Chapter 6

How Do Measurements of Antibiotic Consumption Relate to Antibiotic Resistance?

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1. INTRODUCTION

Currently, we are confronting an epidemic of resistance to antimicrobials. Although the spread of antimicrobial resistance is often due to lack of adherence to infection control measures, selection of resistance due to inappropriate use of antimicrobials may also play a large role. However, antimicrobial resistance is not a new phenomenon, with *Staphylococcus aureus* demonstrating resistance to penicillin soon after its introduction in the 1940s. Initially, resistance was usually related to only a few antimicrobials; however, multidrug resistance is increasingly common. The societal costs of antimicrobial resistance, in terms of morbidity and mortality, are substantial (Lucas *et al*., 1998; Meyer *et al*., 1993). In monetary costs, antibiotics are commonly prescribed drugs and the annual costs to the US healthcare system exceed $7 billion.

Antimicrobial resistance is an incredibly complex problem with no simple solutions. Clonal spread of resistance is facilitated by increased use of day-care centers, international travel, and the transfer of patients to and from hospitals and nursing homes. Antibiotics contribute to selection pressure for resistance due to overuse and misuse of antimicrobials in both inpatient and outpatient settings. In addition, routine use of antimicrobials in the animal husbandry industry is also a factor in resistance. (Smith *et al*., 2002). Multiple drug resistance and delays in development of resistance add to the complexity

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of assessing relationships between antimicrobial use and resistance (Friedrich *et al*., 1999).

Proving a causal relationship between the use of antimicrobials and development of resistance is very difficult; however they have been linked by a substantial amount of evidence. Unfortunately, there are many confounding factors and most of the studies that have examined relationships between antibiotic use and resistance have been hampered by inability to control confounding variables (Austin *et al*., 1999a; Levin, 2001; Lipsitch *et al*., 2000a). Therefore, changes in resistance patterns seen after changes in antimicrobial usage patterns may be due to other factors such as changes in infection control measures that may prevent detection of these relationships. Although direct evidence is lacking, there is compelling evidence that resistance is proportional to antimicrobial usage. McGowan, (1983) and Archibald *et al*. (1997) found resistance to be proportional to antimicrobial usage for Enterococci, Staphylococci and Pseudomonads in studies that compared antibiotic use and resistance in an intensive care unit (ICU) to other patient-care areas of the institution. Moreover, controlling antibiotic use has been shown to reverse trends in resistance (Arason *et al*., 1996; McNulty *et al*., 1997; Rahal *et al*., 1998; Seppala *et al*., 1997).

Although one might attempt to prevent or reverse antimicrobial resistance by interventions in infection control and antimicrobial use as separate entities, this approach may be too simplistic. In modeling relationships between antimicrobial use and resistance with vancomycin-resistant enterococci (VRE) in an ICU, Austin *et al*. (1999a) found infection control measures such as handwashing and cohorting of nursing staff closely linked with antimicrobial use control. This analysis suggested that the impact of infection control measures might be negated by inappropriate antibiotic use. Furthermore, antibiotic use is related to infection control since antibiotics can affect the transmission of organisms.

Thus, it is not surprising that it has been recommended that more attention be paid to monitoring antibiotic usage. Indeed, the Society for Healthcare Epidemiology of America (SHEA) suggests measuring antibiotic usage to compare usage trends, to provide a benchmark for costs analyses and to facilitate the assessment of relationships with both adverse events and the development of resistance. Guidelines by SHEA and the Infectious Diseases Society of America (IDSA) (Shlaes *et al*., 1997) suggest monitoring use of antimicrobials by hospital location or prescribing service as well as monitoring the relationship between antibiotic use and resistance.

Historically, as resistance has developed to an antimicrobial, we have been able to depend on the development of new antimicrobials. However, we are now in an era of minimal development of new antimicrobials, especially those directed at Gram-negative aerobic infections. Therefore, we must pay close

attention to the proper use of infection control measures and the appropriate use of antimicrobials.

Quantitative relationships between antibiotic use and resistance have not been well studied. However, defining these relationships is important because antibiotic use is one variable upon which we may be able to exert some control. Various measures of antimicrobial use such as the defined daily dose (DDD), grams purchased or administered, days of antimicrobial therapy, the mean daily dose, and the number of doses administered have been utilized in assessing drug use-susceptibility relationships. Differences in these measures and evidence of their relationships with resistance will be discussed.

2. ANTIMICROBIAL USAGE DATA

Most investigations of antimicrobial use have been performed in hospitals, where access to usage data may be readily available. However, some studies have examined antimicrobial usage in the community, and yet others have involved nationwide antibiotic use. In hospitals, antibiotic usage data is usually obtained from either hospital purchase or pharmacy dispensing records, or drug administration records on individual patients. Although dispensing or administration records may record patient-specific information, these data are often aggregated for a specific drug. This is referred to as aggregate or "group level" data. When related to cumulative susceptibility data, relationships between antimicrobial use and resistance are often referred to as ecological studies. Purchase records, which have no patient-specific information, always fall into this category. However, non-aggregated dispensing or preferably, administration records are patient-specific data. This distinction is important since studies have revealed divergent results when these two types of data have been evaluated. Harbarth *et al*. (2001) studied both individual patient data such as days of antibiotic exposure and the average number of doses per day and aggregate data, reported as DDDs over a 5-year period in a single institution. The studies evaluated whether resistance of nosocomial isolates of *Enterobacteriaceae* or *Pseudomonas* species was related to in-hospital exposure to fluoroquinolones, third-generation cephalosporins, ampicillin/sulbactam, or imipenem. With aggregate level data, increases in DDDs of fluoroquinolones, third generation cephalosporins and ampicillin/sulbactam were noted; however, the proportion of isolates that were susceptible was stable. Relationships between antibiotic use and resistance were weak and only significant for ampicillin/sulbactam at the specific hospital ward level. In contrast, with patient level data, each drug or drug class evaluated was found to be a strong risk factor for resistance to that drug class. In studies involving patient level data, selection of the proper control group may be important (Harris,

2002) and reliance on patients with susceptible isolates as a control group may be insufficient.

With either type of data, one must decide if all use of a specific drug will be included. For example, only antibiotics selected for therapeutic use may be evaluated or those used for prophylaxis may be included. Furthermore, non-systemic uses such as antibiotics used in surgical repair materials or for topical administration may be included. Most evaluations have assumed that all of an administered drug is available systemically; however, exposure to antibiotics with low oral bioavailability may be overestimated unless corrected for bioavailability. Furthermore, those drugs with poor bioavailability may maintain higher concentrations in the gastrointestinal tract and have a significant impact on alterations of flora. Thus, depending on the type and location of organisms, the systemic availability of antimicrobials should be considered. In addition, high protein binding can limit the concentration of the unbound, pharmacologically active concentration of an antimicrobial. Thus, correction for protein binding may be important for highly bound drugs.

