Measurement of Adult Antibacterial Drug Use in 130 US Hospitals: Comparison of Defined Daily Dose and Days of Therapy

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(See the editorial commentary by Monnet on pages 671–3)

Background. Hospitals are advised to measure antibiotic use and monitor its relationship to resistance. The World Health Organization’s recommended metric is the defined daily dose (DDD). An alternative measure is the number of days of therapy (DOT). The purpose of this study was to contrast these measures.

Methods. We measured the use of 50 antibacterial drugs that were administered to adults who were discharged from 130 US hospitals during 1 August 2002–31 July 2003.

Results. Of 1,795,504 patients, 1,074,174 received at least 1 dose of an antibacterial drug (59.8%). The mean (standard deviation) of total antibacterial drug use measured by the number of DDDs per 1000 patient-days and the number of DOTs per 1000 patient-days were not significantly different (792 ± 147 and 776 ± 120, respectively; P = .137), although the correlation was poor (r = .603). For some individual drugs, such as levofloxacin and linezolid, there was no significant difference between DDDs per 1000 patient-days and DOTs per 1000 patient-days, because the administered daily dosage was nearly equivalent to the DDD. When the administered dosage exceeded the DDD, such as for ampicillin-sulbactam and cefepime, estimates of use based on DDDs per 1000 patient-days significantly exceeded those based on DOTs per 1000 patient-days (P < .001). When the administered dosage was less than the DDD, such as for piperacillin-tazobactam and ceftriaxone, estimates of use based on DDDs per 1000 patient-days were significantly lower than those based on DOTs per 1000 patient-days (P < .001).

Conclusion. The measurement of aggregate hospital antibiotic use by DDDs per 1000 patient-days and DOTs per 1000 patient-days is discordant for many frequently used antibacterial drugs, because the administered dose is dissimilar from the DDD recommended by the World Health Organization. DDD methods are useful for benchmarking purposes but cannot be used to make inferences about the number of DOTs or relative use for many antibacterial drugs.

Antibiotic use significantly contributes to increasing rates of resistant pathogens [1–2]. Many organizations have recommended that aggregated antibacterial drug use at the local and national levels should be monitored to better understand the relationship between the use of antibacterial drugs and emerging bacterial resistance [1–4]. Antibacterial use in hospitals has proved to be difficult to measure, however, and early estimates simply reported the proportion of patients who received antibacterials during hospitalization [5–7]. More recently, the aggregate volume of antibacterial use has been measured among networks of hospitals, most notably those participating in the Center for Disease Control and Prevention’s (CDC) National Nosocomial Infection Surveillance (NNIS) project [8] and in the CDC Project ICARE [9].

The specific metric that best quantifies antibiotic use remains unresolved. The most common methodology uses the defined daily dose (DDD), as promoted by the World Health Organization (WHO) [10]. The WHO-assigned DDD “is the assumed average maintenance dose per day for a drug used for its main indication in adults” [10]. To estimate antibiotic use in a hospital, the total number of grams of each antibiotic used (pur-
chased, dispensed, or administered) are summed during the period of interest, usually 1 calendar year, and divided by the WHO-assigned DDD. Dividing total grams of use by the DDD (grams/day) yields an estimate of the number of days of antibiotic therapy. Expressing antibiotic use by DDDs per 1000 patient-days allows a hospital to compare their antibiotic use with other hospitals’ antibiotic use, regardless of differences in formulary composition, antibiotic potency, and hospital census. Standardized comparisons of health care information are often called “benchmarking” [11–14]. Most hospitals report consumption by DDDs per 1000 patient-days, including NNIS [8], Project ICARE [9], a consortium of 140 European Union hospitals that contribute data to the Antimicrobial Resistance Prevention and Control project [15], and others [16–20]. An Infectious Diseases Society of America practice guideline for implementation of hospital antimicrobial stewardship programs recommends monitoring antimicrobial use by DDDs per 1000 patient-days [4]. Development of DDD methodology has been a major advance in attempts to promote standardized comparisons [15, 17, 19, 21–23].

