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Review Article

Prevalence of carbapenem-resistant *Enterobacterales* (CRE) in Somalia: A systematic review and meta-analysis

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ABSTRACT

Antimicrobial resistance remains a major challenge in public health. Many reports of resistance to common antibiotics have been documented. The carbapenems are one of the last line antibiotics against many members of the *Enterobacterales*. However, the actual prevalence of carbapenem-resistant *Enterobacterales* in Somalia is unknown. Thus, this present investigation was done to ascertain the actual prevalence. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline in the conduct of this study. Searches were conducted in electronic databases such as PubMed, Web of Science, Scopus, ScienceDirect, and Google Scholar to find published articles providing information on the prevalence of carbapenem-resistant *Enterobacterales* in Somalia. Data were extracted and analyzed using the OpenMeta analyst software. Study quality was evaluated using the JBI prevalence tool. The resistance rate of *Enterobacterales* to carbapenems were estimated using the random-effect model. A pooled resistance rate of 4.3% (95% CI, 2.5–7.2) was obtained for imipenem, 2.8% (95% CI, 0.8–8.8) for meropenem, and 13.9% (95% CI, 3.1–44.7) for ertapenem. The heterogeneity test showed low heterogeneity, except for studies contributing to the estimated resistance to ertapenem which had a high heterogeneity (I^2=91.52%; Q=11.788; p<0.001). This first systematic review and meta-analysis suggests that carbapenem antibiotics can be relied on as last line antibiotics to treat *Enterobacterale* infections in Somalia.

1. Introduction

A global priority list of pathogenic bacteria that are resistant to medicines was issued by the World Health Organisation (WHO), and it includes several *Enterobacterales* for which new and novel antibiotics are desperately required.[1] The genus *Brenneria*, *Erwinia*, *Pectobacterium*, *Dickeya*, and *Pantoea* are among the many innocuous symbiotic and harmful strains of the Gram-negative bacteria class *Gammaproteobacteria* that make up the genera within the order *Enterobacterales*.[2] Numerous intestinal and extra intestinal disorders in both humans and animals are caused by the pathogenic strains, which are primarily *Escherichia spp*., *Klebsiella pneumoniae*, serovars of *Salmonella enterica*, *Yersinia pestis*, and species of *Enterobacter*.[3]

When treating diseases caused by *Enterobacteriaceae*, cephamycins and Extended spectrum cephalosporins (ESC) are widely utilized. Given the less likelihood of dual resistance to both tigecycline and colistin among the carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenems, in addition to these antibiotics, are among the last line *anti-Enterobacteriaceae* defense due to the emergence of multidrug resistance.[4,5] By substituting a carbon atom for a Sulphur atom and adding a double

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bond to the five-membered ring of the penicillin nucleus, carbapenems, which are categorized as β-lactam antibiotics, differ slightly from penicillin. Carbapenems are capable of establishing a strong bond with the bacterial Penicillin-binding proteins (PBPs), which are essential for extension and cross-linkage of the peptidoglycan cell wall, resulting in the lysis of the bacteria.[6]

At present, up to four carbapenems (doripenem, ertapenem, imipenem and meropenem) as well as three others (biapenem, faropenem, and panipenem) have clinical use approval in the United States of America[7] and Canada, respectively. Numerous surveillance studies conducted during the past ten years have documented the rise of CRE.[8] The major mechanisms of resistance to carbapenem in these bacteria involves (i) the presence of β-lactamases (carbapenemases), (ii) the collective effect of other β-lactamases with bacterial cell membrane permeability orchestrated by alteration or mutation in the porins, and/or (iii) elevation in the action of the efflux pump. A fourth means of anti-carbapenem action in Gram-negative bacteria has been described to include alteration of PBPs.[9]

In this work, attempt was made to assess the resistance rates of *Enterobacterales* to carbapenems in Somalia. This systematic review and meta-analysis is, to our knowledge, the first to look into this subject.

2. Materials and Methods

This systematic review and meta-analysis of published research papers was carried out based on the established guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[10] To prevent duplication of previous or ongoing investigations, we searched PROSPERO and other notable databases. The study protocol was thereafter registered in PROSPERO (number: CRD42023455823).

