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Review Article

Antimicrobial Drug Resistance in Taiwan

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Antimicrobial resistance is a major global health threat associated with high mortality rates and high medical costs. Geographic variations in resistance profiles of bacterial and fungal pathogens have had a considerable impact on antimicrobial prescription. In Taiwan, there is an alarmingly high prevalence of penicillin-resistant *Streptococcus pneumoniae*, multidrug-resistant and extensively drug-resistant (XDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*, penicillin- and fluoroquinolone-resistant *Neisseria gonorrhoeae*, and azole-resistant *Candida* species. In addition, the emergence of XDR *Mycobacterium tuberculosis* has illustrated the need for regular monitoring of the resistance profiles of clinical isolates. A few clones of XDR *A. baumannii* and methicillin-resistant *Staphylococcus aureus* of unique sequence type (ST 59) have disseminated in Taiwanese hospital settings. Besides, the existence of a transposon-harboring carbapenemase gene has been verified in XDR *P aeruginosa* strains throughout Taiwan. An end to the worsening trends in the emergence of antimicrobial resistance will require continuous survey of resistance data from clinical isolates and effective implementation of strict infection control policies in healthcare settings and animal husbandry.

Key Words: antimicrobial resistance, extended-spectrum β-lactamase, extensively-drug resistant, multidrug-resistant, Taiwan

Antimicrobial resistance is a persistent worldwide healthcare concern. However, in comparison with Western countries, in Asia there are considerable geographic variations in the resistance of various bacterial and fungal pathogens. In North America and Europe, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA),[1] vancomycin-resistant enterococci (VRE),[2] *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K pneumoniae*,[3] multidrug-resistant (MDR) *Acinetobacter* species,[4,5] and fluoroquinolone- and carbapenem-resistant *Pseudomonas aeruginosa*[5] have been reported and are widespread in hospital settings. In contrast, Taiwan has strikingly high prevalence of penicillin-resistant *Streptococcus pneumoniae*,[6] extensively drug-resistant (XDR) *Acinetobacter baumannii* (15%),[7] extended-spectrum β-lactamase (ESBL)-producing *K pneumoniae* (26%),[8] fluoroquinolone-resistant *Neisseria gonorrhoeae*,[9] MDR *Salmonella enterica* serotype Choleraesuis,[10,11] azole-resistant *Candida* species (particularly, *Candida glabrata*),[12] and the emergence of XDR

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Mycobacterium tuberculosis (XDRTB).[13] The emergence of these resistant species has caused enormous difficulty in managing MDR clinical infections and preventing their dissemination. This paper reviews the resistance profiles of the most important bacterial and fungal pathogens in Taiwan.

MRSA

Infections caused by MRSA are troublesome because of the high degree of difficulty of eradication and limited antimicrobial treatment options. In a medical center in Northern Taiwan (National Taiwan University Hospital, NTUH), MRSA accounted for 74% of all nosocomial *S aureus* isolates in 2000.[14] A longitudinal survey of the prevalence of methicillin resistance in healthcare-associated *S aureus* isolates in NTUH from 1986 through 2009 (Figure 1) found that the proportion of MRSA far exceeded that of methicillin-susceptible isolates after 1996, but this difference then declined markedly after 2007. Many new antibiotic options for the management of MRSA infections have become available in the present decade.[15] However, because of the long-term use of virginiamycin in animal husbandry, quinupristin–dalfopristin had a high non-susceptibility rate (> 30%) to MRSA strains before its launch in Taiwan.[16] Consequently, this agent is not a suitable choice for the management of Taiwanese MRSA infections. Although few Taiwanese MRSA strains have exhibited *in vitro* vancomycin heteroresistance,[17] their clinical significance and actual prevalence needs to be further evaluated.

In addition to nosocomially acquired MRSA, the emergence of community-acquired (CA)-MRSA has also been reported worldwide.[1] By comparison with healthcare-associated MRSA infections, CA-MRSA infections are more likely to involve the skin and soft-tissue[1] and to present as necrotizing pneumonia, especially when caused by isolates that carry the Panton-Valentine leukocidin genes.[18] In a survey by Vandenesch et al, genetically diverse CA-MRSA strains collected outside of Taiwan were noted to share a type IV SCC*mec* cassette, with susceptibility to most antibiotics.[1] Distinct from the findings of foreign surveys, however, some CA-MRSA isolates in Northern Taiwan harbored type V SCC*mec*,[19] with the major clone having sequence type (ST) 59 detected by the multilocus sequence typing method.[20] Although the inappropriate use of empirical antibiotics against CA-MRSA infections appears not to have had a significant impact on mortality,[19,20] timely surgery and monitoring of future changes of

