The Role of the Epidemiologist in Antimicrobial Chemotherapy
- Lessons from Garrod and Finland

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Disclosures: Scientific Advisory Boards
Genentech, Cempra
Forty years on
It is now nearly 40 years since antibacterial chemotherapy began with the sulphonamides, and 30 since penicillin began largely to supersede them. Since then other therapeutic tasks have been taken over by a succession of further antibiotics and synthetics, and scarcely a single bacterial infection remains for which no remedy exists. Mycoses too are provided for, and even fungal infections. The era in

Journal of Antimicrobial Chemotherapy

40
Establishing New Standards
1975-2015

Latest Impact Factor 5.313
Generations of AC Workers

1935

FIRST GENERATION

SECOND GENERATION – TRAINEES OF FIRST GENERATION

THIRD GENERATION - TRAINEES OF SECOND GENERATION

FOURTH GENERATION - TRAINEES OF THIRD GENERATION

2016

New Talent
New Talent
New Talent

ROLLINS SCHOOL OF PUBLIC HEALTH
Generations of AC Workers

1935

FIRST GENERATION

Garrod Finland

SECOND GENERATION – TRAIINEES OF FIRST GENERATION

THIRD GENERATION - TRAIINEES OF SECOND GENERATION

FOURTH GENERATION - TRAIINEES OF THIRD GENERATION

2016

New Talent

New Talent

New Talent

New Talent
Generations of AC Workers

1935

FIRST GENERATION
Garrod  Finland

SECOND GENERATION – TRAINEES OF FIRST GENERATION

1971-3

THIRD GENERATION - TRAINEES OF SECOND GENERATION

2016

FOURTH GENERATION - TRAINEES OF THIRD GENERATION

New Talent

New Talent

New Talent
Garrod and Finland

LP Garrod
1895-1979

Professor of Bacteriology, University of London, St Bartholomew's Hospital

Founding Member, BSAC

Active Editor

Many papers

Many trainees
Excursions into Epidemiology: Selected Studies during the Past Four Decades at Boston City Hospital

Maxwell Finland

From the Channing Laboratory, Thorndike Memorial Laboratory, Harvard Medical Unit, Boston City Hospital, Boston, Massachusetts

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Excursions Into Epidemiology

“It was in 1948 that I first was made aware that much of what we were doing in the hospital was considered to be epidemiology. In that year I was surprised to receive a letter notifying me that I had been elected a member of the American Epidemiological Society, of which, I confess, I had never heard until that time.”

Finland M. J Infect Dis 1973; 128: 76-124
“It was 20 years later that I attained ‘professional status,’ for it was only after I was relegated to emeritus status as a professor of medicine at the university that I was given the title ‘epidemiologist’ at BCH with a salary (equivalent to that of a research fellow) to go with it.”

Finland M. J Infect Dis 1973; 128: 76-124
GOALS OF ANTIMICROBIAL CHEMOTHERAPY

Maintaining value of chemotherapy agents by minimizing resistance, through

1. Maximizing effective treatment and preventive therapy (right indication, drug regimen, dose, administration route, etc.)

2. Recognizing and responding to opportunities for development of new antibacterial drugs
What Does An Antimicrobial Chemotherapy Epidemiologist Do?

Identify Relevant Sources, Collect by Appropriate Methods, Manage, Analyze, Interpret and Report DATA to Drive EFFORTS IN ANTIMICROBIAL CHEMOTHERAPY

- Populations (Groups) are focus rather than individuals
ANTIMICROBIAL CHEMOTHERAPY
AND HEALTHCARE EPIDEMIOLOGY
OVERLAP

- Safety
  - Infection Control
  - Employee (“Occupational”) Health, Personnel Safety
  - Patient Safety/Risk Management

- Quality Improvement/Promotion
  - Antimicrobial Use

- Value
  - Technology Assessment, Product Evaluation, Resource Utilization
  - Drug and Instrument Management
The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *Clostridium difficile*), and the emergence of resistance. Thus, the appropriate use of antimicrobials is an essential part of patient safety.
FOCUS OF PRACTICAL EPIDEMIOLOGY

Question 1 – What Should Be Done?
Collect by appropriate methods, analyze, interpret, and report population-based data to inform plans for treatment, control and prevention (BUT other team members involved in developing and implementing plan)

Question 2 – Is Plan Being Implemented?
Collect, analyze, interpret, and report data on process measures to evaluate implementation of plan elements (BUT other team members involved in interpreting data and further action)

Question 3 – Is Plan Working?
Collect, analyze, interpret, and report data on outcome measures to evaluate effectiveness of plan (BUT other team members involved in using data and further action)

These data lead back to Question 1 – “continuous loop”
The Epidemiologist As A Team Member

**Epidemiologist**

**Q1 What Should Be Done?**
Provides DATA on Occurrence, Trends, Risk Determinants, Etc.

**Q2 Is It Being Done?**
Provides DATA on PROCESS Measures

**Q3 Is It Working?**
Provides DATA on OUTCOME Measures

**Team**

Decides on Appropriate Actions

RETURN TO Q1
Role of Epidemiologist –
This Presentation

Limited to:

- Hospitals and other healthcare institutions
- Bacterial diseases
- High resource settings
The Epidemiologist as a Team Member - QUESTION 1

**Epidemiologist**

Q1 What Should Be Done?
1. Provides Descriptive DATA (Occurrence, Trends, Etc.)
2. Provides DATA on Risk Determinants/Drivers
3. Provides DATA on Special Populations and Settings of Increased Risk
4. Provides MODELS on Potential Future Patterns

**Team**

1. Decides on Appropriate Actions
2. Defines Indicators for Monitoring Implementation for Question 2
1. Providing DATA to Better Define Problems

A return to the pre-antimicrobial era?
The effects of antimicrobial resistance will be felt most acutely in lower-income countries

Baker S. Science 2015; 347: 1064-1066

Outbreak of Colistin-Resistant, Carbapenemase-Producing Klebsiella pneumoniae: Are We at the End of the Road?