The shortcomings of DDD methodology have been recognized [24–28]. First, DDD methods will underestimate antibiotic exposure when the administered daily dose is reduced for a patient with impaired renal function. This is relevant when the proportion of patients with renal insufficiency in 1 hospital is different from that in another hospital. Second, aggregation of total hospital antibiotic use, often obtained from purchase records, will usually include drugs administered to pediatric patients for which DDD methodology does not apply. Finally, if the administered daily dosage differs significantly from the WHO-approved DDD, then DDD methodology will not provide an accurate assessment of the number of days of therapy.

Alternative measures of antibiotic consumption have been proposed. The most common method is direct measure of the number of days of therapy (DOTs) [25–28]. Single institutions have measured their hospital’s consumption for selected antibiotics comparing DDD methods to DOT methods, and they report that these 2 measures may produce divergent results [24–28]. The purpose of this investigation was to measure aggregate antibiotic consumption among a network of 130 US hospitals by both DDD and DOT methods, to contrast these measures, and to identify reasons for similarities and differences.

**METHODS**

**Study Design and Data Source**

The Institutional Review Board of Virginia Commonwealth University (Richmond) approved this study. This was a retrospective analysis of administrative claims data obtained by Solucient (Evanston, IL; http://www.solucient.com/) from 130 hospitals that participate in Acute Care Tracker. Solucient is an information company that serves the health care industry. The Acute Care Tracker database contains drug use and demographic information from patient-level billing data. Data were aggregated to the hospital level. All investigators were blinded to the identity of the study hospitals.

**Hospital Demographic Data**

Demographic characteristics were obtained from the Solucient database. Bed size is reported as the number of licensed beds. Teaching status was determined on the basis of the presence of an accredited residency-training program and membership in the Council of Teaching Hospitals of the American Medical Association. The total number of patient discharges and the duration of hospital stay (in days) for all adult patients were obtained from the Solucient database. Patients could be counted more than once if they were discharged multiple times during the study period.

**Antibacterial Retrieval**

Adult antibacterial drug use was obtained from hospital billing records for individual patients discharged during 1 August 2002–31 July 2003. Patient records were filtered by age, and patients aged <18 years were excluded from the analysis. Antibacterial agents were identified by Solucient’s proprietary Standard Transaction Coding, which uses the American Hospital Formulary Service classification code to identify antibacterial drugs (Code 8:12). Of 78 systemic antibacterial drugs, the 50 most frequently used agents, based on the sum of DOTs per 1000 patient-days for all 130 hospitals, were used during this analysis (a complete list of all 50 drugs is available from R.E.P.). When an antibiotic was available in both an oral and parenteral form, the sum for both routes of administration was reported, unless otherwise stated. The sum of these 50 drugs accounted for 99.8% of the total systemic antibacterial drug use.

Aggregated annualized data from each hospital included the generic name for each antibacterial drug, the route of administration (oral or injection), the number of patients treated, the total days of therapy, the number of doses administered, and the total grams administered. From these data, we calculated additional measures of use, including mg/dose (total grams administered/number of administered doses), the mean number of doses/day (number of doses/days of therapy), the mean treatment days (total days of therapy/number of patients), and the administered daily dose (total grams/days of therapy).

**Measures of Antibacterial Use**

**DDD.** Antibiotic use using the WHO’s DDD recommendations was determined for the 50 most frequently prescribed drugs, as described above. All DDDs were based on the 2005 version of the Anatomical Therapeutic Chemical Classification System and the DDD index [10]. To express aggregate use, total
DDD were normalized per 1000 patient-days to control for differences of hospital census; the WHO currently recommends normalizing consumption to 100 patient-days, but most reports have normalized use to 1000 patient-days, and we have followed this convention.

**DOT.** One DOT represents the administration of a single agent on a given day regardless of the number of doses administered or dosage strength. For example, administration of cefazolin as a single 1000-mg dose or as three 1000-mg doses given 8 hours apart would both represent 1 DOT. A single patient receiving both vancomycin and cefazidime would be recorded as receiving 2 DOTs (1 of vancomycin and 1 of cefazidime). These data were normalized to 1000 patient-days, as described above.

