UTI: The Changing Culture

Dr Ramasubramanian

Chennai
during preparation for pathology
this is so simple to identify

during exam
UTI: Epidemiology

- Definition
- Most frequent bacterial infection in OP setting
- 50% women in their lifetime (20% between 20 – 65)
- Men vs. women (1:50)
- Pathogenesis & public toilets
Understanding UTI

- Pyuria - >10 pus cells / hpf
- Bacteriuria - >10^5 cfu / ml
- UTI – Pyuria + bacteriuria
- Asymptomatic bacteriuria – Absence of genito-urinary symptoms
- Symptomatic UTI – Bacteriuria with genito-urinary symptoms
- Complicated UTI – Underlying condition that increases risk of therapy failing
Classification of UTI

• Uncomplicated UTI:
  – lack structural / functional abnormalities of urinary tract
  – No interference with the normal flow of urine

• Complicated UTI:
  – characterized by the presence of structural or functional abnormalities (e.g. urinary obstructions), metabolic and/or hormonal abnormalities (diabetes mellitus, pregnancy, renal impairment, etc.), and impaired host responses (transplant recipients, neutropenic patients, etc.) or MDRO
## Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Uncomplicated UTI</th>
<th>Complicated UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age/Gender</strong></td>
<td>Sexually active young women</td>
<td>Middle-age men, elderly women</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Community-acquired</td>
<td>Nosocomial</td>
</tr>
<tr>
<td><strong>Comorbid Conditions</strong></td>
<td>Healthy</td>
<td>Functional, metabolic, or structural abnormality</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Localized</td>
<td>Localized</td>
</tr>
<tr>
<td><strong>Consequences</strong></td>
<td>Self-limited</td>
<td>Bacteremia</td>
</tr>
</tbody>
</table>

55yr old lady

- Low grade fever
- Dysuria
- Abd pain
- Urine R/E

CBC – N
USG – KUB - Normal

**URINE:**
- Albumin: Trace
- Sugar (R-): Nil
- Deposits: Plenty of Pus cells are seen/HPF
- 4-5 epithelial cells are seen/HPF
- 4-5 pus cells cast are seen/HPF
Dilemma

• Would you send a urine culture?
• What empiric antibiotic would you start?
• How long would you treat?
• Would you repeat a culture after treatment?
• How would you manage recurrent infections?
Our heads are round so that our thinking can change directions

Picabia
Dilemma

• Would you send a urine culture?

• What empiric antibiotic would you start?

• How long would you treat?

• Would you repeat a culture after treatment?

• How would you manage recurrent infections?
Antibiotic selection considerations

- Bacterial etiology
- Local antibiotic resistance patterns
- Pharmacokinetics
  - Drug concentration in urinary tract
  - Once daily vs multiple daily doses
- Safety (adverse events, allergies)
- Patient age
- Prior antibiotic courses
- Effects on normal enteric and vaginal flora

Hooton TM et al, N Engl J Med 1996; 335; 468-474
Hooton TM, Stamm WE, Infect Dis Clin North Amer 1997;11, 551-581
Dilemma

• Would you send a urine culture?
• What empiric antibiotic would you start?
• How long would you treat?
• Would you repeat a culture after treatment?
• How would you manage recurrent infections?
The Study for Monitoring Antimicrobial Resistance Trends (SMART) began collecting data on UTI in late 2009.

Species distribution of different Gram-negative bacteria associated with urinary tract infection from 14 hospitals of seven countries in Asia. (SMART, 2009)

P.-R. Hsueh et al. Journal of Infection (2011) 63, 114e123
Worldwide increasing prevalence of resistance...e.g., ESBLs

The Indian data is even more disconcerting ...

