

Antimicrobial Resistance in Asia: Current Epidemiology and Clinical Implications

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Antimicrobial resistance has become one of the most serious public health concerns worldwide. Although circumstances may vary by region or country, it is clear that some Asian countries are epicenters of resistance, having seen rapid increases in the prevalence of antimicrobial resistance of major bacterial pathogens. In these locations, however, the public health infrastructure to combat this problem is very poor. The prevalence rates of methicillin-resistant *Staphylococcus aureus* (MRSA), macrolide-resistant *Streptococcus pneumoniae*, and multidrug-resistant enteric pathogens are very high due to the recent emergence of extremely drug-resistant gram-negative bacilli in Asia. Because antimicrobial options for these pathogens are extremely limited, infections caused by antimicrobial-resistant bacteria are often associated with inappropriate antimicrobial therapy and poor clinical outcomes. Physicians should be aware of the current epidemiological status of resistance and understand the appropriate use of antimicrobial agents in clinical practice. This review focuses on describing the epidemiology and clinical implications of antimicrobial-resistant bacterial infections in Asian countries.

Key Words: Antimicrobial resistance, Epidemiology, Bacterial infections, Asia

Introduction

Antimicrobial resistance has become one of the most serious public health concerns worldwide. It is a global rather than a local issue, as antimicrobial resistance can spread between countries or continents. Massive increases in trade and long-distance travel have enabled the rapid spread of resistant pathogens. The spread of New Delhi metallo-beta-lactamase-1 (NDM-1)-an enzyme that makes bacteria such as *Escherichia coli* resistant to antibiotics-from India to

many Western countries is one of the best recent examples of the transmission of antimicrobial resistance between countries, as it showed the critical impact of antimicrobial resistance on not just public health but also economies and trade [1]. Among community pathogens, penicillin- or macrolide-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA), and multidrug-resistant (MDR) enteric pathogens are of major concern in the Asian region. Among nosocomial pathogens, MRSA or glycopeptide-resistant *S. aureus* (vancomycin-intermediate or

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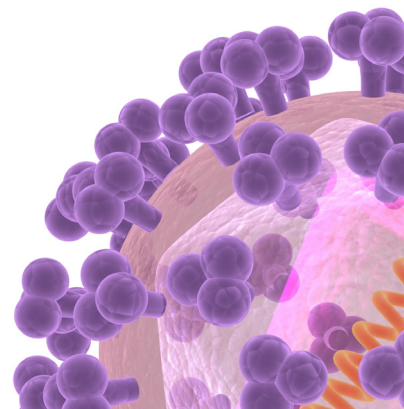
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resistant *S. aureus*, VISA or VRSA, respectively), glycopeptide-resistant enterococci (vancomycin-resistant enterococci, VRE), extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, and MDR nonfermenters are being found with increasing frequency around the world.

Although the circumstances of antimicrobial resistance may vary by region or country, it is clear that Asia is an epicenter of antimicrobial resistance; the prevalence of antimicrobial resistance of major bacterial pathogens has been rapidly increasing. However, public health infrastructures to control the problem are very poor in many countries [2, 3]. Given that more than 70% of the worldwide population lives in the Asia-Pacific region, antimicrobial resistance in this region is, literally, a global problem.

Antimicrobial-resistant *Streptococcus pneumoniae*

According to published reports, very high prevalence rates of beta-lactam and macrolide resistance in *S. pneumoniae* have been found in Asian countries [4, 5]. Particularly, erythromycin resistance has increased dramatically in many Asian countries, where > 70% of clinical isolates were fully resistant [4, 5]. According to a recent prospective surveillance study performed by the Asian Network for Surveillance of Resistant Pathogens (ANSORP), the prevalence rates of penicillin resistance were 0.7% and 57.5% in nonmeningeal and meningeal isolates, respectively, based on the revised CLSI breakpoints for parenteral penicillin (resistant ≥ 8 $\mu\text{g}/\text{ml}$ for nonmeningeal isolates and ≥ 0.12 $\mu\text{g}/\text{ml}$ for meningeal isolates) [4]. Compared with previous ANSORP studies, recent data showed a persistently high prevalence of penicillin nonsusceptibility in Asian countries when previous penicillin susceptibility breakpoints were applied [4-6]. However, according to the revised CLSI breakpoints, the prevalence rate of penicillin-nonsusceptible pneumococci (PNSP) in nonmeningeal isolates was only 4.6%, and fully resistant isolates were found only in China (2.2%) and South Korea (0.3%). Resistance to erythromycin was very prevalent in the region (72.7%); the highest rates were in China (96.4%), Taiwan (84.9%), and Vietnam (80.7%). Multidrug resistance (MDR) was observed in 59.3% of the isolates from Asian countries.

