Measuring Antimicrobial Use: The Way Forward

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(See the article by Polk et al. on pages 664–70)

In 1991, Gerding et al. [1] published the results of their 10-year experience with aminoglycoside use and emergence of aminoglycoside resistance at the Minneapolis Veterans Affairs Medical Center. In this study on the relationship between antimicrobial use and bacterial resistance, consumption data were obtained from pharmacy records and reported as the number of patient-days (of antimicrobial use) per quarter. During about the same time in Europe, hospitals started to report similar data, but they chose to express antimicrobial use as a number of defined daily doses (DDDs) controlled for the population at risk of receiving antimicrobials (e.g., per 100 occupied bed-days or patient-days) [2–4].

The DDD is a measurement unit that was developed by Norwegian researchers together with the Nordic Council on Medicines (Uppsala, Sweden) and was first used in a report in 1976 [5]. The DDD is the assumed average maintenance dose per day for a drug in its main indication for adults. It is a measurement unit to be used during drug use studies and does not necessarily reflect the recommended or prescribed daily dose for individual patients or specific patient groups. Norwegian researchers also developed an Anatomical Therapeutic Chemical (ATC) classification for medicines by modifying and extending the European Pharmaceutical Market Research Association classification system [5].

In 1981, the World Health Organization (WHO) regional office for Europe recommended the ATC/DDD system for international drug use studies. To coordinate activities in the field, a WHO Collaborating Centre for Drug Statistics Methodology was established in Oslo in 1982. Applications for additions or modifications of ATC codes and DDDs are made by users of the system to the WHO Collaborating Centre. These applications are submitted by the WHO Collaborating Centre to a WHO International Working Group for Drug Statistics Methodology, established in 1996, which is in charge of maintaining the ATC/DDD system. The 12 members of this group are experts appointed by the WHO headquarters to represent a wide range of professional backgrounds and the 6 WHO global regions. Extensive information on the ATC/DDD system is available at the WHO Collaborating Centre Web site [5].

Once aware of the DDD methodology, researchers in the United States quickly adopted the DDDs to report hospital antimicrobial use data [6–9]. However, these researchers omitted the fact that, for each antimicrobial, the DDD is a WHO-assigned, international measurement unit, rather than just a methodology to adjust for differences in daily dosages between various antimicrobials when calculating antimicrobial use. This unfortunately led to different “DDDs” being used in Europe and the United States.

Availability of the ATC classification and the DDD definitions without charge on the WHO Collaborating Centre Internet home page [10] and a free tool for calculating antimicrobial use [11] have increased awareness about the ATC/DDD system. The WHO-assigned DDDs were used for most of the recent international or multicenter surveillance studies, both in Europe and in the United States, as well as in Australia [12–18]. The Infectious Diseases Society of America Practice Guideline on antimicrobial stewardship recommends monitoring antimicrobial use by the number of DDDs [19]. Although increased awareness and endorsement of the WHO-assigned DDDs contribute to standardization—and, therefore, comparability—of the reported rates, they also emphasize the limitations of this measurement unit, especially for antimicrobial use in hospitals.

In this issue of Clinical Infectious Diseases, Polk et al. [20] discuss the limitations of the WHO-assigned DDDs and report on discrepancies between these DDDs and the number of days of therapy, which they obtained from patient records. As correctly mentioned by Polk and col-
leagues, many other articles have recently reported or commented on discrepancies between the WHO-assigned DDDs and the doses actually used to treat patients in hospitals [21–29]. The originality of the study by Polk and colleagues was that the analysis was performed on the basis of data from a network of hospitals rather than of data from single institutions. Another limitation of the WHO-assigned DDDs is that they do not exist for every marketed antibiotic, and established surveillance systems, such as the Antimicrobial Use and Resistance component of the National Healthcare Safety Network (formerly NNIS System) [16] or the European Surveillance of Antimicrobial Consumption [13], devised their own “DDDs” for antimicrobials that did not have a WHO-assigned DDD.

The days of therapy methodology proposed by Polk et al. [20] represents an attractive alternative to the DDD methodology and may be the progressive method of study of the relationship between antimicrobial use and resistance. However, days of therapy can only be calculated in institutions that have access to pharmacy data at the patient level. Although this is the case in most US hospitals and in some European hospitals, such data are still rare in Europe and probably even rarer in other parts of the world. Achieving worldwide comparability of antimicrobial-use rates requires a methodology that can be used by all hospitals.

Such a methodology is already in place, and the ATC/DDD system should only require adjustments of the WHO-assigned DDDs; thus, it can reliably be used worldwide, in hospitals, as well as for outpatients. Updates and assignments of new DDDs are based on the proposals of users of the ATC/DDD system to the WHO Collaborating Centre for Drug Statistics Methodology. The way forward—and our responsibility and challenge for the coming years—therefore, is to support and advise the WHO Collaborating Centre in its efforts for maintaining an international system for measuring drug use.

Judging from the recent literature [20–29], many DDD revisions are needed for antimicrobials and because of the global implications of these revisions, advising the WHO Collaborating Centre may require an intermediate step in the form of an international consensus conference. The resulting consensus proposals for revisions of DDDs should then be submitted for approval to the WHO International Working Group for Drug Statistics Methodology via its official application process [5].

Despite more than 20 years of experience, I concur with Polk et al. [20] that antimicrobial use surveillance and research still is in its infancy. In addition to the evaluation and possible revision of the DDDs, research is needed to solve other issues, such as the measurement of antimicrobial use in pediatric wards when patient-level data are not available [30], or to choose a proper denominator for reporting antimicrobial use rates in hospitals [22, 31]. The measurement of antimicrobial use will never replace antimicrobial prescription audits, and we may never identify the best method for measuring antimicrobial use, but we will hopefully succeed in identifying a set of reliable and standardized indicators to be used for various situations, depending on available data.

Acknowledgments


References

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