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Impact of formulary restriction with prior authorization by an antimicrobial stewardship program

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In an era of increasing antimicrobial resistance and few antimicrobials in the developmental pipeline, many institutions have developed antimicrobial stewardship programs (ASPs) to help implement evidence-based (EB) strategies for ensuring appropriate utilization of these agents. EB strategies for accomplishing this include formulary restriction with prior authorization. Potential limitations to this particular strategy include delays in therapy, prescriber pushback, and unintended increases in use of un-restricted antimicrobials; however, our ASP found that implementing prior authorization for select antimicrobials along with making a significant effort to educate clinicians on criteria for use ensured more appropriate prescribing of these agents, hopefully helping to preserve their utility for years to come.

Introduction

Overutilization of antimicrobial agents is recognized as a significant contributor to the development of antimicrobial resistance.[1] Unfortunately, multi-drug resistance has already emerged in a number of species and there are few antimicrobials in the development pipeline, making this a mounting public health concern. In response, many hospitals have implemented antimicrobial stewardship programs (ASPs). Such programs are critical to preserving the effectiveness of the existing antimicrobial armamentarium.[1] For this reason, the Centers for Disease Control and Prevention (CDC) has launched the Get Smart for Healthcare Campaign in order to encourage responsible antimicrobial utilization and the development of ASPs.[2] The primary goal of an ASP is to optimize clinical outcomes while minimizing the unintended consequences of antimicrobial utilization such as the development of resistance and toxicity.[3,4] Secondary goals include reducing health care costs without adversely impacting patient care.[3] The two primary evidence-based strategies for achieving these goals are (1) prospective audit with intervention and feedback and (2) formulary restriction with prior authorization for select agents.[3,4]

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A simple method for carrying out formulary restrictions is to establish a defined institutional formulary.[3,4] This approach enforces formulary restriction by strictly limiting which antimicrobials are available to prescribers at a given institution. Implementation of an institutional formulary may be the least controversial approach in that it poses minimal threat to the authority of the prescriber. It can also result in substantial cost savings. Nonetheless, it may not be the most effective approach if it primarily serves to limit antimicrobial selection to one of a number of similar drugs.[5] For example, making nafcillin available on the formulary but not oxacillin is unlikely to significantly impact antimicrobial usage or clinical outcomes while it may potentially have some financial effect.[5] Additionally, this approach to formulary restriction could be ineffective in institutions where prescribers are able to circumvent the restriction by ordering unapproved medications via a non-formulary pathway.

Another formulary restriction method is setting institutional utilization criteria.[3,4] This requires the prescriber to indicate appropriate rationale for the selection of a particular agent. This can be accomplished electronically in institutions with computer-physician order entry (CPOE) by requiring the prescriber to select the criteria for use from a pre-populated menu on the order entry screen. In institutions using paper medication orders, this can be done using an antimicrobial-specific order form including check boxes with the appropriate criteria for use. Unfortunately, clinicians can circumvent this type of restriction by listing an unconfirmed diagnosis or differential diagnosis to meet the required criteria for use, a practice that may go unrecognized if the ASP cannot invest additional efforts to validate the appropriateness of criteria selection by medical record reviews.

Lastly, antimicrobial restriction can be accomplished by requiring prior approval for use by an infectious diseases (ID) physician or pharmacist (i.e., preauthorization-based restriction). This approach is typically instituted in the setting of a pre-existing restricted formulary. This method is perhaps the most effective but requires trained personnel to be available for approvals. Integration of this process into workflow can be challenging. For example, after-hours availability of antimicrobials without preauthorization may lead to prescribers inappropriately circumventing the restriction by waiting until after-hours to place orders for restricted antimicrobials.[6] Additionally, this approach could

be perceived as a challenge to physician autonomy so may not be fully embraced by the medical staff.[4] Another potential drawback to this process is the restriction of one agent may result in increased utilization of another agent. This phenomenon has been described figuratively as "squeezing the balloon."[7]

This article outlines our experience with formulary restriction with prior authorization at a large academic medical center and reviews the literature on this topic.

