Universitätsspital Basel

Klinik für Infektiologie & Spitalhygiene

Is Piperacillin-Tazobactam Effective for the Treatment of Pyelonephritis Caused by Extended-Spectrum β-Lactamase–Producing Organisms?

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Clinical Infectious Diseases 2020;71(8):e331–7.

Journal Club 14.12.2020
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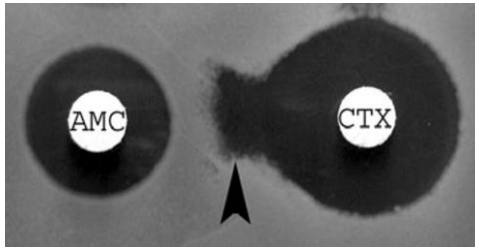
Background:

- ESBL-enzymes inactivate most β-lactam-antibiotics (penicillines, cephalosporines, aztreonam)

- ESBL resistance phenotype



"Double-disk synergy test"

(i) resistance to amino- and carboxy-penicillins, as well as to 2nd-generation and one or several 3rd- and 4th-generation cephalosporins or aztreonam +
(ii) a synergy between these antibiotics and β-lactamase inhibitors

- If an ESBL resistance phenotype is detected, penicillin/β-lactamase combinations such as piperacillin/tazobactam are usually also reported as "resistant"

- However, a large proportion of the currently known ESBL enzymes are sensitive in vitro and in particular the common class A ESBLs of type CTX-M are inhibited by clavulanic acid and tazobactam

Drieux et al. Clin Microbiol Infect 2008;14:90-103.

Background:

- Previous clinical studies on the therapy of ESBL infections with Pip/Taz vs. carbapenems yielded conflicting results

  (methodological weaknesses: underpowered, inhomogenous populations, dosages, microbiological characterisation etc.)

- **MERINO trial 2018:**

  Multi-centre non-inferiority RCT comparing Pip/Taz 4.5g QID to Meropenem 1g TID in ESBL *E. coli* & *Klebsiella pneumoniae* bloodstream infections

  Result: D30-Mortality: Pip/Taz 12.3% (23/187)
  Meropenem 3.7% (7/191)

  Conclusion: Pip/Taz is inferior to Meropenem for treating ESBL *E. coli* & *K. pneumoniae* bacteremia

- Open question after the MERINO trial:

  ″Whether piperacillin/tazobactam remains effective for urinary infections caused by ESBL producers in patients without bloodstream infections remains uncertain″

Harris et al. JAMA 2018;320(10):984-94.

Study design:

- Observational multicentre study (3 hospitals of the Johns Hopkins Health Systems)
- Jan. 2014 – Dez. 2016
- Inclusion criteria: hospitalized adult patients with

  (i) pyelonephritis* due to ESBL-producing *E. coli*, *Klebsiella pneum.*, *Klebsiella oxytoca* or *Proteus mirabilis*
  [*Def.: ≥ 50′000 CFU/ml + pyuria (≥ 10 WBC/HPF) + identification of an ESBL gene + Temp. ≥38.5°C and dysuria + ≥1 of the following symptoms: emesis, rigors, hypotension or flank pain]

  (ii) treated with either Pip/Taz or a carbapenem within 48h from the time the urine culture was obtained and for at least the subsequent 72h

  (iii) in case of switching to an oral regimen (ciprofloxacin, levofloxacin, TMP-SMX) susceptibility of the isolate was demanded

- Exclusion criteria:

  patients with prostatitis, concomitant bacteremia, renal abscesses

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- Primary outcome:

  Recurrent cystitis or pyelonephritis with the same ESBL-producing organism (based on genus, species, ESBL-testing) within 30 days

- Secondary outcomes:

  (i) resolution of symptoms by day-7

  (ii) day-30 mortality

  (iii) identification of a carbapenem resistant gram-negative isolate within 30 days of antibiotic treatment

- Microbiological testing:

  - bacterial identification and antimicrobial susceptibility testing results were done by MALDI-TOF and the BD Phoenix Automated System

