APEC Conference on Strategies Against the Evolving Threats from Antimicrobial Resistance:
From Awareness to Concrete Action

CHINESE TAIPEI

Optimizing Antimicrobial Therapy in The Era of Multi-Drug Resistant Organisms: Impact of Augmented Renal Clearance on Antibiotic Concentration

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Background

Providing appropriate antibiotic therapy in critically ill patients remains challenging in the era of multiple drug resistant organisms (MDRO). The choice of antibiotics is important, but dosing strategies also should be carefully considered. During critical illness, organ dysfunction may alter drug pharmacokinetics and result in inadequate drug exposure. Using strategies to maximize pharmacokinetic (PK) and pharmacodynamic (PD) characteristics in order to optimize antimicrobial activity has been advocated by international guidelines. Moreover, some patients with sepsis may have increased cardiac output and renal blood flow, which lead to augmented renal clearance (ARC, defined as creatinine clearance, CLcr > 130 mL/min). ARC is present in 20-65% of critically ill patients and is associated with sub-therapeutic antibiotic plasma concentration. Therefore, this study aims to evaluate the possible negative effect of ARC on β-lactam antibiotic exposure in critically ill patients and try to figure out optimal dosing way to overcome this problem.

Methods

This is a prospective study, performed in a medical center in Taipei. All adult patients admitted to medical ICUs (MICU) between August 1, 2017 and May 31, 2018 were screened for inclusion. Patients stayed in MICU for more than 72 hours and those who had a Foley catheter for urine collection were enrolled to the study. Exclusion criteria were chronic kidney disease, renal replacement therapy and acute kidney injury when admission. Twenty-four hours urine was collected for calculation of creatinine clearance. Estimated CLcr using Cockcroft-Gault equation was also recorded. Those who treated with broad spectrum β-lactam antibiotics (piperacillin/tazobactam, cefepime or meropenem) had 2 blood samples drawn at steady state: mid-time and trough according to individual antibiotic dosing interval. The probability of target attainment (PTA) were used as surrogate markers for treatment efficacy. PK/PD targets were defined as the time above the minimum inhibitory concentration (T > MIC) or (T > 4XMIC) for ≥50%, ≥100% of the dosing interval. The MIC breakpoint issued by EUCAST for Pseudomonas aeruginosa were used as reference level. Associated data such as patient profile, antibiotic dosing, frequency, infusion time, ICU mortality etc. were all retrieved via electronic database. Data was assessed using descriptive statistics. Fisher's exact test was used to compare the rate of PTA between patient with ARC or not. P-value < 0.05 was considered statistically significant. All statistics were carried out using by Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA) and SPSS 22 (SPSS Inc., Chicago, Illinois, USA).

Results

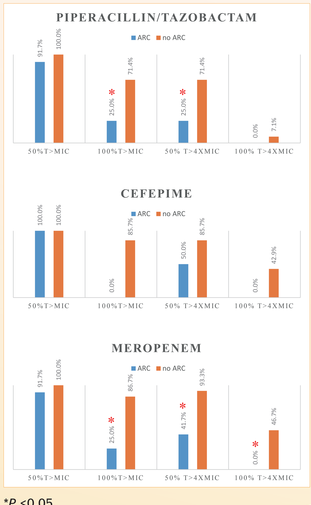
One hundred critically ill patients were enrolled in the study and the median APACHE II score was 19 (IQR: 14-24.75). The characteristics of all patients are shown in Table 1. Patients with ARC were younger than those without. (median age, 53 vs. 63, P<0.05). Obesity was also a significant risk factor for the presence of ARC. The logistic regression analysis showed that an age between 20 and 49 years, and Charlson comorbidity index were the independent predictors of ARC (Odd ratio: 7.34, 1.25 respectively). Sixty-two patients had antibiotic concentrations available for PK/PD analyses. There were no significant differences in target attainment of 50% T>MIC between patients with ARC or not. However, patients who presented with ARC had lower probability of target attainment of 100% T>MIC, which was recommended in neutropenic or critically ill patients. In addition, all patients who received extended infusion (4 hours) of β-lactam antibiotics achieved 100% PTA。

Demographic characteristics of study population

	All people (n=100)	ARC (n=41)	No ARC (n=59)	P-value
Age	60 (47-71)	53 (44.5-69)	63 (53-74)	0.042*
Age <65	57 (57.0%)	27 (65.9%)	30 (50.8%)	0.155
Male	66 (66.0%)	31 (75.6%)	35 (59.3%)	0.091
APACHE II score	19 (14-24.75)	19 (14-26)	19 (13-23)	0.700
SOFA score	5 (4-8)	5 (4-7)	5.5 (4-8)	0.441
Charlson Comorbidity index	5 (4-7)	6 (4-8)	5 (3-6)	0.155
BMI < 18	16 (16.0%)	5 (12.2%)	11 (18.6%)	0.423
Obesity	6 (6.0%)	5 (12.2%)	1 (1.7%)	0.041*
Mechanical ventilator	88 (88.0%)	39 (95.1%)	49 (83.1%)	0.115
Concurrent medications				
Diuretics	25 (25.0%)	7 (17.1%)	18 (30.5%)	0.161
Co-trimoxazole	22 (22.0%)	7 (17.1%)	15 (25.4%)	0.462
Vasopressors	15 (15.0%)	5 (12.2%)	10 (16.9%)	0.580

Notes: Data are presented as number (%) or median (IQR),
*P <0.05

Percentage of target attainment by individual antibiotics



*P <0.05

Conclusion

In critically ill patients who treated with antibiotics, ARC had significantly negative impact on target attainment and may resulted in treatment failure or resistant pathogens. Clinicians should be aware of the possibility of ARC to avoid possible harm. Extended infusion of β-lactam antibiotics may be a practical and economical solution for those who need higher treatment target for better outcome.

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Prevention and Treatment of Multi-Drug Resistant Organisms Related Infections at a Medical Center

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Introduction

Occurrence of multi-drug resistant organisms (MDROs) related colonizations/infections in medical institutions is a major issue. In order to prevent the spread of MDROs, the Infection Control Center Pharmacy Department, and the Information Technology Office at National Taiwan University Hospital have cooperated to establish an automatic surveillance system for MDRO render the clinical staffs could active screen MDROs for high-risk patients, and strengthen infection control measures in clinical practices. The measures include patient placement, MDROs labeling, hand hygiene, contact isolation and environmental cleaning. We educate all patients and train all staffs at NTUH for antimicrobial stewardship and MDROs management every year. The integrated system work successfully through monitoring, notification and intervention to control the infection and prevention of outbreaks of MDROs at NTUH.

Methods

◆Monitoring, notification and intervention of MDROs

1.Introduce an important epidemiological microbiological monitoring system to instantly detect cases of MDRO colonization and infection **(Figure1)**.

