CRITICAL CARE

REVIEW

Pro/con debate: Should antimicrobial stewardship programs be adopted universally in the intensive care unit?

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Abstract

You are director of a large multi-disciplinary ICU. You have recently read that hospital-wide antibiotic stewardship programs have the potential to improve the quality and safety of care, and to reduce the emergence of multi-drug resistant organisms and overall costs. You are considering starting one of these programs in your ICU, but are concerned about the associated infrastructure costs. You are debating whether it is worth bringing the concept forward to your hospital's administration to consider investing in.

Statement for debate

Antibiotic stewardship programs improve patient outcomes and cost-effectiveness in critically ill patients in the ICU.

Introduction

Antibiotic stewardship programs are multidisciplinary initiatives whose primary aim is to optimize antibiotic usage. The Infectious Disease Society of America (IDSA) and the Society for Health Care Epidemiology of America (SHEA) published guidelines for antimicrobial stewardship in 2007 aimed at providing information on how to establish such programs within health care institutions [1]. Because antibiotics are used heavily in the ICU, stewardship programs appear particularly applicable to this setting. Antimicrobial stewardship is broadly defined as a practice that ensures the optimal selection, dose and duration of antimicrobials and leads to the best clinical outcome for the treatment or prevention of infection while producing the fewest possible side effects and the lowest risk for subsequent resistance [2]. Antimicrobial stewardship programs may contain a variety of interventions that are complementary to effective infection prevention and control programs.

Inappropriate antimicrobial usage is a significant problem, with approximately 50% of antimicrobial usage being unnecessary or suboptimal in hospital, community or ambulatory settings [3,4]. A recent study showed that approximately 20% of patients admitted to the ICU with *Clostridium difficile*-associated diarrhoea were receiving antibiotics without any obvious evidence of infection, with an accompanying 28% in-hospital mortality [5]. As a consequence of indiscriminate antibiotic use, there are reported increases in the incidence of infections caused by resistant organisms. A significant correlation was demonstrated between the increase in fluoroquinolone prescriptions in Canada from 0.8 to 5.5 per 100 persons per year and increased ciprofloxacin-resistant *Streptococcus pneumoniae* from 0% to 1.7% [6]. Twelve percent of patients previously exposed to piperacillin-tazobactam were colonized with strains of enterobacteriaceae resistant to this antibiotic [7] and the use of third generation cephalosporins is associated with higher rates of vancomycin-resistant enterococci and extended-spectrum β-lactamase-producing organisms [8]. Antimicrobial resistance emerging in response to the selective pressure exerted by antibiotics is also a clinical phenomenon, with outbreaks of antibiotic-resistant *Pseudomonas aeuroginosa* and *Acinetobacter baumanii-calcoaceticus* occurring in ICUs, where a huge antimicrobial pressure is present [9-11].

Although they are often life-saving, antibiotics can also cause serious harm to patients, including *Clostridium difficile*-associated diarrhoea, antibiotic-resistant infections and invasive candidiasis [12-14]. Antibiotics also result in dangerous drug interactions, life-threatening hypersensitivity reactions, nephrotoxicity, and QT prolongation, to name a few. Inappropriate antibiotic use also contributes to rising drug and hospitalisation costs, and the need to preserve our current antibiotic arsenal

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has assumed greater importance with the paucity of new antibiotic development [15].

Pro: There is justification for implementing antibiotic stewardship programs in the ICU

Clinicians have long been aware of the risks of antibiotic resistance associated with inappropriate antibiotic use, but nonetheless very few effective antibiotic policies have been implemented, and the problem appears to be even worsening [16]. The costs associated with antibiotic usage are also escalating, with systemic antibiotics being the single most costly drug class over the past decade in non-federal hospitals in the United States. In 2007, systemic antibiotics accounted for 11.2% of the pharmacy budget of non-federal hospitals [17]. In addition to direct pharmacy costs, hospitalisation and other infrastructure costs are also increased, ultimately resulting in a greater strain on the healthcare system. Saving antibiotics will save money, and there are a variety of methods to do so.

