WHAT ARE THE CRITICAL TOOLS AND PROCESSES FOR AN EFFECTIVE AND SUCCESSFUL ANTIMICROBIAL STEWARDSHIP PROGRAM?

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Topics to cover

- Key components for “antibiotic management” in a hospital setting
- Focus on “Antimicrobial Stewardship”
  - Definitions
  - Resources and tools needed
- Focus on “Antimicrobial Stewardship” lab tools*
- Measuring success (or failure) of an “Antimicrobial Stewardship” program

This presentation reflects Dr. Miller’s experience as a Clinical Microbiologist and Infectious Diseases physician for over 20 years at McGill University. The opinions and statements herein do not reflect the policy or views of bioMerieux.

* For the in vitro diagnostic assays discussed, please consult the appropriate documents, product monographs and intended uses for each product.
Antimicrobial management in the hospital setting: key components (1)

- **Information, information, information**
  - Local resistance patterns (e.g. by specimen, hospital location, patient type)
  - Local antibiotic consumption (e.g. formulary, restriction policy, “preferences” by surgeons & others)

- **Diagnostic tests for reducing antibiotic use**
  - Biomarkers (WBC, C-reactive protein, Procalcitonin) for making Abx decisions
  - Rapid assays for pinpointing viral or bacterial etiology
  - Rapid & reliable AST for guiding antibiotic choices

- **Infection Prevention & Control Program**
Antimicrobial management in the hospital setting: key components (2)

- **Education, Education, Education**
  - Prophylactic antibiotics (when, dose duration)
  - Duration of antibiotics
  - Etc.

- **Maximal use of vaccination for prevention**
  - Influenza vaccine
  - Pneumococcal vaccine

- **Antibiotic Stewardship program**
DEFINITION

“The optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance.”


Antimicrobial: antibacterial, antiviral, antifungal or antiparasitic
United States
- IDSA supports broad implementation of antimicrobial stewardship programs across all health care settings (http://www.idsociety.org/Stewardship_Policy/#sthash.8v2dnFpa.dpuf)
- SHEA offers guidelines for Antimicrobial Stewardship in acute-care hospitals (http://www.shea-online.org/View/ArticleId/9/Guidelines-for-Developing-an-Institutional-Program-to-Enhance-Antimicrobial-stewardship.aspx)
- The White House advocates “combating drug-resistant bacteria and enhancing good antibiotic stewardship” (https://www.whitehouse.gov/blog/2015/06/02/white-house-hosts-forum-combating-antibiotic-resistance)

Europe

China
- “…regulations for antibiotic use incorporate the internationally accepted notion of antimicrobial stewardship, and include some administrative requirements tailored to the Chinese health-care system” (http://www.chinesemedicalnews.com/2013/02/new-rules-for-rational-antibiotic-use.html)

etc.
But how do you do it?

- **Resources**
  - Money, people

- **Tools**
  - Medical Record tools
  - Pharmacy tools
  - Non-microbiology lab tools
  - Microbiology lab tools
  - Guideline tools

- **Outcome measures**

One example:
http://www.shea-online.org/Portals/0/GNYHA_Antimicrobial_Stewardship_Toolkit_FINALv2%20Dec2011.pdf
A successful program requires SUPPORT

Mandatory to have the support of:

- Hospital administration (all levels)
- Pharmacists
- Nursing
- Laboratories
- Physicians
- ID physicians
- IPC group/committee
- Others
The “team” & their tasks

- **Minimal requirements**
  - Dedicated full-time pharmacist (or equivalent)
  - Dedicated full-time ID physician (or equivalent)

- **Their tasks**
  - Establishing & guiding the “Antimicrobial Stewardship” strategy
  - Managing the day-to-day aspects of the program
    - Tracking the patients, infections, antimicrobials of interest
    - Providing real-time assistance in antimicrobial management
    - Effecting changes in antimicrobial prescriptions
    - Ordering additional tests, as necessary, to guide therapy
  - Educational programs to personnel
  - Providing feedback on the program
1. Choose “low hanging fruit” to start with (demonstrate early success)
e.g. bacteremias, ICU infections, surgical site infections

2. Daily (or twice daily?) review of all pertinent patients
   Positive blood cultures ➔ bacteremias
   ICU rounds ➔ ICU infections
   Surgery rounds & wound cultures ➔ SSIs

3. Use stewardship tools to determine optimal patient management
Antimicrobial Stewardship Tools

INFORMATICS

Antimicrobial Decisions

Non-micro lab data

Micro lab data

Medical Record

Local microbiology epidemiological data

Guidelines (local, regional, national, international)

INFORMATICS

Non-culture results (e.g. antigen, NAAT, serology)
Culture results
Pathogen MICs

Data by body site, hospital location, etc.

