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Research Article

Genetic epidemiology of Plasmid Mediated Class C Beta-Lactamase among Enterobacteriaceae isolates

Epidemiología genética de beta-lactamasa de clase C mediada por plásmidos entre aislados de enterobacterias

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ABSTRACT

Introduction: Plasmid-mediated class C β-lactamase (pAmpC) is a member of broad-spectrum β-lactamase that spreads worldwide. However, its prevalence was under-evaluated.

Objective: To characterize the prevalence and distribution of pAmpC types in 294 cefoxitin (FOX) and third-generation cephalosporin (3GC) resistant Enterobacteriaceae collected in several regions of Thailand and Vietnam in 2018 and 2020.

Methods: Multiplex Polymerase Chain Reaction (PCR) for pAmpC identification was utilized to investigate prevalence and diversification of pAmpC among 294 cefoxitin and third-generation cephalosporin resistant Enterobacteriaceae isolated from Thailand (n= 197) and Vietnam (n= 97).


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Results: The prevalence of pAmpC was 37.1% found in second and third-generation cephalosporin resistant Enterobacteriaceae. CMY-2 like was prominent in Thailand and Vietnam; however, prevalence of CMY-2 was varied in each hospital. DHA contributed 25.7%, ACT/MIR rate was dominant in Chiang Rai hospital, reached 100% in Thanh Hoa Pediatrics hospital. Worrisome, 3.7% - isolates carried two types of pAmpC. The incidence of pAmpC in Vietnam was significantly higher than those in Thailand.

Conclusions: These findings provide evidence-based of highly spreading and diversified distribution of transferable AmpC among Enterobacteriaceae in two Asia-Pacific countries.

Keywords: beta-Lactamases; cephalosporin resistance; enterobacteriaceae; genetic epidemiology.

RESUMEN

Introducción: La β-lactamasa de clase C mediada por plásmidos (pAmpC) es un miembro de la β-lactamasas de amplio espectro que se propaga por todo el mundo. Sin embargo, su prevalencia fue subestimada.

Objetivo: Caracterizar los tipos y la prevalencia y distribución de los tipos pAmpC en 294 enterobacterias resistentes a cefoxitina (FOX) y cefalosporinas de tercera generación (3GC) recolectadas en varias regiones de Tailandia y Vietnam en 2018 y 2020.

Métodos: Se utilizó la reacción en cadena de la polimerasa (PCR) múltiple para la identificación de pAmpC y determinar la prevalencia y diversificación de pAmpC entre 294 enterobacterias resistentes a cefoxitina y cefalosporinas de tercera generación, aisladas en Tailandia (n= 197) y Vietnam (n= 97).

Resultados: La prevalencia de pAmpC fue del 37,1 % encontrada en enterobacterias resistentes a cefalosporinas de segunda y tercera generación. El tipo CMY-2 fue prominente en Tailandia y Vietnam; sin embargo, la prevalencia de CMY-2 varió en cada hospital. El DHA contribuyó con el 25,7 %, la tasa ACT/MIR fue dominante en el hospital de Chiang Rai y alcanzó el 100% en el hospital de Pediatría de Thanh Hoa. Preocupa que el 3,7 %: los aislados portaban dos tipos de pAmpC. La incidencia de pAmpC en Vietnam fue significativamente mayor que en Tailandia.

Conclusiones: Estos hallazgos proporcionaron evidencia basada en una distribución altamente extendida y diversificada de AmpC transferible entre Enterobacteriaceae en 2 países de Asia y el Pacífico.


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Palabras clave: beta-Lactamasas; enterobacterias; epidemiología genética; resistencia a las cefalosporinas.

