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Research Article

In vitro activity of biapenem and comparators against multidrug-resistant and carbapenem-resistant *Acinetobacter baumannii* isolated from tertiary care hospitals in Thailand

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ABSTRACT

Acinetobacter baumannii is one of nosocomial pathogen which emerges as multidrug-resistance worldwide. Multidrug-resistant *A. baumannii* (MDRAB) and carbapenem-resistant *A. baumannii* (CRAB) are highly concerned due to limitation of therapeutic options. Antibacterial activity of biapenem was explored in order to overcome bacterial resistance. A total of 412 *A. baumannii* clinical isolates from 13 tertiary care hospitals in Thailand were collected. MIC values of biapenem and comparators; imipenem, meropenem, colistin, sulbactam, ciprofloxacin ceftazidime and fosfomycin sodium, were determined by broth microdilution method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (2016). In total, 320 isolates (77.67%) were MDRAB and 328 isolates (79.61%) were CRAB while 58 isolates (14.07%) were colistin-resistant AB. *A. baumannii* showed widespread resistance to ceftazidime, ciprofloxacin and carbapenems in more than 90% of the strains; resistance to sulbactam, fosfomycin, and colistin were 85%, 60%, and 15% respectively. By comparison among carbapenems, biapenem showed $MIC_{50/90}$ of 16/32 which were at least 2 folds lower than imipenem and meropenem ($MIC_{50/90}$; 32/128, 32/64, respectively). In addition, 15% of imipenem and meropenem-resistant *A. baumannii* were susceptible to biapenem. Also, 19% of colistin-resistant *A. baumannii* were susceptible to biapenem. Although more than 90% of MDRAB and CRAB were resistant to carbapenems, biapenem showed a good activity over other carbapenems. This drug might be a therapeutic option mono or combination therapy besides other antimicrobial agents.

1. INTRODUCTION

The emerging problem of antibiotic resistance, especially among Gram-negative bacteria (GNB) in nosocomial infection, is a major global concern. The majority of Gram-negative infections in intensive care unit (ICU) are caused by extended spectrum beta-lactamase (ESBL) Enterobacteriaceae, *Pseudomanas aeruginosa*, and *Acinetobacter baumanii*[1]. The increasing of *Acinetobacter* spp. resistance could be an alarming issue. Moreover,

A. baumannii has emerged as multidrug-resistant *A. baumannii* (MDRAB), carbapenem-resistant *A. baumannii* (CRAB), and colistin-resistant strains (CoRAB) which are associated with high mortality rates and longer hospital stays[2]. Carbapenems and colistin have been commonly used as the treatment of choice for MDRAB infections[3]. However, nephrotoxicity and neurotoxicity from colistin use have been reported[4-5]; while, MDRAB isolates which are resistant to carbapenems and colistin have been increasingly reported worldwide[6-7].

Biapenem is a new parenteral carbapenem antibiotic, which are inhibit bacterial cell wall synthesis, and has a wide range of antibacterial activity encompassing many gram-negative and gram-positive aerobic and anaerobic bacteria, including species producing β-lactamases. Biapenem has a penicillin-like five-membered ring, but the sulfur at C-1 in the five-membered ring is replaced with a carbon atom and a double bond between C-2 and C-3 is introduced**.** Moreover, unlike imipenem, biapenem has a 1β-methyl group at the C1 position which is stable to hydrolysis by human renal dihydropeptidase-1 (DHP-1) and it does not require the co-administration of a DHP-1 inhibitor[8]. To counter the increasing prevalence of MDR-AB, biapenem, the latest broad-spectrum carbapenem approved in several countries, is more stable against carbapenemase than other carbapenems[9]. The data from Siriraj Hospital, Thailand showed the susceptibility of biapenem against extended spectrum beta-lactamase (ESBL)-producing *E. coli*, ESBL-producing *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* were 100%, 100%, 70%, and 37% respectively, during 2006 to 2009[10]. Similar to other studies in China[11] and India[12], biapenem showed good activity against ESBL-producing *E. coli, K. pneumoniae*, *P. aeruginosa,* and *A. baumanii.* Thus, biapenem has emerged as a new treatment option for MDRAB infections. Nonetheless, none of prevalence studies which collected large number of *A. baumanii* isolates in tertiary care hospital in Thailand showed susceptibility patterns of biapenem and other antimicrobial agents against these organisms. In this study, we determined the *in vitro* activity of biapenem against *A. baumannii* causing serious infections in hospitalised patients from tertiary care hospitals in Thailand.