Van Duin D, Doi Y. J Clin Microbiol 2015; 53: 3116-3117

A Scary New Superbug Gene Has Reached at Least 19 Countries

Bacteria that resist last-resort drugs were identified two months ago in China. Now scientists are finding them all over.


Jan 22, 2016
POST ANTIBIOTIC ERA

1947

“It is for its power over grave Staphylococcal infections that we always have had most reason to be grateful for the discovery of penicillin, and that power is already on the wane.”

“Polymixin finds its clearest indication in serious infections due to *Ps. pyocyaneae*, an organism which is apt to be resistant to all other drugs whatsoever.”

POST ANTIBIOTIC ERA 1968

“We know now from bitter experience with antibiotics that, in dealing with some bacteria, to have only one antibacterial drug is hopeless. When resistance develops, another must take its place.”

POST ANTIBIOTIC ERA

1978

“Little by little, we are experiencing the erosion of the strongest bulwarks against serious bacterial infections in the modern era.”

In the last several years, the frequency and spectrum of antimicrobial-resistant infections have increased in both the hospital and the community. Certain infections that are essentially untreatable have begun to occur as epidemics both in the developing world and in institutional settings in the United States. The increasing frequency of drug resistance has been attributed to combinations of microbial characteristics, selective pressures of antimicrobial use, and societal and technologic changes that enhance the transmission of drug-resistant organisms. Antimicrobial resistance is resulting in increased morbidity, mortality, and health-care costs. Prevention and control of these infections will require new antimicrobial agents, prudent use of existing agents, new vaccines, and enhanced public health efforts to reduce transmission.
YEAR 2000 BUGS: THE END OF THE ANTIBIOTIC ERA?

*Based on the Robert W. Philip Memorial Lecture delivered at the symposium on Appropriate Antibiotic Prescribing held in the College on 16 June 2000*
POST-ANTIBIOTIC ERA – PUBLIC PERCEPTION?

1. Antibiotic Era = All bacterial infections treatable, so Post-Antibiotic Era = No bacterial infections treatable
2. Antibiotic Era = All bacterial infections treatable, so Post-Antibiotic Era = Some bacterial infections not treatable
BACTERIAL INFECTIONS FOR WHICH RESISTANCE IS A PROBLEM

CDC List:

- **Group 1 - Urgent**
  - Example: Carbapenem-resistant *Enterobacteriaceae*

- **Group 2 - Serious**
  - Example: Multi-drug-resistant *Acinetobacter*

- **Group 3 - Concerning**

- **Need Group 4 - Not a Particular Problem At Present**

http://www.cdc.gov/drugresistance/protecting_patients.html
accessed Jan 13, 2016
CDC – SERIOUS THREATS

Nosocomial Outbreak of Infection With Pan–Drug-Resistant Acinetobacter baumannii in a Tertiary Care University Hospital

Resistant to All Available Drugs

Raquel Valencia, MD, MPH; Luis A. Arroyo, MD; Manuel Conde, MD, MPH, PhD; Josefa M. Aldana, MD, MPH; Maria-José Torres, PhD; Felipe Fernández-Cuenca, PhD; José Garnacho-Montero, MD, PhD; José M. Cisneros, MD, PhD; Carlos Ortiz, MD, PhD; Jerónimo Pachón, MD, PhD; Javier Aznar, MD, PhD

Objective. To describe what is, to our knowledge, the first nosocomial outbreak of infection with pan–drug-resistant (including colistin-resistant) Acinetobacter baumannii, to determine the risk factors associated with these types of infections, and to determine their clinical impact.

Design. Nested case-control cohort study and a clinical-microbiological study.


Patients. Case patients were inpatients who had a pan–drug-resistant A. baumannii isolate recovered from a clinical or surveillance sample obtained at least 48 hours after admission to an intensive care unit (ICU) during the time of the epidemic outbreak. Control patients were patients who were admitted to any of the "boxes" (ie, rooms that partition off a distinct area for a patient’s bed and the equipment needed to care for the patient) of an ICU for at least 48 hours during the time of the epidemic outbreak.

Results. All the clinical isolates had similar antibiotic susceptibility patterns (ie, they were resistant to all the antibiotics tested, including colistin), and, on the basis of repetitive extragenic palindromic–polymerase chain reaction, it was determined that all of them were of the same clone. The previous use of quinolones and glycopeptides and an ICU stay were associated with the acquisition of infection or colonization with pan–drug-resistant A. baumannii. To control this outbreak, we implemented the following multicomponent intervention program: the performance of environmental decontamination of the ICUs involved, an environmental survey, a revision of cleaning protocols, active surveillance for colonization with pan–drug-resistant A. baumannii, educational programs for the staff, and the display of posters that illustrate contact isolation measures and antimicrobial use recommendations.

Conclusions. We were not able to identify the common source for these cases of infection, but the adopted measures have proven to be effective at controlling the outbreak.
Multi-Drug Resistant Acinetobacter spp.

accessed March 3, 2016
“It is well to remember the days before the antimicrobial revolution at a time when there is so much talk of a return to the pre-antibiotic era. Although microbes continue to surprise us with their ingenuity in surviving the antibiotic onslaught, the chances that microbial disease will once more become regularly untreatable is exceedingly remote.

