 hours</td>
</tr>
<tr>
<td>Prostate brachytherapy or cryotherapy</td>
<td>Skin</td>
<td>Uncertain</td>
<td>1st gen. Cephalosporin</td>
<td>Clindamycin**</td>
<td>≤24 hours</td>
</tr>
<tr>
<td>Transrectal prostate biopsy</td>
<td>Intestine††</td>
<td>All</td>
<td>Fluoroquinolone, 1st/2nd/3rd gen. Cephalosporin</td>
<td>- TMP-SMX, Aminoglycoside (Aztreonam†)</td>
<td>≤24 hours</td>
</tr>
</tbody>
</table>
Complications After Prostate Biopsy: Data From SEER-Medicare

Stacy Loeb,* H. Ballentine Carter, Sonja I. Berndt, Winnie Ricker and Edward M. Schaeffer

From the Brady Urological Institute, The Johns Hopkins Medical Institutions (SL, HBC, EMS), Baltimore, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health (SIB), Bethesda and Information Management Services (WRI), Rockville, Maryland

Hospitalizations with infection as primary diagnosis after TRUS Biopsy (black) vs controls (grey): 1991 - 2007

“A likely explanation for the increase in infectious complications is increasing antimicrobial resistance.”

Increasing Hospital Admission Rates for Urological Complications After Transrectal Ultrasound Guided Prostate Biopsy

Robert K. Nam,*,† Refik Sasaki,† Yuna Lee,† Ying Liu,† Calvin Law,† Laurence H. Klotz,‡ D. Andrew Loblaw,† John Trachtenberg,† Aleksandra Stanimirovic,† Andrew E. Simor,† Arun Seth,† David R. Urbach† and Steven A. Narod†
## Post – TRUS Biopsy Infection Studies Since 2009

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No. TRUS</th>
<th>Infections (%)</th>
<th>% E.coli</th>
<th>% FQ Res.</th>
<th>ESBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young et al</td>
<td>US</td>
<td>1,423</td>
<td>5 (0.4)</td>
<td>100%</td>
<td>100%</td>
<td>3 ESBL</td>
</tr>
<tr>
<td>Zaytoun et al</td>
<td>US</td>
<td>1,446</td>
<td>9 (0.6)</td>
<td>78%</td>
<td>57%</td>
<td>0 ESBL</td>
</tr>
<tr>
<td>Womble et al</td>
<td>US</td>
<td>3,911</td>
<td>35 (0.9)</td>
<td>91%</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>Carignan et al</td>
<td>Canada</td>
<td>5,798</td>
<td>48 (0.8)</td>
<td>75%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>Lange et al</td>
<td>Canada</td>
<td>4,749</td>
<td>16 (0.3)</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Hadway et al</td>
<td>UK</td>
<td>256</td>
<td>7 (2.7)</td>
<td>71%</td>
<td>100%</td>
<td>4 ESBL</td>
</tr>
<tr>
<td>Horcajada et al</td>
<td>Spain</td>
<td>411</td>
<td>11 (2.7)</td>
<td>73%</td>
<td>55%</td>
<td>4 ESBL</td>
</tr>
<tr>
<td>Simsir et al</td>
<td>Turkey</td>
<td>2,033</td>
<td>62 (3)</td>
<td>74%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Patel et al</td>
<td>UK</td>
<td>316</td>
<td>10 (3.2)</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Loeb et al</td>
<td>Neth.</td>
<td>10,474</td>
<td>72 (0.7)</td>
<td>88%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Carmignani et</td>
<td>Italy</td>
<td>447</td>
<td>9 (0.2)</td>
<td>89%</td>
<td>88%</td>
<td>6 ESBL</td>
</tr>
</tbody>
</table>
Infection-related hospitalizations after prostate biopsy in a statewide quality improvement collaborative

• Evaluated all MI men that underwent TRUS biopsy from 2012 – 2013
• FQ prescribed in 96% of procedures

• 30 day hospitalization = 0.97%
  – 92% for infectious complications (n=35)
    • 30/33 for E. coli, 3/33 P. aeruginosa
    • 26/33 Resistant to fluoroquinolones

