Antimicrobial Stewardship for Hospitalists

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Infectious Disease
Antimicrobial Stewardship
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Sir Alexander Fleming

“The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and, by exposing his microbes to non-lethal quantities of the drug, educate them to resist penicillin.”

Nobel lecture, 1945
Objectives

- Review scope of problem with MRSA, ESBL, and VRE
- Discuss current regulatory environment
- Review *Clostridium difficile* Infection (CDI)
- Describe resources of VCMC/SPH Antimicrobial Stewardship Program and forthcoming implementation tools
- Discuss stewardship goals and implementation challenges
FIGURE 2-6: Total antibiotic consumption in selected countries, 2000 and 2010

Source: Van Boeckel et al. 2014 (based on IMS MIDAS)
Studies have shown...

- Indication, choice of agent or duration are incorrect up to 50% of the time

- 30% of antibiotics for hospitalized adult patients are unnecessary

- 250,000 *C. difficile* infections (CDI) in hospitalized patients each year = 1 billion dollars/yr
Untoward Effects of Antibiotics

- Antibiotic resistance
- Adverse drug events (ADEs)
  - Hypersensitivity/allergy
  - Drug side effects
  - *Clostridium difficile* infection
  - Antibiotic associated diarrhea/colitis
- Increased health-care costs
In fiscal year 2016, Congress appropriated $160 million for CDC to fight antibiotic resistance (AR), a testament to urgent threat and highest levels of support.
TABLE 3: CDC’s Antibiotic-Resistant Threats in the United States, 2013

**URGENT Threat Level Pathogens (3)**

**Clostridium difficile**

250,000 infections per year requiring hospitalization or affecting hospitalized patients.

14,000 deaths per year.

At least $1 Billion in excess medical costs per year.

*C. difficile* deaths increased 400% between 2000-2007 because of the emergence of a strain resistant to a common antibiotic class (fluoroquinolones).

Almost half of infections occur in people younger than 65, but more than 90% of deaths occur in people 65 and older.

Half of *C. difficile* infections first show symptoms in hospitalized or recently hospitalized patients, and half show symptoms in nursing home patients or in people recently cared for in doctors’ offices and clinics who received antibiotics.

The majority (71%) of pediatric *Clostridium difficile* infections, which are bacterial infections that cause severe diarrhea and are potentially life-threatening, occur among children in the general community, 73% were found to have recently taken antibiotics prescribed in doctor’s offices for other outpatient settings.

**Carbapenem-Resistant Enterobacteriaceae***

Out of ~140,000 healthcare-associated *Enterobacteriaceae* infections per year, more than 9,000 are caused by CRE (7,900 CR-Klebsiella spp; 1,400 CR-E. coli).

44 States have had at least one type of CRE confirmed by CDC testing.

CRE are resistant to nearly all antibiotics including carbapenems—the antibiotic of last resort.

**Neisseria gonorrhoeae*** (Notifiable to CDC)

*Neisseria gonorrhoeae* causes gonorrhea, is the second most common reportable infection in the United States, and is developing resistance to the cephalosporin antibiotics, the last line treatment option for this infection.

Of the 820,000 cases per year, 30% (246,000) now demonstrate resistance to at least one antibiotic.

If cephalosporin-resistant *N. gonorrhoeae* becomes widespread, the public health impact during a 10-year period is estimated to be 75,000 additional cases of pelvic inflammatory disease, 15,000 cases of epididymitis, and 222 additional HIV infections, with an estimated direct medical cost of at least $235 million.
## SERIOUS Threat Level Pathogens (12)

### Multidrug-Resistant *Acinetobacter*

12,000 healthcare-associated *Acinetobacter* infections occur in the U.S. of which 7,000 are multidrug-resistant ~ 500 deaths per year.

At least three different classes of antibiotics no longer cure resistant *Acinetobacter* infections.

### Drug-Resistant *Campylobacter*

*Campylobacter* causes ~1.3 Million infections, 13,000 hospitalizations and 120 deaths each year; 310,000 (25%) drug-resistant *Campylobacter* infections are found each year.

*Campylobacter* drug resistance increased from 13% in 1997 to 25% in 2011.