“That said, resistance is a real and urgent threat that must be addressed if reliable therapy with first-line agents is to remain the norm.”

The **CTEI** (Can’t Treat Every Infection) ERA

Baker S. Science *2015*; 347: 1064-1066
The **CTEI** (Can’t Treat Every Infection) ERA

ANO**THER CTEI** (Can’t Treat Every Infection) ERA
SOME FUTURE ROLES FOR THE EPIDEMIOLOGIST

✧ Example: Providing DATA to better define “SEPSIS”
2. Providing DATA on Risk Determinants/Drivers of Antimicrobial Resistance and its Consequences – Adjusting for Influential Variables
Emergence of Antibiotic Resistance in Hospitals, 1935-1975

“The dominant factor in the emergence and spread of antibiotic-resistant bacterial pathogens, whether in hospital wards or in the community, is clearly the intensive use of the antibiotic agents to which resistance emerges and then spreads.”

Finland M. Rev Infect Dis 1979; 1: 4-21
“... although the link between human antimicrobial use and resistance seems clear cut, this association is complex. Confounding factors mean a uniform approach to understanding resistance cannot be taken.

“These factors include pathogen–drug interactions, pathogen-host interactions, mutation rates of the pathogen, emergence of successful antimicrobial resistant clones, the transmission rates of pathogens between human beings, animals, and the environment, cross-resistance, and selection of co-resistance to unrelated drugs.”

Mortality due to $bla_{KPC}$ *Klebsiella pneumoniae* bacteraemia

Yedidah Fraenkel-Wandel$^{1,2}$†, David Raveh-Brawer$^2$†, Yonit Wiener-Well$^2$, Amos M. Yinnon$^{1,2}$* and Marc V. Assous$^3$

**Conclusions:** The selection of an ESBL/Kp control cohort with a ratio of 1:2 (study versus control group) helped resolve an as yet insufficiently settled question: bacteraemia with KPC/Kp is an independent risk factor for death, justifying the strict adherence to cohorting and isolation procedures.

**Table 2.** Treatment and outcome of admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>ESBL/Kp (n=136)</th>
<th>KPC/Kp (n=68)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial treatment was appropriate</td>
<td>54 (40%)</td>
<td>30 (44%)</td>
<td>NS (0.32)</td>
</tr>
<tr>
<td>empirical treatment with colistin</td>
<td>13 (9.5%)</td>
<td>6 (8.8%)</td>
<td>NS (0.54)</td>
</tr>
<tr>
<td>definite treatment with colistin</td>
<td>59 (43%)</td>
<td>60 (88%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>antibiotic changed due to cultures</td>
<td>110 (81%)</td>
<td>57 (84%)</td>
<td>NS (0.93)</td>
</tr>
<tr>
<td>colistin daily dosage, MU±SD</td>
<td>2.63±1.08</td>
<td>2.42±0.88</td>
<td>0.011</td>
</tr>
<tr>
<td>Admission duration, days, mean±SD</td>
<td>47±49</td>
<td>42±33</td>
<td>NS (0.46)</td>
</tr>
<tr>
<td>Admission duration, days, median (IQR)</td>
<td>32 (15–63)</td>
<td>36 (21–55)</td>
<td>0.012</td>
</tr>
<tr>
<td>Functional status at discharge</td>
<td></td>
<td></td>
<td>NS (0.13)</td>
</tr>
<tr>
<td>independent</td>
<td>43 (32%)</td>
<td>11 (16%)</td>
<td></td>
</tr>
<tr>
<td>dependent</td>
<td>39 (29%)</td>
<td>13 (19%)</td>
<td></td>
</tr>
<tr>
<td>Status on discharge</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>alive (106)</td>
<td>82 (60%)</td>
<td>24 (35%)</td>
<td></td>
</tr>
<tr>
<td>dead (98)</td>
<td>54 (40%)</td>
<td>44 (65%)</td>
<td></td>
</tr>
<tr>
<td>Mortality by initial treatment</td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>treatment appropriate</td>
<td>25/54 (46%)</td>
<td>12/18 (67%)</td>
<td></td>
</tr>
<tr>
<td>treatment inappropriate</td>
<td>29/82 (35%)</td>
<td>32/50 (64%)</td>
<td></td>
</tr>
<tr>
<td>Death by gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male (113)</td>
<td>23/76 (30%)</td>
<td>20/37 (54%)</td>
<td>0.012</td>
</tr>
<tr>
<td>female (91)</td>
<td>31/60 (52%)</td>
<td>24/31 (77%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise indicated.

NS, not significant ($P \geq 0.05$); MU, million units.

$^a$P=0.2.

$^b$P=0.8.
Tools: Multivariate Analysis for Benchmarking

Prevention Status Report | 2013

Healthcare-Associated Infections

Georgia

Central line-associated bloodstream infection—standardized infection ratio

What is a standardized infection ratio (SIR)?

The SIR is a summary measure used to track HAIs over time. It adjusts for the fact that each healthcare facility treats different types of patients. The SIR compares the number of infections reported to the National Healthcare Safety Network in 2011 to the number of infections that would be predicted based on national, historical baseline data:

\[
\text{SIR} = \frac{\text{Observed # of HAIs}}{\text{Predicted # of HAIs}}
\]

How is the standardized infection ratio (SIR) adjusted for risk?