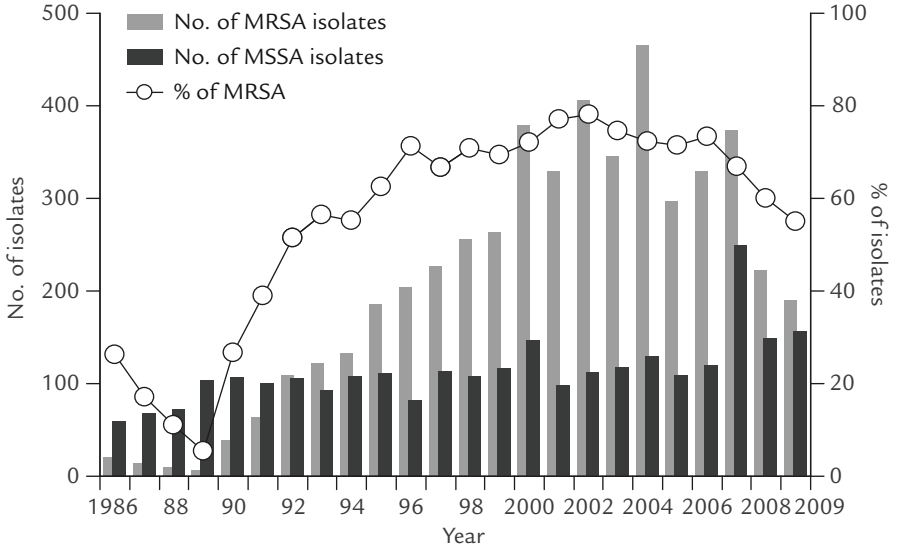

Figure 1. Annual rates of methicillin-resistant *Staphylococcus aureus* among all *S aureus* isolates from patients with healthcare-associated infection at National Taiwan University Hospital, 1986–2009. MSSA = methicillin-susceptible *S aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*.

antimicrobial non-susceptibility of CA-MRSA isolates are still indicated.

S pneumoniae and Haemophilus influenzae

Antimicrobial resistance of *S pneumoniae* and *H influenzae*, two core organisms that cause community-acquired pneumonia and pyogenic meningitis, is a worldwide concern.[21,22] In a longitudinal surveillance of trends in non-susceptibility to penicillin and erythromycin in clinical *S pneumoniae* isolates from 1984 to 2009 in NTUH (Figure 2), > 70% of pneumococci exhibited persistent non-susceptibility to these two important antimicrobials from 1998. In addition, investigation of important pathogens from intensive care units (ICUs) in Taiwan (SMART; Surveillance of Multicenter Antimicrobial Resistance in Taiwan) in 2005 has revealed high rates of non-susceptibility to penicillin (85%), ceftriaxone (66%), and cefepime (57%) against *S pneumoniae*, evaluated by the meningitis criteria.[6] In addition, a significantly increasing prevalence of penicillin-non-susceptible *S pneumoniae* and ceftriaxone-non-susceptible *S pneumoniae* strains has also been found between 2000 and 2005 ($p < 0.05$).[6,23] As a result of the high likelihood of penicillin-non-susceptible *S pneumoniae* exhibiting co-resistance to many non-β-lactam antimicrobials,[24] institution of stricter control policies for prescription of β-lactams is mandatory. Similarly, although no β-lactamase-negative ampicillin-resistant *H influenzae* strain was detected in SMART 2005, high non-susceptibility of *H influenzae* to ampicillin (55%) and cefaclor (45%) was demonstrated.[6] Besides, alertness to the high non-susceptibility rates for imipenem, trimethoprim–sulfamethoxazole, and clarithromycin against ICU *H influenzae* strains (16%, 64%, and 68%, respectively) is required when selecting therapy.[6] Tigecycline exerts good *in vitro* activity against *S pneumonia*e and *H influenza*e isolates, with the minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC_{90}) being 0.03 and 0.25 μg/mL, respectively, which was in accordance with those previously reported.[6,25] Among *S pneumoniae* isolates, resistance to commonly used respiratory fluoroquinolones (such as moxifloxacin and levofloxacin) has remained low (resistance rate < 5%), and tigecycline has exerted potent *in vitro* activity against the isolates tested.[6]

