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Clinical Decision Support Systems and Their Role in Antibiotic Stewardship: a Systematic Review

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Abstract

Purpose of Review The purpose of this article is to perform a systematic review over the past 5 years on the role and effectiveness of clinical decision support systems (CDSSs) on antibiotic stewardship.

Recent Findings CDDS interventions found a significant impact on multiple outcomes relevant to antibiotic stewardship. There are various types of CDSS implementations, both active and passive (provider initiated). Passive interventions were associated with more significant outcomes; however, both interventions appeared effective. In the reviewed literature, CDSSs were consistently associated with decreasing antibiotic consumption and narrowing the spectrum of antibiotic usage. Generally, guideline adherence was improved with CDSS, although this was not universal. The effect on other outcomes, such as mortality, *Clostridiodes difficile* infections, length of stay, and cost, inconsistently showed a significant difference.

Summary Overall, CDDS implementation has effectively decreased antibiotic consumption and improved guideline adherence across the various types of CDSS. Other positive outcomes were noted in certain settings, but were not universal. When creating a new intervention, it is important to identify the optimal structure and deployment of a CDSS for a specific setting.

Keywords Clinical decision support system · CDDS · Decision support system · Antibiotic stewardship · Antimicrobial stewardship

Introduction

Antibiotics have revolutionized modern medicine; however, rising use is threatening the effectiveness of these compounds. Although reports vary, it has been shown that there are high rates of antibiotic misuse. A 2016 JAMA article found that only about 70% of antibiotic use in the USA was appropriate [1]. Generally, reports estimate antibiotic misuse between 20 and 50% [2–7]. This misuse creates a selective pressure leading to antibiotic resistance. In a 2013 report, the CDC estimated that 2 million people in the USA are infected by antibiotic-resistant organisms, leading to 23,000 deaths annually, based on very conservative estimates. It is reported that antibiotic resistance may cost the USA up to $20 billion in excess direct healthcare costs, and $35 billion in lost productivity yearly. In short, it is considered one of the biggest public health care challenges in modern medicine [8]. In order to combat the growing threat of antibiotic resistance, new and innovative interventions are required to curb antibiotic overuse in a safe and effective manner.

The mandate for broad and robust antibiotic stewardship programs (ASPs) is a direct result of this growing threat of antimicrobial resistance. There are many elements that make up a strong ASP. In 2014, the CDC released guidelines, highlighting the 7 core elements of an ASP: leadership, accountability, drug expertise, action, tracking, reporting, and education [9]. Similarly, the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) have released guidelines that include

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recommendations for ASPs to provide education, clinical pathways, and guidelines for antibiotic use [10]. Given the rise of electronic health records, handheld devices, and other advances in information technology, there is great potential to allow for up to date, robust aids and guidelines tailored to specific hospital systems. Unique antimicrobial guides can now be created for individual hospitals. This can potentially go further, with interactive guides giving patient-specific recommendations based on specific risk factors and symptoms, using computer (or clinical) decision support systems (CDSS).

CDSSs are defined as computer applications created to give guidance to practitioners in making both diagnostic and therapeutic choices for patients. This is broadly defined to include a wide array of applications, from pop-up reminders during a patient encounter, to automated order entry, to electronic guides, including dynamic interactive programs that tailor guidelines to specific patients [11]. While this has been applied to many fields in medicine, it can be particularly useful when applied to antibiotic stewardship. This directly applies to the core elements of action and education, and provides clinical pathways and guidelines as recommended by IDSA and SHEA. There have been several review articles looking at CDSS broadly, although specific aspects of CDSS programs have not been explored fully. In this article, a systematic review of the literature was performed, reviewing the current status of interactive, patient-centered CDSS on antibiotic use.

Methods

A systematic literature review was performed using PUBMED on March 27, 2019. An initial search using the term "antibiotic + 'decision support'" was performed. A subsequent search "(antibiotic OR antimicrobial OR antibacterial) + ("Decision Support System" OR CDSS)" was performed. Only English language articles were considered. The search criteria were restricted from studies that were published from January 1, 2014, until present.

CDSS includes a wide spectrum of potential interventions. We defined CDSS as any electronic guidance tailored towards direct antimicrobial and/or infection-related patient care recommendations to providers. This included automatic alerts based on specific antibiotic use and patient symptoms, algorithm-based questionnaires within guides, and specific diagnoses. Only studies assessing antimicrobial use were included. Inclusion criteria included any studies that included a clinical support–based feedback system to help guide antibiotic selection. Providers were defined as physicians, mid-level providers, nursing, and pharmacy. Studies included intensive care unit (ICU), emergency department (ED), and inpatient care. Exclusion criteria included studies that did not have defined outcomes, studies that evaluated electronic-posted guidelines without individualized recommendations tailored to a patient, studies that did not identify electronic intervention(s), and non-human studies. Study quality was grossly estimated as ranging from 1 to 4 (with 4 representing higher quality). One included descriptive studies, and those without statistical representation. Two included observational studies with limitations such as small sample size, missing or ill-defined statistical analyses, or other significant limitations to methodology. Three represented observational studies with more adequate sample size and statistical analyses. Four included experimental studies, such as randomized controlled clinical trials.