2.2. MATERIALS AND METHODS

2.1. Study centers and bacterial isolates

A. baumannii clinical isolates were collected from patients admitted to 13 tertiary care hospitals in Thailand in 2017. These 13 tertiary care hospitals were 4 hospitals from central region including Bangkok, 3 hospitals from northern region, 3 hospitals from north-eastern region, 2 hospitals from southern region, and 1 hospital from eastern region of the country. Non-duplicate consecutive isolates from distinct infectious episodes were obtained from admitted patients. All study isolates were sent to microbiology laboratory (Department of Microbiology, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand).

This study protocol was approved by The Ethics Committee of Faculty of Dentistry/Faculty of Pharmacy, Mahidol University (COA.No.MU-DT/PY-IRB 2017/040.2607).

2.2. Antimicrobial susceptibility testing and interpretation

Antimicrobial susceptibility testing was performed by broth microdilution in cation-adjusted Mueller-Hinton broth (CAMHB) according to Clinical Laboratory Standard Institute (CLSI) guidelines 2016[13]. *A. baumannii* isolates were tested against biapenem and comparators; imipenem, meropenem, colistin, sulbactam, ciprofloxacin, ceftazidime and fosfomycin sodium. The concentration ranges tested in two-fold dilutions were carbapenems (0.125 – 1024 μg /mL), colistin (0.0625 – 512 μg/mL), sulbactam (0.5 – 2048 μg/mL), ciprofloxacin (2 – 512 μg /mL), ceftazidime (0.125-512 μg/mL) and fosfomycin sodium (8-4096 μg/mL). The reference isolates *E. coli ATCC 25922* were used as positive quality control isolates.

MICs and susceptibility rates were interpreted according to the CLSI guidelines (2016)[13]. No breakpoints for fosfomycin sodium are available from the CLSI guidelines. Thus, the CLSI guidelines for Enterobacteriaceae were used for fosfomycin sodium (susceptibility, ≤64 μg/mL; resistance, ≥256 μg/mL)[13]. Additionally, they were divided into the CRAB and MDR groups according to the antimicrobial susceptibility patterns as the following antimicrobial categories: antipseudomonal carbapenems, antipseudomonal fluoroquinolones,

β-lactamase inhibitors, extended-spectrum cephalosporins, and polymyxins. CRAB was defined as acquired nonsusceptible (intermediate or resistant) to at least one carbapenem (excluding ertapenem). MDRAB was defined as non-susceptible to multiple antibiotics, often defined as three or more antimicrobials (e.g. aminoglycoside, ampicillin-sulbactam, antipseudomonal carbapenem, antipseudomonal cephalosporin, and fluoroquinolone)[14].

2.3 Antimicrobial agents

Most antimicrobial agent standard powder including imipenem and cilastatin sodium, meropenem, ciprofloxacin, ceftazidime, sulbactam, colistin sulphate were purchased from Tokyo Chemical Industry, Japan. Biapenem and fosfomycin standard powder were supported by Thai Meiji Pharmaceutical Co., Ltd, Thailand.

2.4 Data analysis

All relevant data including the proportion of resistance pattern, susceptibility of each antimicrobial agent, the MIC range, $MIC_{50/90}$ were performed by using the latest version of the MS Excel 2016. Data were expressed as range, percentage, and mean $\pm$ SD.

3. RESULTS

3.1. Study isolates

A total of 412 *A. baumannii* clinical isolates were submitted to *in vitro* activity testing. All of the isolates were derived from patients with hospital-acquired infections. Three-hundred and twenty-one (77.9%), 37 (8.98%), 23 (5.58%), 19 (4.61%), and 12 (2.91%) of the isolates were obtained from sputum, pus, blood, urine, and other specimens, respectively. *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control (QC) organisms to ensure proper test conditions and procedures for susceptibility testing. The validation of QC results was based on breakpoints in the CLSI recommendations. The MICs of QC strains produced 99.5% within established ranges.

