Challenges and Solutions in the Treatment of CRE infection in Taiwan

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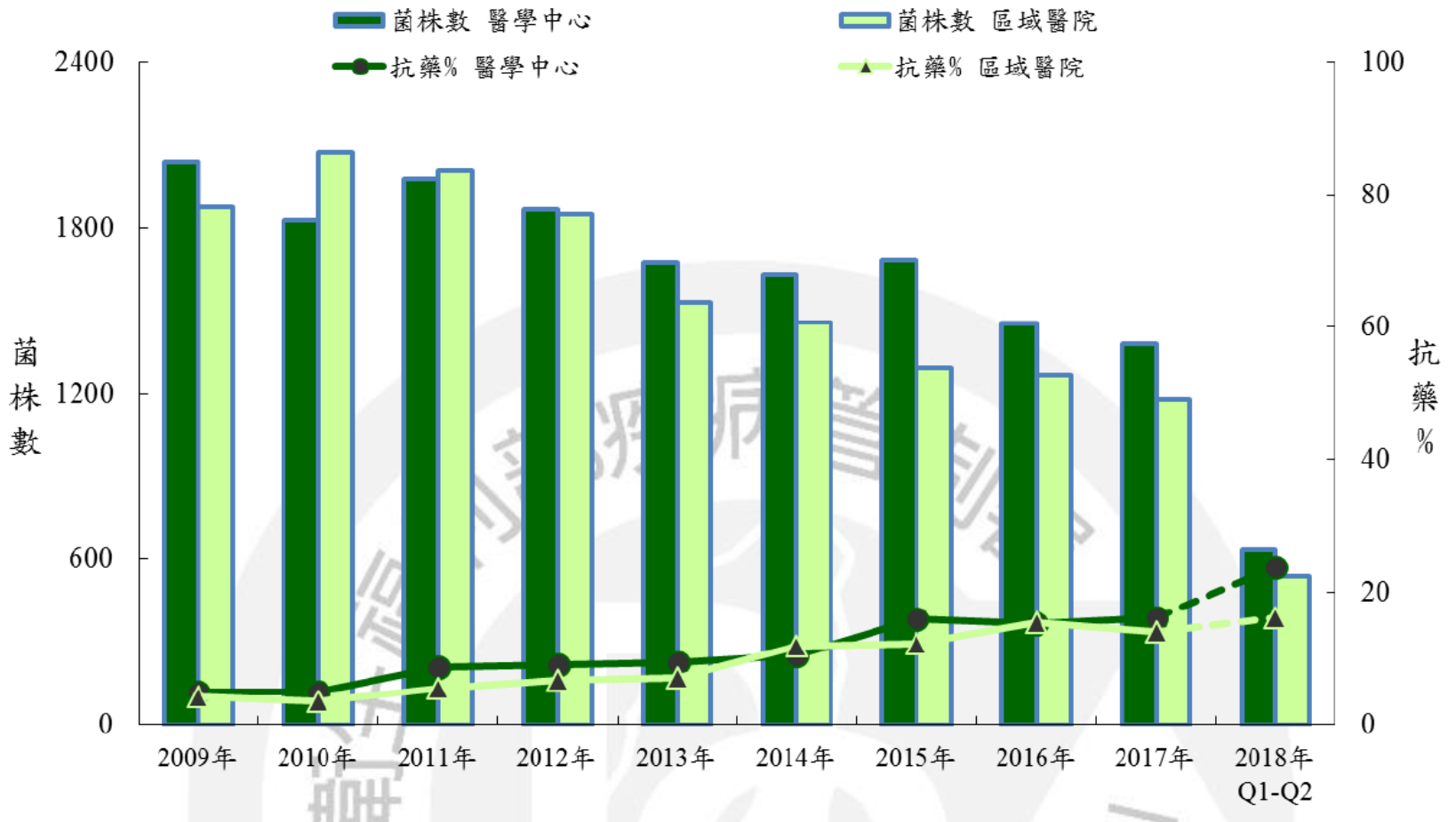
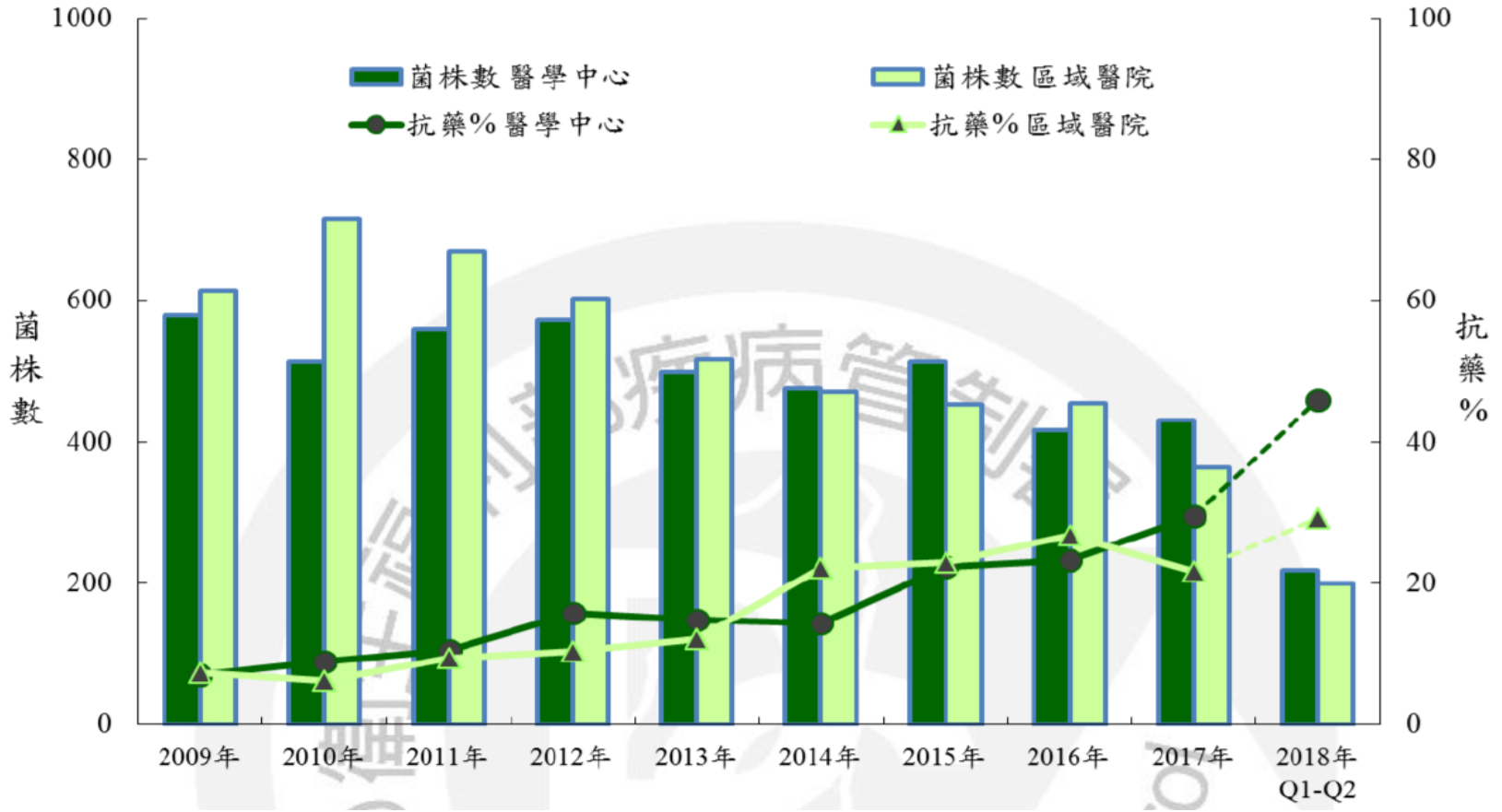
12:10 – 12:40 8 Dec., 2019

CRE = Carbapenem-Resistant Enterobacteriaceae

2009 至 2018 年第 2 季醫學中心及區域醫院加護病房醫療照護相關感染個案分離之 *Enterobacteriaceae* 對 carbapenem 類抗生素具抗藥性(CRE)百分比分布如圖 7。醫學中心加護病房 CRE 比率由 2009 年的 5.0%增加至 2018 年第 2 季 23.7%；區域醫院則由 4.2%上升至 16.0%。



2009 至 2018 年第 2 季醫學中心及區域醫院加護病房醫療照護相關感染個案分離之 *Klebsiella pneumoniae* 對 carbapenem 類抗生素具抗藥性(CRKP)百分比分布如圖 11。醫學中心加護病房之 CRKP 比率由 2009 年的 7.1%增加至 2018 年第 2 季 45.9%；區域醫院則由 7.3%上升至 29.1%。



Impact of CRE

- **US in 2013:** 4% of acute hospital, 18% of long-term acute-care facility
- **Mortality** rate of 40-50% in blood-stream infection of CRE-K.P.
  - Underlying severity
  - Delayed administration of appropriate antimicrobial therapy
- **Factors:** elderly, immunosuppressed, chronically, critically ill, health-care exposure, primary immunodeficiency, solid tumors, lymphoma, organ and bone marrow transplant

MMWR Morb Mortal Wkly Rep 2013;62:165. Patel G. Infect Control Hosp epidemiol 2008;29:1099. Cleve Clin J Med 2013;80:225. Sci Transi Med 2012;4:148. Viale P Expert Rev Anti Infect Ther 2013;11:1053. Zarkotou O. Clin Microbiol Infect 2011;17:1798

Mechanisms of Carbapenem Resistance in Enterobacteriaceae

- **Production of extended-spectrum β-lactamase (ESBL) and/or AmpC β-lactamase** +/- loss of **outer membrane protein** or upregulation of **efflux pump**: CR- *E. coli,* CR- *Enterobacter* spp. in Taiwan
- Production of **carbapenemases :** CR- *K. pneumoniae* in Taiwan

Pfeifer *Int J Med Microbiol* 2010;300:371. Bush K *Curr Opin Microbiol* 2010;13:558. *Future Microbiol* 2007;2:501. Ma L *BMC Infect Dis* 2013;13:599

Mechanisms of Drug Resistance in Enterobacteriaceae

- Tigecycline-resistant *K. pneumoniae*: ramR deficiency and/or widespread mutated tet (A)
- Fosfomycin-resistant genes: FosA subtypes and fosC2
- Colistin-resistant genes: mobilized colistin resistance (*mcr*-1)

Chiu SK. Antimicrob Agetns Chemother 2017;61:e00391. Yang TY,J Microbiol Immunol Infect 2017;10:006

Amber classification
A, B, C, D

Enzyme/ambler classification	Common genetic platform	Species distribution in *Enterobacteriaceae*
KPC (*Klebsiella pneumoniae* carbapenemase)/ class A	*K. pneumoniae* sequence type 258 and ST11 inter alia, transposon Tn4401x	*Klebsiella pneumoniae, Escherichia coli, Enterobacter* sp.; diverse *Enterobacteriaceae*
NDM (New Delhi metallo-beta-lactamase)/class B	Various plasmid types	*K. pneumoniae* and *E. coli* predominantly; diverse *Enterobacteriaceae*
OXA-48 (oxacillinase)/ class D	Incl/M-type plasmid	*K. pneumoniae* predominantly, diverse *Enterobacteriaceae*
VIM (Verona integron-encoded metallo-beta-lactamase)/ class B	Gene cassettes in class 1 integrons	*K. pneumoniae*
IMP/class B	Gene cassettes in class 1 integrons	*K. pneumoniae*
SME/class A	Chromosome	*Serratia marcescens*
DHA-1/class C, in combination with OmpK35/36 loss	Plasmid	*K. pneumoniae*
ACT/class C, in combination with OmpK35/36 loss	Plasmid	*K. pneumoniae*
CTX-M-15/class A, in combination with OmpK35/36 loss	Plasmid	*K. pneumoniae*
SHV-5/class A, in combination with OmpK35/36 loss	Plasmid	*K. pneumoniae*
GES-5/class A, in combination with OmpK35/36 loss	Self-conjugative plasmid	*K. pneumoniae*

