Appropriate Use of Antibiotics

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Outline

• **What** is inappropriate/appropriate use?

• **When** – whenever we encounter a patient, or work in a farm

• **Where** – anywhere, will limit only to healthcare facilities in this talk

• **Why** – everyone know

• **How** – case demo
Concept of appropriate use of antibiotic
Optimal Antimicrobial Therapy

• Clear or convincing evidence of bacterial infection
• Select an agent or a regimen that is “broad” enough but not too broad
• Avoid combinations
• Give antibiotic in a timely manner
Optimal Antimicrobial Therapy

- Follow pharmacokinetics and pharmacodynamics rules
  - Peak, $T_{1/2}$, tissue distribution, route of excretion
- Stop when not in need
- Prophylactic use has its own indications and considerations
Consequence of inappropriate use of antibiotics

• A 90-year-old, ex-police was admitted due to cardiac failure
• He received several drugs, including ceftriaxone for presumed UTI
Consequence of inappropriate use of antibiotics

- Later he developed rashes which was thought to be sepsis.
Consequence of inappropriate use of antibiotics

- All antimicrobial agent was D/C, he did well.
- 2 weeks later, rash popped up again
- He underwent cardiac pace maker placement a week ago and a cephalosporin was prescribed!!!
Pseudomembranous colitis
อัตราการดื้อยาของเชื้อ A. baumannii และอัตราการใช้ยากลุ่ม carbapenem

Microbiology Lab Data, Department of Pathology
The Antimicrobial Committee
Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis

- Original research regarding quantitative relationships between primary care prescribed ATB and subsequent ATBR at the level of the individual
- Not ecological studies
- Antibiotics given by prescription only

Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis

- 5 RCTs, 19 observational studies (2 prospective, 17 retrospective controlled observational or case control studies)
- 22 studies sampled bacteria from patients with symptomatic infection

Forest plot showing individual study and pooled ORs (log scale) for resistance in respiratory tract bacteria and antibiotic exposure

Antibiotics Commonly PRESCRIBED for “URI”

- Amoxicillin
- Amoxi/clav
- Levofloxacin
- Moxifloxacin
- Azithromycin, clarithromycin

Risk factors for acquisition of ESBL producers
What antibiotic would you give?
What antibiotic would you give?
What antibiotic would you give?
Antibiotic Smart Use

• Promote appropriate use of ATB in three common infection in OPD
  – Upper respiratory tract infection
  – Acute diarrhea
  – Clean wound
Throat swab cultures found group A β-hemolytic streptococci in 3.8% of URI patients whereas stool cultures found non-typhoidal *Salmonella* sp. in 14.6% of AD patients. Clinical responses on day 3 after receiving care for URI and AD between the patients who received and who did not receive antibiotics were not significantly different as shown in Table 2.

**Table 2. Clinical response on day 3 after therapy**

<table>
<thead>
<tr>
<th></th>
<th>Improved</th>
<th>Cure</th>
<th>Not Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>URI (N=1,241)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Antibiotics</td>
<td>60.2%</td>
<td>39.1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>• No Antibiotics</td>
<td>62.5%</td>
<td>36.9%</td>
<td>0.6%</td>
</tr>
<tr>
<td><strong>AD (N=210)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Antibiotics</td>
<td>30.0%</td>
<td>67.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>• No Antibiotics</td>
<td>30.6%</td>
<td>69.4%</td>
<td>---</td>
</tr>
</tbody>
</table>
Centor Criteria

- Aid diagnosis of Group A beta-haemolytic streptococcus pharyngitis
  - tonsillar exudate
  - tender anterior cervical lymph nodes
  - absence of cough
  - history of fever
- Presence of 3 or 4 of these signs
  ✔ antibiotic treatment
Asymptomatic Bacteriuria in Young Women With Recurrent UTI: Rx or Not

- 673 consecutive asymptomatic young women with demonstrated bacteriuria
- Group A, not treated (312)
- Group B, treated (361)
- Main outcome: recurrence-free rate at the end of the entire study period

## Main findings

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Enrollment)</th>
<th>First (3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>312</td>
<td>361</td>
</tr>
<tr>
<td>QoL score (±SD)</td>
<td>0.82 ± 0.03</td>
<td>0.81 ± 0.06</td>
</tr>
<tr>
<td>No bacterial growth</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>120 (38.4)</td>
<td>142 (39.3)</td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>102 (32.7)</td>
<td>120 (33.2)</td>
</tr>
</tbody>
</table>