2.Once a notification of MDRO from laboratory, the report will send a brief message to the unit supervisor and the main care physician to remind to set the order of isolation, strengthen the contact isolation to avoid the spread of infection **(Figure2).**

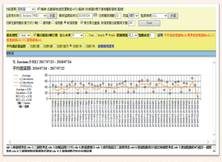

figure1. Epidemiology of important microbial monitoring system

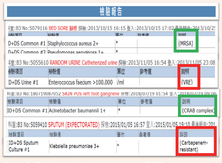

figure2. Test report system labeled MDROs

3.Monitoring the use of antimicrobial agents

(1)The Pharmacy Department conducts monitoring of the consumption of antimicrobial agents (DDD) in all units by month, monitor and report to antimicrobial management team quarterly.

(2)The Infection Control Center analysis trend of MDDRs density and infection density by month, and regularly monitor results of the statistical analysis of clinical MDDRs and consumption of antimicrobial agent (DDD).

◆Formulate infection control policies and strengthen infection control measures

1. Active screening of major MDROs

High-risk groups for MDROs, including patients come from respiratory care centers, security agencies, long-term institutions, and hospitalized patients, they are actively screening with MRSA, CRAB, VRE and CRE and perform preventive contact isolation before results of screening.

2.Treatment of patients with MDROs

(1)Patients with MDROs who are priority arranged to single-patient or general isolation rooms, or the patients with same MDROs are arranged in the same room, and they avoid with low immunity or open wounds in the same room.

(2)Patients with MDROs, their medical record, the door of the hospital room and the bedside have the notice stickers and cards **(Figure3)**.

figure3. isolation label

3.Infection control policy of medical care

(1)The medical staff and caregivers should wear masks, gloves and gowns when exposed to drug-resistant strain patients or their environment, and implement hand hygiene of five moment.

(2)Deal with medical materials

- The work vehicle should not be pushed into the ward or isolated area where the patient with MDROs is located. It is recommended to use the treatment tray and should be disinfected after use.
- The medical material used alone, such as stethoscopes, thermometers, sphygmomanometers, etc.
- It is recommended that the toilet be used separately (such as the potty chair), if the toilet is shared, the toilet should be cleaned before and after the toilet (such as soap water, 0.06% bleach impregnated paper towel) or toilet paper pad.
- The clean staff deal with patients coverlet or clothing, should be worn gloves, masks and gowns and should not be shaken. When the patient discharged or turned, curtains should be replaced of the bed and adjacent beds.

(3)Environmental cleaning

- The medical equipment and patient-specific material are cleaned and disinfected with alcohol or 0.06% bleach, if the infection rate of MDROs is higher or outbreak, the environment is replaced with 0.1% bleach.
- The environmental cleanliness quality is regularly assessed and feedback to the cleaning staff and the responsible person of the compliance management unit, and report in the Infection Control Committee.

◆Education Training

1.In order to strengthen the awareness of medical staffs on the prevention of microbial preparations and MDROs, more than one semi-annual "antimicrobial preparation" education lectures are held every six months to promote the correct use of antimicrobial agents and to avoid the spread of MDROs.

2.In response to international medical treatment, patients and visitors are provided with multi-language contact isolation guides and promotional videos, including Chinese, English, Indonesian and Vietnamese.

◆Regular audits and feedback

The clinical staff are audited of the prevention and treatment measures of MDROs by month. If the results of the audits are unqualified, the unit will be reviewed and improved immediately, and the results of the implementation will be reported to the Infection Control Committee.

Results

The regular monitoring of healthcare-associated infection (HAIs)density has been declining year by year since 2008, and the events of outbreak have also decreased year by year**(Figure4& (Figure5)**.

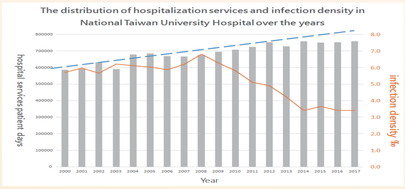

figure4. Hospital associate infection density over the years

figure5. Event of outbreak over the years

Conclusion

Our experience provide the integrated system work successfully through monitoring, notification and intervention to control the infection and prevention of outbreaks of MDROs at hospitals. The recommended strategies are as follows:

Support of leadership is the key to success.
Establish a automatic monitoring information system of MDROs and timely intervention.
Active and early screening of MDROs for high-risk patients.
Education and training of antimicrobial stewardship and MDROs management for medical staffs and patients.
Implement MDROs related infection control policies and regularly audit and feedback.

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Experiences Share of Antibiotic Prescription Consultation, De-escalation and Feedback Mechanism to Enhance the Efficacy of Antibiotics Stewardship

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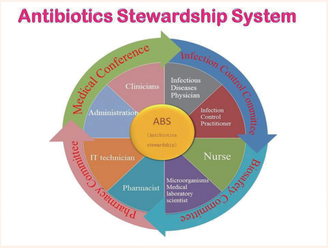
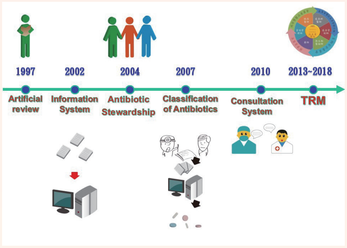
Purpose

Antibiotic stewardship is one of the most important issues for the hospital infection control. The rule and regulation of the stewardship system has been operated for years. However, facing up to the constantly detection of the various multi drug resistance microorganisms, brings out that the rigor examinations and the control execution effectiveness of the antibiotic needs to be reviewed and improved all the time.

Methods

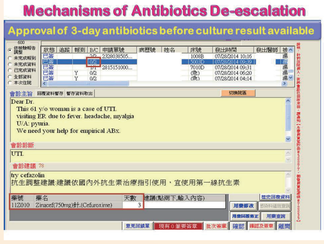
Our hospital has utilizing the database systems to assist executing in the antibiotic medication control since 2004. When antibiotics was prescribed via every medical system, the database system will assist to check the culture reports and consultation records in seven days.



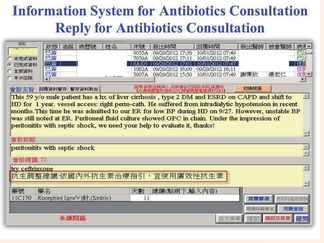


The infectious disease specialist would follow the "laboratory reports", "current medical orders", "nursing records" and "TPR" at the analysis systems to exam then provide the professional commends for the upgrade or downgrade.
For example, before the report of the blood culture, it could only approved three days of antibiotics. And the infectious disease specialist doctors also will control the using of the categories and days then permit to use.
The system also provided "antibiotic adjustment proposals" in order to make the communications and feedbacks between the clinicians and infectious disease doctors.

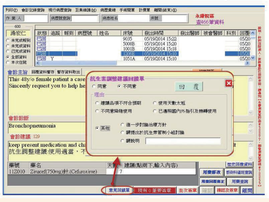
Mechanisms of Antibiotics De-escalation



Information System for Antibiotics Consultation Reply for Antibiotics Consultation



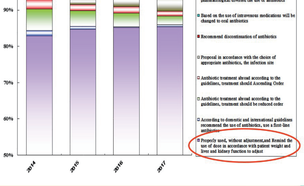
The clinicians and infectious disease doctors communications and feedbacks system.