Education is the cornerstone of any antibiotic stewardship program, with prescriber education and implementation of guidelines and clinical pathways improving antimicrobial prescribing behaviour. For example, studies using algorithms to shorten the course of antimicrobial therapy in ventilator-associated pneumonia led to significantly lower antimicrobial therapy usage with reduction in costs, antimicrobial resistance, and super-infections without adversely affecting the length of stay or mortality [18,19]. The absence of formal antimicrobial stewardship training programs for infectious diseases fellows, board-certified physicians, and pharmacists has recently been a challenge to the education imperative, however [20].

Preauthorisation (also known as formulary restriction) requires approval by a pharmacist or physician prior to clinical use of an antimicrobial. Although preauthorization is thought to be the most effective method of controlling antimicrobial use, it does not alter the duration of therapy or the decision to give or withhold antibiotics. The main benefits of this strategy are the supervision of antibiotic use by experts and substantial cost savings (with some studies demonstrating cost savings upwards of US$800,000) [21,22].

Through prospective audit with interaction and feedback, antimicrobial use is reviewed after antimicrobial therapy has been initiated and recommendations are made with regard to their appropriateness in terms of selection, dose, route and duration. Prospective audit with feedback avoids delays in initiation of therapy and maintenance of prescribers' autonomy, and can be implemented in health care facilities of varying sizes [23,24]. A large teaching hospital reported a 37% reduction in the number of days of unnecessary antibiotics use by decreasing the duration of treatment and by reducing new starts [25]. In another study, antimicrobial suggestions from an infectious disease fellow and a clinical pharmacist resulted in 1.6 fewer days of parenteral therapy and cost savings with no adverse effects on clinical response [23]. Another study demonstrated a sustained decrease in parenteral antibiotics over a 7-year period following introduction of a prospective audit with interaction and feedback [26].

Multiple studies using healthcare information technology, such as computer-assisted decision support designed to provide treatment recommendations, have shown significant reductions in the use of antibiotics and greater de-escalation to narrow-spectrum antimicrobials. Improvements in cost and efficiency of existing stewardship programs, and improved physician knowledge regarding treatment and pathogen prediction were also noted [27-29]. In addition to improving antimicrobial use and patient care (including tracking of antibiotic resistance patterns), such systems can improve surveillance of hospital-acquired infections and adverse drug events when compared to manual surveillance methods [30,31]. In a 15-month study using a web-based antimicrobial approval system linked to national antibiotic guidelines, a sustained reduction in third-generation cephalosporin prescriptions were accompanied by increased concordance with antibiotic guidelines [32]. These benefits have also been noted in an ICU-based study, where investigators used computerised anti-infective programs and were able to document significant reductions in the use of excessive drug dosage, adverse drug events and length of hospital stay and costs [33].

Standardized pre-printed or computer-generated physician order sets can improve the efficiency of antibiotic stewardship programs. In a study looking into their benefits in the management of patients with septic shock in an emergency department, order sets were found to improve initial fluid resuscitation, use of appropriate antibiotics and 28-day mortality [34]. A recent study to evaluate the hospital-wide impact of a standardized order set for the management of severe bacteraemic sepsis has shown that a greater number of patients received appropriate initial antibiotic therapy with decreased incidence of organ failure and improved survival [35].

A survey of 670 US hospitals found that implementation of guideline-recommended practices to control antimicrobial use and optimize the duration of empirical therapy was associated with less antimicrobial resistance, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, fluoroquinolone-resistant *Escherichia coli* and ceftazidime-resistant *Klebsiella* species [36]. Given the relationship between antimicrobial use and antimicrobial resistance, antimicrobial stewardship appears to be a logical first step in the effort to control antimicrobial resistance.