The first report regarding the emergence of fluoroquinolone resistance among *S. pneumoniae* isolates in Asia was from Hong Kong [7], and a subsequent case-control study showed that the presence of chronic obstructive pulmonary disease, nosocomial origin of the bacteria, residence in a nursing home, and

exposure to fluoroquinolones were independently associated with levofloxacin-resistant *S. pneumoniae* colonization or infection [8]. In a Taiwanese hospital, rates of levofloxacin nonsusceptibility of *S. pneumoniae* increased significantly from 1.2% in 2001 to 4.2% in 2007 [9]. The ANSORP study showed that the resistance rates to fluoroquinolones were 1.7%, 0.4%, 1.5%, and 13.4% for levofloxacin, moxifloxacin, gatifloxacin, and ciprofloxacin, respectively, in Asian countries [4]. Isolates from Taiwan (6.5%) and South Korea (4.6%) showed the highest rates of levofloxacin resistance [4]. A case of bacteremic pneumonia caused by an extremely drug-resistant strain of *S. pneumoniae*, nonsusceptible to at least one agent in all classes but vancomycin and linezolid, was reported in Korea [10].

Despite the widespread emergence of *in vitro* resistance in pneumococcal isolates in Asia, the ANSORP studies showed that mortality rates among patients with pneumococcal pneumonia caused by penicillin-, cephalosporin-, or macrolide-resistant strains were not higher than those among patients with antibiotic-susceptible pneumococcal pneumonia [11, 12]. Even though several studies suggested that the outcome of serious pneumococcal infections was not significantly affected by antimicrobial resistance [12, 13], a post-hoc analysis of the ANSORP study showed that levofloxacin resistance was associated with increased mortality in adult patients with invasive pneumococcal diseases [14]. When the 2008 CLSI penicillin breakpoints were applied, a Korean hospital found that fatal outcomes in patients with nonmeningeal pneumococcal bacteremia attributable to penicillin nonsusceptibility were likely to be rare [15]. However, ceftriaxone nonsusceptibility was found to be one of the independent risk factors for 30-day mortality in the study [15].

Methicillin-resistant *Staphylococcus aureus*

Asian countries have shown very high rates (> 50%) of MRSA, which is the most important cause of hospital-acquired infections such as pneumonia, surgical site infections (SSI), and bloodstream infections (Fig. 1). MRSA kills more than 19,000 patients annually in the U.S. alone; thus, many Asian countries could have a huge number of deaths due to this infection [2, 16]. The ANSORP study on *S. aureus* infections in Asia showed that MRSA accounted for 25.5% of community-associated (CA) *S. aureus* infections and 67.4% of healthcare-associated (HA) *S. aureus* infections [4]. The proportion of MRSA among HA *S. aureus* infections was relatively low in India (22.6%) and the Philippines (38.1%), whereas Sri Lanka (86.5%), Korea (77.6%), and Vietnam (74.1%) showed very high rates of MRSA in the ANSORP study.