When the data are risk-adjusted, it makes it possible to fairly compare hospital performance. In this report, the SIRs are adjusted for risk factors that may impact the number of infections reported by a hospital, such as type of patient care location, bed size of the hospital, patient age, and other factors. The SIR is adjusted differently depending on the type of infection measured.

The SIRs for CLABSI and CAUTI are adjusted for:

- Type of patient care location
- Hospital affiliation with a medical school
- Bed size of the patient care location

The SIRs for hospital-onset *C. difficile* and MRSA bloodstream infections are adjusted using slightly different risk factors:

- Facility bed size
- Hospital affiliation with a medical school
- The number of patients admitted to the hospital who already have *C. difficile* or an MRSA bloodstream infection (“community-onset” cases)
- For hospital-onset *C. difficile*, the SIR also adjusts for the type of test the hospital laboratory uses to identify *C. difficile* from patient specimens.

AU Measure

• For each measure and location, we propose summarizing use with a “Standardized Antibiotic Administration Ratio” or “SAAR”.
• SAAR would be a risk adjusted summary measure of AU, where an SAAR of 1.0 would be “expected” use given a particular set of facility characteristics.


NOTE: Will Require Much Higher N of Observations Than Is Currently Available in NHSN
3. Providing DATA to define populations and settings of increased risk for antibacterial resistance, stratified by organism/drug group
Identifying Special Populations At Risk

“... epidemiology separates populations within epidemics into smaller and smaller groups at increasing risk of disease.”

Kuller L. Epidemiology – Then and Now. Am J Epidemiol 2016 (Mar); 183: 372-380
IDENTIFYING THOSE AT SPECIAL RISK

Quantitative Variable (Proportion Not Treatable in Given Population)

- Not Treatable in Overall Population
- Not Treatable in Specific Group (ICU, Dialysis, Etc.)
Resistance - Modern Medicine at Risk

Patients who receive specialized care will be at highest risk

- Cancer chemotherapy
- Complex surgery
- Joint replacements
- Organ transplants
- Chronic conditions (e.g., rheumatoid arthritis)
- Dialysis

CDC slide set at haiwinnablebattle_presentation-2015-final.pptx
Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study

Aude Teillant, Sumanth Gandra, Devra Barter, Daniel J Morgan, Ramanan Laxminarayan

Findings We estimate that between 38.7% and 50.9% of pathogens causing surgical site infections and 26.8% of pathogens causing infections after chemotherapy are resistant to standard prophylactic antibiotics in the USA. A 30% reduction in the efficacy of antibiotic prophylaxis for these procedures would result in 120,000 additional surgical site infections and infections after chemotherapy per year in the USA (ranging from 40,000 for a 10% reduction in efficacy to 280,000 for a 70% reduction in efficacy), and 6,300 infection-related deaths (range: 2,100 for a 10% reduction in efficacy, to 15,000 for a 70% reduction). We estimated that every year, 13,120 infections (42%) after prostate biopsy are attributable to resistance to fluoroquinolones in the USA.

Interpretation Increasing antibiotic resistance potentially threatens the safety and efficacy of surgical procedures and immunosuppressing chemotherapy. More data are needed to establish how antibiotic prophylaxis recommendations should be modified in the context of increasing rates of resistance.
MODELING OF IMPACT OF RESISTANCE IN GROUPS AT SPECIAL RISK

Figure 3: Number of additional deaths per year in the USA under four scenarios of decreased efficacy of antibiotic prophylaxis.

We assessed 10%, 30%, 70%, and 100% decreased antibiotic efficacy by comparison with effect sizes in randomised controlled trials done between 1968 and 2011.

“With the emergence in human beings of plasmid-mediated resistance mechanisms for antimicrobials of crucial importance, such as colistin, consideration of the increased selection pressures created by exposure to these antimicrobials in prophylactic regimes must be deemed a priority. To achieve this, engagement with all clinical specialties to promote clinical leadership of antimicrobial stewardship is crucial.”

SOME CURRENT ROLES FOR THE EPIDEMIOLOGIST

4. Providing MODELS of future resistance patterns
   ∗ Modeling outcome with interventions is priority
Vital Signs: Estimated Effects of a Coordinated Approach for Action to Reduce Antibiotic-Resistant Infections in Health Care Facilities — United States

Rachel B. Slayton, PhD1; Damon Toth, PhD2; Bruce Y. Lee, MD3; Windy Tanner, PhD4; Sarah M. Bartsch, MPH5; Karim Khader, PhD6; Kim Wong, PhD7; Kevin Brown, PhD2; James A. McKinnell, MD5; William Ray4; Loren G. Miller, MD6; Michael Rubin, MD, PhD2; Diane S. Kim7; Fred Adler, PhD8; Chenghua Cao, MPH1; Lacey Avery, MA1; Nathan T.B. Stone, PhD9; Alexander Kallen, MD1; Matthew Samore, MD1; Susan S. Huang, MD7; Scott Fridkin, MD1; John A. Jernigan, MD1

If best infection control practices and antibiotic stewardship were nationally adopted, more than 600,000 infections and 37,000 deaths could be prevented over 5 years.
The Epidemiologist As A Team Member – QUESTION 3

**Epidemiologist**

Q1 What Should Be Done?
- Provides DATA on Occurrence, Trends, Risk Determinants, Etc.

Q2 Is It Being Done?
- Provides DATA on PROCESS Measures

Q3 Is It Working?
- Provides DATA on OUTCOME Measures

**Team**

1. Decides on Appropriate Actions
2. Defines Indicators for Monitoring

Decides on Appropriate Actions

Decides on Appropriate Actions

RETURN TO Q1
5. Providing DATA to monitor PROCESS of Appropriate Antibacterial Use – “Is It Being Done?”

