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Antimicrobial Stewardship (M Stevens, Section Editor)

Basic, Advanced, and Novel Metrics to Guide Antibiotic Use Assessments

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Abstract

Purpose of review This review illustrates relevant and current antibiotic use (AU) metrics and demonstrates their differences. The authors also highlight novel, increasingly complex AU metrics proposed for use in antibiotic stewardship research.
Recent findings Many common antibiotic use metrics (e.g., days of therapy, length of therapy) are well defined, widely generalizable, and commonly used by antimicrobial stewardship programs. Multiple measures are required to comprehensively capture real-world AU, though utilization metrics often lack important contextual information needed to inform antibiotic stewardship strategy. Combining standard AU metrics with meaningful characterization of antibiotic prescriptions, including appropriateness of therapy or antibiotic spectrum, provides important information for developing strategy.
Summary Current antibiotic use metrics are limited by an inability to convey meaningful context. Future research should aim to define generalizable measures that illustrate improved prescribing in addition to volume of use.

Introduction

At the core of antibiotic stewardship lies an inherently unique problem. The goal of antibiotic stewardship programs (ASPs) is to improve antibiotic use (AU), which may include either reductions in antibiotics for patients who do not require them or increases for those who need them. ASPs cannot, and should not, strive towards "zero" AU when measuring over large populations of patients. Clinical outcome measures are important and

highly relevant but often difficult to assess. Adverse drug effects and antibiotic resistance are either rare events or occur slowly over time [1, 2]. Thus, measures of antibiotic utilization are commonly reported as indicators of success for antibiotic stewardship interventions [3].

Antibiotic utilization assessments help stewards understand local antibiotic prescription patterns, assess interventions, and benchmark between facilities [4–7]. Recommended AU metrics for inpatient ASPs include utilization rates that describe volume of antibiotics used (numerators) over person time (denominators) [8]. No single metric, however, can comprehensively represent all aspects of antibiotic decisions, which require nuanced, complex clinical decision-making, and dynamic changes over the course of therapy [9]. Simple calculations of AU do not fully convey critical principles of antibiotic stewardship—the right drug, for the right patient, in the right amount, for the right period of time [10, 11]. In this review, we present the basics of AU metrics within the framework of rates or prevalence. Then, we discuss advanced and novel methods to capture aspects of antibiotic decision-making important to antibiotic stewards.

Utilization rates and prevalence: basic

Utilization rates: numerators

Antibiotic utilization metrics were first developed over four decades ago when data sources were relatively few and estimates of utilization were calculated by simple measures [12]. The first standardized measure of antibiotic utilization was the defined daily dose (DDD), developed by the World Health Organization (WHO) in the 1970s [12]. DDD is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults" [13]. DDD was adopted in Europe in the early 1980s and recommended by the WHO for global use by the late 1990s. DDD is still commonly used in many European countries and by healthcare organizations with limited electronic health record infrastructure [14]. Calculating DDD does not require granular, patient-level data that is only available through electronic medication administration records (eMARs). The WHO continues to promote DDD as the primary AU metric due its simplicity and data accessibility across the spectrum of high and low resource institutions.

However, DDD is an imperfect antibiotic utilization metric if the goal is to define days of antibiotic exposure [15]. By definition, DDD assumes adult dosing for a specific antibiotic and indication and ignores patient level factors that frequently influence dose size or timing. For example, a patient with end-stage renal disease receiving cefazolin 1 g every 24 h will count as one-third DDD per day (1 g over the 3 g reference standard for cefazolin) whereas a patient with normal renal function receiving 2 g every 8 h will count as 2 DDD per day (6 g/3 g). In addition, the assumed dosing standard is insufficient for pediatric patients and suffers when prescribing standards are different between institutions. Discrepancies between DDD and antibiotic treatment days are worse for agents with frequent dosing schedules (e.g., a patient treated with ampicillin-sulbactam may receive over four times the reference DDD for ampicillin) [16, 17]. Importantly, the source of AU data also plays a significant role in the discrepancy, exemplified by Dalton et al. who compared DDD calculated from nursing administration records to DDD derived from pharmacy dispense data and found a 23% lower utilization rate [18].