*Campylobacter* spreads from animals to people through contaminated food, particularly raw or undercooked chicken and unpasteurized milk.

Antibiotic use in food animals can results in resistant *Campylobacter* than can spread to humans.

### Fluconazole-Resistant *Candida*

Out of 46,000 *Candida* yeast infections per year, 3,400 (30%) of patients with bloodstream infections with drug-resistant (DR)-*Candida* die during their hospitalization.

CDC estimates that each case of *Candida* infection results in 3-13 days of additional hospitalization and a total of $6,000-$29,000 in direct healthcare costs per patient.

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### Table 3: CDC’s Antibiotic-Resistant Threats in the United States, 2013
**SERIOUS Threat Level Pathogens (12), continued**

**Extended Spectrum β-Lactamase (ESBL) Producing *Enterobacteriaceae***

Extended Spectrum β-Lactamase (ESBL) is an enzyme that allows bacteria to become resistant to a wide spectrum of penicillins and cephalosporins.

- Of 140,000 *Enterobacteriaceae* infections per year, 26,000 are drug resistant causing 1,700 deaths.
- 26,000 healthcare-associated *Enterobacteriaceae* infections are caused by ESBL-Enteobacteriaceae.
- 26,000 healthcare-associated *Enterobacteriaceae* infections are caused by ESBL-Enterobacteriaceae.

**Vancomycin-Resistant *Enterococcus***

- Of 66,000 *Enterococcus* infections per year, 20,000 are drug resistant causing 1,300 deaths.
- Enterococcus strains resistant to vancomycin leave few or no treatment options.

**Multidrug-Resistant *Pseudomonas aeruginosa***

- Of 51,000 *Pseudomonas* infections per year, 6,700 are multidrug resistant causing 440 deaths.
- 13% of severe healthcare-associated infections caused by *Pseudomonas* are multidrug resistant, meaning nearly all or all antibiotics no longer cure these infections.

**Drug-Resistant Non-Typhoidal *Salmonella*** (Notifiable to CDC)

- Non-typhoidal *Salmonella* causes 1.2 million infections per year, of which 100,000 are drug-resistant resulting in 23,000 hospitalizations and 450 deaths each year.
- Non-typhoidal *Salmonella* results in higher number of hospital stays, length of stay, and treatment costs.

**Drug-Resistant *Salmonella typhi*** (Notifiable to CDC)

- Of 21.7 M *Salmonella typhi* infections worldwide, 5,700 illnesses in the U.S. with 3,800 (67%) of infections are drug-resistant resulting in 620 hospitalizations each year.
- Before the antibiotic era or in areas where antibiotics are unavailable, *Salmonella typhi* results in up to 20% deaths.

**Drug-Resistant *Shigella*** (Notifiable to CDC)

- *Shigella* causes ~ 500,000 illnesses, 5,500 hospitalizations, and 40 deaths each year in the U.S.
- Since 2006, *Shigella* resistance to traditional first-line antibiotics has become so high that physicians must now rely on alternative drugs (ciprofloxacin and azithromycin) to treat infections.

**Methicillin-Resistant *Staphylococcus aureus (MRSA)***

- Over 80,000 invasive MRSA infections and 11,285 related deaths per year (in 2011).
- Severe MRSA infections most commonly occur during or soon after inpatient medical care.
- Between 2005 and 2001, overall rates of invasive MRSA dropped 31% predominantly due to appropriate medical procedures implemented in central-line maintenance.

**Drug-Resistant *Streptococcus pneumoniae*** (Notifiable to CDC)

- Of 4 million disease incidents and 22,000 deaths; 1.2 M are drug resistant (to amoxicillin and azithromycin (Z-Pak) resulting in 19,000 excess hospitalizations and 7,900 deaths.
- In 30% of *S. pneumoniae* cases, the bacteria are fully resistant to one or more antibiotics causing complications in treatment and death.
- Pneumococcal pneumonia accounts for 72% of all direct medical costs for treatment of pneumococcal disease and in excess of $96 million in medical costs per year.
- Pneumococcal conjugate vaccine (PCV) prevents disease, reduces antibiotic-resistance by blocking the transmission of resistant *S. pneumoniae* strains, and protects against 13 strains of Streptococcus.
NOTE: 30 active cases of TB in Ventura County. No MDR’s now. (2 MDRs in last 6 yrs)
ES-1: Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA) in selected countries, 1999–2014