**Statistical analysis.** We used correlation analysis to graphically examine the relationship between the DDWs per 1000 patient-days and the DOTs per 1000 patient-days at each hospital for total antibacterial drug use and for individual drugs. The null hypothesis is that there is no difference in estimates of antibacterial drug use by DDWs and DOT methods. Differences between measures of use (DDDs per 1000 patient-days vs. DOTs per 1000 patient-days) for total antibacterial drug use and for the 10 most commonly used drugs were assessed using paired t-tests. We controlled for inflation of α-error by applying the Bonferroni correction; P < .005 was required to achieve statistical significance. All tests for differences were 2-sided. The power of this analysis to detect small differences in paired measures of DDWs per 1000 patient-days and DOTs per 1000 patient-days for individual drugs is very high. Consequently, we also categorized the importance of the differences between mean DDWs per 1000 patient-days and DOTs per 1000 patient-days as “major” (>25% difference), “moderate” (>5% and <25% difference), and “minor” (<5% difference). Mean values are shown with SDs.

### RESULTS

**Summary of Hospital Demographic Characteristics**

Of the 130 hospitals, 15 (11.5%) were teaching hospitals. All hospitals were general medical-surgical care institutions. The mean number of beds in the hospitals was 288 ± 176 (range, 20–1020), and the mean age of patients was 57.6 ± 4.3 years. Hospitals were located primarily in the South (68 hospitals) and North-Central (51 hospitals) regions of the United State; 10 hospitals were located in the West, and a single hospital was located in the Northeast. Twelve hospitals (9.2%) performed at least 1 solid organ transplantation procedure during the study year.

**Antibacterial Drug Use**

A total of 1,795,504 adult patients were discharged from these 130 hospitals during 1 August 2002–31 July 2003. Of those discharged, 1,074,174 patients (59.8%) received at least 1 dose of an antibacterial drug. Total mean antibacterial drug use measured by DDWs per 1000 patient-days and DOTs per 1000 patient-days was not significantly different (792 ± 147 and 776 ± 120, respectively; P = .137). However, the correlation of total drug use by these 2 measures was relatively poor (r = .603). In many hospitals, the total DDWs per 1000 patient-days was greater than the total DOTs per 1000 patient-days, and in others, there was the reverse relationship. This reflected the relative use of specific antibacterial drugs at each hospital where the DOTs per 1000 patient-days was greater or less than the DDWs per 1000 patient-days. Table 1 summarizes the similarities and differences between measures of aggregate antibacterial

### 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 differencea</th>
<th>DDD, g/dayb</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>.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>Ceftaxime</td>
<td>130</td>
<td>44.9 ± 28.2</td>
<td>62.9 ± 35.9</td>
<td>.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>.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>.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 ± 14.9</td>
<td>.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>.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.

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

b World Health Organization–defined DDD (2005 values [10]).
use by the DDDs per 1000 patient-days and the DOTs per 1000 patient-days for 10 common drugs.

There was excellent agreement between measures of use by the DDDs per 1000 patient-days and the DOTs per 1000 patient-days for antibacterial drugs that are usually given once or twice per day and have a limited range in the administered daily dosage. For example, the estimate of use for intravenous levofloxacin by DDD methods (71.6 ± 58.5 DDDs per 1000 patient-days) was not statistically different from use by DOT methods (70.9 ± 56.8 DOTs per 1000 patient-days; P = .614), and the correlation between these 2 measures was very high (figure 1A). This was because the mean observed dosage for intravenous levofloxacin of 503 ± 101 mg/day (n = 124) was nearly identical to the WHO-recommended DDD (500 mg), and the mean number of doses/day was 1.17 ± 0.19. The same was true for oral linezolid; use by DDD methods was low (1.45 ± 1.57 DDDs per 1000 patient-days) and was not significantly different from that estimated by DOT methods (1.46 ± 1.61 DOTs per 1000 patient-days; P = .669). There was little variability around the mean individual dose of linezolid (595 ± 22 mg; n = 112), and the total daily dosage (1238 ± 316 mg) was very close to the WHO-recommended DDD (1200 mg).