2.1. Patient-specific data

Patient-specific or patient-level antimicrobial use data, used in case control studies, includes collection of the dose, dosing interval and the length of the dosing regimen (Table 1). Depending on the purpose of the study this information may be collected before or after the event of interest. For example, one might study the impact of antecedent antimicrobial use for a fixed period of time prior to detection of a resistant organism. With these data, one could make the distinction between empirical antimicrobial use and that used for directed therapy. Most studies have gathered these data from retrospective chart review, review of pharmacy dispensing records, or medication administration records. With the increasing use of electronic medical records, collection of these data should be less time consuming.

Patient-specific data has several advantages over aggregate data. Most importantly, it allows analysis of the development of resistance that may be due to antecedent and/or concurrent antimicrobial therapy. When other data are collected such as patient demographics, underlying disease states, and the infecting pathogen, one can assess the appropriateness of antimicrobial therapy. Patient-specific data also allows the evaluation of multiple antimicrobial therapy whereas aggregate data usually examines only a single drug. Since a patient's location within a healthcare setting (e.g., an ICU) is known, patient-specific data also facilitates evaluation in specific patient-care areas within an institution. Lastly, since patient-specific data can always be aggregated, comparisons of the relationships with patient-specific and aggregate antimicrobial use data on resistance can be studied. When patient-specific data are analyzed

Table 1. Example of raw antimicrobial use data in specific patients and calculations that may be performed to study aggregate antimicrobial use

	Raw data			Calculations		
Patient	Dose (g)	Dosing interval (hr)	Length of therapy (days)	Doses per day	Grams per day	Grams per course of therapy
1	1	8	10	3	3	30
2	2	8	7	3	6	42
3	1	12	8	2	2	16
Mean	1.3	9.3	8.3	2.7	3.7	29.3
Total			25.0			88.0

without concomitant evaluation of aggregate data, there are some potential disadvantages when compared to aggregate data. In a case control study in which patients are selected based on the occurrence of a specific pathogen, the impact of an antimicrobial on emergence of resistance in other patients, and especially with other organisms, will be missed. In addition, the total amount of selective pressure exerted by an antimicrobial within an institution may be missed if use of that antimicrobial in other patients is not analyzed. Antimicrobial use outside of the patient ward, often referred to as floor stock, such as surgical prophylaxis and dosing in patients undergoing hemodialysis may be excluded if the dispensing records are separate from the primary pharmacy dispensing records. Furthermore, evolving concerns about patient privacy may limit the collection and analysis of patient-specific data (U.S. Office of the Federal Register, 1996).

2.2. Aggregate data

Antimicrobial use data that has been summarized for a group of patients, in which the patient-specific dose, dosing interval, and length of therapy is no longer discernable are referred to as aggregate or group-level data. Aggregate data is most often derived from antimicrobial purchases, but may also be summarized from patient-specific data.

There are several advantages of aggregate antimicrobial use data when compared to patient-specific data. Since aggregate use should capture all of the exposure to an antimicrobial in a healthcare setting, it may better relate to the total microbiological ecology of that setting. Thus, development of resistance to commensal organisms, often called "collateral damage" related to antimicrobial use might be detected with aggregate ecological studies. Purchase data, the most common source of aggregate antimicrobial use data, are usually readily available, and thus, easier to benchmark vs use in other institutions. Furthermore,

when simultaneous pharmacoeconomic studies are a consideration, purchase data may be desirable.

A number of disadvantages exist for aggregate antimicrobial use data. A major limitation is that no distinction can be made between antecedent use prior to the development of a resistant isolate and that administered thereafter, thus precluding assessment of resistance due to poor infection control rather than inappropriate antimicrobial use. Aggregate data, if obtained at the nationwide level, may not allow distinction of antimicrobial use that is not used for treatment of infection (e.g., antimicrobials used in the animal husbandry and horticultural industries) from that used in patients. Since all antimicrobials purchased or dispensed are not administered, aggregate data derived from purchases data may overestimate exposure of an antimicrobial in a specific healthcare setting. When aggregate data are derived from patient-specific data, one can evaluate the impact of antimicrobial use within a specific patient-care area such as an ICU; however, purchase data would preclude such assessment. Lastly, aggregate data apportions antimicrobial use over an entire population of patients, potentially masking the true intensity of antimicrobial exposure.

2.3. Sources of antimicrobial use data

2.3.1. Antimicrobial purchases

Purchase records to estimate antimicrobial use may be obtained from a specific institution, a wholesale distributor, or from government records in countries with nationalized health plans. Through use of purchase records, antimicrobial use in an institution, a community, or a larger geographic region may be assessed. Purchase data may have an advantage over other types of data collection in that total antimicrobial use within a healthcare setting may be captured. Purchase data, often expressed as grams purchased, can also be linked to acquisition costs of antimicrobials; thus, economic analyses will capture total acquisition costs. The major disadvantage of using purchase data to estimate drug exposure in patients is that the drug may never be administered to the patient. Antimicrobials that are purchased may not be dispensed or administered due to wastage after preparation, changes in a prescriber's orders, or destruction of a drug that has exceeded its expiration date. Therefore, purchase data represent the least sophisticated, but most readily available, method of estimating antimicrobial exposure.

2.3.2. Antimicrobial dispensing records

Antimicrobial pharmacy dispensing records may represent a more accurate assessment of antimicrobial use than drug purchases since all antimicrobials

that are purchased are not dispensed. Dispensing records, in which antimicrobials that are dispensed but not administered to a patient are recorded properly, may accurately assess antimicrobial use in a patient population. However, since some of these "returns" may not be recorded, dispensing records are likely to overestimate actual antimicrobial exposure in patients. In some settings, these data are readily available and are preferred over purchase records as a measure of drug use.

2.3.3. Patient administration records

Within an institution, patient administration records may be readily available as an estimate of antimicrobial use. Theoretically, these records should exactly mirror drug use; however, the accuracy of the records should be verified. For example, a dose of an antimicrobial may be charted, yet the drug is still not administered to the patient due to discovery of a drug allergy or difficulty in establishing venous access. In some cases, a partial dose might be administered before an adverse event (e.g., extravasation) is recognized. Although administration records have been difficult to obtain in many settings, increasing use of electronic medical record data may make this information more readily available.

3. ANTIMICROBIAL USAGE MEASURES

From the records described above, one may use or calculate a variety of measures, or metrics, to quantify antimicrobial use. There may be no single ideal measure of antimicrobial use. Indeed, one may choose a measure over another depending on the purpose of the analysis. There may be no single ideal measure that can be used for each drug, drug class, and relationship with resistance. Measures based on patient-specific data allow more flexibility in the analysis of relationships between antimicrobial use and resistance and can also be used to calculate aggregate data.

3.1. Patient-specific measures

Depending on the type of study relating antimicrobial use and resistance, several patient-specific measures have been utilized. In some case control studies, these measures are non-quantitative. For example, one may assess as a binomial variable whether a patient received a specific antimicrobial during a specified period of time without regard to quantity. However, most patient-specific studies assess quantitative antimicrobial use. These measures include the mean daily dosage, the number of antibiotic orders, doses administered, days of therapy, or the number of grams administered to an individual patient.