The studies were categorized by several variables, including active vs passive status and CDSS category, and the following elements were assessed: study design, intervention target, number of subjects, and primary and secondary endpoints. Active was defined as a DSM intervention activating automatically based on a set of criteria. Passive was defined as initiated by the provider. CDSS categories included alert-based, automatic order placement, guideline listing, data collection and compiling, antibiotic/order restriction, diagnostic and/or treatment recommendations, or developmental CDSS that develops new algorithms based on patient data. Primary endpoints included time to antibiotic administration, mortality, adherence to recommendations/guidelines, antibiotic usage, CDSS usage, consultation usage, cost, coverage of organism, dosing, IV to PO, length of stay, urinalysis ordering rate, patient outcomes, user satisfaction, antibiotic resistance rate, performance metrics of developmental algorithms (sensitivity/specificity/positive predictive value/negative predictive value), total interventions made, and workflow. Intervention targets included age category (adult, pediatric, newborn), department (ED, family practice, surgery, junior physicians, ICU, neonatal intensive care unit (NICU), cardiac intensive care unit (CICU) disease type (respiratory, urinary, gastrointestinal (GI), nosocomial infections not otherwise specified (NOS), bacteremia/sepsis). Not all studies had a defined intervention, and some had interventions in multiple subcategories. Statistical significance for both primary and secondary endpoints was recorded, as well as relevant study statistic regarding the primary endpoint. Descriptive statistics were calculated for the categories and subcategories, including total number and percentage. Key studies were described in detail. Descriptive statistics were calculated in SAS 9.4.

Results

Summary of Article Search

The PubMed searches yielded 374 articles. Of them, 305 were not related to either antibiotics or electronic support systems.

Of the remaining 69, 4 were articles related to veterinary medicine, 1 was a field other than ASP/infectious diseases, and 10 were ASP review articles. Of the remaining 54, 7 did not have defined outcomes related to CDSS, as they were descriptive in their implementation of the CDSS, or opinion pieces. One was removed as it focused on identifying risk factors for multidrug-resistant (MDR) organisms, not on CDSS. One was a duplicate study. A total of 45 articles were then reviewed (Fig. 1).

The 45 studies reviewed are summarized in Table 1. Of the 45 studies, 10 (22.2%) were from 2014, 7 (15.6%) were from 2015, 6 (13.3%) were from 2016, 6 (13.3%) were from 2017, 10 (22.2%) were from 2018, and 6 (13.3%) were from 2019. Twenty-four of the 45 interventions were active (53.3%), 15 of 45 were passive (33.3%), 5 of 45 had both an active and passive component (11.1%), and 1 of 45 did not meet criteria for either (2.2%). Nineteen (42.2%) of the CDSS interventions gave specific recommendations, 10 (22.2%) were alert-based, 3 (6.7%) placed orders directly, 7 (15.6%) listed guidelines without offering specific recommendations, 5 (11.1%) collected and compiled data, 4 (8.9%) restricted antibiotics and/or diagnostic orders, and 4 (8.9%) collected data for machine-