Annals of Clinical Microbiology and Antimicrobials 2007; 6:4
Diagnostic Microbiology and Infectious Disease 2002; 44: 367–377
Indian J Med Res December 2004; 120: 553-556

Interscience Conference on Antimicrobial Agents and Chemotherapy (43rd: 2003: Chicago, Ill.).
Clin Microbiol Infect 2008; 14 (Suppl. 1): 154–158
Med Princ Pract 2008;17:32–36
Clinical Infectious Diseases 2001; 32(Suppl 2):S94–103
Rates of E. coli isolates exhibiting extended-spectrum β-lactamase (ESBL) phenotype. All these isolates were collected from patients with urinary tract infection from 14 hospitals of seven countries in Asia. (SMART, 2009)

P.-R. Hsueh et al. Journal of Infection (2011) 63, 114e123
Evaluation of extended spectrum beta lactamase in urinary isolates

Supriya S. Tankhiwale, Suresh V. Jalgaonkar, Sarfraz Ahamad & Umesh Hassani

Department of Microbiology, Government Medical College, Nagpur, India

Results: Of the 217 isolates, 87 were cephotaxime resistant Gram-negative bacilli. Of these, 42 (48.3%) were found to be ESBL producers. Escherichia coli, Klebsiella pneumoniae and Acinetobacter were ESBL producing species. Multidrug resistance was found to be significantly (P<0.05) more in ESBL producing isolates (90.5%) than non ESBL producers (68.9%).

Interpretation & conclusion: In the present study a large number of uropathogens were found to be ESBL producers. Most of the ESBL producing isolates were multidrug resistant. Monitoring of ESBL production and antimicrobial susceptibility testing are necessary to avoid treatment failure in patients with UTI.
E. Coli sensitivity pattern to Ciprofloxacin

- Sensitivity Pattern to Ciprofloxacin
  - 2005: 23.6%
  - 2006: 10.7%
  - 2007: 16.5%
  - 2008: 17.8%
  - 2009: 16.7%
  - 2010: 23.0%

- Average (18.1%)

E. Coli - ESBL producers

- Sensitivity Pattern to ESBL
  - 2005: 61.5%
  - 2006: 64.6%
  - 2007: 78.6%
  - 2008: 75.7%
  - 2009: 74.7%
  - 2010: 75.7%

- Average (71.8%)

- Trend
Risk factors for community acq. ESBL

- DM
- Previous antibiotic exposure
- Previous hospital admission
- Older age
- Male patients
Older Antibiotics

• Mecillinam (UK)
  Only against GNB
  UTI, Salmonellosis
  Stable against betalactamases (400mg BD po 4-7d)

• Fosfomycin (po / iv)
  Uncomplicated UTI – 3g (every 2 days X 3)
  iv 6g QID
  Poor activity against pseudomonas & acinetobacter
Older Antibiotics

• Temocillin (UK)
  Septicemia (2g BID), UTI
  ESBL, AmpC, MBL stable
  Not active against pseudomonas & anerobes

• Nitrofurantoin
  Not active - pseudomonas, proteus, some kleb.
  Quick renal filtration
  Dose – 100mg BD / TID X 5-7d
  Cr cl <60 caution, <10 no use
Limitations

- Nitrofurantoin
- Fosfomycin
- β-lactam-β-lactamase inhibitors – oral vs. parenteral
- Aminoglycosides
- Carbapenems
- Colistin
- Tigecycline
Dilemma

• Would you send a urine culture?
• What empiric antibiotic would you start?
• How long would you treat?
• Would you repeat a culture after treatment?
• How would you manage recurrent infections?
Management of Urinary Tract Infection (UTI)

**Lower UTI** (Cystitis)
- ESBL
  - Nitrofurantoin (3-7 days)
- Non-ESBL
  - Cotrimoxazole, Amoxicillin, Amoxicillin-Clavulanate, Cefuroxime, Ofloxacin, Norfloxacin (3-7 days)

**Upper UTI** (Bacteremic UTI, Pyelonephritis, Urosepsis)
- Pseudomonas
  - Imipenem / Meropenem / BL-BLI+/− Amikacin (7-14 days)
  - ESBL &/or AmpC
    - Ertapenem (10-14 days)
- Non-Pseudomonas
  - Non-ESBL
    - Amoxicillin-Clav, Ampicillin-Sulb, Ofloxacin, Norfloxacin, Ceftriaxone (7-10 days)
    - Vancomycin/Teicoplanin for Resistant GPB

