Faculty of Medicine, Cairo University Postgraduate Research Protocol Template
(Please read carefully provided guidance documents for a comprehensive understanding and proper formulation of your thesis protocol and required forms)

1. Study

a- Proposed Study Title:

Comparative Efficacy and Safety of Colistin–Meropenem Versus Ceftazidime/Avibactam–Aztreonam in Pediatric Patients with Carbapenem-Resistant Enterobacterales Infections

b- Degree:
c- Date of Registration of MSc or MD:

2. Candidate

a. Name:
b. Occupation:
c. Affiliation:
d. Email addresses:
e. Full mailing address:
f. Phone number:

3. Supervisors Contact Information

a. Principal supervisor: Name: Hanaa Ibrahim Rady
Department: Professor of Paediatrics, Faculty of Medicine, Cairo University.
Phone: 01001482444
E-mail address: Hanaaarady@gmail.com

b. Other investigators:

1-Name: Hafez Mahmoud Bazaraa
Department: Professor of Paediatrics- Faculty of Medicine – Cairo University.
Phone: 01222235316
E-mail address: hmbazaraa@kasralainy.edu.eg

2- Name: Walaa Awad Elmeniar
Department: Pharmacy Department, Huddersfield University, UK
Phone: +201007020630 +447438930854
Email: U2469564@unimail.hud.ac.uk
walaaawad8375@yahoo.com

3-Name: Syed Shahzad Hasan
Department: Course Leader, Pharmacy Department, Huddersfield University, UK
Phone: +44 1484 256941
Email: s.hasan@hud.ac

4-Name: Barbara Conway
Department: Head of Pharmacy Department, Huddersfield University, UK
Phone: +441484 256301
Email: B.R.Conway@hud.ac.uk

5-Name: Mahmoud Abdelnaby Mohamed
Department: Clinical Pharmacy Department, Abo-Elreesh Hospital
Phone: 01140148113
Email: ghataty80@gmail.com

4. Background and Rationale:

Carbapenem-resistant organisms (CROs) are one of the increasing threats to public health and impose a significant clinical and economic burden, particularly in paediatric populations. In 2018, the World Health Organisation identified CROs as a priority list of antibiotic-resistant bacteria to encourage antibiotic discovery (Barenghi et al., 2025; Tacconelli et al., 2018). CROs include carbapenem-resistant Enterobacterales (CRE) and multidrug-resistant Pseudomonas. In 2021, carbapenem-resistant organisms (CROs) were responsible for approximately 216,000 deaths globally (Ranjbar & Alam, 2023). In the US, nearly 46,000 patients were infected with CROs, resulting in approximately 4,000 deaths annually (CDC, 2019). CROs increased the length of hospital stay by 42.1%, and the associated medical costs were 50.4% higher compared to those with carbapenem-susceptible infections (Imai et al., 2022).

Colistin is active against MBL enzymes (Zheng et al., 2023) produced by CROs. Consequently, this led to the increased use of colistin and polymyxin B, in combination

(Abdelsalam et al., 2018), as a standard treatment. However, colistin is considered a last-resort antibiotic due to the increased incidence of nephrotoxicity. Thus, it increases the demand for innovative new antibiotics. Since 2014, the US Food and Drug Administration has approved 4 new beta-lactam beta-lactamase inhibitor (BLBLI) combination antibiotics for the treatment of CROs: ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam (Yahav et al., 2020).

Ceftazidime-avibactam (CZA) was approved in 2015 in the US (Zheng et al., 2022). Moreover, it is recommended by many guidelines as a first-line therapy for many infections caused by carbapenem-resistant Enterobacterales (CRE) due to a favourable safety and efficacy profile (Tamma et al., 2024; Paul et al., 2022). Particularly, the incidence of colistin-associated acute kidney injury (AKI) ranges from 25 to 75% compared to 10 to 20% among BLBLIs (Mattos et al., 2019; Rigatto et al., 2016; Rutter & Burgess, 2017).

Although CZA has a favourable safety and efficacy profile, it is ineffective against CRE strains producing New Delhi Metallo-B-Lactamases (MBLs). Furthermore, research has shown that short-term CZA treatment may induce different *blaKPC* gene mutations in pathogens, leading to further resistance, which is against its use as monotherapy (Shi et al., 2022; Tumbarello et al., 2021). Mantzarlis et al., 2025. Reported that when CZA is combined with Aztreonam (AZT) can overcome the MBL gene resistance with a safety profile (Mantzarlis et al., 2025).