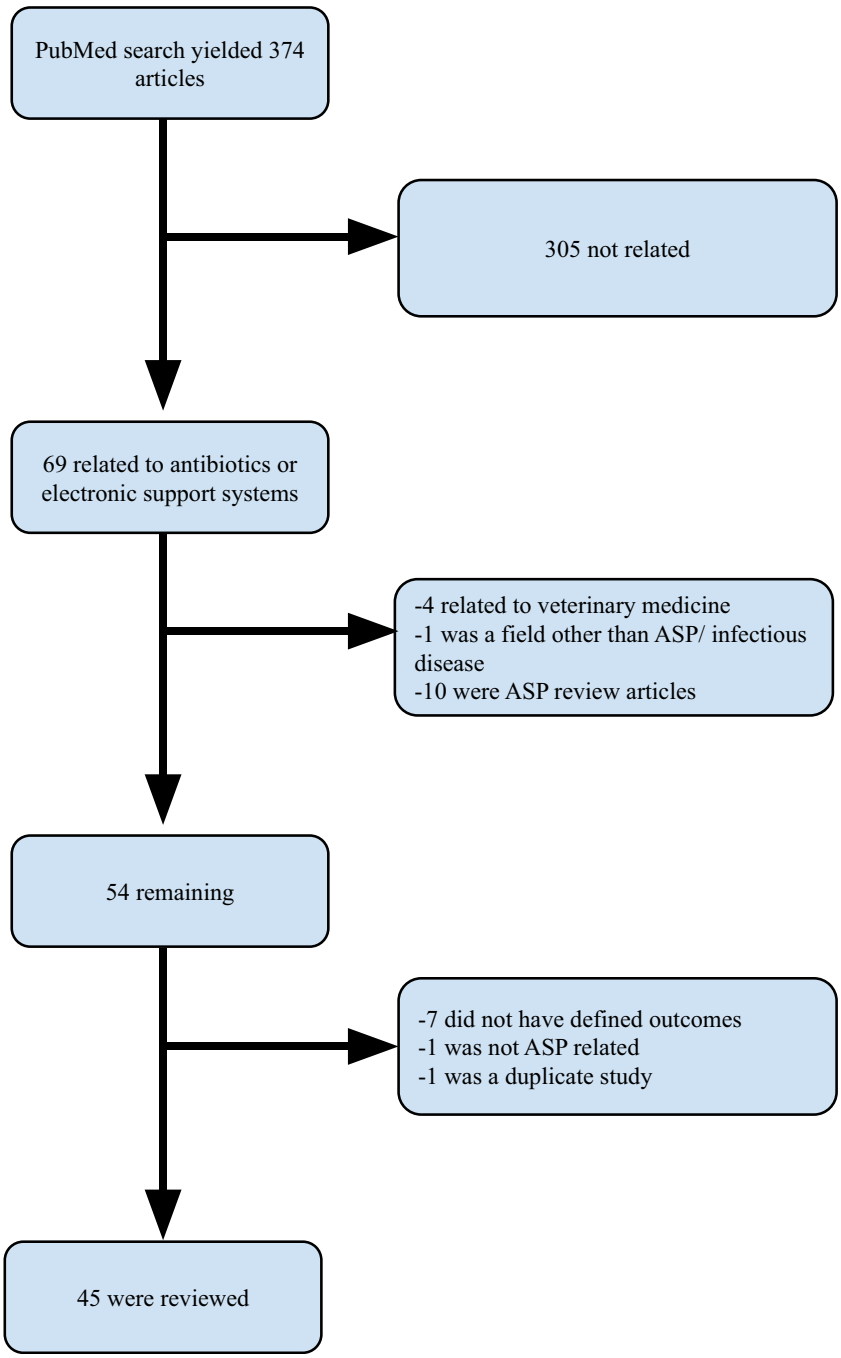

Fig. 1 Flowchart of PubMed search

Table 1 Summary of studies reviewed

Author	Year	Active/ passive	CDSS category	Primary endpoint	Secondary endpoint(s)	Intervention target	Study design	*N*	Statistically significant (primary)	Statistically significant (secondary)	Quality
[12] - Heard	2019	Active	Alert	Total interventions	Types of interventions, time taken		Retrospective cohort	264			**
[13] Mcfadden	2019	Active	Guidelines	Resistance rate		Disease type: Gram-negative bacteremia	Multi-center cohort study	1832			**
[14] - Gulliford	2019	Passive	Recommendation	Antibiotic usage		Disease type: respiratory	Cluster RTC	582,675 pt.*years	Yes		****
[15] - Motaghim	2019	Active	Restriction	Antibiotic usage	Fevers, supplemental O2 usage	Age: pediatric, disease type: pneumonia	Historical control and prospective cohort	241	No	Yes: supplemental O2	***
[16] - Jones	2019	Both	Recommendation	Adherence to guidelines		Disease type: pneumonia	Multi-center retrospective cohort	1722	Yes		***
[17]- Downing	2019	Active	Alert	Adherence to guidelines	Mortality, LOS, transfer to ICU, IV fluids	Disease type: sepsis	RTC, single blind	1123	No	No	****
[18] - Ozkaynak	2018	Active	Developmental	Work flow			Observational	23			*
[19]- Wang	2018	Passive	Data collection	Work flow			Observational				*
[20] - Jung	2018	Active	Order placement	Time to therapy	Mortality, LOS	Disease type: sepsis	Control before and after study	30	Yes	Yes: LOS	***
[21] - Simões	2018	Passive	Recommendation	Not defined			Observational time-motion study				*
[22] - Keller	2018	Active	Alert	Monthly UAs ordered	UC ordered after UA, antibiotic usage		Quasi-experimental prospective interrupted time series		No	Yes	**
[23]- Akhloufi	2018	Active	Alert	IV to PO			Prospective cohort	840			**
[24] - Young	2018	Passive	Recommendation	CDSS usage			Cross-sectional observational study	23,734	Yes		**
[25]- Blanco	2018	Passive	Guidelines	Barriers to use			Observational	34			*
[26] - Gunn	2018	Active	Restriction + alert	Antibiotic usage		Disease type: sinusitis, bronchitis, UTI	Single-center, historical control and prospective cohort	744	Yes		***
[26]- Haque	2018	Passive	Recommendation	Adherence to guidelines		Disease type: cholera	Control before and after study	841	Yes		***
[27] - Giuliano	2017	Passive	Recommendation	User satisfaction	Work flow		Multi-center qualitative interviews	19			*
[28]- Messacar	2017	Active	Recommendation	Time to therapy	Unnecessary antibiotic for contaminants	Age: pediatric, disease type: bacteremia	Pre/post quasi-experimental	300	Yes	Yes	***
[29] - Nault	2017	Active	Data collection + alert	LOS	Antibiotic usage, cost, guideline adherence		Retrospective cohort	40,605 admis-sions	Yes	Yes	***
[30]- Berrevoets	2017	Active	Alert	IV to PO	Median treatment time		Controlled, interrupted time series	5885	Yes	Yes	***
[31] - Bond	2017	Active	Restriction + guidelines	Antibiotic usage	Mortality, cost, HCA-CDI rates, LOS		Interrupted time series	48 months	Yes	Yes: CDI rates, cost	***
[28]- Gifford	2017	Passive	Recommendation	Adherence to guidelines		Disease type: respiratory tract	Retrospective cohort	1131	Yes		***
[32] - Huh	2016	Passive	Recommendation	Antibiotic usage	Resistance rate, cost, LOS		Interrupted time series		Yes	Yes: LOS	**
[33] - Okumura	2016	Active	Restriction	Antibiotic usage	Cost	Department: surgery	Cross-sectional	12 years	Yes	Yes	**
[34] - Caplinger	2016	Active	Alert	Antibiotic usage	Usage in low-risk β-lactam allergy.		Single-center pre/post-intervention retrospective interrupted time series	127	Yes	No	***
[35] - Beaudoin	2016	Active	Developmental	Adherence to guidelines			Single-center prospective observational study	374			*

