CONCISE COMMUNICATION

Lack of Significant Variability among Different Methods for Calculating Antimicrobial Days of Therapy

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Days of therapy (DOTs) are an important measure to quantify antimicrobial use but may not reflect patients' true antimicrobial exposure. Three methods of calculating DOTs were compared to determine whether including "exposure days," when antimicrobials are given less frequently than daily due to renal dysfunction, makes a difference.

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Quantifying antimicrobial use in the hospital setting is an essential component of antimicrobial stewardship. This is due to the association between antimicrobial use and development of resistance and the need for stewardship programs to measure outcomes.[1,2] In recent years, the day of therapy (DOT) has become the preferred measure for aggregate antimicrobial use over the defined daily dose (DDD), because it is more applicable to different populations (adults and pediatrics), less likely to be affected by different dosing schemes, and more applicable to benchmarking.[3] The DOT measures aggregate antimicrobial use by counting each day an antimicrobial was administered to a patient as 1 DOT regardless of dose. However, when renal dysfunction necessitates dosing less frequently than daily, the current DOT measure may not accurately reflect true antimicrobial exposure.

The optimal way to quantify antimicrobial exposure has not been determined. For agents such as ceftriaxone that do not require dose adjustments for organ dysfunction, DOTs equal the number of days on which the drug was administered. However, for agents like levofloxacin that may be dosed every other day or for aminoglycosides or vancomycin that may be dosed even less frequently (every 3–4 days) based on drug levels, calculating DOTs solely on the basis of the number of days on which the drug was administered may not reflect patients' true exposure. Despite not receiving doses on certain days, drug levels may persist and perhaps should count as exposure days (ExDs). If these ExDs are not included when calculating DOTs, then the full impact of antimicrobial exposure on resistance may be underestimated. We performed an analysis of 3 methods for calculating DOTs to assess the impact of ExDs for different antimicrobials and populations.

METHODS

DOTs were measured for antimicrobials dispensed to all adult inpatients at a large (700 bed) academic medical center in New York City, with 5 intensive care units (ICUs, 130 beds) and a considerable solid organ transplant population.

Antimicrobial use provided as doses dispensed for each patient was obtained from pharmacy billing data and included credited doses. Individual patient records were obtained for admissions in 2009 and 2010 and were organized into 3 groups: all locations, ICUs, and non-ICU locations. Five antimicrobials were analyzed based on differing frequency of use and need for dosage adjustment based on renal impairment: ceftriaxone, piperacillin/tazobactam, levofloxacin, tobramycin, and vancomycin (intravenous only).

Data were used to determine total DOTs, total number of antimicrobial courses, and mean duration of therapy. Receiving at least 1 dose of an antimicrobial on a single day was considered 1 DOT.[3] Courses of therapy were determined by start and stop dates. Mean duration of therapy was calculated as the mean number of DOTs per course.

Three methods for calculating DOTs and courses were used. For the "0-day" method, only the actual days on which a patient received an antimicrobial were counted (traditional DOT), and no days were allowed between start and stop dates to be considered a continued course. Two additional methods were used in which ExDs were included in the DOT calculations. For the "2-day" method, an antimicrobial could be stopped and restarted within 2 days to be considered a continued course, and days in between were included as ExDs. For the "custom" method, each antimicrobial was assigned a different allowable "off" time (by adding 1 day to the least frequent dosing interval recommended by institutional dosing guidelines) to be considered a continued course, as follows: levofloxacin, 3 days; tobramycin, 4 days; vancomycin, 4 days; and all others, 2 days.[4] Again, days in between were counted as ExDs and were included in the DOT calculations. Thus, based on the drug, DOTs may be greater for the custom method than for the 2-day method, which in turn may be greater than the 0-day method. Conversely, the fewest number of courses would be expected for the custom method and the greatest number of courses for the 0-day method. Negative binomial regression models were used to compare the differences between the 3 methods regarding calculated DOTs, number of courses, and mean duration (mean days per course). These comparisons were also performed separately according to antimicrobial and the 3 different location types. All statistical analyses were performed with SAS, version 9.3 (SAS).

