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Original Article

Antibiotic spectrum coverage scoring as a potential metric for evaluating the antimicrobial stewardship team activity: a single-center study

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Abstract

Objective: Days of antibiotic spectrum coverage (days of ASC: DASC) is a metric for antibiotic usage calculated by ASC scores for spectrum and addresses limitations of days of therapy (DOT), which does not include spectrum. This study aims to investigate whether ASC-related metrics offer different aspects compared to aggregated DOT for all antibiotics (DOT_{total}) and to assess their correlation in evaluating the impact of antimicrobial stewardship team (AST) programs.

Design: Retrospective.

Setting: A single center within an 845-bed hospital.

Methods: Trends in DOT_{total}, DASC, and the DASC/DOT ratio, representing the average spectrum coverage per therapy day, were analyzed pre- and post-AST programs (April 2018) from January 2015 to December 2023, using interrupted time series analysis. Independent of the DASC/DOT, we also advocated ASC-stratified DOT (ASDOT), which facilitates comprehensive evaluation of DOT across ASC scores of <6, 6–10, and >10, representing narrow-, intermediate-, and broad-spectrum antibiotics.

Results: Among inpatients, AST programs significantly moderated the increasing trends of these metrics. Specifically, although the rates of increase in DOT_{total} and DASC were slowed or plateaued, the DASC/DOT ratio decreased ($P < 0.001$). ASDOT metrics revealed a decrease and subsequent plateau in DOT_{total} for the broad- and intermediate-spectrum antibiotics, with an increase observed for the narrow-spectrum antibiotics ($P < 0.001$ for each). DASC did not provide additional insights in the outpatient's population.

Conclusions: The study demonstrates that ASC-related metrics may yield different and useful conclusions about the effectiveness of AST programs for inpatients.

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Introduction

Antimicrobial resistance (AMR) represents an escalating global challenge, posing a significant threat to human health in the current decade.[1] To promote antimicrobial stewardship programs involving de-escalation practices, antimicrobial stewardship teams (ASTs) have been initiated.[2–5]

Antibiotic use density (AUD) and days of therapy (DOT) have emerged as prevalent metrics for monitoring antibiotic consumption from World Health Organization and the Centers for Disease Control and Prevention (CDC), respectively.[5] These metrics have been adopted nationally through the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) using the same definitions.[6] AUD's reliance on administered doses renders it susceptible to the demographic peculiarities of specific patient groups. DOT offers a dosage-independent measure of antibiotic usage, relying on a standardized dose per day. However, both AUD and DOT are not used for evaluating comprehensive appropriate antibiotic usage

Table 1. Definitions, abbreviations, and equations of metrics

Metric	Abbreviation	Definition	Equation
Days of therapy	DOT	Antibiotic therapy days for an antibiotic.	(Total number of days on which antibiotics were administered or prescribed × 1,000)/(Number of patient days in a specified month)
Aggregated days of therapy	DOT_{total}	Aggregated DOT for all antibiotics.	$\sum$(DOT), for all antibiotics
Antibiotic spectrum coverage	ASC	Antibiotic scores advocated by Kakiuchi et al.[8] (please refer to the detailed scores in Supplementary Text S1 and Table S2).	–
Days of antibiotic spectrum coverage	DASC	DOT for an antibiotic multiplied by the corresponding ASC score and aggregated, as advocated by Kakiuchi et al..[8]	$\sum$(DOT × ASC score), for all antibiotics
Ratio of DASC to aggregated DOT	DASC/DOT	ASC per therapy day, calculated by DASC divided by the aggregated DOT.	$\sum$(DOT × ASC score)/DOT_{total}, for all antibiotics
ASC scores-stratified DOT	ASDOT	Aggregated DOT for antibiotics categorized within an ASC score range.	$\sum$(DOT), for antibiotics categorized into three ranges.

because they are calculated on a per-drug basis, describing trends only roughly in spectrums by evaluating each result. Although a mere aggregated DOT for all antibiotics indicates a potential necessity for antibiotics, it can ignore the spectrum element based on de-escalation efforts.[7]

In 2022, Kakiuchi et al. proposed the days of antibiotic spectrum coverage (DASC) concept, introducing a metric to holistically assess antibiotic usage, including de-escalation activities, through antibiotic spectrum coverage (ASC) scores.[8] A change in DASC can provide comprehensive information on the spectrum. Furthermore, DOT can potentially be upgraded to be evaluated comprehensively to a certain extent based on the stratification by ASC scores (ASC-stratified DOT: ASDOT). Although several studies have explored the utility of ASC-related metrics in antibiotic usage monitoring,[9–12] little information is available about how these complex metrics can yield different results from simpler metrics for comprehensive evaluation of the impact of antimicrobial stewardship team (AST) programs. This study aims to investigate whether different metrics offer different aspects of antibiotic usage and how the metrics are correlated, focusing on ASC-related metrics versus DOT, as an innovative approach for comprehensive antibiotic monitoring.

Methods

Study design, cohort, and consideration of ethics

This monocentric surveillance study was conducted at a tertial referral hospital with 845 beds at Kumamoto City. Most of the patients were Japanese (Asian), with few foreign individuals (Blacks, Whites, and others). Since the study was exempt from being classified as clinical research, an ethical review was not required for this study.