Renal function
Hepatic function
Inflammatory markers (WBC, CRP, PCT)

Drug allergies
Travel/exposure history
Immune status, co-morbidities

Drug allergies
Possible drug interactions
Possible Abx toxicities

Current & previous Abx

Pneumonia guidelines
Sepsis guidelines
CDI guidelines

Pharmacy Records

INFORMATICS
The need for rapid diagnostics to improve Antimicrobial Stewardship
The need for rapid diagnostics to improve Antimicrobial Stewardship

The challenge is to create a cost-effective, accurate, rapid, and easy-to-use test for bacterial infections that will allow health professionals worldwide to administer the right antibiotics at the right time.
The need for rapid diagnostics to improve Antimicrobial Stewardship

U.S. Department of Health and Human Services
National Institutes of Health
Biomedical Advanced Research and Development Authority

PUBLIC CONSULTATION ON ANTIMICROBIAL RESISTANCE
RAPID, POINT-OF-CARE DIAGNOSTIC TEST CHALLENGE

Welcome and Meeting Overview

Robert Eisinger, National Institutes of Health (NIH)

- History and Rationale for the NIH/BARDA Antimicrobial Resistance Diagnostic Challenge
- Alignment with the National Strategy and Action Plan for Combatting Antibacterial Resistance and the Presidential Advisory Council on Combatting Antibiotic-Resistant Bacteria
The need for rapid diagnostics to improve Antimicrobial Stewardship

European Commission launches €1m prize for a diagnostic test to combat antibiotic resistance

Development of a rapid point-of-care test that will reduce the use of antibiotics in a safe way in patients with upper respiratory tract infections. In this context "Upper Respiratory Tract Infections" include pharyngitis, sinusitis, otitis as well as bronchitis.
Antimicrobial Stewardship Lab Tools

**NON-MICROBIOLOGY LAB**
- **Inflammatory markers**
  - WBC (total, bands)
  - C-reactive protein (CRP)
  - Procalcitonin (PCT)
- **Sepsis markers**
  - Lactate
  - Procalcitonin (PCT)
  - Platelets
  - Renal function
  - Hepatic function
- **Indicators at the infection site**
  - Pneumonia: LDH, O₂
  - UTI: pyuria
- **TDM for antimicrobials**
  - Rarely done

**MICROBIOLOGY LAB**
- **Non-culture results**
  - Microscopy (Gram, Z-N & Kinyoun, Acridine)
  - Antigen detection (Legionella urine Ag, “rapid” StrepA Ag, malaria)
  - NAAT (single, multiple, highly multiplex syndromic assays)
  - Serology (viral, toxoplasma)
- **Culture results**
  - Pathogen identification
  - Pathogen susceptibility
What rapid lab tools do we have today to assist with Antimicrobial Stewardship?

- **Inflammatory markers (WBC, CRP, PCT)**
  - Usefulness is dependent on:
    - other clinical variables (e.g. fever, patient’s condition, patient’s immune status)
    - medical condition (e.g. suspected pneumonia, sepsis, pyelonephritis, bone-joint infection)
    - threshold values for each biomarker
    - combination of biomarkers

- Impossible to do a complete review of the literature for these 3 lab indices; many meta-analyses available
NICE guidelines*

“For people presenting with symptoms of lower respiratory tract infection in primary care…..if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed. Use the results of the C-reactive protein test to guide antibiotic prescribing….”

CRP < 20 mg/L: do not routinely offer antibiotic therapy
CRP 20-100 mg/L: consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen)
CRP > 100 mg/L: offer antibiotic therapy

*Pneumonia in adults: diagnosis and management
NICE guidelines [CG191] December 2014
C-reactive protein (CRP)

- COCHRANE review*
  - “Used as an adjunct to a doctor's clinical examination point-of-care tests (e.g. C-reactive protein) can reduce antibiotic use in ARIs in general practice. The possibility of an increased risk of hospital admission suggests that care must be taken in how these tests are used. A more precise effect estimate is needed to assess the costs of the intervention and compare the use of a point-of-care biomarker to other antibiotic-saving strategies.”