3.2. Susceptibility to antimicrobial agents

According to MIC results from the reference BMD method, 412 non-duplicate clinical isolates of *A. baumannii* isolates were classified as 76 non-MDR (18.45%), 320 MDRAB (77.67%), 328 CRAB (79.61%), and 58 CoRAB (14.07%). The antibacterial MIC range, MIC_{50} and MIC_{90} of MDR and CRAB isolates were 4–128 fold higher than non-MDR isolates. Among the non-MDR isolates, the most isolates (≥90%) had MICs of imipenem, meropenem, and biapenem ≤2 μg/mL and MIC_{90} ≤2 μg/mL, whilst only 2.6% of imipenem to non-MDR isolates had MIC>4 μg/mL. On the contrary, the most isolates (>80%) had MICs of meropenem, and biapenem ≥16 μg/mL and MIC_{90} of carbapenems was ≥32 μg/mL, ≥64 μg/mL in MDRAB/CRAB, CoRAB, respectively. Therefore, the MDR *A. baumannii* population had significantly higher MICs and more non-susceptible isolates than the non-MDR isolates. When considered in geographic part and source of specimen, the MIC range, $MIC_{50/90}$ reported no more than 2-fold dilution when compared with the overall mean.

Over 95%of MDRAB and CRAB isolates exhibited high resistance to cephalosporins, ciprofloxacin, and carbapenems including imipenem, meropenem except biapenem (92%). Whereas, colistin was found to be the most effective agent which showed only 14% resistance.

Totally, 328 *A. baumannii* clinical isolates were identified as CRAB, with the MICs of carbapenems ranging from 4 to 1024 μg/mL. The rate of carbapenem resistance was more than 70% while, all carbapenem-resistant isolates had MIC_{90} to imipenem, meropenem >64 μg/mL and biapenem 32 μg/mL. In addition, 320 *A.baumannii* clinical isolates were identified as MDRAB, with >90% of isolates resistant to 3 groups of antimicrobials which were carbapenem, cephalosporins and fluoroquinolones. On the other hand, the rate of colistin resistance was 15% in CRAB and MDRAB while, the MIC_{50} and MIC_{90} were 0.5 and 4 μg/mL, respectively. For colistin testing, 85.9% of *A. baumannii* isolates were classified as susceptible to colistin. Although MDRAB had a broader range of MICs than non-MDR isolates (512–0.0625 μg/mL vs. 4–0.031 μg/mL, respectively), the MIC_{50} and MIC_{90} values of colistin for both groups were not different. Among CoRAB isolates, high rate of resistance (>80%) were found in most antimicrobial agents, but only fosfomycin showed 79.14% of

resistance. MIC range, $MIC_{50/90}$ and percent susceptibility rates for *A. baumannii* isolates were summarized in Table 1. The cumulative MIC distributions of antimicrobial tested against MDRAB, CRAB and CoRAB were shown in Figure 1.

Table 1. MIC values for individual antimicrobial agents of AB, non-MDR, MDRAB, CRAB, and Colistin-resistant AB

