Effects of a Pharmacist-Designed Clinical Decision Support System on Antimicrobial Stewardship

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Abstract

Background Clinical decision support systems (CDSSs) are computer applications, which can be applied to give guidance to practitioners in antimicrobial stewardship (AS) activities; however, further information is needed for their optimal use.

Objectives Our objective was to analyze the implementation of a CDSS program in a second-level hospital, describing alerts, recommendations, and the effects on consumption and clinical outcomes.

Methods In October 2020, a pharmacist-driven CDSS designed for AS was implemented in a second-level hospital. The program provides a list of alerts related to antimicrobial treatment and microbiology, which were automatized for revision by the AS professionals. To analyze the implementation of the CDSS, a pre–post-intervention, retrospective study was designed. AS-triggered alerts and recommendations (total number and rate of acceptance) were compiled. The effect of the CDSS was measured using antimicrobial consumption, duration of antimicrobial treatments, in-hospital mortality, and length of stay (LOS) for patients admitted for infectious causes.

Results The AS team revised a total of 7,543 alerts and 772 patients had at least one recommendation, with an acceptance rate of 79.3%. Antimicrobial consumption decreased from 691.1 to 656.8 defined daily doses (DDD)/1,000 beds-month ($p = 0.04$) and the duration of antimicrobial treatment from 3.6 to 3.3 days ($p < 0.01$). In-hospital mortality decreased from 6.6 to 6.2% ($p = 0.46$) and mean LOS from 7.2 to 6.2 days ($p < 0.01$).

Conclusion The implementation of a CDSS resulted in a significant reduction of antimicrobial DDD, duration of antimicrobial treatments, and hospital LOS. There was no significant difference in mortality.

Keywords
- clinical decision support system
- antimicrobial stewardship
- alert
- optimization

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Background and Significance

Antimicrobial resistance (AMR) poses a major threat to human health,[1–3] and therefore, a range of antimicrobial stewardship (AS) programs have been developed over recent years.[4–6] Specifically, in the hospital setting, AS programs have gained attention as a standard of care, supported by regulatory bodies, accreditation agencies, and quality improvement groups, as well as scientific societies worldwide.[3,7] The activity of these AS teams in hospitals includes both strategic (education and training, writing antimicrobial guidelines, policy, and horizon scanning) and operational roles, including identifying specific patients for clinical review.[2]

Identification and prioritization of relevant cases can be challenging and require significant AS resources and organizational support due to the massive volume of digital health data available to clinicians and difficulty in handling them.[7–10] To address this challenge, clinical decision support systems (CDSSs) have been designed to provide the prescriber with easy and rapid access to information, required to make therapeutic decisions at the point of prescription.[8]

CDSSs are defined as computer applications created to give guidance to practitioners in making both diagnostic and therapeutic choices for patients.[11,12] For AS activities, the role of the CDSSs has turned into an area of great interest with a wide variety of interventions such as helping clinicians in selecting appropriate antimicrobial therapy for various infections and avoiding preventable errors, or decreasing targeted antimicrobial use, antimicrobial drug acquisition costs, and health care-associated *Clostridioides difficile* infection rates.[13–15] However, the major disadvantages of those systems include the financial resources needed for development and maintenance[16] and they are labor intensive for the information technology personnel and not easily shared between institutions that are not part of the same network.[7] Furthermore, information to guide clinicians on those types of alerts that necessitate an intervention is strongly demanded due to the amount of time required by the AS team reviewing alerts and documenting the intervention.[17,18] Because of that, further investigation in this setting is needed, regarding practices of CDSS implementation for AS that resulted in relevant experiences for routine use in hospitals and primary care.

Objectives

The primary objective of our study was to analyze the implementation of a CDSS program in a second-level hospital, describing alerts and recommendations after the initial development. A secondary objective was to evaluate the effects of this program including antimicrobial consumption, duration of antimicrobial treatment, infection-related mortality, and length of stay (LOS).

Methods

Study Setting

This study was conducted at Hospital Universitario Infanta Cristina, a second-level hospital in Parla, Spain. The hospital has 188 beds serving general medicine, surgery, intensive medicine, obstetrics and gynecology, pediatrics, and neonates. The mean number of bed days per year was 48,161 during the 2018 to 2022 period, 2,562 being patients admitted to the intensive care unit (ICU).