*Use of rapid point-of-care testing for infection to guide doctors prescribing antibiotics for acute respiratory infections in primary care settings
Cochrane Review  November 2014
**NICE guidelines***

- "The procalcitonin tests** show promise but there is currently insufficient evidence to recommend their routine adoption in the NHS.
- Further research on procalcitonin tests is recommended for guiding decisions to:
  - stop antibiotic treatment in people with confirmed or highly suspected sepsis in the intensive care unit or
  - start and stop antibiotic treatment in people with suspected bacterial infection presenting to the emergency department.

- Centres currently using procalcitonin tests to guide these decisions are encouraged to participate in research and data collection

**ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay**

*Procalcitonin testing for diagnosing and monitoring sepsis
NICE guidelines [DG18]  October 2015*
COCHRANE review*

“Use of procalcitonin to guide initiation and duration of antibiotic treatment in patients with ARI was not associated with higher mortality rates or treatment failure. Antibiotic consumption was significantly reduced across different clinical settings and ARI diagnoses. Further high-quality research is needed to confirm the safety of this approach for non-European countries and patients in intensive care...........”

*Procalcitonin testing to initiate or discontinue antibiotics in acute respiratory tract infections
Cochrane Review  September 2012
“Procalcitonin guidance for antibiotic discontinuation reduced antibiotic usage in adult patients in ICUs without increasing mortality; however, there was uncertainty related to the evidence on mortality. Furthermore, procalcitonin guidance for initiating and discontinuing antibiotic therapy significantly reduced antibiotic prescription rates and duration of use in patients with acute respiratory tract infections, including acute exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia, and acute bronchitis in the ambulatory care or hospital setting.”
Use of a Combination Biomarker Algorithm To Identify Medical Intensive Care Unit Patients with Suspected Sepsis at Very Low Likelihood of Bacterial Infection

Jennifer H. Han, Irving Nachamkin, Susan E. Coffin, Jeffrey S. Gerber, Barry Fuchs, Charles Garrigan, Xiaoyan Han, Warren B. Bilker, Jacqueline Wise, Pam Tolomeo, Ebbing Lautenbach, for the Prevention Epicenters Program of the Centers for Disease Control Prevention

Clinical Note

Measuring both procalcitonin and C-reactive protein for a diagnosis of sepsis in critically ill patients

Hong-Xiang Li, Zhong-Min Liu, Shu-Jie Zhao, Dong Zhang, Shi-Ji Wang and Yu-Shan Wang

Research

Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections: a prospective study

Kristian Kofod, Ove Andersen, Gitte Kronborg, Michael Tvede, Janne Petersen, Jesper Eugen-Olsen and Klaus Larsen
What rapid lab tools do we have today to assist with Antimicrobial Stewardship?

- **Microbiology-related tools**
  - Antigen detection (StrepA, cryptococcus, malaria, Legionella, S. pneumo, etc)
  - **Single or 2-3 pathogen NAAT assays** (StrepA, FluA/B, FluA/B+RSV)
  - Highly multiplex syndromic NAAT panels (e.g. BioFire, Luminex, GenMark)
  - Rapid bacterial identification (ID) and antimicrobial susceptibility testing (AST) methods
Rapid highly multiplex syndromic panels
(some examples)
Benefits of the syndromic approach

7 of 9 benefits related to antimicrobial stewardship goals

• Faster diagnosis of causative agent of syndrome
• Faster access to specific indicated treatment
• Avoidance of unnecessary treatments (i.e. antibiotics)
• Shorter duration of symptoms if treated quicker
• Less time off work or school
• Shorter stays in clinic, Emergency Dept, or hospital
• Faster implementation of Infection Control precautions to prevent spread of infection to others
• Decreased pharmacy costs
• Decreased overall diagnostic laboratory costs
• Decreased total medical costs per encounter
• Improved patient satisfaction
• Improved overall patient outcomes
Syndromic lab tests: effect on Antimicrobial Stewardship efforts