RESULTS

As expected, for ceftriaxone and piperacillin-tazobactam, the number of DOTs and courses were similar between the 3 methods, as were the mean days per course; DOTs varied by 1% or less between methods (see Table 1). The same was true for levofloxacin, which can be administered as infrequently as every other day. For tobramycin, however, DOTs differed

TABLE 1. Days of Therapy (DOTs), Courses of Therapy, and Mean Duration of Therapy (DOTs per Course) Using 3 Different Methods

	0-Day method			2-Day method			Custom method		
Group, antimicrobial	Total DOTs	Total courses	DOTs/ course	Total DOTs	Total courses	DOTs/ course	Total DOTs	Total courses	DOTs/ course
All									
Ceftriaxone	15,201	3,699	4.1	15,238	3,662	4.2	15,238	3,662	4.2
Levofloxacin IV	11,641	2,544	4.6	11,709	2,477	4.7	11,773	2,445	4.8
Levofloxacin PO	6,941	1,670	4.2	6,967	1,644	4.2	6,987	1,634	4.3
Piperacillin-tazobactam	55,671	11,423	4.9	55,930	11,164	5.0	55,930	11,164	5.0
Tobramycin	12,150	3,590	3.4	12,511	3,229	3.9	12,934	3,050	4.2
Vancomycin IV	49,950	12,913	3.9	51,213	11,652	4.4	53,324	10,761	5.0
Total	155,167	36,985	4.2	157,241	34,914	4.5	159,859	33,802	4.7
ICU									
Ceftriaxone	1,961	562	3.5	1,962	561	3.5	1,962	561	3.5
Levofloxacin IV	4,432	943	4.7	4,461	914	4.9	4,483	903	5.0
Levofloxacin PO	559	156	3.6	561	154	3.6	561	154	3.6
Piperacillin-tazobactam	12,925	2,979	4.3	12,987	2,917	4.5	12,987	2,917	4.5
Tobramycin	5,706	2,091	2.7	5,950	1,847	3.2	6,248	1,723	3.6
Vancomycin IV	18,497	5,206	3.6	19,045	4,658	4.1	19,835	4,328	4.6
Total	44,850	12,177	3.7	45,753	11,274	4.1	46,863	10,809	4.3
Non-ICU									
Ceftriaxone	13,366	3,274	4.1	13,399	3,241	4.1	13,399	3,241	4.1
Levofloxacin IV	7,390	1,784	4.1	7,421	1,754	4.2	7,455	1,737	4.3
Levofloxacin PO	6,414	1,548	4.1	6,439	1,523	4.2	6,457	1,514	4.3
Piperacillin-tazobactam	43,570	9,260	4.7	43,745	9,085	4.8	43,745	9,085	4.8
Tobramycin	6,593	1,727	3.8	6,692	1,628	4.1	6,794	1,583	4.3
Vancomycin IV	32,379	8,873	3.6	32,990	8,264	4.0	34,155	7,770	4.4
Total	112,607	27,430	4.1	113,624	26,416	4.3	114,943	25,851	4.4

NOTE. ICU, intensive care unit; IV, intravenous; PO, per os (by mouth).

by 361 days (3%) between the 0-day and the 2-day method and by 784 days (6.5%) between the 0-day and the custom method. For vancomycin, DOTs differed by 1,263 days (2.5%) between the 0-day and 2-day method and by 3,374 days (6.8%) between the 0-day and custom method. Overall, as expected, DOTs were highest for the custom method as it includes the most ExDs and "lowest" for the 0 day method which includes days of administration only. For both tobramycin and vancomycin, relative differences between methods were most apparent in ICU patients; there was a 9.5% and 7.2% difference in DOTs, respectively, comparing the 0-day and custom methods. Nonetheless, *P*-values for all comparisons were >.8, demonstrating no significant differences using the 3 methods. Similarly, there were no significant differences between number of courses or mean days per course.

DISCUSSION

To our knowledge, this is the first study in which different methods for calculating antimicrobial DOTs were compared. Although the traditional DOT measure was created to capture antimicrobial use, we felt that it was essential to investigate the issue of ExDs and whether they should be included in DOT calculations, because it is ultimately the degree of antimicrobial exposure that leads to resistance.[3] In a previous study, Zagorski and colleagues addressed the same issue but used "stop-start days" (including all days between the first and last day of administration for a given antimicrobial), which would likely lead to greater overestimation of use than our 2-day and custom methods.[5]

Ultimately, we found no significant differences between the 3 different methods of calculating DOTs and courses. We did find, however, that the relative impact of using the 2-day or custom method was greater for ICU patients. Thus, it is possible that for subpopulations where renal dysfunction may be more common, a 2-day or custom method may provide a more accurate measurement of antimicrobial exposure by including ExDs. One could argue that as long as a consistent approach such as the traditional DOT measure is chosen, stewardship programs can accurately track changes in antimicrobial use over time. However, DOTs might fluctuate over time if the proportion of patients with significant renal dysfunction varies. Furthermore, the future possibility of benchmarking between institutions could be affected by relatively different proportions of patients with renal dysfunction or on dialysis. Although our data suggest that the traditional DOT measure is adequate and calculation rules to account for ExDs are not necessary, comparisons should be performed in a variety of different settings before final conclusions are

drawn, and benchmarking between different settings and populations must be performed with caution.

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