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INTRODUCTION

Enterobacteriacae is renowned with widespread on nosocomial infection and high rates of resistance to broad-spectrum β-lactams.[1] Among them, class C cephalosporinase (AmpC) producing organisms are emerged and attracted great concern. The ampC genes locate on both chromosomes and plasmids.[2] Deregulation of cAmpC and acquisition of plasmid-mediated AmpC (pAmpC) β-lactamases are the cause of constitutive overexpression of AmpC β-lactamases.[3] Because of lacking repressors, pAmpCs usually has a resistance pattern similar to that of de-repressed cAmpCs except bla_{DHA-1} gene which is inducible by β-lactams. Therefore, pAmpCs-carrying bacteria constitutively express a large amount of β-lactamases and be considered of significant clinical relevance.[1] Comparing to extended-spectrum β-lactamases (ESBLs), pAmpC β-lactamases have a broader substrate range when they can hydrolyze cephamycins and are not inhibited by commercially available β-lactamase inhibitors.[4] pAmpCs have been assigned as inconsistently conventional β-lactamase taxonomy as CMY (cephamycins), MOX (moxalactam), FOX (cefoxitin), LAT (latamoxef), BIL (Bilal), CFE-1 (ampR gene derived from *C. freundii*), DHA (Dhahran Hospital in Saudi Arabia), MIR (Hospital in Providence, Rhode Island, USA), ACT (AmpC type), and ACC (Ambler class C).[5]

Based on the sequence homology, pAmpCs are grouped into six families, comprising CMY-2 like, DHA, ACT/MIR, MOX/CMY-1 like, FOX, and ACC.[6] The pAmpCs are commonly found on *Escherichia coli*, *Klebsiella pneumoniae* and *Salmonella spp*.[7] and the pAmpC producing Enterobacteriaceae may conceal the detection of ESBLs and *Klebsiella pneumoniae* carbapenemase (KPC) producing isolates.[8]


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Furthermore, the pAmpC is located on transferable components that have high potentiality to spread these resistance genes to other bacteria in nosocomial and community settings. Generally, detection of AmpC β-lactamases is not performed in microbiological laboratories because of lacking approved standard methods. Several phenotypic methods have been developed and only the MAST ID D68C disc test and Tris-EDTA test had good sensitivity and specificity.[9] Additionally, multiple β-lactamases within one organism is a challenge for phenotypic methods. Therefore, molecular methods are assumed as the gold standard of pAmpC identification.[2,10] However, molecular testing is currently not available in most hospitals, particularly in low infrastructure settings.

To reduce the spread of multidrug-resistant bacteria, antibiotic susceptibility surveillance and infection control strategies should be performed regularly. The lack of standard phenotypic methods for pAmpC β-lactamases detection limits the truthful report and epidemiological scenery. Genotypic detection of pAmpC is a beneficial method because it provides a direct and valuable insight into the resistance mechanism which has the ability to spread to other organisms. Several molecular methods have been developed in last decade [3,6,7,11] and these approaches are rapid, high throughput and they can discriminate pAmpC from cAmpC β-lactamases. This study is aimed to determine the prevalence and distribution of pAmpC types in 294 cefoxitin (FOX) and third-generation cephalosporin (3GC) resistant Enterobacteriaceae collected in several regions of Thailand and Vietnam in 2018 and 2020.

METHODS

Study design

A cross-sectional study has been applied in the Quality Control Center for Medical Laboratory-University of Medicine and Pharmacy at Ho Chi Minh City.

Tested organisms

Totally 294 convenient sampling of FOX and 3GC resistant Enterobacteriaceae isolates were selected for detection of pAmpC β-lactamase production and type by molecular method. The first group of 105 isolates was collected in 2018, including 34 isolates from Nakhon Pathom Regional hospital (NPRH)-


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Thailand, 10 isolates from Thanh Hoa Pediatrics hospital (THPH), and 61 isolates from University Medical Center-Ho Chi Minh City (UMC-HCMC)-Vietnam. Second group of 189 isolates was collected in 2020, comprising of 3 hospitals from different parts of Thailand, 64 isolates from NPRH (central Thailand), 56 isolates from Chiang Rai hospital (CRH)-(north, Thailand), and 43 isolates from Buriram hospital (BRH)-(northeast, Thailand) and 26 isolates from UMC-HCMC-Vietnam (south Vietnam).