Fortunately, the development of eMARs allowed for detailed antibiotic administration data from which antibiotic days of therapy (DOT) can also be directly calculated. The DOT metric defines a day of therapy as any calendar day in which at least a single dose of antibiotic is received. Days of therapy are counted separately for each antibiotic agent (i.e., a patient on two different antibiotics simultaneously would count as 2 DOT on a single calendar day), which may limit comparisons of broad-spectrum monotherapy versus combination therapy. Despite this limitation, DOT is the preferred metric over DDD according to joint Infectious Disease Society of America (IDSA) and Society for Healthcare Epidemiology (SHEA) guidelines and expert consensus [8, 19, 20]. DOT does not suffer from the same dose adjustment limitations as DDD, and there is less discrepancy between antibiotic agents [16]. DOT is required in the National Health Safety Network (NHSN) AU option for reporting and tracking antibiotic use [21]. DOT calculation requires electronic medication administration records which may be prohibitive in institutions that do not have access to robust data infrastructure and resources. Ultimately, both DDD and DOT metrics provide valuable means of analyzing AU and should be employed depending on local resources and data collection capabilities, with preference for DOT where able.

Utilization rates: denominators

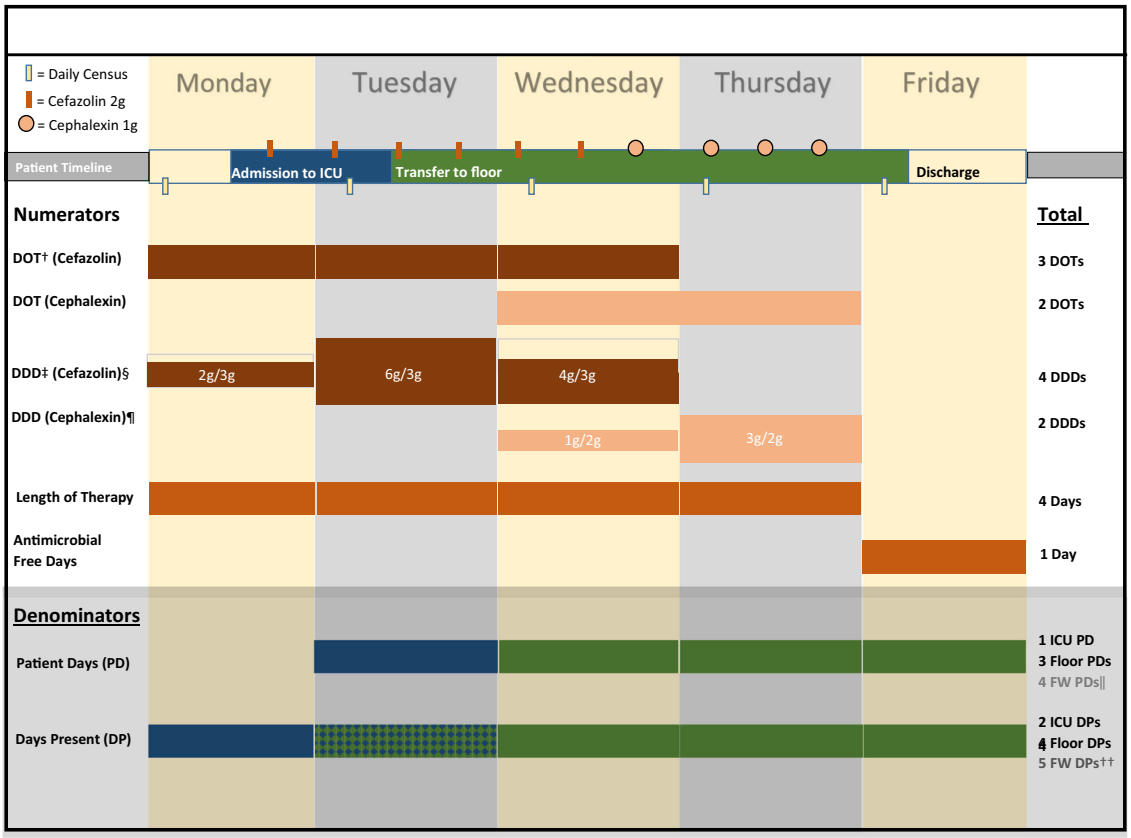
A carefully chosen utilization denominator is required to meaningfully interpret AU data over wide populations of patients. The purpose of the rate denominator is to calculate "time at risk" for antibiotic exposure. Utilization rates are then presented as DOT (or DDD) per 1000 days at risk in order to account for variable volumes of time at risk when comparing rates over time or among differing locations or facilities. For most inpatient ASPs, the targeted population for analysis includes all hospitalized patients. Currently, the most commonly used denominator to capture time at risk and patient volume is patient days. Patient days are calculated by a manual or electronic daily census that measures the total number of occupied beds on inpatient wards per calendar day. Unfortunately, in its simplicity, this measure can be subject to error due to complex bed movement or partial days of exposure. Time at risk may not be captured if a patient was not present on a specific ward at the time of the census count; however, they might be captured in the numerator of days of therapy if at least one dose was given during that partial day. For infrequent events, such as healthcare-associated infections, this potential error does not have a large effect. Antibiotic administration events, however, are very frequent, thus more potential for measurement error. This potential for numerator/denominator mismatch was the rationale for developing a new denominator specifically for AU rates: days present.

