

Making Sense of Antimicrobial Resistance Surveillance: A successful intervention

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Abstract

Background: The intensive care units are epicenters for the emergence of antibiotic resistant Gram-negative bacteria because of the high use of antibiotics, prolonged hospital stay, reduced patient immunity, use of medical devices, and the frequent contact between healthcare workers and patients. Surveillance of bacterial resistance is the key element to understand the size of the problem, drive interventions, and measures the effect of these measures. Several reports have linked the use of third generation cephalosporins with β -lactam resistance in gram-negative bacteria. Several strategies were introduced by the Antibiotic Stewardship Programs to reduce antibiotic resistance but the efficacies of these interventions are not well studied.

Methods: The Microbiology Laboratory of Hamad Medical Corporation (HMC) monitors antimicrobial resistance by continuous surveillance using the National Committee for Clinical Laboratory Standards (NCCLS) - currently Clinical Laboratory Standards Institute interpretive criteria. Surveillance data were released annually and shared with clinicians and policy makers for review of the antibiotic policy and the antibiotic formulary.

Results: Surveillance data in 2001 showed high level β -lactam antibiotics resistance and high level production of extended spectrum β -lactamases (ESBL) among gram-negative bacteria. As a result, the Hospital Antibiotic Policy Committee decided to withdraw ceftazidime a third-generation cephalosporin known to be a strong inducer of ESBL, from the hospital formulary. Subsequent resistance surveillance over the following three years in the Medical Intensive Care unit (MICU) demonstrated a gradual drop in the resistance of *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli*; the commonest isolated gram negative bacteria from MICU), not only to third and fourth generation cephalosporins, but also to Piperacillin – Tazobactam in spite of the increased use of the later drug in the MICU.

Discussion and conclusion: Antibiotic resistance is an increasing global problem. Surveillance studies are needed to monitor resistance development, to guide local empirical therapy, and to implement timely and adequate countermeasures. Since resistance development is an evolutionary process, constant surveillance is necessary to gain insight into the problem in a timely fashion. Several measures were taken including antibiotic cycling, antibiotic rotation and restriction. Restriction of the use of Ceftazidime resulted in a significant drop in the resistance of the common Gram-negative bacteria to the beta-lactam antibiotics. The sustainability and efficacy of these measures need to be monitored over time.

Keywords: Antimicrobial, Surveillance, Intervention

Introduction

Antibiotics resistance has emerged as an important determinant of mortality and morbidity for patients in the intensive care units. This is largely due to the increasing presence of pathogenic organisms with resistance to the commonly used antibiotics resulting in inappropriate antimicrobial therapy [1]. There is also indirect evidence of a relationship between antimicrobial use and bacterial resistance [2, 3]. The main forces driving the increase in antimicrobial-resistant bacteria are poor infection prevention and control practices and injudicious use of antibiotics. Once these factors are addressed, specific antibiotic utilization strategies may help decrease or prevent the emergence of resistance. These strategies include antibiotic

restriction, combination therapy, and antibiotic cycling or rotation [4]. Hence the first steps towards preventing or decreasing the incidence of resistance are effective infection prevention and control policies and improved antimicrobial stewardship [5]. Although infection prevention and control policies are unlikely to prevent resistance from emerging, they are essential to decrease the spread of antimicrobial-resistant bacteria [5].

Many studies have shown that as much as 50% of antimicrobial use is inappropriate [6,7]. Excessive and inappropriate antimicrobial use results in strong selective pressure that facilitates the emergence of antimicrobial-resistant pathogens. Optimizing the selection, dosage, and duration of antimicrobial therapy to prevent and treat infections is essential. Such optimization is often achievable for individual

patients but more difficult to achieve on a population-wide basis. Some classes of antibiotics, despite optimal dosing and duration of therapy, may allow for the selection of resistant organism or may induce resistance. Restriction, cycling or rotating antibiotics within or between classes, by altering the selective pressure for bacteria to develop resistance will help combat resistance to any particular antibiotic, and be an important component of Antimicrobial Stewardship Programs [4].

Surveillance was defined by Centers for Diseases Control and Prevention USA (CDC) as systematic, ongoing data collection, analysis and reporting process that quantitatively monitors temporal trends in the occurrence and distribution of susceptibility and resistance to antimicrobials agents, and provides information useful as a guide to medical practice including therapeutics, antimicrobial stewardship, and disease control activities [8].

The main objective of Surveillance is to detect shift in susceptibility of various organisms to various antibacterial agents and to inform prescribes and antibiotic policy makers of such changes as soon as possible. If an increase in resistance is noted in any species, information from surveillance studies can help detect appropriate therapy to treat emerging resistant pathogens and to allow strategies to be formulated aimed at reducing and preventing any further development of resistance through a proper stewardship program and appropriate infection control practices [9, 10].

Several hospitals demonstrated reduced resistance to ceftazidime after reduction in its use [11,12]. Antibiotic restriction as a utilization strategy involves the selective removal or control of specific agents or classes of antibiotics without the intent to reintroduce them at a future date. This has been successful in decreasing established resistance to the agent being restricted and probably to related antibiotics [13].