Before the implementation of the CDSSs, the activities of the ASP team were focused on the revision of restricted antimicrobials, classified as those having a broad spectrum of activity and/or high ecological effect. Those included carbapenems (meropenem, imipenem/cilastatin, and ertapenem), piperacillin/tazobactam, daptomycin, linezolid, tigecycline, ceftazidime/avibactam, ceftolozane/tazobactam, echinocandins (caspofungin and anidulafungin), liposomal amphotericin B, and voriconazole. The infectious diseases (ID) specialist analyzed the adequacy of those antimicrobials to make recommendations to the primary provider. There was no defined method for identifying patients with AS-related intervention opportunities or for performing prospective interventions and feedback for selected interventions.

In June 2020, an AS pharmacist held the coordination of the AS program and in October 2020, a commercial CDSS designed for AS was implemented with a new methodology including its use and access shared by the pharmacist and one ID specialist. This methodology was registered in a new protocol for use in the hospital and approved by the medical director.

Description of the Clinical Decision Support Systems and Implementation

WASPSS (Wise Antimicrobial Stewardship Support System) is a software package developed as a research project of the University of Murcia, funded by the Ministry of Economy and Competitiveness of the Spanish Government. It is composed of daily microbiology, biochemistry, and hematology results (extracted from Servolab laboratory information management system), currently prescribed antimicrobials, and demographic information (extracted from Selene electronic health record [EHR] system). This program provides a list of basic AS-related alerts (►Table 1) which can be modified by the CDSS technician. After the implementation, some custom-built alerts were added to the program, which are also shown in ►Table 1.

The program allows the user to create "work lists" to automatize triggered alert revisions by the AS professionals. Three lists were created: List 1 including microbiology alerts ("bacteremia," "stool sample with *Clostridioides difficile*," "multidrug resistance [Magiorakos[19]]," and "culture with positive result"); List 2 including "start of restricted antimicrobial," "duration of intravenous antimicrobial $\geq$ 7 days," "course of empiric treatment $\geq$10 days," "course of targeted treatment $\geq$10 days," "antimicrobials with good oral bioavailability $\geq$72 hours," "antimicrobials with narrow therapeutic index $\geq$ 72 hours (without levels)," "dosage adjustment in renal impairment," and "duplicated therapy"; and List 3 including "duration of broad-spectrum antimicrobial (BSA) $\geq$ 72 hours." Lists 1 and 2 were revised by the ASP pharmacist; and List 3 by the ID physician. These alerts can be marked as "revised with AS intervention" or "revised without AS intervention" depending on the need to make or not to make a recommendation.

Table 1 Alerts included in the CDSS

Type	List	Subtype	Name of alert	Antimicrobials included
Basic	3	Treatment	Duration of broad-spectrum antimicrobial (BSA) ≥72 h	Ertapenem, imipenem, meropenem, daptomycin, linezolid, piperacillin/tazobactam, and tigecycline
Custom-built	2	Treatment	Duration of intravenous antimicrobial ≥7 d	All intravenous antimicrobials
Basic	2	Treatment	Antimicrobials with good oral bioavailability ≥72 h	Considered as oral bioavailability >90%: Fluoroquinolones, clindamycin, cotrimoxazole, doxycycline, linezolid, metronidazole, fluconazole, and voriconazole
Basic	2	Treatment	Course of empiric treatment ≥10 d	All antimicrobials
Custom-built	2	Treatment	Dosage adjustment in renal impairment	Antimicrobials which need adjustment in renal insufficiency
Basic	2	Treatment	Start of restricted antimicrobial	Daptomycin, linezolid, tigecycline, ceftolozane/tazobactam, ceftazidime/avibactam, ceftaroline, dalbavancin, and fidaxomicin
Custom-built	2	Microbiology	Culture with positive result	Any culture with a positive result, excluding surveillance detection
Basic	1	Microbiology	Bacteremia	Blood culture with a positive result
Basic	1	Microbiology	Multidrug resistance (Magiorakos)	Nonsusceptibility to at least one agent in three or more antimicrobial categories
Basic	2	Treatment	Course of targeted treatment ≥10 d	All antimicrobials
Basic	2	Treatment	Antimicrobials with narrow therapeutic index ≥72 h (without levels)	Vancomycin, tobramycin, gentamycin, amikacin
Basic	2	Treatment	Duplicated therapy	Antimicrobials from the same ATC pharmacological subgroup
Basic	1	Microbiology	Stool sample with *Clostridioides difficile*	Detection of toxigenic *Clostridioides difficile*

Abbreviations: ATC, Anatomical Therapeutic Chemical; CDSS, clinical decision support systems.

