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Surveillance of Ceftolozane/Tazobactam Antimicrobial Activity Tested Against Contemporary Gram-Negative Organisms and *Streptococcus pneumoniae* Isolated in Australia

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Amended Abstract

Objectives: Ceftolozane/tazobactam (TOL/TAZ) was approved by the Therapeutic Goods Administration in November 2015 for the treatment of adult patients with complicated intra-abdominal infections (in combination with metronidazole), acute pyelonephritis, and complicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. TOL/TAZ is currently in clinical development in patients with ventilator-associated bacterial pneumonia. The Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS), a global surveillance program in which methods for isolate collection, centralized reporting, and analysis have been standardized, evaluates the in vitro activity of ceftolozane/tazobactam.

Methods: In 2013 and 2014, a total of 1573 Gram-negative, nonduplicate, clinical isolates were collected from hospitalized patients in 8 medical centers in 5 Australian cities (n centers): Sydney (3), Adelaide (2), Brisbane (1), Melbourne (1), and Perth (1). In addition, 74 *Streptococcus pneumoniae* isolates were collected from these sites in 2014 only. Isolates were tested for antibacterial susceptibility (S) by broth microdilution, and extended-spectrum β-lactamase (ESBL) phenotype was determined per Clinical Laboratory and Standards Institute (CLSI) guidelines. CLSI breakpoints were used to determine % S.

Results: Against 249 isolates of *P. aeruginosa*, TOL/TAZ (93.6% S) was the most active β-lactam agent tested and demonstrated greater activity than piperacillin-tazobactam (PIP/TAZ, 76.7% S), ceftazidime (CAZ, 79.9% S), cefepime (88.4% S), and meropenem (MER, 91.2% S). Also against *P. aeruginosa,* except for colistin (98.6% S), TOL/TAZ was the most active agent tested, compared with amikacin (93.1% S), gentamicin (90% S), and levofloxacin (84.3% S). Against 523 Enterobacteriaceae (ENT), TOL/TAZ was more active (97.1% S) than PIP/TAZ (93.5% S) and CAZ (92.9% S) but less active than MER (99.6% S, Table). TOL/TAZ was very active against all ESBL-phenotype *E. coli* (n = 27, 10.7% of isolates, 100.0% S) and most of the 7 *K. pneumoniae* ESBL-phenotype strains (7.1% of isolates, 71.4% S). TOL/TAZ in vitro activity against *S. pneumoniae* ($MIC_{50/90}$, 0.12/8 µg/mL), as with other β-lactam agents tested, varied according to *S. pneumoniae* susceptibility to penicillin (PEN).

Conclusion: PACTS surveillance showed that TOL/TAZ demonstrated good activity against *P. aeruginosa* (including CAZ- and MEM-resistant strains), ENT (including most ESBL strains), and penicillin-susceptible *S. pneumoniae* isolated from patients in Australian hospitals during 2013 and 2014.

Organism or phenotype (n)	TOL/TAZ $MIC_{50/90}$ / % S†	PIP/TAZ $MIC_{50/90}$ / % S†	CAZ $MIC_{50/90}$ / % S†	MER $MIC_{50/90}$ / % S†
Enterobacteriaceae (523)	0.25 / 1 / 97.1	2 / 8 / 93.5	0.25 / 1 / 92.9	≤0.06 / ≤0.06 / 99.6
E. coli (253)	0.25 / 0.25 / 100.0	2 / 8 / 96.4	≤0.12 / 0.5 / 95.7	≤0.06 / ≤0.06 / 100.0
ESBL-phenotype (27)	0.5 / 1 / 100.0	8 / 64 / 85.2	4 / >16 / 59.3	≤0.06 / ≤0.06 / 100.0
K. pneumoniae (99)	0.25 / 0.5 / 98.0	4 / 8 / 96.0	≤0.12 / 0.5 / 96.0	≤0.06 / ≤0.06 / 99.0
ESBL-phenotype (7)	0.5 / –‡ / 71.4	>64 / –‡ / 42.9	16 / –‡ / 42.9	≤0.06 / –‡ / 85.7
K. oxytoca (35)	0.25 / 1 / 100.0	2 / 16 / 94.3	≤0.12 / 0.5 / 97.1	≤0.06 / ≤0.06 / 100.0
E. cloacae (46)	0.5 / 8 / 84.8	2 / 64 / 78.3	0.25 / >16 / 78.3	≤0.06 / 0.12 / 97.8
P. mirabilis (13)	0.5 / 0.5 / 100.0	≤0.5 / ≤0.5 / 100.0	≤0.12 / ≤0.12 / 100.0	0.06 / 0.12 / 100.0
P. aeruginosa (249)	1 / 4 / 93.6	8 / >64 / 76.7	4 / >16 / 79.9	0.25 / 2 / 91.2