Type of organisms	Antimicrobial agents							
	Imipenem	**Meropenem**	**Biapenem**	**Colistin**	**Sulbactam**	**Ceftazidime**	**Ciprofloxacin**	**Fosfomycin**
MDRAB (N=320)								
- %susceptible	2.81	3.13	7.92	84.68	7.62	0	0.94	40
- MIC_{50}	32	32	16	0.5	32	>512	64	256
- MIC_{90}	128	64	32	4	128	>512	>256	1024
- MIC range	0.25-1024	0.125-256	0.125-256	0.063-512	1-2048	16->512	0.5->512	32->2048
CRAB (N=328)								
- %susceptible	-	1.52	8.23	85.06	11.89	2.74	3.35	40.85
- MIC_{50}	32	32	16	0.5	32	>512	64	256
- MIC_{90}	128	64	32	4	128	>512	256	1024
- MIC range	4-1024	0.5-256	0.125-256	0.063-512	0.5-2048	2->512	0.125->512	32->2048
CoRAB (N=58)								
- %susceptible	10.34	17.24	17.24	0	17.24	10.34	10.34	20.68
- MIC_{50}	32	32	16	4	32	>512	64	256
- MIC_{90}	128	128	32	16	128	>512	>256	1024
- MIC range	0.25-1024	0.25-256	0.125-256	4-512	0.5-2048	4->512	0.5->512	64->2048
Non- MDRAB (N=76)								
- %susceptible	94.74	96.05	97.37	93.42	85.52	76.32	78.94	48.68
- MIC_{50}	0.5	0.5	0.125	0.25	2	8	0.5	128
- MIC_{90}	2	1	0.25	2	32	512	8	512
- MIC range	0.125-16	0.063-4	0.015-4	0.03-4	0.5-512	2->512	0.125-128	8-1024
Total (N=412)								
- %susceptible	19.67	20.87	26.21	85.92	31.55	18.20	17.96	40.78
- MIC_{50}	32	32	8	0.5	16	>512	64	256
- MIC_{90}	64	64	32	4	128	>512	256	1024
- MIC range	0.125-1024	0.063-256	0.016-256	0.03-512	0.5-2048	2->512	0.125->512	8->2048