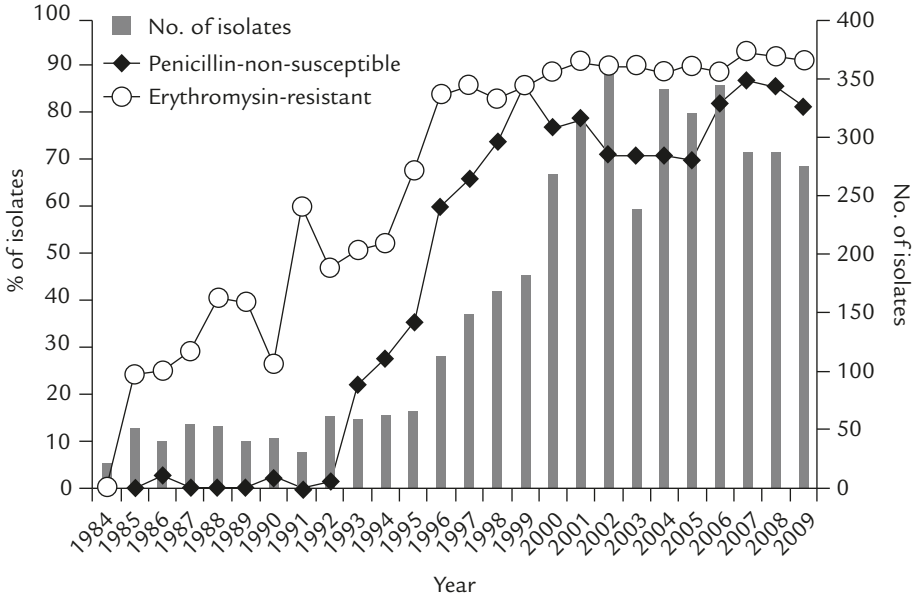

Figure 2. Trends of non-susceptibility to penicillin and erythromycin among clinical isolates of *Streptococcus pneumoniae* as determined by the disk diffusion method at National Taiwan University Hospital, 1984–2009.

VRE

Enterococci that exhibit resistance to vancomycin have been a great problem in the present decade.[2] Patients with VRE bloodstream infection have been shown to have a higher mortality rate than those with vancomycin-susceptible enterococcal bacteremia (odds ratio: 2.52).[26] In addition, nosocomial and inter-hospital dissemination of some VRE clones with long-term persistence has been reported in many countries.[27,28] Longitudinal surveillance (1996–2009) of annual rates of enterococci with resistance to vancomyin in NTUH (Figure 3) has revealed a gradually rising prevalence of VRE. Clonal spread of CC17 VRE (*Enterococcus faecium*) with multilocus sequence type 78 (ST78) and a novel ST444 has been reported in Taiwan.[29] These findings indicate the need for early detection and further prevention of spread of VRE in healthcare settings.

S enterica serotype Choleraesuis

S enterica serotype Choleraesuis, unlike other non-typhoidal *Salmonella*, is a frequent cause of septicemic episodes, which may involve mycotic aneurysm and osteomyelitis.[10,30] The MDR phenotype (defined as resistance to ampicillin, chloramphenicol, and trimethoprim–sulfamethoxazole) among Taiwanese *S enterica* serotype Choleraesuis has been reported.[31] Characteristically, the rapidly increasing prevalence of ciprofloxacin-resistant *S Choleraesuis*, which shares an identical pulsotype with that of swine isolates, is a noteworthy problem in our country.[30,32] In the latest Asian joint survey of non-typhoid *Salmonella*,[11] the prevalence of reduced susceptibility (MIC: 0.125–1.0 μg/mL) and absolute resistance (MIC ≥ 4 μg/mL) to ciprofloxacin in Taiwanese *S Choleraesuis* isolates was 61.5% and 30.1%, respectively. In contrast to overall non-typhoidal strains, the prevalence of reduced susceptibility to ceftriaxone (MIC: 2–8 μg/mL) for *S Choleraesuis* isolates in Taiwan was markedly low (38% *vs*. 10%).[11,33] Imipenem appears to be effective for treatment of tenaciously cefotaxime- and ciprofloxacin-resistant *S Choleraesuis* infection.[34] Periodic monitoring of the antimicrobial utilization in animal husbandry and of the evolutionary trends of resistance to fluoroquinolones and ceftriaxone in MDR *S Choleraesuis* provides essential information for the selection of appropriate therapy.