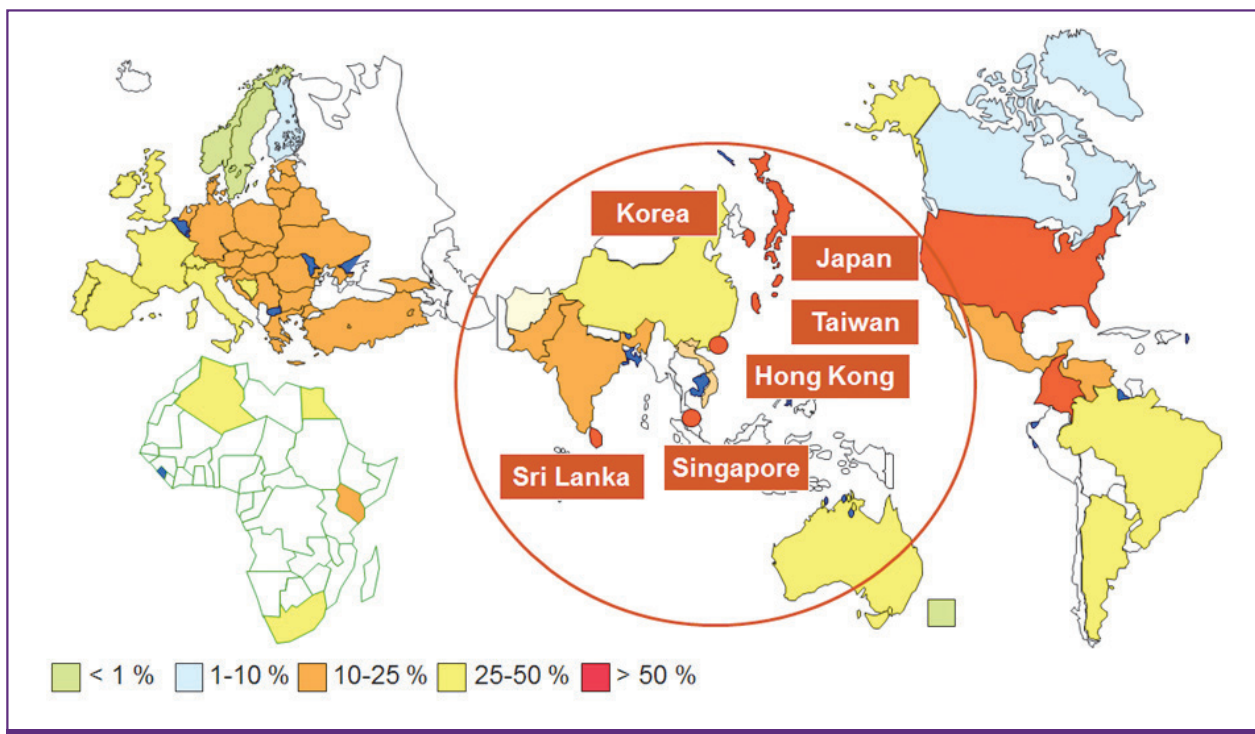


Figure 1. Prevalence of methicillin resistance among *S. aureus* isolates. Some Asian countries have shown the highest prevalence rates of MRSA.

Hospital acquired pneumonia (HAP) caused by *S. aureus* in Asian countries had high resistance rates to oxacillin (82.1%), ciprofloxacin (78.2%), clindamycin (64.2%), erythromycin (76.5%), and tetracycline (70.9%)[17]. Among all *S. aureus* isolates causing ventilator-associated pneumonia in Chinese hospitals, 45.7% were methicillin-resistant [18].

In recent years, community-associated MRSA (CA-MRSA) infections have emerged worldwide [19, 20]. The ANSORP study showed that the proportion of MRSA in CA *S. aureus* infections varied by country: Sri Lanka (38.8%); Taiwan (34.8%); the Philippines (30.1%); Vietnam (30.1%); Korea (15.6%); Hong Kong (8.5%); India (4.3%); and Thailand (2.5%) [21]. In a study on CA-MRSA among patients with purulent skin and soft tissue infections in Hong Kong, 10.4% (13/125) of all *S. aureus* isolates and 5% (12/241) of all abscesses were attributed to pantonvaletine leukocidin (PVL)-positive CA-MRSA [22]. A prospective cohort study on MRSA carriage conducted over 1 month at a children's hospital in Cambodia identified MRSA carriage in 87 (3.5%) of 2,485 children who came to the outpatient department and in 6 (4.1%) of 145 inpatients [23]. In a Taiwanese hospital, the number of adult patients with CA-MRSA bacteremia increased over time, and the disease was associated with more cases of necrotizing pneumonia and cutaneous abscess but fewer cases of endovascular infection compared with CA-MSSA bacteremia [24]. Patients with CA-MRSA bacteremia

did not experience higher mortality than patients with CA-MSSA, even though most of the former did not receive empirical glycopeptide therapy [24].

A systematic review and meta-analysis showed that the mortality rate of MRSA bacteremia was significantly higher than that of MSSA bacteremia [25]. The ANSORP study, which included 4,949 patients with *S. aureus* infection in Asian countries, showed that methicillin resistance adversely affected the outcomes of patients with *S. aureus* infection, especially in patients with cancer or renal disease, and in those with *S. aureus* bacteremia, although MRSA infection was not found to be significantly associated with higher mortality in the overall patient population [26]. In a study on *S. aureus* bacteremia in northern Thailand, a higher mortality rate (52%) than that in industrialized countries was reported, and mortality rates for MRSA and MSSA were 67% and 46%, respectively ($P=0.11$) [27].