- **More appropriate isolation of patients with respiratory illness**
  - Rapid multiplex PCR vs conventional testing\(^1\)
    - 1,447 vs 2,116 isolation days (755 days or 32% less)
  - Rapid multiplex PCR vs conventional methods\(^2\)
    - A saving in isolation days with rapid multiplex PCR in 50% of 800 patients

- **More appropriate isolation of patients with diarrhea; enhanced detection of etiology\(^3\)**
  - 60.0% of patients who tested positive with rapid multiplex PCR were never placed in appropriate isolation (109.1 patient-days)
  - 20.3% rapid multiplex PCR-negative patients could have been removed from isolation (181.2 patient-days)
  - 42.9% patients had a nosocomial infection

*Sources: 1-Goldenberg (Journ Inf 2015); 2-Halligan (CMI 2013); 3-Rand (DMID 2015)*
In summary, the RRP impacted patient care, resulting in less antibiotic use and shorter time in the hospital following admission.
Syndromic lab tests: effect on Antimicrobial Stewardship efforts

Implementation of FilmArray Respiratory Viral Panel in a Core Laboratory Improves Testing Turnaround Time and Patient Care

Min Xu, MD, PhD,1,3 Xuan Qin, PhD,1,3 Michael L. Astion, MD, PhD,1,3 Joe C. Rutledge, MD,1,3 Joanne Simpson, MT,1 Keith R. Jerome, MD, PhD,3 Janet A. Englund, MD,2,4 Danielle M. Zerr, MD,2,4 Russell T. Migita, MD,2,4 Shannon Rich, MT,1 John C. Childs, MT,1 Anne Cent, MS,3 and Mark A. Del Beccaro, MD2,4

Seattle Children’s Hospital

“The average and median turnaround time were 1.6 and 1.4 hours, respectively, in contrast to 7.0 and 6.5 hours documented 1 year previously.”

“Overall, 79 patients (81%) were given oseltamivir in a timely manner…….”

Source: Am J Clin Path 2013
 Syndromic lab tests: effect on Antimicrobial Stewardship efforts

FilmArray Gastrointestinal Panel
1 Test. 23 Targets. All in about an hour.
- Bacteria
  - Aeromonas
  - Campylobacter
  - Clostridium difficile (Toxin A/B)
  - Plesiomonas shigelloides
  - Salmonella
  - Yersinia enterocolitica
  - Vibrio
  - Vibrio cholerae
- Protozoa
  - Cryptosporidium
  - Cyclospora cayetanensis
  - Entamoeba histolytica
  - Giardia lamblia
- Viruses
  - Adenovirus, F 40/41
  - Astrovirus
  - Norovirus GII/III
  - Rotavirus A, B

FilmArray Respiratory Panel
1 Test. 20 Respiratory Pathogens. All in about an hour.
- Viruses
  - Adenovirus
  - Coronavirus HKU1
  - Coronavirus NL63
  - Coronavirus
  - Coronavirus
  - Human Rhinovirus
  - Human Metapneumovirus
- Bacteria
  - Bordetella
  - Chlamydia
  - Mycoplasma

FilmArray® Meningitis/Encephalitis Panel
1 Test. 14 Targets. All in about an hour.
- Bacteria
  - Escherichia coli K1
  - Haemophilus influenzae
  - Listeria monocytogenes
  - Neisseria meningitidis
  - Streptococcus agalactiae
  - Streptococcus pneumoniae
- Viruses
  - Cytomegalovirus (CMV)
  - Enterovirus
  - Herpes simplex virus 1 (HSV-1)
  - Herpes simplex virus 2 (HSV-2)
  - Human herpesvirus 6 (HHV-6)
  - Human parechovirus
  - Varicella zoster virus (VZV)
- Fungi
  - Cryptococcus neoformans/gattii
Rapid bacterial ID and AST methods
(Maldi-ToF +/- rapid AST)

- Tan KE (JCM 2012)
  - Time to ID by 1.4d (5-6d for difficult bacteria)
  - Savings in lab reagents & labor costs of $102,000 in 1st 12 months

- Tamma PD (ICHE 2013)
  - 29% results would result in appropriate Abx Rx (49% if stewardship done)
  - Time to optimal Abx Rx by 1.6d; 116 days of antibiotics avoided