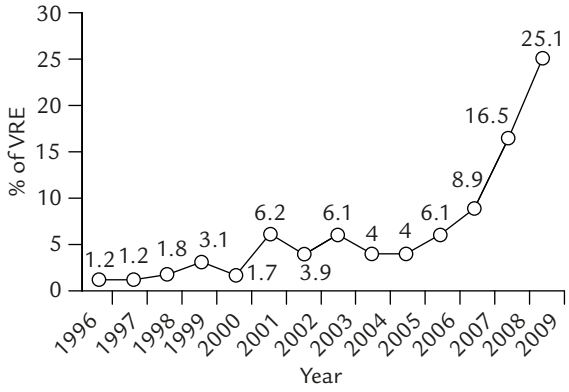

Figure 3. Annual rates of vancomycin-resistant enterococci among all enterococcal isolates from patients with healthcare-associated infection at National Taiwan University Hospital, 1996–2009. VRE = vancomycin-resistant enterococci.

K pneumoniae and Escherichia coli

The *K pneumoniae* isolates in Taiwan, with virulence genes including *rmpA* and *magA*, are known to cause many metastatic infections.[35] In addition, the rapidly rising prevalences of ESBL production among *E coli* (14% in 2005) and *K pneumoniae* (11% in 2000, and 26% in 2005, $p = 0.002$) isolates in ICUs in Taiwan are also a notable focus of resistance.[8,23] *K pneumoniae* is also the most likely pathogen to produce ESBL among *Enterobacteriaceae* isolated in the ICU.[8] In an investigation in the Asia–Pacific region, the nosocomially acquired (≥ 48 hours) intra-abdominal *K pneumoniae* isolates were shown to have a significantly higher probability of producing ESBLs than CA ones.[36] Owing to the high ESBL prevalence (which also contributes the high possibility of non-susceptibility to ciprofloxacin[37]) in *K pneumonia* and *E coli*, the third-generation cephalosporins and fluoroquinolones are not optimal choices against nosocomial *K pneumoniae* infections,[8] and carbapenems are some of the most effective agents against nosocomial

K pneumoniae.[8,36] However, the emergence of profoundly high MIC_{90s} for meropenem and ertapenem (2 μg/mL and 8 μg/mL, respectively) against Taiwanese ESBL-producing *K pneumoniae* strains has also demonstrated the need for close monitoring of the evolution of their resistance.[38] The tigecycline MIC_{90s} for overall *K pneumoniae* isolates collected in SMART 2005, and ESBL-producing *K pneumoniae* strains collected in TIST (Tigecycline *in-vitro* Surveillance in Taiwan, 2006–07), were all 2 μg/mL.[8,39] However, in one *in vitro* susceptibility study among intra-abdominal ESBL-producing *K pneumoniae* isolates, 17% (4/24) exhibited tigecycline MIC levels ≥ 2 μg/mL.[40] Due to its bacteriostatic mechanism and relatively low serum concentration (< 1 μg/mL, sampled after at least 6 doses with standard-dose administration),[41] prudent use of this valuable agent as an alternative to carbapenems should be considered.

P aeruginosa

P aeruginosa is of great concern as a nosocomial pathogen. It is notorious for having multiple mechanisms of antimicrobial resistance (including loss of the outer membrane protein, overexpression of multidrug efflux genes, interplay between impermeability and certain β-lactamases, and carbapenemases).[42] Although the prevalence of carbapenem-non-susceptible (CNS) *P aeruginosa* was not as high as that of the CNS *A baumannii* in SMART 2005 data,[7] horizontal dissemination of mobile Tn*6001*, which contains a bla_{VIM-3}-harboring integron In450, has been reported in CNS and XDR *P aeruginosa* strains collected from medical centers throughout Taiwan.[43] In addition, data from SMART 2005 have shown that all (3/3) XDR *P aeruginosa* strains (defined as resistant to all common antipseudomonal agents except colistin) also exhibited non-susceptibility to colistin.[7] A longitudinal survey of antimicrobial resistance of clinical *P aeruginosa* isolates since 1999 in NTUH (Figure 4) has found a fluctuating annual prevalence of ciprofloxacin non-susceptibility in *P aeruginosa*. Other investigations have suggested that increased consumption of levofloxacin is associated with the decline