†Susceptible (S) breakpoint established by CLSI (2016).
‡Insufficient data to determine MIC_{90}.

Introduction

- Ceftolozane, a novel oxyiminoaminothiazolyl cephalosporin with potent activity against Enterobacteriaceae (similar to other oxyiminoaminothiazolyl cephalosporins), has shown greater activity than ceftazidime against *Pseudomonas aeruginosa*
- Ceftolozane has stability against many *P. aeruginosa* resistance mechanisms, including ampicillin C (AmpC) hyperproduction and efflux mechanisms; furthermore, ceftolozane is little affected by porin deficiency. However, as with other oxyiminoaminothiazolyl cephalosporins, ceftolozane activity is compromised in bacteria that produce extended-spectrum β-lactamases (ESBLs), stably derepressed AmpC β-lactamases, and carbapenemases
- Tazobactam, a penicillanic acid sulfone, is a well-established β-lactamase inhibitor that extends the spectrum of β-lactam agents
- Ceftolozane/tazobactam is a novel antibacterial with activity against *P. aeruginosa*, including drug-resistant strains and other common Gram-negative pathogens, including most ESBL-producing Enterobacteriaceae
- In the past decade, the number of nosocomial infections caused by *P. aeruginosa* and Enterobacteriaceae in intensive care units worldwide increased, along with antimicrobial resistance, with associated increases in morbidity and mortality rates
- Empirical and targeted therapies to treat infections caused by these organisms are becoming increasingly limited
- Ceftolozane/tazobactam was approved by the Therapeutic Goods Administration in November 2015 for the treatment of adult patients with complicated intra-abdominal infections (in combination with metronidazole), acute pyelonephritis, and complicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *P. aeruginosa*
- Ceftolozane/tazobactam is in clinical development in patients with ventilator-associated bacterial pneumonia
- In the current study, we evaluated the potency of ceftolozane/tazobactam and comparator drugs against a large, contemporary (2013-2014) collection of clinically derived Enterobacteriaceae, *P. aeruginosa*, and *Streptococcus pneumoniae* obtained from patients in Australian hospitals

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Materials and Methods

Sampling sites and organisms

- Enterobacteriaceae, *P. aeruginosa*, and *S. pneumoniae* isolates were consecutively collected in 2013 and 2014 from 8 medical centers in Australia by the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS)
- 8 medical centers in 5 Australian cities participated: Sydney (3), Adelaide (2), Brisbane (1), Melbourne (1), and Perth (1). In addition, 74 *S. pneumoniae* isolates were collected from these sites in 2014 only
- All organisms were isolated from documented infections, and only 1 strain per patient-infection episode was included in the surveillance collection

Antimicrobial susceptibility testing

- Minimum inhibitory concentration (MIC) values for ceftolozane/tazobactam (tazobactam fixed at 4 µg/mL) and comparator agents were determined using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution reference method (M07-A10)
- Quality control ranges and interpretive criteria for comparator compounds used the CLSI M100-S26 and 2016 European Committee on Antimicrobial Susceptibility Testing version 6.0 (EUCAST v6.0) guidelines
- The ESBL phenotype was defined as an MIC of ≥2 µg/mL for ceftazidime *or* ceftriaxone *or* aztreonam

