

## Research Article

# Antibiotic efficacy patterns in the critically ill

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### ABSTRACT

**Background:** Knowledge of antibiotic sensitivity patterns in the critically ill would lead to better outcomes by refinement of empirical therapy. The aim of the study was to analyze the antibiotic sensitivity patterns of pathogens in the critically ill.

**Methods:** Retrospective analytical study of 267 culture samples from critically ill patients was done. Data was collected from hospital medical records department and analyzed.

**Results:** In case of community-acquired infections, carbapenems and piperacillin-tazobactam had high efficacy for UTI; carbapenems, aminoglycosides and levofloxacin had intermediate efficacy for pneumonia; aminoglycosides, piperacillin-tazobactam, carbapenems and quinolones had intermediate efficacy for soft tissue infections; and linezolid and vancomycin had high efficacy for blood borne sepsis of unknown source. In case of hospital acquired infections, carbapenems and aztreonam had intermediate efficacy for UTI; aminoglycosides had intermediate efficacy for blood borne sepsis of unknown source and aminoglycosides had high efficacy for CLABSI. Only colistin and tigecycline demonstrated high efficacy for VAP. Colistin and tigecycline showed high efficacy for community and hospital acquired UTI, pneumonia and soft tissue infections as well as gram negative CLABSI and hospital acquired blood borne sepsis of unknown source.

**Conclusions:** The study shows that in critically ill, in general, carbapenems are fast losing their efficacy. Colistin and tigecycline are effective even against MDR pathogens in their spectrum. Fluoroquinolones and cephalosporins have poor efficacy overall to be recommended for empirical therapy. Piperacillin-tazobactam is not satisfactory for many critical infections. Amikacin has variable efficacy. Linezolid, vancomycin and teicoplanin are highly active against MRSA and Enterococcus infections.

**Keywords:** Antibiotics, Critically ill, Efficacy rates

### INTRODUCTION

In many infectious diseases, empirical therapy needs to be started before the exact pathogen and its drug sensitivity patterns are known. But empirical therapy of infection has become highly speculative because of unprecedented increase in antibiotic resistance.<sup>1</sup>

During empirical management, particularly in the critically ill, under-treatment with less sensitive antibiotics would lead to loss of valuable time, spread of infection, increase in morbidity and mortality and delayed recovery; whereas, antibiotic abuse would lead to antibiotic resistance and higher treatment cost.<sup>2,3</sup> Because antimicrobial resistance among pathogens varies from

region to region, it is stressed that empirical therapeutic choices be based on the local resistance patterns.<sup>4</sup>

Therefore, a proper knowledge of local antibiotic sensitivity and resistance patterns for various pathogens in the critically ill patients is of paramount importance in the empirical management of serious infections as the first few hours of sepsis management are critical in determining the outcome.<sup>5</sup>

The study was done to evaluate the antibiotic resistance and sensitivity patterns of the pathogens in the critically ill patients. The results will be useful in refinement of the empirical antibiotic therapy in critically ill thereby leading to better outcomes.<sup>6</sup> The data will also be of help in understanding the pathogen characteristics of serious infections better.

## METHODS

A retrospective analytical study was done from the case records of patients aged more than 18 years admitted in critically ill state in ICU with serious infections during the period of January 2015 to April 2016. The data was collected from the ICU records, microbiology department and hospital records department. Only those patients who had proved positive cultures were included in the study. Patients with culture reports with doubtful clinical significance were excluded from the study. Non serious infections and non-critically ill patients were not included in the study. A total of 267 samples were analyzed. The samples included sputum, ET aspirate, blood, urine, catheter tip, pus, CSF, ascitic fluid and pleural fluid.