Metrics for antibiotic usage

We evaluated DOT for each antimicrobial by the equations below (Table 1):

$$DOT = \frac{\text{Total number of days on which antibiotics were administered or prescribed} \times 1,000}{\text{Number of patient days in a specified month}}$$

Any antibiotic is calculated as one DOT for a one-day dosing. Ideally, the calculated value should also imply the spectrum to evaluate a comprehensive appropriate antibiotic usage for both antibiotic pressure against acquired resistance and ASTs. To address this expectation, ASC scoring has been advocated (Table 1), and the summary is shown in Supplementary Text S1.[8] By incorporating the ASC score into DOT and aggregating, a comprehensive evaluation of appropriate antibiotic usage may be visualized as DASC using the following equation (Table 1).

$$DASC = \sum(DOT \times ASC\ score)$$

For inpatients, the duration of antibiotic administration was recorded, whereas for outpatients, the duration of prescriptions was considered.[13] The foundational study[8] enumerated ASC scores for 77 antibiotics. Additionally, ASC scores for another 14 antibiotics, unique to the Japanese market, were derived from a preceding study.[9] We further established ASC scores for an additional 16 antibiotics, as elaborated in Supplementary Table S1. A comprehensive summary of ASC scores for all evaluated antibiotics is provided in Supplementary Table S2. Accordingly, we computed the DASC for the 77 antibiotics identified in the original study,[8] omitting others. To assess the influence of local antibiotic usage patterns, we also calculated the DASC for all antibiotics listed in Supplementary Table S2. The potential advantage of DASC lies in the comprehensive evaluation of appropriate antibiotic usage by taking ASC into account, in contrast to DOT_{total} and each DOT individually.

Importantly, DASC is also affected by the potential necessity of antibiotic. While DASC can be an essential metric for antibiotic pressure against acquired resistance, a further metric is necessary to evaluate de-escalation more specifically promoted by ASTs. To address this expectation, the DASC/DOT ratio, representing the average spectrum coverage per therapy day, calculated by DASC divided by the aggregated DOT for all antibiotics (DOT_{total}), was
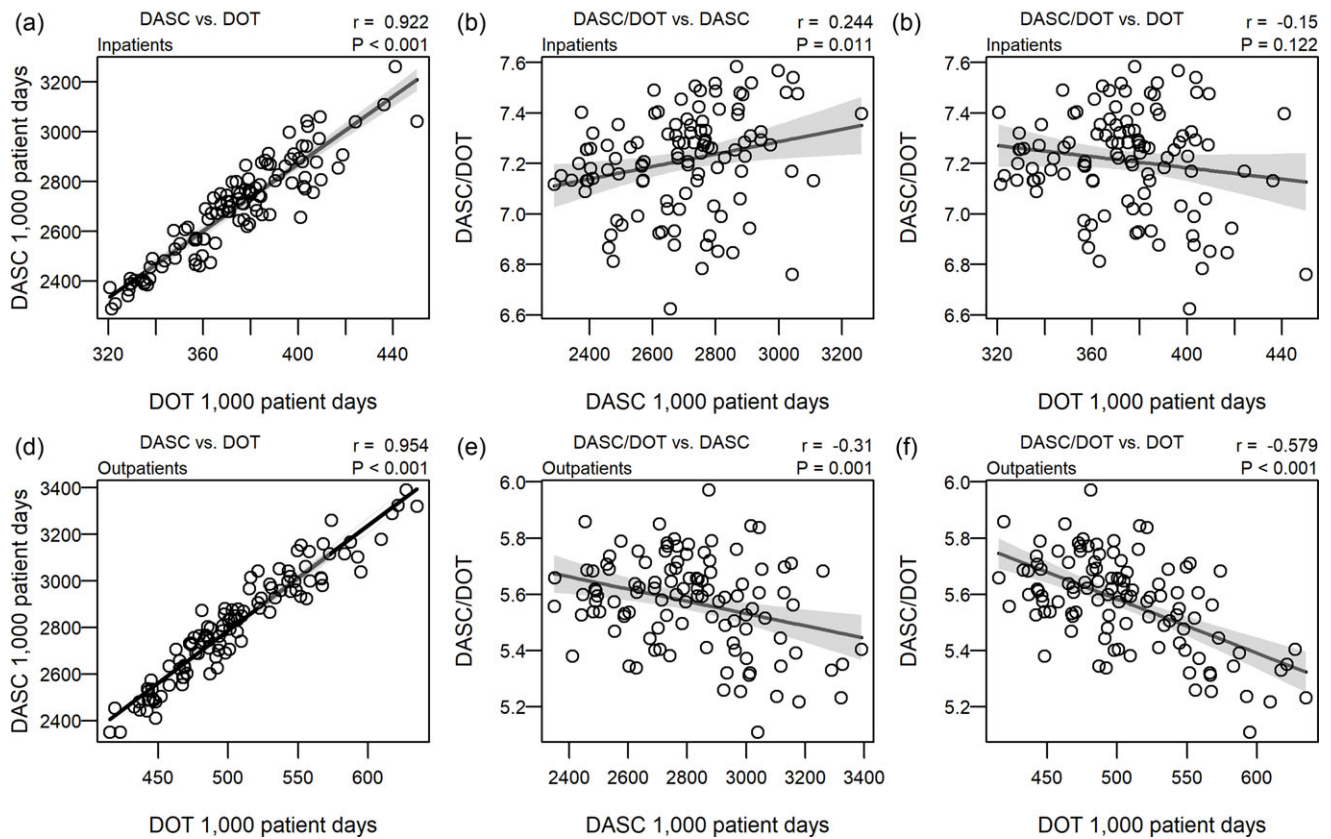
Figure 1. Correlation between days of therapy (DOT), days of antibiotic spectrum coverage (DASC), and DASC/DOT ratio. The panels in the upper (a–c) and lower (d–f) rows present the results for inpatients and outpatients, respectively. The panels on left (a and d), center (b and e), and right (c and f) represent the results for DASC versus DOT_{total}, DASC/DOT ratio versus DASC, and DASC/DOT versus DOT_{total}. The lines and grey areas represent the data fitted to the model and the corresponding 95% confidence interval.

advocated[8] and examined in the present study (Table 1). The DASC/DOT ratio was reported not to correlate with the DOT_{total}.[8] Hence, the DASC/DOT ratio can evaluate AST activity more specifically.

