Title

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Journal

Journal of Antimicrobial Chemotherapy, 76(8)

ISSN

0305-7453

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Publication Date

2021-07-15

DOI

10.1093/jac/dkab138

The feasibility of implementing antibiotic restrictions for fluoroquinolones and cephalosporins: a mixed-methods study across 15 Veterans Health Administration hospitals

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Running title: Feasibility of antibiotic restrictions

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Abstract: 249
Word count: 3,481

Abstract

Introduction: The optimal method for implementing hospital-level restrictions for antibiotics that carry a high-risk of *Clostridioides difficile* infection has not been identified. We aimed to explore barriers and facilitators to implementing restrictions for fluoroquinolones and third/fourth-generation cephalosporins.

Methods: This mixed methods study across a convenience sample of 15 acute-care hospitals within the Veterans Health Administration included electronic surveys and semi-structured interviews (9/2018-5/2019). Surveys on stewardship strategies were administered at each hospital and summarized with descriptive statistics. Interviews were performed with 30 antibiotic stewardship program (ASP) champions and, at five sites, 19 additional stakeholders; transcripts were analyzed using thematic content analysis.

Results: The most restricted agent was moxifloxacin, which was restricted at 12 (80%) sites. None of the 15 hospitals restricted ceftriaxone. Interviews identified differing opinions on the feasibility of restricting third/fourth-generation cephalosporins and fluoroquinolones. Some participants felt that restrictions could be implemented in a way that was not burdensome to clinicians and did not interfere with timely antibiotic administration. Others expressed concerns about restricting these agents, particularly through prior approval, given their frequent use, the difficulty of enforcing restrictions, and potential unintended consequences of steering clinicians towards non-restricted antibiotics. A variety of stewardship strategies were perceived to be effective at reducing the use of these agents.

Conclusions: Across 15 hospitals, there were differing opinions on the feasibility of implementing antibiotic restrictions for third/fourth-generation cephalosporins and fluoroquinolones. While the perceived barrier to implementing restrictions was

frequently high, many hospitals were effectively using restrictions and reported few barriers to their use.

Introduction

Clostridioides difficile infection (CDI) is the most common healthcare-associated infection in the United States.[1] In 2017, there were an estimated 223,900 hospitalizations and 12,800 deaths due to CDI.[2]

Antibiotic stewardship is an important strategy for controlling CDI. Hospitals that have reduced their use of fluoroquinolones and advanced-generation cephalosporins have achieved reductions in CDI.[3-5] In England, national reductions in CDI were largely driven by restricting fluoroquinolone use.[6] According to a 2014 meta-analysis, antibiotic restrictions are more effective than persuasive strategies, such as prospective audit-and-feedback, at reducing CDI.[7] The use of antibiotic restrictions can also decrease antibiotic resistance, especially among gram-negative bacteria.[8, 9]

While antibiotic restrictions are considered a core strategy for antibiotic stewardship, the implementation of restrictions can be difficult, as it requires leadership support and sufficient stewardship resources.[10] There is little data on how many hospitals in the United States are restricting antibiotic agents that carry a high-risk of CDI. In a 2015 survey of all hospitals within the Veterans Health Administration (VHA), less than 20% of hospitals restricted cefepime, 11% restricted ciprofloxacin, and 10% restricted levofloxacin.[11] In general, efforts to control the use of fluoroquinolones and third/fourth-generation cephalosporins can be complicated by clinicians' strong preference for prescribing some agents within these classes.[12]

Given the substantial burden of CDI, there is a need to decrease the use of antibiotic agents that are strongly associated with an increased risk of CDI. However, the optimal approach to implementing antibiotic restrictions for high-risk antibiotic agents is unclear. In this study, we explored barriers and facilitators to implementing antibiotic restrictions for fluoroquinolones and third/fourth-generation cephalosporins across 15 hospitals within VHA.

Methods

The study was approved by the Veterans Affairs Central Institutional Review Board and Research and Development Committee at the Iowa City Veterans Affairs Medical Center. Both electronic surveys were designated as non-human subjects research. For the semi-structured interviews, informed consent was reviewed but not documented with all participants.

Setting and Sample

In 2014, the VHA mandated that all of its hospitals develop and maintain an antibiotic stewardship program (ASP).[13] A major part of this directive is that each hospital is required to identify an antibiotic stewardship pharmacist and physician champion. Under VHA policy, the pharmacist and physician champions are co-leaders of the ASP. Each hospital is allowed to make its own decisions about how specific antibiotic agents are managed locally.[13]

The Veterans Affairs-Centers for Disease Control and Prevention Problem-Based Research Network (VA-CDC PBRN) included 15 geographically-dispersed VHA medical centers. Each site had a local site investigator (LSI) and a dedicated research coordinator; the data and implementation cores were based in Iowa City,

Iowa. We performed a mixed-methods study across this convenience sample of 15 hospitals from February 2018 to May 2019. Data on antibiotic use at these 15 hospitals has been previously published (cite Suda K, et al. ICHE 2021).