Vancomycin-nonsusceptible *Staphylococcus aureus*

Although the prevalence of VISA or VRSA infections is low in Asia [21], a significant problem associated with MRSA is the subpopulation of MRSA with reduced vancomycin susceptibility (also known as heterogeneous vancomycin-intermediate-resistant *S. aureus*, hVISA), particularly in Japan

[2, 28]. However, multinational surveillance studies in Asia have found that the prevalence of MRSA with reduced vancomycin susceptibility ranges from 0.7% to 4.3% [29, 30]. In the ANSORP study on HAP in Asian countries, VISA or VRSA was not found [17]. Clonal dissemination of VISA has been reported in a Taiwanese hospital [31]. The hVISA phenotype was present in more than one-third of MRSA isolates in a Korean hospital [32] and was independently associated with a vancomycin MIC ≥ 2 mg/L, rifampicin resistance, prior vancomycin therapy, and use of immunosuppressive therapy. Compared with vancomycin-susceptible *S. aureus*, hVISA and VISA infections were found to be associated with a longer period of prior glycopeptide use, bone/joint and prosthetic infections, and treatment failure, as evidenced by the longer bacteremic and culture positivity periods in a Singapore hospital [33]. There was, however, no significant difference in overall patient mortality or hospitalization costs between the two groups [33].

Vancomycin-resistant *Enterococcus* (VRE)

The prevalence of VRE, which emerged in the late 1980s, has risen rapidly in many countries. Its prevalence among clinical isolates has been estimated to range from 12% to 21% in Korea, and similar estimates have been made in Taiwan [2, 34, 35]. The prevalence of non-duplicated blood VRE isolates in a Taiwanese hospital increased significantly from 3.9% in 2003 to 18.9% in 2010 [36]. In Chinese hospitals, the prevalence of VRE increased from 0 in 2005 to 4.9% in 2010, and among the VRE isolates, the *vanA* gene was the most prevalent gene [37]. Among patients admitted to the ICU in a Korean hospital, 3.4% carried VRE; independent risk factors for VRE carriage at ICU admission were ICU readmission during hospitalization, chronic obstructive lung disease, recent antibiotic treatment, and recent vancomycin use [38]. In addition, the increment of VRE colonization pressure was significantly associated with vancomycin consumption 1 week before and moderately associated with that of the corresponding week [39].

A systematic review and meta-analysis showed that vancomycin resistance was independently associated with increased mortality among patients with enterococcal bloodstream infections [40]. Additionally, enterococcal bacteremia was associated with increased risk of mortality in recipients of allogeneic hematopoietic stem cell transplantation [41]. On the other hand, among patients with VRE bacteremia in a Korean hospital, mortality did not differ between those receiving anti-VRE therapy later than 72 h after the onset of bacteremia and those receiving treatment within 72 h; these

findings suggest that, despite antibiotic therapy to fight VRE, patients with VRE bacteremia eventually have a higher risk of death because of severe illness at the onset of bacteremia [42].

ESBL-producing Enterobacteriaceae

The Study for Monitoring Antimicrobial Resistance Trends (SMART) was initiated in 2002 to longitudinally monitor the *in vitro* susceptibility profiles of aerobic and facultative gram-negative bacilli isolated from patients with intra-abdominal infections, and it was expanded to include surveillance of gram-negative pathogens causing urinary tract infections in the Asia-Pacific region [43, 44]. Data from previous SMART studies have revealed that the levels of antimicrobial resistance are highest in countries in the Asia-Pacific region. Among gram-negative bacilli collected from intra-abdominal infections in the Asia-Pacific region during 2007, 42.2% and 35.8% of *E. coli* and *Klebsiella* spp., respectively, were ESBL positive [45]. Moreover, the ESBL rates in India for *E. coli*, *K. pneumoniae*, and *K. oxytoca* were 79.0%, 69.4%, and 100%, respectively [45]. Among Enterobacteriaceae isolates collected from 8 tertiary-care hospitals in various regions of Korea, ESBL positivity of *K. pneumoniae* isolates was 22.4%, while that of *E. coli* isolates was 10.2% [46]. The prevalences of Enterobacteriaceae isolates with ESBL were 26% in *K. pneumoniae*, 14% in *E. coli*, and 13% in *Proteus mirabilis*, and a significantly rising prevalence of ESBL production among *K. pneumoniae* was noted in Taiwanese intensive care units [47]. In a Korean hospital, antibiotic resistance in bacteremic biliary tract infections has increased markedly over the past 10 years, and almost half of the nosocomial bacteremic biliary tract infections caused by common gram-negative pathogens during 2005-2009 could not be treated with third-generation cephalosporins [48]. Figure 2