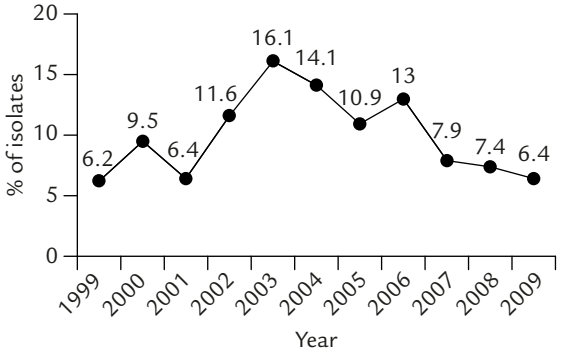

Figure 4. Annual rates of ciprofloxacin non-susceptibility among *Pseudomonas aeruginosa* isolates from patients with healthcare-associated infection at National Taiwan University Hospital, 1999–2009.

of susceptibility to ciprofloxacin for *P aeruginosa* isolates,[44,45] which might partly explain this evolutionary trend of ciprofloxacin resistance. Nevertheless, due to the recent lack of new effective antipseudomonal agents and to avoid progression of resistance, control of dissemination by specific measures remains an important task.

A baumannii and other Acinetobacter species

Clinical infections caused by MDR *A. baumannii* (defined as isolates resistant to ≥ 3 different classes of antimicrobials) and *Acinetobacter* species have been verified to culminate in high in-hospital attributable (21.8%) and overall (26–60%) mortality rates.[4,46,47] For more than a decade, the selection of appropriate antimicrobials and the control of nosocomial infection caused by MDR *A baumannii* have been persistent worldwide problems.[48,49] Multiple resistance mechanisms may exist in a single *Acinetobacter* species.[42] In theory, hospital-acquired *A baumannii* as well as *P aeruginosa* are unlikely to present with markedly different MDR antibiogram prevalence. However, in contrast with *P aeruginosa*, clinical *A baumannii* strains are more likely to exhibit an *in vitro* MDR phenotype in Taiwan.[7,48] Consequently, the gradually rising prevalence of *A baumannii* that is resistant to imipenem (which are also usually the MDR isolates), which is the main antibiotic of last resort for critically ill patients, is an important focus that requires close monitoring in Taiwan (22% in 2000 *vs*. 25% in 2005),[7,23] as

well as in other countries.[50] In significant contrast with non-*baumannii Acinetobacter* spp., the oxacillinase (Ambler class D β-lactamase) genes, located in plasmids and downstream to IS*Aba3* and IS*1008* (two promoters for the transcription control of bla_{OXA} genes), have been demonstrated to play an important role in conferring non-susceptibility to imipenem for *A baumannii* isolates in Taiwan.[51,52] Besides, the class I integron that harbors the bla_{IMP-1} gene has been identified in a carbapenem-resistant clone in a Southern Taiwanese medical center.[53] These impressive findings correspond temporally with the alarming fact that intra-hospital clonal spread of MDR *A baumannii* and inter-hospital dissemination of certain clones of XDR *A baumannii* (defined as isolates resistant to all antimicrobial agents except colistin or tigecycline) have been documented in major teaching hospitals in Taiwan.[7,53] Although tigecycline was previously considered a promising agent against MDR- and colistin-resistant *A baumannii*,[54] Taiwanese ICU *A baumannii* have a tigecycline MIC90 of 4 μg/mL,[7] which is higher than that in Greece.[54] Furthermore, virtually all of the colistin-resistant *A baumannii* strains in SMART 2005 also exhibited non-susceptibility to tigecycline.[7] A few reports have suggested that the combination of some antibiotics would exert *in vitro* synergistic effects against MDR *A baumannii*.[55,56] However, large-scale prospective clinical surveys are needed to determine whether combination therapy against this problematic pathogen is effective. Thus, strict infection control policy remains of the utmost importance.

N gonorrhoeae

The annual number of new cases of confirmed infection caused by *N gonorrhoeae*, one of the pathogens of sexually transmitted diseases, has shown a gradually increasing trend (from 7.1 in 2008 to 9.3 in 2009 per 100,000 population) in Taiwan.[57] In our country, the prevalence of penicillin resistance in *N gonorrhoeae* was markedly high (88.8%) before 1990.[58] In addition, the rapid upsurge of prevalence of ciprofloxacin resistance in Northern Taiwan (87.5% in 2002, and 93.1% in 2003) is alarming.[9] The occurrence of multiple (mostly > 2) mutations in the *parA* and *gyrC* gene has been verified to confer prominent ciprofloxacin resistance (MIC: 4 to ≥ 16 μg/mL) in *N gonorrhoeae* isolates.[9] Besides, the resistance mechanisms that mediate non-susceptibility to other agents (including penicillin, tetracycline, macrolides, and cefixime) have been elucidated in the present decade.[59,60] According to the *in vitro* susceptibility of endemic surveys, ceftriaxone should be seriously considered as one of the first-line options with regard to the management of gonorrhea in Taiwan.