Expert opinion on Pharmacotherapy 2016;17:761

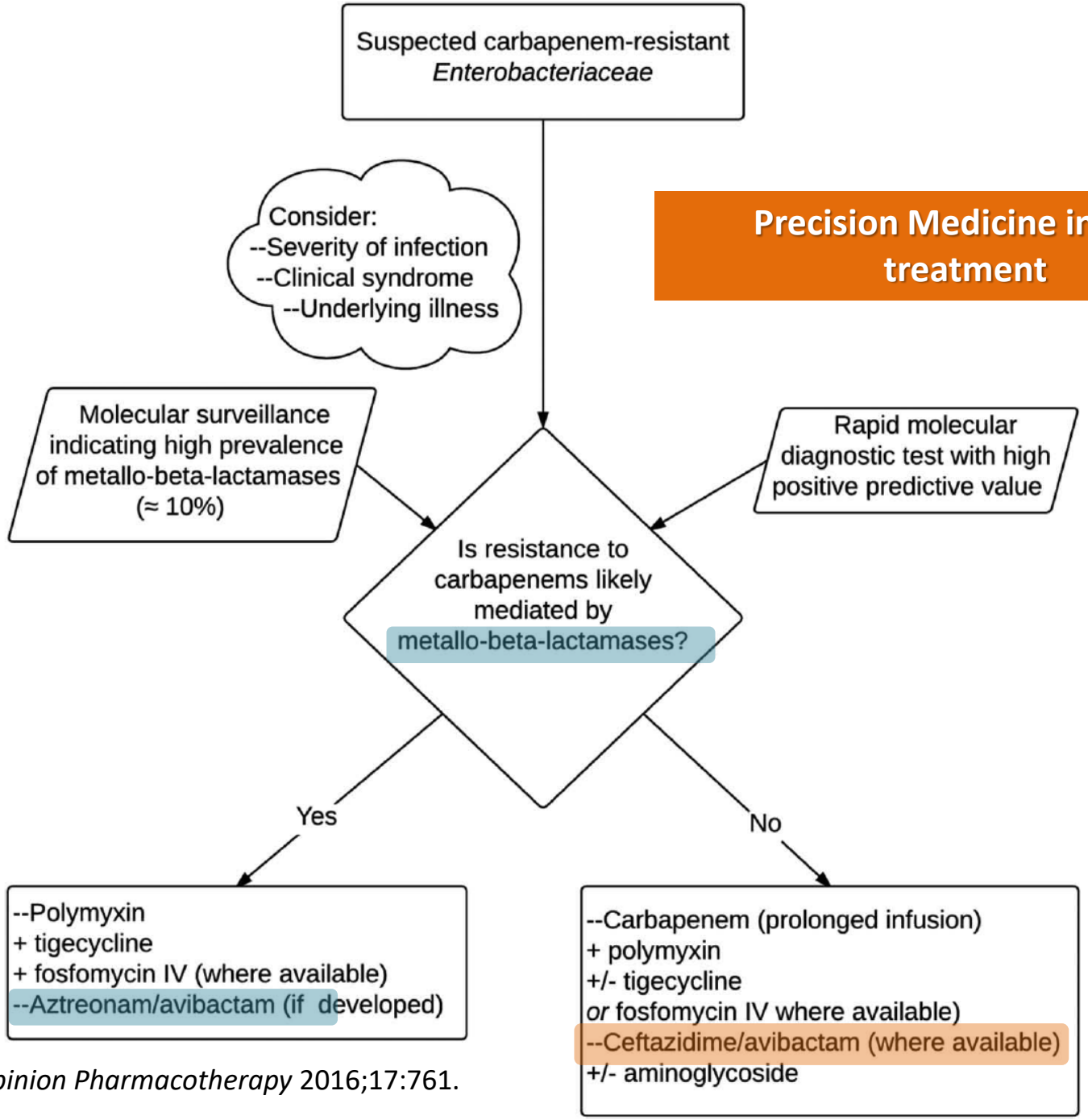
Major Carbapenemases in *Enterobacteriaceae*

Carbapenemase	KPC	MBLs (NDM, VIM, IMP)	OXA-48
Ambler molecular class	A	B	D
Substrates of hydrolysis	All β-lactams	All β-lactams except for aztreonam	Penicillins and carbapenems
Inhibited by classic β-lactamase inhibitors	Minimally	No	No
Inhibited by avibactam	Yes	No	Yes
Inhibited by vaborbactam	Yes	No	No
Inhibited by relebactam	Yes	No	No
Common species in *Enterobacteriaceae*	*K. pneumoniae, E. coli, Enterobacter* spp.	NDM: *K. pneumoniae, E. coli* VIM: *K. pneumoniae* IMP: *K. pneumoniae*	*K. pneumoniae*

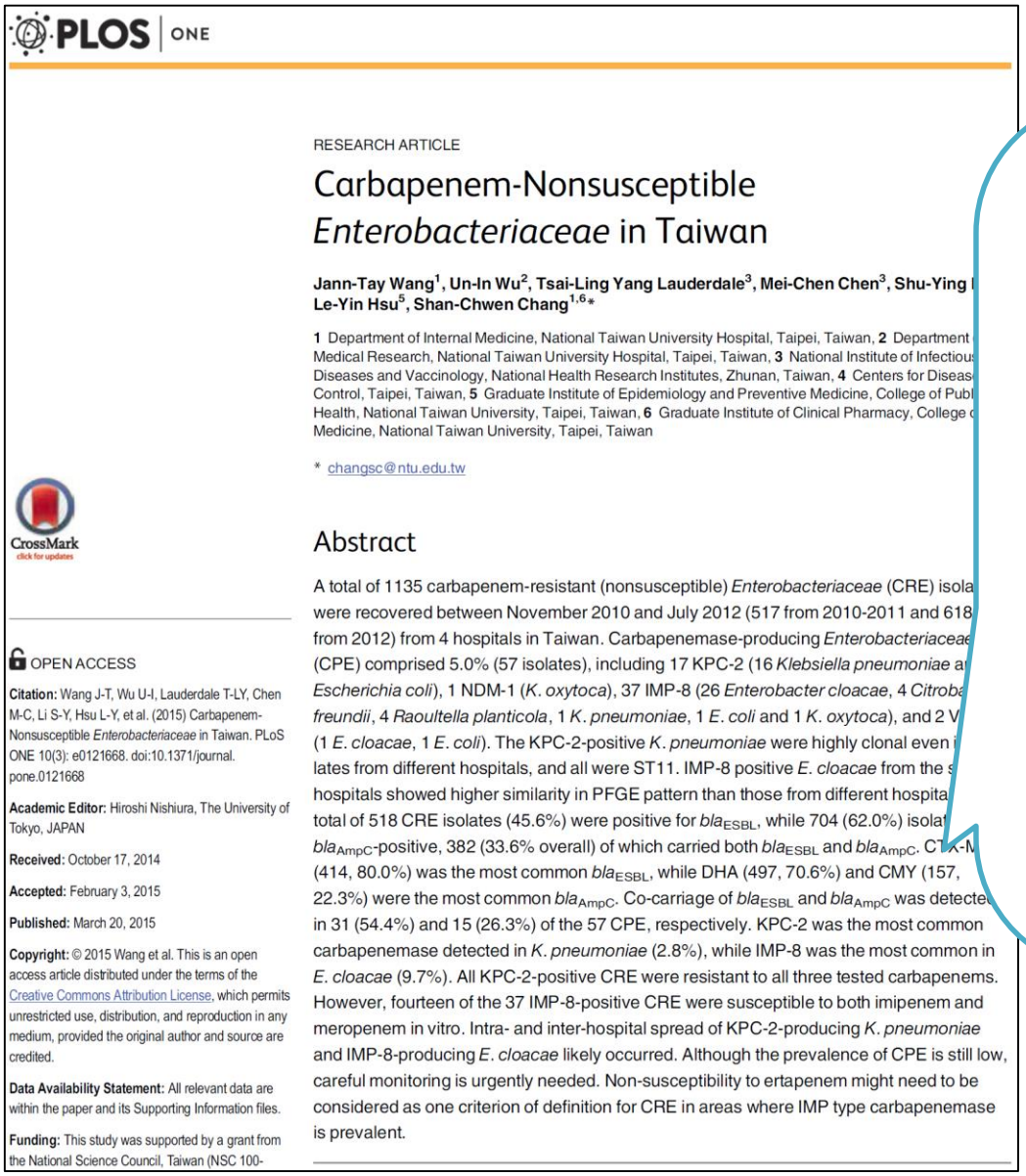
KPC, Klebsiella pneumoniae carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; VIM, Verona integrin-encoded metallo-β-lactamase; IMP, imipenemase; OXA, oxacillinase.

Sheu CC *Front Microbiol* 2019;10:80

Precision Medicine in CR-E treatment



Expert Opinion Pharmacotherapy 2016;17:761.



PLOS ONE

RESEARCH ARTICLE

Carbapenem-Nonsusceptible *Enterobacteriaceae* in Taiwan

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Abstract

A total of 1135 carbapenem-resistant (nonsusceptible) *Enterobacteriaceae* (CRE) isola
were recovered between November 2010 and July 2012 (517 from 2010-2011 and 618
from 2012) from 4 hospitals in Taiwan. Carbapenemase-producing *Enterobacteriaceae*
(CPE) comprised 5.0% (57 isolates), including 17 KPC-2 (16 *Klebsiella pneumoniae* a
Escherichia coli), 1 NDM-1 (*K. oxytoca*), 37 IMP-8 (26 *Enterobacter cloacae*, 4 *Citroba
freundii*, 4 *Raoultella planticola*, 1 *K. pneumoniae*, 1 *E. coli* and 1 *K. oxytoca*), and 2 V
(1 *E. cloacae*, 1 *E. coli*). The KPC-2-positive *K. pneumoniae* were highly clonal even
lates from different hospitals, and all were ST11. IMP-8 positive *E. cloacae* from the s
hospitals showed higher similarity in PFGE pattern than those from different hospita
total of 518 CRE isolates (45.6%) were positive for bla_{ESBL}, while 704 (62.0%) isola
bla_{AmpC}-positive, 382 (33.6% overall) of which carried both bla_{ESBL} and bla_{AmpC}. CT-X-M
(414, 80.0%) was the most common bla_{ESBL}, while DHA (497, 70.6%) and CMY (157,
22.3%) were the most common bla_{AmpC}. Co-carriage of bla_{ESBL} and bla_{AmpC} was detecte
in 31 (54.4%) and 15 (26.3%) of the 57 CPE, respectively. KPC-2 was the most common
carbapenemase detected in *K. pneumoniae* (2.8%), while IMP-8 was the most common in
E. cloacae (9.7%). All KPC-2-positive CRE were resistant to all three tested carbapenems.
However, fourteen of the 37 IMP-8-positive CRE were susceptible to both imipenem and
meropenem in vitro. Intra- and inter-hospital spread of KPC-2-producing *K. pneumoniae*
and IMP-8-producing *E. cloacae* likely occurred. Although the prevalence of CPE is still low,
careful monitoring is urgently needed. Non-susceptibility to ertapenem might need to be
considered as one criterion of definition for CRE in areas where IMP type carbapenemase
is prevalent.

OPEN ACCESS

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

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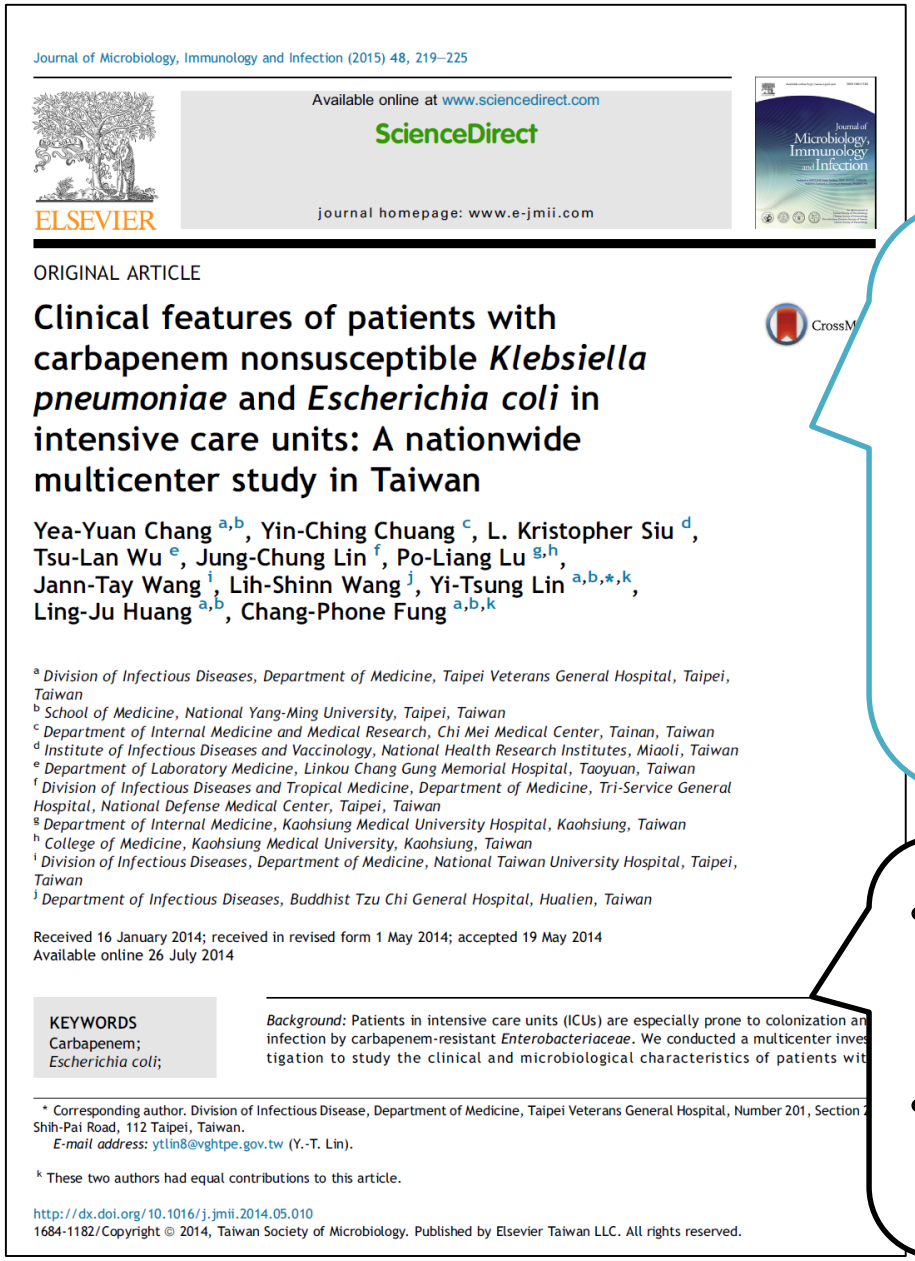
1135 carbapenem-resistant Enterobacteriacea (**2010.11-2012.7, variable sources**)