  - ESBL genes were identified by a DNA microarray-based assay testing for $bla_{CTX\text{-}M\ [1, 2, 8/25, 9]}$, $bla_{TEM\ [E104K, R164S, R164H, G238S]}$, $bla_{SHV\ [G238A, G238S, E240K]}$

- Analysis: Propensity score method

1. Propensity score (PS) generation for each patient
   by multivariable logistic regression:
   - dependent variable: exposure to Pip/Taz
   - independent variables: age, gender, diabetes, chronic kidney disease, urinary catheter, immunosuppression, ICU status, …

2. Creation of a new pseudo-population by «inverse probability of treatment weighting« (IPTW)

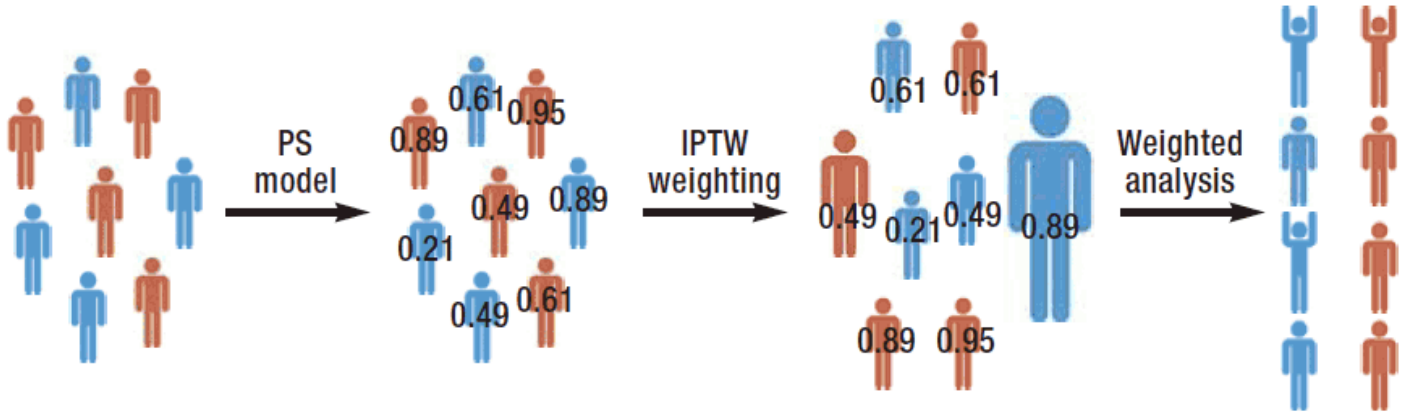

Table 1. Baseline Characteristics

Variable	Full Cohort				Propensity Score–Weighted Cohort[a]			
	Piperacillin-Tazobactam, n = 47; 25%	Carbapenem, n = 141; 75%	*P* Value	Standardized Mean Differences	Piperacillin-Tazobactam, n = 45; 24%	Carbapenem, n = 141; 76%	*P* Value	Standardized Mean Differences
Age, years, median (IQR)	62 (48–73)	63 (49–74)	.986	0.003	64 (50–72)	63 (49–74)	.886	0.023
Female gender (%)	32 (68.1)	95 (67.4)	.928	−0.047	32 (71.1)	96 (68.1)	.756	−0.055
Race/ethnicity								
Black	15 (31.9)	44 (31.2)	.928	0.030	16 (35.6)	44 (31.2)	.643	0.084
White	24 (51.1)	74 (52.5)	.866	−0.049	22 (48.9)	74 (52.5)	.705	−0.068
Asian	5 (10.6)	11 (7.8)	.546	0.105	4 (8.9)	10 (7.1)	.602	0.079
Latino	2 (4.3)	8 (5.7)	.707	−0.060	2 (4.4)	8 (5.7)	.715	−0.063
Other	1 (2.1)	4 (2.8)	.794	−0.042	1 (2.2)	4 (2.8)	.582	−0.092
Preexisting medical conditions								
Diabetes	11 (23.4)	41 (29.1)	.451	−0.116	13 (28.9)	39 (27.7)	.970	0.007
Chronic kidney disease	6 (12.8)	21 (14.9)	.719	−0.053	5 (11.1)	20 (14.2)	.741	−0.057