Specimen collection is usually done in our hospital as follows. Specimens relevant for the clinical condition are collected aseptically in appropriate sterile containers and transported immediately for processing to the microbiology laboratory which functions round the clock. Gram stained smears of the specimens are examined for presence of bacteria and other signs of inflammation. Urine specimens are inoculated on to nutrient agar and MacConkey agar plates with calibrated inoculation loop (for determining colony count). Pus/swab, and exudate specimens are inoculated on to blood agar, MacConkey agar and brain heart infusion broth. Sputum (and other respiratory) specimens are inoculated on to blood agar and MacConkey agar plates. All the inoculated media are incubated aerobically at 37° C except blood agars inoculated with respiratory samples which are incubated in candle jar at 37° C. Blood specimens are directly inoculated into brain heart infusion broth and processed conventionally. Any growth obtained in culture is subjected to biochemical tests and bacterial pathogens identified as per standard microbiological techniques. Antibiotic susceptibility testing is done as per CLSI (Clinical Laboratory Standards Institute) guidelines for disk diffusion method.<sup>7</sup>

The data collected and analyzed included age, gender, diagnosis, whether infection was hospital or community acquired, the specimen analyzed, the pathogen, and its resistance and sensitivity patterns to antibiotics tested.

The efficacy rate of an antibiotic for a specific type of infection, was calculated from the formula, efficacy rate = (S+I)/N where S= number of samples sensitive to the antibiotic, I = number of samples intermediately sensitive to the antibiotic, N=number of samples tested for the antibiotic.<sup>6</sup> The efficacy rates of the antibiotics for an infection in which the number of samples tested for that particular antibiotic were insufficient when correlated with the types of pathogens isolated and number of samples were omitted and not calculated and interpreted in the study. Similarly, the efficacy rates of the antibiotics which were tested only for certain specific pathogens (because of their limited spectrum of activity against those pathogens) were not extrapolated as the overall efficacy rates for that particular infection syndrome as the results would be falsely high. For example, the overall efficacy rate of linezolid in critically ill UTI cannot be said to be 100% just because it has been tested only for *Staph. aureus* and found to be sensitive in all *Staph. aureus* specimens.

The efficacy patterns of the antibiotics were analyzed separately for UTI (from urine samples), pneumonia (from sputum, ET aspirate and pleural fluid), soft tissue infections (from pus), blood borne sepsis (sepsis of unknown source with positive blood culture) and CLABSI (central line associated blood stream infection, from catheter tip culture) after classifying as community acquired (CA) and hospital acquired (HA) infections. Positive blood cultures obtained from UTI, pneumonia and soft tissue infection cases were grouped according to the primary diagnosis. Based on their efficacy rates for a critical infection, antibiotics were considered to be as having low efficacy (<50%), intermediate efficacy (≥50% and <75%) and high efficacy (≥75%). Antibiotic efficacy for atypical organisms and anaerobic pathogens was not assessed in this study.

The study was approved by the ethical committee of Velammal Medical College Hospital and Research Institute, Tamil Nadu, India. The data was analyzed using SPSS software. Descriptive analysis was used in the processing and analysis of data.

## RESULTS

### General patient characteristics

267 samples were collected and analyzed for the pattern and the total number of patients sampled numbered 132 (95 males and 37 females) as at times multiple samples were taken from a single patient. There were 24 patients in <30 years' age group, 170 patients in 30-60 years' age group and 73 patients in >60 years' age group (Table 1). Samples from UTI were 56 (CA-33 and HA-23),

pneumonia 118 (CA-29 and HA-89), soft tissue 66 (CA-55 and HA-16), abdominal infections 4 (CA-2 and HA-2), blood borne sepsis of unknown source 13 (CA-5 and HA-8) and CLABSI 9 (Table 2).

**Table 1: Patient characteristics.**

Characteristics	Patients	Samples	
Gender	Male	95	206
	Female	37	61
Age group	<30 years	8	24
	30-60 years	76	170
	>60 years	48	73
Total	132	267	

**Table 2: Samples.**

Sample	CA	HA	Total
Urine	33	23	56
Respiratory	29	89	118
Pus	51	15	66
GI	2	2	4
Blood	5	8	13
CSF	1	0	1
Catheter	0	9	9
Total	121	146	267

Pathogen characteristics and antibiotic efficacy patterns: (Table 3, Table 4). Critically ill community acquired infections: (n indicates number of samples).

#### Urinary tract infection

Among critically ill patients with community acquired infections, in UTI (n=33), the leading pathogens were *E.coli* (19), *Klebsiella* (6), *Pseudomonas* (3) and *Enterococcus* (3).

