Strategies for Stewardship and Tool for Implementation

Kenneth Lawrence, PharmD
Department of Pharmacy
Division of Geographic Medicine and Infectious Disease

Tufts Medical Center
Main actions to prevent and control antimicrobial resistance

- **Prudent use of antimicrobials**
  (only when needed, correct dose, dose intervals, duration)

- **Infection control**
  (hand hygiene, screening, isolation)

- **New antibiotics**
  (with a novel mechanism of action, research, development)
Get Smart 2010

Each year

- 2 million patients develop bacterial HAI
- 90,000 people die
- More than 70% of these infections are resistant to at least one class of antibiotics

Antibiotic resistance is associated with:

- Increased risk of hospitalization
- Increased length of stay
- Increased hospital costs
- Increased risk of ICU transfer
- Increased mortality

• Decreasing inappropriate antibiotic use is the best way to control the development of resistance
Antimicrobial Resistance: A local, national, and international problem…. Massachusetts:
- Between 2000 and 2007, 3-fold increase in C. diff as a primary diagnosis for hospitalization and >4-fold increase in deaths
- Over 1/3 of Streptococcus pneumoniae isolates in MA are resistant to penicillin and 20% could not be treated with other common antibiotics
- State DPH reported 67 cases of fluoroquinolone-resistant N. gonorrheae in 2006, up from 2 cases in 2001
Bad Bugs: No Drugs, No ESKAPE

- **Enterococcus**
- **S. aureus**
- **Klebsiella spp.**
- **Acinetobacter**
- **P. aeruginosa**
- **Enterobacter spp.**

Source: The Epidemic of Antibiotic-Resistant Infections. CID 2008;46 (15 January)

What is Antimicrobial Stewardship?

• Antimicrobial stewardship involves the **optimal selection, dose and duration** of an antibiotic resulting in the cure or prevention of infection with **minimal unintended consequences** to the patient including emergence of resistance, adverse drug events, and cost.

**Ultimate goal is improved patient care and healthcare outcomes**

Dellit TH, et al. CID 2007;44:159-77,
Get Smart: Know When Antibiotics Work

Goals:
- promoting adherence to appropriate prescribing guidelines
- decreasing demand for inappropriate antibiotics

National campaign to target five conditions that accounted for >75% of all office based antibiotic prescribing:
- Otitis media
- Sinusitis
- Pharyngitis
- Bronchitis
- The common cold

www.cdc.gov/getsmart
Get Smart 2010
Targeting Healthcare settings

Mission: To optimize the use of antimicrobial agents in inpatient healthcare settings

Goals:
• Improve patient safety through better treatment of infections
• Reduce the emergence of antimicrobial resistant pathogens
• Encourage better use of antimicrobials in healthcare settings
Get **SMART** about Stewardship

- **Starting off** – choosing the appropriate empiric regimen
  - “front end”
- **Maintenance of therapy**: Targeting, de-escalating, and discontinuing therapy
  - “back end”
- **Are you treating infection or colonization?**
  - Using current quality measures to promote ASP
- **Route**: IV or PO
  - Empowering your pharmacist
- **Time**: Stop antibiotics as early as possible
  - Harnessing your resources
Antimicrobial Stewardship Strategies at Tufts Medical Center

• Prospective audit with intervention and feedback
• Formulary restriction and preauthorization (pg 6858)

Supplemental Strategies

– Education: “AMT Question of the Week”
– Antimicrobial guidelines and disease management
– Dose optimization via PK-PD: extended dosing of Zosyn
– De-escalation/Streamlining: MR/pages to change treatment
– Antimicrobial order forms/order sets if CPOE
– IV-PO switch: automated by pharmacy
– Computerized decision support (Sentri7 and Safety Surveillor)
Starting off - “Front End”

- Also referred to as “preauthorization” or “pre-prescription approval”
- Restriction at the time the antimicrobial is prescribed:
  - Formulary vs. non-formulary
  - Target specific antimicrobials associated with high rates of resistance or $$$
  - May target a specific disease or indication
- In order to receive restricted antibiotics, a prescriber must have clearance from a member of the stewardship team
- Performed by either an infectious diseases physician, a clinical pharmacist with infectious diseases training, or a member of the antimicrobial support team
- Requires resources early in the intervention process
**ADULT ANTIMICROBIAL ORDER SHEET**