Table 1 (continued)

Author	Year	Active/ passive	CDSS category	Primary endpoint	Secondary endpoint(s)	Intervention target	Study design	*N*	Statistically significant (primary)	Statistically significant (secondary)	Quality
					Identification of inappropriate prescriptions						
[36]- Chow	2016	Both	Recommendation	Adherence to recommendations	Department usage		Multiphase cohort study	9072	Yes	Yes	**
[37] - Chow	2016	Both	Recommendation	Adherence to recommendations		Department: ICU, disease type: pneumonia	Single-center prospective cohort study	283	Yes		***
[38]- Tsoukalas	2015	Active	Developmental	Patient outcome	Mortality and LOS	Disease type: sepsis	Retrospective cohort	1492 patients	Yes	Yes	***
[39] - Dean	2015	Active	Alert + recommendation	Mortality	Results by disease state	Department: ED, disease type: CAP/HCAP	Prospective, controlled, quasi-experimental	4758	No	Yes: CAP mortality	***
[40]- Chow	2015	Both	Recommendation	Mortality	CDI, MDRO infections		Prospective cohort study	1886	No	No	***
[41] - Faine	2015	Active	Order placement	Dosing	Mortality, LOS	Department: ED	Retrospective before-after cohort study	278	Yes	No	***
[42]- Diasinos	2015	Passive	Recommendation	Dosing			Retrospective cohort + interview	68			**
[43] - Michaelidis	2015	N/A	Not described	Cost	Antibiotic usage	Department: ambulatory disease type: acute bronchitis	Clinical trial-based cost-effectiveness analysis	5 years	Yes: printed decision support superior	Yes(variable)	**
[44] - Kannry	2015	Both	Recommendation	Adherence to recommendations			Observational study				*
[45] - Payne	2014	Passive	Guidelines	User satisfaction		Department: junior physicians	Pilot study - descriptive survey	39 junior doctors			*
[46]- Mani	2014	Active	Developmental	Sensitivity, specificity, PPV NPV		Age: neonates, disease type: sepsis	Single-center retrospective cohort - 9 algorithms assessed	299 patients	Yes		***
[47] - Fonzo-christe	2014	Active	Recommendation	Dosing	Gentamicin concentrations	Age: <30 days old	Retrospective historically controlled cohort	134	Yes	Yes	***
[48] - Rodriguez-Maresca	2014	Passive	Data collection + recommendation	Coverage of organism	Mortality, LOS	Department: ICU disease type: nosocomial infections	Prospective quasi-experimental study	218	Yes	No	***
[49] - Arobe	2014	Passive	Recommendation	Coverage of organism	Mortality, LOS		Retrospective and prospective cohort	511 patients	Yes	No	***
[50]- Gulliford	2014	Active	Data collection + guidelines	Consultation usage	Rate of antibiotic prescribing	Department: family practice	Cluster RCT	603,409 patients	Yes	Yes	****
[51] - Hum	2014	Passive	Recommendation	CDSS usage	Providers perceptions	Age: newborn, department: NICU	Multi-center prospective cohort and interview	2009 patients			**
[52]- May	2014	Active	Alert + order placement	Adherence to guidelines		Age: pediatric, department: cardiac ICU	Retrospective cohort	114 patients	No		**
[53] - Demonchy	2014	Active	Data collection + guidelines	Adherence to guidelines		Department: ED, disease type: UTI	Multi-center prospective before and after controlled cohort	912 patients	Yes* (1 of 3 EDs)		***
[54]- Nachtigal	2014	Passive	Guidelines	Adherence to guidelines	Mortality, antibiotic-free days	Department: ICU	Prospective before/after cohort	1316 patients	Yes	Yes	***

based learning/CDSS development (Fig. 2). Of the primary outcomes, 2 of the 45 studies (4.4%) measured the time from intervention to antibiotic administration, 7 (15.6%) measured antibiotic usage, 2 (4.4%) measured mortality, 11 (24.4%) measured adherence to national guidelines and/or hospital recommendations, 2 (4.4%) measured CDSS usage, 1 (2.2%) measured consultation rates, 1 (2.2%) measured cost, 2 (4.4%) measured whether the empiric antibiotic covered the infectious organism isolated, 3 (6.7%) assessed antibiotic dosing, 2 (4.4%) assessed IV to PO conversion rates, 1 (2.2.%) length of stay, 1 (2.2%) assessed urinalysis rates, 1 (2.2%) assessed general patient outcomes, 2 (4.4%) assessed user satisfaction with the CDSS, 1 (2.2%) assessed antimicrobial resistance rates, 1 (2.2%) assessed sensitivity/specificity/PPV/NPV of CDSS algorithms created, 1 (2.2%) assessed total number of interventions, 2 (4.4%) assessed ASP work flow, 1 (2.2%) assessed barriers to use, and 1 (2.2%) was purely descriptive with no defined outcomes.