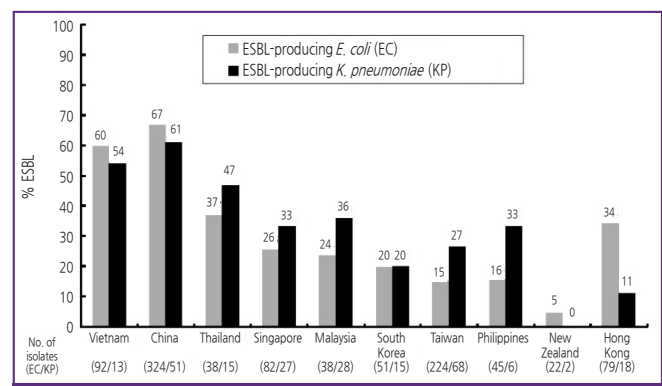


Figure 2. Prevalence of ESBL-producers among *E. coli* and *K. pneumoniae* isolates causing urinary tract infections by country in the Asia-Pacific region, adopted from reference [44].

shows the prevalence of ESBL-producers among *E. coli* and *K. pneumoniae* isolates causing urinary tract infections in the Asia-Pacific region [44].

ESBL-producing *E. coli* are increasingly prevalent pathogens in community and healthcare settings. The international dissemination of blaCTX-M ESBL genes and ST131 over the last decade has been described as a pandemic. CTX-M-producing *E. coli* and ST131 have emerged as a significant cause of both community-onset and hospital-acquired infections in Asian countries, including Korea [49], Taiwan [50], China [51], Hong Kong [52], Japan [53], Malaysia [54], and Thailand [55], and the incidence of serious infections due to CTX-M-producing *E. coli* likely will continue to increase. CTX-M-producing *E. coli* have been highly endemic worldwide. In a Taiwanese hospital, patients with clone ST131 were more likely to have secondary bacteremia and noncatheterized urinary tract infections [50]. Although more virulence factors have been detected in ST131, patients with the ST131 clone in ESBL-producing *E. coli* bacteremia did not exhibit a higher mortality rate [50].

A systematic review and meta-analysis showed that ESBL production is associated with increased mortality and a delay in effective therapy in Enterobacteriaceae bacteremia [56]. In a study in Korea, ESBL-producing bacteremia was the most important risk factor associated with 30-day mortality in patients with hematologic malignancy, along with ICU care and a higher Pitt bacteremia score [57], although the difference in the mortality rates for ESBL bacteremia and non-ESBL bacteremia was not significant in another study [58]. A Korean nationwide study on community-onset bacteremia caused by ESBL-producing *E. coli* showed that ESBL production was an independent factor associated with mortality after adjusting for confounding variables, suggesting that ESBL-producing *E. coli* is a significant cause of bacteremia even in patients with community-onset infections [59]. However, in other studies on community-onset bacteremia caused by ESBL-producing *E. coli* or *K. pneumoniae*, increased mortality was not statistically associated with either ESBL production or inappropriate empirical therapy [60, 61]. Similarly, in a Chinese study regarding community-acquired intra-abdominal infections caused by ESBL-producing bacteremia, patients with ESBL-positive infections had similar resolution rates at discharge compared to those with ESBL-negative infection, despite poorer first-line antibiotic responses [62]. However, ESBL-positive infections led to significantly higher costs from hospitalization and intravenous antibiotics, as well as longer hospital stays [62].

Carbapenem-resistant Enterobacteriaceae

Carbapenem-resistant Enterobacteriaceae (CRE) are particularly problematic, given the frequency with which *Enterobacteriaceae* cause infections and the potential for widespread transmission of carbapenem resistance via mobile genetic elements [63]. The most important carbapenemases among *Enterobacteriaceae* clinical isolates are KPC and NDM. While KPC-producing organisms are rarely reported in Asian countries [64, 65], NDM-producing organisms are prevalent among *Enterobacteriaceae* in India and Pakistan, even in community-onset infections [1]. NDM-1 carbapenemase-producing *Enterobacteriaceae* strains have been detected worldwide [2].