Measures that include the intensity of the dose, such as mean daily dose or grams administered may be preferred over measures such as the number of doses or number of prescriptions that fail to account for dose intensity. Thus, the mean daily dose, also referred to as the prescribed daily dose (PDD) may be useful.

Other measures such as the number of days of antimicrobial therapy may be independent of dose; thus, allowing assessment of dosage independent of length of therapy. Integrated, or hybrid, measures such as the total number of grams administered to a patient may account for both of these independent factors, daily dosage and length of therapy (calculation in Table 1). This may be useful since it is plausible that development of resistance with specific organisms may be due primarily to either the length of antimicrobial exposure or the intensity of the daily dose rather than a hybrid measure such as total grams. If one calculates the average length of therapy from days of therapy in individual patients, antibiotic stop order policies may create a problem. For example, if an institution uses a stop order policy that could discontinue a planned 10-day regimen after only 5 days, continuation of the drug regimen may result in a new antibiotic order. In this situation, it would appear that there were two drug orders, each with a 5-day length of therapy. Many hospital information systems would not indicate that the length of therapy in that patient was actually 10 days. Although total grams of an antimicrobial administered to a patient can be derived from patient-specific data, grams of use are usually obtained from purchase records and will be discussed as an aggregate marker of drug usage.

3.2. Aggregate measures

As mentioned above, one may derive patient-specific data from dispensing or administration records and then use either averages or totals of aggregate data to describe antimicrobial use. Although the average daily dose and average length of therapy have been used as antimicrobial use measures, most aggregate data involve total measures.

3.2.1. Number of prescriptions

Aggregate measures such as the total number of prescriptions, doses, vials, or packages have been used to estimate antimicrobial use; however, these measures provide no direct information on antimicrobial exposure in patients. In limited situations however, these measures may sufficiently estimate use when all patients are given a fixed dose and/or fixed dosing interval. In an analysis by White (2002) over a 9-year period in a large teaching hospital, the correlation between the number of orders for ceftazidime with grams administered

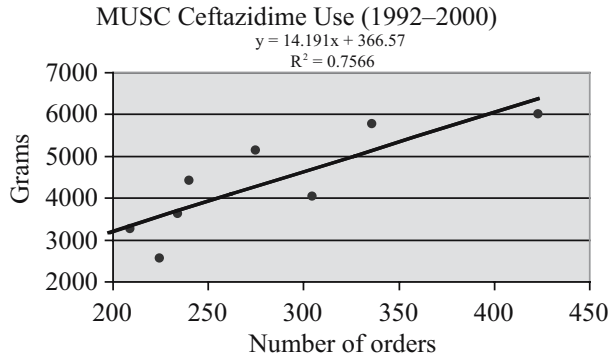

Figure 1. Plot of the number of grams used vs the number of orders for ceftazidime between 1992–2000 at a large teaching institution (White, 2002).

was strong ($R^2 = 0.757$) (see Figure 1). Although correlations of these measures and a more quantitative measure such as grams may be strong, grams as a measure of use provide more quantitative information.

3.2.2. Expenditures

Historically, antimicrobial expenditures were used to estimate antimicrobial usage. Although this measure may still be a reasonable approximation of use in some circumstances, it may differ significantly from actual usage (Rifenburg *et al*., 1999). The major limitation with expenditures is that the acquisition cost of an antimicrobial may change over time. In a longitudinal analysis of antimicrobial use, or when use is related to the development of resistance, substantial changes in acquisition costs during the period of analysis significantly limit the usefulness of this measure. However, expenditure may be one of the easiest measures to obtain.

3.2.3. Grams

Although total grams of an antimicrobial used in a healthcare setting in a fixed period of time can be derived from patient-specific data, grams used are usually obtained from purchase data. As mentioned above, grams can be considered to be a hybrid, rather than independent measure of use since the daily dosage and the length of therapy are either used in the calculation of grams or inherent in the measure if purchased grams are used. If one is analyzing use of only a single drug over time, total grams is a valid measure of use. However,

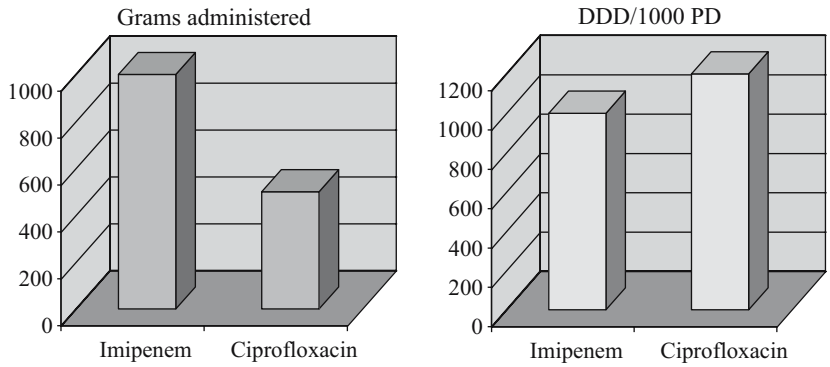

Figure 2. Comparison of grams administered to DDD/1,000 patient-days (PD) of Imipenem and Ciprofloxacin (DDD for Imipenem = 2 g/day, Ciprofloxacin = 0.8 g/day, patient-days = 500) (White, 2002).

when one compares the use of two or more antimicrobials with different daily gram dosages, problems arise. For example, if a drug that is given in a higher gram dosage (e.g., imipenem) is compared to a drug with a lower gram dosage (e.g., ciprofloxacin), differences in use are difficult to discern (Figure 2). Thus, a measure to normalize drugs with different gram daily dosages was needed, especially when evaluating total antimicrobial use for a class of antimicrobials. The DDD was established to alleviate this problem. When one compares grams from one institution to another in an attempt to benchmark antimicrobial use, the source of the data for the grams used may be important. In a comparison of antimicrobial use among 10 hospitals, the source of the grams reported varied from grams dispensed (5 hospitals) to grams purchased (4 hospitals) to grams removed based on storeroom records (Lesch *et al*., 2001). Obviously collection of data from these varied sources makes meaningful surveillance of drug use among multiple institutions more difficult.

3.2.4. Defined daily dose (DDD) method

The DDD method is used to measure and compare antimicrobial use within a population of patients. It has primarily been used to assess antibiotic consumption within an institution, but has also been used to estimate non-hospital consumption within a specific geographic region or country (Ruiz-Bremon *et al*., 2000). In the calculation of DDDs as a measure of antimicrobial use, the total grams used are divided by the DDD, which represents a typical adult daily dosage. This calculation is usually reported as a normalized value of DDD/1,000 patient or inhabitant-days.