This study aims to determine which regimen offers superior clinical and microbiological outcomes, with acceptable safety in paediatric patients.

4. **Objectives:** (describe specific objectives or hypotheses behind the study)

Primary Objective:

To compare the efficacy and safety of Colistin and Meropenem Versus Ceftazidime/avibactam and Aztreonam in paediatric patients infected with CRE infections in critical care settings.

Secondary Objectives:

- Decrease the incidence of colistin-induced AKI. Prevent the emergence of colistin resistance, to preserve it as a last resort in other gram-negative organisms, when there are limited choices.

5. Study Design:

A- Nature of the study

- Prospective study **√** ■
- Retrospective study

B- Design of the study: (Please insert √ in front of the suitable design)

1-	Case series	
2-	Qualitative	
3-	Survey	
4-	Cross sectional analytic	
5-	Case-control	
6-	Cohort (Longitudinal)	
7-	Randomized Clinical Trial	**√**
8-	Non-randomized clinical trial	
9-	Animal study	
10-	Cellular study	

- **Other study design:** ☐

Please describe:

- **Study Methods**

Prospective randomised controlled trial.

- **Study setting:**

Pediatric ICU at Abo Elreesh Mounira Children's Hospital, Cairo University

- **Population of study:** (Please provide all details regarding participants, including gender, age range and disease conditions. Indicate if this protocol involves children, prisoners, pregnant women or cognitively impaired or mentally disabled subjects. Also, indicate if participants will be divided into groups and mention the characteristics of and number of participants in each group adequately.

This prospective study will be conducted on hospitalised pediatric patients in the PICU who are infected with CRE and require combination therapy.

- **Study location:** (Please provide where the study will be conducted and from where study participants will be recruited)

The study will be conducted at the Pediatric ICU at Abo Elreesh Mounira Children's Hospital, Cairo University, after ethical approval.

- **Inclusion criteria:**
  - Age more than 3 months for both sexes.
  - Hospitalised patients with proven infection.
  - Culture or biofire showed Carbapenem-Resistant Enterobacterales.

- **Exclusion criteria:**
  - Co-infection with other microorganisms in conjunction with CRE.
  - Empirical use.
  - Duration of treatment combination is less than 48 hours.
  - Expected survival is less than 48 hours**.**
  - Known allergy to study drugs.
  - Renal replacement therapy.

- **Methodology in detail:** (the description should be chronological, starting with randomization method in detail, if RCT, group allocation and characteristics of each group. Also, indicate what would be done to participants initially and at follow-up visits, including the follow-up duration, if applicable.

This study will be a Prospective, open-label (due to differing administration routes and dosing schedules), parallel-group, randomised controlled trial.

Randomization & Allocation

- **Method:** Computer-generated random sequence (1:1 ratio).
- **Allocation concealment:** Sealed opaque envelopes.
- **Stratification:**
  - Infection type (bloodstream vs non-bloodstream).
- **CONSORT study flow diagram will be used**.

Arm A (Control group): Meropenem+ Colistin

- **Meropenem:** standard paediatric dosing per weight
  - 40 mg/kg/dose every 8 hours; maximum dose: 2,000 mg/dose
- **Colistin:** weight-based IV dosing per hospital protocol and renal function.
  - Mild to moderate infections: 75.000 IU/Kg every 12hours in normal renal function
  - Severe or life-threatening infections: loading dose 150.000 IU/kg followed by the maintenance dose after 12 hours in creatinine clearance >40 ml/min, or after 24 hours if crcl ≤ 40ml/min. Maintenance dose is 75.000 IU/Kg every 8 hours in normal renal function.
  - Renal impairment: dose adjustment according to hospital protocol (see Table 1, supplementary materials)

Duration: 7–14 days, depending on the infection site.

Arm B (Case group): Ceftazidime–avibactam + Aztreonam

- **Ceftazidime–avibactam:** standard paediatric dosing per weight and age.
  - Infants ≥3 months to <6 months:40 mg ceftazidime/kg/dose every 8 hours
  - Infants ≥ 6 months, children, adolescents <18 years:50 mg ceftazidime/kg/dose every 8 hours, maximum dose 2000 mg ceftazidime/dose
  - Adolescents≥ 18 years: 2000 mg ceftazidime every 8 hours

- **Aztreonam:** standard paediatric dosing per weight.
  - Mild to moderate infection: 30 mg/kg every 8 hours, maximum 3000 mg/day
  - Severe infections: 40 mg/kg every 8 hours, maximum 8000 mg/day

- **Duration:** 7–14 days, depending on the infection site.