- Carbapenemase: 5.0% (A: 17 KPC-2, B:1 NDM-1, 37 IMP-8, 2 VIM-1)
- bal_{ESBL}: 45.6% (414 CTM-X)
- bal_{AmpC}: 62.0% (497 DHA, 157 CMY)

Wang JT. *PLoS One* 2015;10:e0121668



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ORIGINAL ARTICLE

Clinical features of patients with carbapenem nonsusceptible *Klebsiella pneumoniae* and *Escherichia coli* in intensive care units: A nationwide multicenter study in Taiwan

Yea-Yuan Chang [a,b], Yin-Ching Chuang [c], L. Kristopher Siu [d], Tsu-Lan Wu [e], Jung-Chung Lin [f], Po-Liang Lu [g,h], Jann-Tay Wang [i], Lih-Shinn Wang [j], Yi-Tsung Lin [a,b,*,k], Ling-Ju Huang [a,b], Chang-Phone Fung [a,b,k]

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Available online 26 July 2014

KEYWORDS
Carbapenem;
Escherichia coli;

Background: Patients in intensive care units (ICUs) are especially prone to colonization an
infection by carbapenem-resistant *Enterobacteriaceae*. We conducted a multicenter inves
tigation to study the clinical and microbiological characteristics of patients wit

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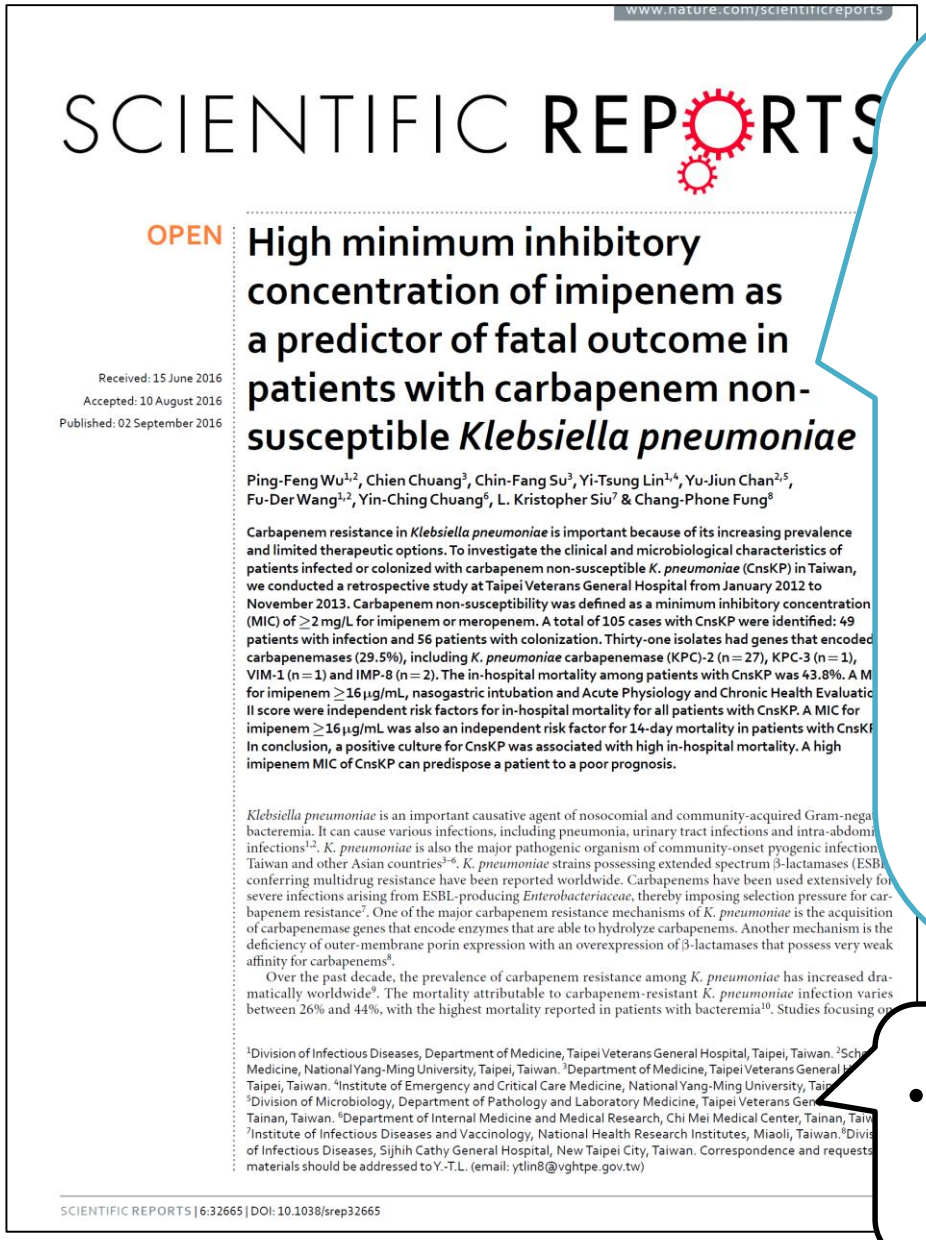
66 CR-E (46 infections, 20 colonization, 60 KP, 6 E. coli) (**2012, ICU**)

- Carbapenemase: 28.8%, 19/66 (A: 14 KPC-2, B:1 NDM-1, 1 IMP-8, 3 VIM-1)
- bal_{AmpC} or ESBL = 71.2%, 47/66

- In-hospital mortality for CRE-infection = 50% (23/46)
- Independent factor of septic shock for 30-day mortality

Chang YY. *J Microbiol Immunol Infect* 2015;48:219



www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

High minimum inhibitory concentration of imipenem as a predictor of fatal outcome in patients with carbapenem non-susceptible *Klebsiella pneumoniae*

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Ping-Feng Wu[1,2], Chien Chuang[3], Chin-Fang Su[3], Yi-Tsung Lin[1,4], Yu-Jiun Chan[2,5], Fu-Der Wang[1,2], Yin-Ching Chuang[6], L. Kristopher Siu[7] & Chang-Phone Fung[8]

Carbapenem resistance in *Klebsiella pneumoniae* is important because of its increasing prevalence and limited therapeutic options. To investigate the clinical and microbiological characteristics of patients infected or colonized with carbapenem non-susceptible *K. pneumoniae* (CnsKP) in Taiwan, we conducted a retrospective study at Taipei Veterans General Hospital from January 2012 to November 2013. Carbapenem non-susceptibility was defined as a minimum inhibitory concentration (MIC) of ≥2 mg/L for imipenem or meropenem. A total of 105 cases with CnsKP were identified: 49 patients with infection and 56 patients with colonization. Thirty-one isolates had genes that encoded carbapenemases (29.5%), including *K. pneumoniae* carbapenemase (KPC)-2 (n = 27), KPC-3 (n = 1), VIM-1 (n = 1) and IMP-8 (n = 2). The in-hospital mortality among patients with CnsKP was 43.8%. A M for imipenem ≥16 μg/mL, nasogastric intubation and Acute Physiology and Chronic Health Evaluatic II score were independent risk factors for in-hospital mortality for all patients with CnsKP. A MIC for imipenem ≥16 μg/mL was also an independent risk factor for 14-day mortality in patients with CnsK In conclusion, a positive culture for CnsKP was associated with high in-hospital mortality. A high imipenem MIC of CnsKP can predispose a patient to a poor prognosis.

Klebsiella pneumoniae is an important causative agent of nosocomial and community-acquired Gram-nega bacteremia. It can cause various infections, including pneumonia, urinary tract infections and intra-abdomi infections[1,2]. *K. pneumoniae* is also the major pathogenic organism of community-onset pyogenic infection Taiwan and other Asian countries[3–6]. *K. pneumoniae* strains possessing extended spectrum β-lactamases (ESB conferring multidrug resistance have been reported worldwide. Carbapenems have been used extensively fo severe infections arising from ESBL-producing *Enterobacteriaceae*, thereby imposing selection pressure for car- bapenem resistance[7]. One of the major carbapenem resistance mechanisms of *K. pneumoniae* is the acquisition of carbapenemase genes that encode enzymes that are able to hydrolyze carbapenems. Another mechanism is the deficiency of outer-membrane porin expression with an overexpression of β-lactamases that possess very weak affinity for carbapenems[8].

Over the past decade, the prevalence of carbapenem resistance among *K. pneumoniae* has increased dra- matically worldwide[9]. The mortality attributable to carbapenem-resistant *K. pneumoniae* infection varies between 26% and 44%, with the highest mortality reported in patients with bacteremia[10]. Studies focusing on

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105 CR-KP (49 infections, 56 colonization) (**2012.1 – 2013.12, VGHTPE**)

- Carbapenemase: 29.5%, 31/105 (A: 27 KPC-2, 1 KPC-3, B:2 IMP-8, 1 VIM-1)
- bal_{AmpC} or ESBL = 70.5%, 74/105 (55 Amp-C β-lactamase with all DHA-1, ESBL with 38 CTX-M-9, 12 CTX-M-1, 49 SHV)

- In-hospital mortality for CR-KP infection = 63.3% (31/49)

Wu PF. *Sci Rep* 2016;6:32665

SCIENTIFIC REPORTS

OPEN

Carbapenem Nonsusceptible *Klebsiella pneumoniae* in Taiwan: Dissemination and Increasing Resistance of Carbapenemase Producers During 2012–2015

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Sheng-Kang Chiu[1], Ling Ma[2], Ming-Chin Chan[3], Yi-Tsung Lin[4], Chang-Phone Fung[5], Tsu-L
Wu[6], Yin-Ching Chuang[7], Po-Liang Lu[8], Jann-Tay Wang[9], Jung-Chung Lin[1] & Kuo-Ming Ye

Before 2011, the prevalence rates of carbapenemase-producing *Klebsiella pneumoniae* (CPKP) amc carbapenem nonsusceptible *K. pneumoniae* (CnSKP) isolates were below 10% in Taiwan. The study presents the dissemination and increased antimicrobial resistance of CPKP from January 2012 to A 2015, as shown by Taiwanese multicenter surveillance. Isolates with minimum inhibitory concentr (MICs) of >1 μg/mL for imipenem or meropenem were collected, screened for various carbapenem genes by PCR, and tested for antimicrobial susceptibility. Among 1,457 CnSKP isolates, 1,250 wer collected from medical centers. The CnSKP prevalence in medical centers increased by 1.7-fold dur the study. Among all CnSKP isolates, 457 were CPKP. The CPKP rate among CnSKP increased by 1.5 fold and reached 36.8% in 2015. The CPKP nonsusceptibility rate to aztreonam, fluoroquinolones, a aminoglycosides increased yearly. Six CPKP isolates carried dual carbapenemase genes. Three Ambl classes were identified in 451 isolates with a single carbapenemase: classes A (315 bla_{KPC-2}, 2 bla_{KPC-3}, 2 bla_{KPC-17}, 2 bla_{KPC-34}), B (26 bla_{IMP-8}, 2 bla_{NDM-1}, 36 bla_{VIM-1}), and D (40 bla_{OXA-48}). The bla_{OXA-48} rate among CPKP increased by 6-fold over three years. Most KPC and OXA-48 producers were ST11. CnSKP was increasingly prevalent, owing to CPKP dissemination. Additionally, CPKP became more resistant during the study period.

Klebsiella pneumoniae is a common cause of bacteremia, pneumonia, urinary tract infection, and liver abscess[1]. β-lactam antibiotics are often deemed the primary therapeutic option for these infections[2]. Among the β-lactams, carbapenems are considered the antibiotics of last resort[3]. Once *K. pneumoniae* isolates become nonsusceptible to carbapenems, they are often resistant to all currently available β-lactams and frequently resistant to non-β-lactam antibiotics[4]. In the clinical context, the emergence of carbapenem non-susceptible *K. pneumoniae* (CnSKP) poses a serious threat to patient survival because CnSKP infections have limited treatment options and are associated with high mortality[5].