For a number of antibacterial drugs, the measure of use by DDDs per 1000 patient-days was significantly lower than that by DOTs per 1000 patient-days. For example, ceftriaxone use by DDD methods (44.9 ± 28.2 DDDs per 1000 patient-days) was significantly less than use by DOT methods (62.9 ± 35.9 DOTs per 1000 patient-days; P < .0001). The correlation between these 2 measures revealed that the DDDs per 1000 patient-days value was lower than the DOTs per 1000 patient-days value for most hospitals (figure 1B). The mean administered daily dose of ceftriaxone was 1103 ± 217 mg (n = 130), but the WHO-recommended DDD is nearly twice as high (2000 mg). Similarly, piperacillin-tazobactam use by DDD methods (30.3 ± 20.3 DDDs per 1000 patient-days) was significantly lower than use by DOT methods (42.7 ± 28.5 DOTs per 1000 patient-days; P < .0001). The mean administered dose for piperacillin-tazobactam was 2906 ± 523 mg (n = 128), but the mean administered daily dose (10113 ± 2656 mg) was less than the WHO-recommended DDD (14,000 mg).

Finally, some antibacterial drugs were usually administered at a dosage that exceeded the WHO-recommended DDD; measures of antibiotic use by DDDs per 1000 patient-days were consequently greater than those by DOTs per 1000 patient-days. The most extreme example of this was ampicillin-sulbactam (figure 1C). The WHO-recommended DDD for ampicillin in combination with sulbactam is 2000 mg. However, the mean daily ampicillin dose actually administered was 8120 ± 1776 mg (n = 129), which reflected an average individual dose of 2.47 g that was administered an average of 3.33 times/day. Consequently, estimates of the use of ampicillin-
sulbactam by DDD methods (88.7 ± 63.0 DDDs per 1000 patient-days) far exceeded those by DOT methods (22.1 ± 16.2 DOTs per 1000 patient-days; P < .0001). A less extreme example is cefepime; use by DDD methods (21.9 ± 29.3 DDDs per 1000 patient-days) was significantly greater than use by DOT methods (15.3 ± 17.3 DOTs per 1000 patient-days; P < .001). The WHO-recommended DDD for cefepime is 2000 mg, whereas the mean administered daily dose was ∼50% greater (2927 ± 959 mg; n = 112). The mean administered cefepime dose (1399 ± 344 mg) reflects use of both the 1-g and 2-g dosages, depending upon severity of illness and pathogen susceptibility.

**DISCUSSION**

To our knowledge, this analysis of methods to measure adult antibacterial drug consumption in US hospitals is the largest of its kind. Specifically, the exclusion of pediatric patient data and the inclusion of all commonly used antibacterial agents are notable extensions of previous investigations [24–28]. Furthermore, reports from single institutions may lack generalizability, because they reflect local formulary decisions, prescribing patterns, and patient mix. Finally, the current data update investigations from 25–30 years ago and suggest that the proportion of patients in US hospitals who receive antibacterial drugs is substantially greater than has previously been reported [5–7].

The advantages and disadvantages of DDD and DOT methods to measure aggregate antibacterial use in hospitals can be summarized (table 2). The main advantage of DDD methodology is that antibacterial use across a wide number of countries and health care settings can be compared using standardized methods. Many national and international organizations report antibiotic consumption data using DDD methodology, and the marked variability in use that has been observed is being investigated [15, 21]. Antibiotic consumption using DDD methodology has been linked to outcomes such as bacterial resistance [20, 29, 30] and *Clostridium difficile* disease [31]. A final advantage of DDD methodology is that it may be used with relative ease in countries where automation of administration records is not developed and where counting packages and vials that have been purchased or dispensed is more feasible than measurement of the number of days of antibiotic therapy. Additional refinement of DDD methods, such as DDDs per 1000 admissions may prove helpful with additional investigation [32]. On the other hand, the limitations of DDD methods are substantial and were it feasible to measure DOTs with ease, it is difficult to escape the conclusion that DOT methodology is a superior measure of use.