To better understand each hospital's antibiotic management process, two electronic surveys were administered (February 2018 and April 2018). Each version of the survey reflected three domains of the Consolidated Framework for Implementation Research, specifically inner setting, outer setting, and characteristics of individuals.[14] Prior to deployment, one ASP physician champion and one ASP pharmacist champion provided feedback on a pilot version of each survey. Each survey was then distributed electronically to each of the 15 sites, and either the ASP physician or pharmacist champion at each hospital completed it. Copies of each survey can be found in the supplemental material.

After the electronic surveys were completed, semi-structured interviews were conducted. The semi-structured interview guides were developed by the study team, which included physicians and pharmacists with antibiotic stewardship expertise and social scientists with qualitative training. The interview guides, which are included as supplemental material, were designed to be comprehensive and elicit perspectives on barriers and facilitators to the adoption of restrictive policies for fluoroquinolones and third/fourth-generation cephalosporins.

Prior to conducting the interviews, local research coordinators participated in approximately 15 hours of didactic training. The training introduced research coordinators to antibiotic classes and general infectious diseases knowledge; it also covered how to conduct qualitative interviews. Training sessions were conducted by experts in each of the content areas. In addition, research coordinators were assigned a mentor (CCG, SHS, EEC) by the qualitative lead (HSR). Each mentor had

qualitative method expertise. At the end of the didactic training, research coordinators conducted practice interviews with their mentor and, when approved by their mentor, conducted a final practice interview with an Infectious Disease pharmacist fellow.

We used purposeful sampling to select participants for the semi-structured interviews. The interview participants were sampled based on their role at the facility and their knowledge about organizational culture and local antibiotic-prescribing practices. LSIs provided a list of potential interviewees, but LSIs did not supervise any of the participants who were invited to participate to avoid coercion.

Each research coordinator conducted semi-structured interviews with the ASP physician and pharmacist champions at their respective hospital from September 2018 to February 2019. All interviews focused on the hospital's current practices for optimizing the use of fluoroquinolones and third/fourth-generation cephalosporins, particularly the use of restrictive policies. Specific questions were asked about the use of prior approval, prospective audit-and-feedback, clinical guidelines, order sets and criteria for use. For the sake of our analysis, restrictive policies included any of the following strategies: prior approval, designating an antibiotic as non-formulary, limiting the use of an antibiotic to specified indications (e.g., prophylaxis for urological procedures), only allowing the antibiotic to be prescribed through an order set or a clinical decision support system (CDSS), and/or restricting the antibiotic to a specific service (e.g. restricted to Infectious Diseases). These strategies were all classified as "restrictions" because there was some type of obstacle to the prescriber ordering the antibiotic.

Additional semi-structured interviews with key stakeholders were conducted at five of the hospitals from December 2018 to May 2019. Key stakeholders

included the hospital's pharmacy administrator and a diverse group of clinicians, including hospitalists, ICU physicians, and emergency department (ED) providers. To help understand a range of perspectives on implementing restrictions, these five hospitals were purposefully sampled to include two sites that currently had restrictions in place, two sites that would be targeted to implement restrictions, and one site that was in the process of changing how they implement restrictions.

All interviews were audio-recorded on encrypted recorders and transcribed. Of the 30 interviews with the ASP physician and pharmacist champions, 28 (93%) were conducted in person and 2 (7%) over the phone. One ASP interview was not recorded due to a recording error, so analysis was performed on notes taken during the interview. An additional 19 interviews were completed in-person with key stakeholders: 5 pharmacy administrators, 5 hospitalists, 5 ICU physicians, and 4 ED providers. One stakeholder interview was not recorded due to a recording error, but detailed written notes were used for analysis. In all, 49 participant interviews were included in the analysis across the 15 hospitals.

Data Analysis

Transcripts were uploaded into MAXQDA, a qualitative data management and analysis software program (VERBI Software, Berlin, Germany). An interdisciplinary team of physicians with antibiotic stewardship expertise and qualitative analysts developed a codebook based on the interview guide (deductive) and interview responses (inductive).[15, 16] Almost 20% of the ASP champion interview transcripts were coded via group consensus, a process that involved analysis team members individually coding transcripts prior to meetings and then reaching final coding consensus after group discussion. Another 20% were coded by pairs of team members. The remaining 60% of transcripts were coded by a mix of paired and

individual coding during the same time period as the group consensus coding; questions were brought to the full analysis team for resolution. This process helped to ensure coding consistency across all transcripts.