High efficacy rates ( $\geq 75\%$ ) were observed with colistin (100%), tigecycline (100%), imipenem (87%), piperacillin-tazobactam (77%) and meropenem (75%). Intermediate efficacy rates (75-50%) were observed with cefoperazone-sulbactam (67%) and netilmicin (67%). Poor efficacy rates ( $<50\%$ ) were observed with ceftriaxone (12%), cefepime (28%), levofloxacin (39%) and gentamicin (40%). Ceftazidime and cefepime were sensitive in all *Pseudomonas* urinary specimens.

#### Pneumonia

In respiratory tract infections (n=29), *Klebsiella* (9), *Acinetobacter* (8) and *CoNS* (4) were the pathogens frequently isolated.

High efficacy rates ( $\geq 75\%$ ) were observed with colistin (100%) and tigecycline (100%). Intermediate efficacy rates (75-50%) were observed with meropenem (71%), amikacin (65%), netilmicin (63%), imipenem (55%), levofloxacin (54%) and gentamicin (50%). Poor efficacy rates ( $< 50\%$ ) were seen with ceftriaxone (11%), aztreonam (25%), cefepime (27%), ofloxacin (29%), ciprofloxacin (48%) and piperacillin-tazobactam (48%). All *Staph.aureus* and *CoNS* specimens were sensitive to linezolid.

#### Soft tissue infections

In soft tissue infections (n=51), the most common organisms were *Pseudomonas* (11), *Klebsiella* (9) and *E.coli* (9). High efficacy rates ( $\geq 75\%$ ) were seen with tigecycline (100%), colistin (96%) and amikacin (75%). Intermediate efficacy rates (75-50%) were observed with netilmicin (69%), piperacillin-tazobactam (66%), imipenem (63%), meropenem (62%), levofloxacin (57%), gentamicin (56%) and ofloxacin (53%).

**Table 3: Pathogen characteristics.**

Organism	Urine		Resp.		Pus		GI		Blood		CSF		Catheter	
	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA
<i>Klebsiella</i>	6	9	9	24	9	7	-	-	-	2	1	-	-	3
<i>Pseudomonas</i>	3	6	1	22	11	3	1	-	-	1	-	-	-	1
<i>E. coli</i>	19	-	3	6	9	3	1	-	-	-	-	-	-	-
<i>Enterococcus</i>	3	1	-	-	2	-	-	-	3	2	-	-	-	-
<i>Citrobacter</i>	1	-	2	1	-	1	-	-	-	-	-	-	-	-
<i>Enterobacter</i>	1	2	-	1	-	-	-	-	-	-	-	-	-	-
<i>Staphylococcus</i>	-	-	2	1	5	-	-	1	1	-	-	-	-	3
<i>CoNS</i>	-	-	4	1	3	-	-	1	-	1	-	-	-	1
<i>Acinetobacter</i>	-	-	8	33	3	1	-	-	1	2	-	-	-	-
<i>Proteus</i>	-	4	-	-	2	-	-	-	-	-	-	-	-	-
Others	-	1	-	-	7	-	-	-	-	-	-	-	-	1
Total	33	23	29	89	51	15	2	2	5	8	1	-	-	9
	56		118		66		4		13		1			9