Studies were also divided by intervention target. Of the 45 studies, 6 (13.3%) intervened on pediatric patients. Of these 6, 3 (50%) assessed the neonatal/newborn population. Twelve of the 45 (26.7%) studies assessed specific departments. Three of the 12 (25.0%) focused on emergency departments, 2 of the 12 (16.7%) assessed family practice/ambulatory settings, 1 of 12 (8.3%) assessed surgical staff, 3 of 12 (25.0%) assessed medical ICUs, 1 of 12 (8.3%) assessed NICUs, 1 of 12 (8.3%) assessed cardiac ICUs, and 1 of 12 (8.3%) assessed junior physicians. Seventeen of the 45 (37.8%) studies intervened on specific organ systems/disease types. Seven of the 17 (41.2%) intervened on respiratory tract infections, 1 of 17 (5.9%) assessed urinary infections, 1 of 17 (5.9%) intervened on both respiratory and urinary infections, 1 (5.9%) intervened on gastrointestinal infections, 1 (5.9%) on nosocomial infections not otherwise specified, and 6 (35.3%) intervened on bacteremia/sepsis (Fig. 3).

Of the 45 studies, 13 (28.9%) were descriptive, and one other did not include statistics that would show statistical significance. Of the 32 remaining, 26 (81.3%) found significance in the primary outcome. Of the 45 articles, 22(48.9%) assessed significance of secondary outcomes, of which 16 (72.7%) found a significant effect in at least one secondary outcome. A total of 29 of the 32 (90.6%) studies found a statistically significant result in at least one measure.

Antibiotic Consumption Rates

Antibiotic consumption/prescribing rates were a common outcome, with 11 studies having this as the primary or secondary endpoint [14, 15, 22, 26, 29, 31–34, 43, 50, 55]. Of the 11 studies, 10 (90.9%) found a statistically significant decrease in consumption. In one study, a single-centered prospective cohort implemented an electronic-based antibiotic restriction and approval section, coupled with a best practice alert on fluoroquinolone use in sinusitis, bronchitis, and urinary tract infections. Fluoroquinolone use in the CDSS group was 62/394 (15.7%), compared with 86/350 (24.6%) in the control group ($p = 0.0035$). Of note, no patients in this study qualified for the diagnosis of acute sinusitis [26]. Another study assessed the use of anti-pseudomonal carbapenems (APC) in patients with a beta-lactam allergy. In this study, information regarding beta-lactam cross-reactivity was inserted