A subgroup of analysis team members performed the analysis on key stakeholder interview transcripts. The established codebook was used for this analysis with both inductive and deductive codes added. This subgroup coded 47% of the transcripts by group consensus. Another 53% was coded by pairs of team members from the subgroup. Like the initial analysis, paired coding took place during the same time period as the group consensus coding and questions were discussed and resolved in the larger subgroup setting.

Results

Characteristics of participating hospitals

The baseline characteristics of the 15 participating hospitals and their ASPs are shown in Table 1. Table 2 shows which antibiotic stewardship strategies were in place across the 15 hospitals at the time of the study, based on responses to the interviews and both electronic surveys (100% response rate).

Moxifloxacin was the most restricted antibiotic, as it was restricted at 12 (80%) sites. Only 5 (33%) sites were using a restrictive strategy for ciprofloxacin, and 6 (40%) had restrictions for levofloxacin. Seven (47%) hospitals restricted ceftazidime, 8 (53%) restricted cefepime, and none restricted ceftriaxone.

Prospective audit-and-feedback was used at varying levels of frequency across sites, most commonly for ceftazidime and cefepime, each at 7 (47%) sites. Six (40%) sites used prospective audit-and-feedback for ciprofloxacin, six (40%) for levofloxacin, and 5 (33%) for moxifloxacin.

No sites had restricted all third/fourth generation cephalosporins and fluoroquinolones. Sites with the most restrictions had restricted ceftazidime, cefepime, and at least 2 of the fluoroquinolones (sites 1, 3, 6). All other hospitals reported restrictions for no more than 2 of the antibiotics of interest (i.e., third/fourth-generation cephalosporins and fluoroquinolones). Two sites had no restrictions in place for third/fourth-generation cephalosporins and fluoroquinolones but instead relied on prospective audit-and-feedback to manage these agents.

Perceptions of antibiotic restrictions

There were differing opinions on the feasibility of implementing prior approval for these antibiotics (Table 3). Some interview participants described prior approval policies as "burdensome," "cumbersome," "chaotic," "really difficult," "very tough" and "not acceptable" to clinicians. Others described prior approval for these antibiotics as “practical” and "moderately" or "potentially" acceptable to clinicians. One hospital had implemented prior approval policies in 1985 and had sustained these restrictions up to the present day (site 1).

Participants that were actively using prior approval for these agents were more positive about the feasibility of this strategy. At these hospitals, clinicians seemed to adapt their prescribing practices after implementation of the restriction; however, it was often necessary to educate clinicians who were new to the facility. When restricted agents were requested, the approval process was described as smooth. At one site that had prior approval for ceftazidime and cefepime, the ASP pharmacist champion said:

> “The approval is relatively without impediment if the scenario is reasonable, because we all have sort of that general mindset of what’s an appropriate

use of a third-generation or fourth-generation cephalosporin, if you will, and if it meets it, sure" (site 1).

To prevent delays in antibiotic administration, the first dose of a restricted agent could be given without review, particularly during off-hours. Subsequent doses of a restricted agent could be denied by the stewardship team if they were felt to be inappropriate. Only 2 sites (1 and 6) reported 24/7 coverage for prior approval of these agents.

When clinicians called to request a restricted agent through the prior approval process, these conversations were viewed as opportunities to teach about antibiotic stewardship.

- "The inpatient doctors don't really mind asking for approval because, basically, they're getting advice. Sometimes, they call for approval when they don't even tell us [*stewardship team*] what they want to be approved. They want us to suggest what antibiotic to use" (ASP physician champion, site 3).
- "When you call ID (Infectious Diseases) about these restricted drugs a lot of times you get a collegial sort of re-education and suggestions and….I think that's a good thing" (ICU physician, site 4).

Restrictive policies other than prior approval were being used at some hospitals, and participants generally perceived these strategies to be more feasible than implementing prior approval. For example, at site 10, certain antibiotic agents (ceftazidime, cefepime and parenteral levofloxacin) were restricted to the Infectious Disease service, but clinicians could still order these restricted antibiotics if they used the hospital's CDSS. While the CDSS was designed to guide clinicians to the optimal antibiotic choice, the system was imperfect. One ED provider acknowledged

working around the CDSS system to find the desired antibiotic: “we are unfortunately forced to pick different diseases which are not applicable to the patient” (site 10). Two hospitals (sites 5 and 13) had “criteria for use” that applied to cefepime, ceftazidime, ciprofloxacin and levofloxacin. The ASP pharmacist champion at site 5 explained, “as long as the provider uses it [the antibiotic] based on the guidelines that we outlined, then the providers can have that agent.”

Table 4 shows how often ASP physicians and pharmacists felt that “further restrictions” on fluoroquinolones and third/fourth-generation cephalosporins would be beneficial. Participants demonstrated more interest in implementing further restrictions for fluoroquinolones than for third/fourth-generation cephalosporins. ASP physician and pharmacist champions at the same hospital often did not agree in their assessments.

