Growing problem of multidrug-resistant 
Acinetobacter baumannii in Thailand

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Abstract

Acinetobacter species have become important pathogens in health care settings and are now responsible for substantial mortality and mortality. The resistance among Acinetobacter spp. has also been continuously rising since 2000. Multidrug-resistance (MDR), is defined as simultaneous resistance to fluoroquinolones, aminoglycoside, and third-generation cephalosporins. Data reviewed from Thailand’s national surveillance mechanism shows that in 2009, at least 62% of isolates of this bacterium were carbapenem and multidrug-resistant. This paper provides a brief summary of our experience.

Introduction

Antimicrobial resistance has become a major health care challenge over the past few decades. Various bacterial species have developed an ability to survive in hostile environments of heavy antimicrobial pressure. For example, methicillin-resistant Staphylococcus aureus (MRSA) has been problematic since 1980s, initially among hospitalized patients, and is now becoming more common in communities in some countries. Extended-spectrum β-lactamase (ESBL) producing organisms were first reported from Germany and have now spread around the globe such that community-acquired strains were also found in many areas. However, the most worrisome trait is the simultaneous resistance to multiple antibiotics among Pseudomonas aeruginosa and Acinetobacter baumannii. These organisms are frequently resistant to carbapenems, the broadest antibiotic available to date, as well as to broad-spectrum cephalosporins, aminoglycosides, and fluoroquinolones.

The National Antimicrobial Resistance Surveillance Centre, Thailand, (NARST), which is the national antimicrobial surveillance system under the administration of the Ministry of Public Health with support from the World Health Organization (WHO), has been monitoring the situation of antibiotic resistance among common bacterial pathogens since 1998. In the beginning, bacterial species that showed high resistance rates were P. aeruginosa and MRSA. However, it was noted that resistance among Acinetobacter spp., has been continuously rising since 2000. Multidrug-resistance (MDR), defined as simultaneous resistance to fluoroquinolones, aminoglycoside, and third-generation cephalosporins in the NARST report published in 2009, was estimated to be at least 62% of carbapenem-resistant A. baumannii. This led to training of microbiology laboratory personnel in the surveillance network in 60...
hospitals around the country to be aware of this particular bacterial species. Because MDR is defined differently in various literatures, this article will focus mainly on carbapenem resistance.

**Prevalence of carbapenem- and multidrug-resistant A. baumannii in Thailand**

During 2000-2005, 28 hospitals in the surveillance network submitted their results of susceptibility tests to NARST. In 2000, over 5000 isolates of A. baumannii were identified from various types of clinical specimens. This number almost doubled in 2005, when nearly 100,000 isolates were identified. Approximately 60% were found in respiratory tract specimens. Resistance to carbapenem was the most dramatic in that the rate of resistance was only 2.1% in 2000 and sharply increased to 46.7% in the last year. The next prominent resistant phenotype was the resistant to cefoperazone/sulbactam, which used to be the drug of choice for the treatment of infections caused by A. baumannii. In 2000, 97% of isolates were susceptible to this b-lactam/β-lactamase inhibitor combination due to dual antimicrobial activity of the two compounds. In contrast, only 88% remained susceptible to this agent in the last year of that study period. The highest carbapenem-resistance rates were found in the northeastern region, northern region, and Bangkok, respectively. Furthermore, over 50% of A. baumannii were not only resistant to carbapenems, but also to many other broad-spectrum agents such as ceftazidime, cefoperazone/sulbactam, ciprofloxacin, and amikacin. In accordance with reports from around the world, a high rate of resistance was seen in intensive care units (ICU). For example, the overall rates of imipenem-resistance in ICUs were 64% and 48% in non-ICU populations in 2005.1