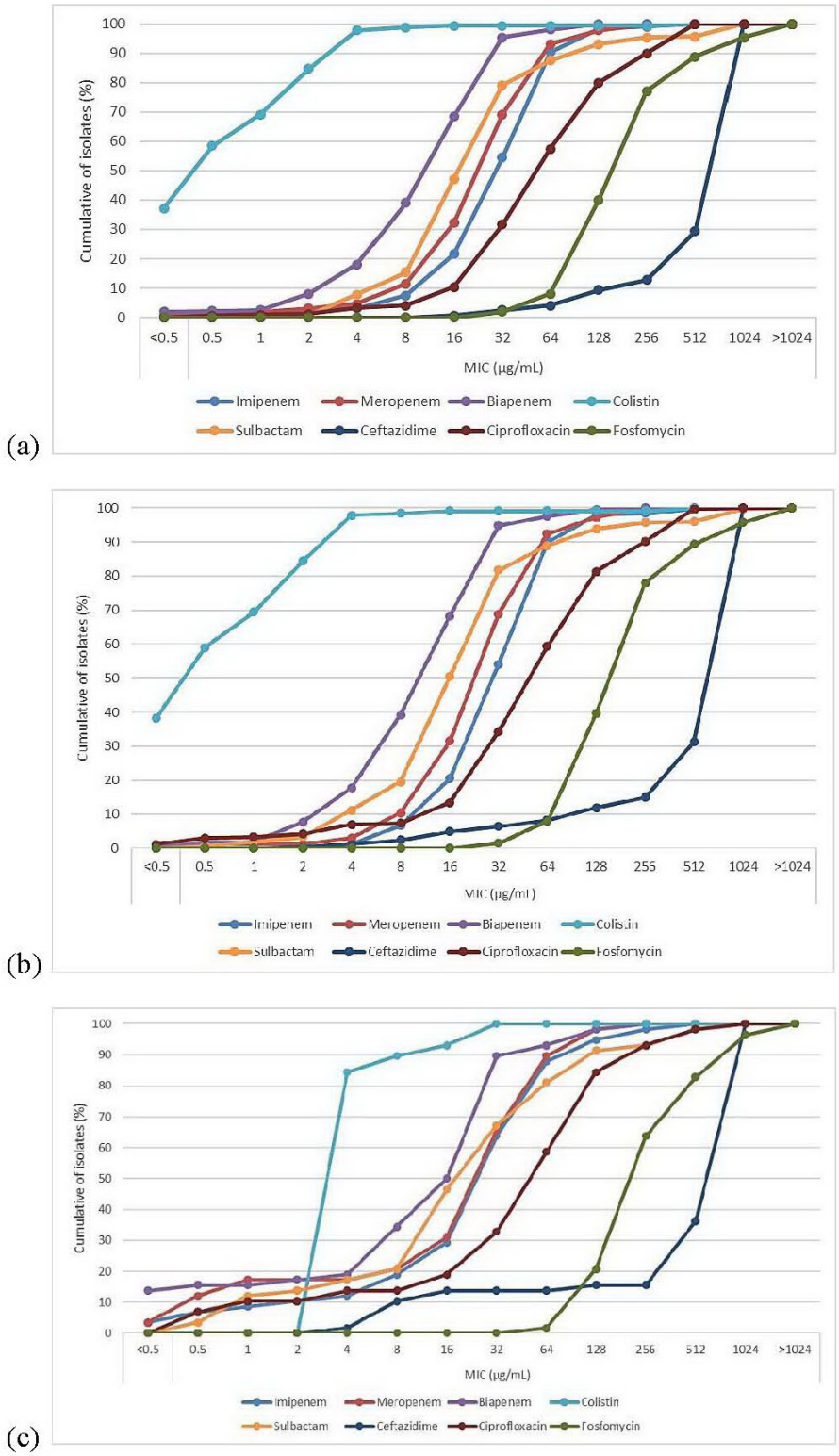

Figure 1. Cumulative minimum inhibitory concentration (MIC) distribution for all antimicrobial tested against (a) MDRAB, (b) CRAB and (c) Colistin-resistant AB

Biapenem has higher activity against *A. baumannii* when compared with other carbapenems, as shown in this study, with an overall MIC_{90} of 32 µg/mL for biapenem amongst MDR, CRAB, and CoRAB isolates which was lower than that of imipenem and meropenem at least 2 to 4-fold dilution. Moreover, ≥15% of isolates which were resistant to imipenem and/or meropenem showed susceptible to biapenem.

4. DISCUSSION

The prevalence of antibiotic-resistant pathogens such as *A. baumannii* is increasing worldwide and specifically in the Asia-Pacific region[15-16]. This dilemma is complicated by limited available antimicrobial choices and the recognition of problems with antimicrobial use. In present study, from 2016 till 2017, a significant increase of multidrug-resistant and carbapenem-resistant *A. baumannii* in a tertiary care hospital in Thailand during 2016 till 2017 was observed. Carbapenem resistance rates were high for MDRAB and CRAB, in which imipenem and meropenem were less active than biapenem. Based on MIC_{90} values, biapenem was 2-fold and 4-fold more active against MDRAB and CRAB than imipenem and meropenem respectively. Most of *A. baumannii* remained highly susceptible to colistin. These results are consistent with the prevalence of CRAB and MDRAB in Southeast Asia[15-16].

Result from the Comparative Activity of Carbapenems Testing (COMPACT) Asia-Pacific Study during the latter half of 2008 and early 2009, showed MICs for carbapenems including doripenem, meropenem and imipenem against *A. baumannii* of >64 µg/mL for both MIC50 and MIC90. Susceptibility rates for *A. baumannii* were approximately 20-30% for all carbapenems tested[17]. Similarly, the COMPACT II Asia-Pacific Study during April-July 2010 showed 73% of *A. baumannii* not susceptible to carbapenems and $MIC_{50/90}$ were 32/>64 µg/mL[18]. Data according to the latest NARST report, over 70% of isolates tested (42,212 isolates) between January and December 2018 were found to be resistant to carbapenem, ampicillin/sulbactam, and piperacillin/tazobactam which was a significant increase from 58.2% (13,645 isolates) in 2010[19-20].