Data collection:

Data will be collected from day 1 of admission or appearance of signs and symptoms of infection, and followed up every 24 hours using a designed data collection sheet (see Supplementary Table 2), and will continue for 14 days.

Data analysis:

The data will be extracted in Microsoft Office Excel 2016. Comparison between different outcomes in both groups will be done, and an appropriate statistical test will be used. Comparing clinical success rate using the Chi-square test, Continuous variables using the t-test and Mortality using Kaplan–Meier survival curves. Multivariable logistic regression to adjust for confounders. Subgroup analysis by pathogen genotype (KPC vs MBL producer) or by bloodstream vs non-bloodstream may be used if there is sufficient sample size.

- **Intervention:**

☐ Diagnostic intervention (please describe):

■ Therapeutic intervention (please describe):

☐ No intervention

- **Does the research involve?**

  ■ Human participants

  ☐ Biological samples/Tissues

  ☐ Identifiable private data/Information

- **Type of consent of study participants:**

  ■ Written consent

  ☐ No consent needed (Please justify)

- **Potential risks:**
  (Please mention all risks involved, even mild ones as pain, discomfort, chance of infection or psychological effects)

All treatment options are approved in paediatrics and will be used in the approved doses and according to renal function. According to the literature, both combinations are suitable for all resistance genes produced by CRE. These combinations will be used when there are no other sensitive antibiotics in the culture; they will be used as a life-saving option for the patients. Colistin may induce AKI; thus, renal function test and urine output will be monitored cautiously, and other nephrotoxic medications will be avoided if applicable.
Meropenem, ceftazidime/avibactam, and aztreonam may induce hypersensitivity reactions. Patient will be monitored closely during administration, and if there is any history of allergic reaction, the patient will be excluded from the study and another appropriate antibiotic will be given. Gastrointestinal disturbances are common side effects of antibiotics, and symptomatic treatment will be provided. Superinfection with C.difficile or fungal infection is common with prolonged use of antibiotics, therefore, the shortest effective duration will be followed. Patients will be admitted in the critical care unit under clinical and laboratory monitoring. If any intolerable and unmanageable side effects occur, the culprit antibiotic will be discontinued immediately, and appropriate treatment will be given to minimize harm and ensure patient safety.

- **Confidentiality of data:** (Please explain how privacy and confidentiality of data and records will be maintained)

All information collected during this study will be kept confidential, with accessibility restricted to the authorised members of the research team only, and will be used for research purposes only. No personal identifiers (name, ID, medical record number) will be used in data collection or data analysis. Study results will be reported in aggregate form only, and no individual participant will be identifiable. After the period of the study, data will be securely destroyed according to the institutional guidelines.

9- Study outcomes:

- **Primary outcomes** (Most important measurable outcomes)
  - Clinical success rate at day 7-14, defined as the resolution of symptoms and no need for antibiotic change.

- ***Secondary outcomes***
  - Microbiological eradication at day 7 and day 14
  - Day 7 and day 14 mortality.
  - Time to fever resolution.
  - Length of ICU stay.
  - Incidence of AKI defined by KDIGO criteria.
  - Adverse events (nephrotoxicity, hepatotoxicity, hypersensitivity, others)
  - Monitoring response to treatment and persistence of the same organisms in subsequent cultures, denoting clinical failure

10- Sample size and technique (number of study subjects included and justification, including the clinical and statistical assumptions supporting sample size calculation)

The minimum required sample size was calculated to achieve a power of 80% (at an alpha error of 0.05). According to the literature, the clinical success rate with colistin is approximately 50%. Whereas with ceftazidime/avibactam and aztreonam is approximately 80%. Thus, the required sample size is 76 patients, 38 patients in each group. In either case, we add 10% for dropouts.

11- Statistical analysis (Please describe your data analysis plan)

Comparing clinical success rate using the Chi-square test, Continuous variables using the t-test and Mortality using Kaplan–Meier survival curves. Multivariable logistic regression to adjust for confounders. Subgroup analysis by pathogen genotype (KPC vs MBL producer) or by bloodstream vs non-bloodstream may be used if there is sufficient sample size.