Days present, also referred to as "patient days present," was developed specifically for the Centers for Disease Control (CDC) NHSN AU option, which aimed to capture unit- and facility- level estimates of antibiotic exposure for the purposes of surveillance and benchmarking [21]. A single day present counts for a location if any amount of time in a calendar day is spent by a patient in that location [22]. Days present counts will always be equal to or greater than patient days counts, because an additional partial day is

counted at either the end or beginning of the stay. While days present remove the possibility that person time at risk will be missed, it can lead to confusion in counts of partial calendar days attributed to a location. For example, if a patient moves from an ICU to a ward within a single calendar day, 2 days present will be counted in unit-level counts: one for the ICU and one for the ward. In facility-wide days present counts, however this transfer day would only be counted as a single day. Days present cannot be summed across units to obtain the count for facility-wide days present, unlike patient days counts which attributes a single calendar day to only one unit (Fig. 1) [22]. Consistency in denominator use is essential for meaningful comparisons of AU between institutions and units.

Prevalence of antibiotic exposures

Instead of rates that use denominators of person time, an alternative measure calculates antibiotic exposure per admission or per patient, referred to as prevalence. Antibiotic prevalence is generally obtained by survey assessments and defined as the number of patients receiving antimicrobials (or a specific agent or



† DOT = Days of Therapy
‡ DDD = Defined Daily Dose
§ World Health Organization DDD Index reference for cefazolin is 3g per day
¶ World Health Organization DDD Index reference for cephalexin is 2g per day
‖ Facility Wide Patient Days – Additive across unit patient days
†† Facility Wide Days Present – Not additive across unit days present

Fig. 1. Example comparison of antibiotic utilization metrics.

class) divided by the total number of surveyed patients. The advantage of using antibiotic prevalence measures is their interpretability. Clinicians think of impacts on "whole" patients; thus, a prevalence measure can provide greater influence for those without training in standard stewardship AU metrics, which includes clinical audiences, hospital leadership, and the wider public. Point-prevalence measurements are also useful for large-scale epidemiologic evaluations aiming to call attention to public health concerns, such as those conducted by the CDC's Emerging Infections Program (EIP) or the Australian National Antimicrobial Prescribing Survey (NAPS) [23–26]. For example, when outlining the impact of antibiotic stewardship, presenting the fact that 60% of hospitalized patients are antibiotic-exposed may have more impact on hospital leadership decision-making than presenting a measure of 800 antibiotic days per 1000 patient days.

Utilization metrics: advanced

Antibiotic duration

A key goal for many ASPs is to promote shorter durations of antibiotic therapy when clinically appropriate. Length of therapy (LOT), also referred to as antibiotic duration, can be captured for hospitalized patients with the same eMAR datasets as DOT. LOT is defined as the number of calendar days of antibiotic therapy regardless of the number of agents used (Fig. 1) [27]. LOT is equal to DOT when calculated for individual antibiotics (e.g., vancomycin). When applied to a class, group, or all antibiotics, LOT can assess durations of therapy when there are switches within that group (see example of cefazolin and cephalexin in Fig. 1). LOT is useful when evaluating antibiotic prescribing in patient admission-level assessments and specific syndromes.