Example calculation of the defined daily dose (DDD) assuming the following:

Grams of use	= 600 g
DDD	= 3 g per day
Patient days during that time period	= 2,000 days
Then, DDD/1,000 patient-days	= (600 g/3 g per day)/2,000 days × 1,000
	= 100

The DDD has been in use since the 1970s, when it was originated by Norwegian researchers. Those researchers, who collaborated with the Norwegian Medical Depot (NMD), developed a system known as the Anatomic Therapeutic Chemical (ATC) classification. They developed a unit of measurement called the DDD that was intended to be used in drug utilization evaluations (World Health Organization, 2002). In 1981, the ATC/DDD system was recommended as a drug use measure by the WHO office in Europe. In 1982, the WHO Collaborating Centre for Drug Statistics Methodology was established to oversee the use of the DDD method. In 1996, this responsibility was transferred to WHO world headquarters in Geneva to promote the DDD as an international standard. Currently, the WHO International Working Group for Drug Statistics advises the WHO Collaborating Centre for Drug Statistics Methodology on use of DDD methodology. In this method, the DDD is the assumed average maintenance dose per day (in grams) for a drug used for its main indication in adults. DDDs are usually based on the monotherapy dosage and on treatment rather than prophylaxis. Furthermore, if a drug is used for more than one indication, different DDDs may be assigned for each indication, thus introducing some potential confusion regarding the appropriate DDD value. DDDs are assigned only for drugs that have been given an ATC code and are reviewed periodically. Antimicrobials are not reviewed and assigned a DDD by the WHO Collaborating Centre until requested from a user of the system (manufacturers, regulatory agencies, and researchers), so DDDs of antimicrobials may not be assigned in a timely manner. Also, since access to DDD values has been expensive, some organizations and authors have utilized non-WHO defined daily doses in DDD calculations (CDC, 2001). With DDD values becoming more accessible, perhaps these problems will subside.

The major advantage of the DDD method is that comparisons of antimicrobial consumption in a population are more meaningful than when simple comparisons of grams are used (Figure 2).

In recent years, the DDD method has become the standard for benchmarking antimicrobial use among institutions or geographic areas. Since DDDs are additive, one may examine total antibiotic exposure within and between drug classes, institutions, regions, and countries.

Although the DDD methodology has much utility in evaluating antimicrobial use, there are several drawbacks that make it less than ideal. A criticism of the method is that the DDD may represent a dose that is seldom used in common clinical practice. Indeed, this can be the case since the DDD may actually represent an average of two or more dosages that are commonly used. Also, since adult doses are the basis for the DDD, these calculations are not as meaningful when used with pediatric antimicrobial use data. Since the DDD is based on the typical adult dose, there is no provision for drug dosages that need to be altered in patients with reduced renal function. When investigators have compared the average daily dosages of antimicrobials (also known as the prescribed daily dose, or PDD) in their institutions, there have been large differences between those dosages and those recommended for calculation of DDDs. Although the DDD is a standard that is useful for benchmarking, the PDD may better represent local usage patterns. Moreover, if the PDD is lower than the DDD, then DDD calculations will underestimate the number of doses or days of therapy (Resi *et al*., 2001).

In a study to compare DDD values to PDD values, Paterson *et al*. (2002) studied piperacillin/tazobactam, levofloxacin, and cefepime over a 2-month period in a large medical center with over 100 ICU beds. Mean PDD were 60% of the DDD for cefepime (2.4 vs 4 g), 85% for intravenous levofloxacin (0.4 vs 0.5 g), 203% for oral levofloxacin (0.4 vs 0.2 g), and 92% for piperacillin/tazobactam (12.35 vs 13.5 g). PDDs were lower in the ICU than the non-ICU setting for piperacillin/tazobactam. The author suggested that the differences observed were likely due to dosage adjustments for renal dysfunction and the DDD values for oral use. Similar variations between the PDDs and DDDs were reported by White (2002), see Table 2.

Although DDD changes over time are not common, there have been some changes that have occurred with antimicrobials (Table 3). Obviously, this

Table 2. Comparison of DDD and mean daily dose values at a large teaching hospital

Drug	DDD (g/day), NNIS	Mean daily dose (g), MUSC	Mean daily dose/DDD (%)
Ceftazidime	3.0	3.7	123
Cefotaxime	3.0	4.4	146
Imipenem	2.0	1.7	85
Nafcillin	4.0	9.6	240
Piperacillin/tazobactam	13.5	11.9	88
Vancomycin	2.0	1.6	80

Note: NNIS = National Nosocomial Infection Surveillance System, MUSC = Medical University of South Carolina.
Source: CDC (2001); White (2002).

Table 3. Example of some antimicrobials for which the DDD has been changed over time

	WHO DDDs (g/day)		
Drug	Pre-1992	1992–2000	Post-2000
Cefoperazone	2	6	4
Ceftazidime	4	6	4
Cefuroxime IV	2	4	3

Source: WHO (2002).

makes assessment of trends in antimicrobial use more difficult (Ronning *et al*., 2000). Since DDD calculations do not take repeated courses of treatment into account, Resi *et al*. (2001) have proposed a "therapeutic course" metric as a complement to the DDD system. In this system, the therapeutic course system would account for all prescriptions within a given time frame as the same course of therapy. Although this may be a useful adjunct to DDD calculations, selection of the time frame that would constitute a therapeutic course would likely be a point of much debate.

3.2.5. Pharmacokinetic estimates of antimicrobial exposure

Given that there are known relationships between antimicrobial exposure and both clinical outcome and resistance (Craig and Andes, 1996; Drusano, 2003; Thomas *et al*., 1998), it would be desirable to measure or estimate antimicrobial exposure in individual patients. The measures of antimicrobial use that have been reviewed fail to account for differences in drug exposure in patients due to intrapatient and interpatient variability. For example, when grams are used (or DDDs as a derivation of grams), the calculations assume that any gram of an antimicrobial administered to a patient will have the same impact on the development of resistance as any gram administered at a different time to that same patient. Furthermore, those calculations assume that the same dose of an antimicrobial will have the same impact on resistance in different patients. These assumptions are invalid due to known interpatient and intrapatient variability in pharmacokinetic profiles. Ultimately, estimations of drug use may be replaced by estimates of drug exposure in patients. To this end, one needs either direct measurements of drug concentrations in individual patients or precise estimations of drug exposure using population pharmacokinetic estimates. These estimates are unlikely to be made in large populations since assays of antimicrobial concentrations sufficient to estimate drug exposure are invasive and costly. Estimates of drug exposure from population pharmacokinetic values is more likely to occur, but may be prone to error if

population pharmacokinetic studies are not representative of the underlying populations of interest. A potential disadvantage of this method is that drug concentrations at sites of contact with organisms that may develop resistance may be poorly characterized. For example, if a drug has low systemic concentrations due to poor oral absorption and serum concentrations are measured, drug contact with organisms in the gastrointestinal tract may be underestimated.