Results

- Against 249 isolates of *P. aeruginosa*, ceftolozane/tazobactam ($MIC_{50/90}$, 1/4 µg/mL; 93.6% susceptible [S]) was the most active β-lactam agent tested and demonstrated greater activity than piperacillin/tazobactam (76.7% S), ceftazidime (79.9% S), cefepime (88.4% S), and meropenem (91.2% S; **Tables 1 and 2**)
- Except for colistin (98.6% S), ceftolozane/tazobactam was the most active agent tested against *P. aeruginosa* compared with amikacin (93.1% S), gentamicin (90.0% S), and levofloxacin (84.3% S; **Table 2**)
- 20.1% of the *P. aeruginosa* strains were ceftazidime nonsusceptible, and 68.0% of these ceftazidime-nonsusceptible strains were susceptible to ceftolozane/tazobactam
- 8.8% of *P. aeruginosa* strains were meropenem nonsusceptible, and the ceftolozane/tazobactam susceptibility rate against these strains was 63.6% (**Table 1**)
- Ceftolozane/tazobactam was very active ($MIC_{50/90}$, 0.25/1 µg/mL; **Table 1**) against 523 Enterobacteriaceae, with CLSI/EUCAST breakpoint susceptibility rates of 97.1%/94.6% (**Table 2**)
- Meropenem (99.6% [CLSI]/99.8% S [EUCAST]; MIC_{50}, ≤0.06 µg/mL) was the most active agent tested against Enterobacteriaceae (**Table 2**)
- ESBL phenotype represented 10.7% (27 of 253) of *E. coli* isolates, and 100.0%/96.3% (CLSI/EUCAST) of these isolates were susceptible to ceftolozane/tazobactam (**Table 1**)
- ESBL phenotype represented 7.1% (7 of 99) of *K. pneumoniae* isolates and 71.4%/57.1% (CLSI/EUCAST) of these isolates were susceptible to ceftolozane/tazobactam (**Table 1**)
- Ceftolozane/tazobactam showed good activity against *Enterobacter cloacae* ($MIC_{50/90}$, 0.5/8 µg/mL; 84.8% [CLSI]/82.6% [EUCAST] S), *Klebsiella oxytoca* ($MIC_{50/90}$, 0.25/1 µg/mL; 100.0%/91.4% S), and *Proteus mirabilis* ($MIC_{50/90}$, 0.5/0.5 µg/mL; 100.0% S; **Table 2**)
- Ceftolozane/tazobactam in vitro activity ($MIC_{50/90}$, 0.12/8 µg/mL), as with other β-lactams, varied according to *S. pneumoniae* susceptibility to penicillin (**Tables 1 and 2**)

Table 1. Activity and cumulative % distribution of ceftolozane/tazobactam tested against bacterial isolates from Australia (2013-2014)

Organism (No.)	Cumulative % Inhibited at Ceftolozane/Tazobactam MIC, µg/mL								$MIC_{50/90}$ µg/mL
	≤0.25	0.5	1	2	4	8	16	>16	
Enterobacteriaceae (523)	70.9	87.6	**94.6**	97.1	97.7	98.3	99.0	100.0	0.25 / 1
E. coli (253)	91.3	98.0	**99.6**	100.0					0.25 / 0.25
E. coli-ESBL (27)	48.1	85.2	**96.3**	100.0					0.5 / 1
K. pneumoniae (99)	72.7	91.9	**96.0**	98.0	98.0	98.0	99.0	100.0	0.25 / 0.5
K. pneumoniae-ESBL (7)	28.6	57.1	**57.1**	71.4	71.4	71.4	85.7	100.0	0.5 / –
K. oxytoca (35)	80.0	88.6	**91.4**	100.0					0.25 / 1
E. cloacae (46)	41.3	69.6	**82.6**	84.8	87.0	91.3	91.3	100.0	0.5 / 8
P. mirabilis (13)	15.4	**100.0**							0.5 / 0.5
P. aeruginosa (249)	5.6	43.0	84.3	88.8	**93.6**	97.6	98.0	100.0	1 / 4
P. aeruginosa-CAZ-NS (50)	0.0	8.0	32.0	44.0	**68.0**	88.0	90.0	100.0	4 / 16
P. aeruginosa-MER-NS (22)	0.0	0.0	31.8	40.9	**63.6**	77.3	81.8	100.0	4 / >32
S. pneumoniae (74)	64.9	67.6	70.3	73.0	82.4	90.5	100.0		0.12 / 8

