An Overview of Antimicrobial Use

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November 13, 2012
Disclosures

- No financial disclosures or conflicts of interest relative to this presentation.
Antimicrobials present unique management challenges

- 200-300 million antibiotics are prescribed annually
  - 45% for outpatient use
- 25-40% of hospitalized patients receive antibiotics
  - 10-70% are unnecessary or sub-optimal
  - 5% of hospitalized patients who receive antibiotics experience an adverse reaction
- Antibiotics are unlike any other drugs, in that use of the agent in one patient can compromise its efficacy in another (“Societal Drugs”)

Slide courtesy of Sara Cosgrove, MD  Johns Hopkins University
Why evaluate antimicrobial use?

- Monitor precious resources
- Examine the relationship of use and development of resistance
- Monitor the impact of stewardship interventions
### Metrics for measurement

#### TABLE 2. Numerators Used in Antimicrobial Utilization Measures and Their Definitions

<table>
<thead>
<tr>
<th>Measure</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial-days</td>
<td>Sum of the calendar days on which each antimicrobial drug was administered</td>
<td>2 drugs given for 5 days followed by a different drug given for 5 days to 1 patient = 15 antimicrobial-days</td>
</tr>
<tr>
<td>Patient-days receiving antimicrobials</td>
<td>Sum of the calendar days on which one or more antimicrobial drugs was administered</td>
<td>2 drugs given for 5 days followed by a different drug given for 5 days to 1 patient = 10 patient-days receiving antimicrobials</td>
</tr>
<tr>
<td>Antimicrobial starts</td>
<td>Sum of the calendar days on which each new antimicrobial drug was started, following 3 or more days without exposure to that drug</td>
<td>2 drugs given for 5 days followed by a different drug given for 5 days to 1 patient = 3 antimicrobial starts</td>
</tr>
<tr>
<td>Antimicrobial courses</td>
<td>Sum of the calendar days on which any antimicrobial drug was started, following 3 or more days without exposure to any antimicrobial drug</td>
<td>2 drugs given for 5 days followed by a different drug given for 5 days to 1 patient = 1 antimicrobial course</td>
</tr>
<tr>
<td>Defined daily doses (DDDs)</td>
<td>World Health Organization–standardized conversion of aggregate drug dosing data into number of doses&lt;sup&gt;26&lt;/sup&gt;</td>
<td>200 grams of vancomycin dispensed divided by 2 grams per vancomycin DDD = 100 DDDs of vancomycin</td>
</tr>
</tbody>
</table>

Definition and general considerations

Definition and introduction
The basic definition of the defined daily dose (DDD) is:

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

A DDD will only be assigned for drugs that already have an ATC code.

It should be emphasised that the defined daily dose is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose. Doses for individual patients and patient groups will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations.

For the optimal use of drugs, it is important to recognise that genetic polymorphism due to ethnic differences can result in variations in pharmaco-kinetics of drugs. The DDD should reflect the global dosage irrespective of genetic variations of drug metabolism.

Drug consumption data presented in DDDs only give a rough estimate of consumption and not an exact picture of actual use. The DDD provide a fixed unit of measurement independent of price and dosage form (e.g. tablet strength) enabling the researcher to assess trends in drug
Guidelines for ATC classification and DDD assignment 2012

http://www.whocc.no/atc_ddd_publications/guidelines/
Defined Daily Doses

- Utilizes the Anatomical Therapeutic Chemical (ATC) classification system
- The DDD is defined as the average daily maintenance dose per day for a drug for its main indication in adults.
- “Drug consumption data presented in DDDs only give a rough estimate of consumption and not an exact picture of actual use.”
- Weight based dosing assumes 70 kg
ATC/DDD Index 2012

A searchable version of the complete ATC index with DDDs is available below. The search options enable you to find ATC codes and DDDs for substance name and/or ATC levels. In your search result you may choose to show or hide the text from the Guidelines for ATC classification and DDD assignment linked to the ATC level. The text in the Guidelines will give information related to the background for the ATC and DDD assignment.

Search query

ATC code  or  name

ATC code

- All ATC levels are searchable.
- A search will result in showing the exact substance/level and all ATC levels above (up to 1st ATC level).

Name

- "Name" is defined as the name of the substance (normally the INN name) or the name of the ATC level. Note that trademarks are not searchable.
- A minimum of three letters must be entered in the name box. Select a query that contain part of or a query that start with the letter entered.
- For ATC combination levels, please note that all active ingredients would normally not be searchable.