*BL-BLI*: Empiric in mild cases; De-escalation if sensitive & patient stable; Definitive
Dilemma

- Would you send a urine culture?
- What empiric antibiotic would you start?
- How long would you treat?
- Would you repeat a culture after treatment?
- How would you manage recurrent infections?
Asymptomatic bacteriuria (ASB)

- Definition
- Pyuria accompanying ASB
- Progression
- Indications for therapy – Pregnancy, urethral manipulation
- Screening not recommended – non-pregnant women, diabetics, elderly, spinal cord injury, catheterized patients
Asymptomatic bacteriuria

• In children
• In pregnancy
• In pre-op patients
• In immuno-compromised pts
• In diabetics
• In catheterised pts
Dilemma

• Would you send a urine culture?
• What empiric antibiotic would you start?
• How long would you treat?
• Would you repeat a culture after treatment?
• How would you manage recurrent infections?
Three urologic factors—namely, incontinence (41% of case patients vs. 9.0% of control patients; ), presence of a cystocele P  0.001 (19% vs. 0%; P  0.001), and postvoiding residual urine (28% vs. 2.0%; P = 0.00008)—were all strongly associated with recurrent UTI. Multivariate analysis showed that urinary incontinence (odds ratio [OR], 5.79; 95% confidence interval [CI], 2.05–16.42;P = 0.0009), a history of UTI before menopause (OR, 4.85; 95% CI, 1.7–13.84; P = 0.003), and nonsecretor status (OR, 2.9; 95% CI, 1.28–6.25; P = 0.005) were most strongly associated with recurrent UTI in postmenopausal women.
Managing Recurrent UTI

- History – post-coital, episodic chills, prostatic symp.
- Examination – phimosis, balano-posthitis
- Obstruction (papillary necrosis)
- Imaging
- Prostatitis
- Cystoscopy
- Chronic suppressive prophylaxis
Evidence does not make decisions, people do.

Bryan Haynes
Indian scenario: lessons learnt...

IT HAPPENS ONLY IN INDIA

EMERGENCY CLINIC
Dr. R.S. Chaudhary (Advocate)
B.J.M. (Lucknow)
Physician & Surgeon
Skin Specialist
UTI in India - 2017

- Safe (AG)
- Susceptibility pattern (FQ)
- Cost (Carbapenems)
- Ease of administration – OPAT
- Efficacy / urinary concn.
- Preventing recurrence
EFFICACY & COST OF ERTAPENEM AS OPAT IN ACUTE PYELONEPHRITIS DUE TO ESBL PRODUCING ENTEROBACTERIACEAE

V.Ramasubramanian1, P.Muralidharan2, S.Nambi1, S.Pavithra1, S.Puthran2, T.Petigara1.
1 Apollo Hospital, Chennai, 2 KIMS Trivandrum, 3 MSD Pharmaceuticals Pvt. Ltd, Mumbai.

INTRODUCTION
Acute pyelonephritis (APN) is associated with significant morbidity & often requires hospitalization. However, OPAT could be a clinically effective cost saving option in select patients.

AIM
Primary objective was to evaluate the clinical response of Ertapenem in ESBL positive APN. Secondary objective was to evaluate the cost effectiveness of Ertapenem under OPAT vs inpatient settings.

METHODS AND MATERIALS
A retrospective analysis was conducted at 2 centers for ESBL positive APN from 2010-2014. Patient demographics, clinical response & treatment costs were collected from hospital records. Response to Ertapenem & cost of treatment in inpatient vs OPAT settings were compared using Pearson's chi square or Fisher's exact test for categorical variables. ANOVA (or Kruskal Wallis) was used for continuous variables.

Inclusion/Exclusion Criteria: Data of all adult patients with a diagnosis of APN & who received more than 3 doses of Ertapenem therapy were included for analysis. APN was defined as patients with fever, flank pain or costovertebral angle tenderness, pyuria ≥5 WBCs/HPF or urinary symptoms and confirmed ESBL enterobacteriaceae on urine culture. Patients who required concomitant antimicrobials in addition to Ertapenem were excluded.