**DATE:** [Insert Date]

**TIME:** [Insert Time]

**Patient Allergies:**
- [ ] Suspected Infection
- [ ] Documented Infection
- [ ] List pathogen(s) isolated
- [ ] Other

**Serum Creatinine:** [Insert Value]

**Body Weight (Kg):** [Insert Value]

**Calculated Values:**
- [ ] Calculated

**BW Calculations:**
- [ ] BW (m/male) = 50 kg + [2.3 x (84 - height in feet)]
- [ ] BW (female) = 45 kg + [2.3 x (84 - height in feet)]

**CRI Calculation:**
- [ ] CRI = [Insert Value]

**DRUGS THAT MAY BE PRESCRIBED WITHOUT RESTRICTION:**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Amoxicillin/Clavulanate</td>
<td>1.5g</td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
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<tr>
<td>Amikacin</td>
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<td></td>
<td></td>
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<tr>
<td>Cefazolin</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1g</td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
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<tr>
<td>Ceftiraxime</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
</tr>
<tr>
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<td>IV</td>
<td>Q24h</td>
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<tr>
<td>Clarithromycin</td>
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<td>Clindamycin</td>
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<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
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<tr>
<td>Dicloxacillin</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
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<tr>
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<td>PO</td>
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<td>IV</td>
<td></td>
<td></td>
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<tr>
<td>Imipenem</td>
<td>400mg</td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
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<tr>
<td>Levofloxacin</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
</tr>
<tr>
<td>Meropenem</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
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**DRUGS FOR WHICH RESTRICTIONS MAY APPLY:**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
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<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
</tr>
<tr>
<td>Cefazolin</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
</tr>
<tr>
<td>Ceftiraxime</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
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<tr>
<td>Dicloxacillin</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
</tr>
<tr>
<td>Imipenem</td>
<td>3.375g</td>
<td>IV, over 4h</td>
<td>Q24h</td>
<td>Doses</td>
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<tr>
<td>Loperamide</td>
<td></td>
<td>IV</td>
<td></td>
<td></td>
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<tr>
<td>Meropenem</td>
<td></td>
<td>IV</td>
<td>Q24h</td>
<td>Doses</td>
</tr>
</tbody>
</table>

**Sign:** [Insert Signature]

**Page 8**
Maintenance of therapy: Targeting, de-escalating, and discontinuing therapy

• Empiric regimen is often NOT the regimen that needs to be continued for the full treatment course

• GET CULTURES and use the data to target therapy using the most narrow spectrum agent possible.

• Take an “Antibiotic Time Out” – reassess after 48-72 hours
"Back end"

- Also called “post prescription review”
- Prescribers are allowed to order antibiotics upon admission
- Antibiotic orders are reviewed at specified intervals after initiation
- May be restricted to particular patient populations
  - Ex: Cefepime and Zosyn in ICU for up to 72 hours
  - Ex: Echinocandins in candidemia
- May be restricted to formulary drugs or by using a clinic pathway or protocol
  - Ex: Pneumonia or ABSSTI protocol
Getting started is as easy as 123 and ABC

**Getting Started…**

1. Review Blood and urine cultures that grow organisms
2. Review of Key “Never” Combinations
   1. Metronidazole and Zosyn
   2. Cefazolin and cefepime
   3. Levofloxacin and azithromycin
3. Align the formulary with Local susceptibility data

**Focus on the basics…**

A. Appropriate indication, dose, and duration
   - Guidelines
   - Order sets
B. Take an antibiotic Break
   - Review of all orders after 48 hours to assess for appropriate therapy
C. Get Cultures

http://www.cdc.gov/getsmart/healthcare/improve-efforts/clinicians.html
http://www.cdc.gov/getsmart/healthcare/improve-efforts/start.html
Antimicrobial Stewardship Care Bundle