The efficacy of antimicrobial stewardship programs has been the subject of a recent Cochrane systematic review, examining 66 studies from 1980 to 2003 [37]. The main interventions analyzed in the review were targeted to decrease treatment (57 studies), increase treatment (6 studies) or both (3 studies). The interventions addressed the antibiotic regimen (61 studies), the duration of treatment (10 studies), the timing of first dose (6 studies), or the decision to prescribe antibiotics (1 study). Optimization of antibiotic use was seen in 81% of the studies aimed at improving antimicrobial utilization. Significant improvements in microbiological outcome (for example, prevalence of antibiotic-resistant bacteria) and clinical outcomes (for example, mortality and length of hospital stay) were also noted in some studies. Recent observational studies (subsequent to the Cochrane review) have demonstrated that reducing antimicrobial pressure correlates with improved antimicrobial susceptibility of pathogens [38,39].

Antimicrobial stewardship programs using the methods described above will promote the optimal use of antimicrobial therapy, leading to the best clinical outcome for patients. The relative paucity of outcome data demonstrating the benefits of antimicrobial stewardship is likely due to its infancy: antimicrobial stewardship programs today are where infection control programs were roughly 30 years ago [40,41]. Because antimicrobials are widely prescribed in the ICU, with an apparent mortality benefit with appropriate therapy [42], using the best available methods to optimize their use through antimicrobial stewardship is crucial.

Con: The evidence for effectiveness of antimicrobial stewardship is lacking

Despite the publication of guidelines for improving the use of antimicrobial agents in the United States, a great deal of scepticism about the effectiveness and acceptability of antimicrobial stewardship programs persists. In a survey conducted by the United States Centers for Disease Control and Prevention's National Nosocomial Infections Surveillance Systems, only 40% of selected hospitals had antibiotic restriction policies and 60% used stop orders [43]. Antimicrobial stewardship programs are also 50% less likely to be implemented in community hospitals compared to academic hospitals [44]. Two years after the publication of the IDSA/SHEA antibiotic stewardship guidelines [1] only 48% of survey respondents stated that their hospital had a program [41].

Reduction in the incidence of bacterial resistance is touted as the main advantage of antimicrobial stewardship programs, but lacks scientific evidence to support it. In a recent survey of 33 US hospitals, there was no significant correlation between antibiotic guideline adherence by physicians and resistance rates [45]. Antibiotic use in ICUs may be the consequence rather than the cause of resistance, and there is a risk that stewardship, with its emphasis on decreased antibiotic use, could lead to a substantial increase in patient risk. It is also important to note that neither the published guidelines nor the important stewardship articles identify safety as an endpoint.

Another potentially adverse consequence of antibiotic restriction is the emergence of new resistance patterns replacing the old ones. A study documenting the introduction of new guidelines that restricted cephalosporin use was primarily aimed at reducing the incidence of cephalosporin-resistant *Klebsiella* spp. Even though the primary aim was achieved, this occurred at the expense of increased imipenem usage with the subsequent increase in incidence of imipenem-resistant *P. aeuroginosa* by about 69% [46]. Thus, formulary restriction does not necessarily prevent the potential overuse of available broad spectrum antibiotics in routine practice [47]. Rather, a significant change in clinical thinking to reduce our dependence on and abuse of antibiotics is needed.

Antimicrobial stewardship programs form only one strategy for minimizing the incidence of resistance, and must partner with infection control measures, including surveillance, outbreak investigation, disinfection and sterilization, and environmental hygiene. Of the studies reported to be beneficial, it remains unclear as to whether the reported improvements in resistance rates are related to antimicrobial stewardship programs, infection control measures or both.

Although healthcare information technology is believed to be a key component of antimicrobial stewardship programs, detailed information on the resources required to implement and maintain these sophisticated computer programs is not widely available. It is also not clear whether the reported cost-effectiveness of many of these stewardship programs takes into account the overall cost of these interventions above and beyond the pharmacy-related costs and expenses associated with development and distribution of educational materials.