Cirrhosis	2 (4.3)	10 (7.1)	.491	−0.118	2 (4.4)	9 (6.4)	.666	−0.076
Renal transplant	4 (8.5)	16 (11.3)	.585	−0.088	5 (11.1)	15 (10.6)	.960	−0.009
Solid organ transplant, other than renal transplant	4 (8.5)	18 (12.8)	.432	−0.131	5 (11.1)	16 (11.3)	.818	−0.043
Bone marrow transplant within past 12 months	1 (2.1)	4 (2.8)	.794	−0.042	2 (4.4)	4 (2.8)	.806	0.053
Chemotherapy within past 6 months	3 (6.4)	10 (7.1)	.868	−0.022	4 (8.9)	10 (7.1)	.823	0.045
Immunosuppressive therapy within the past 30 days[b]	5 (10.6)	23 (16.3)	.344	−0.158	7 (15.6)	21 (14.9)	.997	−0.001
Urologic abnormalities								
Foley catheter, not removed	5 (10.6)	17 (12.1)	.793	−0.037	5 (11.1)	16 (11.3)	.939	−0.014
Intermittent catheterization	8 (17.0)	32 (22.7)	.410	−0.132	8 (17.8)	30 (21.3)	.756	−0.058
Nephrostomy tube or suprapubic catheter	3 (6.4)	2 (1.4)	.067	0.261	1 (2.2)	4 (2.8)	.963	0.006
Nephrolithiasis	1 (2.1)	8 (5.7)	.324	−0.180	2 (4.4)	7 (5.0)	.783	−0.061
Prior genitourinary surgery	4 (8.5)	6 (4.3)	.260	0.180	3 (6.7)	8 (5.7)	.799	0.040
Persistence of urinary hardware throughout antibiotic treatment	5 (10.6)	14 (9.9)	.889	0.031	4 (8.9)	15 (10.6)	.854	−0.034
ICU admission for pyelonephritis	11 (23.4)	38 (27.0)	.684	−0.069	13 (28.9)	38 (27.0)	.825	0.042
Vasopressors	2 (4.3)	8 (5.7)	.729	−0.060	2 (4.4)	7 (5.0)	.625	−0.075
Pathogen								
Escherichia coli	29 (61.7)	77 (54.6)	.396	0.126	25 (55.6)	79 (56.0)	.970	0.007
Klebsiella pneumoniae	13 (27.7)	44 (31.2)	.647	−0.064	15 (33.3)	43 (30.5)	.704	0.072
Klebsiella oxytoca	2 (4.3)	4 (2.8)	.632	0.081	1 (2.2)	4 (2.8)	.990	0.002
Proteus mirabilis	3 (6.4)	16 (11.3)	.328	−0.169	3 (6.7)	14 (9.9)	.469	−0.129