The OSUWMC Experience

The Ohio State University Wexner Medical Center (OSUWMC) is a 1,229 bed tertiary care academic medical center located in Columbus, Ohio. Expansion of the ASP at OSUWMC occurred in 2008. The ASP core members include ID-trained physicians and pharmacists, clinical microbiologists and a data manager. Initial efforts at antimicrobial restriction entailed the development of OSUWMC-specific utilization criteria for select antimicrobials including linezolid, daptomycin, tigecycline, colistin, piperacillin-tazobactam and imipenem. These criteria were available to prescribers on the OSUWMC ASP website and some were built into the CPOE system, requiring the prescriber to select the indication for use at the point of order entry. In addition, the ASP physicians/pharmacists monitored the use of these agents daily by way of an electronically-generated report from the electronic medical record system. Daily review of this report allowed for prospective audit with feedback along with education to the prescribers without direct prescribing restriction.

In 2010, doripenem replaced imipenem as the OSUWMC Formulary anti-Pseudomonal carbapenem (i.e., class 2 carbapenem) and prior authorization was required for its utilization. Ertapenem was retained on the formulary as a non-Pseudomonal carbapenem as well. This formulary change was based on a pharmacodynamic analysis of 64 OSUWMC *Pseudomonas aeruginosa* isolates that identified 4 h [extended-infusion (EI)] doripenem infusions as the optimal anti-Pseudomonal carbapenem for our patients.[8] That is, the cumulative fraction of response was determined to be 94% for EI doripenem as compared with 78% for imipenem which cannot be administered as an extended-infusion due to stability limitations.[8] This made the formulary change the right decision for our patients despite the fact that doripenem was more expensive than imipenem.

In order to facilitate this process change, ASP developed criteria for doripenem use that were subsequently approved by the Antibiotic Subcommittee and the Pharmacy and Therapeutics Committee. Once approved for formulary addition, doripenem was also built in the Integrated Healthcare Information System (IHIS) with a STAT first dose in order to help ensure timely order processing and delivery. Significant educational efforts were made at this time to inform the Medical and Pharmacy Staff of this change and its rationale to ensure appropriate utilization of this agent in hopes of preserving its activity against multi-drug resistant Gram negative organisms.

The prior authorization system was set up such that prior authorization is required at the point of CPOE from 8 a.m.–10 p.m. seven days per week. An order question stating, "This medication requires prior approval by the Antimicrobial Stewardship Program. Enter the approval code here:" must be completed in order for the pharmacist to process the order. If it is not complete, the prescriber is notified and instructed to contact the ASP for approval. Each day, one of the pharmacist or physician members of the ASP team takes calls for doripenem approval via pager system. Additionally, ID fellows participate in the ASP call schedule during their ASP rotation(s). When applicable, ID fellow recommendations are reviewed daily with one of the ASP physicians who provides feedback to them as part of their education and for quality assurance.[9] All participants in the call schedule have the ability to access electronic medical records remotely so that the patient chart can be accessed during the conversation with the prescriber even during evening hours. This is to ensure that the information is correct and complete as prior studies have reported problems in this area.[10] If approval for doripenem use is granted, an approval code is given to the prescriber for entry into the medication order as mentioned previously. Alternative therapy is recommended if doripenem is not considered to be appropriate.

During the hours of 10 p.m.–8 a.m., doripenem may be ordered without prior authorization to prevent delay in appropriate treatment throughout the overnight hours. A member of the ASP team then reviews the orders for appropriateness according to OSUWMC criteria for use on the following business day. If the order is deemed appropriate an approval code is added to the order. If the order is not considered appropriate, the medical team is contacted and alternative therapy is recommended. This process ensures all orders for doripenem have been reviewed, even orders placed during the overnight hours when doripenem does not require prior approval.

During the initial implementation phase (October 2010 through April 2011), all ASP members were required to enter details regarding each call he/she took into an electronic database including the date/time of the request, time to call return, length of call, requesting physician/team, therapeutic indication and approval status. At the end of this timeframe, the ASP data manager summarized the data and all team members reviewed it to ensure that the process did not create any delays in time to antimicrobial therapy. The ASP then presented the data to the Antibiotic Subcommittee and Pharmacy and Therapeutics Committee for quality review.