WASPSS also allows the user to register the recommendations which were made either face-to-face, by phone, or by typing a note in the EHR. The form for recommendations includes the fields: AS evaluation, type of recommendation, mean of contact, and primary provider decision. All of the recommendations required provider approval.

The implementation of this CDSS in our hospital supported the validation and usefulness of the system for the daily activities of the AS team. All the AS alerts generated by the CDSS and included in the work lists were revised once a day (at 10:00 a.m.) by the pharmacist and the ID physician, from Monday to Friday. Alerts were triggered at 2 a.m. and contained information regarding the location of the patient, antimicrobials prescribed, and laboratory results that were subsequently that could be broadened with clinical data from the EHR. Contacting primary providers required typing recommendations in the EHR as the system did not provide bidirectional entries or calling by phone after the physician rounds at 1 p.m.

Study Design

To analyze the implementation of the CDSS in our setting, a pre–postintervention study was designed. The preintervention group included patients admitted to the hospital between April 1, 2018, and September 30, 2020, and the postintervention group those admitted to the hospital between October 1, 2020, and March 31, 2023. Patients admitted to the ICU were not considered for the study as their program for electronic prescription was not linked to WASPSS.

For the postintervention group, AS-triggered alerts were measured, including type and actionability. Actionable alerts were defined as those that led directly to an AS recommendation which were recorded in the CDSS. Reasons for nonactionable alerts included duration of treatments that were already defined in the EHR, discharges from the hospital, treatments that were no longer active, and clinical assessment by the ID physician considering the antimicrobial as an appropriate treatment. Clinical features of these recommendations were compiled, including demographic characteristics of the patient (age and gender), primary service, type of infection, antimicrobial drug with Anatomical Therapeutic Chemical (ATC) code, route of administration, associated alert, type of recommendation, clinical decision, time to decision, and method of contact. The total number of AS recommendations and the rate of acceptance (%) were measured. The acceptance rate was calculated by dividing the number of recommendations, which were accepted by the primary provider by the total number of recommendations made by the AS team.

Study Outcomes

To evaluate the antimicrobial consumption, the defined daily doses (DDDs) per 1,000 beds-month were used. DDDs were defined as the sum of dosage during the entire hospitalization divided by the daily average maintenance dose for a given drug used for its main indication in adult patients at 70 kg body weight. Pediatrics and nephrology patients were not considered in these usage measures as DDD does not reflect the real dosage in this population and patients admitted to the emergency department because they could not be considered as a real hospitalization. Variations in consumption after the implementation of the CDSS were measured for overall antimicrobials and stratified by the ATC group: antibacterials for systemic use (J01) and antifungals for systemic use (J02). Targeted antimicrobials defined by the AS group to reduce their use were also compared: intravenous (IV) antimicrobials, carbapenems, and IV antimicrobials with good oral bioavailability (fluoroquinolones, clindamycin, cotrimoxazole, doxycycline, linezolid, metronidazole, fluconazole, and voriconazole). Overall expenditures were calculated in €/1,000 beds-month.

To quantify the duration of treatments, all antimicrobials prescribed during the pre- and postintervention period were compiled, recording the date of start and end of treatment. Antimicrobials prescribed for patients in the emergency department were not considered, as well as those with duration <24 hours. Duration of IV antimicrobials and BSA (ertapenem, imipenem, meropenem, daptomycin, linezolid, piperacillin/tazobactam, and tigecycline) were also measured, including the proportion of patients who were prescribed IV antimicrobials for more than 7 days and BSA for more than 72 hours (as defined in basic alerts of the CDSS).

Clinical outcomes for the pre- and postintervention study were also evaluated, including in-hospital mortality (proportion of patients who died during their hospitalization) and LOS for patients admitted due to infectious disease reasons.

Antimicrobial usage and duration of treatments were extracted from FarmaTools prescription software and clinical outcomes (in-hospital mortality and LOS) from the CMBD registry of the hospital.

Statistical Analysis

Continuous variables were described either by the median and interquartile range (median [IQR]) or mean and standard deviation (mean ± standard deviation) and categorical variables by absolute and relative frequencies. The Wilcoxon signed-rank test was used for comparisons between two continuous variables. The χ^2 test or Fisher's exact test was used to compare two categorical variables. A p-value < 0.05 was considered statistically significant. Computer support used for the statistical analysis was Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX, United States).