*CDDEP 2015*
FIGURE 1-2: Percentage of extended-spectrum beta-lactamase producing *Escherichia coli*, by country (most recent year, 2011–2014)
RE 1-3: Percentage of carbapenem-resistant *Klebsiella pneumoniae*, by country (most recent year, 2011–2014)

ce: CDDEP 2015, WHO 2014 and PAHO, forthcoming
MRSA

- MRSA incidence has **declined** in incidence in Europe, **United States** and Canada over past eight years, to 18%, 44%, and 16%, respectively (EARS-Net 2014; CDDEP 2015b; Public Health Agency of Canada 2015)
- Declined in South Africa (28%), where stewardship is taking hold (Kariuki and Dougan 2014; CDDEP 2015b)
- **Still rising** (AGAR 2013; CDDEP 2015b) at 47% in India in 2014 and 90% in Latin American hospitals in 2013 (PAHO)
Extended-Spectrum Beta-Lactamases (ESBL)

- Inactivate most penicillins, cephalosporins, & monobactams
- Most common bacteria are Klebsiella, E.coli, & Proteus
- Agents that are active against ESBLs:
  - Carbapenems – Imipenem, Meropenem, Ertapenem
  - Cephemycins – Cefoxitin & Cefotetan (based on observational studies only for non severe urinary sources, recommended in France)
  - Cefepime : breakpoint issues, assumption for use is challenged. May consider if 2gq8 if mild disease, urinary source, and MIC less than equal to 2. (Recent national shortage)
  - Piptazobactam
  - Ceftolozane-Tazobactam
  - Ceftazidime-Avibactam
Piptazobactam (PTZ) for ESBLs

- Piptazobactam- In vitro sensitivity does not always translate to 100% in vivo
- Some say 30-50% active against ESBL (if MIC less than or equal to 4)
- Existing evidence indicates low-moderate severity, urinary sources with low MICs, PTZ works as well as carbapenems (at dose 4.5g q 6 hrs)
# Piptazobactam for ESBLs

## Meropenem vs. PTZ for Definitive Treatment of Bloodstream Infections Due to Ceftriaxone Non-Susceptible E. coli and Klebsiella spp. (MERINO trial)

<table>
<thead>
<tr>
<th>Objective</th>
<th>To determine if PTZ results in equivalent outcomes as meropenem for ceftriaxone non-susceptible bacteremia</th>
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<tbody>
<tr>
<td>Methods</td>
<td>- Multicenter, randomized, open-label, non-inferiority trial</td>
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<td>- Meropenem (1 g q8h) vs. PTZ (4.5 g q6h)</td>
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<td>- Target enrollment is 454 patients</td>
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<td>- Estimated study completion date: December 2018</td>
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<td>- Clinicaltrials.gov: NCT02176122</td>
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Ceftolozane-Tazobactam or Ceftazidime-Avibactam for ESBL

- Ceftolozane-Tazobactam: Activity against ESBL E coli > ESBL Klebsiella. Need more data. Probably similar to Piptazobactam.
- Ceftazidime-Avibactam - more favorable for use than the previous. Excellent in vitro activity against ESBL. Need more data.
ESBL Summary

• For mild-moderate infections, particularly those from urinary sources or with low MICs, non-carbapenems can be considered early on, with PTZ having the most favorable data available. We may also consider Cefoxitin.

• For severe, invasive infections, carbapenems are still first-line option.
CRE

- Carbapenem-Resistant Enterobacteriaceae (CRE) are resistant even to last-resort carbapenems.
- Over past decade, members of the Enterobacteriaceae family of bacteria have begun to develop resistant to carbapenems and these resistant bacteria have spread throughout the U.S./world.
  - Klebsiella spp., especially *K. pneumoniae*
  - *E. coli*
  - *Enterobacter* spp.
CRE: Just Another Type of MDRO?