CAZ = ceftazidime; ESBL = extended-spectrum β-lactamase; MER = meropenem; NS = nonsusceptible.
Bold values represent % susceptible by EUCAST breakpoints and underlined values represent % susceptible by CLSI/FDA breakpoints. There are no EUCAST or CLSI/FDA breakpoints for *S. pneumoniae*.

Table 2. Activity of ceftolozane/tazobactam and comparator antimicrobial agents when tested against bacterial isolates from Australia (2013-2014)

Organisms (no. tested)/ Antimicrobial Agent	MIC µg/mL		% S / % I / % R	
	MIC_{50}	MIC_{90}	CLSI†	EUCAST†
All Enterobacteriaceae (523)‡				
Ceftolozane/tazobactam	0.25	1	97.1 / 0.6 / 2.3	94.6 / –§ / 5.4
Ceftazidime	0.25	1	92.9 / 0.8 / 6.3	90.2 / 2.7 / 7.1
Cefepime	≤0.5	≤0.5	95.0 / 1.7 / 3.3	93.9 / 1.9 / 4.2
Ceftriaxone	≤0.06	2	89.3 / 1.3 / 9.4	89.3 / 1.3 / 9.4
Piperacillin/tazobactam	2	8	93.5 / 3.3 / 3.3	90.6 / 2.9 / 6.5
Meropenem	≤0.06	≤0.06	99.6 / 0.2 / 0.2	99.8 / 0.0 / 0.2
Levofloxacin	≤0.12	0.5	94.0 / 0.4 / 5.6	93.9 / 0.2 / 5.9
Gentamicin	≤1	2	94.1 / 0.6 / 5.4	93.5 / 0.6 / 5.9
Tigecycline¶	0.12	0.5	99.6 / 0.4 / 0.0	98.1 / 1.5 / 0.4
Colistin	≤0.5	>8	– / – / –	87.2 / – / 12.8
E. coli (253)				
Ceftolozane/tazobactam	0.25	0.25	100.0 / 0.0 / 0.0	99.6 / – / 0.4
Ceftazidime	≤0.12	0.5	95.7 / 1.2 / 3.2	92.1 / 3.6 / 4.3
Cefepime	≤0.5	≤0.5	93.3 / 2.4 / 4.3	92.1 / 1.6 / 6.3
Ceftriaxone	≤0.06	0.5	91.7 / 0.0 / 8.3	91.7 / 0.0 / 8.3
Piperacillin/tazobactam	2	8	96.4 / 1.2 / 2.4	94.1 / 2.4 / 3.6
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	1	90.1 / 0.0 / 9.9	90.1 / 0.0 / 9.9
Gentamicin	≤1	2	91.3 / 0.4 / 8.3	90.5 / 0.8 / 8.7
Tigecycline¶	0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Colistin	≤0.5	≤0.5	– / – / –	100.0 / – / 0.0
K. pneumoniae (99)				
Ceftolozane/tazobactam	0.25	0.5	98.0 / 0.0 / 2.0	96.0 / – / 4.0
Ceftazidime	≤0.12	0.5	96.0 / 0.0 / 4.0	92.9 / 3.0 / 4.0
Cefepime	≤0.5	≤0.5	98.0 / 0.0 / 2.0	98.0 / 0.0 / 2.0
Ceftriaxone	≤0.06	0.12	94.9 / 1.0 / 4.0	94.9 / 1.0 / 4.0
Piperacillin/tazobactam	4	8	96.0 / 0.0 / 4.0	92.9 / 3.0 / 4.0
Meropenem	≤0.06	≤0.06	99.0 / 0.0 / 1.0	99.0 / 0.0 / 1.0
Levofloxacin	≤0.12	0.5	98.0 / 0.0 / 2.0	97.0 / 1.0 / 2.0
Gentamicin	≤1	≤1	98.0 / 1.0 / 1.0	98.0 / 0.0 / 2.0
Tigecycline¶	0.25	0.5	100.0 / 0.0 / 0.0	97.0 / 3.0 / 0.0
Colistin	≤0.5	1	– / – / –	100.0 / – / 0.0
K. oxytoca (35)				
Ceftolozane/tazobactam	0.25	1	100.0 / 0.0 / 0.0	91.4 / – / 8.6
Ceftazidime	≤0.12	0.5	97.1 / 0.0 / 2.9	97.1 / 0.0 / 2.9
Cefepime	≤0.5	≤0.5	97.1 / 0.0 / 2.9	94.3 / 2.9 / 2.9
Ceftriaxone	≤0.06	2	85.7 / 5.7 / 8.6	85.7 / 5.7 / 8.6
Piperacillin/tazobactam	2	16	94.3 / 0.0 / 5.7	88.6 / 5.7 / 5.7