The aforementioned audit included 328 doripenem requests occurring between October 4, 2010 and April 30, 2011.[11] The data were analyzed using Microsoft Excel and STATA 11. The Wilcoxon ranksum test was used to determine p values with two-tailed p values ≤ 0.05 being considered statistically significant. The results indicate that this process does not impede patient care at OSUWMC as the mean time to return a page was 2.7 min ($\pm$ 4.4) and the mean call length was 4 min ($\pm$ 3.2).[11] It also revealed that although 56% of indications for use were categorized as "other" (i.e., fell outside the approved criteria), 18% of requests were for empiric broad-spectrum therapy in patients with both a penicillin and cephalosporin allergy, which was an approved criteria for use.[11] Several of the requests for doripenem that fell outside of the approved criteria for use were for patients with febrile

neutropenia clinically decompensating on alternative therapy. As a result, this was later added to the list of approved criteria for use. Other criteria for use included confirmed *Pseudomonas* species only susceptible to doripenem and aminoglycosides (10%), infection with an extended-spectrum β-lactamase (ESBL)-producing organism (8%), concurrent infection with *Pseudomonas* species and an extended-spectrum β-lactamase (ESBL)-producing organism or other multidrug-resistant Gram-negative (5%) and confirmed *Acinetobacter* species susceptible to doripenem (3%).[11]

Another important finding was that although 91% of doripenem requests were approved, mean doripenem use was significantly lower than prior mean imipenem use over a 10 mo period (11 antimicrobial days/1,000 patient days vs. 27 antimicrobial days/1,000 patient days; $p = 0.0008$).[11,12] Despite this decrease in anti-Pseudomonal carbapenem use, no significant increase in ertapenem, cefepime or piperacillin-tazobactam utilization was observed (data not shown).

Based on the success of the doripenem restriction process, fidaxomicin was recently added to the list of antimicrobials requiring pre-authorization. Similar to doripenem, the ASP created criteria for fidaxomicin use that were approved by the Antibiotic Subcommittee and Pharmacy and Therapeutics Committee at the time of formulary addition.

Discussion

Early efforts at antimicrobial stewardship involved strategies such as defining criteria for use and in some cases requiring prior authorization by an ID physician. One metric of the success of ASPs has been economic. Some institutions were able to show cost-savings without adversely affecting patient outcomes.[13-15] For example, Coleman and colleagues investigated the impact of strengthening a parenteral antibiotic control policy and instituting continuous ID physician reviews of the appropriateness of antimicrobials on cost and patient outcomes.[13] They found these measures to result in an annual cost reduction of $91,200 as well as no significant difference in overall mortality ($p = 0.22$). Similarly, Woodward and colleagues demonstrated a monthly cost-savings of $34,597 by strictly enforcing formulary restrictions of aminoglycosides, vancomycin, and cephalosporins with no detrimental changes in the hospital length of stay or mortality in the months following the implementation of these restrictions.[14] From an economic perspective, restriction policies can reduce drug use and drug costs.

While many ASPs have focused on reduction in drug costs as the primary metric for the success of their programs, we have demonstrated that appropriate antimicrobial use stemming from various ASP interventions has resulted in improved patient outcomes including shorter hospitalizations with associated cost reductions.[12,16]

Another metric for ASP success has been the impact of limiting inappropriate antimicrobial use on improved antimicrobial susceptibilities, decreased colonization with multidrug-resistant organisms and fewer outbreaks with resistant organisms.[17-21] Some programs have implemented general antimicrobial restrictions aimed at decreasing overall antimicrobial use. In one institution, orders for intravenous amikacin, ceftazidime, ciprofloxacin, fluconazole, ofloxacin, ticarcillin/clavulanate, piperacillin/tazobactam and aztreonam were not dispensed unless the prescriber received prior authorization from an ID physician.[17] This program resulted in a 32% decrease in total parenteral antimicrobial expenditures while β-lactam and quinolone susceptibilities increased most notably in the inpatient setting.[17] Meanwhile, other programs have aimed at decreasing the utilization of select antimicrobials in an effort to decrease the selective pressure on certain organisms. Quale and colleagues published their experience with restricting the use of cefotaxime and vancomycin and adding β-lactamase inhibitors to replace third-generation cephalosporins in an effort to better control outbreaks of vancomycin-resistant Enterococcus (VRE) in their institution.[20] In doing so, they found a decrease in point prevalence of fecal colonization with VRE from 47% to 15% ($p < 0.001$) and in the number of patients with VRE culture positive specimens over time.[20]