Several ASP champions and key stakeholders raised concerns about restricting third/fourth-generation cephalosporins and fluoroquinolones. These concerns included a desire for maintaining prescriber autonomy and clinicians’ strong preference for prescribing these agents. According to one ICU physician, “I think quinolones partly became king because they were just so convenient and you could give somebody one pill potentially just once a day and treat their pneumonia and who doesn’t love that?” (site 10).

Some participants felt that the additional workload required to enforce new restrictions would be prohibitively large. According to the ASP pharmacist champion at a site without any restrictions for third/fourth-generation cephalosporins, “The reason why we probably don’t do it [*restrict third-generation cephalosporins*] is because the volume of these that we would have to approve would go on our clinical pharmacy staff and we don’t have the bandwidth to take on that high of a

prescribing volume, so some things in our model would have to change if we were to do something like that" (site 15).

Participants also expressed concern about the unintended consequences of restricting fluoroquinolones and third/fourth-generation cephalosporins. According to one ICU physician, "I really worry that by restricting these options, you might find the use of other agents that have an even broader antimicrobial profile to be used more frequently. That would be my big concern" (site 11).

Many sites were using prospective audit-and-feedback to improve prescribing of fluoroquinolones and third/fourth-generation cephalosporins. At some of these sites, participants questioned the added benefit of restricting these agents: "Because we do prospective audit-and-feedback and we have good results, we just get people off of those things fairly quickly here. So, I'm not so sure that's there's much bang for your buck in restricting them" (ASP physician champion, site 14). However, other sites had concerns about the practicality of prospective audit-and-feedback, "The difficulty with prospective audit and feedback is, even though it's quite useful and I think talking to providers is very useful, it is resource-heavy" (ASP physician champion, site 10).

Discussion

In this mixed-methods study across 15 hospitals, we found differing opinions on the feasibility of implementing antibiotic restrictions for fluoroquinolones and third/fourth-generation cephalosporins. While some hospitals had effectively operationalized antibiotic restrictions for these agents, many ASP champions and stakeholders had concerns about the acceptability, safety, and unintended consequences of restrictive policies, particularly prior approval. Our findings suggest that the perceived barrier to implementing restrictive policies can be high,

but once the restrictions are established, these types of policies can be acceptable to clinicians.

Whether deemed clinical inertia or organizational culture, some sites had clearly established norms where restrictions were accepted, and the ASP champions could envision introducing additional restrictions. These hospitals had established a general understanding of what constitutes appropriate use of a restricted agent. In addition, some sites discussed restrictions as an opportunity for education and reported clinicians using the prior approval process to ask for advice. However, other sites questioned the benefit of disrupting the current culture because clinicians may feel “attacked” while restrictions would create additional workload and have potential unintended consequences. In addition, some sites felt that their hospital’s use of fluoroquinolones and third/fourth-generation cephalosporins was within target so there was not much “bang for your buck” by adding restrictions. There seemed to be a major dividing line between ASPs with and without restrictions, as the former had already established norms around restrictions while the latter would have to disrupt the norm to implement restrictions. If restrictions are to be more widely implemented, more research is needed on how hospitals can move from a culture in which restrictions are viewed as an attack to a culture where restrictions are viewed as an opportunity to improve patient care.

Prior antibiotic stewardship studies have highlighted concerns about antibiotic restrictions, which were echoed by many participants in our study. For example, studies have raised concerns about antibiotic restrictions delaying antibiotic treatment while also undermining trust between ASP personnel and frontline clinicians.[17-19] In studies across French and US hospitals, antibiotic stewards strived to collaborate with clinicians while trying to minimize perceptions that they

were policing antibiotic use.[20 21] An additional concern is that restrictions of these high-risk CDI agents can lead to greater use of other broad-spectrum agents. In England, reductions in fluoroquinolone and cephalosporin use were associated with increased use of beta-lactam, beta-lactamase inhibitor combinations and carbapenems.[22]

Restrictions can take many different forms, and some types of restrictive strategies seem to be more acceptable than others. In our study, several participants had concerns about the use of prior approval, but participants thought that a variety of other strategies could be effective at decreasing the use of fluoroquinolones and third/fourth-generation cephalosporins. Some sites expressed a preference for only allowing clinicians to order restricted antibiotics through a CDSS or order sets—strategies that may exert less direct control over prescribing than prior approval. Many sites were using prospective audit-and-feedback, which is a purely persuasive strategy that can be resource-intensive. A 2014 meta-analysis found that restrictive policies are more effective than persuasive strategies at reducing CDI.[7] However, prospective audit-and-feedback is also effective at reducing the use of high-risk agents and in reducing CDI.[23-26] Furthermore, persuasive strategies, particularly those that involve feedback, have been shown to enhance the beneficial effect that antibiotic restrictions have on general antibiotic use.[27]. While both persuasive and restrictive stewardship strategies likely have a role in CDI prevention, reducing the initiation of high-risk antibiotics through restrictive approaches may be more impactful on CDI than simply shortening duration through persuasive strategies, as certain antibiotics may cause more rapid disruption of the intestinal microbiota.