**Table 4: Antibiotic efficacy rates (part 1 of 2).**

Drug	UTI		Pneumonia		Soft tissue inf.	
	CA	HA	CA	HA	CA	HA
Amikacin	75% (n=24)	33% (n=15)	65% (n=20)	27% (n=73)	75% (n=32)	33% (n=12)
Gentamicin	40% (n=15)	27% (n=11)	50% (n=14)	26% (n=38)	56% (n=25)	22% (n=9)
Netilmicin	67% (n=12)	29% (n=14)	63% (n=16)	39% (n=54)	69% (n=26)	0% (n=10)
Cefepime	28% (n=25)	21% (n=19)	27% (n=15)	16% (n=55)	34% (n=32)	22% (n=9)
Ceftriaxone	12% (n=25)	29% (n=14)	11% (n=18)	8% (n=64)	22% (n=18)	20% (n=10)
Ceftazidime	100% (n=3)	29% (n=7)	NA	29% (n=24)	46% (n=13)	0% (n=3)
Cefoperazone Sulbactam	67% (n=3)	NA	-	0% (n=3)	NA	0% (n=3)
Piperacillin Tazobactam	77% (n=26)	53% (n=19)	48% (n=21)	20% (n=77)	66% (n=35)	18% (n=11)
Ampicillin Sulbactam	NA	-	NA	67% (n=12)	NA	NA
Ampicillin	67% (n=3)	NA	-	0% (n=3)	-	-
Ciprofloxacin	12% (n=26)	17% (n=18)	48% (n=21)	12% (n=74)	45% (n=29)	7% (n=15)
Levofloxacin	39% (n=31)	17% (n=18)	54% (n=26)	26% (n=73)	57% (n=37)	20% (n=15)
Ofloxacin	67% (n=3)	14% (n=7)	29% (n=7)	15% (n=20)	55% (n=11)	0% (n=4)
Imipenem	87% (n=23)	58% (n=19)	55% (n=20)	24% (n=68)	63% (n=27)	30% (n=10)
Meropenem	75% (n=12)	58% (n=12)	71% (n=17)	23% (n=64)	62% (n=29)	10% (n=10)
Aztreonam	25% (n=12)	62% (n=13)	25% (n=8)	22% (n=50)	10% (n=20)	33% (n=12)
Linezolid	NA	NA	100% (n=7)	NA	86% (n=7)	-
Vancomycin	-	-	NA	-	-	-
Teicoplanin	NA	-	-	-	NA	-
Clindamycin	-	-	67% (n=3)	NA	43% (n=7)	-
Colistin	100% (n=10)	92% (n=12)	100% (n=8)	98% (n=62)	96% (n=23)	100% (n=12)
Tigecycline	100% (n=5)	100% (n=5)	88% (n=8)	97% (n=29)	100% (n=4)	80% (n=5)
Minocycline	NA	-	NA	13% (n=8)	67% (n=3)	-

**Table 5: Antibiotic efficacy rates (part 2 of 2).**

Drug	GI		Blood sepsis		CSF	CLABSI
	CA	HA	CA	HA	CA	HA
Amikacin	50% (n=2)	100% (n=2)	50% (n=2)	67% (n=6)	100% (n=1)	75% (n=8)
Gentamicin	100% (n=2)	-	67% (n=3)	50% (n=4)	100% (n=1)	100% (n=3)
Netilmicin	0% (n=1)	100% (n=1)	NA	0% (n=3)	100% (n=1)	-
Cefepime	0% (n=2)	-	-	0% (n=2)	100% (n=1)	0% (n=2)
Ceftriaxone	0% (n=1)	-	NA	0% (n=5)	100% (n=1)	0% (n=2)
Ceftazidime	0% (n=1)	-	50% (n=2)	NA	-	0% (n=2)
Cefoperazone Sulbactam	-	-	-	NA	-	0% (n=3)
Piperacillin Tazobactam	100% (n=2)	-	NA	25% (n=4)	100% (n=1)	0% (n=2)
Ampicillin Sulbactam	-	-	50% (n=2)	NA	-	-
Ampicillin	-	-	33% (n=3)	-	-	-
Ciprofloxacin	0% (n=1)	50% (n=2)	20% (n=5)	0% (n=6)	100% (n=1)	13% (n=8)
Levofloxacin	0% (n=2)	50% (n=2)	50% (n=4)	38% (n=8)	100% (n=1)	29% (n=7)
Ofloxacin	-	100% (n=1)	-	-	100% (n=1)	0% (n=4)
Imipenem	50% (n=2)	-	NA	40% (n=5)	100% (n=1)	40% (n=5)
Meropenem	0% (n=1)	-	-	0% (n=4)	-	0% (n=2)
Aztreonam	0% (n=2)	-	-	0% (n=2)	100% (n=1)	NA
Linezolid	-	NA	100% (n=3)	NA	-	67% (n=3)
Vancomycin	-	-	100% (n=1)	NA	-	-
Teicoplanin	-	100% (n=1)	100% (n=3)	NA	-	-
Clindamycin	-	100% (n=2)	-	-	-	25% (n=4)
Colistin	100% (n=1)	-	NA	100% (n=4)	100% (n=1)	100% (n=3)
Tigecycline	-	-	-	100% (n=3)	100% (n=1)	100% (n=3)
Minocycline	-	-	-	-	-	-

Poor efficacy rates (<50%) were observed with aztreonam (10%), ceftriaxone (22%), cefepime (34%), ciprofloxacin (45%) and ceftazidime (46%). All *Staph. aureus* (5) and *Enterococcus* (2) specimens were sensitive to linezolid. 2 out of 3 CoNS specimens were sensitive to linezolid.