Among the eight antibiotics tested, MDRAB and CRAB showed widespread resistance to ceftazidime, ciprofloxacin and carbapenems in more than 90% of the strains. The reason of high resistance rate could be explained by two factors which were the pathogenic organisms, and the host status. The first reason was that the pathogens were obtained from tertiary care hospitals in Thailand, where risk of drug resistance organisms was high. In contrast to the NARST report[19-20], specimens were collected from various types of hospitals. The cause of high resistance rates of infection in tertiary care hospitals was finally derived from several factors including the inappropriateness of antibiotic use. In particular, prior antibiotic use, such as carbapenems, was an important factor that contributed to the selection of such organisms[21]. The second reason was patients admitted in tertiary care hospitals were most likely had high risk of *A. baumannii* resistance because physiological defense barriers were interrupted by several treatment modalities. Consequently, patients might suffer from infections caused by MDR pathogens. These conditions of the patient generally require broad spectrum antibiotics, and thus lead to highly resistance pattern. In addition, there were other precipitating factors such as ventilator support, urinary and/or intravenous catheter. These all increased the risk of colonization or infection with *A. baumannii*[22].

However, more than 15% of imipenem and meropenem resistant strains were sensitive to biapenem. Several explanations include structure relationship of biapenem and the different resistance mechanisms. The bla_{OXA-23} was reported as the OXA-type carbapenemase-encoding genes in Thailand. Biapenem has good activity against *A. baumannii* which expresses the OXA-type carbapenemase. Biapenem affects to class B, D carbapenemase enzyme in several ways. These are binding carbepenemase residue structures which reveal the conformational change at the active site, strong hydrogen bond with composition of NDM-1 which affects on biapenem binding and hydrolysis against Gram negative bacteria[9].

From this *in vitro* data, it can be proposed that biapenem might have role in the treatment of MDRAB, CRAB, and CoRAB in two means which are increasing dose of biapenem and/ or use as combination with other antimicrobial agents. Available pharmacokinetic/pharmacodynamic data

on biapenem, the finding of a significant correlation between drug concentrations and the probability of attaining pharmacodynamic target (PTA) in various populations showed >75%PTA values for achieving ≥40%T>MIC at MIC 4 μg/mL for doses of standard regimen and extended infusion (3-h infusion). With only a dose of 300mg q8h (3-h infusion) and 600 mg q8h (3-h infusion) could be achieved PTA >75% for ≥40%T>MIC at MIC 8 μg/mL. However, no regimens achieved PTA ≥ 80% at MIC 32 μg/mL, which was MIC_{90} of this study[23]. Thus, further investigation on increased dose of biapenem might be needed. Additionally, the role of biapenem in combination with other antimicrobial agents might be possible. The findings of this study showed higher susceptibility to fosfomycin, sulbactam and colistin for both MDRAB and CRAB than other antimicrobials. The synergistic or additive effect of carbapenem with fosfomycin, sulbactam and colistin were reported against *A. baumannii*[24-25]. Therefore, the rates of synergy and characterise of biapenem in combination with colistin, fosfomycin, and sulbactam against carbapenem-resistant *A. baumannii* should be further studied utilizing checkerboard and time–kill experiments.

The strengths of this study lie in the large number of isolates from several tertiary-care hospitals across Thailand, and probably attributable to the infection control and antimicrobial overuse in place in each center. However, this study still has several limitations that should be noted. First, the study was not able to evaluate the information regarding antimicrobial administration, which could be one of the risk factors for MDRAB and CRAB acquisition. Second, some antimicrobials were not tested in this study which were amikacin and tigecycline. Last genotypic mechanism could not be detected.

5. CONCLUSIONS

A. baumannii resistance seems to be a complex phenomenon, in which isolates of different sources and different resistance patterns. Our data supported that, colistin was found to be better against MDRAB and CRAB compared to other antimicrobial agents. However, prudent use of colistin is needed to avoid an increase in colistin-resistance mechanisms. While biapenem showed a good activity over other carbapenems against the MDRAB, CRAB and CoRAB. Accordingly, this drug might be a therapeutic option which might be used as high dose monotherapy or in combination for highly resistant bacteria. Further studies are needed to figure out the appropriate dose of biapenem and role of combination therapy with other antimicrobials against *A. baumannii* resistance strains.

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Conflict of interest (If any)

This study protocol was principally initiated by all investigators. Biapenem and fosfomycin standard powder were supported by Thai Meiji Co.,Ltd., Thailand. The company had no role in protocol development, data collection, data analysis, results, discussion and conclusion of this work. The authors had no conflict of interest in this work.

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Ethical approval

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