RESULTS
100 patients were evaluated for response to Ertapenem in APN [hospital only (10), hospital/OPAT (63), OPAT only (27)]. Diabetes (71%), hypertension (40%), renal (19%) & cardiac (11%) disorders were the major co-morbidities. Fever (85%), abdominal pain (45%), dysuria (41%), vomiting (36%) & chills (35%) were main presenting features.

Baseline urine cultures were ESBL positive with 98% prevalence of GNB (E.coli 89%, Klebsiella 9%). Only Ertapenem, Imipenem & Meropenem showed 100% sensitivity to ESBL positive GNB. Complete clinical resolution with Ertapenem was seen in 96%, absence in 2 & information was unavailable for 2 patients. Amongst patients showing complete resolution, 82 received definitive & 14 received empirical treatment with Ertapenem. 60 patients received Ertapenem both during IP & OPAT, 26 only as OPAT & 10 only as inpatients.

A significant reduction in treatment costs was seen in patients who received Ertapenem as OPAT (p < 0.05). Median charges (IQR 2014) were - Hospital only (2,64,302), Hospital/OPAT (1,89,554) and OPAT only (41,380).

CONCLUSIONS
Ertapenem showed 100% sensitivity & complete clinical resolution for 96% patients with APN due to ESBL Enterobacteriaceae. It was administered as OPAT in 90% patients & significantly reduced overall treatment costs. Additional studies monitoring adverse events are needed to better define when in-hospital treatment is required.

References:
TABLE 1: CLINICAL OUTCOMES

<table>
<thead>
<tr>
<th>RESPONSE BY TREATMENT GROUP</th>
<th>CLINICAL RESOLUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital only (n = 10)</td>
<td>YES (100%)</td>
</tr>
<tr>
<td>Hospital + OPAT (n = 63)</td>
<td>60 (95%)</td>
</tr>
<tr>
<td>OPAT only (n = 27)</td>
<td>26 (96%)</td>
</tr>
</tbody>
</table>

TABLE 2: PER PATIENT CHARGES BY TREATMENT GROUP (INR 2014) - APOLLO

<table>
<thead>
<tr>
<th>GROUP</th>
<th>N</th>
<th>MEAN</th>
<th>MEDIAN</th>
<th>MIN</th>
<th>MAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital only*</td>
<td>5</td>
<td>3,40,670</td>
<td>2,04,302</td>
<td>67,304</td>
<td>6,84,224</td>
</tr>
<tr>
<td>Hospital + OPAT</td>
<td>41</td>
<td>2,03,268</td>
<td>1,89,554</td>
<td>72,308</td>
<td>5,82,416</td>
</tr>
<tr>
<td>OPAT only**</td>
<td>22</td>
<td>37,497</td>
<td>41,380</td>
<td>14,750</td>
<td>44,180</td>
</tr>
</tbody>
</table>

*One patient was excluded from hospital only group who had 2 hospital days | **One patient was excluded from OPAT only group who had 3 OPAT days

TABLE 3: PER PATIENT CHARGES BY TREATMENT GROUP (INR 2014) - KIMS

<table>
<thead>
<tr>
<th>GROUP</th>
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<th>MIN</th>
<th>MAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital only</td>
<td>4</td>
<td>1,61,406</td>
<td>1,23,510</td>
<td>30,574</td>
<td>3,48,029</td>
</tr>
<tr>
<td>Hospital + OPAT</td>
<td>22</td>
<td>87,103</td>
<td>81,716</td>
<td>30,508</td>
<td>1,79,557</td>
</tr>
<tr>
<td>OPAT only**</td>
<td>4</td>
<td>21,589</td>
<td>17,718</td>
<td>13,598</td>
<td>37,320</td>
</tr>
</tbody>
</table>

CONCLUSION

Ertapenem showed 100% sensitivity & complete clinical resolution for 96% patients with APN due to ESBL Enterobacteriaceae. It was administered as OPAT in 90% patients & significantly reduced overall treatment costs. Additional studies monitoring adverse events are needed to better define when in-hospital treatment is required.

REFERENCES:
Thank you