Results

Analysis of the Implementation

During the postintervention period, a total of 7,543 alerts were revised by the AS team and 1,076 required an AS recommendation (11.1%). Of these, 864 (80.3%) were made by the AS pharmacist and 212 (19.7%) by the ID physician. Recommendations and revisions by alert type are presented in ►Table 2.

The clinical features of the recommendations are described in ►Table 3. The most frequent antimicrobial drug included in the recommendations was piperacillin/tazobactam (17.7%), followed by meropenem (10.3%), linezolid (9.9%), levofloxacin (9.3%), and ceftriaxone (8.9%). Of these recommendations, 853 were accepted (79.3%), 151 had no possible follow-up (hospital discharge or care transitions) (14.0%), and 72 were rejected (6.7%). The median time until clinical decision was 4 hours (24). The type of communication for the recommendations was 70.8% notes in the EHR (762/1,076), 18.0% phone calls (194/1,076), 8.0% face-to-face communication (86/1,076), 0.5% phone messages (5/1,076), and 2.7% not registered (29/1,076).

Study Outcomes

After the implementation of the CDSS, the median overall antimicrobial consumption decreased from 691.1 (107.4) to 656.8 (80.2) DDD/1,000 beds-month ($p = 0.04$), showing a relative reduction of 9.3%. A significant reduction was observed when stratifying by antibiotics, J01 (673.4 [93.4] to 621.7 [69.3], $p < 0.01$), but an increase was observed in antifungals, J02 (18.5 to 22.8, $p = 0.06$). Relative reductions of 5.5, 8.3, and 17.3% were recorded for IV antimicrobials, fluoroquinolones, and IV antimicrobials with good oral bioavailability (►Table 4). Overall expenditure of antimicrobials varied from €3,162.4 to 2,946.0/1,000 beds-month ($p = 0.34$), with a relative reduction of 6.8%.

The median duration of antimicrobial treatment decreased from 3.6 (3.9) to 3.3 (3.9) days in the postintervention period ($p < 0.01$). Regarding IV antimicrobials, this duration was reduced from 3.5 (3.9) to 3.3 (4.0) ($p = 0.02$). No differences were found for BSA (5.1 [4.6] vs. 5.0 [4.8] days) ($p = 0.13$). The proportion of patients having a prescription of IV antimicrobial > 7 days was 17.2% in the preintervention group and 16.9% in the postintervention group ($p = 0.55$), 75.8 versus 72.6% ($p < 0.01$) for BSA ≥ 72 hours.

For clinical outcomes, in-hospital mortality for those patients admitted for infectious causes decreased from 6.6% (233/3,497) to 6.2% (177/2,852) showing no statistically significant differences ($p = 0.46$). Mean LOS was 7.2 ± 8.6 days in the preintervention period and 6.2 ± 9.3 days in the postintervention period ($p < 0.01$) in this group of patients. Mortality and LOS by type of infection are displayed in ►Table 4.

Discussion

We analyzed here the implementation of a CDSS designed for AS activities (WASPSS), describing the type of alerts, recommendations, and clinical outcomes that were achieved in the postimplementation period. We found a significant decrease in antimicrobial consumption, duration of treatments, and infection-related LOS, not reaching statistical significance for overall expenditure and infection-related mortality. The WASPSS program was developed as a brand-new project in