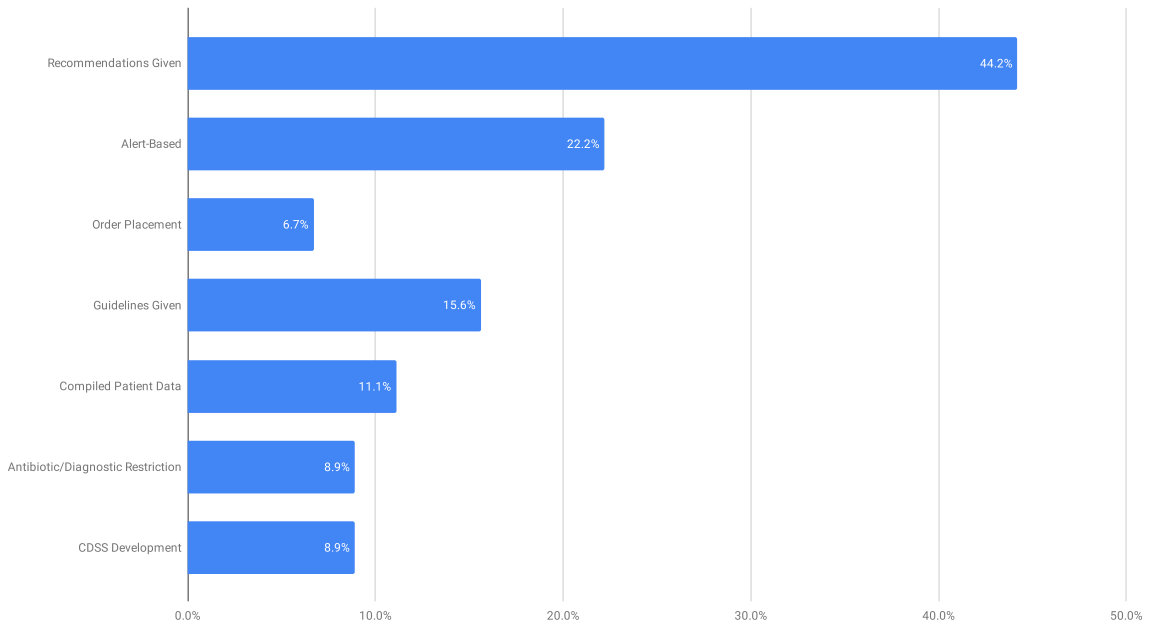

Fig. 2 Major categories of clinical decision support systems

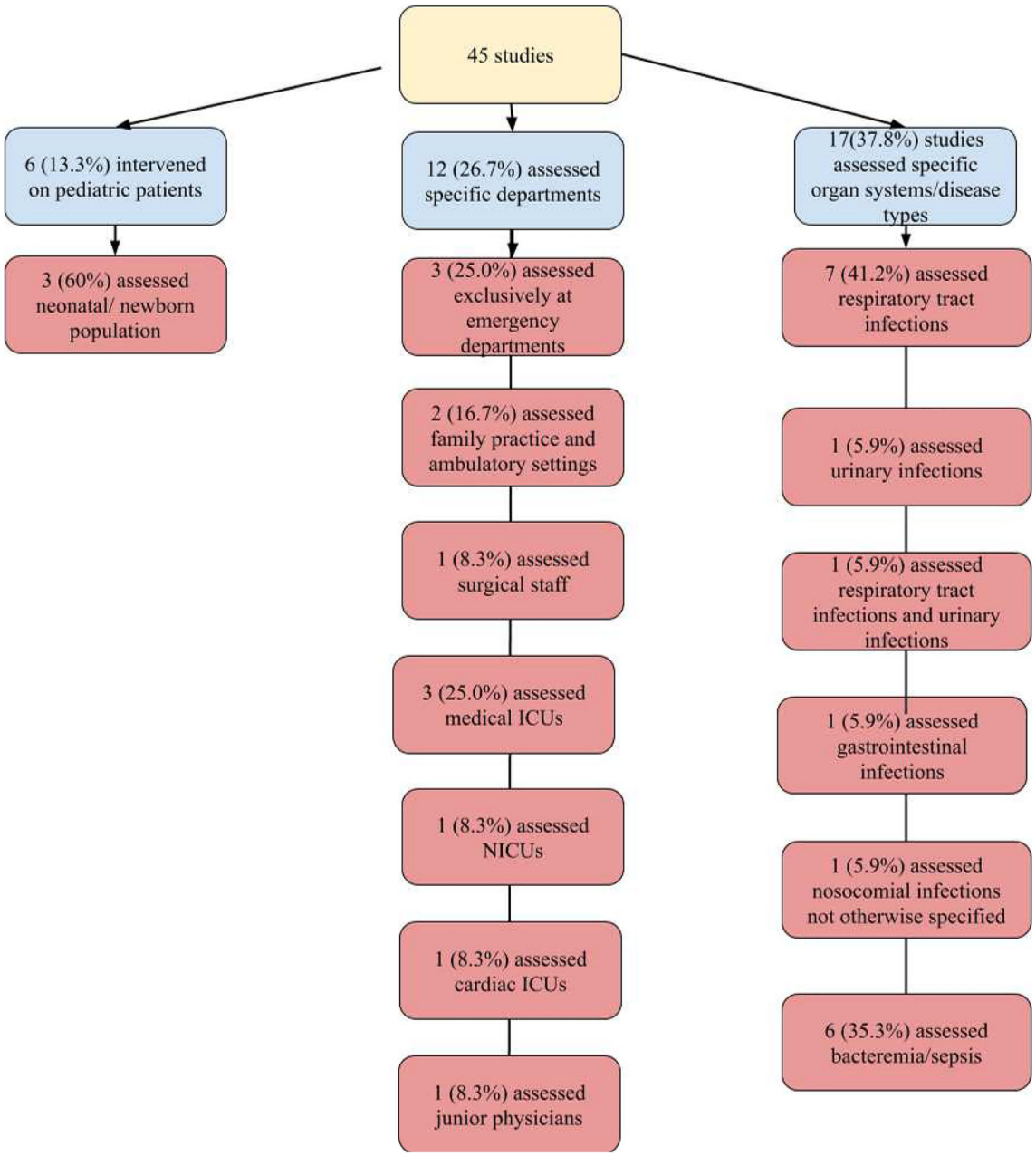

Fig. 3 Studies divided by intervention target

into a CDSS. Aggregate monthly APC initiations decreased from 7.01 to 6.14 per 1000 patient-days ($p = 0.03$). No adverse events were observed [34]. Conversely, a 2019 study created an automated antibiotic restriction protocol for presumptive uncomplicated community-acquired pneumonia. Pre- and post-intervention antibiotic consumption were not significantly changed, although both arms noted high use of narrow-spectrum penicillins (81.3% vs 77.6% ($p = 0.47$)), and macrolides (53.7% vs 61.7% $p = 0.21$). Supplemental oxygen use was increased from 30.6% to 54.2% ($p < 0.001$), which was a secondary outcome of the study [15]. One study assessed cefazolin use in surgical prophylaxis. This cross-sectional analysis used computerized provider order entry (CPOE) and CDSS, measuring cefazolin usage and cost analysis. A reduction of 6.31 to 2.15 defined daily doses/100 bed-days, over a 9-year period, with reduced cost, was found [33].

Adherence to Guidelines/Recommendations

Many studies assessed the effect of CDSS on adherence to recommendations or national guidelines [16, 17, 29, 35–37, 44, 52–54, 56, 57]. These studies inconsistently showed good adherence to following CDSS recommendations. A recent

study in patients with pneumonia found that 90% of recommendations to reject broad-spectrum antibiotics by their CDSS were followed [16]. Conversely, a study of 3 French EDs assessed a CDSS for community-acquired UTIs, over a 30-week period. Overall adherence to national guidelines of antibiotic prescribing improved in only 1 of the 3 locations. The CDSS was used in 59% of cases, and in that subset, appropriate use significantly improved. However, overall implementation of the CDSS was not statistically significant in the 3 settings combined [53].