4. NORMALIZATION OF USE DATA

It is common practice to normalize aggregate antimicrobial use data to account for differences in census within an institution or geographic area. This is usually accomplished by correcting the use data so that it reflects a rate of use per unit of time, for example, 1,000 days. This day term is often referred to as patient-days since one calculates this denominator by multiplying the number of patients within the institution in a given period of time by the length of hospitalization (in days) and correcting it to a value such as 1,000. Patient-days are also referred to as occupied bed-days. Correction for changes in the population in this manner allows one to see "true" changes in rates of antimicrobial use rather than fluctuations that may simply reflect changes in the population over time or differences in two or more populations. Although it is always useful to normalize the data to detect the true rate of use, normalization is of little value when small changes in census occur. For example, census changes in smaller patient-care areas may be very important whereas institution-wide fluctuations in census may be minimal; thus, normalization may have only a minimal impact (Figure 3). Obviously, if there are no changes in the number of patient-days over time, non-normalized measures (e.g., grams) and the normalized measures (e.g., grams/patient-day) would perfectly correlate. These calculations mathematically spread the use over the entire population rather than the population that actually received the antimicrobial of interest. Thus normalized values such as grams per patient-day will not reflect average grams per day doses of an antimicrobial.

The most common denominator for normalizing antimicrobial use within an institution in the United States is 1,000 patient-days. In Europe, the European Surveillance of Antimicrobial Consumption (www.ua.ac.be/main.asp?c=*ESAC) recommends use of bed-days, which are calculated by multiplying the number of beds by the occupancy by the length of time of the study. The denominator for use in primary healthcare settings and thus, within a geographic region, is usually inhabitant-days per unit of time, which is calculated by multiplying the number of inhabitants in an area by the number of days studied. For example, 7 DDD/inhabitant/year is equivalent to each inhabitant of an area receiving a 7-day course of that antimicrobial during a 1-year period. If certain

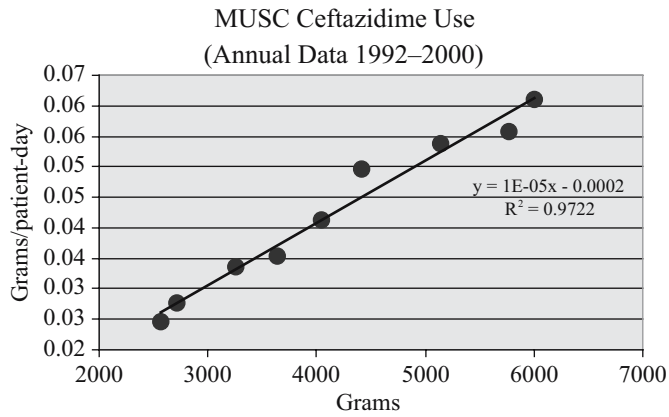

Figure 3. Example of the impact of small changes in patient-days when normalizing grams of use data (White, 2002).

antimicrobials are used only in patients of specific ages, one can utilize the number of inhabitants in that age range when those data are available. The number of admissions or discharges can also be used to estimate the percentage of patients exposed to antimicrobials. Other factors that have been used to calculate rates of use are use per number of beds or occupied beds. However, factors that fail to take length of stay into account are probably less useful; thus patient-days, bed-days, and inhabitant-days are preferred. When patient-specific antimicrobial use data are available, there is no need to normalize the data since the antimicrobial exposure reflects only the patients who received antimicrobials.

5. RELATIONSHIPS BETWEEN MEASURES OF ANTIMICROBIAL USAGE AND RESISTANCE

Establishing a causal relationship between antimicrobial exposure and development of resistance is very difficult since a myriad of factors other than antimicrobial use may contribute to the emergence of resistance (McGowan, 1983). Although the spread of resistant organisms from patient to patient is important, selection pressure from antimicrobials may largely contribute to the emergence of resistance. Levy (1994) suggests that the intensity of antimicrobial use in a population is the most important factor in the selection of resistance and that a threshold may exist that may differ for a specific patient as compared to a population. Furthermore, this threshold may differ among various populations. Since prospective randomized controlled trials of the development of resistance are not

performed and would be unethical, most studies are observational and retrospective. Thus, lack of control of confounding variables is a major limitation in these studies and most studies involve a small number of patients and are performed in a single institution. Furthermore, these evaluations have utilized different measures of antibiotic use such as DDDs, grams, days of therapy, and the number of prescriptions over various periods of time. Although antimicrobial use is usually evaluated in discrete time intervals, cumulative use data may be more likely to detect relationships with changes in susceptibility (White and Bosso, 2003).

Statistical evaluation of antimicrobial use-susceptibility relationships has included linear, multiple and logistic regression analysis (Bonapace *et al.*, 2000a, b; Burgess and Jones, 2002; Enzweiler *et al.*, 2000a; Friedrich *et al*., 1999; Johnson *et al*., 2002a, b; Polk *et al*., 2002) as well as time-series analysis (Monnet and Lopez-Lozano, 2002). Mathematical modeling of relationships between antimicrobial use and resistance and the relative contribution of infection control measures has greatly enhanced our understanding of the complexity of the relationships. (Austin and Anderson, 1999; Austin *et al*., 1999b; Levin *et al*., 1997; Lipsitch *et al*., 2000b; Lipsitch and Samore, 2002).

Although we often refer to studies of resistance, many studies evaluate the relationship between antimicrobial use and changes in the percentage of isolates categorized as susceptible rather than resistant. This is not surprising given that antibiograms, the basis for most institutional surveillance studies, report percentage susceptibility rather than percentage resistance. Due to the intermediate category, susceptibility and resistance do not necessarily trend in opposite directions and evaluations with one category may not result in the same conclusions as using another category. Aggregate studies using antibiogram data undoubtedly combine data from pathogens as well as colonizing organisms, which may complicate evaluation of relationships between antimicrobial use and resistance. In an evaluation of 10 years of data in a large teaching hospital, Enzweiler *et al*. (2002c) found that changes in percentage resistance were often more useful than tracking of percentage susceptibility. In that study, clinically relevant changes were detected earlier, in some cases, years earlier, when using percentage resistance rather than percentage susceptibility. Moreover, institution-wide rather than unit-specific data are usually used to assess relationships between antimicrobial use and resistance. Although clinically relevant relationships may be detected, institution-wide data may mask important relationships occurring in specific patient-care areas within the institution (White *et al*., 2000).

Adding to the complexity of detection of relationships between antimicrobial use and resistance may be the pattern of use in a specific institution. For example, one institution may use an antimicrobial as monotherapy while another consistently uses it as part of combination therapy. This may be important since in

mathematical models, combination therapy is better than antimicrobial cycling in prevention of resistance. Typically, the rise in resistance is faster than the decline when selection pressure is removed since the costs of resistance in the absence of antimicrobial pressure is less than the benefit of resistance when pressure is present. Thus, declining susceptibility due to increasing antimicrobial use may be easier to detect than increasing susceptibility when antimicrobial use declines (Bonhoeffer *et al*., 1997). Further complicating detection of relationships between use and susceptibility is simultaneous resistance to multiple antimicrobials. In a study evaluating the relationship between multiple antimicrobials and resistance in Gram-negative aerobes, Friedrich *et al*. (1999) found that with relationships involving increasing antimicrobial use with declining susceptibility, more than one antimicrobial was statistically associated with the changes in susceptibility (mean 1.7, range 1–14) to any single agent. When combinations of resistance mechanisms are present, associations between antimicrobial use and resistance may be quite complex. Ryan *et al*. (2002) reported on the relationships between fluoroquinolone and carbapenem use with resistance of *P. aeruginosa*. Meropenem and ciprofloxacin, but not imipenem, susceptibility patterns were associated with carbapenem and fluoroquinolone use ($p < 0.0001$). Although not directly evaluated in this study, the authors attributed these effects to a combination of mutations, changes in porins, or drug efflux mechanisms.