Results

The infection control team also performed the statistical analysis regularly according to this information and most of the clinicians can identify to list the proper prescription by the infectious disease specialist professional advices. Antibiotics appropriate ratio about 80%.

Suggestion for Antibiotics Adjustment



Conclusion

The infectious disease specialist, the infection control and antibiotic teams working so hard for the execution and declaration for the antibiotic. The clinicians can use antibiotics correctly via ASP. We wish the antibiotics stewardship effectiveness and experiences can be shared with the partner hospital and take this as a reference to carry out the policy.

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Ten-Year Experience of Healthcare Information System-based Online Prospective Auditing Antibiotics Stewardship Programs in A Tertiary Hospital in Chinese Taipei

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Background

The overuse of antimicrobial agents has raised alert around the world in recent decades since antibiotic-resistant bacterial strains have been springing up in many medical centers even local medical departments. Besides, the inappropriate use of antimicrobial agents has adverse impact on patient safety and outcome at individual patient level. More and more Antibiotics Stewardship Programs (ASP) are developed accordingly to survey and optimize comprehensive antibiotics use. Standardized guidelines and experience are required to construct the ASP system and offer feasible recommendations for the clinicians acting as a gatekeeper of ASP. Many studies have been working on the efficacy of ASP, including reduction and controlling specific antimicrobial-resistant strains. There have also been studies on clinicians' attitude, re-education, and system modification for continuously improving and reforming ASP system. However, very little is known about physicians' behavior within the structure of ASP and the interaction between prescribing and stewardship physicians.

Methods

In this study we reviewed the data of our Healthcare Information System (HIS) based electronic online stewardship program to summarize the details of inappropriate use defined by stewardship physicians. We also analyze the interaction between prescribing and stewardship physicians. The database was of the consecutive10-years from 2008 to 2017. All statistical analyses were performed using SAS Enterprice Guide version 5.1.

Results

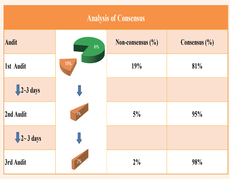
Antimicrobial consumption was calculated in DDDs per 1000 patient-days. There was an increase in restricted use antibiotics (240.69±29.67 in 2008-2012 vs 316.73±35.82 in 2013-2017, p<0.01) with decrease in non-restricted use antibiotics. Comparing the recent 5 years to the first 5 years, stewardship physicians issued more advice on the appropriateness of use (3439.8±829.44 in 2008-2012 vs 5642.6±997.52 in 2013-2017, p< 0.01). There were more recommendations for microbiology based de-escalation (1506.6±332.63 in 2008-2012 vs 1947.2±187.74 in 2013-2017, p= 0.028) and more stop advice for no more indication after adequate length of duration (1736.6±235.94 in 2008-2012 vs 2671.2±567.6 in 2013-2017, p= 0.01). For initial disagreement, consensus can be reached in one week for more than 98% of the cases. The gross mortality for all hospitalized patients remained unchanged (R2=0.002).

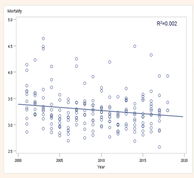
	DDDs/1000 Patient-Days (Mean±SD)			
Category of antimicrobial	2008-2017	2008-2012	2013-2017	*p*
Oral antimicrobials	354.17±34.55	364.07±37.54	344.26±28.88	0.07
Non-restricted antimicrobials	422.04±69.39	464.87±57.93	379.21±51.62	<0.01**
Restricted antimicrobials	278.71±50.36	240.69±29.67	316.73±35.82	<0.01**
Restricted antimicrobials 1	122.66±21.81	107.56±11.19	137.77±19.26	0.12
Restricted antimicrobials 2	156.05±35.31	133.13±26.91	178.96±27.01	<0.01**
Total	1054.92±64.04	1069.64±64.95	1040.2±61.18	0.144

	Prescriptions (yearly Mean)			
Category	2008-2017	2008-2012	2013-2017	*p*
A. Escalation	464.0	525.0	403.0	0.12
B. De-escalation	3963.4	3251.2	4675.6	0.16
C. Inappropriate choice	4541.2	3439.8	5642.6	<0.01**
D. Regimen problem	1834.8	1853.2	1816.4	0.87
E. No (more) indication	2203.9	1736.6	2671.2	0.01*
F. Bedside consultation	629.8	684.6	575.0	0.27
G. Others	643.4	457.8	829.0	0.02*
Total	14280.5	11948.2	16612.8	0.03*

		Prescriptions (yearly Mean)			
Category	Subcategory	2008-2017	2008-2012	2013-2017	*p*
A. Escalation	111. Empiric	178.2	203.0	153.4	0.34
	122. Microbiology interpretation	274.8	315.6	234.0	0.021*
	133. Combination therapy	11.0	6.4	15.6	0.073
B. De-escalation	211. Empiric	1842.4	1554.4	2130.4	0.434
	222. Microbiology interpretation	1726.4	1506.6	1947.2	0.028*
	233. Monotherapy	394.6	191.2	598.0	0.003**
C. Inappropriate choice	311. Inappropriate choice	4037.9	2774.6	5301.2	0.003**
	322. PK/PD consideration	86.6	109.8	63.4	0.098
	333. Cost benefit	406.6	539.6	273.6	0.055
	344. Allergy	2.5	3.3	1.3	0.225
	355. Microbiology interpretation	9.0	14.5	3.8	0.158
D. Regimen problem	411. Dosage	944.8	925.2	964.4	0.743
	422. Dosing interval	890.0	928.0	852.0	0.556
E. No (more) indication	511. No more indicated	476.0	253.0	666.0	0.003**
	522. Not baterial infection	737.1	754.4	719.8	0.73
	533. Contamination/colonization	103.3	99.0	107.6	0.665
	544. ASB	126.8	127.0	126.6	0.983
	555. No relevant medical record	699.3	464.6	934.0	0.014*
	566. Allergy	23.8	13.4	34.2	0.049*
	577. AAD	5.6	5.0	6.5	0.205
	588. Others	42.1	38.0	28.7	0.696
F. Bedside consultation	60F. Bedside consultation	629.8	684.6	575.0	0.272
G. Others	70G. Others	643.4	457.8	829.0	0.019*

*p< 0.05; * * p< 0.01





Conclusion

Our HIS-based antibiotics stewardship platform of real-time and interactive intervention is an efficient system:

Restricted antibiotics use maintains an increasing trend despite active stewardship. This increase may be more in the absence of stewardship.

Stewardship physicians are more and more willing to provide advice with maturation of the stewardship platform.

There is significant increase in microbiology based de-escalation and call for stop advice.

Consensus between stewardship and prescription physicians can be reached for more than 98% in about one week in our dynamically interactive operation system.

Inappropriate antimicrobial uses were informed and changed based on consensus without compromising patient safety and clinical outcomes.