12- Source of funding: (Please include source of funding, even if self-funding)

- Faculty of Medicine, Cairo University ■
- Other sources: ☐

  Please specify: There is no direct funding from any agents. However, the facilities of Cairo university hospital will be used in this study. Because the study subjects will receive

treatment at Cairo university hospital.

13- Time plan:

- When to start (**the start date should be after getting REC approval**)?
mediately after obtaining the approval

-When expected to finish? 6-12 months

- When to publish? after finishing the data collection and writing phases (2-3 months)

14- References:

Abdelsalam, M. F. A., Abdalla, M. S., & El-Abhar, H. S. E. D. (2018). Prospective, comparative clinical study between high-dose colistin monotherapy and colistin–meropenem combination therapy for treatment of hospital-acquired pneumonia and ventilator-associated pneumonia caused by multidrug-resistant Klebsiella pneumoniae. *Journal of global antimicrobial resistance*, *15*, 127-135.

Barenghi, L., Pellegrini, M., & Barenghi, A. (2025). WHO's global research priorities for Antimicrobial resistance in human health. *The Lancet Microbe*.

CDC, A. (2019). Antibiotic resistance threats in the United States. *US Department of Health and Human Services: Washington, DC, USA*, *1*, 67-100.

Imai, S., Inoue, N., & Nagai, H. (2022). Economic and clinical burden from carbapenem-resistant Bacterial infections and factors contributing: a retrospective study using electronic medical records in Japan. *BMC infectious diseases*, *22*(1), 581.

Mantzarlis, K., Manoulakas, E., Papadopoulos, D., Katseli, K., Makrygianni, A., Leontopoulou, V., ... & Dimopoulos, G. (2025). Ceftazidime-Avibactam Plus Aztreonam for

the Treatment of Blood Stream Infection Caused by Klebsiella pneumoniae Resistant to All Beta-Lactam/Beta-Lactamase Inhibitor Combinations. *Antibiotics*, *14*(8), 806.

Mattos, K. P. H., Gouvea, I. R., Quintanilha, J. C., Cursino, M. A., Vasconcelos, P. E., & Moriel, P. (2019). Polymyxin B clinical outcomes: a prospective study of patients undergoing intravenous treatment. *Journal of clinical pharmacy and therapeutics*, *44*(3), 415-419.

Paul, M., Carrara, E., Retamar, P., Tängdén, T., Bitterman, R., Bonomo, R. A., ... & Rodríguez-Baño, J. (2022). European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by the European Society of Intensive Care Medicine). *Clinical Microbiology and Infection*, *28*(4), 521-547.

Ranjbar, R., & Alam, M. (2023). Antimicrobial Resistance Collaborators (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Evidence-based nursing*.

Rigatto, M. H., Oliveira, M. S., Perdigão-Neto, L. V., Levin, A. S., Carrilho, C. M., Tanita, M. T., ... & Zavascki, A. P. (2016). Multicenter prospective cohort study of renal failure in patients treated with colistin versus polymyxin B. *Antimicrobial agents and chemotherapy*, *60*(4), 2443-2449.

Rutter, W. C., & Burgess, D. S. (2017). Acute Kidney Injury in Patients Treated with IV Beta-Lactam/Beta-Lactamase Inhibitor Combinations. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *37*(5), 593-598.

Shi, Q., Han, R., Guo, Y., Yang, Y., Wu, S., Ding, L., ... & Hu, F. (2022). Multiple novel

ceftazidime-avibactam-resistant variants of bla KPC-2-positive Klebsiella pneumoniae in two patients. *Microbiology Spectrum*, *10*(3), e01714-21.

Shields, R. K., Nguyen, M. H., Chen, L., Press, E. G., Kreiswirth, B. N., & Clancy, C. J. (2018). Pneumonia and renal replacement therapy are risk factors for ceftazidime-avibactam treatment failures and resistance among patients with carbapenem-resistant Enterobacteriaceae infections. *Antimicrobial agents and chemotherapy*, *62*(5), 10-1128.

Tamma, P. D., Heil, E. L., Justo, J. A., Mathers, A. J., Satlin, M. J., & Bonomo, R. A. (2024). IDSA GUIDELINES.