## Main findings

<table>
<thead>
<tr>
<th></th>
<th>Second (6 months)</th>
<th>Third (12 months)</th>
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<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>23</td>
<td>98</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>278</td>
<td>231</td>
</tr>
<tr>
<td>QoL score (±SD)</td>
<td>0.81 ± 0.06</td>
<td>0.52 ± 0.01</td>
</tr>
<tr>
<td>No bacterial growth</td>
<td>27 (9.7)</td>
<td>21 (9.0)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>68 (24.4)</td>
<td>142 (61.5)</td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>149 (53.5)</td>
<td>36 (15.6)</td>
</tr>
</tbody>
</table>

Infectious Diseases in Surgery

- Antibiotic prophylaxis in surgery
- Post operative infection
  - UTI
  - Pneumonia
  - Phlebitis
  - Wound infection
  - Specific infections related to surgery i.e. intra-abdominal abscess, anastomosis leakage, biliary infection post biliary surgery
Antimicrobial Prophylaxis in Surgery

• Prevent postoperative infection of the surgical site
• An anti-infective drug should be:
  active against the pathogens most likely to contaminate the wound
  given in an appropriate dosage and at a time that ensures adequate concentrations at the incision site during the period of potential contamination
  safe
  administered for the shortest effective period to minimize adverse effects, development of resistance, and cost.
Antimicrobial Prophylaxis in Surgery

• clean operations: *S. aureus* and *S. epidermidis*
  – **Cefazolin**: relatively long duration of action, effective against the organisms most commonly encountered in surgery, low cost

• clean-contaminated operations: GI and GU pathogen—*Escherichia coli, Proteus* species, *Klebsiella* species, staphylococci, streptococci, enterococci, anaerobes; *Bacteroides* species
  – Cefoxitin
Antimicrobial Prophylaxis in Surgery

• Timing: within 30 minutes to 1 hour before the incision, at the time of induction of anesthesia

• Duration: should be 24 hours or less, with the exception of cardiothoracic procedures (up to 48 hours’ duration)

• Redosing: base on renal function, if
  – Operation is expected to last > 6-8 hours.
  – Prolonged or excessive bleeding
  – Factors that may shorten the half-life of the antimicrobial (e.g., extensive burns).
Ertapenem versus Cefotetan Prophylaxis in Elective Colorectal Surgery

Kamal M.F. Itani, M.D., Samuel E. Wilson, M.D., Samir S. Awad, M.D., Erin H. Jensen, M.S., Tyler S. Finn, B.A., and Murray A. Abramson, M.D., M.P.H.
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<tr>
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<tbody>
<tr>
<td></td>
<td>Ertapenem (N = 338)</td>
<td>Cefotetan (N = 334) Absolute Difference</td>
</tr>
<tr>
<td></td>
<td>no. (%)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Any failure</td>
<td>95 (28.0)</td>
<td>143 (42.8)</td>
</tr>
<tr>
<td>Surgical-site infection</td>
<td>62 (18.1)</td>
<td>104 (31.1)</td>
</tr>
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NNIS index category 3 SSI rate ≈13.3% during 2002-2004

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<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Any failure</td>
<td>182 (40.2)</td>
<td>229 (50.9)</td>
</tr>
<tr>
<td>Surgical-site infection</td>
<td>78 (17.1)</td>
<td>118 (26.2)</td>
</tr>
</tbody>
</table>
Risk factors for the acquisition of carbapenem-resistant *E. coli* among hospitalized patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% C.I.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem use</td>
<td>6.50</td>
<td>2.33–18.16</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Metronidazole use</td>
<td>4.25</td>
<td>1.56–11.59</td>
<td>0.005</td>
</tr>
<tr>
<td>Presence of biliary drainage catheter</td>
<td>4.59</td>
<td>1.18–17.78</td>
<td>0.028</td>
</tr>
<tr>
<td>Prior hospital stay (&lt;1 year)</td>
<td>1.02</td>
<td>1.00–1.03</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Predictors of Carbapenem-R *K. pneumoniae* Acquisition among Hospitalized Adults and Effect of Acquisition on Mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission (within 2 wk)</td>
<td>0.031</td>
<td>4.68 (1.15–19.09)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>0.006</td>
<td>12.69 (2.09–77.10)</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>0.032</td>
<td>3.57 (1.11–11.42)</td>
</tr>
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Example 1

- ผู้ป่วยหญิง อายุ 80 ปี มา admit ด้วยปัญหา NSTEMI CAG plan CABG
- หลัง admit ผู้ป่วยได้รับ imipenem เป็น antibiotic prophylaxis ก่อนผ่าตัดประมาณ 2 วัน
- ขณะผ่าตัดมีปัญหา BP drop และมีสาย A line + C line จากห้องผ่าตัด
Example 1

