Predominance of international clone 2 multidrug-resistant Acinetobacter baumannii clinical isolates in Thailand: a nationwide study

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Abstract

Background: Acinetobacter baumannii has emerged as one of the common multidrug resistance pathogens causing hospital-acquired infections. This study was conducted to elucidate the distribution of antimicrobial resistance genes in the bacterial population in Thailand. Multidrug-resistant A. baumannii (MDR A. baumannii) isolates were characterized phenotypically, and the molecular epidemiology of clinical isolates in 11 tertiary hospitals was investigated at a country-wide level.

Methods: A total of 135 nonrepetitive MDR A. baumannii isolates collected from tertiary care hospitals across 5 regions of Thailand were examined for antibiotic susceptibility, resistance genes, and sequence types. Multilocus sequence typing (MLST) was performed to characterize the spread of regional lineages.

Results: ST2 belonging to IC2 was the most dominant sequence type in Thailand (65.19%), and to a lesser extent, there was also evidence of the spread of ST16 (10.37%), ST129 (3.70%), ST16 (2.96%), ST98 (2.96%), ST25 (2.96%), ST215 (2.22%), ST338 (1.48%), and ST745 (1.48%). The novel sequence types ST1551, ST1552, ST1553, and ST1557 were also identified in this study. Among these, the blaoxa-23 gene was by far the most widespread in MDR A. baumannii, while the blaoxa-24/40 and blaoxa-58 genes appeared to be less dominant in this region. The results demonstrated that the predominant class D carbapenemase was blaOXA-23, followed by the class B carbapenemase blaNDM-like, while the mcr-1 gene was not observed in any isolate. Most of the MDR A. baumannii isolates were resistant to ceftriaxone (99.23%), gentamicin (91.85%), amikacin (82.96%), and ciprofloxacin (97.78%), while all of them were resistant to carbapenems. The results suggested that colistin could still be effective against MDR A. baumannii in this region.

Conclusion: This is the first molecular epidemiological analysis of MDR A. baumannii clinical isolates at the national level in Thailand to date. Studies on the clonal relatedness of MDR A. baumannii isolates could generate useful data to understand the local epidemiology and international comparisons of nosocomial outbreaks.

Keywords: MDR, Molecular epidemiology, Carbapenemases, MLST, Antimicrobial resistance, Sequence type, A. baumannii

Background

Antimicrobial resistance (AMR) has emerged as a silent health threat over the last two decades. It has been estimated that AMR could be the major cause of mortality worldwide by 2050 [1]. Among antimicrobial-resistant bacteria, Acinetobacter baumannii is a prominent
member of the notorious “ESKAPE” group of pathogens, along with Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species [2]. The most common infections caused by A. baumannii are related to nosocomial infections, including ventilation-associated pneumonia, skin and soft tissue infections, and bloodstream infections [3, 4]. This organism is well known for its remarkable ability to resist almost all available antibiotics due to its capability of adapting and acquiring resistance genes. Moreover, A. baumannii is frequently found to be resistant to a class of last-resort antibiotics, carbapenems, and these strains are known as carbapenem-resistant A. baumannii (CRAB). Colistin, an alternative antibiotic, has shown some promising activity against resistant A. baumannii. Unfortunately, an increase in the colistin resistance rate has been reported worldwide, along with reports on multidrug-resistant (MDR) and pandrug-resistant (PDR) A. baumannii [5]. In Thailand, A. baumannii was described as strongly associated with multidrug or carbapenem resistance and has caused nosocomial outbreaks. The presence of MDR A. baumannii has been reported in all regions of Thailand since 2000 [6]. According to the annual national antimicrobial report 2019, the National Antimicrobial Resistance Surveillance Center, Thailand (NARST), A. baumannii complex isolates showed less than 50% susceptibility rates with almost all the currently used antibiotics except colistin [7]. In addition, PDR A. baumannii has emerged in regional hospitals in Thailand [8–10].