Another method to show the impact of ASP initiatives focused on shorter antibiotic durations is the inverse of LOT: antimicrobial-free days. This is the count of hospital days where patients received no antibiotics, and has been used as an outcome in syndrome-specific trials focused on antibiotic duration [28, 29]. Chastre et al. used antimicrobial free days as a primary outcome when studying 8- versus 15-day therapy for ventilator-associated pneumonia. Antibiotic-free days were simpler to report among patients that received complicated courses of antibiotics over the 28-day follow-up period, whereas length of therapy would be difficult to define [28].

Days of therapy avoided (DOTA) attempts to quantify the direct impact of ASP interventions in avoiding antibiotic exposures [30]. DOTA estimates the difference between the initial planned antibiotic days and the antibiotic days after prospective audit and feedback. This estimate was promoted to measure cost savings attributable to stewardship intervention by using the average wholesale price per day of antibiotics and multiplying by DOTA. However, DOTA can be time intensive to calculate as users must estimate the originally planned duration and then input cost information for each prospective audit and feedback event. Further, the value of days of therapy avoided goes beyond pharmacy acquisition costs.

The antibiotic durations metrics described above are limited to the inpatient setting. The total duration of antibiotic therapy can be interrupted by hospital discharge for many inpatients, after which prescribing data must come from a source other than eMARs. Prior studies have indicated that up to two-thirds of antibiotic courses for common infections are completed outpatient and up to 40% of total antibiotic days occur post-discharge [31, 32]. Stewardship

interventions that target total durations of therapy require accurate measurements of AU occurring post-discharge. To date, estimates of post-discharge duration have largely come from chart review of discharge prescriptions or electronic prescriptions orders data, which both have feasibility limitations [33•]. Further, discharge prescriptions duration counts capture the "intended" days of antibiotic therapy, but assume patient adherence. Despite the feasibility barriers in capturing post-discharge antibiotic days, these data are important to understand the full impact of decisions made and attributable to the inpatient stay. Thus, total duration, rather than inpatient duration, may be more meaningful to stewards and clinicians working to improve antibiotic management decisions.

Class switching and squeezing the balloon

Analyses of antibiotic use often require assessments of both targeted agents and agents that not targeted by an intervention. The "squeezing of the balloon" effect has been well described in response to stewardship interventions focused on reducing use of specific agents or classes of antibiotics [34–36]. Aldeyab et al. identified low prescribing rates of cephalosporins and fluoroquinolones after institutional restriction, yet also noted a relative increase in penicillin plus beta-lactamase antibiotics [37]. Thus, tracking non-targeted antibiotic agents is important for understanding unintended consequence of stewardship interventions.

Interventions may also impact the use of single agents versus combination therapies and may raise DOT measures, such as recommending avoidance of fluoroquinolones in favor of a cephalosporin plus a macrolide for CAP. Thus, alternative AU metrics used as adjuncts to overall or agent-specific DOT rates may be necessary to fully represent the impact or intent of the intervention. If the goal of the intervention was to target duration regardless of the number of agents, LOT may be more appropriate than DOT. Also, trending the ratio of DOT/LOT over time may better illustrate whether DOT rate increases were a result of combination therapies or other factors [27].

In some scenarios, class switching or squeezing of the balloon may occur after discharge. For example, many inpatient ASPs promote avoidance of fluoroquinolones in response to emerging safety data and *C. difficile*. However, clinicians may switch from inpatient therapy to a fluoroquinolone for discharge due to dosing simplicity, despite the safety risks [33•, 38•]. Inpatient ASPs that only focus on inpatient AU and do not quantify post-discharge antibiotic exposures would miss important opportunities to impact antibiotic decisions made at transitions of care.

Benchmarking antibiotic use

Comparing rates of antibiotic use among different facilities or hospital units has the potential to help ASPs understand patterns of use within their facility and identify targets for intervention. These external comparisons, also known as benchmarks, can identify facilities or units with "different" AU rates compared to a standard population of pooled data. Importantly, they do not measure appropriate or inappropriate AU and thus serve to identify AU patterns that warrant local investigation for possible stewardship intervention. The known challenges in providing adequate risk-adjustment for benchmarked AU comparisons make these comparisons inappropriate for public reporting, regulatory

programs, or pay for performance [39].