5.1. Relationships based on patient-specific data

Patient-specific data are used in case control studies in which antecedent antimicrobial use is associated with the development of resistance. In the case control studies, resistant isolates are identified and risk factors are examined. In other prospective studies, the antimicrobials that may increase the risk of colonization with resistant isolates are examined. In these studies, antimicrobial use may be quantitative (e.g., number of antibiotic courses, grams, number of days of therapy, etc.) or non-quantitative (e.g., binomial data regarding drug exposure of a certain intensity or length of therapy). Since the length of drug exposure prior to development of resistance is not known and whose ascertainment may be the purpose of the study, the length of time for the evaluation of antecedent drug use is not standardized.

Numerous studies have evaluated prior antibiotic use and development of resistance. In investigations of the association of antecedent vancomycin use and development of vancomycin-resistant enterococci (VRE), several studies found relationships between vancomycin and development of VRE colonization or infection (Ena *et al*., 1993; Frieden *et al*., 1993; Yates, 1999). In a meta-analysis of 20 studies of vancomycin use and the selection of resistance in

enterococci, there was however, no statistically significant relationship. The author suggested that the design of the individual studies and differences in control group selection, length of hospital stay, and publication bias, likely had a great impact on whether such an association was detected (Carmeli *et al*., 1999). Exposure to broad-spectrum antimicrobials without activity against enterococci was found to be strongly related to colonization with VRE. In this study, the total number of days of antimicrobial exposure was correlated with the prevalence of VRE (Tokars *et al*., 1999). Yet others have suggested that antimicrobials with significant activity against anaerobes, rather than vancomycin use, may be important in selection of VRE (Donskey *et al*., 2000; Yates, 1999).

In a prospective, observational study, Chow *et al*. (1991) evaluated the emergence of resistance during antibiotic therapy in 129 patients with Enterobacter bacteremia. Previous administration of a third generation cephalosporin was more likely than other antimicrobials to be associated with multiresistant Enterobacter isolates in an initial blood culture ($p < 0.001$). Emergence of resistance to a third generation cephalosporin was more frequent than to aminoglycosides ($p = 0.001$) or other β-lactam agents ($p = 0.002$). In a 5-year case control study of piperacillin-tazobactam resistant *P. aeruginosa*, Harris *et al*. (2002a) found a number of factors and antimicrobials associated with resistance. The length of time a patient was at risk for the development of resistance, a transfer from one patient-care area to another, ICU stay, and the number of admissions in the previous year were risk factors for the development of *P. aeruginosa* resistant to piperacillin-tazobactam. The odds ratio (OR) for several antimicrobials including piperacillin-tazobactam, OR 6.82, imipenem, OR 2.42, broad-spectrum cephalosporins, OR 2.38, aminoglycosides, OR 2.18, and vancomycin, OR 1.87 indicated an association with resistance. Interestingly, in almost half of the cases of piperacillin-tazobactam resistant *P. aeruginosa*, the patient did not receive piperacillin-tazobactam. In contrast, in an evaluation of the impact of broad-spectrum antibiotics on detection of resistant isolates, Richard *et al*. (2001) found that fluoroquinolones were associated with the development of fluoroquinolone-resistant Gram-negative bacilli in gastrointestinal flora. This study illustrate the complexity of relationships between antimicrobial use and resistance and the value in examining patient-specific antecedent antimicrobial use.

5.2. Relationships based on aggregate usage

Many studies have examined the relationship between aggregate antimicrobial use and resistance. (Arason *et al*., 1996; Ballow and Schentag, 1992; Chen *et al*., 1999; Dahms *et al*., 1998; Enzweiler *et al*., 2002a, b; Janoir *et al*., 1996; Lopez-Lozano *et al*., 2000; McNulty *et al*., 1997; Polk *et al*., 2001;

Rahal *et al*., 1998; Rice *et al*., 1996; Seppala *et al*., 1997; Tokars *et al*., 1999; Tornieporth *et al*., 1996). As one might expect, most of these have been conducted in hospital settings; however, several have been analyses of nationwide data. In these studies, various measures of antimicrobial use have been utilized; however, the DDD is the most common metric.

In a nationwide analysis conducted in Finland, resistance of Group A Streptococci was associated with macrolide use expressed in DDD/1,000 patient-days. Erythromycin resistance increased from 5% in 1988 to 19% in 1993 while macrolide use increased 3-fold. Upon reduction of macrolide use by 50%, resistance to Group A Streptococci also declined by approximately 9% (Seppala *et al*., 1997). In a similar analysis in Canada, Chen *et al*. (1999) evaluated the resistance of *Streptococcus pneumoniae* to fluoroquinolones. Fluoroquinolone use, rose from 0.8 prescriptions/person/year in 1988 to 5.5 prescriptions/person/year in 1997. During that time, *S. pneumoniae* with reduced susceptibility to fluoroquinolones (ciprofloxacin MIC $\geq$ 4 mg/L) increased from 0% in 1988–93 to 1.7% in 1997–8. Janoir *et al*. (1996) also evaluated the relationship between fluoroquinolone use, as DDD/1,000 inhabitants and fluoroquinolone resistance with *S. pneumoniae*. As fluoroquinolone use increased from 0.9 DDD/1,000 inhabitants in 1985 to 2.2 DDD/1,000 inhabitants in 1997, ciprofloxacin-resistant *S. pneumoniae* increased from 0.9% to 3%. In another evaluation of resistance to *S. pneumoniae*, Arason *et al*. (1996) examined the relationships between total antibiotic use, expressed as DDD/inhabitant and drug-resistant *S. pneumoniae* (DRSP) after the percent of DRSP increased to 20% and total antibiotic use increased to 23.2 DDD/inhabitant. From 1992 to 1995, antibiotic use decreased to 20.2 DDD/inhabitant while the percentage DRSP decreased by 5%.

In a study involving 18 hospitals, Ballow and Schentag (1992) studied the relationships between ceftazidime use and susceptibility of *Enterobacter cloacae* to ceftazidime. There was covariance in susceptibility of *E. cloacae* to ceftazidime, piperacillin, mezlocillin, cefotaxime, and ceftriaxone. Although only 10 of the 18 hospitals individually showed a linear relationship between ceftazidime use, expressed as grams/quarter/bed and susceptibility of *E. cloacae* to ceftazidime, overall the relationship was significant ($p < 0.02$). In two hospitals there was a relationship between declining ceftazidime use and increasing susceptibility of *E. cloacae*. Using a multiple hospital database, Polk *et al*. (2001) evaluated total fluoroquinolone use and resistance. Using total fluoroquinolone use as DDD/1,000 patient-days, there was a strong relationship with the prevalence of ciprofloxacin-resistant *P. aeruginosa* ($r = 0.54, p = 0.01$).