Among the many mechanisms conferring resistance to carbapenems, carbapenemases can efficiently hydrolyze carbapenems and have become an important cause of antimicrobial resistance[6]. Many carbapenemases have

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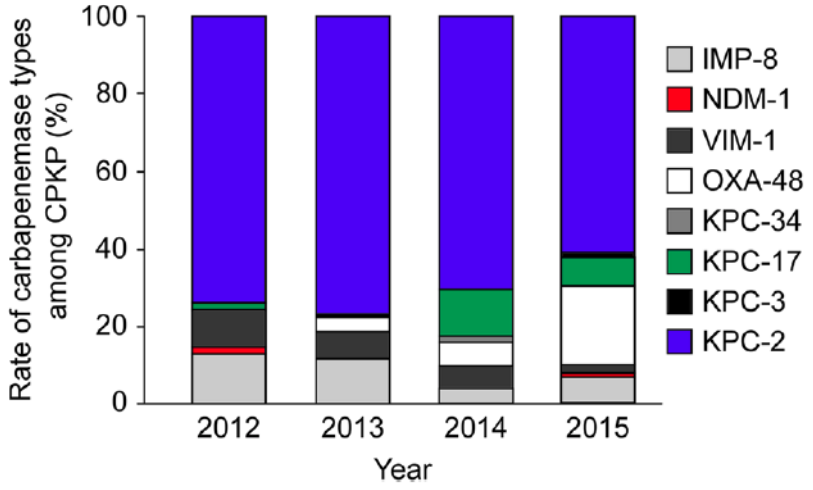
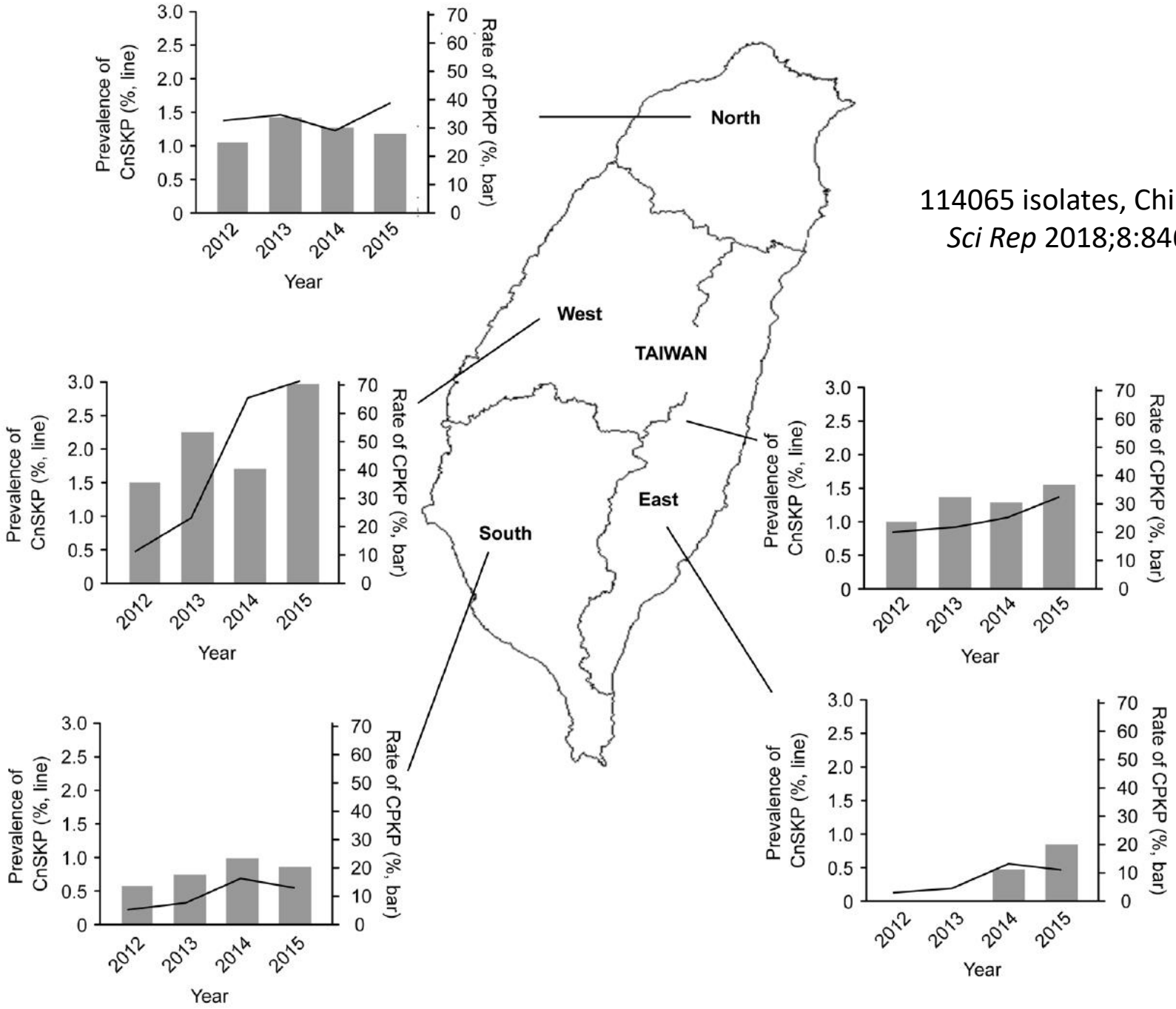
Chiu SK. *Sci Rep* 2018;8:8468

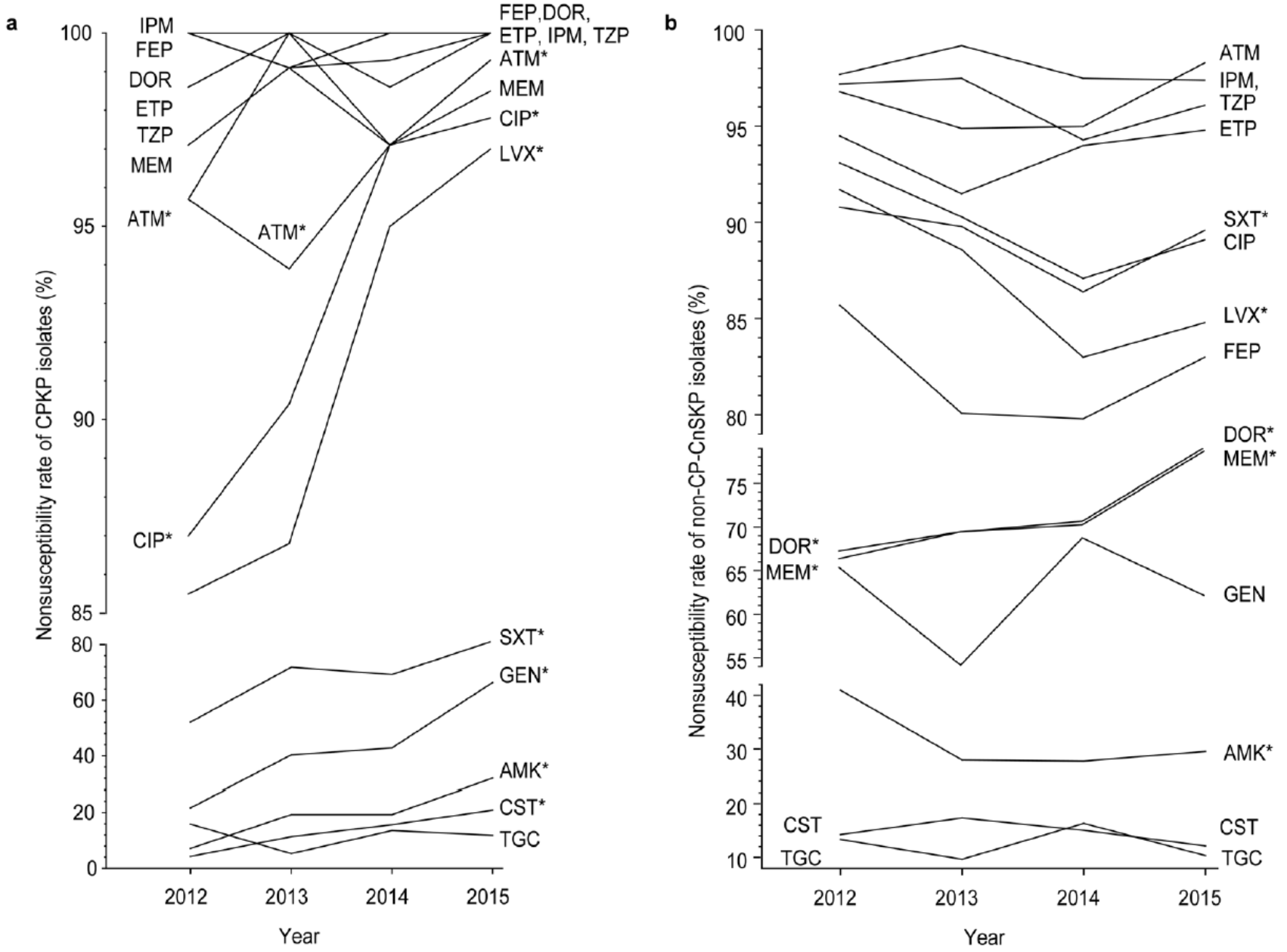
1457 CR-KP (1250 from medical centers) (**2012.1 – 2015.8**)

- Carbapenemase: 31.4%, 457/1457 (A: 315 KPC-2, 2 KPC-3, 2 KPC-34; B : 2 NDM-1, 26 IMP-8, 36 VIM-1; D = 40 bla_{OXA-48})
- Non-CP-CnSKP = 1000/1457





114065 isolates, Chiu SK.
Sci Rep 2018;8:8468



Chiu SK. *Sci Rep* 2018;8:8468

Infection and Drug Resistance

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ORIGINAL RESEARCH

Resistance mechanisms and molecular epidemiology of carbapenem-nonsusceptible *Escherichia coli* in Taiwan, 2012-2015

This article was published in the following Dove Press journal:
Infection and Drug Resistance

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L Kristopher Siu[2]
Jann-Tay Wang[3]
Tsu-Lan Wu[4]
Yu-Hui Chen[5,6]
Yin-Ching Chuang[7,8]
Jung-Chung Lin[9]
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Purpose: This study aimed to investigate the resistance mechanisms and molecular epidemiology of carbapenem-nonsusceptible *Escherichia coli* (CnsEC) in Taiwan.

Patients and methods: From 2012 to 2015, 237 *E. coli* isolates with minimum inhibitory concentrations of imipenem or meropenem >1 μg/mL were collected in a nationwide surveillance and subjected to polymerase chain reaction (PCR) for carbapenemase, AmpC-type β-lactamase, and extended spectrum β-lactamase (ESBL) genes. We evaluated outer membrane proteins (OmpF and OmpC) loss and conducted multilocus sequence typing and pulsed-field gel electrophoresis (PFGE). Isolates that were resistant to all carbapenems were designated as pan-carbapenem-resistant *E. coli* (pCREC) in this study.

Results: The predominant resistance mechanism of CnsEC in Taiwan was the CMY-2 β-lactamase in combination with OmpF and OmpC loss. Sequence type 131 was the most prevalent type (29.2%). Among 237 CnsEC isolates, 106 (44.7%) isolates were pCREC and 18 (7.59%) produced carbapenemase. The prevalence of carbapenemases increased from 6% in 2012 to 11.36% in 2015. Various carbapenemases including KPC-2, IMP-8, NDM-1, NDM-5, VIM-1, OXA-48, and OXA-181 were identified, with NDM-1 being the most common (38.9%) carbapenemase. Comparison between pCREC and non-pCREC among the non-carbapenemase-producing CnsEC isolates revealed SHV, CMY, co-carriage of SHV and CTX-M and concurrent loss of both OmpF and OmpC were more commonly detected in the pCREC group. PFGE revealed no nationwide clonal spread of carbapenemase-producing *E. coli*.

Conclusion: NDM-1 was the most common carbapenemase and combination of CMY-2 and concurrent OmpF and OmpC porin loss was the most prevalent resistance mechanism in CnsEC in Taiwan.