DDD
Defined daily dose examples

- Cefepime = 2 grams (1 gram every 12 hours)
  - At OSUWMC we give 2 grams every 8 hours
- Vancomycin = 2 grams (1 gram every 12 hours)
  - At OSUWMC this would be an estimated standard dose
- Daptomycin = 0.28 grams (4 mg/kg) daily
  - At OSUWMC we may give 6-10 mg/kg
- Linezolid = 1.2 grams (600 mg twice daily)
  - At OSUWMC this would be an estimated standard dose
Measurement of Adult Antibacterial Drug Use in 130 US Hospitals: Comparison of Defined Daily Dose and Days of Therapy

Ronald E. Polk,¹ Christina Fox,¹ Anne Mahoney,² Jim Letcavage,² and Conan MacDougall¹,*
¹School of Pharmacy, Department of Pharmacy, Virginia Commonwealth University, Medical College of Virginia Campus, Richmond, Virginia; and ²Solvicent, Evanston, Illinois
Methods

- Antimicrobial use data from 130 hospitals obtained from Solucient (www.solucient.com) and examined through the Acute Care Tracker database.
- Calculated the DDD using the WHO methodology.
- Calculated antimicrobials days of therapy defined as the 1 DOT=administration of a single antimicrobial regardless of the number of doses administered or the dosage strength.

Table 1. Comparison of aggregate drug use by defined daily dose (DDDs) per 1000 patient-days and days of therapy (DOTs) per 1000 patient-days for 10 common antibacterial drugs.

<table>
<thead>
<tr>
<th>Parenteral antibiotic</th>
<th>No. of hospitals</th>
<th>Mean DDDs per 1000 patient-days ± SD</th>
<th>Mean DOTs per 1000 patient-days ± SD</th>
<th>P</th>
<th>Mean difference between DDD and DOT, %</th>
<th>Importance of the mean difference&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DDD&lt;sub&gt;b&lt;/sub&gt;, g/day</th>
<th>Mean administered daily dose, g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>130</td>
<td>80.3 ± 35.4</td>
<td>94.3 ± 27.7</td>
<td>&lt;.0001</td>
<td>−17.4</td>
<td>Moderate</td>
<td>3</td>
<td>2.46</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>123</td>
<td>75.6 ± 57.5</td>
<td>74.9 ± 55.8</td>
<td>.3</td>
<td>0.7</td>
<td>Minor</td>
<td>0.5</td>
<td>0.51</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>53</td>
<td>56.5 ± 67.9</td>
<td>52.1 ± 48.6</td>
<td>.4</td>
<td>7.9</td>
<td>Moderate</td>
<td>0.4</td>
<td>0.42</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>130</td>
<td>44.9 ± 28.2</td>
<td>62.9 ± 35.9</td>
<td>&lt;.0001</td>
<td>−28.6</td>
<td>Major</td>
<td>2</td>
<td>1.46</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>130</td>
<td>46.1 ± 39.0</td>
<td>52.7 ± 26.6</td>
<td>.013</td>
<td>−6.6</td>
<td>Moderate</td>
<td>2</td>
<td>1.63</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>127</td>
<td>30.3 ± 20.3</td>
<td>42.7 ± 28.5</td>
<td>&lt;.0001</td>
<td>−40.9</td>
<td>Major</td>
<td>14</td>
<td>10.1</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>126</td>
<td>28.1 ± 14.3</td>
<td>32.8 ± 15.4</td>
<td>&lt;.0001</td>
<td>−7.0</td>
<td>Moderate</td>
<td>1.5</td>
<td>1.32</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>130</td>
<td>20.8 ± 17.1</td>
<td>18.0 ± 14.8</td>
<td>&lt;.0001</td>
<td>13.4</td>
<td>Moderate</td>
<td>0.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>123</td>
<td>18.0 ± 22.1</td>
<td>13.5 ± 16.3</td>
<td>&lt;.0001</td>
<td>24.9</td>
<td>Moderate</td>
<td>0.5</td>
<td>0.72</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>129</td>
<td>21.7 ± 12.5</td>
<td>22.3 ± 10.8</td>
<td>.23</td>
<td>−2.8</td>
<td>Minor</td>
<td>1.8</td>
<td>1.79</td>
</tr>
</tbody>
</table>

NOTE. The larger the difference between the administered daily dose and the DDD, the larger the difference in the measure of aggregate use by DDDs per 1000 patient-days and DOTs per 1000 patient-days.