Moreover, an evaluation may be expected to exhibit which antibiotics in each spectrum category (broad, intermediate, and narrow) alter. Of note, ASC score may also provide an advantage over DOT by allowing antibiotics to be categorized comprehensively into specific spectrum to a certain extent. Therefore, we analyzed the ASC scores-stratified DOT (ASDOT), as introduced in the Introduction section, to gather more granular insights (Table 1). The present study preliminary investigated the categorization of antibiotics by ASC scores into three groups. First, ASC scores less than 6 were considered to be in the narrow-spectrum category, which includes cefazolin and ampicillin. Second, those greater than 10 were considered to be in the broad-spectrum category, which includes meropenem, tazobactam/piperacillin, and levofloxacin, which can be used empirically in the treatment of critically ill patients with suspected infection. Finally, those with scores between 6 and 10 were considered to be in the intermediate-spectrum category, which includes ceftriaxone, sulbactam/ampicillin, cefepime, colistin, linezolid, and ceftazidime.

Correlations between DOT_{total}, DASC, and DASC/DOT were analyzed by Pearson' correlation tests for inpatients and outpatients. The effect of the AST programs on these metrics and ASDOT for inpatients and outpatients were compared using interrupted time series (ITS) analysis with ordinary least squares

estimation.[14] The hypothesis was that the AST programs would result in a random change in the slopes. These analyses spanned the periods before and after April 2018, coinciding with the assignment of a full-time equivalent (FTE) pharmacist specialized in AST practices, as described in Supplementary Text S2. The statistical model was defined as follows:

$$Y = B0 + B1 \times T1 + B2 \times D + B3 \times T2 + e$$

where Y represents an outcome, specifically the DOT_{total}, DASC, or DASC/DOT_{total}. B0 represents the intercept. B1 and T1 represent the slope and time during the preimplementation term, respectively. B2 and D represent the immediate effect after the start of implementation and a dummy variable indicating observation collected pre- or post-implementation, respectively. B3 and T2 represent the slope and time during the post-implementation term, respectively (note: T2 is equal to zero during the pre-implementation term). The term e represents the additive residual variability. No covariates were applied in the ITS analysis. T1 spanned from January 2015 to March 2018 (39 mo), and T2 spanned from April 2018 to December 2023 (69 mo). AST was preliminarily implemented in April 2016, although we did not take advantage of it in the analyses. We did not include a wash-in period in our analysis while the program was getting up and running.

Data acquisition

Data regarding antibiotic usage were collected from medical records intended for expense claims. These records are integral to
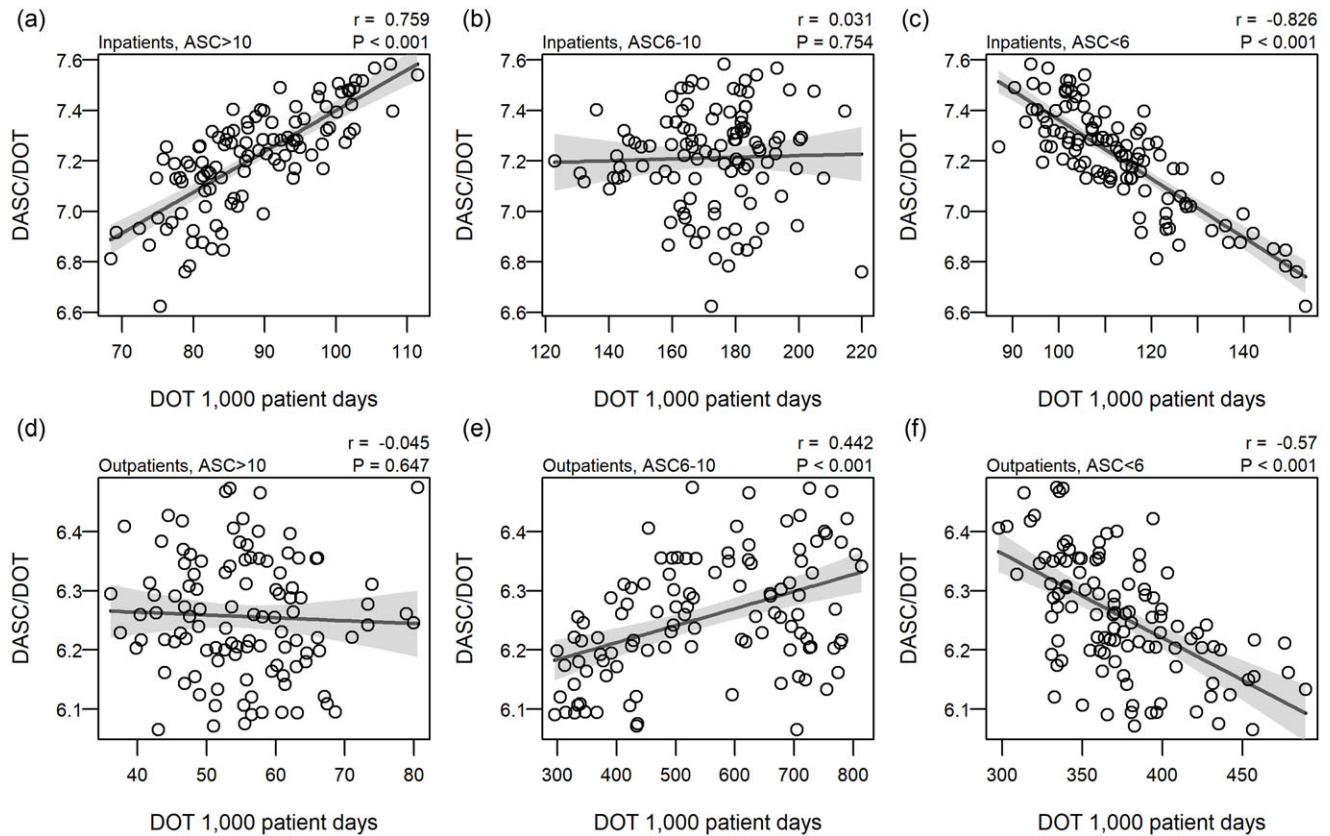
Figure 2. Correlation between days of antibiotic spectrum coverage/days of therapy (DASC/DOT) ratio for 77 antibiotics and DOT for antibiotic spectrum coverage (ASC)-stratified antibiotics. The panels in the upper (a–c) and lower (d–f) rows present the results for inpatients and outpatients, respectively. The panels on left (a and d), center (b and e), and right (c and f) represent the results based on DOT for ASC-stratified antibiotics (>10, 6–10, and <6). The lines and grey areas represent the data fitted to the model and the corresponding 95% confidence interval.