Keywords: multidrug resistance, carbapenemase, Enterobacteriaceae, epidemiology

Introduction

Escherichia coli is one of the most common human pathogen, the major etiology of community-acquired urinary tract infection and a major nosocomial Gram negative bacteria.[1,2] In the late 1990s, extended spectrum β-lactamase (ESBL)-producing *E. coli* infections emerged.[3] Since the worldwide propagation of ESBL-producing *Enterobacteriaceae*, carbapenems have been the prevailing treatment of such infections. Carbapenem resistance in *Enterobacteriaceae* was relatively uncommon before 2000. Nevertheless, the prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) rose markedly in the following decade.[4] The United States Centers for Disease Control and Prevention (CDC) listed CRE as an urgent threat that requires intensive monitoring

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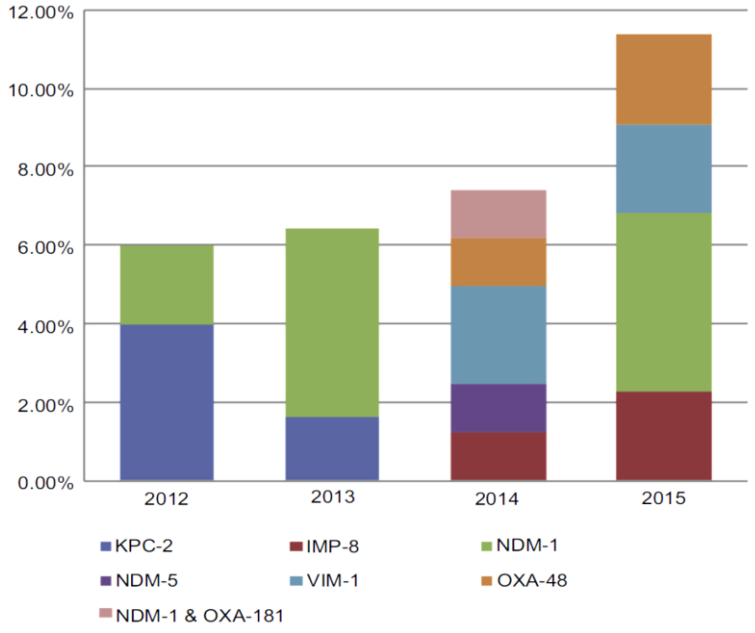
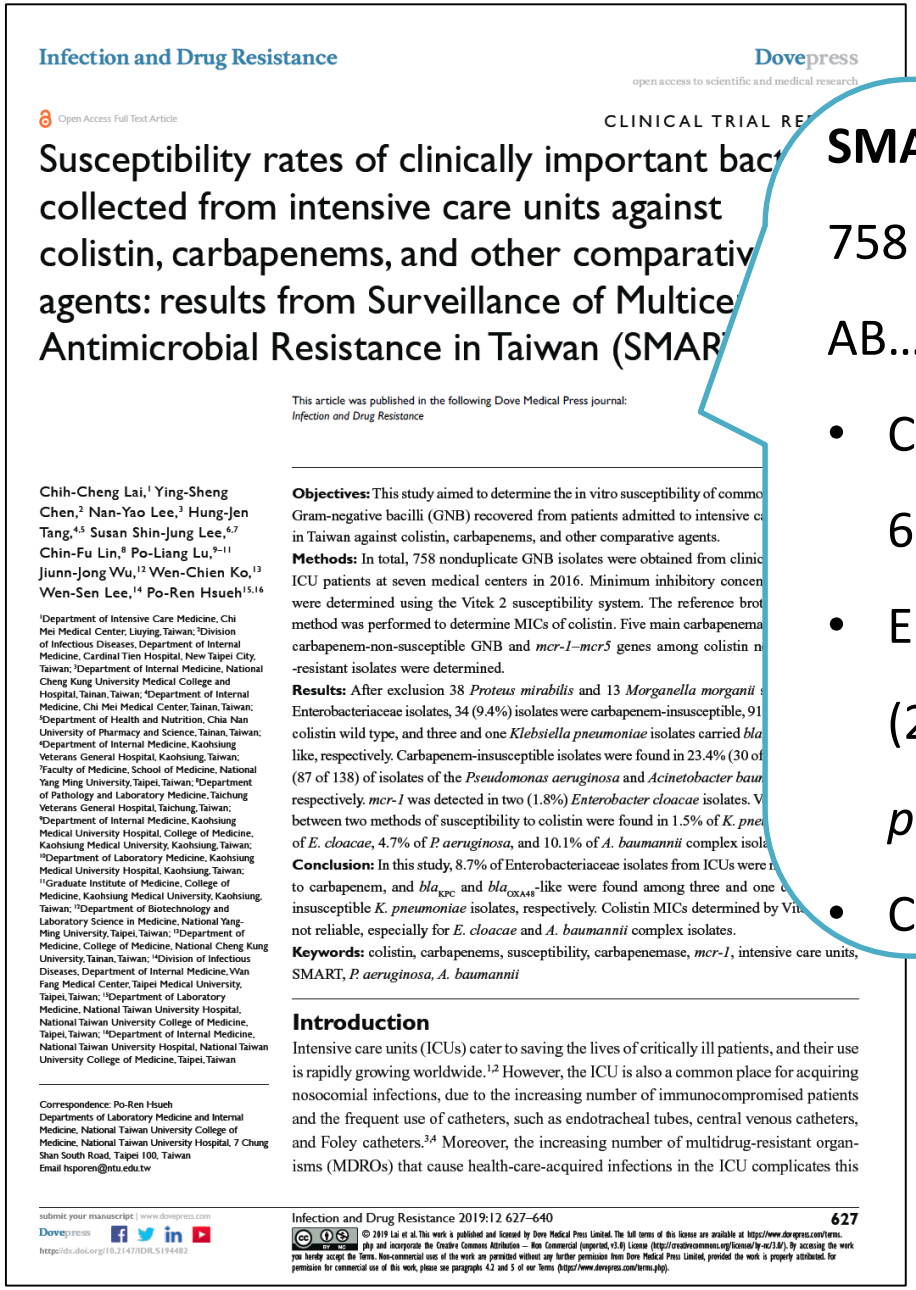
237 CR-E coli (12 medical centers, 9 LH)

(**2012.1 – 2015.9**)

- Carbapenemase: 7.59%, 18/237 (A : 3 KPC-2; B : 7 NDM-1, 1 NMD-5, 2 IMP-8, 3 VIM-1; D : 2 bla_{OXA-48})
- Non-CP-CnSKP = 86.5% AmpC, 43.5% ESBL



Chang YT. *Infect Drug Resist* 2019;12:2113



Infection and Drug Resistance

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CLINICAL TRIAL RE

Susceptibility rates of clinically important bact
collected from intensive care units against
colistin, carbapenems, and other comparativ
agents: results from Surveillance of Multice
Antimicrobial Resistance in Taiwan (SMAR

This article was published in the following Dove Medical Press journal:
Infection and Drug Resistance

Chih-Cheng Lai,[1] Ying-Sheng Chen,[2] Nan-Yao Lee,[3] Hung-Jen Tang,[4,5] Susan Shin-Jung Lee,[6,7] Chin-Fu Lin,[8] Po-Liang Lu,[9–11] Jiunn-Jong Wu,[12] Wen-Chien Ko,[13] Wen-Sen Lee,[14] Po-Ren Hsueh[15,16]

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Email hsporen@ntu.edu.tw

Objectives: This study aimed to determine the in vitro susceptibility of commo
Gram-negative bacilli (GNB) recovered from patients admitted to intensive c
in Taiwan against colistin, carbapenems, and other comparative agents.
Methods: In total, 758 nonduplicate GNB isolates were obtained from clinic
ICU patients at seven medical centers in 2016. Minimum inhibitory concen
were determined using the Vitek 2 susceptibility system. The reference brot
method was performed to determine MICs of colistin. Five main carbapenema
carbapenem-non-susceptible GNB and *mcr-1–mcr5* genes among colistin n
-resistant isolates were determined.
Results: After exclusion 38 *Proteus mirabilis* and 13 *Morganella morganii*
Enterobacteriaceae isolates, 34 (9.4%) isolates were carbapenem-insusceptible, 91
colistin wild type, and three and one *Klebsiella pneumoniae* isolates carried *bla*
like, respectively. Carbapenem-insusceptible isolates were found in 23.4% (30 of
(87 of 138) of isolates of the *Pseudomonas aeruginosa* and *Acinetobacter bau*
respectively. *mcr-1* was detected in two (1.8%) *Enterobacter cloacae* isolates. V
between two methods of susceptibility to colistin were found in 1.5% of *K. pne*
of *E. cloacae*, 4.7% of *P. aeruginosa*, and 10.1% of *A. baumannii* complex isol
Conclusion: In this study, 8.7% of Enterobacteriaceae isolates from ICUs were
to carbapenem, and bla_{KPC} and bla_{OXA48}-like were found among three and one
insusceptible *K. pneumoniae* isolates, respectively. Colistin MICs determined by Vi
not reliable, especially for *E. cloacae* and *A. baumannii* complex isolates.

Keywords: colistin, carbapenems, susceptibility, carbapenemase, *mcr-1*, intensive care units, SMART, *P. aeruginosa, A. baumannii*

Introduction

Intensive care units (ICUs) cater to saving the lives of critically ill patients, and their use is rapidly growing worldwide.[1,2] However, the ICU is also a common place for acquiring nosocomial infections, due to the increasing number of immunocompromised patients and the frequent use of catheters, such as endotracheal tubes, central venous catheters, and Foley catheters.[3,4] Moreover, the increasing number of multidrug-resistant organisms (MDROs) that cause health-care-acquired infections in the ICU complicates this

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http://dx.doi.org/10.2147/IDR.S194482

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SMART 2016, 7 ICU of medical centers

758 GNB (121 E coli, 137 KP, 128 PA, 138 AB…)

- CR-E 9.4%, 34/361; CR-PA 20.3%, CR-AB 62.3%
- Enterobaceriaceae: CR- *E. cloacae* (21.6%), *C. freundii* (20.0%), *K. pneumoniae* (13.1%), *E. coli* (2.5%)
- CP-KP: 3 bla_{KPC}, 1 bla_{OXA48} (0.5%, 4/758)

Lai CC. *Infect Drug Resist* 2019;12:627

Infection and Drug Resistance

Open Access Full Text Article

ORIGINAL

In vitro activity of ceftazidime–avibactam, ceftolozane–tazobactam, and other comp agents against clinically important Gram-nega bacilli: results from the 2017 Surveillance of Multicenter Antimicrobial Resistance in Taiwa (SMART)

This article was published in the following Dove Press journal:
Infection and Drug Resistance

Shio-Shin Jean,[1,2] Min-Chi Lu,[3] Zhi-Yuan Shi,[4] Shu-Hui Tseng,[5] Ting-Shu Wu,[6] Po-Liang Lu,[7] Pei-Lan Shao,[8] Wen-Chien Ko,[9] Fu-Der Wang,[10,11] Po-Ren Hsueh[12,13]

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Objectives: We investigated the in vitro antimicrobial susceptibilities of clinically
Gram-negative bacteria (GNB) from 16 major teaching hospitals in Taiwan in 2017.
Materials and methods: *Escherichia coli* (n=686) and *Klebsiella pneumoniae* bloodstream
isolates (n=673), non-typhoid *Salmonella* (NTS; n=221) from
(n=21) from fecal samples, and *Neisseria gonorrhoeae* (n=129
collected. Antibiotic minimum inhibitory concentrations (MIC
microdilution method. Alleles encoding *K. pneumoniae* carb
metallo-β-lactamases (NDMs), Verona integron-encoded metallo
48-like, and *mcr*-1-5 genes were detected by molecular method
Results: Five (0.7%) *E. coli* isolates harbored *mcr*-1 alleles. T
four (0.6%), and one (0.15%) *K. pneumoniae* isolates contain
bla $_{NDM}$, respectively. Three (1.4%) NTS and no *Shigella* isolat
one (10.5%) *K. pneumoniae* isolates displayed non-susceptibi
Phenotypically extended-spectrum β-lactamase (ESBL)-pr
showed significantly higher rates of ertapenem, tigecycline, ar
TAZ) NS (40.2%, 16.3%, and 71%–80%, respectively) than
phenotypes (5.4%, 0.7%, and 18%–28%, respectively). All ph
coli isolates were ceftazidime–avibactam (CAZ–AVB) suscep
K. pneumoniae isolates showed CAZ–AVB NS. Hospital-acqu
significantly less susceptible to ertapenem and CLZ–TAZ than
Conclusion: Third-generation cephalosporins remain the
Shigella, and gonococcal infections in Taiwan. Hospital-acq
producing *K. pneumoniae* are a heavy resistance burden in T
Keywords: Enterobacteriaceae, *Neisseria gonorrhoeae*, e
carbapenemase, ceftolozane–tazobactam, ceftazidime–aviba

Introduction

Infections that become septicemic conditions, regardles
community or hospitals, are typically associated with

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Infection and Drug Resistance 2018:11 1983–1992