- Prospective audit system
  - Stewardship program
  - Outcomes
    - Reason for treatment, cultures, empirical, and de-escalation
    - LOS, mortality, and % interventions accepted

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Control Phase</th>
<th>Intervention Phase</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented indication for antibiotic therapy</td>
<td>76/80 (95)</td>
<td>80/80 (100)</td>
<td>0.12</td>
</tr>
<tr>
<td>Appropriate cultures collected</td>
<td>70/80 (87)</td>
<td>76/80 (95)</td>
<td>0.09</td>
</tr>
<tr>
<td>Appropriate empirical therapy</td>
<td>55/80 (69)</td>
<td>65/80 (81)</td>
<td>0.06</td>
</tr>
<tr>
<td>Appropriate deescalation³</td>
<td>41/57 (72)</td>
<td>52/58 (90)</td>
<td>0.01</td>
</tr>
<tr>
<td>All indicators concurrently</td>
<td>13/80 (16)</td>
<td>43/80 (54)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mortality Associated With Initial Inadequate* Therapy in Critically Ill Patients With VAP or Septicemia, Severe Sepsis, or Community-Acquired Bloodstream Infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Infection Type</th>
<th>Initial Adequate Therapy</th>
<th>Initial Inadequate Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luna (1997)</td>
<td>VAP†1</td>
<td>91%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Rello (1997)</td>
<td>VAP†2</td>
<td>37%</td>
<td>38%</td>
</tr>
<tr>
<td>Kollef (1998)</td>
<td>VAP†3</td>
<td>60.8%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Ibrahim (2000)</td>
<td>Septicemia, severe sepsis, or bloodstream infection ‡4</td>
<td>61.9%</td>
<td>28.4%</td>
</tr>
<tr>
<td>Harbarth (2003)</td>
<td>Severe sepsis†5</td>
<td>39%</td>
<td>24%</td>
</tr>
<tr>
<td>Vallés (2003)</td>
<td>Bloodstream infection†6</td>
<td>63%</td>
<td>30.6%</td>
</tr>
</tbody>
</table>


VENTILATOR-ASSOCIATED/HEALTHCARE-ASSOCIATED/HOSPITAL-ACQUIRED PNEUMONIA
ORDER SHEET for ADULT PATIENTS

DATE: ___________________  TIME: ___________________
(24-hour clock)

PATIENT IDENTIFICATION
- Allergies:
- Weight (Kg):
- Serum Creatine:
- Creatinine Clearance (mL/min):

MEDICATION ORDERS ONLY
(INCLUDES IV MEDICATIONS)

Order Set A. No Risk factors for Multi-drug Resistant Organisms
(see Risk Assessment for Multi-drug Resistant Organisms)
- Ceftriaxone 1g IV Q24 hours x 72 hours OR
- Meropenem 4g IV or PO Q24 hours x 72 hours
- Consider adding Vancomycin if history of infection or colonization with MRSA
- Vancomycin 0.5-1g IV or PO Q24 hours x 72 hours
- Consider adding Azithromycin for coverage of atypical pathogens
- Azithromycin 500mg PO Q24 hours x 72 hours

Order Set B. Risk factors for Multi-drug Resistant Organisms AND Not Intubated
- Drug 1: Cefepime 2g IV Q8 hours x 72 hours OR
- Drug 2: Vancomycin 1g IV Q24 hours

Order Set C. Risk factors for Multi-drug Resistant Organisms
(see Risk Assessment for Multi-drug Resistant Organisms) AND Intubated:
- Drug 1: Cefepime 2g IV Q8 hours x 72 hours OR
- Drug 2: Tobramycin 40mg IV ONCE

Risk Assessment for Multi-drug Resistant Organisms
Step 1: My patient has a new pneumonia that developed in the hospital AND:
- Is currently hospitalized for 5 days or more OR
- Has received antibiotics for 5 days or more in the last 30 days OR
- Has immunosuppressive disease or therapy

Step 2: My patient has pneumonia and one or more of the following:
- Risk factors for drug-resistant organisms.