• เมื่อออกจากห้องผ่าตัดผู้ป่วยได้รับการทำ central line ใหม่อีกครั้ง เพราะเส้นที่ทำมาจากห้องผ่าตัดใช้การไม่ได้

• แพทย์ได้พยายามแทงเส้นใหม่ประมาณ 5 ครั้ง จึงสำเร็จ

• ต่อมาผู้ป่วยพบเหนื่อยมากขึ้น CXR มี new multiple patchy infiltrations consistent with blood-borne pneumonia ผู้ป่วยยังได้ imipenem ตามเดิม
Example 1

• 3 วันต่อมาอาการไม่ดีขึ้น ยังมีอาการหนอนเหนื่อย เสมหะมาก vital sign unstable (on inotropic drug)
• ได้ add Vancomycin + Amikacin 1 dose
• ผล sputum culture =Carbapenem-R Acinetobacter baumanii และ MRSA
Example 1

- หลังจากนั้น pneumonia progress to ARDS มี septic shock อีก 2 ครั้ง source คิดว่าน่าจะเป็นมาจากปอด แต่ยังเชื่อมไม่ได้ชัดเจน
- ท้ายสุดคิดว่าน่าจะมี candidemia ร่วมด้วย
- ผู้ป่วยเสียชีวิต
Example 2

- ชายอายุ 82 ปี admit ด้วยปัญหา heart filure
- ทำ cardiac cath พบว่ามี triple vessel disease; plan ทำ CABG
- ผู้ป่วยปัสสาวะไม่ออกระหว่างการทำ cath จึงคะASA 4 ปัสสาวะไว้
- หลังจากนั้น 1 วัน ผู้ป่วยมีอาการไข้หน้าส้น UA มี WBC 50-100/HPF
Example 2

- sang blood, urine culture
- Start antibiotic
  - ????
- Patient received meropenem 3 days, then switched to "simple" *E. coli* for culture positive. Antibiotic was changed to ceftriaxone for 10 days, UA was normal.
- Performed CABG 2 days later.
Example 2

• Which antibiotic for surgical prophylaxis?
Surgical Prophylaxis: Summary

• NO broad-spectrum antibiotic for prophylaxis, almost absolutely
• NO carbapenem, vancomycin, or ciprofloxacin
• Give at the right time, right dose, with supplemental dose
• NOT beyond 24 hours after surgery
Infectious Diseases at ER

- Bacterial sepsis is common
- Most common causes of community-acquired sepsis: *E. coli*, streptococci, *B. pseudomallei*, and salmonella
- Most common anatomical sites: respiratory tract, intra-abdominal, urinary tract, skin and soft tissue
Case 1

- 65-year-old man with IHD, HTN, CKD
- High fever for 1 week
History of present illness

• 1 month PTA:
  – Cough with sputum, no hemoptysis
  – Fever in the evening
  – Fatigue, N/V, weight loss 3 kg
History of present illness

- 1 wk PTA:
  - High fever
  - Dyspnea, no PND, no edema
  - Decreased urination

PH: Old pulmonary TB Dx 30 years, treated for 1 year >> no symptom
Physical Examination

- V/S: T 37°C, PR 96/min, RR 30/min, BP 80/50 mmHg
- GA: Tachypnea, drowsy, follow to simple command
- Lungs: trachea in midline, medium crepitation both lung, decreased breath sound and decreased vocal resonance RLL
Problem list

- Shock DDx: hypovolemic, antihypertensive, sepsis
- HTN, IHD
- ARF ontop CKD with acidosis
Laboratory results

• WBC: 19,770 cells/mm$^3$, Plt 522,000; 90% PMN
• U/A: WBC 3-5/HPF, RBC 10-15/HPF
• Na 131 mEq/mL, K 5.7 mEq/mL, Cl 98 mEq/mL, CO$_2$ 13.4 mEq/mL
• ABG: metabolic acidosis with respiratory alkalosis
Management at ER

- Dx: “CAP”
- Antibiotics: ceftriaxone + clarithromycin
- Admit 7SW
- Admission day 5: dyspnea, cardiac arrest
Microbiological results

- Mycobacterium H/C: *M. tuberculosis*
- Pleural fluid Mycobacterium C/S: no growth 60 days
**Case 2**

<table>
<thead>
<tr>
<th>Pt ID</th>
<th>Route</th>
<th>Drug</th>
<th>D/C Date</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

- **Diagnosis:** Pneumonia
- **Plan:**
  - Azithromycin 500 mg
  - Bisulfram 1x3 daily
  - Clamicit 1900x3
  - Paracetamol 500mg 6 hourly
- **Notes:**
  - No underlying disease
  - Diagnosed: 12/07/2016
  - Discharged: 04/08/2016
  - Comment: Tensive Tension