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The Prevalence Survey of Colistin Resistance Gene *mcr-1* in *Escherichia coli* Conducted at a Medical Center

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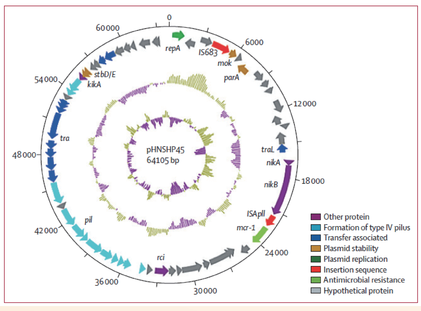
Introduction

Since the beginning of the 20th century, various natural antibiotics have been discovered, including penicillin and streptomycin, which opened the era of antibiotics. This discovery enables humans the edge in fighting bacteria. However, along with the use of antibiotics, the problem of drug resistance has become more and more serious. Significant increase in multidrug resistant bacteria in recent years has caused therapeutic difficulties. These serious concerns have been catalysed by the rapid increase in carbapenemase producing Enterobacteriaceae expressing enzymes such as KPC-2 *(Klebsiella pneumoniae carbapenemase-2)* and NDM-1 (New Delhi metallo-β-lactamase-1). For this reason, the colistin remains the last line of defense against many Gram-negative bacilli.

Typically, colistin resistance is due to chromosomal mutations. The resistance genes are generally not transmissible between bacteria and so have not disseminated widely. *In The Lancet Infectious Diseases*, Yi-Yun Liu and his colleagues reported the finding of a transferable plasmid-mediated colistin resistance gene, *mcr-1* (Figure.1), detected in *Escherichia coli* isolates from animals, food and patients in China. Moreover, they found *mcr-1* in K. *pneumoniae* isolates from patients. Horizontal gene transfer represents a paradigm shift in colistin resistance, which until then only was found to be mediated by chromosomal mutations and thus spread by vertical transmission. This will increase risks and harms to human health and public health. TSAR (Taiwan Surveillance of Antimicrobial Resistance) also conducted a similar survey. The survey revealed that the prevalence of the *mcr-1* gene in E. coli in Chinese Taipei was approximately 0.6% in 2014. The purpose of this study is to investigate prevalence of *mcr-1* in *E. coli* in our hospital as well as to analyze its current trend in the location.

Fig1:Structure of plasmid pHNSHP45 carrying *mcr-1 from E. coli strain SHP45*



Materials and methods

Bacterial isolates

One thousand two hundred and ninety-three *E.coli* isolates from clinical specimen identified by MALDI-TOF MS were collected during June to July in 2016. Among 1293 isolates, 1011 were obtained from urinary tract, 41 from respiratory tract, 69 from wound, and 173 from blood and body fluid. Antimicrobial susceptibility testing was performed by Kirby Bauer disc diffusion method following the Clinical and Laboratory Standards Institute (CLSI) guidelines against 5 different antimicrobial agents, including carbapenem、aminoglycosides、β- lactam/β-lactamase inhibitor combine、cephalosporine 、 fluoroquinolone.

Screen method for colistin resistant strain

Inoculated isolates on screen agar contained 2μg/ml colistin sulfate and incubated them for 24 hours at 35°C. Selected Colonies that grew on screen agar and carried out PCR for further mcr-1 gene detection.

PCR method for mcr-1 gene detection

The primers specific for *mcr-1* gene were CLR5-F (5'-CGGTCAGTCCGTTTGTTC-3') and CLR5-R(5'-CTTGGTCGGTCTG TAGGG-3'). Thermal cycling parameters were denatured at 95°C for 15 min, followed by 30 cycles of 94 °C for 30 sec, 52°C for 30 sec, and 72°C for 30 sec, with a final extension step at 72 °C for 10 min. The resulting fragments were electrophoresed in a 2 % agarose gel, stained with ethidium bromide, and visualized under UV light. The target's fragment size was 308 kb. (Liu YY, Wang Y, et al. Lancet Infect Dis 2016; 16: 161-8) (Figure 2).

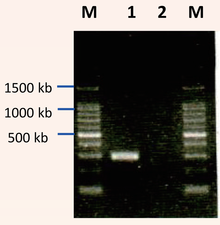


Fig2: PCR amplification of *mcr-1* at 308 bp.
M marker, Line 1: positive, Line2 : negative

Results and discussion

1.By culturing *E.coli* in 2μg/ml colistin sulfate screen agar, 204 isolates grew out from 1293 collected from clinical specimens at a ratio of 15.8%. 10 isolates were detected with *mcr-1* by PCR (0.77%). See table 1.

Table1：Results of PCR and colistin resistant strains screen in *E. coli*

	Total isolate 1293	
	Colistin screen agar positive	*mcr-1* PCR positive
isolate No.	204	10
isolate %	15.8	0.77

2.Among 10 isolates were detected with *mcr-1* by PCR, 7 were isolated from urine, 1 from blood, sputum, and wound individually. Besides, the susceptible rate against carbapenem、aminoglycosides、β- lactam/β-lactamase inhibitor combine、cephalosporine IV、fluoroquinolone was 90, 90, 90, 50, 40% separately. Additionally, isolate from blood was found resistance to carbapenem、cephalosporine、fluoroquinolone while isolate from sputum hold the resistance to aminoglycosides、cephalosporine、fluoroquinolone. Both were multidrug resistant bacteria.（Table 2）

Table 2： Results of antimicrobial susceptibility test on mcr-1 positive E. coli isolates

source	aminoglycoside		fluoroquinolone	carbapenem	b-lactam/ b-lactamase inhibitor combine	cephalosporin I	cephalosporin II	cephalosporin III	cephalosporin IV
	Amikacin	Gentamicin	Ciprofloxacin	Ertapenem	Piperacillin-tazobactam	cefazolin	cefuroxime	ceftriaxone	cefepime
Urine	S	S	R	S	S	R	R	R	S
Urine	S	S	S	S	S	R	R	R	S
Urine	S	S	R	S	S	R	R	R	I
Blood	S	S	R	I	R	R	R	R	R
Sputum	S	R	R	S	S	R	R	R	R
Urine	S	S	S	S	S	R	S	S	S
Urine	S	S	R	S	S	R	R	R	R
Pus	S	S	S	S	S	R	R	R	S
Urine	S	S	S	S	S	R	R	R	R
Urine	S	S	R	S	S	I	S	S	S
No.(%) of susceptable	10(100)	9(90)	4(40)	9(90)	9(90)	0(0)	2(20)	2(20)	50(50)

Conclusion

The investigation demonstrated that the prevalence of *mcr-1* in *E.coli* in our hospital was 0.77%. Comparing with the data of TSAR (0.6％, 2014), there was no notable increase. Thus, the dissemination of *mcr-1* in Chinese Taipei was not as serious as the areas in China and economies in South East Asia during the period of 2014-2016. Besides cephalosporine、fluoroquinolone, it was a relief to find that the susceptible rate toward carbapenem、aminoglycosides、β- lactam/β-lactamase inhibitor combine still remained 90% in *mcr-1* positive *E.coli*. A screen on *mcr-1* in *E. coli* routine basis may not be necessary, however surveillance over *mcr-1* spread must be taken periodically to prevent any outbreaks occur in the future.