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	≤0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Gentamicin	≤1	≤1	97.1 / 0.0 / 2.9	97.1 / 0.0 / 2.9
Tigecycline¶	0.25	0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Colistin	≤0.5	≤0.5	– / – / –	100.0 / – / 0.0
E. cloacae (46)				
Ceftolozane/tazobactam	0.5	8	84.8 / 2.2 / 13.0	82.6 / – / 17.4
Ceftazidime	0.25	>16	78.3 / 0.0 / 21.7	78.3 / 0.0 / 21.7
Cefepime	≤0.5	4	89.1 / 6.5 / 4.3	87.0 / 8.7 / 4.3
Ceftriaxone	0.25	>8	76.1 / 2.2 / 21.7	76.1 / 2.2 / 21.7
Piperacillin/tazobactam	2	64	78.3 / 15.2 / 6.5	78.3 / 0.0 / 21.7
Meropenem	≤0.06	0.12	97.8 / 2.2 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	0.5	98.0 / 0.0 / 2.0	97.0 / 1.0 / 2.0
Gentamicin	≤1	4	91.3 / 0.0 / 8.7	89.1 / 2.2 / 8.7
Tigecycline¶	0.25	0.5	97.8 / 2.2 / 0.0	97.8 / 0.0 / 2.2
Colistin	≤0.5	>8	– / – / –	73.9 / – / 26.1
P. mirabilis (13)				
Ceftolozane/tazobactam	0.5	0.5	100.0 / 0.0 / 0.0	100.0 / – / 0.0
Ceftazidime	≤0.12	≤0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Cefepime	≤0.5	≤0.5	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ceftriaxone	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Piperacillin/tazobactam	≤0.5	≤0.5	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Meropenem	0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Gentamicin	≤1	≤1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Tigecycline¶	1	2	100.0 / 0.0 / 0.0	76.9 / 23.1 / 0.0
Colistin	>8	>8	– / – / –	0.0 / – / 100.0
P. aeruginosa (249)				
Ceftolozane/tazobactam	1	4	93.6 / 4.0 / 2.4	93.6 / – / 6.4
Ceftazidime	4	>16	79.9 / 8.0 / 12.0	79.9 / – / 20.1
Cefepime	2	16	88.4 / 3.6 / 8.0	88.4 / – / 11.6
Meropenem	0.25	2	91.2 / 3.6 / 5.2	91.2 / 5.6 / 3.2
Piperacillin/tazobactam	8	>64	76.7 / 12.0 / 11.2	76.7 / – / 23.3
Levofloxacin	0.5	44	84.3 / 7.6 / 8.0	74.3 / 10.0 / 15.7
Gentamicin	≤1	8	90.0 / 2.4 / 7.6	90.0 / – / 10.0
Amikacin	2	8	93.1 / 2.6 / 4.3	92.2 / 0.9 / 6.9
Colistin	1	2	98.6 / 0.4 / 0.0	100.0 / – / 0.0
S. pneumoniae (74)				
Ceftolozane/tazobactam	0.12	8	– / – / –	– / – / –
Amoxicillin/clavulanate	≤1	4	89.2 / 1.4 / 9.5	– / – / –
Penicillin††	≤0.06	2	68.9 / 17.6 / 13.5	68.9 / – / 31.1
Penicillin‡‡	≤0.06	2	91.9 / 8.1 / 0.0	68.9 / 23.0 / 8.1
Ceftriaxone§§	≤0.06	1	91.9 / 8.1 / 0.0	82.4 / 17.6 / 0.0
Imipenem	≤0.12	0.5	85.1 / 14.9 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	≤0.12	>16	70.3 / 0.0 / 29.7	70.3 / 0.0 / 29.7
Levofloxacin	1	2	95.9 / 0.0 / 4.1	95.9 / – / 4.1
Tetracycline	≤0.5	>8	71.6 / 0.0 / 28.4	71.6 / 0.0 / 28.4
Tigecycline¶	0.03	0.03	100.0 / – / –	– / – / –
Trimethoprim/sulfamethoxazole	≤0.5	>4	64.9 / 6.8 / 28.4	71.6 / 0.0 / 28.4
Linezolid	0.5	1	100.0 / – / –	100.0 / 0.0 / 0.0
Vancomycin	0.25	0.5	100.0 / – / –	100.0 / – / 0.0