The CDC developed the standardized antimicrobial administration ratio (SAAR) to provide risk-adjusted benchmark comparisons to a national standard AU dataset [40, 41]. The NHSN AU Option receives voluntarily reported, monthly estimates of unit and facility-wide antibiotic utilization for selected antimicrobials in days of therapy with denominators of days present [42]. The SAAR "calculates the ratio of observed antibiotic use to predicted antibiotic use, based on modeled data from all reporting hospitals and allows hospitals to compare their antibiotic use with similar facilities" [22]. SAAR models include a limited number of risk-adjustment variables self-reported through the NHSN annual survey. SAAR output can provide benchmarks for facility-wide AU estimates or specific units including selected location types. In December 2018, the SAAR baseline population was updated to include 2017 annualized data, which included a larger sample of hospitals than the 2014 baseline. The larger dataset allowed NHSN to expand the types of locations for which benchmarks were available (Table 1). Antibiotic agent groups were updated to provide distinct adult and pediatric groups and new categories were added. Given these additions, the number of unit-specific and SAAR group-specific benchmarks available for local comparisons more than doubled.

Many facilities have established data repositories to compare AU rate estimates within healthcare systems and collaborative groups to motivate improvements in stewardship [16, 43, 44]. However, the ability to provide robust, risk-adjusted estimates based on patient case mix is limited. If available, risk-adjustments are likely inadequate to fully account for non-modifiable differences in patient populations among facilities [4]. Thus, risk-adjustment methods for AU benchmarking is an area of active investigation and development. Improvements in risk-adjusted comparisons could provide more meaningful and actionable data for local ASPs to use to guide local investigations, develop ASP strategy, and demonstrate impact [45, 46•, 47].

Utilization metrics: novel concepts

Antibiotic spectrum and de-escalation

Antibiotic spectrum is a qualitative description of the number of bacterial pathogens for which an antimicrobial regimen has activity, ranging from "broad" to "narrow." Transitioning from broad to narrow is a process called antibiotic de-escalation. The rationale for de-escalation is to avoid selective pressure that leads to acquired resistance and other negative effects, such as *C. difficile*. Standardized definitions of broad- versus narrow-spectrum agents have not yet been established. Similarly, no standard definition of antibiotic de-escalation exists [19, 48]. Prior investigators have considered de-escalation to be a reduction in antibiotic spectrum measured at two distinct time points, yet some consider de-escalation to be a comprehensive concept to include other factors in addition to spectrum: whether an agent is restricted by the ASP, non-formulary, high cost, high risk for causing adverse events, or available only in intravenous formulation. We outline several proposed definitions for defining spectrum and de-escalation to highlight differences in methods.

Multiple investigators have proposed methods of assigning scores to antibiotic agents and classes to define antibiotic spectrum (Table 2). Most investigations focused on treatment for pneumonia and intensive care unit patients [48,

Table 1. Summary of changes from 2014 to 2017 Baseline National Healthcare Safety Network Standardized Antimicrobial Administration Ratio (SAAR) methods (References: Van Santen et al. CID; NHSN AUR Team December Quarterly AU Users Call Slide Presentation. December 12, 2018)

2014 baseline SAAR methods	2017 baseline SAAR methods
Adult and pediatric units modeled together.	Adult and pediatric units modeled separately.
Baseline hospital population included 77 hospitals.	Baseline hospital population included 449 hospitals in adult models, 109 hospitals in pediatric models.
Antibiotic groups were the same for both adult and pediatric units: - Broad spectrum agents predominantly used for hospital-onset/multi-drug resistant bacteria - Broad spectrum agents predominantly used for community-acquired infection - Anti-MRSA agents - Agents predominantly used for surgical site infection prophylaxis - All antibacterial agents	Antibiotic groups were distinct for pediatric and adult SAAR models and included the following groups: - Broad spectrum antibacterial agents predominantly used for hospital-onset infections - Broad spectrum antibacterial agents predominantly used for community-acquired infections - Antibacterial agents predominantly used for resistant Gram-positive infections (e.g., MRSA) - Narrow spectrum beta-lactam agents - Antibacterial agents posing the highest risk for *C. difficile* - Antifungal agents predominantly used for invasive candidiasis - Azithromycin (pediatric models only) - All antibacterial agents
Included units were medical, surgical, or medical/surgical ICUs and wards for adult and pediatrics.	Included units were the following: - Adult: medical, surgical, and medical/surgical ICUs and wards, hematology-oncology wards, adult step-down units - Pediatric: medical and medical/surgical ICUs; medical, medical/surgical, and surgical wards
20 separate unit-specific SAARs available for comparison to local data.	44 separate unit-specific SAARs available for comparison to local data.
Risk-adjustment variables included the following:* - Location type - Interaction of location type and ICU - Total number of hospital beds - Total number of hospital ICU beds - Medical school affiliation - Location bed size	Risk-adjustment variables included those from 2014 plus the following:* - Facility type - Interaction of location type with facility type - Percentage of beds that are ICU beds (total no. of ICU beds/total no. of hospital beds) - Average hospital length of stay (total annual patient days/total annual admissions)