the nationwide surveillance system in Japan, focusing on AUD and DOT under the J-SIPHE framework. The raw CSV data files, stratified by inpatient and outpatient status and submitted by our institution to J-SIPHE, were analyzed using R statistical software (version 4.3.2, https://www.r-project.org/). This analysis facilitated the detailed calculation of the doses utilized and the days accounted for each antibiotic on a monthly basis. Additionally, the monthly counts of inpatients and outpatients from January 2015 to December 2023 were extracted from the hospital's management database. Our evaluation encompassed both parenteral and oral antibiotics for inpatient treatments, along with oral antibiotics for outpatient care.

Statistical corrections

Given that twenty-one ITS analyses and six Pearson's correlation tests were planned, we applied the Bonferroni correction to set the threshold for statistical significance at a P value of 0.002. This adjustment minimizes the risk of false-positive results.

Results

Number of included patients and correlations between DOT_{total}, DASC, and DASC/DOT

The study included a median (minimum–maximum) of 19,910 (17,555–21,548) inpatients days and 20,012 (16,075–22,937) prescription days for outpatients per month. The DASC and DOT_{total} were strongly correlated for both inpatients and outpatients (Figures 1a and 1d). For inpatients, the DASC/DOT ratio showed little and not significant correlation with the DASC ($r = 0.244$, Figure 1b) and DOT_{total} ($r = -0.150$, Figure 1c). For outpatients, the DASC/DOT ratio exhibited statistically significant correlations with both the DASC ($r = -0.310$, Figure 1e) and DOT_{total} ($r = -0.579$, Figure 1f).

Correlations between the DASC/DOT ratio for 77 antibiotics and ASDOT are shown in Figure 2. The DASC/DOT and DOT for antibiotics with ASC scores > 10 were correlated for inpatients but not for outpatients (Figure 2a and 2d). The DASC/DOT and DOT for antibiotics with ASC scores < 6 were correlated both for inpatients and outpatients (Figure 2c and 2f).