Molecular techniques have been applied to monitor the epidemiology and evolution of drug-resistant bacteria. Popular techniques include whole-genome sequencing (WGS), multilocus sequence typing (MLST), and pulsed-field gel electrophoresis (PFGE) [5]. PFGE is recognized as the standard method even in this era of sequence-based methods, while WGS is the best method that can provide much information. However, both WGS and PFGE are quite laborious and require specific equipment that is available in only some laboratories. Therefore, MLST is now widely referred to as an additional tool for global epidemiological research that allows the recognition of epidemics and virulence of A. baumannii clones and the monitoring of their spread at both the national and international levels. The molecular epidemiology of A. baumannii has been extensively studied in outbreaks of infection in many countries worldwide. However, little is known about the clonality and genetic relatedness of MDR A. baumannii isolates in Thailand. There were some sporadic reports that focused on a few hospitals in the region. To date, two systematic MLST schemes, namely, the Oxford scheme developed by Burtual et al. and the alternative Pasteur MLST scheme, are now well recognized and acknowledged [11, 12]. These two schemes compare seven housekeeping genes and have three genes in common, namely, cpn60, gltA, and recA. Gaiarsa et al. compared those two schemes and proposed that the Pasteur scheme was more appropriate for population biology and epidemiology studies of A. baumannii and related species [13]. Therefore, the Pasteur MLST scheme was referenced in the present study to elucidate the epidemiology of MDR A. baumannii in a nationwide study across Thailand. Moreover, the antimicrobial resistance profiles contributing to drugs frequently used in Thailand for MDR A. baumannii infections were phenotypically and genetically characterized.

Materials and methods
Bacterial collection
A. baumannii clinical isolates were collected during 2016–2017 from 11 hospitals in 5 regions of Thailand, including the capital city, central region, northern region, southern region, and northeastern region. Bacteria were preliminarily identified as the genus Acinetobacter by microbiological and biochemical methods. All the isolates were genotypically confirmed as A. baumannii by the presence of the blaOXA-51-like gene [14]. The antibiotic susceptibility profiles of A. baumannii in this study were determined by the broth microdilution method according to the Clinical and Laboratory Standards Institute guidelines [15]. MDR A. baumannii in this study was defined as nonsusceptible to at least 1 agent in at least 3 antimicrobial categories, including aminoglycosides, fluoroquinolones, carbapenems, cephalosporins, folate pathway inhibitors, penicillins, beta-lactamase inhibitors, tetracyclines, and polymyxins [16]. The samples were stored as glycerol stocks at -80 °C until use.

Detection of antibiotic resistance genes
The specific primers and PCR conditions for ndm-type and blaOXA-type carbapenemase detection were used as previously published (Table 1) [17, 18]. E. coli ATCC BAA 2469 was purchased from the American Type Culture Collection, USA, and used as a positive control for ndm-type carbapenemase. The blaOXA-51-like gene, an intrinsic enzyme marker, was used as a marker for the identification of A. baumannii according to the study by [14].

The mcr-1 gene from the PubMed database was used as a template to design a set of primers (Table 1). Total genomic DNA of MDR A. baumannii was used as a template for the PCR (10 µL buffer, 0.2 mM dNTPs, 1 U of DNA polymerase, 0.2 mM each primer, and 2 mM MgCl2). The PCR conditions were as follows: 3 min of initial denaturation at 95 °C, followed by 30 cycles of 30 s of denaturation at 95 °C, 30 s of annealing at 61 °C, and 30 s
of elongation at 72 °C and a final elongation at 72 °C for 5 min. The PCR products were analyzed by 1% agarose gel electrophoresis, dyed with ethidium bromide and visualized under a UV transilluminator. *E. coli* NCTC 13846 was purchased from the American Type Culture Collection, USA, and used as a positive control.