M tuberculosis

Taiwan is an endemic country for *M tuberculosis*. From the data provided by the Taiwan Surveillance of Drug Resistance in Tuberculosis (TB), high resistant rates against the first-line anti-TB drugs (including: 11.3% to isoniazid; 7.5% to rifampicin; 20.4% to any first-line agent, including isoniazid, rifampicin, ethambutol, and pyrazinamide; and 5.3% MDR to both isoniazid and rifampicin) were reported in 2004, which were higher than those in a global survey (6.6%, 2.2%, 10.4%, and 1.7%, respectively).[61,62] Fluoroquinolones are often considered the preferred alternative agents for managing drug-resistant TB. Nevertheless, a study by Wang et al has suggested that any resistance to first-line anti-TB agents or prior anti-TB management was well-correlated with TB resistance to fluoroquinolones.[63] In addition, XDR-TB (MDR isolates resistant to any fluoroquinolone and ≥ 1 of the three injectable anti-TB drugs, capreomycin, kanamycin, and amikacin) has emerged in Taiwan.[13,61] In surveillance of the antimicrobial non-susceptibility of XDR-TB isolates collected in 2004–2005, the resistance rates to second-line anti-TB drugs (including fluoroquinolone, kanamycin, ethionamide, and para-aminosalicylate) exceeded 15%, and the fluoroquinolone resistance rate among Taiwanese MDR strains was as high as 42.8%.[61] In the most recent Taiwanese studies, about one-half of MDR- and XDR-TB strains belonged to the Beijing family genotype, by spoligotyping analysis,[64] and most patients

with XDR-TB infection had pulmonary cavitary lesions and a previous history of anti-TB treatment,[13,64] which escalates the degree of difficulty of successful eradication. To implement an effective infection control policy for prevention of the dissemination of MDR- and XDR-TB, continuous monitoring of their prevalence and prudent use of fluoroquinolone agents are mandatory.

Candida species

Invasive candidiasis has emerged as an important nosocomial infection, especially in critically ill patients, who have crude mortality rates 5–10-fold higher than those of the entire hospital population, and may be as high as 60%.[65,66] Although there is a markedly different regional prevalence in the etiology of invasive candidiasis in Asia-Pacific countries,[67] *C albicans* accounted for > 50% of invasive isolates of *Candida* spp. in Taiwan, followed by *Candida tropicalis* (18%), *C glabrata* (16%), and *Candida parapsilosis* (10%).[67] The fungemia caused by *C glabrata*, which almost always occurs in patients with underlying comorbidity, and shows high non-susceptibility to fluconazole (i.e. only 22% of organisms have MICs ≤ 8 μg/mL), presents a considerable crisis in the selection of appropriate therapy. Fortunately, it can be successfully managed by echinocandins and new tri-azoles.[12,68] In contrast with invasive *C glabrata* strains, all of the other three *Candida* spp. (collected from 1999 to 2007 in Northern Taiwan) have exhibited ≥ 95% susceptibility to fluconazole.[62] To decrease the in-hospital mortality rate, regular surveillance of the epidemiology and resistance load for candidiasis is crucial to determine the best treatment options for all high-risk patients.

Conclusions

Many measures have been taken in our country to reduce the heavy antimicrobial resistance load and control its escalating trends. The Bureau of National Health Insurance in Taiwan has implemented a strict policy on antibiotic prescription in hospitals and drug stores, especially for the treatment of trivial upper respiratory tract infection and inappropriate use in surgical prophylaxis. In addition, the enhancement of hand-washing maneuvers in healthcare settings and the establishment of standards of practice for performance of invasive procedures in hospitals have been widely promoted. The Council of Agriculture in Taiwan has prohibited the use of several antimicrobials that were previously used as growth promoters or prophylactic agents in animal husbandry over the past three decades. This is predicted to result in a decline of resistance of human pathogens that originate from food-producing animals. Finally, to provide timely revision of infection control policy, continued nationwide surveillance of antimicrobial resistance remains a necessity in Taiwan. These measures provide the best prospect of halting the rise of resistance as well as the requisite information to encourage appropriate utilization of antibiotics in specific patient populations, especially those who are critically ill.

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