What makes CRE special?
- No decolonization strategy
- Few treatment options available
- High mortality rate (50% or more in some studies)
- Resistance can hop between many Enterobacteriaceae (over 70 bacteria in family)
- High speed/rate of resistance transfer

NEED GOOD INFECTION CONTROL STRATEGY REGIONALLY
2012 CDC CRE Toolkit

- Facility-level recommendations
  - Acute care
  - Long-term care

- Health department involvement
  - Varies depending on regional prevalence
  - Focused emphasis on preventing further transmission and widespread emergence of CRE

Critical Opportunity for CRE Control: “Detect and Protect”
Vancomycin-Resistant Enterococci (VRE)

- Heavy use of Vancomycin $\rightarrow$ development of VRE
- Need to distinguish between colonization vs. pathogen
- VRE infections require “bigger gun” antibiotics
  - Quinupristin/Dalfopristin, Daptomycin, or Linezolid
  - Much more expensive
- Strategies to lower VRE rates:
  - Limit the use of vancomycin and/or de-escalate early on, e.g. cellulitis, line infections, meningitis, etc
  - Limit duration of empiric therapy (use of procalcitonin)
REPORT TO THE PRESIDENT ON
COMBATING ANTIBIOTIC RESISTANCE

Executive Office of the President
President’s Council of Advisors on
Science and Technology

September 2014
CMS Regulations

- The Joint Commission announced new Medication Management (MM) standard for hospitals, critical access hospitals, and nursing care centers.
- Standard MM.09.01.01 addresses antimicrobial stewardship and becomes effective January 1, 2017.
SB 739

- Requires general acute care hospitals develop process for evaluating use of antibiotics.
- California is first state to pass this kind of legislation. Based on its success, several other states are planning to implement similar legislation. I.e. Missouri

- Joint Commission is making it a national requirement.
Core Elements for Antibiotic Stewardship Programs

Summary of Core Elements:

- Leadership commitment from administration
- Single leader responsible for outcomes
- Single pharmacy leader
- Antibiotic use tracking
- Regular reporting on antibiotic use and resistance
- Educating providers on use and resistance
- Specific improvement interventions

http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html
IDSA/SHEA Antimicrobial Stewardship Guidelines

- A multidisciplinary ASP team includes an **ID physician and pharmacist** and other key stakeholders
- Two core strategies were recommended
  - Prospective audit with intervention and feedback
  - Formulary restriction and preauthorization
- Other recommended strategies
  - Education
  - Guidelines and clinical pathways
  - Order forms
  - De-escalation
  - Dose optimization
  - IV to PO conversion

IDSA=Infectious Diseases Society of America
SHEA=Society for Healthcare Epidemiology of America

Vital Signs: Improving Antibiotic Use Among Hospitalized Patients

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On March 4, 2014, this report was posted as an MMWR Early Release on the MMWR website (http://www.cdc.gov/mmwr).

**Background:** Antibiotics are essential to effectively treat many hospitalized patients. However, when antibiotics are prescribed incorrectly, they offer little benefit to patients and potentially expose them to risks for complications, including *Clostridium difficile* infection (CDI) and antibiotic-resistant infections. Information is needed on the frequency of incorrect prescribing in hospitals and how improved prescribing will benefit patients.

**Methods:** A national administrative database (MarketScan Hospital Drug Database) and CDC’s Emerging Infections Program (EIP) data were analyzed to assess the potential for improvement of inpatient antibiotic prescribing. Variability in days of therapy for selected antibiotics reported to the National Healthcare Safety Network (NHSN) antimicrobial use option was computed. The impact of reducing inpatient antibiotic exposure on incidence of CDI was modeled using data from two U.S. hospitals.

**Results:** In 2010, 55.7% of patients discharged from 323 hospitals received antibiotics during their hospitalization. EIP reviewed patients’ records from 183 hospitals to describe inpatient antibiotic use; antibiotic prescribing potentially could be improved in 37.2% of the most common prescription scenarios reviewed. There were threefold differences in usage rates among 26 medical/surgical wards reporting to NHSN. Models estimate that the total direct and indirect effects from a 30% reduction in use of broad-spectrum antibiotics will result in a 26% reduction in CDI.

**Conclusions:** Antibiotic prescribing for inpatients is common, and there is ample opportunity to improve use and patient safety by reducing incorrect antibiotic prescribing.