Ultimately, the processes an ASP decides to implement are likely influenced by the availability of resources, the organizational culture of the hospital, and the perceived value of the new processes. Several participants described how the need to reduce the use of high-risk CDI antibiotics should be weighed against the potentially adverse consequences of prescribing alternate agents. This suggests that participants did not see CDI reduction as the primary purpose of their ASP.

To fully leverage stewardship processes for CDI prevention, hospitals would have to restrict all fluoroquinolones or both third/fourth-generation cephalosporins and fluoroquinolones.[3, 4, 6] In our cohort, none of the hospitals had restricted ceftriaxone and only a few sites had restricted all types of fluoroquinolones. ASP champions disagreed on whether further restrictions would be beneficial. Clinicians strongly prefer to use some antibiotics in each of these high-risk classes, so it is particularly challenging to restrict all agents. To overcome this barrier, there is likely a need for more persuasive evidence on the benefits of restrictions. Given the concerns raised by our study's participants, this evidence would need to show how substituting piperacillin-tazobactam or other broad-spectrum antibiotics for third/fourth-generation cephalosporins would influence local rates of antibiotic resistance. Studies would also need to evaluate the efficacy of using more narrow-spectrum empiric therapy for indications when ceftriaxone is often prescribed, such as community-acquired pneumonia and urinary tract infections.

Our study is not without limitations. First, while the semi-structured interview guide included questions about specific types of restrictive policies, both interviewers and participants often used the word "restrictions" without specifying which type of restrictive strategy they were discussing. There are a variety of ways to restrict antibiotics, and perceptions will differ based on the specific type of

strategy. We have tried to limit our analysis to situations where the strategy being discussed was clear. Second, our interviews did not specifically explore why restrictions had been implemented at each site, although we can speculate that harm reduction and cost containment were likely motivating factors. Third, it is unclear whether our findings are generalizable to non-VHA hospitals.

In conclusion, in this mixed-methods study across 15 VHA hospitals, we found differing opinions on the feasibility of implementing restrictions for third/fourth-generation cephalosporins and fluoroquinolones. While the perceived barrier to implementing restrictions--especially prior approval--was high at many hospitals, other hospitals that had implemented some types of restrictions reported lower barriers to their use. In short, experience implementing restrictions influences perceptions of barriers . Broader implementation of restrictive strategies may require changing the perceptions of ASP champions and frontline clinicians.

Acknowledgement: none

Funding: This work was supported by the VA-CDC Practice-Based Research Network, which was funded collaboratively by the VA Health Services Research and Development (HSR&D) service and the Centers for Disease Control and Prevention. It was also supported by a Career Development Award (CDA 16-204, DJL) and the Collaborative Research to Enhance and Advance Transformation and Excellence program (CRE 12-289, HSR) from the VA HSR&D.

Transparency declaration: None to declare

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States Government. The findings and conclusions in this article are those of

406 the authors and do not necessarily represent the official position of the Centers for
407 Disease Control and Prevention (CDC).
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Table 1. Characteristics of 15 participating Veterans Health Administration hospitals and their antibiotic stewardship programs

Characteristic	N (%)
US Census Regions	
Midwest	6 (40)
Northeast	1 (7)
South	5 (33)
West	3 (20)
Acute-care beds	
≥100	10 (67)
<100	5 (33)
VHA Hospital Complexity Level[1]	
1a	10 (67)
1b	4 (26)
1c	1 (7)
ASP leader	
Co-led by physician and pharmacist	12 (80)
Physician	2 (13)
Pharmacist	1 (7)
ASP pharmacist's time commitment to ASP	10 (67)
76-100%	3 (20)
26-50%	2 (13)
No time	
Clinical pharmacists routinely round with inpatient providers	13 (87)

Abbreviations: VHA Veterans Health Administration; ASP antibiotic stewardship program

1. The Veterans Health Administration classifies its medical facilities at the following levels of complexity: 1a, 1b, 1c, 2, or 3. A hospital's complexity level is based on its patient population, clinical services, education and research. The most complex hospitals are level 1a, and the least complex are level 3.