Continuing surveillance performed after the above data were published revealed an even more difficult situation. Overall, carbapenem-resistance rates increased to 59.1% in 2009. A high rate of resistance was seen in all hospitals in the network. These hospitals are mainly medium-sized, secondary to tertiary care hospitals. A few hospitals were large (>500-1000 beds) and were also university-affiliated. One tertiary-care, university-affiliated hospital in the eastern region reported up to 76.1% resistance. This figure was similar to what we found in Bangkok where at least three university hospitals which are not in NARST reported a similar rate of resistance. However, if one explores further into each individual area of the hospital, the highest rate of resistance will be found in the ICU. In these university hospitals, only 10% to 15% of A. baumannii in ICUs are still susceptible to carbapenems, and most of these isolates are resistant to almost all available antimicrobial agents in the hospitals. Another unpleasant fact is that nearly all these ICU isolates are now almost completely resistant to major classes of antibiotics including carbapenems, third- and fourth-generation cephalosporins, aminoglycosides, and fluoroquinolones. In addition, resistance to cefoperazone/sulbactam is also increasing, which further limits treatment options for these problematic organisms. The only two antibiotics that might still be used with little hope are tigecycline and colistin. Tigecycline is a minocycline derivative that has bacteriostatic activity against several bacterial species including carbapenems, third- and fourth-generation cephalosporins, aminoglycosides, and fluoroquinolones. In addition, resistance to cefoperazone/sulbactam is also increasing, which further limits treatment options for these problematic organisms. The only two antibiotics that might still be used with little hope are tigecycline and colistin. Tigecycline is a minocycline derivative that has bacteriostatic activity against several bacterial species including carbapenems, third- and fourth-generation cephalosporins, aminoglycosides, and fluoroquinolones. In addition, resistance to cefoperazone/sulbactam is also increasing, which further limits treatment options for these problematic organisms. The only two antibiotics that might still be used with little hope are tigecycline and colistin. Tigecycline is a minocycline derivative that has bacteriostatic activity against several bacterial species including carbapenems, third- and fourth-generation cephalosporins, aminoglycosides, and fluoroquinolones. In addition, resistance to cefoperazone/sulbactam is also increasing, which further limits treatment options for these problematic organisms. The only two antibiotics that might still be used with little hope are tigecycline and colistin. Tigecycline is a minocycline derivative that has bacteriostatic activity against several bacterial species including carbapenems, third- and fourth-generation cephalosporins, aminoglycosides, and fluoroquinolones. In addition, resistance to cefoperazone/sulbactam is also increasing, which further limits treatment options for these problematic organisms. The only two antibiotics that might still be used with little hope are tigecycline and colistin. Tigecycline is a minocycline derivative that has bacteriostatic activity against several bacterial species including carbapenems, third- and fourth-generation cephalosporins, aminoglycosides, and fluoroquinolones. In addition, resistance to cefoperazone/sulbactam is also increasing, which further limits treatment options for these problematic organisms.
A. baumannii and the susceptibility test should be performed using the broth dilution technique, which is not routinely done in microbiology laboratories in developing countries. Therefore, if one wants to prescribe this agent for patients, close monitoring of clinical response is critical. Secondly, resistance can emerge easily during therapy. Lastly, colistin can lead to impaired renal function and/or neurotoxicity in a large number of patients. These factors are therefore limitations for clinical use of colistin.

Factors influencing epidemiology of carbapenem- and multidrug-resistant A. baumannii

It has been well documented that the emergence and increasing rate of resistance to an antibiotic correlates with the use of that particular agent. In the case of carbapenem-resistance, studies regarding this correlation have been published as well. Our observation found that carbapenems have been used increasingly in the past two decades. From 1994 to 2001, the rate of carbapenem use in a university hospital was lower than 10 defined daily doses (DDD) per 1000 patient-days. During that period, the carbapenem-resistant A. baumannii ranged between 2% and 10%. From 2001 onwards, carbapenems were used increasingly every year until in 2009 when the rate of use was about 54 DDD/1000 patient-days. Along with this increased use, the rate of carbapenem-resistant A. baumannii increased dramatically until 2009 when it reached about 76% as mentioned earlier. The driving force leading to increased use of carbapenem in healthcare facilities is the emergence and spread of extended-spectrum β-lactamase producing Gram-negative bacilli, mainly enterobacteriaceae, in hospitals nationwide. Polwichai P et al. pointed out that the prevalence of ESBL-producing E. coli and K. pneumoniae increased gradually from around 20% in 2000 to 40% in 2005. In the early years of the epidemic, ESBL-producers were mainly hospital isolates. However, community-onset infections caused by these organisms have been increasingly reported. The production of this type of enzyme has been associated with poor outcome when a third-generation cephalosporin was used and many cases needed to change the antibiotic to one of carbapenems. Furthermore, a higher proportion of community strains of E. coli have become resistant to fluoroquinolones and gentamicin, other alternatives to β-lactam agents. Because of widespread concern regarding multidrug-resistance, particularly ESBL producers, many practicing physicians now choose a carbapenem as empirical therapy while waiting for the results of microbiologic studies. Once the results of the cultures have been reported, we would expect physicians to adjust the regimen accordingly, but this was not true in all circumstances. Other forms of inappropriate use of carbapenems included use as routine surgical prophylaxis or prescribed to patients whose fever did not respond to other antibiotics even though the cause of fever might not be an infectious process. Frequently, patients came to medical care because of high fever and physicians tend to prescribe a carbapenem because of the misconception that an antibiotic that has the broadest spectrum of coverage would be “the best” for their patients.