TEAM develops guides/indicators

TEAM evaluates results
“... if the pace of discovery were slowed, or even if we had a moratorium for a year or two, it might not be a bad thing. There is a possibility that not many new antibiotics remain to be discovered, and if so it is better that they should be introduced one by one at fairly long intervals. My main reason for this suggestion is that the rapid expansion of choice for the clinician has far outrun his capacity for learning about these drugs and their different merits and indications.”

Garrod LP. Antimicrobial Agents Chemotherapy 1965; 1107-1114.
The main recommendations are designed to promote and monitor sensible antimicrobial use through stewardship teams to review prescribing and resistance data and to provide feedback, education, and training to prescribers. Specific guidance is given on clinical assessment and documentation of diagnosis, obtaining microbiological samples, watchful waiting or delayed prescribing, and taking the time to discuss with patients the likely cause of their symptoms. Above all, prescribers need to ensure “the right antibiotic, at the right dose at the right time”, when a prescription is needed, and must resist pressure to prescribe unless warranted. According to NICE, “9 out of 10 GPs say...”
Results: The majority of CCGs and acute trusts reported reviewing national AMS toolkits formally or informally (60% and 87%, respectively). However, only 13% of CCGs and 46% of acute trusts had developed an action plan for the implementation of these toolkits.

Conclusions: The majority of healthcare organizations review national AMS toolkits; however, implementation of the toolkits, through the development of action plans to deliver AMS interventions, requires improvement.

Findings: The survey was completed by 14 of the 15 AMTs (response rate 93 %). Results demonstrated good compliance with 9 of the 10 key European indicators included in the survey; 7 (50 %) of AMTs achieved all 9 indicators and 14 (100 %) of AMTs achieved at least 6 out of 9 indicators (67 %).
SOME CURRENT ROLES FOR THE EPIDEMIOLOGIST

6. Providing DATA on effectiveness of control measures or new drugs – “Is It Working?”
   - OUTCOME measures
Impact of Antimicrobial Stewardship - Multiple OUTCOME Measurements

“Measurement for improvement is not focused on judging whether data meet a compliance threshold or target but rather is a means of determining whether the changes we make to improve are effective and to what degree.”

Universal Screening and Decolonization for Control of MRSA in Nursing Homes: A Cluster Randomized Controlled Study

RESULTS. NHs were randomly allocated to a control group (51 NHs, 2,412 residents) or an intervention group (53 NHs, 2,338 residents). Characteristics of NHs and residents were similar in both groups. The mean screening rates were 86% (range, 27%–100%) in control NHs and 87% (20%–100%) in intervention NHs. Prevalence of MRSA carriage averaged 8.9% in both control NHs (range, 0%–43%) and intervention NHs (range, 0%–38%) at baseline, and this rate significantly declined to 6.6% in control NHs and to 5.8% in intervention NHs after 12 months. However, the decline did not differ between groups (P = .66).

CONCLUSION. Universal screening followed by decolonization of carriers did not significantly reduce the prevalence of the MRSA carriage rate at 1 year compared with standard precautions.

Comparison of control strategies for methicillin-resistant Staphylococcus aureus

Mary T. Bessesen MD a, *, Karla Lopez BSN b, Karen Guerin MS c, Karen Hendrickson BSN d, Shavetta Williams MSPH d, Susan O'Connor-Wright MS d, Donald Granger MD d, e

Conclusion: Significant reductions in MRSA HAI were associated with implementation of the MRSA control bundle. The bundle that included full contact precautions for colonized patients was no more effective in prevention of MRSA transmissions than a similar bundle that omitted the use of cover gowns.

Amer J Infect Control 2015 (April); 36: 401-408

Amer J Infect Control 2013; 41: 1048-1052
Is It Working? YES – and Sustainable

Strict Infection Control Leads to Low Incidence of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection over 20 Years

Andreas F. Widmer, MD, MS;¹ Botond Lakatos, MD;¹ Reno Frei, MD²

Infect Control Hosp Epidemiol 2015; 36: 702-709

Time series analysis of the impact of an intervention in Tayside, Scotland to reduce primary care broad-spectrum antimicrobial use

Virginia Hernandez-Santiago*, Charis A. Marwick, Andrea Patton, Peter G. Davey, Peter T. Donnan and Bruce Guthrie

**Conclusions:** A real-world intervention to reduce primary care prescribing of antimicrobials associated with CDI led to large, sustained reductions in the targeted prescribing, largely due to substitution with guideline-recommended antimicrobials rather than by avoiding antimicrobial use altogether. Further research is needed to examine the impact on antimicrobial resistance.

J Antimicrob Chemother 2015; 70: 2397-2404
Show Me the Money: Long-Term Financial Impact of an Antimicrobial Stewardship Program

James R. Beardsley, PharmD;¹
John C. Williamson, PharmD;¹
James W. Johnson, PharmD;¹ Vera P. Luther, MD;²
Rebekah H. Wrenn, PharmD;¹ Christopher C. Ohl, MD²

The financial impact of an antimicrobial stewardship program in operation for more than 11 years was determined by calculating the reduction in antimicrobial expenditures minus program labor costs. Depending on the method of inflation adjustment used, the program was associated with average cost savings of $920,070 to $2,064,441 per year.