Table 2. Antibiotic stewardship strategies for managing inpatient use of third/fourth-generation cephalosporins and fluoroquinolones at 15 Veterans Health Administration hospitals[1,2]

	Ceftriaxone			Ceftazidime			Cefepime			Ciprofloxacin			Levofloxacin			Moxifloxacin		
	Restrictio	PAF	Neither	Restrictio	PAF	Neither	Restrictio	PAF	Neither	Restrictio	PAF	Neither	Restrictio	PAF	Neither	Restrictio	PAF	Neither
Totals	0	4	11	7	7	5	8	7	4	5	6	7	6	6	6	12	5	1
Site 1		X		X	X		X	X		X	X		X	X		X	X	
Site 2			X	--[4]	X		X	X				X[5]			X[5]			X[5]
Site 3			X[3]	X			X					X	X			X		
Site 4			X			X	X					X			X	X		
Site 5			X	X			X			X			X			X		
Site 6			X	X	X		X	X		X	X		X	X		X	X	
Site 7		X			X			X			X			X			X	
Site 8			X			X			X			X			X	X		
Site 9		X		X	X			X			X			X		X	X	
Site 10			X	X			X					X[5]			X[5]	X		
Site 11			X			X			X			X			X	X		
Site 12			X			X			X			X			X	X		
Site 13			X	X	X		X	X		X	X		X	X		X		
Site 14		X			X			X			X			X			X	
Site 15			X			X			X	X			X			X		

Abbreviations: PAF prospective audit-and-feedback

1. Reported strategies are based on each site's responses to the two electronic surveys. If a site gave discordant responses to the two surveys, we used the interview transcripts to resolve any discrepancies.

2. Restrictions included prior approval, designating an antibiotic as non-formulary, limiting use of the antibiotic to specified indications, only allowing the antibiotic to be prescribed through an order set or a clinical decision support system, and/or restricting the antibiotic to a specific service (e.g. restricted to Infectious Diseases).
3. This site only required prior authorization if two-gram doses of parenteral ceftriaxone were ordered. For this table, this site was classified as not having a restrictive policy for ceftriaxone.
4. This site gave conflicting responses, so it is unclear whether ceftazidime was restricted.
5. Some sites only restricted and/or audited parenteral forms of certain fluoroquinolones. For this table, these sites were classified as not having a stewardship process for fluoroquinolones.

Table 3. Sample quotations from semi-structured interviews with antibiotic stewardship champions and other clinicians across 15 Veterans Health Administration hospitals

FACTORS THAT FACILITATE RESTRICTONS FOR THIRD/FOURTH-GENERATION CEPHALOSPORINS AND FLUOROQUINOLONES	
The approval process for antibiotic restrictions can be done in a way that is not onerous to clinicians.	
ICU physician, site 11	"They [the residents] would have to put in an emergency non-formulary consult request and I've typically found that those are approved in a very timely manner, and so it does not lead to any particularly onerous restrictions in workflow."
ICU physician, site 10	"I think, for me in ICU, it's fine because we are a multidisciplinary team and we round together every day with pharmacy and so for us, I don't have any real complaints about it.…We order things and if there's something wrong with how we've ordered it or there's a restriction placed on it, the PharmD is with us and just says 'Oh, by the way, this has to be fixed,' or whatever. And so…it's fine 'cause it's very little adverse impact on our workflow."
Clinicians eventually adapt their practices once antibiotic restrictions have been implemented.	
Pharmacy administrator, site 4	"I think that at the VA, folks are used to guided prescribing and they appreciate the need to restrict and have bumpers around antimicrobial prescribing."
ASP pharmacist, site 13	"We already require prior approval so that they're used to that but the third generation [cephalosporins] would be new to them and I think it would be hard for them to get used to that, but.…if they had guidelines or something.…they could probably get used to it and it would be ok."
ASP pharmacist, site 3	"Where they [the physicians-in-training] come from, sometimes it won't be restricted, like the quinolones, but they learn quickly.…It's just the learning process."
Pharmacy administrator, site 10	"We do get put in a position of being the enforcer of the policy.…If it's a restricted antibiotic, then we will call the provider and sometimes we do get pushback from them because they're frustrated, 'cause now they have to go through an extra step of finding it and going into CDSS [Clinical Decision Support System] and ordering it. Sometimes it's because they're relatively new providers, or we get, especially in the ER, providers who are just here occasionally...I would say probably 90% of the time.…it's like, "Oh yeah, I--," especially residents, 'cause they're new here, going, "Oh yeah, that's right, I need to go through CDSS," so they're very open to, to using it."
To address concerns about the timeliness of antibiotic administration, hospitals can allow the first antibiotic dose without approval.	
ASP pharmacist, site 9	"None of our antibiotics are prior approvals. It's all retrospective, so they can order it and we'll give it to 'em and then they need to get it approved afterwards.…There's not a large motivation to change our restriction to be prospective because then we could delay patient care."
ASP pharmacist, site 10	"We don't staff the first dose, but it's important that people be able to get their first dose on time.…I think after 24 hours or after 48 hours or.…after a certain amount of time, it is much more feasible, much more logistically feasible. And then, at that point, you can do one-on-one education. Of course, you know, we're a 24-7 facility and like somebody coming in at 2:00 in the morning, we don't talk to that person that was ordering at 2:00 in the morning."