Multidrug-resistant Nonfermenters

The rate of carbapenem-resistant *Pseudomonas aeruginosa* is very high, and MDR nonfermenters are highly prevalent in Asian countries [34, 35]. In the ANSORP study on HAP, resistance rates of *P. aeruginosa* to ceftazidime, cefepime, piperacillin-tazobactam, imipenem, and ciprofloxacin were 34.7%, 27.7%, 36.9%, 27.2%, and 30.1%, respectively [17]. The resistance rate of *P. aeruginosa* to imipenem was the highest in China (56.9%). HAP associated with *Acinetobacter* spp. in Asian countries showed a very high rate of resistance to imipenem, at 67.3%; the rate was especially high in Malaysia (86.7%), Thailand (81.4%), India (85.7%), and China (58.9%) [17]. MDR and XDR rates of *Acinetobacter* spp. were 82.0% and 51.1%, respectively. The prevalence of imipenem-resistant *A. baumannii* has been rising gradually in Korea, as well as in China and Taiwan [34, 66-68]. Rates of carbapenem-resistant *Acinetobacter* spp. and

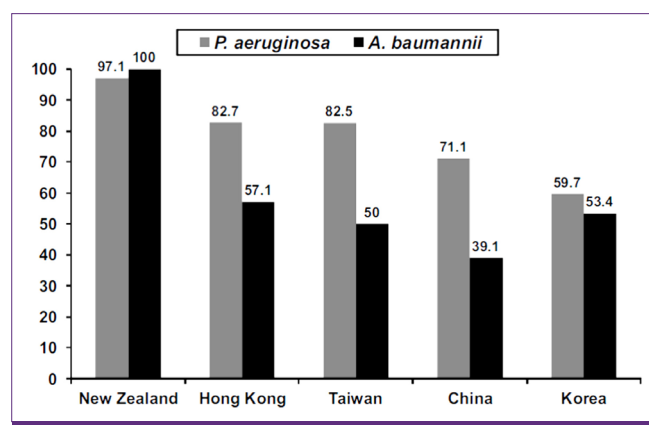


Figure 3. Susceptibility to imipenem among isolates of *P. aeruginosa* and *A. baumannii* obtained from patients with intra-abdominal infections in selected countries in the Asia-Pacific region, adopted from reference [70].

P. aeruginosa were very high, and MDR nonfermenters were highly prevalent in Asian countries [17, 34, 35]. In a surveillance study in the Asia-Pacific region, 29.8% of *P. aeruginosa* and 73.0% of *A. baumannii* isolates were not susceptible to at least one carbapenem, whereas the majority of Enterobacteriaceae (97.2%) were susceptible to all carbapenems [69]. The SMART study on intra-abdominal infections in the Asia-Pacific region showed that *A. baumannii* exhibited very high rates of resistance to most antimicrobial agents, including imipenem [70]. Figure 3 shows the results of antimicrobial susceptibility to imipenem among isolates of *P. aeruginosa* and *A. baumannii* obtained from patients with intra-abdominal infections in selected countries in the Asia-Pacific region [70].

Despite the high prevalence of MDR or XDR *Pseudomonas* and *Acinetobacter* in Asia [2, 68], the clinical consequences of antimicrobial resistance are not fully understood in many Asian countries. In a Korean hospital, antimicrobial resistance, especially to ceftazidime and imipenem, adversely affected the outcomes of patients with *P. aeruginosa* bacteremia [71]. In a multicenter study in Taiwan, patients with carbapenem-resistant *A. baumannii* bacteremia had a higher mortality rate than patients with carbapenem-susceptible *A. baumannii* bacteremia (46.0% vs. 28.3%, $P=0.04$), and multivariate analysis showed that carbapenem resistance was one of the independent variables associated with mortality in patients with *A. baumannii* bacteremia [72]. In a previous study in Korea, imipenem resistance had a significant impact on mortality among patients with *Acinetobacter* bacteremia, and this was mainly attributable to the higher rate of discordant antimicrobial therapy [73]. The ANSORP study showing a high prevalence of MDR nonfermenters in HAP demonstrated that discordant initial empirical antimicrobial therapy significantly increases the likelihood of pneumonia-related mortality [17].

Conclusions

Asia is one of the epicenters of antimicrobial resistance worldwide, and this is an increasing public health concern. MDR pathogens have been widely disseminated, both in hospitals and throughout communities, in many countries. Continuous surveillance is essential for providing information on the magnitude of, and trends in, antimicrobial resistance. Given the devastating impact of this problem on human lives and public health, future strategies should be developed based on multifaceted collaboration among all relevant stakeholders in the Asia-Pacific region. Comprehensive strategies for the control

and prevention of antimicrobial resistance are urgently needed in the region.

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