In addition to inappropriate use of carbapenems and other broad-spectrum agents, inadequate infection control measures is another important aspect of the endemicity. Hospitals in Thailand were mainly built so that many patients stay in a common large room consisting of 4 to 30 beds. Spaces between beds are usually small. In many circumstances, these “common wards” were not meant to function as intensive care units but they were modified to accommodate critically-ill patients due to limited space in the hospitals. Old buildings may not have an adequate number of sinks for hand washing. Medications are prepared in a designated area in each patient care unit, where it might be near a sink, which
creates a moist environment, not at the pharmacy department. Along with limited space and suboptimal design, the numbers of healthcare workers are also limited. The nurse: patient ratio had hardly ever been at 1:1, but mostly is around 1:2-8. With this working environment, it is easy for any bacterial pathogens to spread from person to person via the hands of health-care personnel and/or contaminated inanimate objects.

Resources for isolation in hospitals are also limited. In order to isolate patients who carry MDR pathogen effectively, an adequate number of single-bed isolation rooms equipped with bathroom and necessary space for keeping patient care items in place is needed. Hand hygiene facilities including sink, soap, and paper towels for hand washing and alcohol-based hand rub solution should also be easily accessible in the room. Water-proof isolation gowns, gloves, and surgical masks are essential items as well as medical instruments and devices such as sphygmanometer, blood pressure cuffs, and stethoscopes. However, all these resources are limited in most hospitals.

The higher the prevalence, the more resources and efforts are needed to bring the epidemic under control. Since the prevalence of carbapenem-resistance and other epidemiologically important type of resistance have reached high levels in many hospitals, it is a true challenge for health-care providers to work tirelessly to reduce the magnitude of this problem.

Examples of efforts to reduce the prevalence of MDR A. baumannii

Controlling MDR A. baumannii is not an easy task because the epidemiology of MDR A. baumannii is complicated. In brief, its emergence and spread in healthcare facilities involved both inappropriate uses of broad-spectrum antimicrobial agents and inadequate infection control. Therefore, multifaceted intervention is the only possible means to control the epidemic. These measures include an antimicrobial stewardship programme, education for health-care workers of all disciplines, standard and contact precautions, an effective hand hygiene campaign, and/or active surveillance culture for early detection. These efforts have been tried in many hospitals in Thailand. Some of these have been published in medical journals. For example, a medical school in central Bangkok has been trying to establish an antimicrobial stewardship programme focusing on carbapenems via the use of an antibiotic order form. This programme resulted in a stable rate of carbapenem use in the institution despite increasing prevalence of ESBL producers. However, it has not affected the prevalence of MDR A. baumannii since many other broad-spectrum antibiotics were not included in the order form because of the manpower limitation to closely monitor the use of these agents. In addition, isolation precautions have not been fully implemented. This particular university hospital is now using a computer-assisted antimicrobial prescription programme with direct linkage to microbiology data so that more antibiotics can be included; the prescriptions are easier for monitoring and feedback; and educational messages can be placed for prescribing physicians. The initial phase of the use of such a programme resulted in a significantly decreased use of carbapenems. Another university hospital has implemented multifaceted interventions in the ICU including an educational programme, introduction of an antibiogram, use of antibiotic prescription forms, and prescribing controls. After the intervention, the inappropriate use of broad-spectrum antibiotics was significantly reduced. The incidence of infections due to several MDR pathogens such as MRSA, ESBL-producing E. coli and Klebsiella pneumoniae, and third-generation cephalosporin–resistant A. baumannii was significantly decreased. The total cost–saving value of these interventions was estimated to be US$32,231.5 The authors further expanded the intervention to regular wards that had 30 beds and where the
nurse-patient ratio was 1:8. They created a cohort area in addition to the isolation measures. The intervention brought about successful reduction of MDR pathogens as well. According to our personal conversation with colleagues in many hospitals, we are aware that, in fact, efforts to control MDR A. baumannii are under way in their areas.

In summary, antimicrobial resistance in A. baumannii, particularly resistance to carbapenems and other broad-spectrum antibiotics, is a challenge for healthcare services worldwide. Its emergence and spread are tied closely with inappropriate use of antibiotics, not only carbapenem itself, but also other broad-spectrum agents such as third- and fourth-generation cephalosporins. Inadequate infection control efforts further aggravate the problems. Interventions that encompass these two major aspects have been demonstrated to work well even in areas with limited resources like Thailand. We therefore encourage all health-care sectors to create such programmes taking into account normal practice, culture, and resources available for practicality of the intervention. With determined efforts, we should be successful, at least in retarding the accelerated increase in the incidence of these pathogens before we are left in a world that seems to have no effective antibiotics to fight against serious bacterial infections.

References and bibliography