#### *Blood borne sepsis of unknown source*

In blood borne sepsis of unknown source (n=5), *Enterococcus* (3) accounted for most infections.

High efficacy rates ( $\geq 75\%$ ) were observed with linezolid (100%), vancomycin (100%) and teicoplanin (100%). Intermediate efficacy rates (75-50%) were observed with gentamicin (67%), levofloxacin (50%) and ampicillin-sulbactam (50%). Poor efficacy rates (< 50%) were observed with ciprofloxacin (20%) and ampicillin (33%).

#### *Abdominal infections*

*Pseudomonas* and *E.coli* accounted one each for the abdominal infections. Gentamicin, piperacillin-tazobactam and colistin were efficacious in both the specimens whereas amikacin and imipenem were efficacious in one specimen. Aztreonam, ceftriaxone, cefepime, ceftazidime, netilmicin, ciprofloxacin and meropenem were resistant in both.

#### *Cerebrospinal fluid*

One CSF sample from meningitis which was due to *Klebsiella* was sensitive to amikacin, gentamycin, netilmicin, ceftriaxone, cefepime, ciprofloxacin, ofloxacin, levofloxacin, piperacillin-tazobactam, imipenem, aztreonam, colistin and tigecycline.

#### *Critically ill hospital acquired infections*

##### *Urinary tract infection*

In UTI (n=23), the leading pathogens were *Klebsiella* (9), *Pseudomonas* (6), and *Proteus* (4).

High efficacy rates ( $\geq 75\%$ ) were observed with colistin (100%) and tigecycline (100%). Intermediate efficacy rates (75-50%) were observed with aztreonam (62%), imipenem (58%) and meropenem (58%). Poor efficacy rates (<50%) were observed with ofloxacin (14%), ciprofloxacin (17%), levofloxacin (17%), cefepime (21%), gentamicin (27%), netilmicin (29%), ceftriaxone (29%), ceftazidime (29%) and amikacin (33%).

##### *Pneumonia*

In respiratory tract infections (n=89), majority of cases were VAP (ventilator associated pneumonia).

*Acinetobacter* (33), *Klebsiella* (24) and *Pseudomonas* (22) were the leading organisms isolated.

High efficacy rates ( $\geq 75\%$ ) were observed with colistin (98%) and tigecycline (97%). Poor efficacy rates (<50%) were seen with cefoperazone-sulbactam (0%), ceftriaxone (8%), ciprofloxacin (12%), minocycline (13%), cefepime (16%), piperacillin-tazobactam (20%), meropenem (23%), imipenem (24%), gentamicin (26%), amikacin (33%) and netilmicin (39%).

#### *Soft tissue infections*

In soft tissue infections (n=15), the common organisms were *Klebsiella* (7), *Pseudomonas* (3) and *E.coli* (3).

High efficacy rates ( $\geq 75\%$ ) were observed with colistin (100%) and tigecycline (80%). Poor efficacy rates (<50%) were observed with cefoperazone-sulbactam (0%), ciprofloxacin (7%), meropenem (10%), piperacillin-tazobactam (18%), ceftriaxone (20%), cefepime (22%), gentamicin (22%), imipenem (30%), amikacin (33%) and aztreonam (33%).

#### *Blood borne sepsis of unknown source*

In blood borne sepsis (n=8), *Klebsiella*, *Acinetobacter* and *Enterococcus* accounted for 2 cases each. Colistin and tigecycline were 100% sensitive in gram negative pathogen samples. Intermediate efficacy rates (75-50%) were observed with amikacin (67%) and gentamicin (50%). Poor efficacy rates (<50%) were observed with levofloxacin (38%), imipenem (40%), piperacillin-tazobactam (25%), cefepime (0%), ceftriaxone (0%), ciprofloxacin (0%), netilmicin (0%), meropenem (0%) and aztreonam (0%). Teicoplanin was sensitive to both the specimens of *Enterococcus* tested.