The first step towards decreasing the emergence and spread of antibiotic resistant bacteria is optimizing infection control policies and antimicrobial stewardship. If these are not in place before antibiotic restriction strategies and other interventions are employed, resistance rates are unlikely to stabilize or decrease.

We here present the effect of restricting the use of ceftazidime on the resistance of Gram-negative bacteria in the MICU.

Materials & Methods

In 2001 Hamad Medical Corporation-Qatar had 4 main Hospitals, Hamad General Hospital, with 5 intensive care units, Rumailah Hospital, The Women's Hospital and Al Amal cancer Hospital. Besides these hospitals there were more than 24 health centers for Primary health care. Specimens from all these locations were processed in the Microbiology laboratory. Isolates were identified to the species level and tested for their susceptibility to a wide range of antibiotics by the Vitek 2 instrument (biomerieux, France). Organisms not included in the Vitek 2 data base were tested by API (biomerieux, France) and E test (AB Biodisk, solution, Sweden). The antibiotics selected were appropriate to the range of organisms anticipated and/or the disease and body site, taking account of the ones available in the hospital formulary, as well as those that provide reference information, or help to elucidate resistance mechanisms. The Microbiology laboratory had very comprehensive quality control procedures for media, reagents, antimicrobials and

equipment and was enrolled in an External Proficiency Tests (College of American Pathologists). For interpretation of MICs NCCLS guidelines were followed. The percentage resistant isolates were calculated by using resistant bacteria isolated from clinical samples as numerator; excluding duplicate isolates. The denominator was the number of strains of the same species, isolated under the same condition. Intermediately resistant isolates were pooled with the resistant ones.

According to the NCLSI guidelines, a minimum of twenty strains was required for separate reporting. The critical resistance level beyond which isolates of a particular species can be regarded as resistant and cannot be used for empirical therapy was > 10-20% of isolates. However a lower percentage can be used depending on the severity of infection and the availability of other therapeutic options.

Both continuous and targeted surveillance were released annually and distributed to the concerned. Resistance pattern were calculated by location, by body sites and for specific organisms from our routine susceptibility data following NCCLS. The use of routine susceptibility data is now accepted widely, as opposed to the costly and labor intensive active surveillance, as it can produce a great deal of useful, easily acceptable and sufficiently accurate information [14,15].

Results

Our continuous surveillance data showed increased resistance to third generation cephalosporins and increased production of ESBLs among the 3 commonly isolated Gram-negative bacilli from the MICU; *P.aeruginosa*, *E-coli* and *K. pneumoniae*. This particular class of antibiotics is notorious for its ability to rapidly select for high level β -lactamase-producing organisms, leading to resistance not only to the cephalosporins but also to many other β -lactam antibiotics [16-18]. Ceftazidime, a third generation cephalosporin, is a strong inducer of ESBL. It slowly penetrates the Gram-negative cell wall and slowly accumulates in the bacterial periplasmic space; this allows time for the common β -lactamases (TEM and SHV enzymes) to mutate by substituting one or more amino acid in the protein chain of the enzyme. This change results in a mutation of the enzyme to an ESBL.

In October 2001 The Antibiotic Policy Committee decided to remove Ceftazidime from the hospital formulary and replace it by Cefepime, a fourth generation cephalosporin. The effect of this on resistance of the common gram-negative organisms isolated from the MICU patients was evaluated.

Piperacillin- Tazobactam was introduced at the end of 1997. Ceftazidime and Ceftriaxone were the most commonly used antibiotics in MICU. Resistance of *E.coli* and *K.pneumoniae* to Ceftazidime was found to be almost similar to that of cefotaxime/ceftriaxone and Cefepime while in *P. aeruginosa* resistance to cefepime was similar to that of ceftazidime. Hence we analyzed the resistance of the commonest isolates to ceftazidime and Piperacillin-Tazobactam, assuming ceftazidime as the representative of the third and fourth generation cephalosporins. (Figure 1, 2 & 3) show the resistance of the three isolates to these two antibiotics, four years before the cessation of ceftazidime (98,99,2000,2001) and three years after (2002, 2003,2004). As shown in the figures the resistance to both ceftazidime and piperacillin-tazobactam increased to reach a peak in 2001. After removal of ceftazidime at the end of 2001

there was a statistically significant drop in the resistance of all three organisms for both drugs. This occurred despite increased rate of utilization of Piperacillin- Tazobactam (Tables 1,2).