Interrupted time series analysis for inpatients

We conducted the ITS analyses on the DOT_{total}, DASC, and DASC/DOT ratio for inpatients (Figure 3). The AST programs significantly plateaued the DASC and decreased the DASC/DOT to less than 7 (both $P < 0.001$, Figure 3b and 3c), although the change in the DOT_{total} did not reach a predefined significant level ($P = 0.015$, Figure 3a). Notably, the DOT_{total} and DASC for parenteral antibiotics decreased but showed variability (Figure 3d and 3e), while the DASC/DOT ratio apparently decreased (Figure 3f). Conversely, the AST programs did not affect the increasing trends of the DOT_{total} and DASC for oral antibiotics
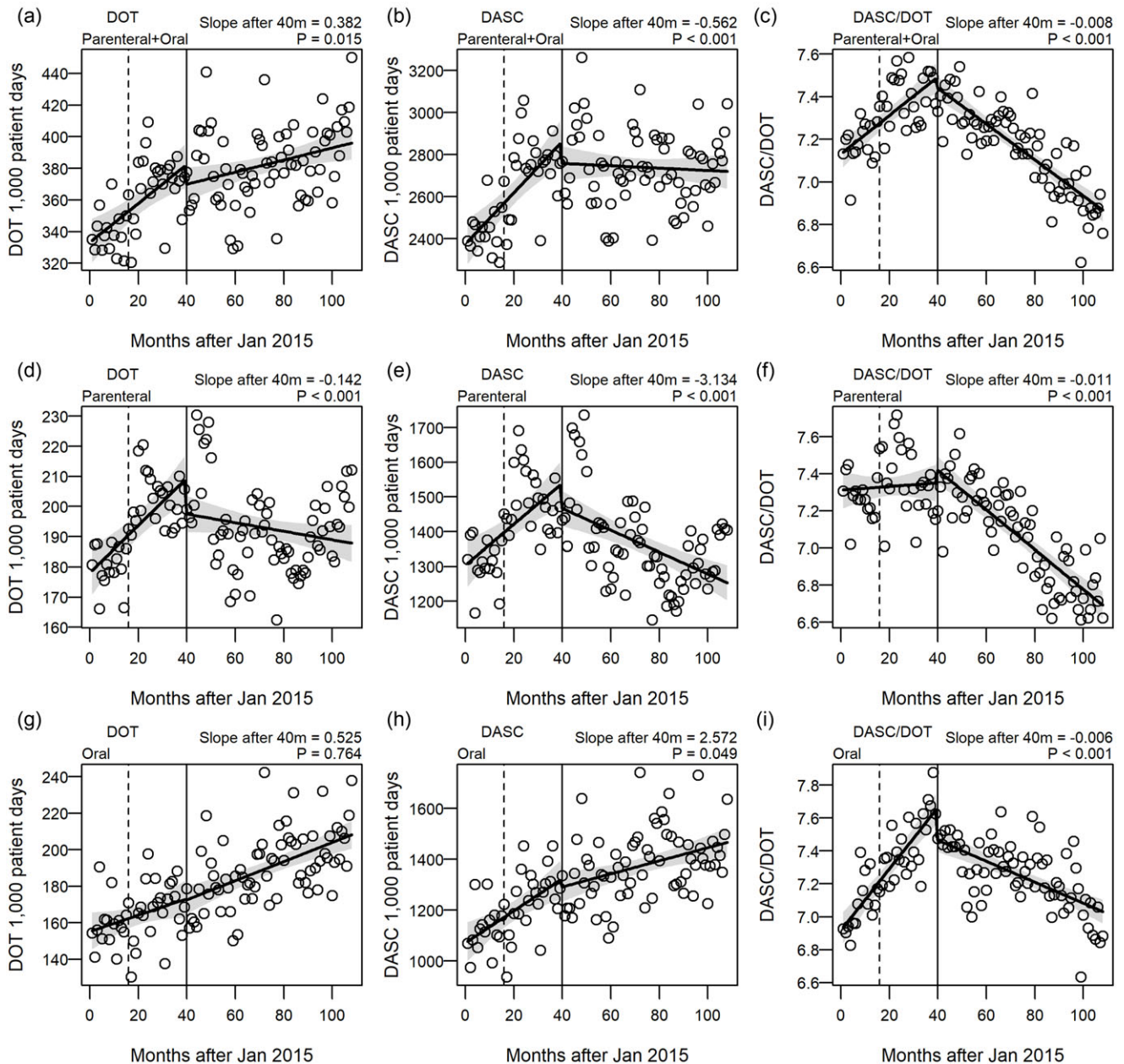
Figure 3. Impact of antimicrobial stewardship team (AST) programs on days of therapy (DOT), days of antibiotic spectrum coverage (DASC), and DASC/DOT ratio based on antibiotic spectrum coverage (ASC) scores for 77 antibiotics in inpatients. The panels in the upper (a–c), middle (d–f), and lower (g–i) rows display total (parenteral and oral), parenteral, and oral antibiotics, respectively. The panels in the left (a, d, g), center (b, e, h), and right (c, f, i) columns represent for the DOT$_{total}$, DASC, and DASC/DOT ratio, respectively. The lines and grey areas represent the data fitted to the model and the corresponding 95% confidence interval by interrupted time series analysis, with the interruption set at 40 months. The vertical dotted and continuous lines signify the preliminary and full AST programs at 16 months (with a full-time equivalent (FTE) of 0.7) and 40 months (with an FTE of 1.5) after January 2015, respectively.

(Figure 3g and 3h). Nevertheless, the DASC/DOT ratio significantly reduced (Figure 3i).