The most significant limitation of DDD methods results from differences between the administered daily dose, also called the prescribed daily dose, and the WHO-recommended DDD. The most extreme example in the present investigation is for ampicillin-sulbactam; this problem has been previously noted for β-lactamase–inhibitor combinations [24, 28]. DDD methodology overestimates the number of days of therapy by ∼4-fold, because the WHO-recommended DDD for ampicillin (alone or combined with sulbactam) is 2 g, whereas the mean administered daily dose was >8 g. This discrepancy produces an inaccurate assessment of relative antibiotic use as, for example, in the 2004 NNIS data [8]. According to DDD methods, the ampicillin group of antibiotics appears to be the most commonly prescribed antibiotic class in most patient care areas of the NNIS hospitals. However, this simply reflects a WHO-recommended DDD value that is far lower than the dose used for clinical practice. This is problematic, because a hospital that uses a great deal of ampicillin-sulbactam will appear to have a relatively large total DDDs per 1000 patient-days, compared with a hospital that uses little or none. The WHO is aware of this and states, “It should be emphasized that the defined daily

<table>
<thead>
<tr>
<th>Measurement method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined Daily Dose</td>
<td>(1) Allows standardized comparisons of aggregate antibiotic use between hospitals in different locations and countries; (2) allows for an estimate of use in countries with limited access to computerized pharmacy data; (3) will change the estimate of drug use if the recommended daily dose is altered and the approved DDD does not change</td>
<td>(1) Will not accurately estimate DOT when the administered daily dose is not equal to the DDD and, therefore, cannot be used to compare relative use between different antibiotic classes; (2) cannot be used in children; (3) will underestimate use for drugs that require reduced dosage when excretory function is impaired, such as with renal impairment; (4) approved DDDs may change as new dosages are approved for existing drugs, which can create confusion when comparing use over time</td>
</tr>
<tr>
<td>Days of Therapy</td>
<td>(1) Can be used to measure antimicrobial use in children; (2) not influenced by changes in the recommended DDD; (3) not influenced by discrepancies between the DDD and the preferred daily dose</td>
<td>(1) Will overestimate use for drugs that are given in multiple doses per day; (2) more difficult to measure without computerized pharmacy records</td>
</tr>
</tbody>
</table>
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 pharmokinetic considerations” [10].

Estimates of antibacterial use using DDD methods will remain open to criticism because the prescribed dosage often deviates from the “usual” daily dose, depending on location of the infection, pathogen susceptibility, excretory status of the patient, and other issues. For example, during the first half of this investigation, the approved dose of levofloxacin for most hospital infections was 500 mg, and the mean administered dose was nearly identical to the DDD. On 5 November 2002, the FDA approved a 750-mg daily dose for treatment of hospital-acquired pneumonia. If a hospital were to treat all patients with this higher dosage, the total number of aggregated grams would increase by 50%, and—assuming that the DOTs remained unchanged—the DDD measure of use will also increase by 50%. However, the measure of levofloxacin use by DOT would not change. The effect, if any, of this increased dosage on bacterial resistance is unknown, and therefore, it will be important to have a method that recognizes this change, such as the DDD method, and a method that is independent of dosage, such as the DOT method. An investigator, or a hospital antibiotic-management program that is tracking use to link to resistance, will probably wish to measure both DDDs per 1000 patient-days and DOTs per 1000 patient-days, because it is unknown which of these measures is most predictive of resistance.

There are limitations to our investigation. The most important is that administrative claims databases have generally not been extensively validated [33]. Although the great majority of the data that were obtained during our investigation are consistent with expectations, some data are likely inaccurate. For example, outlier data points for the correlation analyses (figure 1) may result from submission of data that are not coded correctly. We decided to include these data in the analysis because they were relatively infrequent and were thus unlikely to substantially alter the comparisons of mean DDDs per 1000 patient-days and DOTs per 1000 patient-days. However, these outliers may have had an effect on correlation assessments.

Measurement of antibacterial use at the national and local levels is recommended by most professional organizations and national task forces that are concerned about the rising rate of bacterial resistance. The acquisition of reliable consumption data is in its infancy, and the relationships between use and outcomes, such as bacterial resistance, remain unclear. We believe that additional work must be done before definitive recommendations can be made as to the best method of measuring use. In the mean time, individual hospitals should decide their main purpose for measuring antibacterial use and select ≥1 method that will allow them to achieve their goals.

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