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CHINESE TAIPEI

Epidemiological Study of HIV-1 Drug Resistance in Treatment Naïve and Experienced Patients at a Medical Center

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Introduction

Development of HIV-1 drug resistance mutations to the viral proteins proteases, reverse transcriptase and integrase can undermine the effectiveness of treatment regimens. Therefore, monitoring of clinical isolates for HIV drug resistance mutations is critical not only for the management of patients, but also for policy makers forecasting drug needs following initial treatment. Genotypic testing for HIV-1 drug resistance is useful for selecting antiretroviral drug regimens for naïve and treatment failure patients, but the optimal means for interpreting the test results is limited because differences in web-based interpretation tools and definitions for levels of resistances.

Materials and Methods

A prospective study was conducted in antiretroviral therapy-naïve and experienced HIV-1-infected individuals at VGHKS from January 2013 to Dec 2017 in Chinese Taipei. Drug resistance genotyping was performed on subjects' plasma samples. Drug resistance mutations were determined by ViroSeqTM system. In house PCR and Illumina MiSeq sequencing were used for integrase inhibitors (INSTI) resistance. The resistance profile was evaluated using the Stanford Database program.

Results

Our study showed that a total of 224 HIV-1 infected treatment naïve patients had tested for resistance in 2013 to 2017, of whom 97% were infected by MSM and 3% were infected by heterosexual. The prevalence rate for syphilis infection was 32%, hepatitis A 11%, hepatitis B 8% and hepatitis C 2%. Subtype B HIV-1strains were found in 96% of the individuals and subtype CRF01_AE in 4%.(Table.1) The resistance rates to any classes of antiretroviral therapy (NRTI, NNRTI, PI and INSTI) were 8.9%. The prevalence rate for NRTI, NNRTI, PI and INSTI resistance was 4%, 5.8%, 0.4% and 0.9%, respectively.(Figure.1) The most common NRTI resistance associated mutation was M184V (1.3%) and K65R (1.3%).The most common NNRTI resistance associated mutation was V179D (4.4%), V106I (2.7%) and K103N (1.3%). The most PI resistance associated mutation was L10I (13.3%), A71T (5.8%), L10V (4.0%) and A71V (3.5%). The most common INSTI resistance associated mutation was G163K (0.4%) and E138A (0.4%).(Figure.3). 52 HIV-1 infected treatment failure patients had tested for resistance, of whom 90% were infected by MSM. Subtype B HIV-1strains were found in 92% of the individuals. (Table 2). The resistance rates to any classes of antiretroviral therapy (NRTI, NNRTI, PI and INSTI) were 77%. The prevalence rate for NRTI, NNRTI, PI and INSTI resistance was 65%, 48%,12% and 37%, respectively. (Figure 2 and 4). Among the 38 patients had simultaneously Illumina MiSeq sequencing and population sequencing, none had INSTI resistance associated mutation by population sequencing but the Illumina MiSeq sequencing detected 4 more INSTI resistance associated mutations (G163R 3.25%, S153Y 1.36%, S153F 3.21% and Y143H 2.06%). Table 3-4, Figure 5.

Table.1 Demographic data among treatment-naïve of HIV-1 infected patients (n=224)

Parameters		Patient Numbers (%)
Gender	Male	224 (100)
	Female	0 (0)
Age	Median (IQR)	26 (23-31)
Age cut piont	< 35	190 (85)
	≥ 35	34 (15)
Risk factor	Heterosexual	7 (3)
	MSM	217 (97)
Any class resistance (n=218)	Y	18 (8)
	N	200 (92)
HIV subtype (n=218)	non-B	8 (4)
	B	210 (96)
CD4 (cell/ul)	Minimum	7
	Maximum	1098
	Median (IQR)	305 (207-429)
CD4 cut point (cell/ul) (n=223)	< 200	50 (22)
	≥ 200	173 (78)
Viral load (Log)	Minimum	2.6
	Maximum	7.0
	Median (IQR)	4.8 (4.4-5.1)
Viral load cut point (Log) (n=223)	< 4	16 (7)
	≥ 4	207 (93)
Syphilis (n=223)	Negative	151 (68)
	Positive	72 (32)
IHA-AMEBIASIS (n=202)	≤ 128	197 (98)
	≥ 256	5 (2)
TOXOPLASMA-IgG (n=223)	Negative	207 (93)
	Positive	16 (7)
CMV-IgG (n=222)	Negative	4 (2)
	Positive	218 (98)
CRYPTOCOCCUS Ag (n=223)	Negative	222 (99.6)
	Positive	1 (0.4)
HAV Ab (n=223)	Negative	199 (89)
	Positive	24 (11)
HBs Ab (n=223)	Negative	117 (52)
	Positive	106 (48)
HBs Ag (n=223)	Negative	204 (92)
	Positive	19 (8)
HBc Ab (n=223)	Negative	170 (76)
	Positive	53 (24)
HCV Ab (n=223)	Negative	219 (98)
	Positive	4 (2)

Table.2 Demographic data among treatment-failure HIV-1 infected patients (n=52)

Parameters		Patient Numbers (%)
Gender	Male	51 (98)
	Female	1 (2)
Age	Median (IQR)	34 (29-41)
Age cut point (n=51)	< 35	27 (53)
	≥ 35	24 (47)
Risk factor (n=50)	Heterosexual	5 (10)
	MSM	45 (90)
Any class resistance	Y	40 (77)
	N	12 (23)
HIV subtype (n=49)	non-B	4 (8)
	B	45 (92)
CD4 (cell/ul)	Minimum	6
	Maximum	865
	Median (IQR)	245 (160-406)
CD4 cut point (cell/ul) (n=51)	< 200	18 (35)
	≥ 200	33 (65)
Viral load (Log)	Minimum	3.5
	Maximum	5.8
	Median (IQR)	4.4 (3.9-4.9)
Viral load cut point (Log) (n=223)	< 4	15 (29)
	≥ 4	37 (71)

Table.3 Demographic data among HIV-1 infected patients with NGS analysis (n=38)

Parameters		Patient Numbers (%)
Gender	Male	38 (100)
	Female	0 (0)
Age	Median (IQR)	25 (23-34)
Age cut piont	< 35	29 (76)
	≥ 35	9 (24)
Risk factor	Heterosexual	1 (3)
	MSM	37 (97)
Any class resistance	Y	2 (5)
	N	36 (95)
HIV subtype	non-B	4 (10)
	B	34 (90)
CD4 (cell/ul)	Minimum	91
	Maximum	668
	Median (IQR)	337 (234-438)
CD4 cut point (cell/ul)	< 200	8 (21)
	≥ 200	30 (79)
	< 350	20 (53)
	≥ 350	18 (47)
Viral load (Log)	Minimum	3.5
	Maximum	7.0
	Median (IQR)	4.9 (4.6-5.3)
Viral load cut point (Log)	< 4	1 (3)
	≥ 4	37 (97)
Syphilis	Negative	26 (68)
	Positive	12 (32)
IHA-AMEBIASIS	≤ 128	36 (95)
	≥ 256	2 (5)
TOXOPLASMA-IgG	Negative	35 (92)
	Positive	3 (8)
CMV-IgG	Negative	0 (0)
	Positive	38 (100)
CRYPTOCOCCUS Ag	Negative	38 (100)
	Positive	0 (0)
HAV Ab	Negative	34 (90)
	Positive	4 (10)
HBs Ab	Negative	24 (63)
	Positive	14 (37)
HBs Ag	Negative	33 (87)
	Positive	5 (13)
HBc Ab	Negative	28 (74)
	Positive	10 (26)
HCV Ab	Negative	38 (100)
	Positive	0 (0)