**Multilocus sequence typing (MLST)**
All MDR *A. baumannii* isolates were identified by MLST as described by Diancourt et al. [12]. The MLST profiles were analyzed by using the MLST Pasteur scheme (https://pubmlst.org/abaumannii/). Briefly, total genomic DNA of MDR *A. baumannii* was extracted by the Gentra Puregene Yeast/Bact. Kit (Qiagen, Germany). Seven housekeeping genes (cpn60, fusA, gltA, pyrG, recA, rplB and rpoB) were amplified by PCR with the recommended conditions and primers (Table 1) using a T100 Thermal Cycler (Bio-Rad, USA). PCR products were sequenced by Bio Basic Inc., Singapore. All DNA sequences were searched for exactly matched locus numbers. Sequence types (STs) were determined by combination of each locus number of each gene.

A new allele number was assigned when the gene was not exactly matched with the existing locus number. PCR products of new loci were amplified and submitted for sequencing to confirm the sequence. New STs were assigned when no STs existed for the combination of all exactly matched loci. All the new alleles and STs information is available at https://pubmlst.org/organisms/acinetobacter-baumannii [19].

**Clonal complex analysis using GOeBURST**
All STs of MDR *A. baumannii* isolates were further analyzed for the clonal complex using Phyloviz 2.0. The program is available at http://www.phyloviz.net/ [20]. A group of STs sharing at least five alleles (DLVs) were allocated to the same clonal complex. All STs in this study were analyzed for MLST relevance with full MSTs.

**Results**

**Antimicrobial resistance pattern of MDR *A. baumannii* clinical isolates**
A total of 135 nonrepetitive isolates were collected and confirmed to be MDR *A. baumannii* by phenotypic and genotypic methods. The vast majority (109/135, 80.74%)
of the isolates were recovered from sputa. The remaining isolates were from pus (14/135, 10.37%), urine (7/135, 5.19%), tissue (3/135, 2.22%), and respiratory tract secretions (2/135, 1.48%) (Fig. 1a). The Acinetobacter isolates were phenotypically identified by microbiological and biochemical methods. The molecular detection of the \textit{bla}oxa-51-like gene revealed a 353-bp band in all clinical isolates, which preliminarily confirmed the identity of the clinical isolates as \textit{A. baumannii}. All clinical isolates were subjected to antimicrobial susceptibility testing with
the drugs currently used for A. baumannii treatment. Most of the clinical isolates were resistant to ceftazidime (134/135, 99.23%), gentamicin (124/135, 91.85%), amikacin (112/135, 82.96%), ciprofloxacin (132/135, 97.78%), or colistin (20/135, 14.81%), while all the isolates were resistant to carbapenems (imipenem, meropenem, and doripenem). Interestingly, all the isolates showed high resistance to all three carbapenem antibiotics, except two isolates that were still susceptible to both imipenem and meropenem. Notably, 17 out of 135 isolates were resistant to all eight tested antibiotics (Fig. 1b).

**Occurrence of antimicrobial resistance genes in MDR A. baumannii**

One of the most important carbapenem resistance mechanisms is the production of class D β-lactamases (e.g., oxacillinase; OXA). This study demonstrated that a majority of the class D β-lactamases among MDR A. baumannii isolates in Thailand were blaoxa-23-like (125/135, 92.59%), followed by blaoxa-24-like (20/135, 14.81%), and only two isolates carried the blaoxa-58-like gene (1.48%). Notably, MDR A. baumannii isolates carrying blaoxa-24-like or blaoxa-58-like genes also carried the blaoxa-23-like gene, indicating the presence of three OXA carbapenemase-encoding genes (including the intrinsic blaoxa-51-like gene) in these isolates, while A. baumannii ATCC 19606, a standard control strain, exhibited only the intrinsic blaoxa-51-like gene (Fig. 2).

In addition, 6 isolates of MDR A. baumannii were found to harbor NDM-type carbapenemases collected from two distinct regional hospitals. With an occurrence rate of 4.44%, the data revealed the limited spread of ndm-harboring A. baumannii isolates in Thailand. Further investigation was performed because colistin is one of the most commonly used drugs in Thailand. Fortunately, the mcr-1 gene was not detected in any MDR A. baumannii isolates in this study. Although colistin resistance phenotypically appeared in some isolates (14.07%), no association with the genotypic presence of the mcr gene was identified.