What to do? A few options

| Nothing. These Infections are relatively rare with low mortality. |
| Offer alternative prophylaxis based on risk factors for antimicrobial resistance. |
| Give alternative prophylaxis in those with FQ resistance on a rectal culture screen. |
What to do? A few options

Offer alternative prophylaxis based on risk factors for antimicrobial resistance.
### Risk Factors

#### For Post Biopsy Infection
- Medical Co-morbidities
  - Diabetes
- Recent hospitalization
- Recent travel
- Prior antibiotic use
- Urological pathology
- Long term catheters
- Asymptomatic bacteriuria
- Prostate size, malignancy
- Number of cores
- Second TRUS biopsy
- Lack of prebiopsy enema

#### For FQ resistant *E. coli*
- Prior antibiotic use
- Travel

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**Not enough consistent data for a universal recommendation!**
Pre – TRUS Biopsy Urine Culture

• Value of routine urine culture and prebiopsy treatment of asymptomatic bacteriuria remains controversial

• Conflicting studies: some yes, some no

What to do? A few options

- Nothing. These infections are relatively rare with low mortality.
- Offer alternative prophylaxis based on risk factors for antimicrobial resistance.
- Give alternative prophylaxis in those with FQ resistance on a rectal culture screen.
Role of Targeted Antimicrobial Prophylaxis

• Is fecal carriage of FQ resistant *E. coli* a risk factor?

Prospective Belgium Study\(^1\)
- 58 with FQ Res Organism → 7 infections
- 178 with FQ Sen Organism → 0 infections

• Approximately 20% with stool carriage\(^{1,2}\)

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\(^1\)Clin Microbiol Infect 2012; 18: 575–581
\(^2\)J Urol 2011; 185; 1283-1288
Targeted Antimicrobial Prophylaxis Using Rectal Swab Cultures in Men Undergoing Transrectal Ultrasound Guided Prostate Biopsy is Associated With Reduced Incidence of Postoperative Infectious Complications and Cost of Care

Aisha K. Taylor, Teresa R. Zembower, Robert B. Nadler, Marc H. Scheetz, John P. Cashy, Diana Bowen, Adam B. Murphy, Eliodi Dielubanza and Anthony J. Schaeffer*,†

From the Department of Urology (AKT, RBN, JFC, DB, ABM, ED, AJS) and Department of Medicine, Division of Infectious Diseases (TRJ), Northwestern University Feinberg School of Medicine, Department of Pharmacy, Northwestern Memorial Hospital (MHS), Chicago, and Department of Pharmacy Practice, Midwestern University Chicago College of Pharmacy (MHS), Downers Grove, Illinois

**Purpose:** We evaluated targeted antimicrobial prophylaxis in men undergoing transrectal ultrasound guided prostate biopsy based on rectal swab culture results.

**Materials and Methods:** From July 2010 to March 2011 we studied differences in postoperative infections between men who received targeted vs standard empirical ciprofloxacin prophylaxis before transrectal ultrasound guided prostate biopsy. Targeted prophylaxis used rectal swab cultures plated on selective media containing ciprofloxacin to identify fluoroquinolone resistant bacteria. Patients with fluoroquinolone susceptible organisms received ciprofloxacin while those with fluoroquinolone resistant organisms received directed antimicrobial prophylaxis. We identified men with infections within 30 days after transrectal ultrasound guided prostate biopsy using the electronic medical record.