Tumbarello, M., Raffaelli, F., Giannella, M., Mantengoli, E., Mularoni, A., Venditti, M., ... & Viale, P. (2021). Ceftazidime-avibactam use for Klebsiella pneumoniae carbapenemase–producing K. pneumoniae infections: a retrospective observational multicenter study. *Clinical Infectious Diseases*, *73*(9), 1664-1676.

Yahav, D., Giske, C. G., Grāmatniece, A., Abodakpi, H., Tam, V. H., & Leibovici, L. (2020). New β-lactam–β-lactamase inhibitor combinations. *Clinical microbiology reviews*, *34*(1), 10-1128.

Zheng, G., Cai, J., Zhang, L., Chen, D., Wang, L., Qiu, Y., ... & He, J. (2022). Ceftazidime/avibactam-based versus polymyxin B-based therapeutic regimens for the treatment of carbapenem-resistant Klebsiella pneumoniae infection in critically ill patients: a retrospective cohort study. *Infectious Diseases and Therapy*, *11*(5), 1917-1934.

Zheng, Z., Shao, Z., Lu, L., Tang, S., Shi, K., Gong, F., & Liu, J. (2023). Ceftazidime/avibactam combined with colistin: a novel attempt to treat carbapenem-resistant

Gram-negative bacilli infection. *BMC infectious diseases*, *23*(1), 709.

Supplementary materials

Table 1: Colistin Renal dose adjustment according to the local hospital protocol

Doses in renal impairement

*Doses Based on Ideal Body Weight

Cr Cl	Recommended dose %	Recommended dose IU/Kg
40 - 59	80 % standard Dose divided every 12 hours	120.000 IU/Kg divided every 12 hours
20 - 39	60 % standard Dose divided every 12 hours	90.000 IU/Kg divided every 12 hours
5- 19	50 % standard Dose once daily dose	75.000 IU/Kg once daily dose
< 5	40 % standard Dose once daily dose	60.000 IU/kg once daily dose
CRRT	Standard dose provided dialysis at least 8 h in previous 12 hours	150.000 IU/Kg provided dialysis at least 8 h in previous 12 hours
IHD/ SLED	**Non Dialysis day** : 40% standard dose once daily **Dialysis Day** : 40% standard dose once daily+ supplement 4% standard dose for each hour of dialysis (example nearly 15% of standard dose in 4 hours dialysis session) given after dialysis session	**IHD:** **Non Dialysis day:** 60.000IU/Kg once daily **Dialysis Day:** 60.000IU/Kg + Supplement 6000 IU/Kg for reach hour of dialysis session Example: 60.000 IU/Kg + supplement 24.000 IU/Kg if 4 hours dialysis session given after dialysis session

Table 2: Data collection sheet 7th PICU for each patient for 14-day follow-up

Age	
Gender	
Date of admission	
Date of discharge	
Cause(s) of admision	
Other Underlying diseases	
History of Previous ABX used	
PIM 3 Score on admission	
Sepsis? / septic shock? On admission	
Start day	
ABX use and dose	
Length of therapy for the combination	
Length of therapy for one ABX	
Stop date for CZA	

Stop date for MER											
Stop date for COL											
Stop date for AZT											
Cause of early discontinuation of ABX											
Use of other antibiotics During combination											
Source of infection											
Culture(source, pathogen)											
Culture sensitivity											
Biofire results											
ABX started based on culture or biofire results?											
Days	Baseline	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Use of a vasoactive agent											
Mode of oxygenation/setting before starting ABX)											
Organ dysfunction (renal or liver?											
ABX used											
Average Fever (for 7 days) starting with baseline before starting ABX											
CRP day after day, starting with baseline before starting ABX											
Average BP/HR (for 7 days) starting with baseline before starting ABX											

CBC (WBCs, shift, Platelets)											
Outcomes											
Microbial clearance after 7 days? Follow-up culture	Date: result:										
Total cost of the ABX course	Cost of CZA vial: Cost of COL vial: Cost of MER vial: Cost of AZT vial: Regimen`s total cost :						Total cost of CZA vials used: Total cost of COL vials used: Total cost of MER vials used: Total cost of AZT vials used:				
Clinically improved? Totally /partially/No improvement/deteriorated ?											
Mortality 7 days											
Mortality 14 days											
LOS											
Acute kidney injury											
Other ADR											

1- Please fill in all the included sections and don't delete any part of the template
2- For choice brackets, please just use the fill-in function in word