*Infect Control Hosp Epidemiol 2012;33(4):398-400*
Is It Working? YES — and Leverage

Association Between Outpatient Antibiotic Prescribing Practices and Community-Associated Clostridium difficile Infection

Results. Healthcare providers prescribed 5.2 million courses of antibiotics among adults in the surveillance population in 2010, for an average of 0.73 per person. Across surveillance sites, antibiotic prescription rates (0.50–0.88 prescriptions per capita) and unadjusted CA-CDI rates (40.7–139.3 cases per 100 000 persons) varied. In regression modeling, reducing antibiotic prescribing rates by 10% among persons ≥20 years old was associated with a 17% (95% confidence interval, 6.0%–26.3%; \( P = .032 \)) decrease in CA-CDI rates after adjusting for age, gender, race, and type of diagnostic assay. Reductions in prescribing penicillins and amoxicillin/clavulanic acid were associated with the greatest decreases in CA-CDI rates.

Conclusions. Community-associated CDI prevention should include reducing unnecessary outpatient antibiotic use. A modest reduction of 10% in outpatient antibiotic prescribing can have a disproportionate impact on reducing CA-CDI rates.

Dantes R, et al. Open Forum Infect Dis 2015; 2(3); ofv113
SOME CURRENT ROLES FOR THE EPIDEMIOLOGIST

7. Providing Outcome DATA targeted to Action

Example: Targeted Assessment for Prevention (TAP)
Targeted Assessment for Prevention of Healthcare-Associated Infections: A New Prioritization Metric

OBJECTIVE. To develop a method for calculating the number of healthcare-associated infections (HAIs) that must be prevented to reach a HAI reduction goal and identifying and prioritizing healthcare facilities where the largest reductions can be achieved.

SETTING. Acute care hospitals that report HAI data to the Centers for Disease Control and Prevention’s National Healthcare Safety Network.

METHODS. The cumulative attributable difference (CAD) is calculated by subtracting a numerical prevention target from an observed number of HAIs. The prevention target is the product of the predicted number of HAIs and a standardized infection ratio goal, which represents a HAI reduction goal. The CAD is a numeric value that if positive is the number of infections to prevent to reach the HAI reduction goal. We calculated the CAD for catheter-associated urinary tract infections for each of the 3,639 hospitals that reported such data to National Healthcare Safety Network in 2013 and ranked the hospitals by their CAD values in descending order.

RESULTS. Of 1,578 hospitals with positive CAD values, preventing 10,040 catheter-associated urinary tract infections at 293 hospitals (19%) with the highest CAD would enable achievement of the national 25% catheter-associated urinary tract infection reduction goal.

CONCLUSION. The CAD is a new metric that facilitates ranking of facilities, and locations within facilities, to prioritize HAI prevention efforts where the greatest impact can be achieved toward a HAI reduction goal.

Soe MM, et al. Infect Control Hosp Epidemiol 2015 (Dec); 36: 1379-1384
The Five "W"s of the Targeted Assessment for Prevention (TAP) Strategy

WHAT is the TAP strategy?
The Targeted Assessment for Prevention (TAP) strategy is a method developed by the Centers for Disease Control and Prevention (CDC) to use data for action to prevent healthcare-associated infections (HAIs). The TAP strategy targets healthcare facilities and specific units within facilities with a disproportionate burden of HAIs so that gaps in infection prevention in the targeted locations can be addressed. The TAP report uses a metric called the cumulative attributable difference (CAD). The CAD is the number of infections that must be prevented to achieve a HAI reduction goal and is calculated by subtracting a numerical prevention target from an observed number of HAIs. The TAP report allows for the ranking of facilities, or locations within individual facilities, by the CAD to prioritize prevention efforts where they will have their greatest impact.
TAP report capability in NHSN for CLABSI, CAUTI, CDI

http://health.state.tn.us/ceds/HAI/calculator.shtml
NHSN Data for Action: Targeted Assessment for Prevention (TAP)

NHSN Data

Rank Hospitals by Excess* Infections

Target hospitals with highest excess numbers of infections

Technical Assistance

* Based on a set benchmark defined at a national, state, or group level

- QIOs
- HENs
- State Health Departments
- Other partners
You are receiving this letter because 2014 HAI data indicate your facility has not met the 2013 national HAI reduction goals for at least one of three targeted HAIIs—CLABSI, CAUTI or CDI. The table below indicates the HAIIs for which your facility has an occurrence above the national goals set by the Department of Health and Human Services in the National HAI Action Plan. The cumulative attributable difference (CAD) is the number of infections that must be prevented within your facility to achieve the national standardized infection ratio (SIR) goal.

MetaStar, Inc. and the Wisconsin Hospital Association (WHA) provide HAI reduction consultative services, including education and peer networking, to Wisconsin healthcare facilities at no cost. The tradition of collaboration among Wisconsin hospitals is a proven method for improving healthcare quality, and DPH strongly encourages your facility to participate in one of the collaborative HAI reduction groups led by these organizations. We also encourage you to

Cumulative Attributable Difference: An Infection Metric That Reflects a Value System

The second assumption is unlikely to be true because of the law of diminishing marginal returns, which states that, at some point, additional units of an input will yield fewer units of the output.\textsuperscript{5,8–10} In the case of infection control, this means that as HAIs decrease, increasingly greater effort and resources will be needed to yield further reductions in HAIs. From a healthcare network perspective, it is conceivable that it may be more costly to prevent a single additional infection in a large hospital with a moderate HAI rate than in a small hospital with a high HAI rate. As a consequence, the potential impact of an intervention (the count of HAIs prevented) may not correlate with CAD.

A complicating factor is that poorly performing hospitals may be poorly performing because of local difficulties in the implementation of preventive strategies. Thus, even though the law of diminishing returns can help us predict changes in marginal returns at the same hospital, it remains difficult to predict the difference in cost of preventing 1 more infection in a high-CAD hospital versus a low-CAD hospital. More research is needed on this point.