We subsequently present the results for ASDOT (Figure 4). The AST programs significantly reduced the increasing trend of the DOT$_{total}$ for the combined parenteral and oral antibiotics with ASC scores > 10 ($P < 0.001$, Figure 4a) and moderated the increase for those with scores of 6–10 ($P < 0.001$, Figure 4b). A similar reduction was observed in the analyses for parenteral antibiotics with ASC scores ≥ 6 (Figure 4d and 4e). In contrast, the DOT$_{total}$ for the combined parenteral and oral antibiotics with ASC scores < 6 showed a significant increase ($P < 0.001$, Figure 4c), and the increasing trend persisted for parenteral antibiotics with ASC scores < 6, regardless of AST programs (Figure 4f). While the AST programs did not show a reduction in the use of oral antibiotics, it did moderate the increasing trend for those with ASC scores ≥ 6 ($P < 0.001$, Figure 4g and 4h). An upward trend was also noted for oral antibiotics with ASC scores < 6 ($P < 0.001$, Figure 4i).
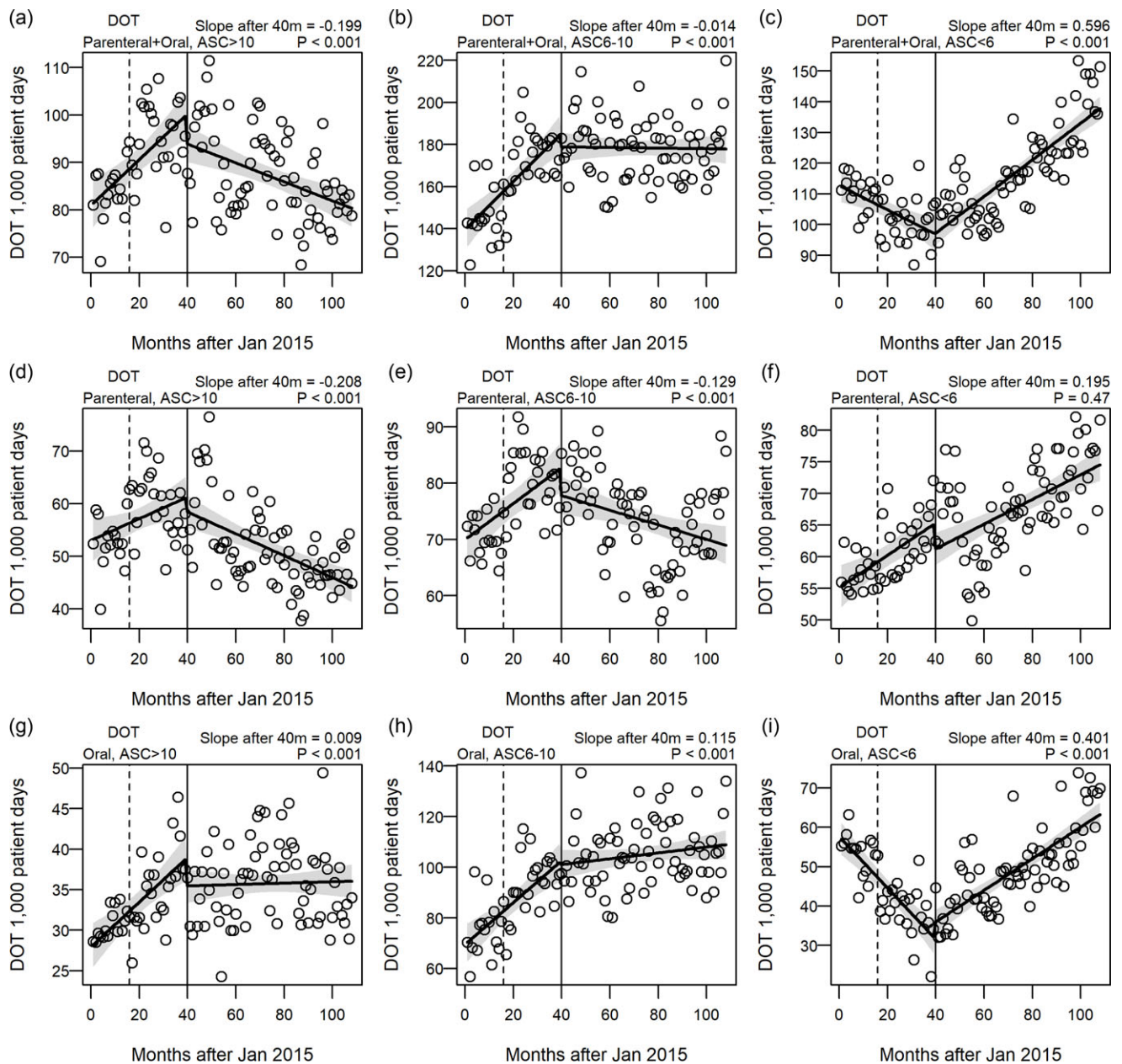
Figure 4. Impact of antimicrobial stewardship team (AST) programs on days of therapy (DOT) stratified by antibiotic spectrum coverage (ASC) scores for 77 antibiotics in inpatients. The panels in the upper (a–c), middle (d–f), and lower (g–i) rows display total (parenteral and oral), parenteral, and oral antibiotics, respectively. The panels in the left (a, d, g), center (b, e, h), and right (c, f, i) columns correspond to antibiotics with ASC scores > 10, 6–10, and < 6, respectively. The lines and grey areas represent the data fitted to the model and the corresponding 95% confidence interval by interrupted time series analysis, with the interruption set at 40 months. The vertical dotted and continuous lines signify the preliminary and full AST programs at 16 months (with a full-time equivalent (FTE) of 0.7) and 40 months (with an FTE of 1.5) after January 2015, respectively. Stratification details are depicted on the top-left of each panel.

Notably, although the linear regression lines after 40 months for the DOT_{total} of both broad- and intermediate-spectrum parenteral antibiotics exhibited negative slopes (−0.208 and −0.129), the detailed datapoints seemed to increase after approximately 80 months (September 2021, as depicted in Figure 4d and 4e). Likely associated with this trend, the DOT_{total} for all parenteral antibiotics might have increased at the time despite the overall negative slope (−0.142, Figure 3d), whereas the use of narrow-spectrum antibiotics continued to rise (Figure 4c, 4f, and 4i). In contrast, the DASC/DOT ratio showed an apparently different trend from the DOT_{total} and was minimally affected (Figure 3c, 1f, and 3i).

The influence of local antibiotic usage patterns was minimal (Supplementary Figures S3–4).