Antimicrobial susceptibility testing

The antimicrobial susceptibility testing (AST) was performed by disk diffusion method following the instruction of The Clinical & Laboratory Standards Institute (CLSI) and *E. coli* American Type Culture Collection (ATCC) 25922, 35218 and *Pseudomonas aeruginosa* ATCC 27853 were used as reference strains for quality control.[12] The antibiotic disks comprising cefoxitin (FOX; 30 µg), cefotaxime (CTX; 30 µg), ceftazidime (CAZ; 30 µg), cefpodoxime (CPD; 30 µg), cefepime (FEP; 30 µg), ertapenem (ETP; 10 µg), meropenem (MEM; 10 µg), ceftazidime/clavulanic acid (CAZ-CA; 30/10 µg), cefotaxime/clavulanic acid (CTX-CA; 30/10 µg), were purchased from Oxoid, England.

Molecular detection of pAmpC types

Enterobacteriaceae were grown on McConkey agar and several colonies were suspended in distilled water to a turbid at 0.5 McFarland No.1. The bacterial suspension was heated for 10 min and the supernatant was used as a DNA template.

The pAmpC types were characterized by utilizing inhouse developed method.[13] In brief, a 20 µL of total PCR reaction contains 2 µL DNA template, 2 µL PCR buffer (10X), 2 µL dNTP mix (2 mM each), a variable concentration of primers (Bio Basic Inc., Canada) including 20 ρM of AmpC-F and AmpC-R, 4 ρM of MOX-F, ECB-R, ACC-F, ACC-R, DHA-F, and DHA-F, 8 ρM of CIT-F, 2 ρM of FOX-R, and 0.5 U i-TaqTM DNA Polymerase (iNtRON Biotechnology, Korea). Distilled water was added to reach the expected volume. Amplification was performed by following thermal cycling conditions: 1 cycle of initial denaturation at 94 °C in 3 min, then 35 cycles consisting of 20 s at 94 °C, 15 s at 60 °C, and 45 s at 72 °C, and final extension step 3 min at 72 °C. The amplicons were resolved by electrophoresis on a 2% agarose gel (Research Organics INC., USA) and stained with ethidium bromide. A Genesnap (Syngene, USA) was used for PCR band detection and imaging. By applying this method, 6 different groups of pAmpC genes have been detected (table 1).


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Table 1 - The correlation between six designed groups and detected pAmpC genes

No.	Designed group	Target gene	Variants coverage
1	MOX	*bla*$_{MOX}$	MOX 1- 12, CMY-1, CMY 8-11, CMY-19
2	ECB	*bla*$_{ECB}$	ACT 1-10, ACT 12-38; MIR 1-19
3	CIT	*bla*$_{CIT}$	CMY 2-7, CMY 12-18, CMY 20-140; LAT-1; CFE-1
4	FOX	*bla*$_{FOX}$	FOX 1-10, FOX-12
5	DHA	*bla*$_{DHA}$	DHA 1-7, DHA-9,10, DHA 12-23
6	ACC	*bla*$_{ACC}$	ACC 1-5

MOX: MOX (moxalactam) and CMY-1 liked (cephamycins); ECB: MIR (Hospital in Providence, Rhode Island, USA) and ACT (AmpC type); CIT: CMY-2 liked, LAT (latamoxef), BIL (Bilal) and CFE-1 (ampR gene derived from *C. freundii*); FOX (cefoxitin); DHA (Dhahran Hospital in Saudi Arabia); ACC (Ambler class C).

RESULTS

The results show that 109 out of 294 (37.1%) isolates of cefoxitin and 3GC resistant Enterobacteriaceae produced pAmpC β-lactamases. Because of the high prevalence of carbapenem-resistant Enterobacteriaceae (CRE) in this study, the positive rate of pAmpC was 47.1% (98/208) in FOX-R, ESC-R, and carbapenem (CAR) susceptible isolates. The 109 pAmpC producing isolates were highly found in *E. coli* (56.9%), followed by *Klebsiella spp*. (24.8%), and *Enterobacter spp*. (17.4%) respectively. Three clusters of pAmpC (CMY-2 like, DHA, and ACT/MIR) were presented while MOX/CMY-1 like, FOX and ACC types were absent in this study. The CMY-2 like cluster was the most prominent (47.7%) while DHA and ACT/MIR clusters were found in similar rates of 25.7% and 22.9% respectively (table 2). Moreover, 11 (3.7%) isolates carried two types of pAmpC β-lactamases. Remarkably, all pAmpC positive *Enterobacter spp*. Possessed ACT/MIR type whereas most *E. coli* and *Klebsiella spp*. harbored the CMY-2 like type (75.8%) and DHA type (74.1%), respectively.