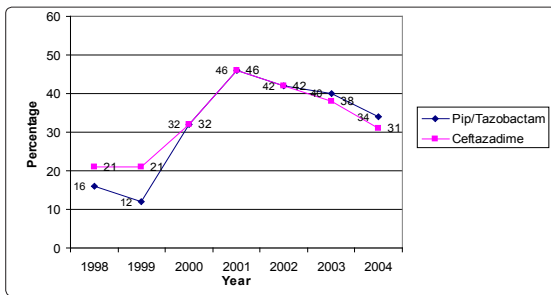


Figure 1: % Resistance of *P. aeruginosa* to ceftazidime and Pip/ Tazobactam

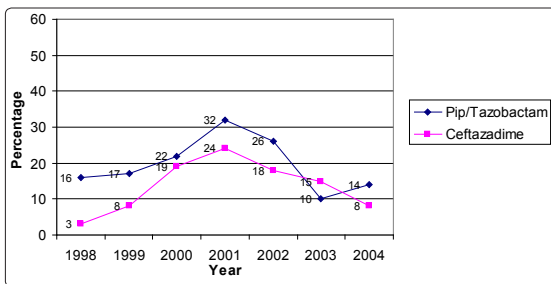


Figure 2: % Resistance of *E.coli* to ceftazidime and Pip/ Tazobactam

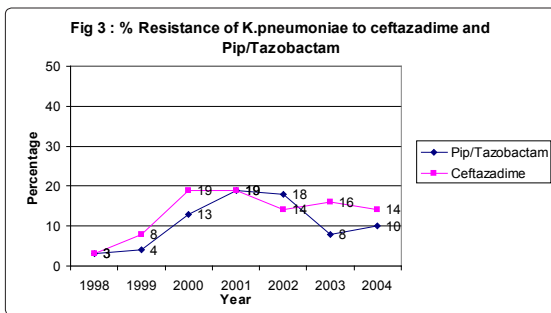


Figure 3: % Resistance of *K.pneumoniae* to ceftazidime and Pip/ Tazobactam

Table 1: % resistance of *P.aeruginosa*, *E.coli* and *K.pneumoniae* to Ceftazidime: 1998-2004: P value

Organism	Pip/Tazobactam% resistance 1998-2004							
	1998	1999	2000	2001	2002	2003	2004	2004
<i>P.aeruginosa</i>	16	12	32	46	42	38	34	34
<i>E.coli</i>	16	17	22	32	26	10	14	14
<i>K.pneumoniae</i>	3	4	13	19	18	8	10	10

Table 2: % resistance of *P.aeruginosa*, *E.coli* and *K.pneumoniae* to Pip/Tazobactam: 1998-2004: P value

Organism	Ceftazidime% resistance 1998-2004							
	1998	1999	2000	2001	2002	2003	2004	2004
<i>P.aeruginosa</i>	21	21	32	46	42	38	31	<0.001
<i>E.coli</i>	3	8	19	24	18	15	8	0.003
<i>K.pneumoniae</i>	3	8	19	19	14	16	14	0.001

Discussion

Surveillance studies provide a tool for intervention based on the data obtained, for instance surveillance data can lead to removal of a given drug from an accepted official list of medications. However there is an important controversy regarding the resistance rate that an antibiotic has to attain in a particular setting for declassification of its use. Controversy also exists regarding the relationship between antimicrobial use and resistance. There is indirect evidence of a relationship between antimicrobial use and bacterial resistance. Antimicrobial use is the major, but not the only factor determining resistance in a defined ecologic system such as the hospital. This explains why some studies failed to demonstrate a relationship [19-21]. Unfortunately these studies only identified association or dose effect relationship between antimicrobial use and resistance at the group level and did not study variations of these two variables overtime. Such variations, i.e. changes in antimicrobial use followed by changes in resistance, in the same direction, are probably the most convincing since they take into account the time sequence between the suspected cause and the observed effect as reported from various hospitals and countries [22-24]. In our hospital we demonstrated that after the introduction of ceftazidime into the hospital formulary, the resistance of *P. aeruginosa* and members of the family Enterobacteriaceae rose from 0% to as high as 46%. Once ceftazidime was withdrawn, a steady drop in resistance was observed not only for ceftazidime, but for other third and fourth generation cephalosporins, as well as for Piperacillin - Tazobactam despite the constant increase of its use. This was also observed by others [25].

However in our MICU Ceftriaxone which is also a strong inducer of ESBL was used as the main antibiotic. In a recent drug use review, we estimated that ceftriaxone was prescribed in 57% of patients admitted to the MICU as an empirical therapy either alone or in combination with other antibiotics [26]. Reduction in the use of Ceftriaxone may be followed by further drop in the resistance of gram-negative bacteria to cephalosporin as well as β -lactam- β -lactamase inhibitors. Ceftriaxone can be reserved for treating patients with meningitides, while antimicrobials like cefepime and Piperacillin-Tazobactam, which are less inducer, can be used for treating other infections.

Conclusion

We conclude that the selection of resistance is an inevitable consequence of antibiotic usage. Regular surveillance of antimicrobial resistance is essential to detect and monitor the development of resistance, but for the results to be of value, the information gathered must be utilized not only in formulating empirical therapy but also for strategic intervention to prevent the increase and spread of resistance [27-30].

This trial, will provide further insight in the restriction of antibiotics and guide future practice guidelines and clinical practice. Nevertheless, strategies incorporating multiple interventions including infection prevention and control, shorter courses of treatment, de-escalation of antibiotics on the basis of culture and other antimicrobial stewardship strategies, are most likely to be successful.

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