<sup>a</sup> Major (>25% difference), moderate (>5% and <25% difference), and minor (<5% difference) importance.

<sup>b</sup> World Health Organization–defined DDD (2005 values [10]).
When the administered dose is similar to the recommended DDD then correlation is good between the two methods.
When the administered dose is lower than the recommended DDD then the DDD are significantly lower than the DOT

When the administered dose is greater than the recommended DDD then the DDD are significantly greater than the DOT

Other difficulties with DDD measurement

- Applicable only to adults; cannot be used for pediatric populations
- Not applicable to renal failure patients with reduced dosing.
Deriving Measures of Intensive Care Unit Antimicrobial Use from Computerized Pharmacy Data: Methods, Validation, and Overcoming Barriers

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Infect Control Hosp Epidemiol 2011;32:472-480
<table>
<thead>
<tr>
<th>Data source</th>
<th>Events measured</th>
<th>Logic applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy dispensing</td>
<td>Antimicrobial doses dispensed from pharmacy</td>
<td>One or more doses of each antimicrobial dispensed during an ICU-day constitutes an antimicrobial-day; 1 or more doses of any antimicrobial dispensed during an ICU-day constitutes a patient-day receiving antimicrobials.</td>
</tr>
<tr>
<td>Physician orders (CPOE)</td>
<td>Antimicrobial start and stop orders; days of admission to and discharge from the ICU</td>
<td>ICU-days on which each antimicrobial is ordered for continuous scheduled administration; subsequent ICU-days are counted as antimicrobial-days until either the discontinuation of that drug or discharge from the ICU. ICU-days on which any antimicrobial is ordered and subsequent ICU-days are counted as patient-days receiving antimicrobials until either the discontinuation of all antimicrobials has been ordered or until discharge from the ICU.</td>
</tr>
<tr>
<td>Medication administration (eMAR)</td>
<td>Antimicrobial doses administered by a nurse</td>
<td>One or more doses of each antimicrobial administered during an ICU-day constitutes an antimicrobial-day; 1 or more doses of any antimicrobial administered during an ICU-day constitutes a patient-day receiving antimicrobials.</td>
</tr>
</tbody>
</table>

**Note.** CPOE, computerized provider order entry; eMAR, electronic medication administration record; ICU, intensive care unit.

* Numerator events are counted only through the calendar day before discharge from the ICU.
OBJECTIVE. To outline methods for deriving and validating intensive care unit (ICU) antimicrobial utilization (AU) measures from computerized data and to describe programming problems that emerged.

DESIGN. Retrospective evaluation of computerized pharmacy and administrative data.

SETTING. ICUs from 4 academic medical centers over 36 months.

INTERVENTIONS. Investigators separately developed and validated programming code to report AU measures in selected ICUs. Use of antibacterial and antifungal drugs for systemic administration was categorized and expressed as antimicrobial-days (each day that each antimicrobial drug was given to each patient) and patient-days receiving antimicrobials (each day that any antimicrobial drug was given to each patient). Monthly rates were compiled and analyzed centrally, with ICU patient-days as the denominator. Results were validated against data collected from manual review of medical records. Frequent discussion among investigators aided identification and correction of programming problems.

RESULTS. AU data were successfully programmed through a reiterative process of computer code revision. After identifying and resolving major programming errors, comparison of computerized patient-level data with data collected by manual review of medical records revealed discrepancies in antimicrobial-days and patient-days receiving antimicrobials that ranged from less than 1% to 17.7%. The hospital from which numerator data were derived from electronic records of medication administration had the least discrepant results.

CONCLUSIONS. Computerized AU measures can be derived feasibly, but threats to validity must be sought out and corrected. The magnitude of discrepancies between computerized AU data and a gold standard based on manual review of medical records varies, with electronic records of medication administration providing maximal accuracy.

Infect Control Hosp Epidemiol 2011;32(5):472-480
European Antimicrobial Resistance Surveillance Network (EARS-NET)

- Formerly was European Antimicrobial Resistance Surveillance System (EARSS)
European Antimicrobial Resistance Surveillance Network (EARS-Net)

EARS-Net is a European wide network of national surveillance systems, providing European reference data on antimicrobial resistance for public health purposes. The network is coordinated and funded by the European Centre for Disease Prevention and Control.

The coordination of EARS-Net, the European Antimicrobial Resistance Surveillance Network (former EARSS), was transferred from the Dutch National Institute for Public Health and the Environment (RIVM) to the European Centre for Disease Prevention and Control (ECDC) in January 2010.