Table.4 Overall frequency (%) of integrase inhibitor resistance-associated mutations among HIV-1 infected patients by NGS analysis (n=38) (no data for 9, 30)

mutation / sample	Y143H	L74M	E92G	T97A	S147G	S153F	S153Y	G163R
1					0.51			
2					0.51			
3								
4								
5					0.51			
6					0.68			
7					0.52			
8					0.58			
10					0.54			
11								
12			0.5					
13					0.47			
14								
15								
16					0.58			
17				0.53	0.5			3.25
18				0.97			1.36	
19		0.47						
20				0.59	0.47			
21								
22								
23	2.06							
24			0.5		0.58			
25								
26								
27					0.5			
28								
29	0.78							
31		0.51	0.49					
32			0.49					
33								
34					0.61			
35								
36								
37						3.21		
38					0.75			
39								
40								

Figure.1 Percentage of drug resistance and drug resistance-associated mutation in treatment-naive of HIV-1 infected patients

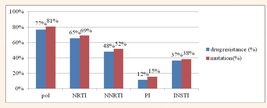

Figure.2 Percentage of drug resistance and drug resistance-associated mutation in treatment-failure HIV-1 infected patients

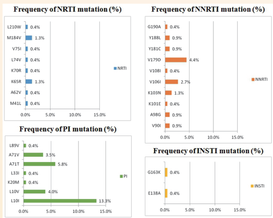

Figure.3 Frequency of drug resistance-associated mutation in treatment-naive of HIV-1 infected patients

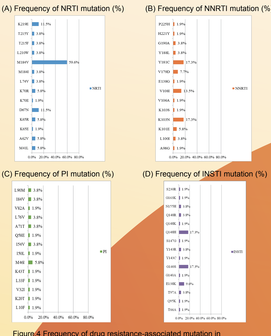

Figure.4 Frequency of drug resistance-associated mutation in treatment-failure HIV-1 infected patients

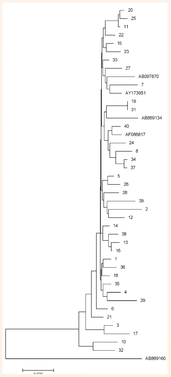

Figure.5 Evolutionary relationships of taxa. (Neighbor-Joining analysis of B type *integrase* sequences.)

Conclusion

Our findings showed the high rate of HIV drug resistance (8.9% and 77%) to any four classes of antiretroviral regimens in treatment naïve and virological failure patients, respectively. Illumina MiSeq sequencing detected more INSTI resistance associated mutations at a low frequency. The clinical implications need further study.

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CHINESE TAIPEI

Evaluation of a Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry Assisted, Selective Broth Method to Screen for Carbapenem-Resistant Enterobacteriaceae in Patients at High Risk

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Introduction

The discovery of NDM-1 in 2010 caused great concern in the world, and the increasing trend of drug-resistant strains gradually gained attention. As carbapenem antibiotics are broad-spectrum β-lactams, they are often used to treat multidrug-resistant bacteria. In recent years, intestinal bacteria have become increasingly resistant to carbapenem-resistant Enterobacteriaceae (CRE). The increase has made infection control even more difficult, the availability of antibiotics has been limited, and even drug-free access has become a dilemma.

Rapid detection of CRE is critical to make optimal hospital control decisions and help to take action to prevent and control the infections. There are several laboratory techniques to perform CRE screening. Conventional methods are mainly relied on cultures. Identification and susceptibility are based on colonies isolated after incubation. Improved methods, such as PCR-based methods can detect CRE directly from specimens and significantly reduce identification turnaround times. However, the higher cost of PCR-based methods is a major obstacle for extensive use. Therefore, current methods used for CRE screening in most laboratories are still culture dependent. The turnaround time are 48-72 hours, which means patients may probably need to be put under pre-emptive contact isolation for 2-3 days. Contact isolation itself has known to have several drawbacks, such as decreasing the frequency of contacts between health care workers and patients, producing psychological impact, and of course, leading to more costs. It may also arouse the ethical concern if final culture results are negative. Thus, a laboratory method with higher accuracy, lower cost and shorter turnaround time for CRE screening is crucial.

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a rapid and inexpensive method used widely to identify clinical microorganisms in recent years. The method was reported to have a high accuracy for bacteria detection within 30-60 minutes. However, MALDI-TOF MS is not able to provide information of drug resistance. Another day for susceptibility testing is still required.

In this study, we developed a home-made CRE selective broth which include antibiotics for selection of CRE and inhibiting gram-positive bacteria and yeast are included. Whenever bacteria grow, it is probably carbapenem-resistant gram-negative bacilli. Detection of Enterobacteriaceae is based on its ability to ferment glucose and turn yellow in the present of phenol red. Suspected CRE will be confirmed with MALDI-TOF MS. Thus, further susceptibility testing is not needed and turnaround time is shortened for at least one day.

We aim to increase our understanding on the epidemiology of the important MDROs in our hospital. In addition, we will determine the distribution of their genotypes and corresponding phenotypes, and investigate their impact on clinical manifestation and hospital infection control.

Results

Speicmens: 14 speicmens, from Dec. 2017-Mar. 2018

Specimens submitted for CRE detection (n=14)

CRE borth Culture negative (n=6)	CRE broth Culture positive (n=8)	
	Yellow (n=4)	Red (n=4)
	K. pneumoniae (n=1) *E. coli* (n=1) *E. aerogenes* (n=1) K. *pneumoniae*+*S. maltophilia* (n=1)	*P. aeruginosa* (n=1) CoNS (n=2) Yeast (n=1)

CRE Detected by CRE Broth

	CRE broth		
No.	MS identification	Susceptibility results	Laboratory reports
1	*K. pneumoniae* (n=1)	Carbapenem-resistant	CRE
2	*E. coli* (n=1)	Carbapenem-resistant	Culture negative for CRE (Growth for *E. coli*)
3	*E. aerogenes* (n=1)	Carbapenem-resistant	CRE
4	*S. maltophilia* (n=1)	Carbapenem-resistant	Culture negative for CRE (Growth for *K. pneumoniae* and *S. maltophilia*)

Discussion

CRE broth detected all 4 specimens with CRE (100%)
Current Lab method detected 2/4 (50%)
All 4 CRE were detected within 20 hrs, compared to 3.75 days in Lab method

Materials And Methods

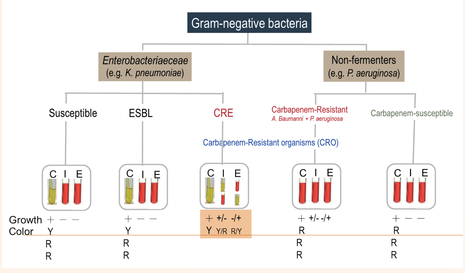
Specimen collection and processing.