In a study of ceftazidime-resistant *Klebsiella pneumoniae*, ceftazidime use was found to be a risk factor for development of resistance. In this study, there was a strong association between ceftazidime use in a specific patient-care area, in grams, and prevalence of ceftazidime-resistant *K. pneumoniae*

(Rice *et al*., 1990). In response to an outbreak of ceftazidime-resistant extended-spectrum β-lactamase (ESBL) producing *K. pneumoniae*, the use of cephalosporins was restricted. Although the restriction program was successful in reducing cephalosporin use and reducing ceftazidime-resistant ESBL *K. pneumoniae* infections by 44%, imipenem use increased and imipenem-resistant *P. aeruginosa* increased by 57% (Rahal *et al*., 1998). In an evaluation of antimicrobial use over a 10-year period in a single institution, Enzweiler *et al*. (2002a) found numerous strong linear relationships between antimicrobial use, in DDD/1,000 patient-days, and percentage susceptibility. Of these relationships, most occurred when antimicrobial use was increasing while susceptibility was decreasing; however, relationships were also found where antimicrobial use was declining while susceptibility was increasing.

In the examples above, relationships with resistance were demonstrated with various measures of antimicrobial use. Since many of these measures are highly correlated, it is not surprising that various measures may lead one to the same conclusions. However, these studies did not evaluate which measure may have resulted in the strongest relationship with resistance.

5.2.1. Comparison of various measures of antimicrobial use

Although there have been numerous studies using both patient-specific and aggregate antimicrobial use measures, only a few have compared these measures to each other or with respect to relationships to resistance (Bonapace *et al*., 2000b; Burgess and Jones, 2002; Enzweiler *et al*., 2001, 2002b; Johnson *et al*., 2002b; Polk *et al*., 2002). Each of these studies is discussed below.

Using 8 years of data from a single institution, Bonapace *et al*. (2000b) evaluated the relationships between four measures of antimicrobial use for 19 antimicrobials (13 β-lactams, 3 aminoglycosides, 2 fluoroquinolones, and trimethoprim/sulfamethoxazole) and changes in susceptibility to eight Gram-negative aerobes (*A. baumannii*, *E. coli*, *E. aerogenes*, *E. cloacae*, *P. mirabilis*, *P. aeruginosa*, *S. marcescens*, *K. pneumoniae*). Using hospital-wide patient-specific antimicrobial use data, aggregate measures of antimicrobial use were calculated and included total grams, grams/patient-day, days of antimicrobial therapy, and the mean daily dose. Relationships between each of these measures and percentage susceptibility for each organism were assessed by linear regression and only the strongest relationships ($R^2 \geq 0.5$) were further evaluated. Discordance was defined as a regression line slope in the opposite direction from the relationships found with the other measures of drug use (Figure 4). Of the 142 relationships that met the study criteria, in 39% of instances, there was concordance (agreement in the regression line slope) among all four measures of use. When one of the four measures was discordant with the others, it most frequently occurred with the mean daily dose (57% of discordant occurrences). Interestingly, although the mean daily dose was most frequently

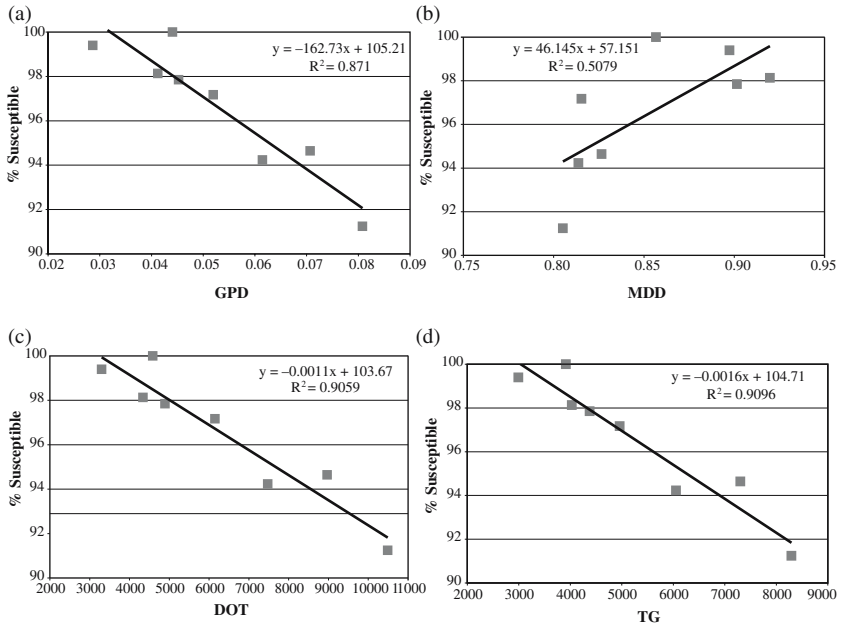

Figure 4. Example of relationships between different aggregate measures of antimicrobial use and percentage susceptibility. (GPD = grams/patient-day, MDD = mean daily dose, TG = total grams, DOT = days of antibiotic therapy) (Bonapace *et al*., 2000b).

discordant, it was most strongly correlated with changes in susceptibility. There were no apparent trends of discordance among specific antimicrobials or organisms. As expected, some measures of use were highly correlated with each other. Positive correlations between measures of use were strong for total grams vs total grams/patient-day ($r = 0.985$) and days of antibiotic therapy ($r = 0.943$). Days of antibiotic therapy were also highly correlated with total grams/patient-day ($r = 0.928$). However, the mean daily dose was negatively and poorly correlated to each of the other measures of use.

In another study assessing differences in measures of antimicrobial use, Enzweiler *et al*. (2001) evaluated correlations among five measures of use. From patient-specific antimicrobial use data collected from 1992–9 in seven ICUs, the combined ICU, the non-ICU area, and hospital-wide data, the following aggregate measures of use were calculated for 34 antimicrobials: grams, grams/patient-day, DDD/1,000 patient-days, days of antibiotic therapy, and the mean daily dose. Using DDD/1,000 patient-days as a standard, the correlation of the other measures to DDD/1,000 patient-days was assessed. In all instances, grams, grams/patient-day, and days of antibiotic therapy were positively correlated with DDD/1,000 patient-days. Since DDD calculations are

derived from grams and then normalized for patient-days, the correlation between DDD/1,000 patient-days and grams/patient-day was 1.00. Similarly, with grams, although not normalized to patient-days, the correlation with DDD/1,000 patient-days was high ($r = 0.8-1.0$) with only 3% of correlations with $r < 0.9$. Days of antibiotic therapy were not as highly correlated to DDD/1,000 patient-days ($r = 0.23-0.99$); however, only 7% of the correlations were lower than 0.7. Correlations between the mean daily dose and DDD/1,000 patient-days were poor and were negatively correlated in 33% of the comparisons.