When antibiotic restrictions are in place, the process of requesting approval is often a teachable moment about optimal antibiotic-prescribing.	
Pharmacy administrator, site 10	"It [CDSS] is viewed very positively…. because it does help them [physicians], lead them to making the right decision."
ASP pharmacist, site 11	"If we are talking about implementing an order set, then the order set could simply guide them *[clinicians]* into choosing something different without maybe having to go through a restrictive process."
ASP physician, site 13	"I think that having the order sets right now makes it much more acceptable because that really does screen out a lot of unnecessary use."
Showing clinicians data that demonstrates the rationale for antibiotic restrictions helps achieve clinician buy-in for the restriction.	
Hospitalist, site 11	"I think if it [restrictions] could be shown that it was beneficial, I think people would get onboard."
ASP pharmacist, site 11	"If you implement this [prior approval for third/fourth generation cephalosporins and fluoroquinolones], then you need to REALLY inform [clinicians] before implementing as to why to get their buy-in, if you want it to go through smoother."
ASP pharmacist, site 9	"If I have data that says that we will benefit from something and that there is something that we can do to change practice to improve patient care, people get behind that like this. But if we go and say, 'We're gonna just restrict this drug because we feel like restricting it and it might do something and I have no data to support that we have an existing problem,'…the people aren't gonna like that. I wouldn't like that."
ASP pharmacist, site 15	"I will say they [clinicians] have responded well to our other initiatives to decrease quinolone use, education and the clinical guidelines and so if we get the volume [of fluoroquinolone use] low enough, at least in the inpatient setting theoretically, so where it's manageable for us, we could potentially restrict quinolones and I think it would be more acceptable because of all the documented dangers of those medications."
ASP pharmacist, site 7	"I think that one [restricting fluoroquinolones] is a little more straightforward simply because we have the FDA's backing. There's warnings in place that suggest we should be using alternatives and the safety concerns with fluoroquinolones, so I think we have some leverage there to allow that to really get buy-in from the providers with fluoroquinolone restrictions and criteria of use. I think it would be a little bit more challenging with the third-gen cephalosporins."
BARRIERS TO USING RESTRICTIONS FOR THIRD/FOURTH-GENERATION CEPHALOSPORINS AND FLUOROQUINOLONES	
Clinicians commonly prescribe third-generation cephalosporins and fluoroquinolones; they appreciate their benefits.	
ASP physician, site 15	"Restriction of a third-generation cephalosporin would be difficult for the providers, really. I think they want to use those quite often. Um, the fourth generation, I think, would be understandable. You know? They see that as very broad, but they see ceftriaxone as something that's reasonable to use."
ASP pharmacist, site 7	"It would get somewhat complex with regards to, 'What are we using in place of a third-gen cephalosporin?'"

ASP pharmacist, site 4	"We are using ceftriaxone as the workhorse cephalosporin for community-acquired pneumonia in inpatients that are admitted to the hospital."
ED provider, site 10	"Let's say we take levofloxacin. The ease of single once-a-day dosing, that is a big deal for us….in our opinion, it improves patient compliance."
Restricting antibiotics interferes with physicians' autonomy.	
Pharmacy administrator, site 13	*[How would your facility's culture affect the success of **prior approval** for third or fourth generation cephalosporin and/or fluoroquinolones?] "I think* it would be difficult initially for pharmacists to have to do extra steps since we are lacking some staff but I think it would be harder for the physicians if they are used to freely prescribing."
Pharmacy administrator, site 11	"They [the prescribers] do not like others telling them what they can prescribe and what they can't prescribe."
ASP physician, site 7	"The providers don't like restrictions. They want to just prescribe what they want to give the patient, because they feel like that's the best thing to do. So if the stewardship team's always butting heads with providers and trying to restrict these drugs, I think it works against the sort of collaborative multidisciplinary environment we're trying to create."
Antibiotic restrictions may delay the timely administration of antibiotics.	
ICU physician, site 13	Requiring prior approval for third/fourth generation cephalosporins and fluoroquinolones "…would make me very sad because I think people would die if they had septic shock, if I had to delay antibiotic delivery."
ASP pharmacist, site 3	"I think one of the biggest issues [with requiring prior approval for all fluoroquinolones] is timeliness. The big thing is always getting antibiotics in a timely manner."
Pharmacy administrator, site 10	"I would say sometimes it [prior approval of antibiotics] does delay patient care, particularly in the ER setting, where…you want to get that antibiotic in within the-the first hour of the diagnosis of sepsis."
Enforcing antibiotic restrictions is resource-intensive.	
Hospitalist, site 13	Ceftriaxone "is our drug of choice for community-acquired pneumonia, which we see frequently here. So, I think that would be a hard because that'd mean a lot of extra phone calls."
ASP physician, site 7	"I think one reason we haven't implemented them is because implementing restrictions requires certain resources and it requires people's time and people to be available off-hours and on weekends to enforce these restrictions."
ASP physician, site 8	"Formulary restrictions, they can be a bit challenging because somebody has to be there to do it 24-7. So, somebody wants it in the middle of the night, they want to start somebody on a medication, you have to be able to look and say, 'Yes,' or, 'No.' So there's a 24-7 availability issue."
ASP pharmacist, site 15	"We have to be careful how much we restrict because, again, the volume of the workload can be unmanageable if you continue to restrict more things. So, even though from a stewardship perspective I would love to say, 'Oh yeah, let's restrict everything,' we can't actually do that because of the barriers to implementation and time."
ASP physician, site 6	"I think it would be quite a large burden on the ID pharmacist to review every single case where ceftriaxone was used."