- Perez KK (J Infect 2014)
  - ICU and overall LOS; reduced time to optimal Abx Rx
  - in overall 30-day mortality

- Huang AM (CID 2013)
  - time to effective Abx Rx by 10 hrs & to optimal Abx Rx by 43 hrs
  - ICU mortality in GN bacteremia; ICU LOS

- Nagel JL (JCM 2014)
  - Abx Rx & vancomycin TDM in CoNS blood culture contamination
  - mortality in real CoNS bacteremia patients
Rapid bacterial ID and AST methods
(Multiplex ID/AST from BC⁺)

Implementation and performance of the BioFire FilmArray® Blood Culture Identification panel with antimicrobial treatment recommendations for bloodstream infections at a midwestern academic tertiary hospital

Timothy R. Southern a,b, Trevor C. VanSchooneveld c, Dianna L. Bannister d, TeAnne L. Brown d, Amy S. Crismon d, Sarah N. Buss a,b, Peter C. Iwen a,b, Paul D. Fey a

“...the FilmArray® BCID panel is a rapid and reliable test for the detection of common bloodstream pathogens, and therapeutic decisions can be based upon panel results.

Randomized Trial of Rapid Multiplex Polymerase Chain Reaction–Based Blood Culture Identification and Susceptibility Testing

Rita Banerjee,1,4 Christine B. Teng,2,4 Scott A. Cunningham,3 Shorry M. Ihdo,3 James M. Stockelberg,4 James P. Moriarty,5 Nilay D. Shah,6 Jayewant N. Mandrekar,7 and Robin Fetter7

“...reduced treatment of contaminants and use of broadspectrum antimicrobials. Addition of antimicrobial stewardship enhanced antimicrobial de-escalation.
Rapid detection of candidemia

- Innovative PCR-based detection of candida directly from a blood specimen, using T2 Biosystems’ T2Candida assay

Potential to reduce the amount and duration of “empiric” antifungals in high-risk patients

T2 Magnetic Resonance Assay for the Rapid Diagnosis of Candidemia in Whole Blood: A Clinical Trial

Eleftherios Mylonakis1, Cornelius J. Clancy2, Luis Ostrosky-Zeichner3, Kevin W. Garey4, George J. Atanagad6, Jose A. Vazquez5, Jeffrey S. Croeger7, Marc A. Judson5, Yuka–Marie Vinagre8, Stephen O. Heard10, Fainarci N. Zervou4, Ioannis M. Zacharioudakis1, Dimitrios P. Kontoyiannis1, and Peter G. Pappas12

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Outcome measures: how to define “success” or “failure”

- **Programmatic**
  - Number and type of interventions and/or recommendations
  - Rates of clinician acceptance or implementation of recommendations

- **Antimicrobial Usage**
  - Quantity of total or targeted antimicrobial use (e.g., in defined daily doses, days of therapy, or grams)
  - Duration of antimicrobial therapy
  - Percentage of oral vs. intravenous drug administration for agents with both oral and intravenous formulations

- **Clinical**
  - All-cause mortality
  - Infection-related mortality
  - Duration of hospitalization
  - Rates of readmission (14-day; 30-day; same diagnosis)
  - Clinical cure (how to define?)
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- **Microbiologic**
  - Surveillance for organisms resistant to certain antimicrobials
  - Surveillance for multi-drug resistant organisms (to define)
  - Number of infections due to specified organisms
  - Rate of isolation of resistant organisms
  - Incidence of *C. difficile* infection

- **Costs**
  - Antimicrobial expenditures (total; by class; by disease indication)
Outcome measures: how to define “success” or “failure”

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Antimicrobial Stewardship programs can be highly effective. They do not happen “by magic” or through wishful thinking; appropriate planning and adequate resources are necessary to ensure success. Aside from the right people, the necessary tools must be present to facilitate the work. Informatics are crucial to ensure program efficiency. Laboratory tools have the potential to positively impact stewardship activities. Biomarkers & rapid micro lab innovations can benefit stewardship programs; despite the lab costs generated, overall hospital expenses can be reduced and patient outcomes improved. Relevant outcome measures must be used to assess the success of the program; feedback to stakeholders is crucial to ensure continued support.
Thank you.