Baseline characteristics were considered balanced if the SMDs were less than 10%

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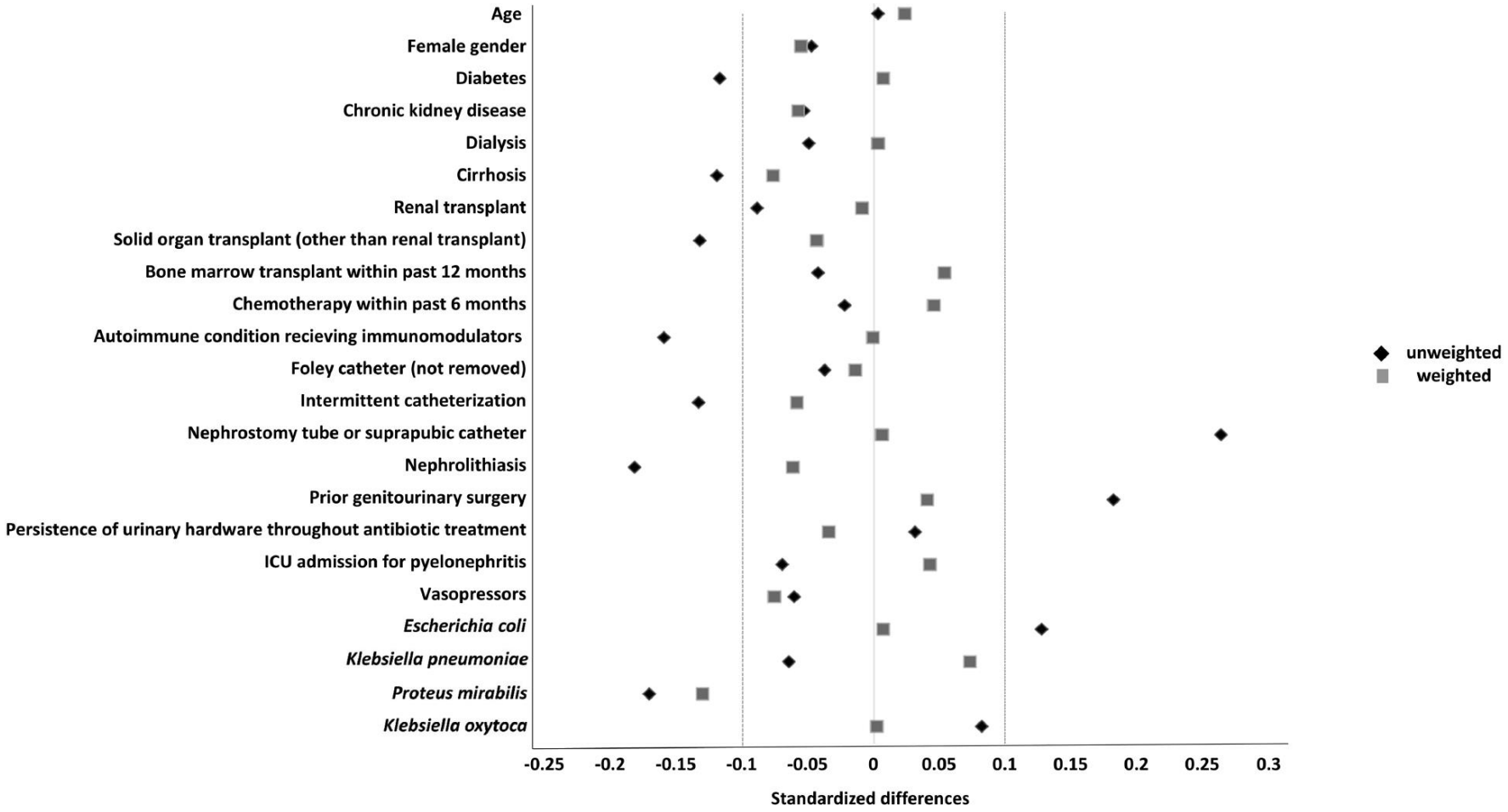

Baseline characteristics were considered balanced if the SMDs were less than 10%

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Results:

- N=186 Pip/Taz: 45 (24%)
  Carbapenem: 141 (76%)

Patients:

- median age 63 (IQR 49–74)
- 68% females
- 47% immunocompromising conditions
- 46% underlying urologic abnormalities
- 26% ICU patients

Pathogens:

- 56% *E. coli*
- 30% *K. pneumoniae*
- 10% *P. mirabilis*
- 3% *K. oxytoca*

Table 2. Antibiotic Treatment Regimens in the PS-Weighted Cohort

	Piperacillin-Tazobactam, n = 45; 24%	Carbapenem, n = 141; 76%
Antibiotic initiated within 24 hours of urine culture collection		
Ceftriaxone	2 (4.4)	14 (9.9)
Cefepime	0	11 (7.8)
Piperacillin-tazobactam	43 (95.5)	14 (9.9)
Ertapenem	0	51 (36.2)
Meropenem	0	47 (33.3)
Fluoroquinolone	0	4 (2.8)
Oral step-down therapy		
Trimethoprim-sulfamethoxazole	3 (6.7)	3 (2.1)
Ciprofloxacin	6 (13.3)	8 (5.7)
Duration of therapy		
Total duration, median (IQR)	9 (7–12)	10 (7–14)
Duration of study drug, median (IQR)	8 (7–10)	8 (7–13)

Regimens/dosing:

Pip/Taz: 81%: 3.375g QID
19%: 4.5g QID

Ertapenem: 1g OD

Meropenem: 1g TID

Results:

Outcomes	Pip/Taz N (%)	Carbapenem N (%)	p-value
Primary outcome: Recurrence with the same ESBL-producing organism ≤ 30 days	9 (20)	35 (25)	0.52
Secondary outcomes:			
► Resolution of symptoms by day-7	42 (93)	125 (89)	0.37
► Day-30 mortality	2 (4)	10 (7)	0.36
► Identification of a carbapenem resistant gram-negative isolate within 30 days of antibiotic treatment	1 (2)	11 (8)	0.09

P. aeruginosa

3 *E. coli*
4 *K. pneumoniae*
3 *P. aeruginosa*
1 *A. baumannii*

*

* 5 treated with Ertapenem, 6 treated with Meropenem

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Conclusion:

- In hospitalized patients with non-bacteremic pyelonephritis caused by ESBL-producing organisms treatment with Pip/Taz may result in similar clinical outcomes as carbapenem therapy

- Although not achieving statistically significance, 2% of patients receiving Pip/Taz, compared to 8% of patients receiving a carbapenem, had an incident carbapenem-resistant organism recovered from clinical culture within 30 days of antibiotic treatment

Limitations:

- Observational design (propensity score method: potential for unmeasured confounding)
- Unability to differentiate recurrent from persistent ESBL infection
- Study limited to bla_{CTX-M}, bla_{TEM}, bla_{SHV} genes from one region
- No testing for bla_{OXA-1}
- It is unclear whether the results can be extended to other members of the Enterobacterales family that are ESBL-producing or to regions where OXA-1 production may be more prominent
- Most critical: the low sample size…

Needed sample-size for a non-inferiority trial:

Significance level (alpha)	5%
Power (1-beta)	80%
Percentage 'success' in control group	75 %
Percentage 'success' in experimental group	75 %
Non-inferiority limit, d	5 %

Calculate sample size

Sample size required per group	928
Total sample size required	1856

Significance level (alpha)	5%
Power (1-beta)	80%
Percentage 'success' in control group	75 %
Percentage 'success' in experimental group	75 %
Non-inferiority limit, d	10 %

Calculate sample size

Sample size required per group	232
Total sample size required	464

Also just published:

Efficacy of β-lactam/β-lactamase inhibitors to treat ESBL-producing Enterobacterales bacteremia secondary to urinary tract infection in kidney transplant recipients (INCREMENT-SOT Project)

Pierrotti et al. Transpl Infect Dis 2020 Nov;e13520. doi: 10.1111/tid.13520.

Methods: We retrospectively evaluated 306 kidney transplant recipients admitted to 30 centers from January 2014 to October 2016. Therapeutic failure (lack of cure or clinical improvement and/or death from any cause) at days 7 and 30 from ESBL-E BSI onset were primary and secondary study outcomes, respectively.

Conclusions: Our data suggest that therapy based on β-lactam/β-lactamase may be as effective as carbapenem-containing regimens.

General thoughts:

Table 1. Potentially Favorable Circumstances for Noncarbapenem-β-Lactams in the Treatment of Extended-Spectrum β-Lactamase Infections

• What if noncarbapenem β-lactam minimum inhibitory concentrations are low?
• What if high-dose, frequent-interval βL-βLIs or cefepime is administered?
• What if extended-infusion noncarbapenem β-lactams are administered?
• If carbapenem antibiotics are administered when the burden of bacteria is highest, can therapy be transitioned to a noncarbapenem after a short period of time?
• If a βL-βLI is administered, does the type of β-lactamase inhibitor matter (eg, tazobactam, sulbactam, clavulanic acid, or avibactam)?
• Does it matter if the ESBL resistance mechanism is a bla_{TEM} type, bla_{CTX-M} type, or bla_{SHV} type?
• Does the genus or species of the ESBL producer matter?
• Does the source of bacteremia and if source control measures were taken matter?
• Should the severity of illness determine if a carbapenem or noncarbapenem agent is administered?

Abbreviations: βL-βLI, β-lactam–β-lactamase inhibitor; ESBL, extended-spectrum β-lactamase.

Vielen Dank für die Aufmerksamkeit