*Updated 18/08/2016 by xxxxxx.*
Case 3

HCV CHB abs NM HT

Foliv 1x1, NPH 1x 50cc hs, lactulose 30ml od

PB drawing not well co-operative mark pale, much jaundice

Hb 8.6, Abdl soft

Imp: Hepatic Encephalopathy

Rs: - lactulose 30ml c until dry (CO2 fl)
- 6/m plt 80 x1000
- supportive tx.
What is your idea?
Case 3

- WBC 26.7 k, 92% PMN, 2% band; Plt 14,000
- Admitted ICU
- ต่อม มาผู ป่วยชัก ตรวจพบ stiffness of neck
Case 3

- H/C: group B streptococcus
- The patient was in a stage of profound shock and finally passed away
Skin Infections

This patient was bitten by a cat

What antibiotic should be given?

How good is cloxacillin?
Skin Infections

• No obvious injury: skin flora – strep/staph
• Previous surgery: Group A β-hemolytic streptococci
Skin Infections

• Water or water-animal exposure: *Aeromonas* spp, *Vibrio* spp.

• Dog (severe) and cat bite: *Pasteurella multocida* and other mouth flora

• Soil: atypical pathogens – non-tuberculous mycobacterium, *Nocardia* spp., deep-seated mycoses
Case 4

Ceftriaxone + amox/clavulanate

Diagnosis
A Miracle Combination
Combination therapy

• Synergistic effects: β-lactam + aminoglycoside against enterococci and other strep with high PCN MIC
• Broaden coverage in area with high MDR incidence
• Prevent the emergence of resistance during treatment: TB, HIV
Current Evidence

• Combination $\beta$-lactam + aminoglycoside resulted in similar clinical outcome for Gm neg sepsis, except *P. aeruginosa*
Adverse Effects of double β-lactam

• Mostly indifferent or additive in their effects; rarely does synergy occur.
• Antagonism can sometimes be seen (i.e., cefoxitin or imipenem)
Overlapping Spectrum in Antimicrobial Regimens

• Vancomycin +
  – Linezolid, fosfomycin, tigecycline, daptomycin
  – Cefepime
    • (cefpeme=ceftazidime + one anti-staph)

• Carbapenem + metronidazole in intra-abdominal infection
Case

• 57 year-old-female with
  – Multiple sclerosis
  – Hypothyroid from post I-131
  – Right leg DVT from Protein S deficiency
• 4 วันก่อนมา รพ. คลื่นไส้ อาเจียน ถ่ายเหลว มาตรวจที่ OPD ได้ ciprofloxacin po
• 1 วันก่อนมา รพ. อาเจียนเป็นเลือดคล้ำ ปัสสาวะและ ผู้จาระเป็นเลือดคล้ำ
• Hct 33% → 24%
• INR >12
• Whole abdominal CT: intramural hemorrhage of the proximal jejunum
Current medications

- Prednisolone (5 mg) 4 tabs po EOD
- Azathioprine (50 mg) 1 tab po OD
- Warfarin (5 mg) 1 tab po OD
- Ezetrol (10 mg) 1 tab po OD
- Euthyrox (0.1 ug) 1 tab po OD
- CaCO3 (600 mg) 1 tab po tid
Drug Interactions!

Warfarin:

- Effect & INR profoundly increased by
  - Trimethoprim/sulfamethoxazole
  - Metronidazole
- Significantly increased with
  - Fluconazole, ciprofloxacin
Drug Interactions!

- Multivalent Cations (Ca, Mg, Fe), and tube feeding decrease absorption of fluoroquinolones and tetracyclines
What should be a better alternative?

• To give or not to give an antibiotic
• If not, what data is needed to support requirement of ATB therapy
• If there are indications for an antibiotic, what would be the most appropriate agent?
Drug Interactions!

• Drugs cleared by CYP 450
  Statins, Cyclosporine, Benzodiazepines, Theophylline, Anticonvulsants, oral hypoglycemics
  – Levels increased by (Metabolism inhibited by)
    » Macrolides (Erythromycin)
    » Azoles (Fluconazole, Itraconazole)
    » Protease inhibitors
    » Ciprofloxacin
  – Levels decreased by (Metabolism induced by)
    » Rifampin, rifabutin

• Oral Contraceptives
  – Decreased with rifampin & nafcillin +/- others
Appropriate antimicrobial therapy

• Saves life
• Minimal unintended consequences
• Depends on ability to
  – Make a microbiologic diagnosis
  – Applying pharmacological principles to clinical practice
• AND MIND SET