Table 2 Revision and recommendations by alert type

Name of alert	Total number	Revised with AS intervention		Acceptance rate, *n* (%)	Revised without AS intervention, *n* (%)
		Type	*n* (%)		
Duration of BSA ≥ 72 h	1,622	Total	212 (13.1)	187 (88.2)	1,410 (86.9)
		De-escalate therapy	96 (45.3)		
		Stop therapy	72 (34.0)		
		Substitution to other antimicrobial	15 (7.1)		
		Duration adjustment	11 (5.2)		
		Dosage adjustment	10 (4.7)		
		Start of new antimicrobials	3 (1.4)		
		Interval adjustment	2 (0.9)		
		CPK monitoring	1 (0.5)		
		Others	1 (0.5)		
Duration of intravenous antimicrobial ≥7 d	1,135	Total	167 (14.7)	132 (79.0)	968 (85.3)
		Stop therapy	138 (82.6)		
		Dosage adjustment	9 (5.4)		
		De-escalate therapy	7 (4.2)		
		Duration adjustment	7 (4.2)		
		Substitution to other antimicrobial	3 (1.8)		
		Interval adjustment	1 (0.6)		
		Transition from IV to oral therapy	1 (0.6)		
		Others	1 (0.6)		
Antimicrobials with good oral bioavailability ≥72 h	855	Total	210 (24.6)	136 (64.8)	645 (75.4)
		Transition from IV to oral therapy	176 (83.8)		
		Stop therapy	14 (6.7)		
		Substitution to other antimicrobial	5 (2.4)		
		Duration adjustment	4 (1.9)		
		Dosage adjustment	3 (1.4)		
		Interval adjustment	3 (1.4)		
		De-escalate therapy	3 (1.4)		
		Others	2 (1.0)		
Course of empiric treatment ≥10 d	802	Total	94 (11.7)	76 (80.9)	708 (88.3)
		Stop therapy	71 (75.5)		
		De-escalate therapy	6 (6.4)		
		Duration adjustment	5 (5.3)		
		Dosage adjustment	4 (4.3)		
		Transition from IV to oral therapy	3 (3.2)		
		Substitution to other antimicrobial	2 (2.1)		
		Interval adjustment	1 (1.1)		
		Start of new antimicrobial	1 (1.1)		
		Others	1 (1.1)		
Dosage adjustment in renal impairment	787	Total	99 (12.6)	75 (75.8)	688 (87.4)
		Dosage adjustment	71 (71.7)		
		Interval adjustment	23 (23.2)		
		Stop therapy	3 (3.0)		
		De-escalate therapy	1 (1.0)		
		Substitution to other antimicrobial	1 (1.0)		

(*Continued*)

Table 2 (*Continued*)

Name of alert	Total number	Revised with AS intervention		Acceptance rate, *n* (%)	Revised without AS intervention, *n* (%)
		Type	*n* (%)		
Start of restricted antimicrobial	665	Total	63 (9.5)	59 (93.4)	602 (90.5)
		SSRI discontinuation	16 (25.4)		
		De-escalate therapy	12 (19.0)		
		Substitution to other antimicrobial	11 (17.4)		
		Stop therapy	7 (11.1)		
		CPK monitoring	5 (7.9)		
		Dosage adjustment	3 (4.8)		
		Duration adjustment	2 (3.2)		
		Others	7 (11.1)		
Culture with positive result	403	Total	155 (38.5)	131 (84.5)	248 (61.5)
		De-escalate therapy	69 (44.5)		
		Substitution to other antimicrobial	39 (25.2)		
		Stop therapy	27 (17.4)		
		Dosage adjustment	8 (5.2)		
		Start of new antimicrobial	5 (3.2)		
		Duration adjustment	3 (1.9)		
		Interval adjustment	2 (1.3)		
		Transition from IV to oral therapy	1 (0.6)		
		Others	1 (0.6)		
Bacteremia[a]	303	Total	58 (19.1)	–	245 (80.9)
Multidrug resistance (Magiorakos)[a]	291	Total	58 (19.9)	–	233 (80.0)
Course of targeted treatment ≥10 d	268	Total	5 (1.9)	3 (60.0)	263 (98.1)
		Stop therapy	4 (80.0)		
		De-escalate therapy	1 (20.0)		
Antimicrobials with narrow therapeutic index ≥72 h (without levels)	191	Total	64 (33.5)	48 (75.0)	127 (66.5)
		Drug monitoring	43 (67.2)		
		Stop therapy	9 (14.1)		
		Dosage adjustment	6 (9.4)		
		Interval adjustment	3 (4.7)		
		Substitution to other antimicrobial	1 (1.6)		
		Others	2 (3.1)		
Duplicated therapy	175	Total	7 (3.1)	6 (85.7)	168 (73.4)
		Stop therapy	4 (57.1)		
		Dosage adjustment	3 (42.9)		
Stool sample with *Clostridioides difficile*[a]	54	Total	4 (6.7)	–	50 (83.3)

Abbreviations: AS, antimicrobial stewardship; BSA, broad-spectrum antimicrobial; CPK, creatine phosphokinase; IV, intravenous; SSRI, selective serotonin reuptake inhibitors.
[a]Microbiologic alerts that were revised together with "Culture with positive result" and therefore, their types and acceptance rates are not displayed.

Spain, compiling information from EHR (antimicrobial prescription) and laboratory results (microbiological, biochemical, and hematological) to help physicians in making therapeutic decisions. To our knowledge, this is the first study in our country reporting experience in this type of program, included in the routine use of an AS team and specifically applied to a second-level hospital.