SOME CURRENT ROLES FOR THE EPIDEMIOLOGIST

8. Careful evaluation of new DATA methods and tools
“Despite their importance, most international surveillance systems outside Europe have not been formally assessed in terms of validity, sustainability, and long-term effects on antibiotic resistance.

“The evidence base to determine the most cost-effective systems for surveillance of antibiotic use and resistance remains weak worldwide.”

Dar OA et al. Lancet 2016 (Jan 16); 387: 285-295
VALIDATION OF DATA

Lessons learned from initial reporting of carbapenem-resistant *Enterobacteriaceae* in New York State hospitals, 2013-2014

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**Background:** Carbapenem-resistant *Enterobacteriaceae* (CRE) are an urgent concern in health care in the United States because of high attributable mortality and versatile resistance mechanisms. CRE reporting was mandated in New York State (NYS) hospitals in July 2013.

**Methods:** Infection preventionists from the NYS Department of Health audited hospital-reported CRE data by comparing laboratory records with cases reported to the National Healthcare Safety Network (NHSN). Information regarding microbiology laboratory testing methodologies was obtained through a survey in October 2013.

**Results:** There were 1,151 CRE laboratory reports audited, with 13.6% determined not to have been reported to the NHSN when they should have been and 4.6% determined to be reported in error. There were a variety of errors, including lapses in surveillance and misinterpretation of the surveillance definition.

**Conclusion:** Educational initiatives that include microbiology laboratory staff, improvements in the use of laboratory information systems to communicate with infection prevention, and updated NHSN definitions should improve the accuracy and consistency of CRE reporting in NYS.
KEY POINT: THE EPIDEMIOLOGIST DEPENDS ON THE REST OF THE TEAM

- DATA are NECESSARY but not SUFFICIENT for success
  - Example 1: DOOR/RADAR
isolated\textsuperscript{14} or in those artificially habituated.\textsuperscript{15} The discovery of TC was welcomed on other grounds than these. TC produced higher and better-sustained levels of antibiotic activity in the blood than OTC\textsuperscript{16} and more particularly than CTC, the exceptional instability of which explains this difference. Moreover, TC was found less apt to produce gastro-intestinal side-effects, notably the acute enterocolitis caused by resistant staphylococci, which had proved to be so dangerous a complication of therapy with CTC and particularly OTC.\textsuperscript{3-8}
Tool: Stratified Analysis

A Chance to Change the Paradigm of Outcome Assessment of Antimicrobial Stewardship Programs

“We believe that interventions that are used to modify care processes or bacterial ecology should no longer be evaluated in a unidirectional way, since their effects could be complex and eventually unintended. *Investigators should be compelled to probe not only the efficacy of their interventions but also their safety at a patient to patient level.*”

“DOOR/RADAR is a composite score designed to compare strategies of antibiotic optimization. It uses a two-step classification of all patients in the sample.”

1. Classification of clinical benefit for each patient on the basis of safety and efficacy
2. Measure total days of antimicrobial use within each clinical benefit stratum. Compare for the two groups. Assess impact of intervention on reducing antimicrobial use after stratifying for clinical outcome in each individual patient, rather than for the group as a whole.

1. If clinical outcome worse for intervention group, do NOT assess antibiotic use intervention
2. If clinical outcome same or better for intervention group, assess antibiotic use intervention in usual fashion

Can **NOT** Be Done By The Epidemiologist Alone – Requires TEAM input

Table 3. Overall Clinical Outcome for the SCOUT-CAP\(^a\) Trial (From Most to Least Desirable)

1. Survival; adequate clinical response; no adverse events
2. Survival; adequate clinical response; mild adverse event(s)
3. Survival; adequate clinical response; moderate adverse event(s)
4. Survival; adequate clinical response; severe adverse event(s)
5. Survival; inadequate clinical response without additional emergency department or clinic visit or hospitalization
6. Survival; inadequate clinical response with additional emergency department or clinic visit but without hospitalization; any grade of adverse event
7. Survival; inadequate clinical response with hospitalization; any grade of adverse event
8. Death

Adequate clinical response was defined based on absence of all of the following as assessed on day 11–14 after initiation of therapy: (1) fever unless related to a new process that is unrelated to the prior diagnosis of pneumonia, (2) tachypnea, (3) increased work of breathing (retractions, nasal flaring, grunting), and (4) a medically attended visit to an emergency department/clinic or hospitalization for persistent or worsening pneumonia at any time after randomization. This is a draft version from a developing clinical trial.

\(^a\) Short-Course Outpatient Therapy for Community-Acquired Pneumonia in Children.
KEY POINT: THE EPIDEMIOLOGIST DEPENDS ON THE REST OF THE TEAM

- Example 1: DOOR/RADAR
- Example 2: Providing DATA from enhanced post-marketing monitoring of new antibacterial drugs approved by less stringent review
The Pipeline is Not Dry

It is clear that we are entering a new era in the management and treatment of serious infections such as VAP. Within the next 3 to 5 years, new antibiotics directed against multidrug-resistant gram-negative bacteria will become available, including carbavance, ceftolozane-tazobactam, ceftazidime-avibactam, plazomicin, eravacycline, relebactam, brilacidin, BAL30072, aztreonam-avibactam, carbapenems with ME 1071, and S-649266, a novel siderophore cephalosporin. These agents will provide enhanced activity against β-lactamase producers, carbapenem-resistant bacteria, and, in some, cases even metallo-β-lactamase-producing bacteria. The challenge to ICU clinicians is how to most effectively use these agents, once they become available, to maximize patient benefits while minimizing the emergence of resistance. The use of rapid diagnostics seems to hold

Kollef MH. Chest 2015; 147: 1448-1450
“... some propose that the requirements of adequate and well-controlled trials make the study of new antibiotics infeasible. To address perceived hurdles, these bills propose a regulatory pathway in poorly defined “limited populations” without requiring demonstrated benefits in populations with resistant disease.