FOOTNOTES
- Adjust dose for renal dysfunction. See Tufts Medical Center Antimicrobial Guidelines or Tufts MC Pharmacy website.
- If patient recently received a lactam or quinolone or has history of ESBL, please call AMT for consideration of therapy targeting ESBL.
- If patient has chronic obstructive pulmonary disease or diabetes, please consider de-escalation to a lower-risk antibiotic.
- Physician’s Name (Print:) ___________________________  Physician’s Signature: ___________________________

White - Medical Records  Yellow - Pharmacy  Pager #: ___________________________
Treatment algorithm for HAP/VAP/HCAP

Suspected Ventilator-associated / Healthcare-associated / Hospital-acquired Pneumonia

Obtain lower respiratory tract sample for quantitative culture and microscopy prior to start of therapy. (obtaining cultures should not delay initiation of treatment)

Assess risk factors and initiate treatment

New pneumonia that developed in the hospital
AND ONE OR MORE OF THE FOLLOWING
Current hospitalization 5 days or more?
OR
Antibiotics for 5 days in the last 30 days?
OR
Immunosuppressive disease?

yes

Not intubated
Order Set B

Intubated
Order Set C

no

Recent hospitalization 5 or more days in last 30 days?
OR
Nursing home or long-term care?
OR
Home infusion bx?
OR
Dialysis?
OR
Wound care?
Or
Immunosuppressive Disease

no

Order Set A

yes

Does patient have at least TWO of the following THREE risk factors:
1. Requires ICU admission
2. Three or more days of antibiotics in the past 6 months
3. Inability to perform self care

Order Set A (+Vancomycin)

no

Not intubated
Order Set B

Intubated
Order Set C

yes
Days 2 and 3: Check cultures and clinical response

Has there been clinical improvement in 48-72 hours?

no

Cultures (-)

Search for other sites of infection, other pathogens, or non-infectious diagnosis.

Cultures (+)

Adjust antibiotics to match culture results (de-escalate to narrowest coverage possible). Search for other pathogens and/or sites of infection.

yes

Cultures (-)

Consider non-infectious diagnosis. Consider stopping antibiotics (de-escalate to FQ's).*

Bronchoscopy. colony count \( \geq 10^4 \text{ CFU/ml}^{**} \)

Or

Mini-BAL colony count \( \geq 10^3 \text{ CFU/ml}^{**} \)

no

Consider stopping antibiotics as patient may be colonized.*

yes

Pseudomonas or Acinetobacter isolated?

no

Adjust antibiotics to match culture results (de-escalate to narrowest coverage possible).

Treat for up to 8 days.

yes

Adjust antibiotics to match culture results (de-escalate to narrowest coverage possible).

Treat for up to 14 days.

* These diagnostic tests are not 100% sensitive. If suspicion is high for pneumonia even in the absence of confirmatory microbiologic data then it is reasonable to continue antibiotics and reassess again.

** Pseudomonas pneumonia may be present with colony counts < 10^3
Benefits of a VAP/HAP Protocol at Tufts Medical Center

Duration of antibiotic use and hospital stay

(* p=0.024, (**) p=0.01. Duration of ICU (p=0.97) and hospital (p=0.41) stay were not statistically different.
Are you treating infection or colonization?

- Colonization = bacteria are present at the site sampled, but are not causing disease
- Contamination = bacteria are present in the laboratory sample, but not at the site
- NEITHER requires antibiotics!
- Cultures drawn through a central line should be avoided
- WBCs in the urine ≠ UTI; NO WBCs in the urine = NO UTI
- Candida is a frequent colonizer
The government vs. the microbes
Center for Medicare and Medicaid Services (CMS) Non Payment Conditions

- Object inadvertently left in after surgery
- Air embolism
- Blood incompatibility
- Catheter associated urinary tract infection
- Pressure ulcer (decubitus ulcer)
- Central line associated blood stream infection
- Surgical site infection - Mediastinitis after CABG, post orthopedic surgery, post bariatric surgery
- Certain types of falls and trauma
Working with …