ASP pharmacist, site 7	“We use it [ceftriaxone] quite a bit for different infections so it’ll be hard for providers to have to call for every order.”
Restricting third/fourth-generation cephalosporins and/or fluoroquinolones may result in increased use of other broad-spectrum antibiotics that antibiotic stewardship teams are trying to manage.	
ICU physician, site 11	“You may actually find that by restricting third- and fourth-generation cephalosporins, you may see a rise in carbapenem use, which would, in my mind, be a worse thing.”
ASP pharmacist, site 4	“Requiring prior approval for third and fourth generation cephalosporins and all fluoroquinolones ….would probably shift everybody to using more pip-tazo, which I think we already have an ongoing issue with.”
ASP pharmacist, site 10	“If people want a broad-spectrum antimicrobial, they’re gonna find a way to get one, so I wouldn’t use restriction as our way of trying to decrease resistance, because we might decrease resistance to a fluoroquinolone, but I think we we’d still be prescribing piperacillin-tazobactam. We’d still get a lotta resistance, one way or the other. People would still be using antimicrobials, and any antimicrobial use promotes resistance.”
Persuasive strategies can be leveraged to reduce the use of third/fourth-generation cephalosporins and fluoroquinolones.	
ASP physician, site 9	“I believe more in education and order sets, where you recommend [antibiotics]…so you still get the choice. You’re educating the health care workers.”
ASP physician, site 13	“I think having a prospective audit and intervention and feedback is much better [than antibiotic restrictions] ‘cause explaining to them why you should get a history of your allergy and then not prescribe the quinolone is much more meaningful than saying, ‘No, no, no,’ upfront.”
ASP physician, site 7	“We [the stewardship team] feel like we’ve been able to optimize antibiotic use to a large degree through our current mechanisms of audit and feedback.”
ASP physician, site 14	“The ASP pharmacist does pretty extensive prospective audit and feedback on ceftriaxone….and we get people off of ceftriaxone pretty quickly. My point is that people are fairly appropriately empirically using it and when we [the ASP champions] suggest changes or de-escalation, they [clinicians] do it rapidly. So, I’m not really sure it’s necessary to restrict it. People follow our guidance almost all the time.”

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Table 4. Perceptions of whether further restrictions on fluoroquinolones and third/fourth-generation cephalosporins would be beneficial, based on interview responses of 15 ASP pharmacist and 15 ASP physician champions

	Would further restrictions be beneficial?[1]		Frequency at which a hospital's ASP pharmacist and physician champion agreed on the benefit of further restrictions, n (%)
	ASP pharmacist, n (%)[2]	ASP physician, n (%)	
Fluoroquinolones	YES: 10/14 (71%) NO: 4/14 (29%)	YES: 8/15 (53%) NO: 7/15 (47%)	6/14 agreed YES (43%) 3/14 agreed NO (21%)
Third-generation cephalosporins	YES: 2/15 (13%) NO: 11/15 (73%)	YES: 3/15 (20%) NO: 11/15 (73%)	0/15 agreed YES (0%) 7/15 agreed NO (47%)
Fourth-generation cephalosporins	YES: 3/15 (20%) NO: 10/15 (67%)	YES: 6/15 (40%) NO: 8/15 (53%)	3/15 agreed YES (20%) 7/15 agreed NO (47%)

Abbreviation: ASP antibiotic stewardship program

1. If the respondent expressed uncertainty about the benefit of further restrictions, the response was coded as neither YES nor NO.
2. One of the ASP pharmacist champions was not asked whether further restrictions would be beneficial for fluoroquinolones.