Studies would be done in patients with effective options rather than those with unmet medical needs, allowing approval even with inferior effectiveness in the population studied.

No requirement for diagnostics means that the drugs may be prescribed empirically outside the limited population.

The bills would alter the standard of approval from substantial evidence to “sufficient evidence” derived from “small clinical data sets” and would consider preclinical data, animal models, and pharmacologic data to be “confirmatory evidence.”
Evaluating Drugs for Pan-Resistant Bacteria: A Tradeoff

● PROVING EFFICACY
  ■ Compared to Low or No Effectiveness in Comparator, LESS DATA will be required to show efficacy
    – N of 1 trials
    – Case Series

● PROVING SAFETY
  ■ When Less Data Required to Show Efficacy, Only High-Frequency Adverse Events Will Be Apparent
  ■ This Stresses the Need for MORE DATA to be obtained after the Drug is Approved to monitor for Low Frequency Adverse Events
More Intensive Post-Approval DATA Collection Needed

PROVING SAFETY

When Fewer Data Required to Show Efficacy, Only **High-Frequency** Adverse Events Will Be Apparent

- This Stresses the Need for **MORE DATA** to be obtained after the Drug is Approved to monitor for Low Frequency Adverse Events (Safety, Collateral Damage)

- Plans for Collecting Such Data **Must Include More Intensive Surveillance Than Usual Post-Marketing** (“Phase IV, “pharmacovigilance,” etc.) Studies to Date
Alternatives to antibiotics—a pipeline portfolio review

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Antibiotics have saved countless lives and enabled the development of modern medicine over the past 70 years. However, it is clear that the success of antibiotics might only have been temporary and we now expect a long-term and perhaps never-ending challenge to find new therapies to combat antibiotic-resistant bacteria. A broader approach to address bacterial infection is needed. In this Review, we discuss alternatives to antibiotics, which we defined as non-compound approaches (products other than classic antibacterial agents) that target bacteria or any approaches that target the host. The most advanced approaches are antibodies, probiotics, and vaccines in phase 2 and phase 3 trials. This first wave of alternatives to antibiotics will probably best serve as adjunctive or preventive therapies, which suggests that conventional antibiotics are still needed. Funding of more than £1.5 billion is needed over 10 years to test and develop these alternatives to antibiotics. Investment needs to be partnered with translational expertise and targeted to support the validation of these approaches in phase 2 trials, which would be a catalyst for active engagement and investment by the pharmaceutical and biotechnology industry. Only a sustained, concerted, and coordinated international effort will provide the solutions needed for the future.
More Intensive Post-Approval DATA Collection Needed

Reviving old antibiotics

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Strategies are urgently needed to ‘re-develop’ these drugs using modern standards, integrating new knowledge into regulatory frameworks and communicating the knowledge from the research bench to the bedside. Without a systematic approach to redeveloping these old drugs and rigorously testing them according to today’s standards, there is a significant risk of doing harm to patients and further increasing multidrug resistance.

J Antimicrob Chemother 2015; 70: 2177-2181
More Intensive Post-Approval DATA Collection Needed

Suppression of Emergence of Resistance in Pathogenic Bacteria: Keeping Our Powder Dry, Part 1

In this review, we look at the data for resistance suppression. Approaches include increasing the intensity of therapy to suppress resistant subpopulations; developing concepts of clinical breakpoints to include issues surrounding suppression of resistance; and paying attention to the duration of therapy, which is another important issue for resistance suppression. New understanding of optimizing combination therapy is of interest for difficult-to-treat pathogens like *Pseudomonas aeruginosa*, *Acinetobacter* spp., and multidrug-resistant (MDR) *Enterobacteriaceae*. These lessons need to be applied to our old drugs to preserve them as well and need to be put into national and international antibiotic resistance strategies.

EVALUATING NEW DRUGS

“Finally, the ultimate arbiter on the merits of any drug is the clinical trial, and it is thus to the clinician that we look for the final verdict on utility ... This verdict must take into account side effects, and if any of these is a manifestation of toxicity which could be dangerous, the cost/benefit analysis required may call for exceptional powers of judgment.”*

Can NOT Be Done By The Epidemiologist Alone – Requires TEAM Input

Working Together As A TEAM

The Innovative Medicines Initiative’s New Drugs for Bad Bugs programme: European public–private partnerships for the development of new strategies to tackle antibiotic resistance


Drug firms ask governments to do more in fight against superbugs

DAVOS, SWITZERLAND

More than 80 international drug and biotech firms urged governments to work with them to combat drug-resistant superbugs which could kill tens of millions of people within decades unless progress is made and new antibiotics found.

http://www.reuters.com/article/us-health-antibiotics-superbugs-idUSKCN0UZ009
Generations of AC Workers

1935

FIRST GENERATION
Garrod Finland

SECOND GENERATION – TRAINEES OF FIRST GENERATION

THIRD GENERATION - TRAINEES OF SECOND GENERATION

FOURTH GENERATION - TRAINEES OF THIRD GENERATION

2016 and Beyond – The Future Is Bright!

New Talent

New Talent

New Talent