Similarly, 2 studies assessed CDSS uptake/usage [24, 51]. A study in a neonatal intensive care unit (NICU) assessed the effectiveness of a CDSS. In this study, tool activation aggregated culture results and lab values, along with prescribing recommendations. The study found that providers only viewed prescribing recommendations on 15% of the tool activation, and the tool was only activated by 37% of providers. There were concerns with the tool's visibility as a barrier to use [51]. Another study was a cross-sectional analysis of a smartphone-based mobile app. After implementation, usage was tracked over a 1-year period. They found that over this time, the app was accessed 23,734 times on 5097 unique devices. In addition, utilization increased by an average of 94 devices per month ($p < 0.001$). Usage increased significantly on smartphones ($p < 0.001$), desktops ($p < 0.001$), but not on tablets ($p = 0.14$). The majority of unique devices were desktops (3151, 62.1%), but most sessions were accessed on smartphones (18,860, 79.5%). Mean session duration was 2:22 minutes [24].

Dosing

Three studies assessed tools aimed at dosing management of antibiotics [41, 42, 47]. Two studies focus on gentamicin dosing, and one focused on vancomycin dosing. One study found a statistically significant effect on gentamicin dosing, whereas the other did not. A 2014 study by Fonzo-Christe et al. assessed a CDSS to aid with gentamicin dosing in newborns (< 30 days old); providers received computerized support to assist with once-daily dosing (ODD) or extended-interval dosing (EID). When comparing with the year prior to implementation, ODD or EID was used in 97.7% compared with a control of 61.6% ($p = 0.001$). In addition, the number of blood samples per patient was significantly reduced. Finally the probability of a trough concentration < 1 mg/dl was increased in the CDSS group, with an OR of 2.02 (1.01–4.02 $p = 0.045$) [47].

Conversely, a 2015 study by Diasinos et al. assessed if individualized doing of gentamicin based on computerized support systems was more effective than traditional nomograms, based on 2010 Australian Therapeutic Guidelines. Sixty-eight cases of continued therapy were evaluated. Of this, 55% went unmonitored. Of the 30 that were monitored, only 4 used the available CDSS, and only 1 recommendation was initiated. Physicians were interviewed in phase two of the study. Regarding the computerized dosing tool, the majority of providers did not know that it existed and used the traditional nomogram. One provider noted that it was too difficult to access. Multiple doctors cited "alert-fatigue" as an issue [42].

A 2015 study by Faine et al. assessed vancomycin dosing in the ED for critically ill patients, using an EMR-based dosing tool. Overall, a dose increase from 14.1 to 16.5 was noted with the tool ($p < 0.001$). There was an improvement in the appropriate dosing of the first dose, from 24.0 to 34.3%, although this was not clinically significant ($p = 0.07$). Twenty-eight-day in-hospital morality was a secondary measure, which was not significantly changed [41].

Two studies assessed the impact of CDSS on IV to PO conversion of antibiotics, one directly and one indirectly [23, 30]. A 2017 study by Berrvoets found that, using a combination of an electronic trigger tool that identifies candidates that could be converted to PO therapy, and weekly education sessions, there was a 19% decrease in IV prescriptions lasting > 72 h ($p < 0.01$). The median IV antibiotic days decreased by 0.8 days ($p < 0.05$), which was statistically significant. Secondary analysis showed that providers were 72% adherent to this reminder [30]. A 2018 study by Akhloufi assessed the relevance and usefulness of alerts created by their CDSS. An alert was considered relevant if the antibiotic could be discontinued or switched to PO. 53.5% of the alerts were deemed relevant. However, only 10.1% were clinically useful, as the physician had already chosen to de-escalate therapy prior to the alert [23].

Time to Optimal Therapy

Two studies assessed time to antibiotic therapy in bacteremia/sepsis, both of which found statistically significant outcomes [20, 28]. For instance, one study focusing on bacteremia in a pediatric population assessed the median time to optimal therapy, defined as time from blood culture collection to start of a pathogen-specific regimen, before and after the initiation of a CDSS targeting children with positive blood cultures, in conjunction with a FilmArray blood culture identification panel. The median time to optimal therapy decreased from 60.2 to 26.7 h ($p = 0.001$). As a secondary outcome, unnecessary antibiotic initiation on patients with organisms that were considered contaminants decreased from 76 to 26% ($P < 0.001$) [28].

Mortality

Patient outcomes were also a common primary endpoint in many studies [17, 20, 31, 38–41, 48, 49, 54]. While many found significance in primary and secondary outcomes, results were inconsistent. Ten studies assessed mortality as a

primary or secondary outcome, and only 2 studies found a statistically significant effect (20%). In one study, a data-driven probabilistic framework for clinical decision support in sepsis-related care was implemented. A predictive model was created based on culture results, temperature, respiratory rate, white blood cell count, mean arterial pressure, and lactate levels. Using the partially observable Markov decision process (POMDP), all potential combinations of vancomycin, cefepime, metronidazole, ceftriaxone, meropenem, LOS, and mortality were predicted, and the optimal antibiotic policy was recommended. Favorable patient outcomes were seen in 49% with the data-derived policies vs 37% in alternative policies ($p = <0.001$). When the optimal policy was followed, 387 (25.9%) patients had 90% transitioned to a better patient state, whereas for those that did not, 503 (33.7%) patients had 90% transitioned to a worse state ($p < 0.001$). The system was able to predict mortality rates and LOS with high accuracy (AUC of 0.7 with an accuracy of 0.82, and AUC of 0.69 to 0.73 with accuracy from 0.69 to 0.82, respectively) [38]. Another prospective before and after cohort study implemented a CDSS in an ICU setting. This CDSS offered algorithmic guidelines on treatment options for specific infections, use of antibiotic agents, and microbiologic diagnostics. The primary endpoint was adherence to recommended guidelines, and secondary endpoints were mortality and antibiotic-free days. Guideline adherence improved from 61 to 92% after 1 year of implementation, but this dropped to 76% by year 2, and 71% by year 3 ($p = 0.178$ from year 2 to 3). Mortality for those with low guideline adherence was higher than in those with high guideline adherence (12.3 to 8% ($p = 0.014$)) [54].