RELATED EVENTS
No items found.

RELATED DOCUMENTS
- EARS-Net Microbiological manual
- EARS-Net Reporting protocol 2012

RELATED NEWS

RELATED PUBLICATIONS

RELATED NETWORKS
- Healthcare-associated Infections Surveillance Network (HAI-Net)
- European Surveillance of Antimicrobial Consumption Network (ESAC-Net)
The Relationship between Antimicrobial Use and Antimicrobial Resistance in Europe


In Europe, antimicrobial resistance has been monitored since 1998 by the European Antimicrobial Resistance Surveillance System (EARSS). We examined the relationship between penicillin nonsusceptibility of invasive isolates of *Streptococcus pneumoniae* (an indicator organism) and antibiotic sales. Information was collected on 1998-99 resistance data for invasive isolates of *S. pneumoniae* to penicillin, based on surveillance data from EARSS and on outpatient sales during 1997 for beta-lactam antibiotics and macrolides. Our results show that in Europe antimicrobial resistance is correlated with use of beta-lactam antibiotics and macrolides.

*Emerg Infect Dis* 2002;8:278-282
Figure 2. The logodds of resistance to penicillin among invasive isolates of *Streptococcus pneumoniae* (PNSP; ln(R/(1-R))) is regressed against outpatient sales of beta-lactam antibiotics in 11 European countries; antimicrobial resistance data are from 1998 to 1999 and antibiotic sales data are from 1997. DDD = defined daily dose; BE = Belgium; DE = Germany; FI = Finland; IE = Ireland; IT = Italy; LU = Luxembourg; NL = the Netherlands; PT = Portugal; ES = Spain; SE = Sweden; UK = United Kingdom.

Figure 3. The logodds of resistance of invasive isolates of *Streptococcus pneumoniae* to penicillin (PNSP; ln(R/(1-R))) is regressed against nonadherence rates to antibiotic therapy in four European countries. Nonadherence rates are from 1993; PNSP data are from 1998-99. UK = United Kingdom; BE = Belgium; IT = Italy; ES = Spain.

*Emerg Infect Dis* 2002;8:278-282

Lauri A. Hicks,¹ Yu-Wen Chien,² Thomas H. Taylor Jr,¹ Michael Haber,³ and Keith P. Klugman,⁴ ⁵ on behalf of the Active Bacterial Core Surveillance (ABCs) Team⁰

¹Division of Bacterial Diseases, Centers for Disease Control and Prevention, ²Department of Epidemiology, and ³Department of Biostatistics and Bioinformatics, Rollins School of Public Health, School of Medicine, Emory University, ⁴Hubert Department of Global Health, Rollins School of Public Health, School of Medicine, Emory University, and ⁵Division of Infectious Diseases, School of Medicine, Emory University, Atlanta, Georgia

*Clinical Infect Dis* 2011;53:631-639
Methods

- Accessed antimicrobial resistance data from the CDC Active Bacterial Core (ABC) surveillance network that tracks invasive pneumococcal infections in 7 states
  - Active population based surveillance system
- All isolates from sterile body sites underwent standard susceptibility testing
- Systemic antibiotic prescriptions were extracted from the IMS Health Xponent prescription database which contains 70% of all outpatient prescriptions in the US

*Clinical Infect Dis* 2011;53:631-639
Results

- Yearly outpatient prescriptions decreased during the study time period from 1996-2003
  - 37% decrease for children <5 years
  - 42% decrease for children >5 years
- Sites of high prescribing had higher number of cases of invasive pneumococcal disease resistant to antimicrobials than sites with low prescribing sites
- Cephalosporins and macrolides appeared to select for penicillin and multi-drug resistant strains

*Clinical Infect Dis* 2011;53:631-639
Table 2. Causal associations between antimicrobial use and the emergence of antimicrobial resistance.

Changes in antimicrobial use are paralleled by changes in the prevalence of resistance. Antimicrobial resistance is more prevalent in health care–associated bacterial infections, compared with those from community-acquired infections. Patients with health care–associated infections caused by resistant strains are more likely than control patients to have received prior antimicrobials. Areas within hospitals that have the highest rates of antimicrobial resistance also have the highest rates of antimicrobial use. Increasing duration of patient exposure to antimicrobials increases the likelihood of colonization with resistant organisms.