First, either AS alerts included in our CDSS could be prebuilt (included in the basic version of the program) or custom-built (included later using a request by the AS team). The presence of

Table 3 Clinical features of the AS recommendations

Clinical feature	*n* (%)
Patients	772
Age, median (years)	75 (IQR: 23)
Sex (men)	404 (52.3)
Primary service	
Medical	576 (77.2)
Surgical	196 (25.4)
Type of infection	
Respiratory	336 (31.2)
UTI	259 (24.1)
IAI	251 (23.3)
SSTI	135 (12.6)
Fever syndromes	25 (2.3)
Endovascular	25 (2.3)
Articular	24 (2.2)
Bacteremia	17 (1.6)
CNS infection	4 (0.4)
Antimicrobial drug	
Other β-lactam antibacterials (J01D)	277 (25.7)
Beta-lactam antibacterials, penicillin (J01C)	272 (25.3)
Other antibacterials (J01X)	245 (22.8)
Quinolone antibacterials (J01M)	171 (15.9)
Aminoglycoside antibacterials (J01G)	42 (3.9)
Antimycotics for systemic use (J02A)	29 (2.7)
Macrolides, lincosamides, and streptogramins (J01F)	25 (2.3)
Tetracyclines (J01A)	11 (1.0)
Sulfonamides and trimethoprim (J01E)	4 (0.4)
Route of administration	
IV	949 (88.2)
Oral	127 (11.8)

Abbreviations: CNS, central nervous system; IAI, intra-abdominal infection; IQR, interquartile range; IV, intravenous; SSTI, skin and soft tissue infections; UTI, urinary tract infection.

both basic and customized alerts is common for many applications used for AS,[14,17] even though only 22.2% of those programs have been defined as "alert based"[11]. The most frequent triggered alert was "duration of BSA $\geq$ 72 hours," followed by "duration of intravenous antimicrobial $\geq$ 7 days" and "antimicrobials with good oral bioavailability $\geq$ 72 hours." The initiation of BSA has been defined as an alert in some studies,[20,21] to reduce their use in situations where narrower spectrum antimicrobials were indicated. We included the revision of BSA 72 hours after the initial prescription to optimize recommendations having a great acceptance rate of 88.2%. On the other hand, the use of CDSS for the transition to the oral route in antimicrobials with good oral bioavailability resulted in AS recommendation in 24.6% of cases and 83.8% of the transition from IV to oral therapy. Signs and symptoms (fever, gastrointestinal intolerance…) could not be displayed by the CDSS, which discouraged recommendations for transition to oral therapy, justifying the relatively low percentage. These antimicrobials have been targeted in previous cohorts,[22,23] focused solely on the switch from intravenous to oral therapy; however, as described here, our software displayed a major number of alerts.

To note, 11.1% of all alerts triggered by WASPSS produced an AS recommendation. This rate is comparable to that reported by Heard et al.,[2] where 298 clinical interventions (e.g., stop antimicrobial, dose optimization, intravenous to oral switch, start antimicrobials…) were made over 2,662 cases reviews (11.2%). Slightly higher rates were reported by Schulz et al.[24] (18.9%), however they used best practice alerts only for antimicrobial de-escalation. Excessive warning can result in "alert fatigue," whereby the antimicrobial steward inadvertently disregards clinically relevant alerts.[14] To determine what alerts were more efficient, we calculated the proportion of them requiring AS intervention, showing that the most productive one was "culture with positive result" with a 38.5% rate, including de-escalation, substitution to other antimicrobial and stopping therapy as the common intervention types. This alert included cultures from any source with a positive result, different from other studies focused on candidemia,[25] gram-negative bacteremia,[26] and asymptomatic bacteriuria[27]; both designed as specific AS strategies. The second most efficient alert was "antimicrobials with narrow therapeutic index $\geq$ 72 hours" (33.5%) including vancomycin and aminoglycosides (gentamycin, tobramycin, and amikacin). Monitorization of those antimicrobials was recommended in 67.2% of cases and the alert-driven acceptance rate in this case was 75.0%. This intervention has proved to increase the likelihood of ordering measuring of concentrations, obtaining serum concentration within the therapeutic range, and reducing institutional costs.[9,28] Stool sample with *Clostridioides difficile* (6.7%), duplicated therapy (3.1%), and course of targeted treatment $\geq$10 days (1.9%) were alerts that resulted in the lowest rates of AS interventions, and therefore, optimization was needed. Duplicated therapies considered necessary (e.g., ceftriaxone and ampicillin for bacterial meningitis) were revised and modified with the CDSS technician, and the other two alerts were deactivated according to the decision of the AS team for a subsequent use of the application.