Interrupted time series analysis for outpatients

Figure 5 displays the results of ITS analyses on the DOT_{total}, DASC, and DASC/DOT ratio for oral antibiotics in outpatients. The AST programs seemed to curtail the increase in the DASC/DOT ratio, though it did not reach a predefined significant level ($P = 0.006$, Figure 5c). In contrast, the DOT_{total} and DASC continued to increase regardless of the AST programs
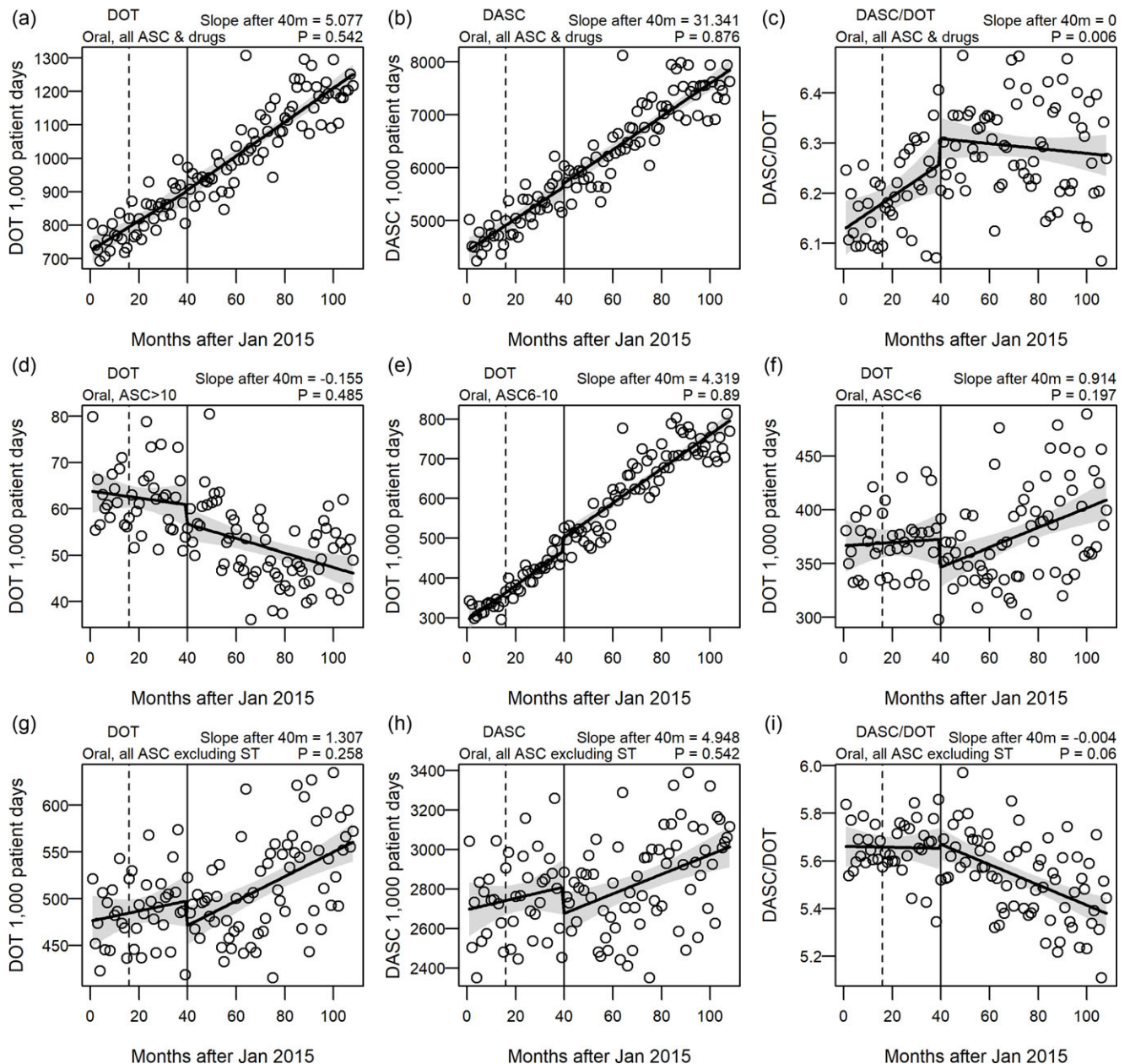
Figure 5. Impact of antimicrobial stewardship team (AST) programs on days of therapy (DOT), days of antibiotic spectrum coverage (DASC), and DASC/DOT ratio based on antibiotic spectrum coverage (ASC) scores for 77 antibiotics in outpatients. The panels in the upper (a–c), middle (d–f), and lower (g–i) rows represent the results for total oral antibiotics (DOT, DASC, and DASC/DOT ratio), DOT stratified by ASC scores (>10, 6–10, and <6), and the results excluding sulfamethoxazole/trimethoprim (DOT, DASC, and DASC/DOT ratio), respectively. The lines and grey areas represent the data fitted to the model and the corresponding 95% confidence interval by interrupted time series analysis, with the interruption set at 40 months. The vertical dotted and continuous lines signify the preliminary and full AST programs at 16 months (with a full-time equivalent (FTE) of 0.7) and 40 months (with an FTE of 1.5) after January 2015, respectively. Stratification by ASC scores are depicted on the top-left of panels d–f. Panels g–i exclude sulfamethoxazole/trimethoprim.

(Figures 5a and 5b), which is different from the results for inpatients (Figure 3a and 3b). This finding is intriguing. For detailed investigations to identify the causal antibiotics, ASDOT efficiently supported this effort. Figure 5d to 5f present changes in ASDOT, which identified that antibiotics with ASC scores of 6–10 exhibited a significant elevation in the DOT$_{total}$ (Figure 5e). Consequently, prophylactic sulfamethoxazole/ trimethoprim (ST, with an ASC score of 7) was identified as the oral antibiotic contributing most to the increase in the

DOT$_{total}$ for ASC scores of 6–10 (Supplementary Figure S2). Therefore, we reevaluated oral antibiotics for outpatients, excluding ST. These adjusted findings are illustrated in Figure 5g to 3i. The DOT$_{total}$ and DASC values remained constant prior to the AST programs but escalated subsequently (Figure 5g and 5h). The trend in the DOT$_{total}$ changes (Figure 5g) paralleled that of antibiotics with ASC scores lower than 6 (Figure 5f). The increase in DASC was mitigated by the reevaluation. Although not statistically significant ($P = 0.06$),

the decrease in the DASC/DOT ratio due to the AST programs might have been more pronounced (Figure 5i).