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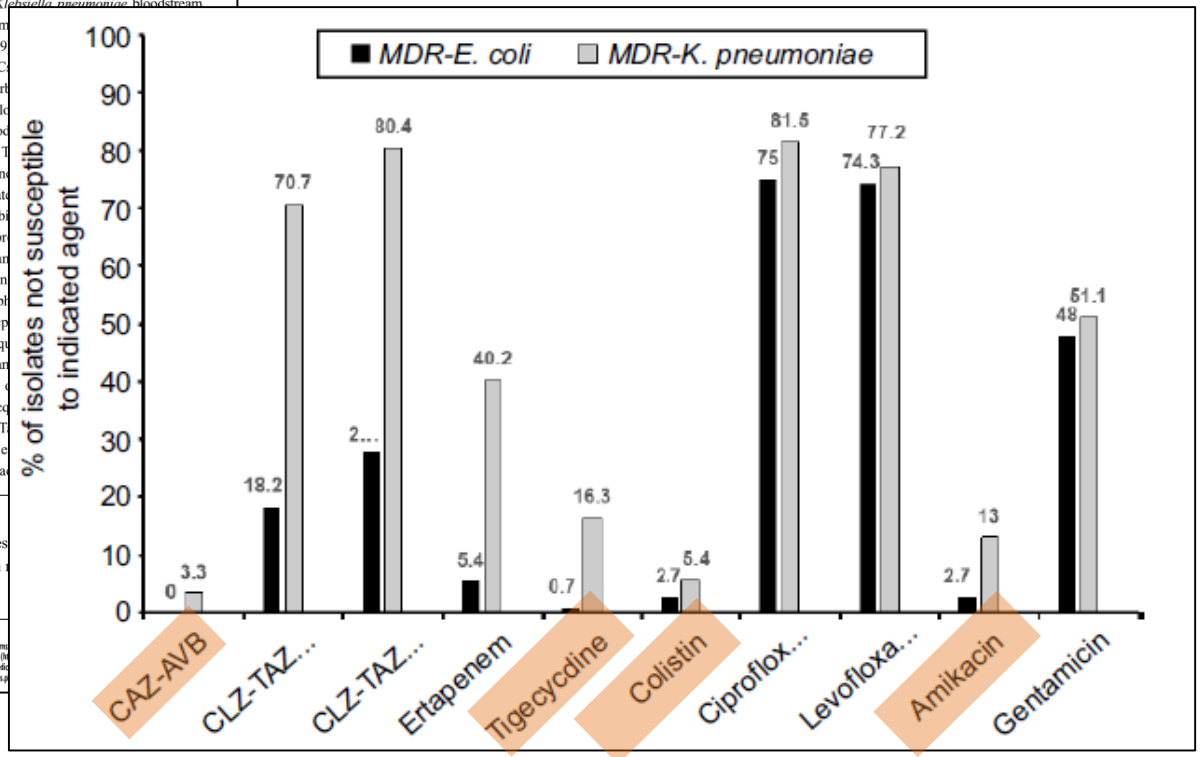
SMART 2017, 16 centers

Bloodstream CR-E. coli = 2.0%, 14/686

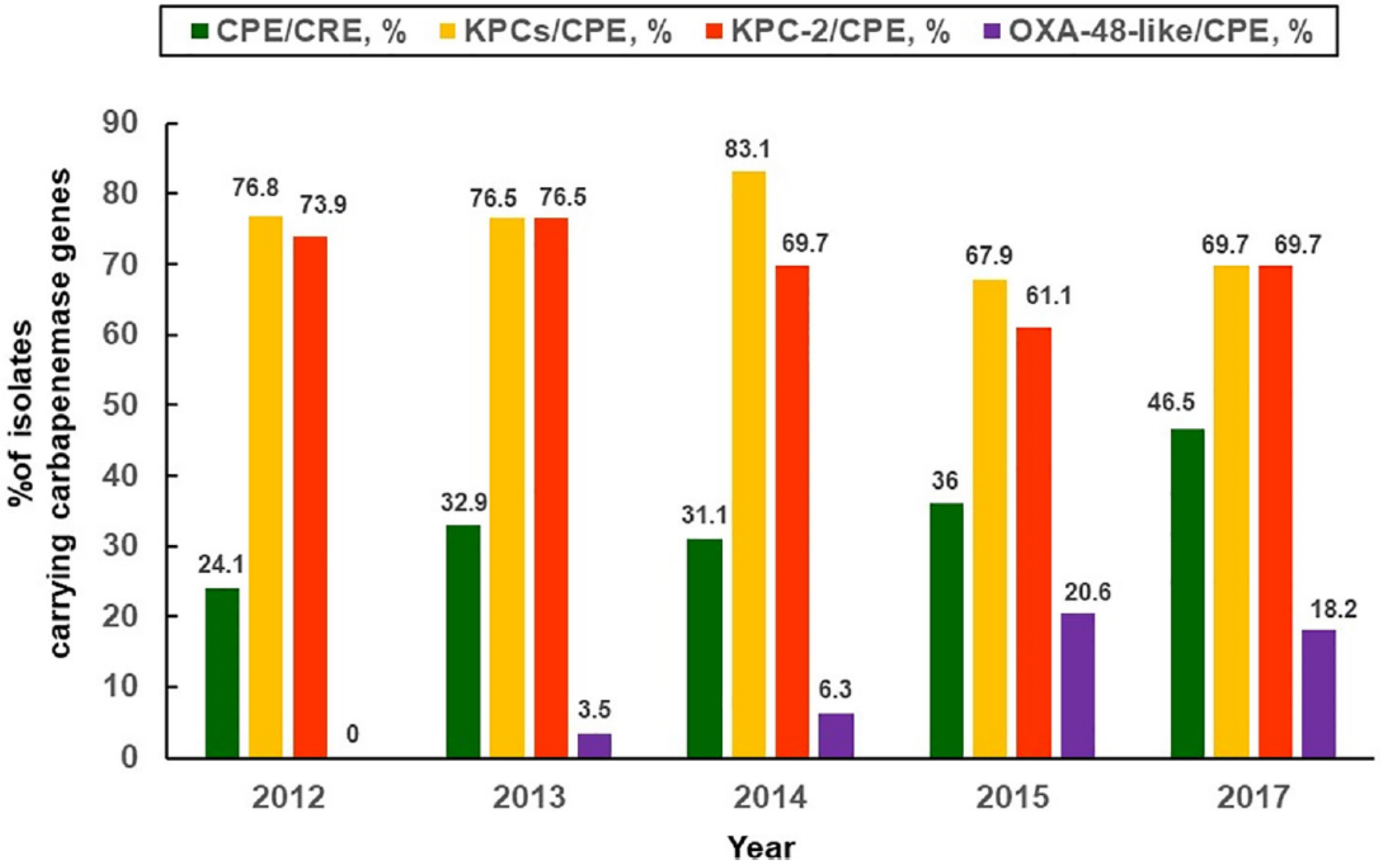
Bloodstream CR-KP = 10.5%, 71/673

85 bloodstream CR-E (14 E coli, 71 KP)

- Carbapenemase: 41.2%, 35/85



Jean SS. *Infect Drug Resist* 2018



Jean SS. *Infect Drug Resist* 2018;11:1983 (SMART **2017**) &
Chiu SK. *Sci Rep* 2018;8:8468 (**2012.1 – 2015.8) for CR-KP**

International Journal of Antimicrobial Agents 54 (2019) 318–328

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journal homepage: www.elsevier.com/locate/ijantimicag

Nationwide surveillance of antimicrobial resistance among cl important Gram-negative bacteria, with an emphasis on carb and colistin: Results from the Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART) in 2018

Yu-Lin Lee[a], Min-Chi Lu[b], Pei-Lan Shao[c], Po-Liang Lu[d], Yen-Hsu Chen[d], Shu-H Wen-Chien Ko[f], Chi-Ying Lin[g], Ting-Shu Wu[h], Muh-Yong Yen[i], Lih-Shinn Wang Chang-Pan Liu[k], Wen-Sen Lee[l], Zhi-Yuan Shi[m], Yao-Shen Chen[n], Fu-Der Wang Shu-Hui Tseng[p], Chao-Nan Lin[q], Yu-Hui Chen[r], Wang-Huei Sheng[s], Chun-Ming Ming-Huei Liao[u], Po-Ren Hsueh[s,v,*]

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2018 SMART, 16 sites

1184 bloodstream GNB (398 E coli, 346 KP, 252 PA, 188 AB, 230 Salmonella, 18 Shigella)

- CR-E coli 2.8%, CR-KP 9.0%, CR-PA 10.3%, CR-AB 43.6%, CR-salmonella spp 0.4%

	Prevalence [*n* (%)]				
	E. coli (*n* = 398)	*K. pneumoniae* (*n* = 346)	*Salmonella* spp. (*n* = 230)	*P. aeruginosa* (*n* = 252)	*A. baumannii* complex
Carbapenem-non-susceptible	11 (2.8)	31 (9.0)	1 (0.4)	26 (10.3)	82 (43.6)
bla_{KPC}	0	15 (48.4)	0	0	0
bla_{OXA-48}	0	2 (6.5)	0	0	0
bla_{NDM-1}	1 (9.1)	0	0	0	0
bla_{VIM}	0	2 (6.5)	0	0	0
High colistin MIC[a]	2 (0.5)	22 (6.4)	82 (35.7)	22 (8.7)	16 (8.5)
mcr-1	1 (50.0)	2 (9.1)	3 (3.7)	0	0

MIC, minimum inhibitory concentration.
[a] An MIC ≥ 2 mg/L among Enterobacteriaceae and an MIC ≥ 4 mg/L among *P. aeruginosa* and *A. baumannii* complex isolates.

Lee YL. *Int J Antimicro Agents* 2019;54:318

European Journal of Clinical Microbiology & Infectious Diseases (2018) 37:651–659
https://doi.org/10.1007/s10096-017-3156-8

ORIGINAL ARTICLE

Treatment outcome of non-carbapenemase-producing carbapenem-resistant *Klebsiella pneumoniae* infections: a mu study in Taiwan

Chin-Fang Su[1] · Chien Chuang[1] · Yi-Tsung Lin[2,3] · Yu-Jiun Chan[2,4,5] · Jung-Chung Lin[6] · Po-Liang
Ching-Tai Huang[8] · Jann-Tay Wang[9] · Yin-Ching Chuang[10] · L. Kristopher Siu[11] · Chang-Phone Fung

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Abstract

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections are associated with high mortality, and ex
treatment are usually based on carbapenemase-producing strains. Non-carbapenemase-producing CRKP is of c
but relevant studies are lacking. This nationwide study aimed to evaluate the outcome of antimicrobial therapy in
carbapenemase-producing CRKP infections. Patients with non-carbapenemase-producing CRKP infections we
hospitals during January 2013 to December 2014 in Taiwan. Carbapenem resistance was defined as reduced st
minimum inhibitory concentration of ≥2 mg/L for imipenem or meropenem. The resistance mechanisms of CR
analyzed, and the clinical data of these patients were collected retrospectively. Independent risk factors of 14-day
determined by Cox regression analysis. A total of 99 patients with non-carbapenemase-producing CRKP infections we
and 14-day mortality was 27.3%. Among 67 patients treated with appropriate antimicrobial therapy, most ($n = 61$) patients received
monotherapy. The 14-day mortality was lower in patients treated with appropriate monotherapy (21.3%) than in the
inappropriate therapy (37.5%). The multivariate regression model identified monotherapy (hazard ratio [HR], 0.30; 95%
interval [CI], 0.13–0.71; $P = 0.005$) as protective factor, and APACHE II scores (HR, 1.09; 95% CI, 1.01–1.18; P
factor associated with 14-day mortality. Tigecycline, colistin, and carbapenem were the most commonly used drug
This study provides evidence supporting the efficacy of monotherapy in the treatment of non-carbapenemase
infections, and provides a future target for antibiotics stewardship for CRKP infection.

Chin-Fang Su and Chien Chuang contributed to this manuscript equally.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10096-017-3156-8) contains supplementary material, which is available to authorized users.

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Research Institutes, Miaoli, Taiwan

[12] Division of Infectious Diseases, Sijhih Cathy
Taipei City, Taiwan

99 non-CP-CRKP (2013.1-2014.12, 16 sites)

- ESBL: 88 SHV, 60 TEM, 45 CTX-M, 17 OXA-1.
- AmpC: 60 DHA-1, 5 CMY-2.
- 54 loss of OmpK35/36 porin, 36 OmpK35, 4 OmpK36

- 14-day mortality 27.3%
- 67.7% (67/99) appropriate antibiotic tx
- 61.6% (61/99) received monotherapy (Tige, Colistin, Carbapenem)
- Independent factors for mortality: monotherapy, appropriate antibiotics & APACHEII

Su CF. *Eur J Clin Microb Infect Dis* 2018;37:651

Polymyxins

- Polymycin B, Polymycin E (colistin, prodrug-colistimethate sodium CMS)
- Mechanism: bind to negatively charged phosphate moieties in the lipid A fracture of LPS (GNB), disruption of cell membrane
- A very narrow therapeutic window: 2 ųg/ml
- Nephrotoxic (2.5ug/ml) and neurotoxic
- 13.5-31.7% of colistin resistant CRE-KP (e.g. modification in lipid A, overexpression protein OprH, alterations in the mgrB gene…)

Landersdorfer CB *Semin Respir Crit Care Med* 2015;36:126. Pena I *Int J Antimicrob Agent* 2014;43:460

Tigecycline

- Mechanism: bacteriostatic, interferes with protein synthesis by binding to 30S ribosomal subunit
- A large volume of distribution (7-10L/kg), 40h of half-life, excreted into feces via bile, very little excreted in urine
- Dosage: 0.60ug/ml after a 100mg infusion, activity based on AUC/MIC>12.5
- High dose : 100mg q12h for VAP
- CRE-KPC/MBLs: MIC_{90} = 1µg/ml, in combination with colistin and carbapenem
- Resistance: multidrug efflux pump (mutation in ramA….)