Another challenge to implementing antimicrobial stewardship in the ICU deals with the confidence intensivists have in the clinical judgement of the stewardship physician. A junior physician might be a less effective antimicrobial stewardship team member because of a perceived or real lack of knowledge and experience [48], but may be utilized because the 'price is right'. In the survey by Pope and colleagues [41], personnel shortages (55%), financial considerations (36%), and resistance from administration (14%) were frequent barriers to establishing antimicrobial stewardship programs. Opposition from prescribing physicians was a barrier to establishing an antimicrobial stewardship program in about 27% of cases.

While antimicrobial stewardship programs have rather consistently shown significant improvement in antimicrobial utilization, there are very few studies examining meaningful clinical outcome measures such as duration of hospitalization, mortality rates, or even quality indicators such as patient satisfaction. In the systematic review by the Cochrane Collaboration on antibiotic stewardship programs, clinical outcomes such as mortality and length of hospital stay were reported in only 15% of the studies [37]. In the 2008 survey by Pope and colleagues [41], only 25% of respondents reported clinical outcomes. Also, none of the studies report any significant reduction in antimicrobial side effects as a result of these interventions.

Conclusion

Hospitals are increasingly implementing antimicrobial stewardship programs in response to increasing antimicrobial resistance (despite aggressive infection control practices), coupled with fewer novel antimicrobials and increasing antimicrobial costs. There is little question that antimicrobial use is causally related to antimicrobial resistance, and there is growing evidence that stewardship measures aimed at optimizing antimicrobial use can reduce antimicrobial resistance while reducing associated costs. Being major foci of antimicrobial resistance and the largest consumers of antimicrobials in most hospitals, ICUs can expect to benefit most from antimicrobial stewardship programs.

Full implementation of antibiotic stewardship programs requires significant investment, however. In the present economic climate, barriers to implementing such programs include personnel shortages, financial cutbacks, and resistance from administration who are reluctant to assume economic risk. Focusing on patient safety initiatives and the benefits of cost savings and cost avoidance may enable hospital administrators to look upon antibiotic stewardship programs favourably [20]. Supplemental strategies such as consultations provided by specialists in infectious diseases might also be used in lieu of clinical decision support systems. Such expertise has been shown to improve antimicrobial use, shorten duration of mechanical ventilation and ICU stay, and to reduce in-hospital and ICU mortality [49], although it is unlikely that a clinical-decision support system would be entirely replaced. In addition to pre-authorization and/or audit-and-feedback approaches, ICUs should consider other strategies to improve antimicrobial utilization. In short, stewardship programs should be adapted according to the individual needs of institutions, but should be adequately resourced to achieve their intended aims.

ICUs are complicated systems, and implementing a complex program into another complex structure raises the potential of unintended (and often unmeasured) adverse consequences. All ICUs should have an antimicrobial stewardship program accompanied by a system to monitor clinically meaningful outcomes such as mortality and length of stay. Monitoring such outcomes presents an excellent opportunity for infection control and other patient quality and safety initiatives, whose aims include prevention of healthcare-associated infections and control of antibiotic-resistant organisms. In the absence of such monitoring, antimicrobial stewardship programs are nothing more than programs to reduce antimicrobial use with a largely unproven effect on patient care. Close collaboration between critical care, infectious disease, infection control, medical informatics, microbiology, and pharmacy staff are needed for the success of an antimicrobial stewardship program. From our experience, leadership and a culture that embraces change is critical to implementation of a successful antimicrobial stewardship program.

Abbreviations

IDSA = Infectious Diseases Society of America; SHEA = Society for Healthcare Epidemiology of America.

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Competing interests

AMM is Director of the Antimicrobial Stewardship Program at Mount Sinai Hospital and University Health Network in Toronto. He receives salary support for his work in this capacity. There are no other competing interests.

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