The influence of local antibiotic usage patterns was minimal (Supplementary Figure S5).

Discussion

This study demonstrated significant variation in DASC and the DASC/DOT ratio between pre- and post-implementation phases of ASTs. Most importantly, while the DASC/DOT ratio may be a complicated metric, it independently captured different conclusions in the comprehensive evaluation of ASTs, differing from simpler metrics (Figure 1). Monitoring ASDOT for either board- or narrow-spectrum antibiotics may be substituted by the DASC/DOT ratio (Figure 2). These findings demonstrated that ASC-related metrics, based on categorizing by spectrum such as ASC scores, provided useful information in the evaluation of ASTs. Many studies demonstrating reduction of broad-spectrum antibiotics by prospective-audit and feedback (PAF) have been available.[15–22] It was logical that the study demonstrated a reduction in the DOT_{total} for broad-spectrum parenteral antibiotics due to PAF (Figure 4d).

Regarding the period after 80 months, the detailed datapoints for the DOT_{total} of both broad- and intermediate-spectrum parenteral antibiotics seemed to increase despite of the negative regression lines (Figure 4d and 4e), this turning point may correlate with the COVID-19 pandemic and the emergence of delta variants. The DOT_{total}, the simplest metric, highlights concerns regarding the functionality of ASTs. On the contrary, it is noteworthy that the DASC/DOT ratio demonstrated that the efficacy of ASTs was maintained (Figure 3c and 3f). As for oral antibiotics, ASTs minimally affected the DOT_{total} (Figure 3g), although the significant curtailing and reduction in the DASC/DOT ratio clearly indicated the efforts of AST (Figure 3i). Therefore, the DASC/DOT ratio could yield original results to evaluate the activity for ASTs. The discussion for FTE and outcomes were additionally described in Supplementary Text S3 and Figure S6.

More specifically, the AST activities decreased the DASC/DOT ratio to less than 7, which aligns with previous reports.[8–12] The ASC scores around 7 correspond to ceftriaxone (6), ceftazidime (6), piperacillin (7), cefepime (8), and tazobactam/ceftolozane (8). Indeed, the evidence supporting a causal relationship suggesting that the use of ceftriaxone versus cefepime reduces AMR is limited. It is a key principle that ceftriaxone does not promote resistance in *Pseudomonas aeruginosa*, whereas cefepime does. Furthermore, the reported DASC/DOT was a median; thus, more drastic changes in DASC/DOT could be observed in individual cases due to de-escalation. With the significant evidence in favor of de-escalation strategies against AMR,[2,3] ASC-related metrics can serve as a powerful tool for assessing AST activities.

ASC scores contributed to facilitating a more comprehensive evaluation of DOT. ASDOT visualized that the DOT_{total} decreased in parenteral antibiotics with ASC scores ≥ 6 (Figure 4d and 4e) while it increased in antibiotics with ASC scores < 6 (Figure 4f and 4i), raising the issue that oral antibiotics with broad-spectrum should be targeted for decrease (Figure 4g). Specifically, the only oral antibiotics with ASC scores > 10 were fluoroquinolones (levofloxacin, moxifloxacin, garenoxacin, tosufloxacin, sitafloxacin, pazufloxacin, lascufloxacin, and prulifloxacin) in the hospital. While parenteral antibiotics with ASC scores > 10 are subject to prescribing notification to the AST in the hospital, such a

regulation might also be considered for these oral antibiotics. The present study demonstrated first that ASDOT allows for comprehensive monitoring of antibiotics across a range of ASC scores. Further stratification by departments would provide valuable insights for individual AST activities.

We also evaluated the DOT_{total} and ASC-related metrics for monitoring oral antibiotics in outpatients for the first time (Figure 5). The increasing trends in the DOT_{total} and DASC was similar to those for inpatients, regardless of the AST programs (Figure 5g and 5h, versus Figure 3g and 3h). Although the negative slope for the DASC/DOT ratio did not demonstrate the statistical significance, this trend may show significance with continuous AST activity.

The study had five additional limitations. First, the practice of de-escalation and step-down therapy was indirectly observed from the results, meaning the appropriateness of the infection treatment could not be directly evaluated. Continuous AST activities and proactive antimicrobial feedback can address this concern. Second, this was a single-center study, so further evaluation in a multicenter setting should be conducted. Third, the ITS analysis cannot control for secular trends that may have led to improvements independent of the AST program. Fourth, the detailed information and demographics of the included population could not be evaluated with the current data acquisition method. Lastly, more complex metrics may compromise generalizability and pose challenges with informatics infrastructure. Determining and acknowledging ASC scores in society is essential to facilitate the metrics.

Conclusions

We demonstrated that ASC-related metrics, the DASC/DOT ratio and ASDOT, offer independent and different measures for assessing ASTs for inpatients, and yield useful information from conventional simpler metrics such as DOT_{total}. ASC-related metrics could be instrumental in enabling comprehensive antibiotic monitoring, incorporating the aspect of the antibiotic spectrum.

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