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Table 2 - Prevalent rates and variation of pAmpC types among cefoxitin and third-generation cephalosporin resistant Enterobacteriaceae

Bacteria	No. of isolates (%)		Distribution of pAmpC types (%)				
	Tested	Positive	CIT*	DHA	ECB**	CIT+DHA	ECB+DHA
E. coli	150	62 (41.3)	75.8	11.3	8.1	4.8	-
bsiella spp.	101	27 (26.7)	18.5	74.1	7.4	-	-
Enterobacter spp.	33	19 (67.6)	-	-	94.7	-	5.3
Other Enterobacteriaceae***	10	1 (10.0)	-	100	-	-	-
Total	294	109 (37.1)	47.7	25.7	22.9	2.8	0.9

* CIT (CMY-2 like, LAT, CFE) types are related to AmpC β-lactamases of *C. freundii* while DHA type and ** ECB (ACT/MIR) type are originated from *M. morganii* and *Enterobacter* spp., respectively [2]. *** *Citrobacter spp*. (3); *Providencia spp*. (2); *Proteus spp*. (2); *Serratia spp*. (2); *Edwardsielleae spp*.(1)

Interestingly, the variation of pAmpC types were not only species of Enterobacteriaceae but also depended on hospitals and periods. Data of collected isolates of 3 hospitals in 2018 showed that over 50% of pAmpC producing isolates collected from Nakhon Pathom Regional hospital, Thailand (NPRH-TH), and University Medical Center-Ho Chi Minh City, Vietnam (UMP-HCMC-VN) carried CMY-2 like types whereas all pAmpC producing isolates collected from Thanh Hoa Pediatrics hospital, Vietnam (THPH-VN) carried ACT/MIR type. In 2020, the data from one region in Vietnam (UMC-HCMC) and 3 regions in Thailand (Nakhon Pathom Regional hospital (NRPH), Chiang Rai hospital (CRH), and Buriram hospital (BRH)) were analyzed. All three main clusters (CIT, DHA, and ECB) were present in all 4 hospitals; however, the prevalent rates were different. The CMY-2 like cluster was prominent in UMC-HCMC and BRH, while DHA was highly presented in NPRH and ACT/MIR in CRH, respectively. Moreover, the change of pAmpC type in collected isolates of NPRH and UMC-HCMC from 2018 to 2020 was also noticed. From UMC-HCMC isolates, the ACT/MIR type was increased from 5.9% in 2018 to 16.7% in 2020. On the other hand, the proportion of CMY-2 like and DHA clusters from NPRH was converted between the year 2018 to 2020 (table 3).

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Table 3 - Distribution of pAmpC types in different regions and time periods (2018 and 2020)

Time	Hospital (n)	pAmpC (%)	Distribution of pAmpC type (%)				
			CIT	DHA	ECB	CIT+DHA	ECB+DHA
2018	THPH (10)	70.0	-	-	100	-	-
	UMC-HCMC (61)	55.7	52.9	33.4	5.9	8.8	-
	NPRH (34)	61.8	52.4	28.6	19.0	-	-
2020	UMC-HCMC (26)	46.2	58.3	25.0	16.7	-	-
	NPRH (64)	18.8	33.3	50.0	16.7	-	-
	CRH (56)	21.4	25.0	8.3	58.3	-	8.3
	BRH (43)	25.6	81.8	9.1	9.1	-	-
Total	VIETNAM (97)	54.6	47.2	26.4	20.8	5.7	-
	THAILAND (197)	28.4	48.2	25.0	25.0	-	1.8

CIT: CMY-2 like, LAT, CFE; ECB: ACT/MIR; UMC-HCMC: University Medical Center-Ho Chi Minh City-Vietnam; THPH: Thanh Hoa Pediatrics Hospital-Vietnam; NPRH: Nakhon Pathom Regional Hospital-Thailand; CRH: Chiang Rai Hospital-Thailand; BRH: Buriram Hospital-Thailand.