Regarding acceptance of AS interventions made using the CDSS, the overall rate was 79.3%. This rate had a wide variability in previous publications, ranging from 4 to >90%. Possible factors influencing providers' decisions on rejecting AS recommendations include undocumented patient comorbidities or allergies, the severity of infection, and additional sources of infection.[29] Ghamrawi et al[17] reported a 70% acceptance rate, which was lower than ours but the proportion of actionable alerts was higher. By type of alert, the greatest rate of acceptance was found for the start of restricted antimicrobial (93.4%) and duration of BSA $\geq$72 hours (88.2%). Jones et al[21] showed a 10% rejection rate for

Table 4 Differences in study outcomes for pre- and postintervention groups

Outcome	Preintervention period	Postintervention	*p*-Value
Antimicrobial consumption, (DDD/1,000 beds-month)			
Overall antimicrobials	691.1	656.8	0.04
Antibiotics (J01)	673.4	621.7	<0.01
Antifungals (J02)	18.5	22.8	0.06
Other β-lactam antibacterials (J01D)	208.4	198.8	0.47
Beta-lactam antibacterials, penicillin (J01C)	210.8	173.9	<0.01
Other antibacterials (J01X)	61.5	93.5	<0.01
Quinolone antibacterials (J01M)	104.4	89.3	0.07
Aminoglycoside antibacterials (J01G)	11.4	8.1	<0.01
Macrolides, lincosamides, and streptogramins (J01F)	76.3	46.0	<0.01
IV antimicrobials	450.6	426.0	0.11
Oral antimicrobials	200.6	209.1	0.66
Carbapenems	42.3	45.6	0.24
IV antimicrobials with good oral bioavailability	76.0	62.8	0.02
Mortality and LOS by the type of infection			
Respiratory ($n = 3,558$)	6.0%	5.0%	0.19
	7.0 d	5.6 d	<0.01
UTI ($n = 727$)	0.6%	0.7%	1.00
	5.1 d	4.3 d	0.01
Sepsis ($n = 621$)	25.6%	32.6%	0.06
	9.5 d	9.9 d	0.66
IAI ($n = 437$)	1.3%	4.5%	0.04
	6.2 d	7.3 d	0.15
SSTI ($n = 416$)	2.0%	1.4%	0.72
	8.3 d	6.2 d	<0.01
Fever syndromes ($n = 227$)	1.8%	0%	0.25
	6.4 d	5.9 d	0.66
Gynecological ($n = 115$)	0%	0%	–
	3.4 d	5.1 d	0.08
Articular ($n = 106$)	2.0%	1.8%	0.91
	16.7 d	13.3 d	0.21
CNS infection ($n = 90$)	0%	2.3%	0.49
	6.3 d	4.4 d	0.19
Endovascular ($n = 52$)	9.7%	14.3%	0.68
	11.2 d	10.1 d	0.68

Abbreviations: CNS, central nervous system; DDD, defined daily doses; IAI, intra-abdominal infection; IV, intravenous; LOS, length of stay; SSTI, skin and soft tissue infections; UTI, urinary tract infection.

those antimicrobials, with differences in pathogen risk assessment, additional patient information, antibiotic properties, and physician preferences being the main reasons. Antimicrobials which were comprised in the AS recommendations often included those with a broad spectrum of activity and/or high ecological effect: piperacillin/tazobactam, meropenem, and linezolid. Due to practical issues, 70.8% of interventions were made by typing a note in the EHR so it could be read by the primary provider, followed by phone calls and face-to-face communication, due to technical characteristics of the CDSS, it did not provide direct communication to the EHR, as reported elsewhere.[7]

To assess the effect of the CDSS on the outcomes of patients admitted to our hospital, we began calculating differences in antimicrobial usage. Antibiotic consumption and prescribing rates have been common indicators in