2.1. Literature search and data sources

We looked for publications describing the prevalence of CRE in Somalia using a combination of key terms including "*Enterobacteriaceae*," "CRE," "*Enterobacterales*," "*Escherichia coli*," "*E. coli*," "*Klebsiella*," "*Shigella*," "*Citrobacter*," "*Enterobacter,*" "Carbapenem," "Imipenem," "Meropenem," "Ertapenem" and "Somalia" in five electronic databases (Google Scholar, Scopus, Pubmed, Web of Science, and Science Direct). The complete search strategy utilized in exploring all the databases is presented in the supplementary document (File S1). No filters for study design, language, or publication year were used to ensure a thorough search. The initial database search was done on July 9, 2023, and an updated and last search, done on July 29, 2023, gave a total of 513 records. The databases' retrieved records were transferred to Mendeley software for the removal of duplicate records and preliminary screening.

2.2. Eligibility criteria

Studies that examined CRE in Somalia were included in this work. The following were not included:

1. Case reports, editorials, letters, review articles, book chapters, and opinions.
2. Articles that examined CRE outside of Somalia.
3. Articles whose complete information was not readily available.

All authors determined the criteria for article screening, selection, and evaluation. Two authors (A.S.A.M. and Y.A.N.) independently screened the publications on the bases of titles and abstracts. The entire texts of the records that passed screening were next evaluated. Conflicts that arose during the screening and assessment phase were resolved by discussion among all the authors.

2.3. Data extraction and quality assessment

Data extraction was done using an excel file that was pre-defined. From the articles that were included, all authors independently extracted the following data: Study name, duration of study, location, period of study, study design, sample type from which *Enterobacterales* were isolated, members and number of *Enterobacterales* tested for carbapenem resistance, and number of resistant isolates.

To evaluate the methodological quality of the studies assessed, the Joanna Briggs Institute (JBI) critical assessment checklist for prevalence data[16,17] (File S2) was employed. The studies were evaluated by two authors (Y.A.N and A.A.I) separately to provide an overall quality mark that spans from 0 to 9. If a study received a 7 or higher, it was deemed to be of satisfactory quality.[18]

2.4. Data synthesis and statistical analysis

The extracted data were examined for possible duplicate data and thereafter, analyzed. The data were analyzed using OpenMeta Analyst software. Summary estimates for resistance to each of carbapenems (Imipenem, Meropenem, and Ertapenem) were derived. The DerSimonian-Laird meta-analysis method and the random effect model were used to obtain the pooled estimates. Cochran's Q test was employed for the assessment of the study-level estimates' heterogeneities, and I^2 statistics was used to quantify them. I^2 values of 25%, 50%, and 75%, respectively, were regarded as low, moderate, and high heterogeneity.[19–21] A p-value of <0.001 was regarded as statistically significant in all tests.

3. Results

3.1. Selection of study

Figure 1 depicts a summary of the procedure of identifying and selecting articles used for this investigation. Upon

Table 1: Major characteristics of the included studies reporting the prevalence of CRE

Study ID [reference]	Location	Study period	Study design	Sample type	Method	Organisms	Total isolates
Ali 2022 [11]	Mogadishu	August 2021–June 2022	Cross-sectional	Middle ear discharge	DDM	*E. coli,* P. mirabilis, Klebsiella spp.	44
Hussein 2022 [12]	Mogadishu	September 2020–September 2021	Retrospective	Hemodialysis catheter tips	DDM	*E. coli*, *K. pneumoniae*	23
Mohamed 2020 [13]	Mogadishu	January 2019–January 2019	Retrospective	Urine	DDM	*E. coli*, *K. pneumoniae*	277
Moussa 2021 [14]	Mogadishu	October 2019 to March 2020	Cross-sectional	Urine, blood, vaginal swab, pus aspirates, stool	DDM	*E. coli*, *Proteus* spp., *Klebsiella* spp., *Salmonella* spp.	77
Ugur 2020 [15]	Mogadishu	2016–2018	Retrospective	Blood	DDM	*E. coli*, *K. pneumoniae*	8

Table 2: Resistance of *Enterobacterales* to carbapenem antibiotics

Carbapenem antibiotics	Number of studies	Resistance rate (%)	95% CI	I2 (%)	Q	Heterogeneity test	
						DF	P value
Imipenem	3	4.3	2.5–7.2	0	0.307	2	0.858
Meropenem	3	2.8	0.8–8.8	31.16	2.905	2	0.234
Ertapenem	2	13.9	3.1–44.7	91.52	11.788	1	<0.001

CI, confidence interval; I^2, Heterogeneity I^2 index; Q, Heterogeneity chi-squared statistic; DF, degrees of freedom.

searching five electronic databases, a total of 513 results were found. After eliminating duplicates and eliminating records that did not fulfil our specified criteria for inclusion, the eligibility of 14 research was evaluated in full text. Five articles were found eligible and were included in the meta-analysis and qualitative synthesis.