Clostridiodes Difficile Rates

Two studies assessed *Clostridiodes difficile* rates, with only 1 finding a statistically significant difference in rates [31, 40]. In this study, from New South Wales, an interrupted time series from 5 hospital systems was performed. The CDSS was an internet browser–based application that handled antibiotic restrictions and approvals, while offering guidance for appropriate use of antibiotics. Endpoints included the effect of the intervention on targeted antimicrobial use, antimicrobial cost, healthcare-associated *Clostridiodes difficile* infection rates, infection-related length of stay, and standardized mortality ratios. Post-intervention, antimicrobials targeted for increased use increased from 223 to 293 defined daily doses/1000 occupied bed-days/month (DDDs/1000 OBDs/month) ($p < 0.01$), and antimicrobials targeted for decreased use fell from 254 to 196 DDDs/1000 OBDs/month ($p < 0.01$). *Clostridiodes difficile* rates decreased post intervention by −0.2 cases/10000 OBDs/month ($p < 0.01$) [31].

Length of Stay

Nine studies assessed LOS as a primary or secondary outcome [17, 20, 29, 31, 32, 38, 41, 48, 49]. Four (44.4%) found a significant change [20, 29, 32, 38]. A 2018 study used a commercially available bedside clinical surveillance system to create a sepsis screen score (SSS), which predicted sepsis in patients. By adding this score to the display, a statistically significant decrease to time from SSS positivity to antibiotic administration (55.3 to 16.2 h) and ICU and hospital length of stay were found ($p < 0.01$) [20]. In another study in 2017, a quasi-experimental retrospective interrupted time series was performed. Pharmacist-led prospective audit and feedback was performed, when triggered by the CDSS, based on published and local guidelines. In total, 40,605 hospitalizations and 35,778 patients were reviewed. A decrease in length of stay by 0.92 days ($p < 0.01$) was noted. Also noted in this study, antibiotic consumption decreased by 28 days of therapy/1000 patient*days ($p = 0.01$), antimicrobial spending with variable price decreased by $13,589 ($p < 0.03$), and non-concordance with local prescribing guidelines decreased by 2.3% ($p = 0.04$). [29]

Cost

Five studies assessed CDSS cost. Of the 5 studies, 2 found clinically significant benefits (40%), 1 found clinically significant increased cost (20%), and 1 showed mixed results (20%) [29, 31–33, 43]. In one 2015 study, a randomly controlled trial of an ambulatory center evaluated printed decision support (PDS) vs computerized decision support (CDS) vs usual care (UC). Of these models, cumulative 5-year cost per 5 cases of acute bronchitis was $2574, compared with $2768 for usual care, and $2805 for computerized clinical support. Using a one-way sensitivity analysis, PDS dominated UC and CDS in cost. Regarding use, there was no significant difference in antibiotic use between PDS and CDS, but both were superior to UC[20]. In contrast, a 2016 cross-sectional study targeting cefazolin dispensing in surgical prophylaxis CDSS was estimated to have reduced cefazolin use from 6.31 DDD/100 bed-days to 2.15 DDD/100 bed-days over a 9-year period ($p < 0.05$), with an estimated savings of $50,433.39 [33]. Finally, a 2017 interrupted time series that was previously discussed assessed cost as a secondary outcome. Initially, cost decreased by AUD $64,551/month ($p < 0.01$), but then subsequently increased by AUD $7273/month ($p < 0.01$) [31].

Conclusion

Our review reveals that CDSS interventions may have a significant impact on multiple outcomes relevant to antibiotic stewardship. Passive (provider initiated) interventions appear

more robust than active interventions (although significant outcomes have been described with both). In the reviewed literature, CDSS was consistently associated with decreasing antibiotic consumption and narrowing the spectrum of antibiotic usage. Generally, guideline adherence was improved with CDSS, although this was not universal. An impact of CDSS on patient outcomes was inconsistently demonstrated.

A major limitation with the existing CDSS literature is great heterogeneity in CDSS interventions and study settings. At this point, it is not clear which CDSS modalities and what outcome and process metrics are optimal for various clinical care settings.

An important consideration is the overall utilization and acceptability of CDSS by providers. In one usage study, implementation of new technology was well received, with increased usage over time, particularly among smartphone usage [24]. In another study, poor utilization of the CDSS was noted. In this study, the authors noted poor visibility, and other issues with EMR upgrade and change that interfered with the rollout of the CDSS [51]. A critical element of CDSS design and implementation is its acceptability and utility to front-line providers. Additionally, potential adverse consequences from the deployment of CDSS need to be considered when being adopted.

While limitations exist, this review details multiple potential options for CDSS ranging from low to high resource utilization. Although CDSS appears promising as a tool to improve antimicrobial prescribing, more studies are needed to determine the most optimal structure and deployment of CDSS for specific settings and interventions.

Compliance with Ethical Standards

Conflict of Interest Barry Rittmann and Michael Stevens declare that they have no conflict of interest.

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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