**MLST profile analysis**

In the present study, extensive efforts were made to genetically characterize MDR A. baumannii for epidemiological investigation in Thailand. According to the Pasteur MLST scheme, the ST2 or International clone 2 was identified as a dominant clone, with 65.19% (88/135) abundance in this region (Fig. 3a). Another

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**Fig. 2** Occurrence of antimicrobial resistance genes among MDR A. baumannii. The graphical chart represents the number of antimicrobial genes detected by PCR among all clinical isolates. The majority of class D β-lactamases was blaOXA-23 followed by blaOXA-24 and blaOXA-58 carbapenemases. Some isolates also carry blaNDM-type carbapenemases. The overlapped circle represents double or triple existence of the genes.
Fig. 3 Multi locus sequence typing population analysis. 

a Graph summary of STs in Thailand. 

b The sequence type distribution in each regions of Thailand.
major clone was ST164 (14/135, 10.37%), and other recognized clones were ST129 (5/135, 3.70%), ST16 (4/135, 2.96%), ST98 (4/135, 2.96%), ST25 (4/135, 2.96%), ST215 (3/135, 2.22%), ST338 (2/135, 1.48%), and ST745 (2/135, 1.48%). The remaining five genotypes (e.g., ST768, ST126, ST1160, ST1250, and ST1253) were also identified. Moreover, four new STs of A. baumannii, namely, ST1551 (ID5087; MTC0480), ST1552 (ID5088; MTC0904), ST1553 (ID5089; MTC0146) and ST1557 (ID 5104; MTC0709), were discovered in this study. Notably, an MDR A. baumannii isolate belonging to ST1553 carried the new allele of the fusA gene, which was identified and assigned a new locus number. The newly discovered STs have been deposited in the Acinetobacter MLST database.

Further analysis of the geographic distribution demonstrated different patterns of genetic variants by region (Fig. 3b). ST2 was found to be a dominant clone in all regions of Thailand with varied distribution percentages. The highest percentage of ST2 (80.56%) was observed in the northern region. There were some variations in the ST clones with the second highest percentages between regions. ST129 was ranked second in the capital city, while ST25 and ST215 were ranked second in the northern and southern regions, respectively. In the central and northeastern regions, the second most distributed ST clone was ST164.

eBURST analysis was performed to assign each ST to the respective clonal complex. The majority of the isolates exhibited a relatively close evolutionary relationship in the phylogenetic tree (Fig. 4). Only one major clonal complex belonging to clonal complex 2 (CC2) was highly prevalent in Thailand. There was no evidence of CC1 being present in this region.

Discussion
A. baumannii is one of the most common emerging nosocomial pathogens, causing significant concern globally. Generally, carbapenems, with the exception of ertapenem, have been the drug of choice for the empirical therapy of A. baumannii infections [21]. However, the emergence of CRAB and MDR A. baumannii at high frequency in many intensive care units has led to therapeutic failure. Although there is no optimal regimen for elimination of highly resistant A. baumannii, colistin is currently recommended for the treatment of serious infections. Other drugs, such as tigecycline and sulfadiazine, have been reported, but combination therapy is preferable [22]. In this study, all MDR A. baumannii isolates were highly resistant to almost all the tested drugs widely used in this region except colistin. The results suggested that colistin could still be used effectively to treat MDR A. baumannii infections in Thailand. This study will also raise awareness regarding the monitoring of antibiotic usage with limited resources.