3.2. Characteristics of the eligible studies

The publications included in this meta-analysis were found to be primarily conducted at Mogadishu, even though the eligibility criteria were not restricted to this location. The articles included both cross-sectional and retrospective studies conducted in hospital settings in the last eight years. In all of the studies, resistance to carbapenem antibiotics were assessed using the Kirby-Bauer disk diffusion method. The clinical sample sources from which members of the *Enterobacterales* were isolated include urine, vaginal swab, blood, etc., with *E. coli* and *K. pneumoniae* being the most frequently identified organism (Table 1).

3.3. Pooled prevalence

Meta-analysis was conducted using data from the 5 included studies. A total of 12 cases of resistance of *Enterobacterales* to imipenem antibiotics was reported among 308 clinical isolates. Resistance cases of 13 and 27 among 398 and 306 clinical isolates were reported for meropenem and ertapenem, respectively. After computing the summary estimate using the random-effect model, a pooled resistance rate of 4.3% (95% CI, 2.5–7.2) was obtained for imipenem, 2.8% (95% CI, 0.8–8.8) for meropenem, and 13.9% (95% CI, 3.1–44.7) for ertapenem (Figure 2, Table 2). The heterogeneity test showed low heterogeneity, except for studies contributing to the estimated resistance to ertapenem which had a high heterogeneity (I^2=91.52%; Q=11.788; p<0.001). Further, all the included publications were found to be of good methodological quality (File S2 and File S3).

4. Discussion

Due to their broad-spectrum activity, β-lactam antibiotics including penicillin and cephalosporins have been widely utilized against pathogenic *Enterobacteriaceae* [22]. This practice has, however, aided in the development and spread of ESBLs and other varieties of β-lactamases. Human medications now contain carbapenems to combat *Enterobacteriaceae's* resistance to extended spectrum cephalosporins (ESC) and cephamycins. The population of CRE is rapidly growing on a global scale. [23,24] The spread of carbapenemase-producing pathogens in humans may be caused by a number of factors, which include but not limited to ongoing antibiotic exposure, the use of