The specimens were collected from patients who received routine active surveillance cultures at the infection ward in Kaohsiung Veterans General hospital. Two samples will be collected on a Copan Amies sterile transport swabs (Copan Diagnostics, Corona, CA) and transported to the microbiology laboratory for the detection of Carbapenem-resistant Enterobacteriaceae(CRE), one tested by routine culture and the other by the study method

Selective CRE broth method.

The CRE selective broth includes Trypticase Soy Broth (BBL), antibiotics including one carbapenem (either 2 μg/ml imipenem or 1 μg/ml ertapenem), 8 μg/ml vancomycin for inhibiting gram positive cocci , 8μg/ml amphotericin B for inhibiting yeasts, and phenol red as indicator.

A swab was put into 0.5 mL sterile NaCl 0.9%, thoroughly vortexed, and 25 μl of this solution was inoculated into 2 ml of selective broths. Adding mineral oil into the broths and were observed for growth after an incubation period of 20, 24, 28, 32 and 48 hours.



MALDI-TOF MS identification method

Positive broths will be centrifuged at 1,000 rpm for 1 minute. The supernatant will be discarded, and the pellet will be resuspended in 0.5 ml of 70% alcohol, vortexed, and then washed once in 0.5 ml of distilled water. After centrifuged at 14000 rpm for 1 minute, the pellet will be spotted onto a MALDI-TOF target plate. The subsequent protein extraction method will be performed only when definite identification is not achieved after performing the washing steps. The pellet will be mixed with 5 μl of acetonitrile (AN) and 5 μl of 20% trifluoroacetic (TFA) acid and incubated for 15 minutes at room temperature. After centrifugation at 14000 rpm for 1 minutes, 2 μl of supernatant will be spotted onto a MALDI-TOF target plate. Each deposit on the target plate will be overlaid with 2 μL of matrix solution [saturated solution of α-HCCA (alpha-cyano-4-hydroxycinnamic acid) in 50% AN and 2.5% TFA]. The matrix-sample will be crystallized by air drying at room temperature for 5 minutes. Following sample preparation, samples will be analyzed with the Vitek MS MALDI-TOF mass spectrometer in linear positive-ion mode, across the mass-to-charge ratio range of 2,000 to 20,000 Da. Each spot will be irradiated with 500 laser shots at 50 Hz. Target plates will be calibrated and quality controlled both before and after data acquisition by using Escherichia coli ATCC 8739. After the acquisition of spectra, data will be transferred from the Vitek MS acquisition station to the Vitek MS analysis server, and identification results will be displayed using Myla v2.4 middleware. The total processing and data analysis time will be approximately 20 min for a single isolate; this time increased by approximately 1 min for each subsequent sample. The Vitek MS identification system is based on comparison of the characteristics of the spectra obtained with the Vitek MS v2.0 database.

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CHINESE TAIPEI

Longitudinal Multicenter Surveillance on AMR

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1National Health Research Institutes (NHRI); 2 National Taiwan University Hospital

Background

Antimicrobial resistance is a global public health threat. Longitudinal surveillance plays an important role in the control of antimicrobial resistance by helping to define the extent of the problem in a region, detect emerging resistance, and identify specific problems that exist locally. Such data can be used to advocate for intervention measures and assess the impact of intervention. In 1998 NHRI implemented the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program to monitor antibiotic resistance of clinical bacterial isolates recovered from inpatients and outpatients. Ten rounds of TSAR have been completed to date.

Methods

Isolates and hospitals. Since 2002, isolates have been collected between July and September biennially from the same 25-28 hospitals located in different regions (Figure 1). Isolate collection protocols have also remained similar (Figure 2).
Phenotypic and genotypic studies. After species confirmation, susceptibility to different antimicrobial agents was determined by broth microdilution following the CLSI guidelines using Sensititre panels (Trek Diagnostics, England). Genotypic studies were performed to investigate mechanisms of resistance and molecular epidemiology of important drug-resistant bacteria.
Data analysis: Susceptibiity analysis was made using the Whonet software. Multivariate analysis was prformed to identify independent factors associated with drug-resistant bacteria.

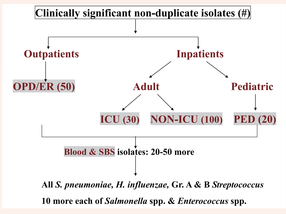


Figure 1 (left). Locations of TSAR Hospitals
Figure 2 (above). TSAR collection protocol

Results

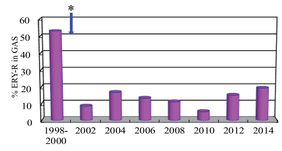
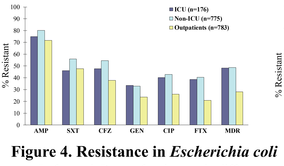


Figure 3. Erythromycin resistance (ERY-R) in Gr. A *Streptococcus* (GAS).
*A policy to restrict outpatient antibiotic use was implemented in 2001.



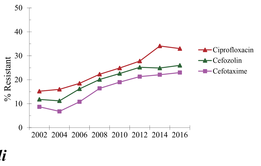


Figure 4. Resistance in *Escherichia coli*
Left panel: Rates of resistance in different patient groups (2012 data).
Right panel: Increasing resistance in outpatient UTI isolates.
(AMP, ampicillin; SXT, trimethoprim/sulfa; CFZ, cefazolin; GEN, gentamicin; CIP, ciprofloxacin; FTX, cefotaxime; MDR, resistant to 3 or more of the agents shown)

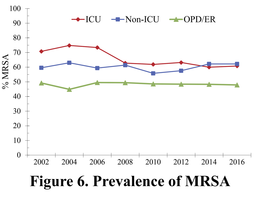


Figure 6. Prevalence of MRSA

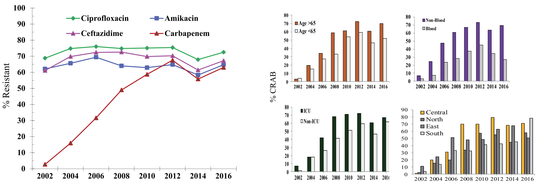


Figure 5. Multidrug-resistant *Acinetobacter calcoaceticus-A. baumannii*
Left panel. Rapid increase of carbapenem-resistant *A. baumannii* (CRAB)
Right panel. Factors associated with CRAB (Age, ward, specimen, regions)

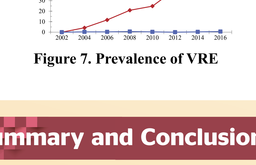


Figure 7. Prevalence of VRE

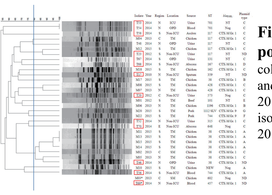


Figure 8. Dendrogram of *mcr*-1 positive *E. coli.* *mcr*-1 (plasmid-mediated colistin-resistance) was detected in 0.1%, 0.1%, and 0.6% of TSAR isolates from 2010, 2012, and 2014, respectively; and 1.1%, 6.6%, and 8.7% of isolates from retailed meat in 2012, 2013, and 2015, respectively.