**Results:** A total of 457 men underwent transrectal ultrasound guided prostate biopsy, of whom 112 (24.5%) had rectal swab obtained while 345 (75.5%) did not. Among those who received targeted prophylaxis 22 (19.6%) men had fluoroquinolone resistant organisms. There were no infectious complications in the 112 men who received targeted antimicrobial prophylaxis, while there were 9 cases (including 1 of sepsis) among the 345 on empirical therapy (p = 0.12). Fluoroquinolone resistant organisms caused 7 of these infections. The total cost of managing infectious complications in patients in the empirical group was $13,219. The calculated cost of targeted vs empirical prophylaxis per 100 men undergoing transrectal ultrasound guided prostate biopsy was $1,345 vs $5,596, respectively. Cost-effectiveness analysis revealed that targeted prophylaxis yielded a cost savings of $4,499 per post-transrectal ultrasound guided prostate biopsy infectious complication averted. Per estimation, 38 men would need to undergo rectal swab before transrectal ultrasound guided prostate biopsy to...
Cost Considerations

Screening (micro)
Labor
Alternative antibiotics
Treatment of fewer infections

Treatment of relatively few infections
An ID physician’s opinion

1. Understand your local microbiology
2. If possible, evaluate risk factors for FQ resistant *E. coli*
   - Recent hospitalization
   - Prior antibiotics
   - Prior cultures
   - Travel
3. Consider rectal screening those with risk factors and work closely with the microbiology laboratory
4. Develop alternative prophylaxis strategy in conjunction with Infectious Diseases
Conclusion

- Resistance is inevitable, antibiotics just speed up the process
- FQ resistance *E. coli* is increasing and not going anywhere
- Stewardship in performing prostate biopsies should not be lost
- Resistance is local
- Prophylaxis will never be perfect
Thank You

Questions?

eddie.stenehjem@imail.org
Asymptomatic Bacteriuria

The Role of Asymptomatic Bacteriuria in Young Women With Recurrent Urinary Tract Infections: To Treat or Not to Treat?

Tommaso Cai,1 Sandra Mazzioli,2 Nicola Mondaini,1 Francesca Meacci,2 Gabriella Nesi,4 Carolina D’Elia,4 Gianni Malossini,1 Vieri Boddi,3 and Riccardo Bartoletti2

1Department of Urology, Santa Chiara Hospital, Trento; 2Sexually Transmitted Disease Centre, Santa Maria Annunziata Hospital, Florence; 3Department of Urology, 4Division of Pathological Anatomy, Department of Critical Care Medicine and Surgery, and 5Department of Public Health and Epidemiology, University of Florence, Italy

Should AB be treated in women affected by recurrent UTI, after antibiotic treatment?
<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≥ 1 Symptomatic UTI in last 12 months</td>
<td>• Cystitis Symptoms</td>
</tr>
<tr>
<td>• ≥10⁵ CFU (100,000) of a uropathogen on 2 consecutive urine Cx</td>
<td>• Abx in past 4 weeks</td>
</tr>
<tr>
<td>– Enteric Gram Negatives</td>
<td>• Urinary Catheter</td>
</tr>
<tr>
<td>– Enterococcus</td>
<td>• Known Urinary/Renal Abnormality</td>
</tr>
<tr>
<td>– S Saprophyticus</td>
<td>• Symptoms or Dx of STD</td>
</tr>
<tr>
<td>– GBS</td>
<td>• Pregnancy/Lactation/Menop</td>
</tr>
<tr>
<td>• Age 18 – 40</td>
<td>• Major Disease</td>
</tr>
<tr>
<td>• Sexually Active</td>
<td>• New Contraception</td>
</tr>
</tbody>
</table>
## Primary Outcome

### Development of symptomatic UTI

<table>
<thead>
<tr>
<th></th>
<th>No Antibiotics</th>
<th>Antibiotics</th>
<th>95% Confidence Interval</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 312</td>
<td>N = 361</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 mo</td>
<td>0%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>3.5%</td>
<td>8.8%</td>
<td>1.01–1.10</td>
<td>0.051</td>
</tr>
<tr>
<td>6 mo</td>
<td>7.6%</td>
<td>29.7%</td>
<td>1.21–1.42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>12 mo</td>
<td>14.7%</td>
<td>73.1%</td>
<td>2.55–3.90</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asx</td>
<td>237/312 (76%)</td>
<td>62/361 (17%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treating asymptomatic bacteriuria leads to more recurrent UTIs

- Who do you treat with asymptomatic bacteriuria:
  - Pregnant
  - Undergoing urologic procedures
  - Kidney transplant
  - Febrile neutropenia