DISCUSSION

The production of pAmpC β-lactamases in Enterobacteriaceae is clinically important because of their ability to hydrolyze a wide range of β-lactams such as broad-spectrum penicillins, extended-spectrum cephalosporins, cephamycins, and monobactams[7] and enzymes cannot be inhibited via commercial β-lactamase inhibitors. In combination to other resistance mechanisms eg. efflux pumps and porin loss, pAmpC even causes low-level resistance to carbapenems.[5]

Several members of Enterobacteriaceae possess cAmpC such as *Enterobacter spp*., *Serratia marcescens*, *C. freundii*, *Providencia spp*. and *M. morganii*, often termed ESCPM group.[14] Herein, it is reported that pAmpC β-lactamases was not only detected in a familiar host, *E. coli* and *Klebsiella spp*. but also found in *Enterobacter spp*. and *Proteus vulgaris*. These results referred to that both cAmpC and pAmpC β-lactamases are possibly presented in one organism. As indicated in table 1, *E. coli* and *K. pneumoniae* were most common agents of pAmpC producing Enterobacteriaceae, however, they mainly carried different enzyme clusters. The CMY-2 like type is derived from *C. freundii*[2] and it is now commonly found in *E. coli* while the DHA has the origin from *M. morganii* and first detected in *S. enteriditis,*[2] and


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are closely related to *Klebsiella spp*., particularly in *K. pneumoniae*. Among Enterobacteriaceae, *E. coli* and *K. pneumoniae* are the most common agents found in both nosocomial and community infection. This result alarms that a transferable resistance mechanism is now spreading in the hospital environment and geographic region. Besides, all Enterobacter isolates were presented the ACT/MIR cluster which is originally from *Enterobacter*.[5] Only 2 and 5 isolates of *Klebsiella spp*. and *E. coli* harbored the ACT/MIR cluster. These results inferred that the ACT/MIR plasmid types are still mainly stored in the original host.

The CMY-2 like pAmpC β-lactamases were highly spread in Sri Lanka, India and Iran.[15,16,17] Furthermore, CMY-2-producing *E. coli* isolates are potential development of cefepime (a member of fourth generation cephalosporin group) resistance.[18] In these data, CMY-2 like was still the most common pAmpC types in both Thailand and Vietnam; however, prevalent rates of CMY-2 like pAmpC β-lactamases were varied depending on regions. In some particular regions. Thanh Hoa Pediatrics hospital (THPH, North Vietnam) and Chiang Rai Regional Hospital (CRH, north Thailand) were dominant with ACT/MIR determinants. The high population density and the weak drug control policies may be the main reasons for the high proportion of antimicrobial drug resistance bacteria including pAmpC producing organism. The coexistence of multiple β-lactamases within one organism is a challenge for phenotypic testing and can rigorously limit therapeutic options. The 3GC resistant Enterobacteriaceae commonly carry ESBLs, thus, the co-production of ESBL and AmpC β-lactamases was also found a high rate in these regions. Furthermore, the resistance to carbapenems is commonly presented as phenotypically resistance to FOX and 3GC that may interfere with the proportion of pAmpC among tested organisms including CRE. By utilizing cefoxitin and 3GC resistant criteria for screening pAmpC, this study may face minor bias (can not cover all cases of bla_{DHA-1} gene which is inducible by β-lactams).[1] However, DHA-type β-lactamase contributed 25.7% among detected pAmpCs.

In conclusion, determining the prevalence and diversified distribution of pAmpC cluster in Enterobacteriaceae is of clinical importance. The prevalence of pAmpC was 37.1% found in second and third-generation cephalosporin resistant Enterobacteriaceae. Three main pAmpC clusters (CIT, DHA, and ECB) were described while MOX, FOX and ACC absented. The variation of pAmpC genes is depend on region and the time of bacteria collection. This finding provide convincing evidence-based data of

pAmpC epidemic and it is necessary to survey the prevalence and genetic distribution of pAmpC β-lactamases in these regions.

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Conflicts of interest

None of conflicts of interest in relation to the work.

Authorship contribution

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Data availability

Raw data is stored in excel files and is ready to be provided upon request.