Summary and Conclusion

Following a policy to restrict antibiotic use for acute upper respiratory infections in outpatients, significant decrease in erythromycin resistance was observed in Group A Streptococcus (Figure 3).
However, multidrug-resistance (MDR) is prevalent in hospitals and outpatient settings and resistance to non-first-line agents continued to increase (Figures 4-7).
Increasing resistance to non-first-line agents indicate the need to reevaluate empirical therapy guidelines for outpatients (Figure 4).
Determination of independent factors associated with resistant bacteria helps to identify at risk groups requiring more focused interventions (Figure 5).
Detection of plasmid-mediated colistin resistance (mcr-1) in E. coli isolated from human clinical samples and retail meat (Figure 8) further support the need for continued monitoring of emerging resistance and investigations of antibiotic use in all sectors.

Acknowledgement: We thank all TSAR hospitals for their long-term participation of the TSAR project.

Asia-Pacific Economic Cooperation

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APEC Conference on Strategies Against the Evolving Threats from Antimicrobial Resistance:
From Awareness to Concrete Action

CHINESE TAIPEI

Experience sharing of Implementing Asia Pacific Antimicrobial Stewardship Preceptorship Program in Chinese Taipei

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Background

Antimicrobial resistance (AMR) is one of the most pressing public health issues the world faces today. Three key strategies are needed to address this urgent problem: infection control and hand hygiene, epidemiology monitoring and antimicrobial stewardship promotion. Antimicrobial stewardship is a systematic process wherein expertise of a multidisciplinary team is integrated in order to improve patient outcomes by optimizing antimicrobial use and minimizing unintended consequences. Linkou Chang Gung Memorial Hospital (CMGH) has been the first in 2004 to establish a computerized system assessing the appropriateness of antimicrobial prescriptions. By the year 2006, an ASP Team has been formed and has now accumulated more than ten years of experience in improving antimicrobial use. Furthermore, Linkou CGMH was selected to serve as one of the model centers assisting in the implementation of the Antimicrobial Stewardship Program led by Our Centers for Disease Control (CDC) from 2013 to 2015.

Objectives and Designs of program

Through the years, Linkou CGMH spares no effort in promoting antimicrobial stewardship. As part of our determination to deliver on the commitment of addressing public health problems, we will continue providing support to the implementation of antimicrobial stewardship across all health care settings locally and abroad. We are looking forward to strengthen our collaborative partnership with all of the members of Asia-Pacific Economic Cooperation (APEC) as we progress along the road to improved patient care. This training program is aim to cultivate preceptor faculty of antimicrobial stewardship and consists of lecture, case discussion, feedback and on-site visiting.

Program Introduction

This 2108 antimicrobial stewardship preceptorship training program is a one year project. It includes pre-training teleconference, one week training course at Linkou CGMH, post-training feedback and on-site visiting. We invited eighteen delegates from four hospitals at Philippines and two hospital at Vietnams to participate in this program. There are four specialties (ID, pharmacist, microbiologist, infection control nurse) and hospital administrates from the participants.

One week training course consisted of lectures, case discussion, clinical wards round, microbiology, pharmacy and infection control units round. We combined lecture teaching and clinical practice to demonstrate our daily antimicrobial stewardship. In the final day's workshop, participants used the US CDC checklist for core elements of hospital antibiotic stewardship program to determine the further actions to improve their antibiotic use.

After training course, we will have teleconference with visiting hospitals for the stewardship implementation follow-up and feedback. In the late 2018, we will arrange on-site visiting to see the result of their antimicrobial stewardship.

Asia Pacific Antimicrobial Stewardship Preceptorship Training Program in Chinese Taipei

Time	Monday	Tuesday	Wednesday	Thursday	Friday
07:30~08:30 (60 mins)				Pediatric ID Morning Meeting	
08:30~08:40 (10 mins)	Opening Remarks	Ward Round	Ward Round		Workshop
08:40~09:30 (50 mins)	Course Introduction and Introduction of AMS			ICN Visiting	
09:30~10:00 (30 mins)	*Coffee Break*				
10:00~11:00 (60 mins)	Introduction of the online prospective antimicrobial audit system		*Coffee Break*		
11:00~12:00 (60 mins)			Journal Meeting	*Coffee Break*	
12:00~13:30 (90 mins)	*Lunch Break*			Combined Case Conference	*Lunch Break*
13:30~14:30 (60 mins)	Healthcare Quality and Patient Safety	The Role of Clinical Microbiologist in AMS	Outcome Measurement	*Coffee Break*	Closing Meeting
14:30~15:30 (60 mins)	The Role of Pharmacist in ASP	Clinical Microbiology Lab Round		Discussion and Feedback	
15:30~15:40 (10 mins)	*Coffee Break*				
15:40~16:40 (60 mins)	Infection control in CGMH	The multidisciplinary teamwork in ASP	Pharmacy Unit Round		
16:40~17:00 (20 mins)	Panel Discussion				

The Core Elements of Hospital Antibiotic Stewardship Programs CHECKLIST

The Core Elements of Hospital Antibiotic Stewardship Programs CHECKLIST (Philippine)	St. Luke's Medical Center	Chang Hua Hospital	Metro Davao Medical and Research Center	Medicus Medical Center
LEADERSHIP SUPPORT				
A. Does your facility have a formal, written statement of support from leadership that supports efforts to improve antibiotic use (antibiotic stewardship)?	Y	Y	Y	Y
B. Does your facility receive any budgeted financial support for antibiotic stewardship activities(e.g., support for salary, training, or IT support)?	Y	Y	Y	Y
ACTIONS TO SUPPORT OPTIMAL ANTIBIOTIC USE				
POLICIES				
A. Does your facility have a policy that requires prescribers to document in the medical record or during order entry a dose, duration, and indication for all antibiotic prescriptions?	Y	N	Y	Y
B. Does your facility have facility-specific treatment recommendations, based on national guidelines and local susceptibility, to assist with antibiotic selection for common clinical conditions?	N	Y	N	Y

Conclusion And Future Prospects

This is a comprehensive antimicrobial stewardship training program, which consisted of pre-training communication, multidisciplinary team lectures, ward/units wound, workshop with feedback, and a final on-site visiting. Participants are not only receive a general course but also an individualized guidance according to their hospital's facilities and policies.

We are looking forward to know the response and result after the training program in late 2018. We are also like to share our experience with the members of APEC and economies in other area those who are in the early stage of developing antimicrobial stewardship program.

Feb, 2018 **Preparatory group meeting** → Apr, 2018 **Teleconference with visiting hospitals** → May~Jan, 2018 **One week training program** → Aug, 2018 **Teleconference with vising hospitals** → Nov, 2018 **On site Visiting**

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