Castanheira M *Antimicrob Agents Chemother* 2008;52:570. De Pascale G *Crit Care* 2014;18:R90

Fosfomycin

- Mechanism: inhibits the first step in synthesis of peptidoglycan by blocking the formation of N-acetylmuramic acid through competitive inhibition of phosphoenol pyruvate syndthetase.
- Antimicrobial spectrum: GPC, GNB
- >50% bioavailable after oral administration, largely excreted unchanged into the urine (e.g. UTI, prostatitis)
- 4g q6h with high-serum concentration
- 20% resistance rate (e.g. fosfomycin-inactivating enzyme..)
- Combination use only

Gobernade M. Rev Esp Quimioter 2003;16:15, Michalopoulos AS Int J Infect Dis 2011;15:e732. Pontikis K. Int J Antimicrob Agents 2014;43:52

Aminoglycosides

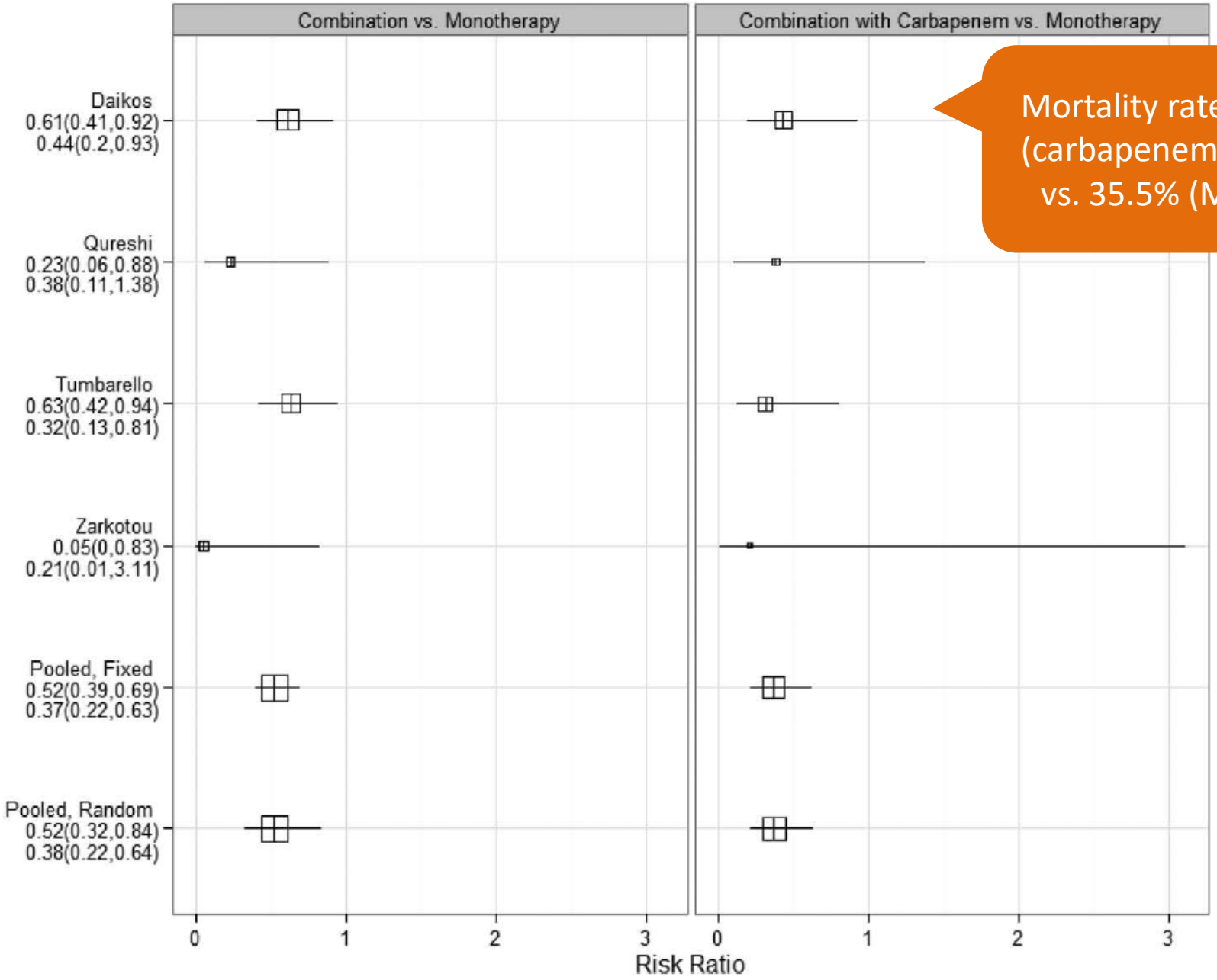
- Mechanism: inhibition of protein synthesis (reduction in carbapenaemase production) + beta-lactam (cell wall synthesis inhibitor)
- Nephrotoxic and ototoxic

Garcia-Salguero C *Antimicrob Angents Chemother* 2015;59:5959

Combination or Monotherapy

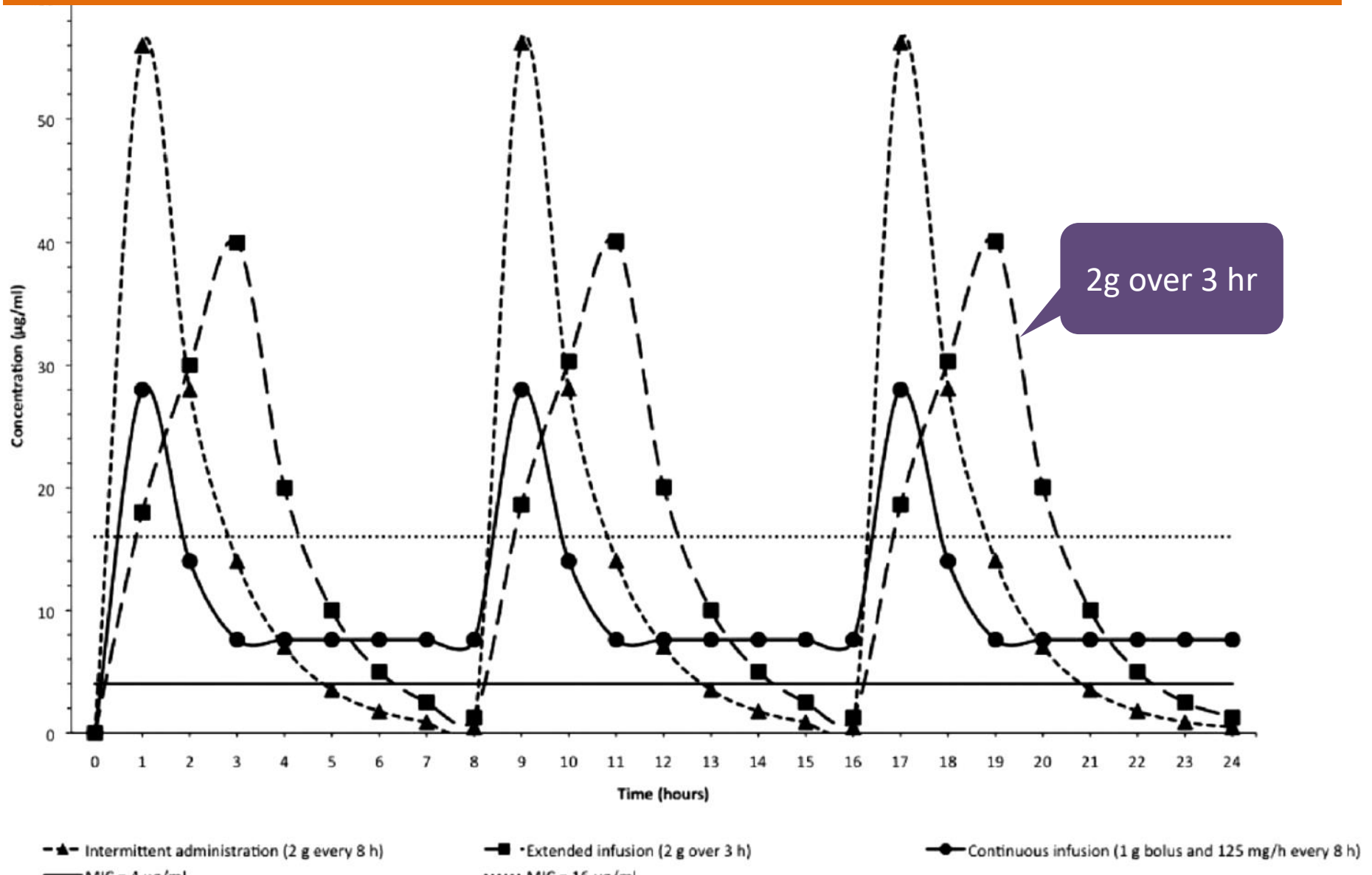
- **Carbapenem** with colistin (polymycin B): synergy rate 55%-67%
- **Carbapenem** + fosfomycin: synergy 70%
- **Colistin** (polymycin B) + rifampin, doxycycline, tigecycline
- **Ertapenem + doripenem**

Zusman O Antimicrob Agents Chemother 2013;57:5104. Jernigan MG Antimicrob Agents Chemother 2012;56:3395. Souli M Antimicrob Agnets Chemother 2011;55:2395



Expert Opinion Pharmacotherapy 2016;17:761. Daikos GL *Antimicrob Agents Chemother* 2014;58:2322

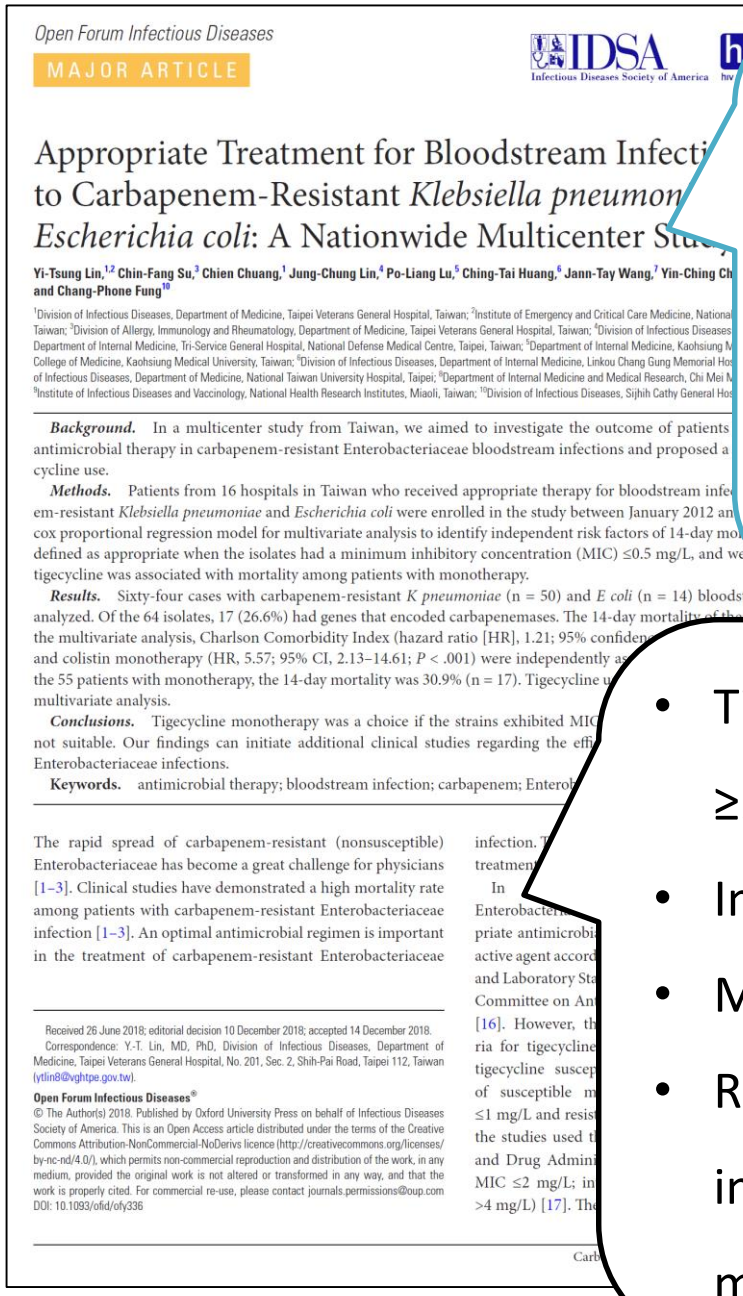
Concentration of meropenem: bactericical acitivity by concentration above MIC for 40-50% of time



Expert Opinion Pharmacotherapy 2016;17:761.