several studies. In two systematic reviews, 10 out of 11 studies (90.0%)[11] and 14 out of 19 studies (73.7%)[30] showed significant decreases in antibiotic usage. On the other hand, Jenkins et al[31] showed that only 1 of 4 studies that focused on antimicrobial consumption had a positive effect (reduction) using a CDSS. We observed a reduction in overall antimicrobial usage from 691.1 to 656.8 DDD/1,000 beds per month. To note, most studies included in the reviews targeted antibiotics (not antifungals), where we also found a significant reduction in consumption from 673.4 to 621.7 DDD/1,000 beds per month ($p < 0.01$). Bond et al[13] stratified differences in consumption for antimicrobials targeted for increased and decreased use, displaying rising and declining rates, respectively. In our study, IV antimicrobials, fluoroquinolones, and IV antimicrobials with good oral bioavailability had relative reductions in their overall usage with statistically significant differences for the last group. A 20% increase in oral compared with IV antimicrobials was also reported by Khadem et al[32] in the 6 months postintervention. We subsequently calculated differences in antimicrobial expenditure, having a relative reduction in €/1,000 beds per month but without significance. Conflicting evidence exists regarding this issue, with CDSS having a positive, negative, or zero effect.[11,30,33] Finally, somewhat reductions appeared in the postintervention period for the proportion of IV antimicrobials with more than 7 days and BSA $\geq$ 72 hours, which were described before as the most recurrent alerts.

Clinical outcomes displayed in this study included mortality and LOS. A paucity quality of evidence is available for CDSS regarding mortality,[8] and Curtis et al[30] calculated a marginal statistically significant effect of this system on mortality (odds ratio = 0.85) showing that only 4 of 20 studies included had relevant reductions. In-hospital mortality for our patients was calculated for those admitted for infectious reasons, who were most often treated with antimicrobials. It resulted in a slightly relevant reduction (6.6–6.2%) without reaching significance. Otherwise, a significant reduction in median LOS for those patients was found ($p < 0.01$). Recently, Yuan et al[33] did not find differences in median LOS or overall mortality in surgical settings. By type of syndrome, significant reductions were found for respiratory infection ($p < 0.01$), urinary tract infection ($p = 0.01$), and skin and soft tissue infections ($p < 0.01$). These results are in accordance with Bond et al,[13] who showed a reduction in LOS for the same types of infections, moreover septicemia. Ridgway et al[29] reported a decrease in LOS for cellulitis but not for other syndromes.

This study has several limitations. First, rates of antimicrobial usage (especially IV antimicrobials) and in-hospital mortality could be deeply influenced by the coronavirus disease pandemic, leading to an increasing number of bacterial coinfection inpatients during the postintervention period (2021–2022) because of second and subsequent surges. However, we reported statistically significant reductions in antibiotic consumption and relative reduction in mortality attributable to infection. Second, the appropriateness of prescribed drugs for our population cannot be evaluated using the measure of antimicrobial consumption (such as septic patients or nosocomial infection), which must be considered on a case-by-case basis. Lastly, this is a single-center study where alert assessment was accomplished by an AS-trained pharmacist with the support of an infectious diseases clinician, but a dual review was not always available due to timely reasons. After all, a single-center study could be reliable because of the different methodologies used in each center, as WASPSS was only evaluated in eight hospitals in Spain.

Conclusion

In conclusion, the implementation of a CDSS in a second-level hospital resulted in a relevant number of AS interventions, turning the work methodology into a personalized and focused manner. Our results showed that antibiotic consumption, use of IV antimicrobials, duration of treatments, and LOS could be improved without affecting mortality using this type of program, therefore being a useful weapon in the fight against inappropriate use of antibiotics and AMR. Further research is needed to elucidate the AS-related alerts that are deemed to be efficient and powerful in the optimization of treatment for infectious syndromes.

Clinical Relevance Statements

This CDSS implementation is generalizable to other institutions considering its simplicity and provides additional evidence about the importance of AS teams in hospitals and primary care centers. The identification of AS alerts with a higher positive predictive value reduces alert fatigue and makes these systems more reliable to apply in the health care setting.

Multiple-Choice Questions

1. Which of the following measures has shown the most relevant reductions after the implementation of CDSS for AS?
   a. Mortality
   b. Length of stay
   c. DDDs/1,000 beds of antimicrobials
   d. Costs of antimicrobials

   Correct Answer: The correct answer is option c. Antimicrobial usage, measured in daily-defined doses per 1,000 beds, has consistently been associated with reduction after the implementation of CDSS for AS activities.

2. What is the estimated percentage of AS alerts that triggered a recommendation in the published evidence?
   a. 0 to 10%
   b. 10 to 20%
   c. 20 to 30%
   d. 30 to 40%

   Correct Answer: The correct answer is option b. The percentage of alerts generated by a CDSS that lead to an AS recommendation ranged from 11 to 18%.

Protection of Human and Animal Subjects

The study was performed in compliance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and was reviewed by the Hospital Universitario Puerta de Hierro Institutional Review Board.

Conflict of Interest

None declared.

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