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; I = intermediate; MIC_{50} = minimum inhibitory concentration to inhibit growth of 50% of isolates; MIC_{90} = minimum inhibitory concentration to inhibit growth of 90% of isolates; no. = number; R = resistant; S = susceptible.
†Criteria as published by CLSI (2015) and EUCAST (2015).
‡Includes *Citrobacter freundii* (5), *C. freundii* species complex (1), *C. koseri* (7), *Enterobacter aerogenes* (16), *Enterobacter asburiae* (3), *E. cloacae* (46), *E. cloacae* species complex (1), *Escherichia coli* (253), *K. oxytoca* (35), *K. pneumoniae* (99), *Leclercia adecarboxylata* (1), *Morganella morganii* (4), *P. mirabilis* (13), *Proteus vulgaris* (1), *Serratia liquefaciens* (1), *Serratia marcescens* (35), unspeciated *Salmonella* (2).
§Dash indicates that no breakpoint was available for interpretation.
¶In the absence of CLSI breakpoints, FDA breakpoints were applied when available (Tygacil [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; December 2014).
††Oral penicillin V breakpoints were used.
‡‡CLSI parenteral (nonmeningitis) and EUCAST "infections other than meningitis" breakpoints used.
§§Nonmeningitis breakpoints used.

Conclusions

- In 2013-2014, ceftolozane/tazobactam showed high potency against contemporary *P. aeruginosa* isolates (including many ceftazidime- and meropenem-nonsusceptible strains) consecutively collected from 8 medical centers in 5 Australian cities
- Ceftolozane/tazobactam showed good activity when tested against Enterobacteriaceae, including ESBL strains, isolated from patients from Australian hospitals during the period 2013-2014
- Ceftolozane/tazobactam in vitro activity, as with other β-lactams, varied according to *S. pneumoniae* susceptibility to penicillin

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