**Implications for Public Health:** Hospital administrators and health-care providers can reduce potential harm and risk for antibiotic resistance by implementing formal programs to improve antibiotic prescribing in hospitals.
Study Objectives and Results

- Potential for improvement of inpatient prescribing
  57.7% of patients received antibiotic during hospitalization
  29.8% received at least one dose of broad spectrum antibiotics

- Opportunities for improvement: **37.2% could have been improved** (lack of diagnostic culture, treating colonization/contamination, failure to de-escalate antibiotics based on culture data).

- Models to illustrate impact of reduced antibiotic exposure on incidence of CDI demonstrate: **30% reduction in broad-spectrum antibiotics will result in 26% reduction in CDI**
Antimicrobial Stewardship

- Improve patient outcome
- Optimize selection, dose and duration of Rx
- Reduce adverse drug events
- Reduce morbidity and mortality
- Limit emergence of antimicrobial resistance
- Reduce length of stay
- Reduce health care expenditures

How best can we achieve these goals?

Nine Factors to Consider When Selecting an Antibiotic

Spectrum of coverage
Patterns of resistance
Evidence or track record for specified infection
Achievable serum, tissue, or body fluid concentration (e.g. cerebrospinal fluid, urine)
Allergy
Toxicity
Formulation (IV vs. PO); if bioavailable
Adherence/convenience (e.g. 2x/day vs. 6x/day)
Cost
Limit Duration of Antibiotic Therapy to the Appropriate Length

Create Clinical Practice Guidelines and/or Refer to IDSA:

- Ventilator-associated pneumonia: 8 days
- Community-acquired pneumonia: 5 days
- Uncomplicated cystitis: 3-5 days
- Pyelonephritis: 7-14 days
- Intra-abdominal with source control: 4-7 days
- Cellulitis: 5-7 days or clinical resolution

Hayashi Y, Paterson DL. Clin Infect Dis 2011; 52:1232
Tenets of Antimicrobial Stewardship

- Re-evaluate, de-escalate or stop therapy at 48-72 hours based on diagnosis and microbiologic results.
- Re-evaluate, de-escalate or stop therapy with transitions of care (e.g. ICU to step-down or ward).
- Do not give antibiotic with overlapping activity.
- Do not “double-cover” gram-negative rods (i.e. *Pseudomonas sp.* except empirically in select critically ill cases or known history).
Tenets of Antimicrobial Stewardship

- Limit duration of surgical prophylaxis to <24 hours perioperatively
- Improve micro and lab capability and use rapid diagnostics if possible
- Procalcitonin as biomarker
- Solicit expert opinion if needed
- Prevent infection
  - Good hand hygiene and infection control practices
  - Early removal of catheters and lines
C. difficile is an “Urgent Threat”

- Over 450,000 cases per year
  - Over 29,000 associated deaths
- Most common cause of healthcare-associated infections in US

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. (%)</th>
<th>Rank</th>
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<tbody>
<tr>
<td>Clostridium difficile</td>
<td>61 (12.1)</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>54 (10.7)</td>
<td>2</td>
</tr>
<tr>
<td>Klebsiella pneumoniae or K. oxytoca</td>
<td>50 (9.9)</td>
<td>3</td>
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<tr>
<td>Escherichia coli</td>
<td>47 (9.3)</td>
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<tr>
<td>Enterococcus species</td>
<td>44 (8.7)</td>
<td>5</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>36 (7.1)</td>
<td>6</td>
</tr>
<tr>
<td>Candida species</td>
<td>32 (6.3)</td>
<td>7</td>
</tr>
<tr>
<td>Streptococcus species</td>
<td>25 (5.0)</td>
<td>8</td>
</tr>
<tr>
<td>Coagulase-negative staphylococcus species</td>
<td>24 (4.8)</td>
<td>9</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>16 (3.2)</td>
<td>10</td>
</tr>
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Lessa. NEJM. 2013; Magill. NEJM. 2014

- 780 people die/day in the US related to Cdiff

Dubberke. Washington University School of Medicine
**Clostridium Difficile Infection**