*Not all risk-adjustment factors were included in all SAAR group models

52]. Investigators from the Veterans Affairs (VA) developed a score which measured the microbial spectrum of antibiotic regimens for treatment of pneumonia using susceptibility data for important respiratory pathogens [53]. Spectrum scores were applied each calendar day and compared at days 2 and 4; decreased scores were considered de-escalation. Using 20 clinical vignettes, investigators validated the VA spectrum score with expert assessments of de-escalation with 86% sensitivity and 96% specificity. The spectrum score was applied to a retrospective cohort of 9319 VA patients hospitalized for healthcare-associated pneumonia. De-escalation was 28% among all patients in the cohort with variability

Table 2. Proposed antibiotic spectrum scoring systems

	Score Calculation	Range	Advantages	Disadvantages
Madaras-Kelly et al. [49] "VA Spectrum Score"	- Antibiotic susceptibility estimates for each organism converted to ordinal scale, weighted, and summed. - Includes 14 organism domains and 10 antibiotic domains.	4.0 (metronidazole) to 49.75 (tigecycline) on a possible 60-point scale.	- Robust methods used to develop score including expert panel (N = 24) and validation with clinical vignettes - Provides a tool to utilize local susceptibility data and create individualized spectrum scores for institutions - Accounts for combination therapy	- Developed to focus on empiric therapy for pneumonia and VA populations, limiting wide application across hospitalized populations. - Unable to compare a standardized score between hospitals if local susceptibility data is used. - Complex calculation and large range. - Interpretability for clinicians and hospital leaders may be limited due to complexity -Score may not correlate with local ASP policy and practice (e.g., restriction)
Gerber et al. [50] "Antibiotic Spectrum Index (ASI)"	– Points awarded to antibiotics with activity against 14 bacterial organisms or MDRO groups (e.g., ampC producers). - Points cumulative if more than one antibiotic.	1 (oxacillin) to 13 (tigecycline) on a possible 14-point scale	- Moderately easy to calculate and interpret - Generalizable across institutions and hospitalized populations (e.g., pediatric and adult, all disease states) - Accounts for combination therapy	- Bacteria of different pathogenicity or disease burden weighted equally - Does not account for local susceptibility patterns - Score may not correlate with local ASP policy and practice (e.g., restriction)
Stenehjem et al. [46•]	Antibiotics classified into 5-point ordinal scale based on antibiotic spectrum and activity against MDRO.	1 (narrow spectrum) to 5 (broad spectrum/MDRO Active)	- Easy to calculate and interpret at bedside - Could be generalizable across institutions, if there is agreement.	- Will not discriminate subtle antibiotic changes within the same category - Category definitions may not correlate with local ASP policy and practice (e.g., restriction) - Combination therapy not addressed - Does not account for local susceptibility patterns
Braykov and Morgan et al. [51]	Antibiotics ranked into 4 categories based on antibiotic spectrum, activity against MDRO,	1 (narrow spectrum) to 4 (restricted, which included carbapenems, tigecycline,	- Easy to calculate and interpret at bedside - "Restricted" category may have practical benefits for local	- Will not discriminate subtle antibiotic changes within the same category

Table 2. (Continued)