In contrast to the success of some of the programs mentioned above, others have shown a lack of an association between antimicrobial restriction and improved organism susceptibilities and patient outcomes.[22,23] For example, Toltzis and colleagues examined whether a ceftazidime restriction policy in a neonatal intensive care unit would decrease the endemic rate of colonization with ceftazidime-resistant Gram-negative bacilli.[22] This policy did result in a 96% reduction in ceftazidime use but there was actually a slight increase in the density of ceftazidime-resistant organisms (1.57 to 2.16 isolates per 100 patient-days) during the study period.[22] Another study assessed the impact of restricting vancomycin and third-generation cephalosporin use on the prevalence of VRE over a 10-y period.[23] Over this timeframe, third-generation cephalosporin use decreased by 85.8% while vancomycin use initially decreased by 23.9% but gradually increased back to pre-restriction use levels, and VRE prevalence increased steadily from 17.4 to 29.6% ($p < 0.001$).[23] Studies like these highlight the fact that formulary restriction alone may not yield the desired results and should be combined with other strategies aimed at reducing inappropriate antimicrobial use. In combination, these approaches may slow the development of resistance but this is most likely to be seen over a prolonged period of time.[24] For this reason, one of the challenges of ASPs in the future will be to conduct additional well designed studies that demonstrate an impact on decreasing resistance and improving clinical outcomes.[25]

Today, mounting concerns regarding Gram-negative multidrug resistance have led some institutions to selectively restrict the use of anti-Pseudomonal carbapenems including meropenem, imipenem and doripenem. In some cases, this type of restriction has been shown to result in improved Pseudomonal susceptibilities to these antimicrobials.[26,27] However, as mentioned previously, this type of restriction may lead to the "squeezing of the balloon" effect in which there is increased use of alternative agents such as piperacillin/tazobactam and cefepime for empiric broad-spectrum treatment and ertapenem for certain resistant Gram-negative organisms.[7] Fortunately, studies to date have indicated that ertapenem utilization does not have a negative impact

on Pseudomonas susceptibility to anti-Pseudomonal carbapenems.[28,29] At OSUWMC, the restriction of doripenem has led to decreased anti-Pseudomonal carbapenem utilization with no significant increase in ertapenem use. Additionally, this change has led to an annual cost savings of $61,000.[30] Nonetheless, judicious use of ertapenem should continue in order to preserve its activity against other multi-drug resistant organisms.

Being that anti-Pseudomonal carbapenems are often used empirically in septic patients, some experts would argue that restriction of these medications could result in worsened patient outcomes as a result of delayed therapy. For this reason, some recommend allowing all first doses while requiring approval for subsequent doses.[31] Data collected at OSUWMC after implementing doripenem restriction revealed a rapid time to page return (mean 2.7 min).[11] In fact, although few studies have shown improved patient outcomes with restriction programs, the transition from imipenem to extended-infusion doripenem has shown a trend toward improved patient outcomes at OSUWMC (i.e., shorter time on mechanical ventilation, shorter intensive care unit and overall length of stay and lower mortality) although none of these findings were statistically significant.[32] In addition to requiring prior authorization for doripenem and fidaxomicin, daily prospective audit with feedback of select antimicrobials continues today as it has proven quite successful in terms of cost savings and improved patient outcomes at our institution.[12,16]

In addition to "squeezing the balloon" and delays in time to medication delivery, additional potential limitations surrounding prior authorization formulary restriction include staffing challenges. At OSUWMC, all pharmacist and physician members of ASP take call approximately 5 d per month in order to cover 365 d per year. By splitting the days equally among all members and not taking call during overnight hours, the burden is minimized for each individual. Another concern may be how to prevent prescribers from waiting until after on-call hours to order restricted medications. At OSUWMC, we have not observed a spike in the ordering of restricted antimicrobials after-hours; however, a member of the ASP team reviews all orders for doripenem each business day. In this manner, orders placed after-hours are assessed for appropriateness in a timely fashion.

Another potential limitation to this approach is the deliberate or unintentional communication of false information by the prescriber in order to obtain antimicrobial approval. In order to minimize the risk of this occurring, ASP members directly view the electronic medical record and patient information concurrent with their discussion with the prescribing team. This real-time chart review also enables the ASP member to make optimal recommendations for alternative therapy when appropriate. Finally, prescriber pushback could be a challenge when implementing prior authorization formulary restrictions. At OSUWMC, concerns surrounding medication delays as a result of this process were voiced by some prescribers prior to implementation. However, these worries were put to rest once we presented data demonstrating that this was not an issue. Prescriber pushback at the point of a medication request can also occur if the medication is not approved. These situations are handled by referring the caller to one of the Infectious Diseases physician members of the ASP team.

Despite potential limitations of formulary restriction including delays in therapy, prescriber pushback, and unintended increases in use of un-restricted antimicrobials, implementing prior authorization for select antimicrobials and making a significant effort to educate clinicians on criteria for use can ensure more appropriate prescribing of these agents and help preserve their utility for years to come.

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