The relationship between four different measures of antimicrobial use and percentage susceptibility were evaluated using 10 years of data in a large teaching hospital. Enzweiler *et al*. (2002a) evaluated 32 antimicrobials with 7 Gram-positive and 8 Gram-negative organisms. From patient-specific antimicrobial use data, the following aggregate use measures were evaluated: grams/1,000 patient-days, days of antibiotic therapy/1,000 patient-days, DDD/1,000 patient-days, and the mean daily dose. Relationships between each of these measures of use and hospital-wide percentage susceptibility calculated on a quarterly, semi-annual, and an annual basis were assessed by linear regression. Only relationships with $R^2 \geq 0.5$ were further analyzed. Using relationships with DDD/1,000 patient-days as a standard and the slope of the regression line as the basis for agreement, there was agreement of the four measures with DDD/1,000 patient-days in less than 50% of the relationships assessed. With both grams/1,000 patient-days and days of antibiotic therapy/1,000 patient-days, there was good agreement with DDD/1,000 patient-days (100% and 77% of occurrences, respectively); however, the mean daily dose agreed poorly with DDD/1,000 patient-days (44% of occurrences).

Johnson *et al*. (2002b) examined the relationships between aggregate fluoroquinolone use in communities surrounding 35 hospitals in a surveillance network with the prevalence of ciprofloxacin-resistant *P. aeruginosa* in 1999 and 2000. Antimicrobial use measures included prescriptions/1,000 population, total grams/1,000 population, and DDD/1,000 population. Significant linear relationships were found using only DDD/1,000 population for total fluoroquinolone use ($R^2 = 0.25$, $p = 0.02$) and levofloxacin use ($R^2 = 0.33$, $p = 0.01$) in 1999 and levofloxacin use ($R^2 = 0.17$, $p = 0.04$) in 2000. Although this study did not directly compare the measures of use, only DDD/1,000 population was found to correlate with resistance.

In a hospital surveillance network, Polk *et al*. (2002) evaluated the relationship between fluoroquinolone use and the prevalence of ciprofloxacin-resistant *P. aeruginosa*. Linear regression was used to assess the relationship between use and resistance. Antimicrobial use, expressed as DDD/1,000 patient-days, was more strongly associated with resistance ($R^2 = 0.486$, $p < 0.001$) than were grams/1,000 patient-days ($R^2 = 0.237$, $p = 0.017$).

In a large teaching hospital, Burgess and Jones (2002) examined biannual drug usage data from 1998–2001 in 12 hospital units for 18 antibiotics and 6 organisms. Linear regression was used to assess relationships between antimicrobial use and percentage susceptibility. Antimicrobial use measures for each drug included: total milligrams, total milligrams/patient-day, DDD, and DDD/1,000 patient-day. Clinically relevant relationships were defined as having an R value of greater than 0.7 with greater than 70% susceptibility. Using these criteria, there were 143 clinically relevant relationships using total milligrams, 136 using DDD, 138 using total milligram/patient-day, and 141 using DDD/1,000 patient-days. In 47% of occurrences, clinically significant relationships were found by all four measures of use.

6. SUMMARY AND RECOMMENDATIONS

It is evident from the comparisons of the antimicrobial use measures discussed above, that several measures are highly correlated. Since DDD calculations are derived from grams, it is not surprising that there is a high degree of covariance among these measures when a specific antimicrobial is evaluated. However, the advantage of the DDD calculation over the use of grams is the ability to calculate antimicrobial use within a drug class, a patient-care area, an institution, a region, or a country. With regard to normalization of data use of patient-days or inhabitant days, may help to establish the true rate of antimicrobial use.

In several of the reports described above, the mean daily dose, the number of days of antimicrobial therapy, grams, and DDDs were compared. Grams and thus DDDs, since they are derived from grams, should be considered hybrid measures of antimicrobial use since they may be calculated from the dose, the dosing interval (comprising the daily dose), and the number of days of antimicrobial therapy. Although it seems intuitive that one would want to use a measure that was derived from both drug dose intensity (daily dose) and the length of therapy, it is very plausible that, with some antimicrobial/organism combinations, one of the measures, daily dose, or length of therapy may be more closely associated with the development of resistance than the other. In that scenario, use of a hybrid measure such as grams or DDDs could potentially mask these relationships. In the reports above, the mean daily dose consistently disagreed with other measures. This is likely due to the amount of relative influence that the daily dose and length of therapy (or days of antibiotic therapy) have on the calculation of total grams. Since the number of days that a patient receives an antimicrobial usually numerically exceeds the daily dose, it should be expected that days of therapy would be in closer agreement with grams and DDDs than would the mean daily dose.

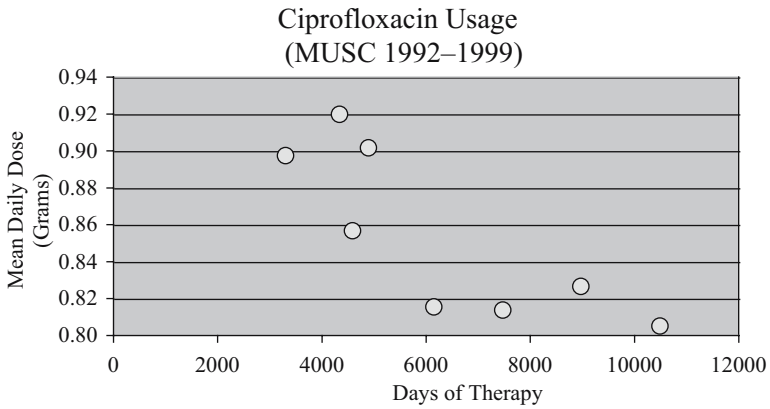

Figure 5. Relationship between total days of therapy with ciprofloxacin and the mean daily dose of ciprofloxacin using 8 years of data at a large teaching hospital (White, 2002).

Interestingly, for some antimicrobials, the correlation between the mean daily dose and days of therapy may be inversely related (White, 2002; Figure 5). This is what one might expect with an antimicrobial in which efficacy is related to dose intensity and thus the area under the serum concentration–time curve (AUC)/MIC relationship (Craig and Andes, 1996). Importantly, it may suggest a relationship that clinicians can manipulate to reduce the length of antimicrobial therapy. Relationships such as this would go undetected if only hybrid measures were analyzed. Therefore, it would be prudent to continue to evaluate these measures as separate entities while also evaluating hybrid measures such as the DDD. Ultimately, the ideal marker may be either direct measurement or an estimate of drug exposure (e.g., AUC).

The ideal marker(s) of antimicrobial use will be selected on the basis of the relative strength of the relationships between various markers and development of resistance. To determine this, improvements in antimicrobial usage data collection and additional research are required. It is likely that no single marker will be optimal for all purposes and may depend on whether one uses it for surveillance of a specific antimicrobial or comparisons with other antimicrobials and whether associations with toxicity or changes in susceptibility are being investigated.

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