NOTE. A causal association between antimicrobial use and the emergence of antimicrobial resistance has been reviewed elsewhere [9, 19–22] and is strongly suggested on the basis of several lines of evidence that are derived from patient and population levels of analysis, colonization and infection data, and retrospective and prospective studies [23–31]. Adapted from [10].

Clinical Infect Dis 2007;44:159-177
Clinical Infect Dis 1997;25:584-599
Predicting Hospital Rates of Fluoroquinolone-Resistant *Pseudomonas aeruginosa* from Fluoroquinolone Use in US Hospitals and Their Surrounding Communities

Ronald E. Polk, Christopher K. Johnson, Donna McClish, Richard P. Wenzel, and Michael B. Edmond

1School of Pharmacy, Department of Pharmacy and School of Medicine, and Departments of Internal Medicine and Biostatistics, Virginia Commonwealth University, Medical College of Virginia Campus, Richmond

*Clinical Infect Dis 2004;39:497-503*
Methods

- Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE). SCOPE is a nosocomial bacteremia surveillance network with about 40 participating hospitals and is coordinated by VA Commonwealth University.

- MediMedia Antimicrobial Information Technology (MMIT) Antimicrobial Monitoring Network involves about 70 nongovernmental hospitals and links drug use to hospital and patient demographic data.

- Data collected from SCOPE and MMIT partnership.

- Number of community prescriptions as outpatients were obtained from IMS Health Xponent database.
Hospital fluoroquinolone use

Clinical Infect Dis 2004;39:497-503
Community fluoroquinolone use

Clinical Infect Dis 2004;39:497-503
Correlation of FQ use with resistance

Clinical Infect Dis 2004;39:497-503
CDC Efforts

- [http://www.cdc.gov/hai/eip/antibiotic-use_techinfo.html](http://www.cdc.gov/hai/eip/antibiotic-use_techinfo.html)
- CDC’s first- ever, large-scale antimicrobial use prevalence survey among U.S. acute care inpatients.
- Phase 1: pilot survey conducted in 2009 in nine acute care hospitals in Jacksonville, FL.
- Phase 2: limited roll-out survey conducted in 2010 in 22 acute care hospitals within the catchment areas of the 10 Emerging Infection Program sites.
- Phase 3: a full-scale survey conducted in 2011 in more than 180 acute care hospitals across the 10 EIP sites.
Results of CDC studies

- Phase 1: Antimicrobial therapy was the most sensitive proxy indicator for HAIs

- Phase 2: Antimicrobial use prevalence was 48.3% (95% CI: 46.2–50.5%). In 731 patients receiving treatment for active infection, vancomycin (218, 29.8%) and piperacillin/tazobactam (139, 19.0%) were the most commonly administered antimicrobials.

- Phase 3: Results still pending.
CDC NHSN AU system

- [http://www.cdc.gov/nhsn/](http://www.cdc.gov/nhsn/)

  The National Healthcare Safety Network (NHSN) is a secure, internet-based surveillance system that integrates and expands legacy patient and healthcare personnel safety surveillance systems managed by the Division of Healthcare Quality Promotion (DHQP) at CDC.

- Collects standardized data on healthcare-associated infections.

- Launching module for collecting antimicrobial use and resistance data
Antimicrobial Use and Resistance (AUR) Option

1. Antimicrobial Use (AU) Option

Objectives: The primary objective of the Antimicrobial Use option is to facilitate risk-adjusted inter- and intra-facility benchmarking of antimicrobial usage. A secondary objective is to evaluate trends of antimicrobial usage over time at the facility and national levels.

Numerator Data (Antimicrobial Days):
Antimicrobial Days (Days of Therapy): Defined as the aggregate sum of days for which any amount of a specific antimicrobial agent was administered to individual patients as documented in the eMAR and/or BCMA. Appendix B provides a list of antimicrobial agents. Aggregate antimicrobial days are reported monthly for inpatient locations, facility-wide-inpatient, and select outpatient acute-care settings (e.g., outpatient

Denominator Data (Days Present and Admissions): The numerator will be analyzed against the denominator of days present and also admissions for facility-wide-inpatient only. The denominators are further defined below.
Monitoring antimicrobial stewardship interventions

![Graph showing antimicrobial usage over time](image)

- **Antimicrobial Days per 1,000 Patient Days**
- **Calendar Year Month**
- **Legend:** IMIPENEM — DORIPENEM

- **Note:** Formulary Restriction Protocol implemented in October 2010.
Questions?