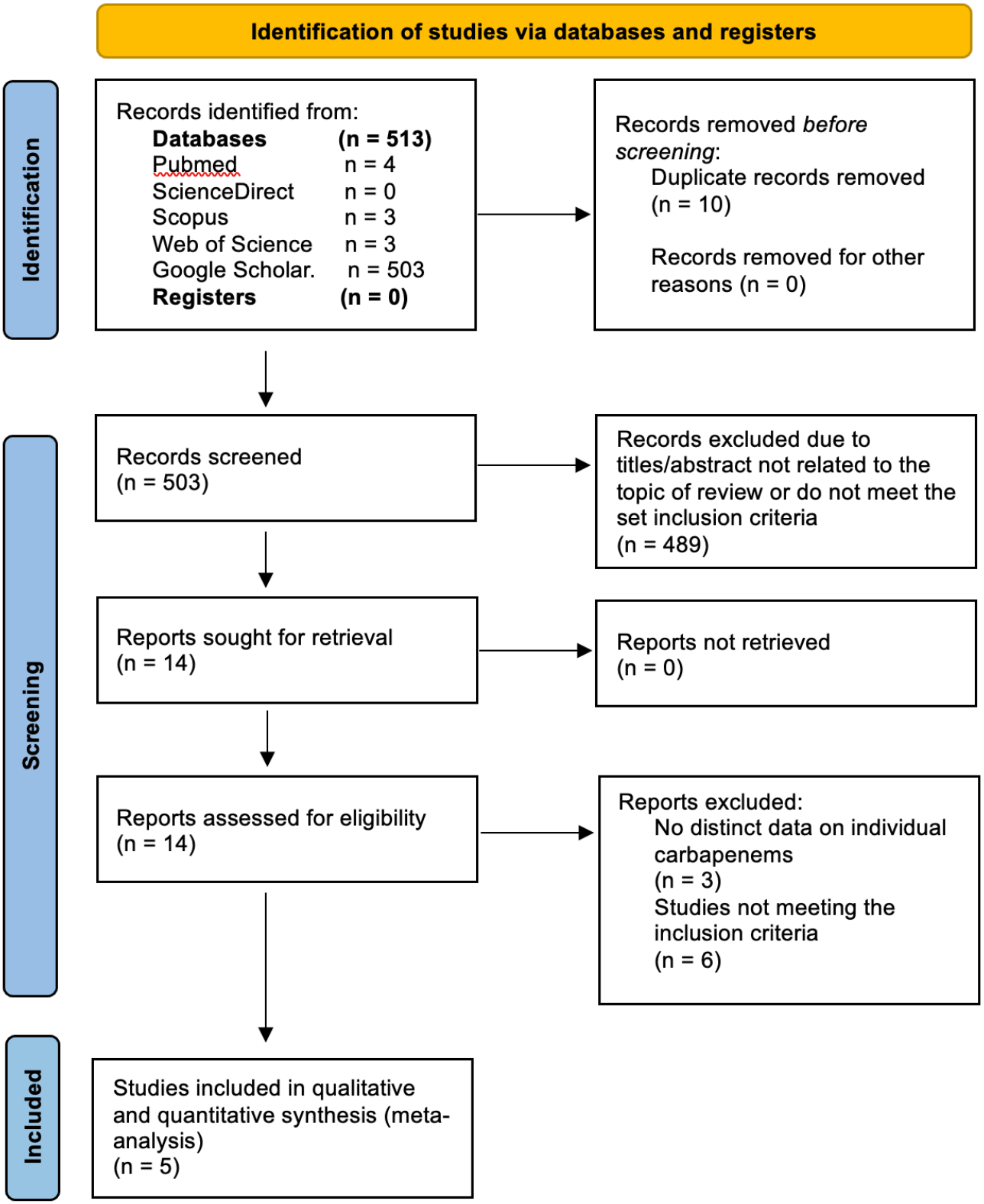

Figure 1: Summary of article search and selection process

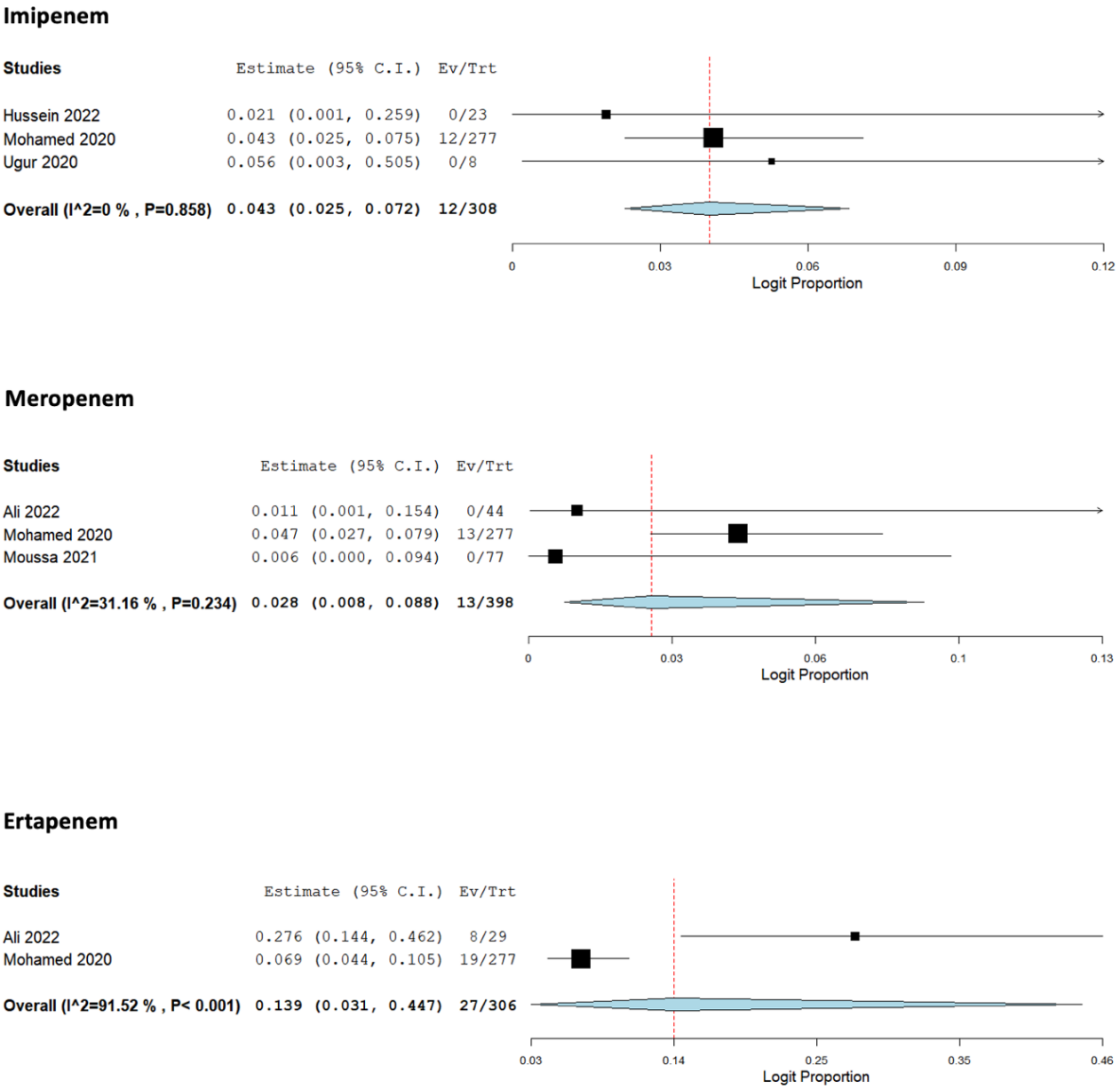

Figure 2: Forest plot of the pooled resistance to carbapenem antibiotics

varying antibiotic doses, and microbial contamination of surgical instruments.[25–27] Because the true resistance rate of *Enterobacterales* to carbapenems in Somailia is not known as various studies report different resistance values, this study used meta-analysis approach to estimate the rates. To our knowledge, this is the first systematic review and meta-analysis to evaluate the prevalence of carbapenem resistant *Enterobacterales* in Somalia.

In this meta-analysis, the utilization of Kirby-Bauer disk diffusion method by the included studies to detect resistance of clinical isolates derived from various clinical specimen types to the major carbapenems revealed a low resistance of *Enterobacterales* to carbapenems, especially meropenem (2.8%) and imipenem (4.3%). There was no report on resistance to doripenem. The low resistance to meropenem and imipenem antibiotics is although surprising because antibiotics usage, like in many other developing countries, are poorly regulated in Somalia.[28,29] This low prevalence is, however, encouraging, as this last line drugs can be relied upon especially in cases of MDR bacteria infections. The prevalence CRE varies across different nations. For instance, much higher prevalence of around 60% and 40% have been reported in Greece and Italy, respectively,[30] despite being more developed than Somalia. However, in

a study involving multiple Asian countries, an average prevalence of less than 1% was reported in the whole culture-positive infections.[31]

This review also identified three retrospective hospital-based studies[32–34] which provided information regarding carbapenem resistance, but the data could not be pooled in the meta-analysis due to the absence of distinct resistance data for each of the carbapenem antibiotics.

This study has some limitations. First, only few publish reports were available on CRE in Somalia despite an exhaustive search of multiple electronic databases. The availability of more reports and larger data would strengthen and increase reliability on the estimated resistance rates. Second, we found all the studies to originate from Mogadishu. Thus, the estimates may not adequately reflect the national resistance rate.

5. Conclusion

The pooled resistance rate of *Enterobacterales* to carbapenem antibiotics was for the first time evaluated with data from Somalia using meta-analysis. There was generally low resistance to the carbapenems, with as low as 2.8% resistance rate for meropenem. This study suggests that the carbapenems can still be depended upon as last line antibiotics for difficult-to-treat pathogenic bacteria in Somalia.

6. Conflict of Interest

None.

7. Source of Funding

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