	Score Calculation	Range	Advantages	Disadvantages
	and typical ASP restriction policies.	linezolid, daptomycin)	institution if it matches local policy	- Category definitions may not correlate with local ASP policy and practice (e.g., restriction) - Highest ranked agent determines spectrum when combination therapy is used. - Does not account for local susceptibility patterns.
Kollef et al. [52]	Antibiotics ranked according to activity against gram-negative organisms, rank assigned according to most potent drug	1 (other) to 5 (carbapenem)	-Easy to calculate and interpret in context of pneumonia	- Developed specifically for ventilator associated pneumonia and gram-negative agents, limiting wide application across hospital populations. - Excludes agents with "broader" gram-positive activity (e.g., vancomycin, daptomycin) - Large number of agents fall into "other" category - Will not discriminate subtle antibiotic changes within the same category - Highest ranked agent determines spectrum when combination therapy is used.

by hospital (95% CI 22–36%) [49]. The VA spectrum score applied to both combination and monotherapy regimens with an objective, electronic definition. Limitations of this score include generalizability to clinical syndromes outside pneumonia or the VA population and complexity in computing and interpreting the score at the bedside for clinicians and stewards. The VA spectrum score also may not reflect local ASP priorities or subjective assessments of de-escalation. For example, the daptomycin spectrum score was 14.25 while trimethoprim-sulfamethoxazole was 33.5, yet daptomycin has been a targeted agent for many ASPs.

The antibiotic spectrum index (ASI) was introduced by Gerber et al. for use in benchmarking antibiotic selection patterns across hospitals [50]. ASI was defined as the count of pathogens, from a specified list, for which an antibiotic regimen was active. Multidrug-resistant pathogens were counted separately. ASI was calculated per antibiotic day, ranging 0 to 14 possible points for an

individual day, and additive if combination therapy was used on the same day. The ASI could be used to compare AU spectrum patterns of use among hospitals, or be trended over time to demonstrate the impact of an initiative. The strengths of the ASI included its application on aggregate electronic data or its relative simplicity in applying to individual patients. ASI also is not specific to any one infectious disease state and could be applied broadly across populations with differing diagnoses.

Other investigators have employed a simple, 4- to 5-point ordinal scale to identify groups of agents considered broad or narrow [46•, 51, 54]. The main advantage to a simple, ranking approach is improved interpretability of the concept for use in educating bedside clinicians and hospital leaders. Further, antibiotic rank decisions can include additional parameters important to stewards. In contrast to the VA Spectrum score, Stenehjem et al. considered daptomycin to be on the high end (rank = 5) of the scale because of its activity against multidrug resistant organisms. Simple ranking scales, however, may fail to detect subtle changes in antibiotic decision-making and thus differences between regimens may be lost. Further, decisions on antibiotic rank, if left up to expert consensus or local practice, could be difficult to standardize between facilities and health systems.

Other approaches to define antibiotic de-escalation have varied in comprehensiveness and resource investment. For example, the ASP at Henry Ford Health System evaluated the effect of a "nudge" message used in respiratory culture reports to specify the absence of MRSA and *P. aeruginosa* [55]. De-escalation events were defined as discontinuation of anti-MRSA or anti-pseudomonal agents after culture results were reported. This de-escalation definition was effective for assessing the targeted intervention, but would have limited applicability across populations of patients and syndromes. In contrast, Braykov and Morgan et al. performed a six-hospital, retrospective cohort study of 730 patients in which infectious diseases specialists evaluated cases to define de-escalation, escalation, or unchanged courses of antibiotics [51]. Similar to estimates from the VA spectrum score, 29% of patients had narrowing or discontinuation of antibiotic therapy. The limitations of such an approach are the time-intensity of chart review, requirements for expert reviewers, and introduction of subjectivity into the definition. De-escalation and spectrum remain concepts to further develop standard, objective methods of measurement before ASPs can widely use them for routine review and strategy decisions.

Antibiotic appropriateness

Antibiotic utilization metrics used in combination with measures of antibiotic appropriateness can better characterize the impact of an ASP intervention. Prior reviews have examined the complexity and difficulty of providing a standard definition of appropriateness of antibiotic therapy, which often require subjective components, expert review, and personnel investment [56, 57]. Demonstrating reduced AU may not be compelling evidence that ASP interventions improved clinical management. Thus, investigators use measures of antibiotic appropriateness to show that reductions in AU were not a result of improperly withholding antibiotics. We provide examples of analytic approaches that combine utilization with concepts of antibiotic appropriateness to illustrate this strategy.