Organism	Resistant to	Primary treatment	Alternative treatment	Comments
ESBL Produced by Enterobacteriaceae, PA	All ceph, FQ, AG, TMP-SMX	MER or IMP	Ceftolozane-tazobactam **Ceftazidime-avibactam** Meropenem-vaborbactam	Pip-tazo discordance For UTI: Nitrofurantoin, Fosfomycin
OXA-48 producing Enterobacteriaceae	All PCNs, FQ, AG, TMP-SMX	If sensitive: Cefepime, Ceftazidime	If critically: **Ceftazidime-avibactam, Aztreonam**	Mediterranean sea
KPC producing Enterobacteriaceae	All PCNs, cepha, aztreonam, carbapnems, FQ, AG, TMP-SMX	**Ceftaz-avi, meropenem-vaborbactam**	MER + **Polymycin B**	For pneumonia: add nebulized colistin 50-75mg bid ERTA + MER (JAC 69:1718,2015)
Metallo-carbapenemase		Ceftaz-avi + aztreonam		

Table 5B: Treatment options for MDR (熱病2019)



Open Forum Infectious Diseases

MAJOR ARTICLE

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Appropriate Treatment for Bloodstream Infecti… to Carbapenem-Resistant *Klebsiella pneumon… Escherichia coli*: A Nationwide Multicenter St…

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Background. In a multicenter study from Taiwan, we aimed to investigate the outcome of patients … antimicrobial therapy in carbapenem-resistant Enterobacteriaceae bloodstream infections and proposed a … cycline use.

Methods. Patients from 16 hospitals in Taiwan who received appropriate therapy for bloodstream infe… em-resistant *Klebsiella pneumoniae* and *Escherichia coli* were enrolled in the study between January 2012 an… cox proportional regression model for multivariate analysis to identify independent risk factors of 14-day mo… defined as appropriate when the isolates had a minimum inhibitory concentration (MIC) ≤0.5 mg/L, and we … tigecycline was associated with mortality among patients with monotherapy.

Results. Sixty-four cases with carbapenem-resistant *K pneumoniae* (n = 50) and *E coli* (n = 14) bloodstream infections were analyzed. Of the 64 isolates, 17 (26.6%) had genes that encoded carbapenemases. The 14-day mortality of these cases was 31.3%. In the multivariate analysis, Charlson Comorbidity Index (hazard ratio [HR], 1.21; 95% confiden… and colistin monotherapy (HR, 5.57; 95% CI, 2.13–14.61; $P < .001$) were independently as… the 55 patients with monotherapy, the 14-day mortality was 30.9% (n = 17). Tigecycline u… multivariate analysis.

Conclusions. Tigecycline monotherapy was a choice if the strains exhibited MIC… not suitable. Our findings can initiate additional clinical studies regarding the effi… Enterobacteriaceae infections.

Keywords. antimicrobial therapy; bloodstream infection; carbapenem; Enterob…

The rapid spread of carbapenem-resistant (nonsusceptible) Enterobacteriaceae has become a great challenge for physicians [1–3]. Clinical studies have demonstrated a high mortality rate among patients with carbapenem-resistant Enterobacteriaceae infection [1–3]. An optimal antimicrobial regimen is important in the treatment of carbapenem-resistant Enterobacteriaceae infection. T… treatmen… In Enterobacteri… priate antimicrobi… active agent accord… and Laboratory Sta… Committee on An… [16]. However, th… ria for tigecycline… tigecycline suscep… of susceptible m… ≤1 mg/L and resist… the studies used t… and Drug Admini… MIC ≤2 mg/L; in… >4 mg/L) [17]. The…

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Carb…

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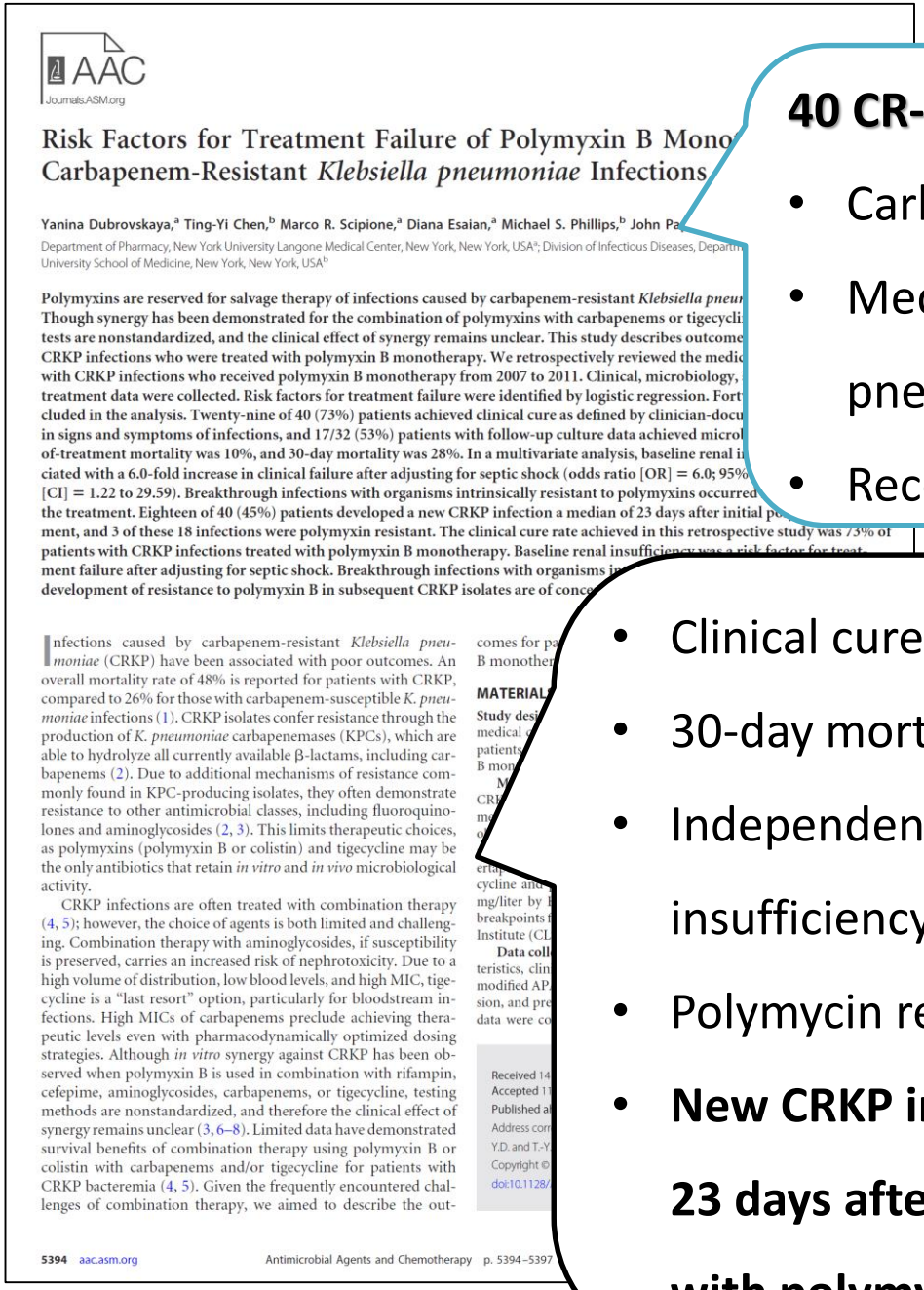
64 CR-E BSI (50 KP, 14 E.coli, 16 sites, **2012.1-2016.6**)

- Carbapenemases: 26.6% (17/64): KP = A: 11 KPC-2, 2 KPC-3, 2 KPC-34; B : 1 NDM-1, 8 IMP-8, 2 VIM-1; D = 1 bla_{OXA-48}. E. coli = 1NDM-1

- Tige MIC: **71.9% ≥0.5mg/L**, 25% 1-2mg/L, 3.1% ≥2mg/L
- Imipenem/meropenem **MIC: 75% ≥8mg/L**
- Monotherapy 86% (55/64) = CLTS 38% ,Tige 20%
- Risk for 14-D mortality: Charison comorbidity index AHR 1.21 (1.03-1.42, p = 0.022), colistin monotherapy AHR 5.57 (2.13-14.61, p <0.001)



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Risk Factors for Treatment Failure of Polymyxin B Mono
Carbapenem-Resistant *Klebsiella pneumoniae* Infections

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**Polymyxins are reserved for salvage therapy of infections caused by carbapenem-resistant *Klebsiella pneu*
Though synergy has been demonstrated for the combination of polymyxins with carbapenems or tigecycli
tests are nonstandardized, and the clinical effect of synergy remains unclear. This study describes outcome
CRKP infections who were treated with polymyxin B monotherapy. We retrospectively reviewed the medic
with CRKP infections who received polymyxin B monotherapy from 2007 to 2011. Clinical, microbiology,
treatment data were collected. Risk factors for treatment failure were identified by logistic regression. Fort
cluded in the analysis. Twenty-nine of 40 (73%) patients achieved clinical cure as defined by clinician-docu
in signs and symptoms of infections, and 17/32 (53%) patients with follow-up culture data achieved microl
of-treatment mortality was 10%, and 30-day mortality was 28%. In a multivariate analysis, baseline renal i
ciated with a 6.0-fold increase in clinical failure after adjusting for septic shock (odds ratio [OR] = 6.0; 95%
[CI] = 1.22 to 29.59). Breakthrough infections with organisms intrinsically resistant to polymyxins occurred
the treatment. Eighteen of 40 (45%) patients developed a new CRKP infection a median of 23 days after initial p
ment, and 3 of these 18 infections were polymyxin resistant. The clinical cure rate achieved in this retrospective study was 73% of
patients with CRKP infections treated with polymyxin B monotherapy. Baseline renal insufficiency was a risk factor for treat
ment failure after adjusting for septic shock. Breakthrough infections with organisms in
development of resistance to polymyxin B in subsequent CRKP isolates are of conc**

Infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) have been associated with poor outcomes. An overall mortality rate of 48% is reported for patients with CRKP, compared to 26% for those with carbapenem-susceptible *K. pneumoniae* infections (1). CRKP isolates confer resistance through the production of *K. pneumoniae* carbapenemases (KPCs), which are able to hydrolyze all currently available β-lactams, including carbapenems (2). Due to additional mechanisms of resistance commonly found in KPC-producing isolates, they often demonstrate resistance to other antimicrobial classes, including fluoroquinolones and aminoglycosides (2, 3). This limits therapeutic choices, as polymyxins (polymyxin B or colistin) and tigecycline may be the only antibiotics that retain *in vitro* and *in vivo* microbiological activity.

CRKP infections are often treated with combination therapy (4, 5); however, the choice of agents is both limited and challenging. Combination therapy with aminoglycosides, if susceptibility is preserved, carries an increased risk of nephrotoxicity. Due to a high volume of distribution, low blood levels, and high MIC, tigecycline is a "last resort" option, particularly for bloodstream infections. High MICs of carbapenems preclude achieving therapeutic levels even with pharmacodynamically optimized dosing strategies. Although *in vitro* synergy against CRKP has been observed when polymyxin B is used in combination with rifampin, cefepime, aminoglycosides, carbapenems, or tigecycline, testing methods are nonstandardized, and therefore the clinical effect of synergy remains unclear (3, 6–8). Limited data have demonstrated survival benefits of combination therapy using polymyxin B or colistin with carbapenems and/or tigecycline for patients with CRKP bacteremia (4, 5). Given the frequently encountered challenges of combination therapy, we aimed to describe the out-

40 CR-KP (50 KP, 14 E.coli, 16 sites, **2007-2012**)

- Carbapenemases and non-CPKP: ?
- Median age 76 yr, 14 bacteremia, 12 UTI, 7 pneumonia, 4 STSI, 2 IAI, 1 osteomyelitis
- Receiving polymycin B monotherapy

- Clinical cure: 73% (29/40)
- 30-day mortality = 28%
- Independent treatment failure: baseline renal insufficiency AOR 6.0 (1.22-29.59) &
- Polymycin resistance during tx = 7.5% (3/40)
- **New CRKP infection in 45% (18/40) at a median 23 days after initial polymycin B tx, 37.5% (3/18) with polymycin B resistance**

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Chemotherapy 2013

Conclusions

- Mortality rate of Bloodstream infections of CRE : 50%
- Current available antibiotics for CRE: colistin, tigecycline, fosfomycin, AK
- A combination therapy for CRE (e.g. carbapenem MIC < 16 ug/ml and prolonged infusion + cilisitn / tige)
- CRE genotyping (A, B, D ?)
- Molecular surveillance study and Amber classification for individualized treatment of CRE