### Antibiotics and CDI Risk

<table>
<thead>
<tr>
<th>Very Commonly Related</th>
<th>Less Commonly Related</th>
<th>Uncommonly Related</th>
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<tbody>
<tr>
<td>Clindamycin</td>
<td>Beta-lactam inhibitors</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Macrolides</td>
<td>Metronidazole</td>
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<tr>
<td>Amoxicillin</td>
<td>Carbapenems</td>
<td>Rifampin</td>
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<tr>
<td>Cephalosporins</td>
<td>Tigecycline</td>
<td>Tetracyclines</td>
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<tr>
<td>Fluoroquinolones</td>
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<td>Daptomycin</td>
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<tr>
<td></td>
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<td>Sulfonamides</td>
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<td>Trimethoprim</td>
</tr>
</tbody>
</table>

Risks remain for weeks to months after antibiotics have stopped

Dubberke. Washington University School of Medicine
Gastric Acid Suppression

• Correlation ≠ Causation
  – *C. difficile* spores are resistant to gastric acid
  – Unclear how gastric acid suppression would predispose

• As many as 60% of prescriptions for non-indicated reasons
  – General good practice: discontinue

Antimicrobial Stewardship at SPH and VCMC

- Restricted Drug Approvals
- Procalcitonin Guideline
- Other guidelines in pipeline: Uncomplicated Cellulitis, Meningitis, Cdiff, Osteomyelitis, Pneumonia
- 48-72 hour Chart Review and direct feedback
- Review of all patients on broad spectrum antibiotics
- ICU rounds
- Physician and Patient education. Antibiotic Time out Standford CME for physicians/pharmacists
- Vancomycin Protocol Revamping to make pharmacy run as well as Aminoglycoside monitoring
- Renal Dose Adjustment of Antibiotics
- Vaccine programs
- Reduce PPI use
48 – 72 hr review in CERNER – Effective NOW!

1. Review diagnosis
2. Antibiotic plan including duration
3. Tailor to microbiology
4. IV to PO switch

De-escalation: Lessons learned

Most common reasons for not de-escalating:

- Lack of conclusive microbiology results
  - Continued use of broad-spectrum
- Diagnostic uncertainty
  - Treatment of fever, colonization and/or contamination
- Insecurity
  - Treatment of noninfectious syndrome associated with fever
- Duration longer than necessary
Challenges

- Difficulty changing prescribing behaviors
- Antibiogram – none at VCMC since 2012 until 2016
- No data collecting capacity (no software for tracking/recording)
- Lab specimen/collection delays at VCMC, no rapid diagnostics
- Literature often not always clear in Infectious Diseases
- Providers perceive autonomy is lost
- Medicolegal implications of responsibility for patients
- Difficulty proving impact of program (Ø national measures)
- Financial pressures dictating decisions
  - Pharmaceutical manufacturers
  - Hospitals
  - Payers (CMS, SNFs)
  - Patients
What can we all do to help?

- Obtain cultures **before** antibiotics unless Septic (in ED and on floors) and then just 2 antibiotics ok.
- Include in progress note **justification** of antibiotics including dose, duration, and micro data supporting decision
- **De-escalate** early and often
- **Transition** from IV to PO early
- Include antibiotic **side effects** in progress notes (creation of system wide Dot phrases pending)
- **Educate** residents and patients using GET SMART CDC handouts
- Educate on asymptomatic bacteruria, **colonization** vs. disease, and dangers of future antibiotics in Cdiff patients
- Give Stewardship team **feedback** often
Microbiology Stewardship
Obtain Cultures Prior to Starting Antibiotics

- Develop a process to ensure cultures are properly and consistently ordered
- Develop a process to ensure cultures are properly and consistently obtained
- Develop processes to ensure cultures are properly and promptly transported and processed (Current work in Progress – see handout for specimen collection)
- Develop standards for and assess reliability of processes for ordering and obtaining a culture
Stewardship Disclaimer

- **Note:** Antimicrobial Stewardship involvement does not equate to a formal ID consult.

- If you believe your patient needs a formal consult, please obtain one after talking to your hospitalist attending ;)

Special Thanks to Core Stewardship Team

- Annette Patterson
- Torri Boghossian
- Jason Arimura
- Tony Dao
- Elvira Barajas
- Heather Scott
- Hospitalists, Surgeons and Admin for all the support
KEEP CALM AND DO Antimicrobial Stewardship
References


References