#### *Central line associated blood stream infection (CLABSI)*

Central line associated blood stream infections (CLABSI) (n=9), were most often due to *Klebsiella* (3) and *Staph. aureus* (3). Colistin and tigecycline were sensitive to all gram negative organisms tested (3 each). High efficacy rates ( $\geq 75\%$ ) were observed with amikacin (75%). Poor efficacy rates ( $\leq 50\%$ ) were observed with meropenem (0%) ofloxacin (0%), ceftriaxone (0%), cefoperazone-sulbactam (0%), ceftazidime (0%), cefepime (0%), piperacillin-tazobactam (0%), ciprofloxacin (13%), levofloxacin (29%) and imipenem (40%). Linezolid was sensitive in 2 out of 3 *Staph.aureus* specimens.

#### *Abdominal infections*

In case of community-acquired infections, carbapenems and piperacillin-tazobactam had high efficacy for UTI; carbapenems, aminoglycosides and levofloxacin had intermediate efficacy for pneumonia; aminoglycosides,

piperacillin-tazobactam, carbapenems and quinolones had intermediate efficacy for soft tissue infections; and linezolid and vancomycin had high efficacy for blood borne sepsis of unknown source.

Abdominal infections (n=2), were contributed by *Staph.aureus* and CoNS (one each). Amikacin, netilmicin, linezolid, ofloxacin, clindamycin and teicoplanin were sensitive in both the samples studied. Ciprofloxacin and levofloxacin were sensitive in only one sample.

Overall, out of 9 *Staph. aureus* samples tested for methicillin resistance, 8 were MRSA and except one MRSA sample all were sensitive to linezolid. The efficacy rate of linezolid for *Enterococcus* was 100%. Vancomycin was efficacious in all the 3 samples tested for *Enterococcus* (2) and MRSA (1). Teicoplanin was sensitive to all samples tested for *Enterococcus* (6), CoNS (2) and MRSA (2). Amikacin was efficacious in 6 out of 8 MRSA cases.

## DISCUSSION

In case of community-acquired infections, carbapenems and piperacillin-tazobactam had high efficacy for UTI; carbapenems, aminoglycosides and levofloxacin had intermediate efficacy for pneumonia; aminoglycosides, piperacillin-tazobactam, carbapenems and quinolones had intermediate efficacy for soft tissue infections; and linezolid and vancomycin had high efficacy for blood borne sepsis of unknown source. Poor efficacy rates were noted with cephalosporins and fluoroquinolones for UTI and pneumonia; and cephalosporins for soft tissue infections.<sup>1</sup>

In case of hospital acquired infections, carbapenems and aztreonam had intermediate efficacy for UTI; aminoglycosides had intermediate efficacy for blood borne sepsis of unknown source; and aminoglycosides had high efficacy for CLABSI. Only colistin and tigecycline demonstrated high efficacy for VAP. Poor efficacy rates were observed with cephalosporins, fluoroquinolones, amikacin for UTI; cephalosporins, fluoroquinolones, carbapenems, piperacillin-tazobactam for VAP, soft tissue infections, CLABSI and blood sepsis of unknown source; and also with aminoglycosides for VAP and soft tissue infections.<sup>8</sup>

Reserve drugs, colistin and tigecycline showed high efficacy for community and hospital acquired UTI, pneumonia and soft tissue infections as well as gram negative CLABSI and hospital acquired blood borne sepsis of unknown source.<sup>8</sup>

Because of widespread and irrational use of antibiotics, antibiotic resistance has increased exponentially causing grave prognosis in the management of infectious diseases.<sup>2</sup> The study results also indicate the same. The knowledge of local resistance patterns should guide the

treating doctors in the rational decision of choosing an empirical antibiotic.<sup>2,4</sup>

## CONCLUSION

The study shows that in critically ill patients, even higher antibiotics like carbapenems are fast losing their efficacy due to MDR organisms particularly in hospital acquired infections because of widespread use. Reserve drugs, colistin and tigecycline are highly efficacious against the pathogens in their spectrum even against MDR strains in hospital acquired setting. Cephalosporins have also lost their efficacy in the treatment of critically ill infections. Fluoroquinolones cannot be recommended for critically ill infections due to lack of efficacy in general. Linezolid, vancomycin and teicoplanin can be recommended for empirical treatment of suspected MRSA and *Enterococcus* infections. Piperacillin-tazobactam has declined in efficacy particularly in hospital acquired infections. Amikacin has variable rates of efficacy in different infections.

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