To date, the emergence of carbapenem resistance among MDR A. baumannii has been progressively increasing globally. It was clearly demonstrated in this study that the rate of resistance to carbapenems, including imipenem, meropenem, and doripenem, was extremely high (>90%) among MDR A. baumannii. One of the most important carbapenem resistance mechanisms is the production of class D β-lactamases (oxacillinase; OXA). This group of enzymes can hydrolyze oxacillin and third-generation cephalosporins but possesses weak activity against carbapenems [23]. This study demonstrated that the presence of the blaOXA-23 gene was closely correlated with carbapenem resistance, and this gene was predominantly carried in MDR A. baumannii isolates. Of these genes, the blaOXA-23 gene was by far the most widespread in MDR A. baumannii, while the blaOXA-24/40 and blaOXA-58 genes appeared to be less dominant in this region. The prevalence of the blaOXA-23-like gene was found to be relatively high worldwide [5, 24, 25]. Thirapanmethie et al. also reported that the OXA-23-like gene was the most common carbapenemase gene among CRAB clinical isolates in Thailand (68.31%) [26]. In addition, many new enzyme variants of OXA-24/40-like carbapenemases have been reported, including OXA-72. In fact, the blaOXA-72 gene was first identified in an A. baumannii isolate from Thailand in 2004. Since then, this variant has disseminated in healthcare settings and environments around the world, especially Asia and Southeast Europe, which could be of interest for further investigation [27–30].

Gram-negative pathogens carrying NDM-type β-lactamases have been discovered worldwide, with high occurrence in India and China [31]. The presence of blaNDM-1 demonstrates a pattern of resistance to all β-lactam agents except monobactams. In Thailand, NDM-type carbapenemase was first detected in Gram-negative pathogens in 2012 [32]. A. baumannii carrying NDM-type carbapenemase was later identified in 2018 from the 2013–2014 specimen collection [33]. In the present study, only 4.44% of MDR A. baumannii isolates were found to harbor ndm-type carbapenemases, and these isolates were collected from two distinct regional hospitals, indicating the limited distribution of this gene type in Thailand.

Colistin is an antibiotic that is highly recommended for use against drug-resistant bacteria. Mobile colistin resistance (MCR-1) was discovered in Escherichia coli in 2015 [34]. Since then, many mcr gene families (mcr-1, -2, -3, -4, -5, -6, -7, -8, -9) have been sporadically reported in Gram-negative bacteria [34–38]. This gene family was also recognized as the latest threat
in the antibiotic era since the \textit{mcr} gene was found on transferable plasmids. Fortunately, the \textit{mcr-1} gene was not detected in any MDR \textit{A. baumannii} isolates in this study. Although colistin resistance phenotypically appeared in some isolates (14.07\%), no association with the genotypic presence of the \textit{mcr} gene was identified. This could be explained by other colistin resistance mechanisms reported in MDR \textit{A. baumannii}, namely, loss of lipopolysaccharide (LPS) production and mutation of the PmrAB system [39].
To date, a total of 1395 STs have been submitted to the Acinetobacter MLST database [40]. In the present study, extensive efforts were made to genetically characterize MDR A. baumannii by MLST analysis for epidemiological investigation in Thailand. MLST has been extensively utilized for genotyping bacteria and allows this genetic information to be placed in a global context. According to the Pasteur MLST scheme, the ST2 or International clone 2 was found to be a dominant clone in all regions of Thailand. A total of 18 ST genotypes played a crucial role in nosocomial infection and spread in Thailand. Moreover, four new STs of A. baumannii (ST1551, ST1552, ST1553, and ST1557) were discovered in this study. ST2 has circulated intensively in the rest of the world, including Thailand, as indicated in this study [41, 42]. ST164, ST129, ST25, and ST215 were the common STs in our local settings, as each of them was found in different regions of Thailand. In 2006, a single ST2 isolate obtained from patients hospitalized in intensive care units in Thailand was identified [25]. According to the Acinetobacter MLST database, some Thai ST2 clones and an ST215 A. baumannii clone have been present in the database since 2010, indicating local distribution over time [36]. Our previous work demonstrated that most carbapenem-resistant Acinetobacter baumannii isolates (CRAB) in Thailand were ST2 clones, but some belonged to ST25, ST98, ST129, ST164, ST215, ST338, and ST745 [26]. In Asia, ST2 has been reported as the most prevalent sequence type of CRAB in China and Lebanon [24, 43, 44]. Sequence typing of A. baumannii distributed in Thailand was conducted in a study of 23 samples from a single hospital setting using the Oxford MLST scheme [45]. It was reported that ST195, which belongs to the clonal cluster of IC2, was the dominant clone, followed by ST342. In 2013, the Asian Network for Surveillance of Resistant Pathogens (ANSORP) surveillance study, which randomly selected 30 Thai hospital-associated pneumonia isolates, revealed a high prevalence of ST195, along with some amounts of ST92, ST346, ST88, ST365, ST395, ST208, ST398, and ST399 [46]. However, our study focused on the clonal relatedness of MDR A. baumannii using the Pasteur MLST scheme. ST2 classified in IC2 was identified as a dominant clone among MDR A. baumannii. Other major clones were incomparable with the previous study since the difference scheme of MLST was assigned.