• Surgical Care Improvement Project (SCIP) to develop pre/post antibiotic guidelines

• Collaborate closely with Infection Control on the development of bundles for the prevention of HAIs

• Work with hospitalists and nursing specialists (i.e. wound care nurses, ostomy nurses, etc) to develop understanding of colonization vs infection
Route: IV or PO

- Many drugs are highly available in the PO form.
- The oral route is less expensive, allows for earlier removal of lines and decreased length of stay.
- Patients on oral antimicrobials with clearly documented reasons for continued hospital stay are not at risk for claims rejection by payors.
Tufts Pharmacy IV to PO switch program

• Pharmacists may dispense, and nurses may administer to inpatients equivalent oral doses of certain highly bioavailable IV medications

• Criteria:
  – Functioning GI tract (taking oral fluids and medications or enteral feeds)
  – No evidence of severe nausea, diarrhea, GI bleeding, high NG output, etc
  – Normal stable vital signs
  – WBC between 4,000 and 11,000 cells /microliter
  – No life threatening infection
Pharmacists driven initiatives

- Pharmacokinetic dosing or monitoring of aminoglycosides or vancomycin
  - automatic dosing of AG’s and vanco by pharmacy rather than clinicians
- Automatic Drug conversion
  - Ex: transfers from outside hospital automatically transitioned to formulary drugs
- Alternative dosing regimens
  - Continuous or prolonged infusions of β-lactam
  - Increased frequency of dosing (e.g., meropenem)
Time: Stop antibiotics as early as possible

• “We know everything about antibiotics except how much to give.” — Maxwell Finland (one of the forefathers of antibiotic therapy)

• Longer is not better

• CAP guidelines and clinical trials suggest good results with 5 days of antibiotics if patient meets clinical criteria

• Intra-abdominal infection guidelines: 4-7 days unless difficult to control the source of infection
Comparison Between 8-Day and 15-Day Treatments for VAP

Diagnostic and Pathogen Identification Techniques

• Biomarkers
  – Procalcitonin
  – CRP
• PNA FISH
• PCR
• E-test of patient samples
Decision Support for Antimicrobial Stewardship

<table>
<thead>
<tr>
<th>Lists</th>
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<td>Pharmacy Monitoring *</td>
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<td>Koppa IV *</td>
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<td>Argetoban or Lepirudin *</td>
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<td>Warfarin Daily Monitoring - TEST *</td>
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<td>Vitamin K Use *</td>
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<tr>
<td>Heparin Dosing Study *</td>
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<tr>
<td>Antimic Stewardship *</td>
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<tr>
<td>Daptomycin without CK Check *</td>
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<tr>
<td>Vanco Trough &gt; 20 or &lt; 10 *</td>
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<td>Metronidazole AND Other Drugs with Anaerobic Activ *</td>
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<td>IV to PO - Anti-infectives *</td>
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<td>IV to PO - Other *</td>
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</table>
Computer Surveillance and Decision Support in Antimicrobial Stewardship

• Sentri7
• SafetySurveillor
• TheraDoc
• Computerized physician order entry
• Benchmarking and local antimicrobials point prevalence surveys (state may consider doing this)
Behind the scenes: Infection Control and AMT

- Web-based infection control surveillance system/antimicrobial management program
- ADT, Microbiology, and Pharmacy data interfaces
  - OR data and Radiology data are in progress
- Ability to alert AMT to inappropriate antimicrobial use in real time and evaluation of antibiotic use trends.
Conclusions

• Antimicrobial resistance is a major patient safety and patient care issue, LIVES are at stake.
• Healthcare providers have a moral obligation to ensure that the currently available antimicrobials, as well as those yet to be developed remain the powerful tools that penicillin was in the 1940s.
• Antimicrobial stewardship strategies are the best way to achieve this goal.
The Future of Stewardship = YOU

• Appropriate antibiotic use is a patient safety priority
• Antibiotics are a shared resource – and becoming a scarce resource.
• Inappropriate antibiotic use and resistant infections = Billions of $$ in excess healthcare costs
• To combat resistance: Think globally, act locally