The most robust example of surveillance for both antibiotic prevalence and appropriateness is the previously mentioned National Antimicrobial Prescribing Survey (NAPS) organized by the Australian National Centre for Antimicrobial Stewardship (NCAS) [25, 26]. The voluntary survey is performed annually and documents antibiotic agents and indications for inpatients. Auditors make assessments of appropriateness based on adherence to national guidelines in multiple domains (choice, dose, route, duration) categorized into five categories: optimal, adequate, suboptimal, inadequate, or not assessable. The key to success for this survey is the endorsement of a standardized set of national guidelines developed for the purpose of promoting antimicrobial stewardship; this is a critical achievement that other practice settings currently lack. Prevalence surveys of this scale can be challenging to organize, require personnel dedicated to administering the survey, and may require adjudication of complex cases by expert review with elements of subjectivity. These detailed data create a comprehensive and flexible method to benchmark AU and assist participating hospitals in understanding progress and opportunities in antibiotic stewardship. This understanding can then lead to meaningful development of inpatient ASP strategy both locally and nationally [58].

Antibiotic utilization assessed among highly selected populations can identify instances of inappropriate prescribing. This approach is commonly employed in the outpatient setting using electronic data, and limited to patient encounters of low complexity given the difficulty in identifying "no antibiotic needed" scenarios reliably. For example, the percent of encounters with diagnosis codes for viral upper respiratory infection receiving antibiotics can be used as a measure of performance for individual provider feedback [59••]. Data feedback, however, can result in unintended behavioral changes impacting the selection of the patient population for assessment. Prescribers may code infections differently in order to avoid assessments of AU. Therefore, denominator size must be tracked along with prescribing rates. Further, complex clinical cases are generally excluded from assessments, which may result in small, over-selected evaluable populations. These measures then become less effective at driving behavior change over large populations of patients.

Alternate measures of outpatient prescribing can assess broader populations of patients. Choice of antibiotic for a defined condition can be measured as the percent of encounters with guideline concordant antibiotics prescribed [60]. This metric does not seek 100% concordance unless the population is selected to avoid scenarios where going "off guideline" is an appropriate clinical choice. Investigators can alternatively use assessments of "comprehensive" management to assess multiple factors (choice, dose, duration) or the inverse: "imperfect" or "suboptimal" prescribing. The latter are more complex to achieve with electronically-derived definitions and subject to similar feasibility and resource challenges as described above.

Ideally, investigators combine measures of antibiotic utilization with measures of appropriateness to fully understand the effects of stewardship strategies. For example, Tamma et al. aimed to compare two core ASP strategies: post-prescription audit and feedback versus pre-prescription authorization [61••]. The primary outcome was AU in days of therapy per 1000 patient days. Secondary outcomes included assessments of local guideline concordance at day 1 and day 3. Antibiotic therapy was guideline-noncompliant in 34% and 41% of patients on days 1 and 3 in the preauthorization group and in 57% and

36% respectively in the post-prescription audit and feedback group. Ultimately, reduced antibiotic use in the post-prescription audit and feedback group was attributed to a larger impact on antibiotic duration and post-discharge antibiotic therapy. A robust understanding of how the two strategies differed in impacting antibiotic management would not have been clear had guideline concordance not been assessed along with AU rates.

Conclusion

Understanding AU is fundamental to improve patient care, prevent unnecessary harm, and combat antimicrobial resistance through antibiotic stewardship. Current metrics widely used to describe utilization patterns are well defined, though subtle nuances require careful interpretation and additional investigation for complete understanding. Current metrics do not convey important contextual information inherent to antibiotic prescribing. Prescriptions that are "too broad" or "off guideline" are difficult to define on objective scales with feasible data capture, yet measuring these events are essential for developing antibiotic stewardship strategy. Further development of unique and sophisticated metrics will be required to better capture and quantify this context.

Compliance with ethical standards

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Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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This study post-prescription review with feedback versus preauthorization was robustly designed to evaluate both antibiotic utilization and guideline concordance, answering not only whether there was an effect on antibiotic use but how it occurred.

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