eBURST analysis was used to analyze the MLST data to determine the evolutionary relationships among the isolates. According to the eBURST analysis, most MDR A. baumannii isolates belonged to major clonal complex 2 (CC2), indicating a single dominant lineage in Thailand. Although CC1 and CC2 have been identified as the key clonal lineages globally, no isolates belonging to CC1 were detected in this study. CC2 was by far the most abundant A. baumannii clone, with a broad international distribution over many continents [26, 47–50]. CC2 in the Pasteur scheme corresponds to CC92 in the Oxford scheme and international clone II, as previously identified [42]. The majority of MDR A. baumannii clones in Thailand belonged to the dominant clonal complex 2, which was similar to the results for other neighboring countries in this region. Tada et al. suggested that ST2 MDR A. baumannii isolates were mainly spreading in medical settings in Myanmar [48]. In Malaysia, most of the isolates were grouped under CC92 in the Oxford scheme comparable to CC2 in the Pasteur scheme [51]. Schultz et al. reported that the majority of the CRAB isolates causing ventilator-associated pneumonia (VAP) in Vietnamese ICUs during 2009–2012 were oxa23-positive global clone GC2 [52].

**Conclusion**

In summary, our study reported the relative prevalence of MDR A. baumannii isolates that were genetically diverse, belonging to 18 distinct STs. The majority of the MLST genotyped isolates in this study fell into one of seven genotypes within a single clonal complex known as IC2. The predominance of IC2 in Thailand was consistent with the high distribution of this clone worldwide. Notably, four new MLST genotypes were discovered in Thailand. The predominant class D carbapenemase was blaOXA-23-like, followed by the class B carbapenemase blaNDM-like. Fortunately, none of the MDR A. baumannii isolates carried the mcr-1 gene. The present study population was unique and represented the nationwide characterized collection of MDR A. baumannii isolates in Thailand reported to date. The data provide knowledge for the evolutionary study and international comparisons of nosocomial outbreaks in the future (Additional file 1).

**Abbreviations**

AMR: Antimicrobial resistance; WGS: Whole genome sequencing; MLST: Multilocus sequence typing; PFGE: Pulse field gel electrophoresis; IMP: Imipenem; MER: Meropenem; DOR: Doripenem; CTZ: Ceftazidime; GEN: Gentamicin; AMK: Amikacin; CIP: Ciprofloxacin; COL: Colistin; bia: Beta-lactamase; NDM: New delhi metallo-beta-lactamase; MCR: Mobilized colistin resistance; OXA: Oxacillinase; MFD: Multidrug resistant; PDR: Pan-drug resistant; CRAB: Carbapenem resistant-Acinetobacter baumannii; ST: Sequence type; IC: International clone; CC: Clonal complex; GC: Global clone.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12941-021-00424-z.

Additional file 1.
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Authors’ contributions
PKh contributed to methodology, investigation, software and data curator, writing—original draft. PK contributed to methodology and investigation. MTC contributed to conceptualization, methodology, supervision, writing—review and editing, and funding acquisition.

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Declarations

Ethics approval and consent to participate
The study was approved by the Ethical Review Committee, Faculty of Dentistry and Faculty of Pharmacy, Mahidol University (MU-ĐT/PHY-IRB 2016/008.0404).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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