# Meta-analysis of Randomized Control Trials Evaluating New Beta-Lactamase Combination Antibiotics

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# Background

- Ceftolozane/ Tazobactam (C/T), Ceftazidime/ Avibactam (C/A), Meropenem/ Vaborbactam (M/V) and Imipenem/ Relebactam (I/R) are new combination beta-lactam/ beta-lactamase inhibitor antibiotics primarily used to treat multidrug-resistant (MDR) Gramnegative infections.
- This study synthesized outcomes of comparative observational studies and randomized control trials (RCTs) that evaluated clinical success of these antibiotics compared to other therapies.

### Methods

- PubMed, EMBASE, and Google Scholar were searched from January 1<sup>st</sup>, 2013 through September 2<sup>nd</sup>, 2020 for comparative observational studies and RCTs of C/T, C/A, M/V and I/R.
- Study and patient demographics were collected along with clinical success rates.
- Meta-analysis was used to determine the pooled clinical success rates of C/T, C/A, M/V, and I/R.
  - Clinical success was defined as the resolution of all signs and symptoms of infection such that no further intervention was needed.
- Heterogeneity and publication bias were assessed via l<sup>2</sup> values and funnel plots, respectively.

#### Results

Table1: Demographics of Included Articles

Variable Name	Randomized Control Trials (n=17)	Observational Studies (n=8)
Duration of Study (mos)	23.0	49.6
Sample Size	8,238	828
Location	Global=16 Asia=1	USA=5 Spain=2 Italy=1
Number of Sites	84.5	8
Antibiotic under Investigation	C/A=8 C/T=3 I/R=3 M/V=2	C/A=4 C/T=4

Figure 1: Diagram of Search Results

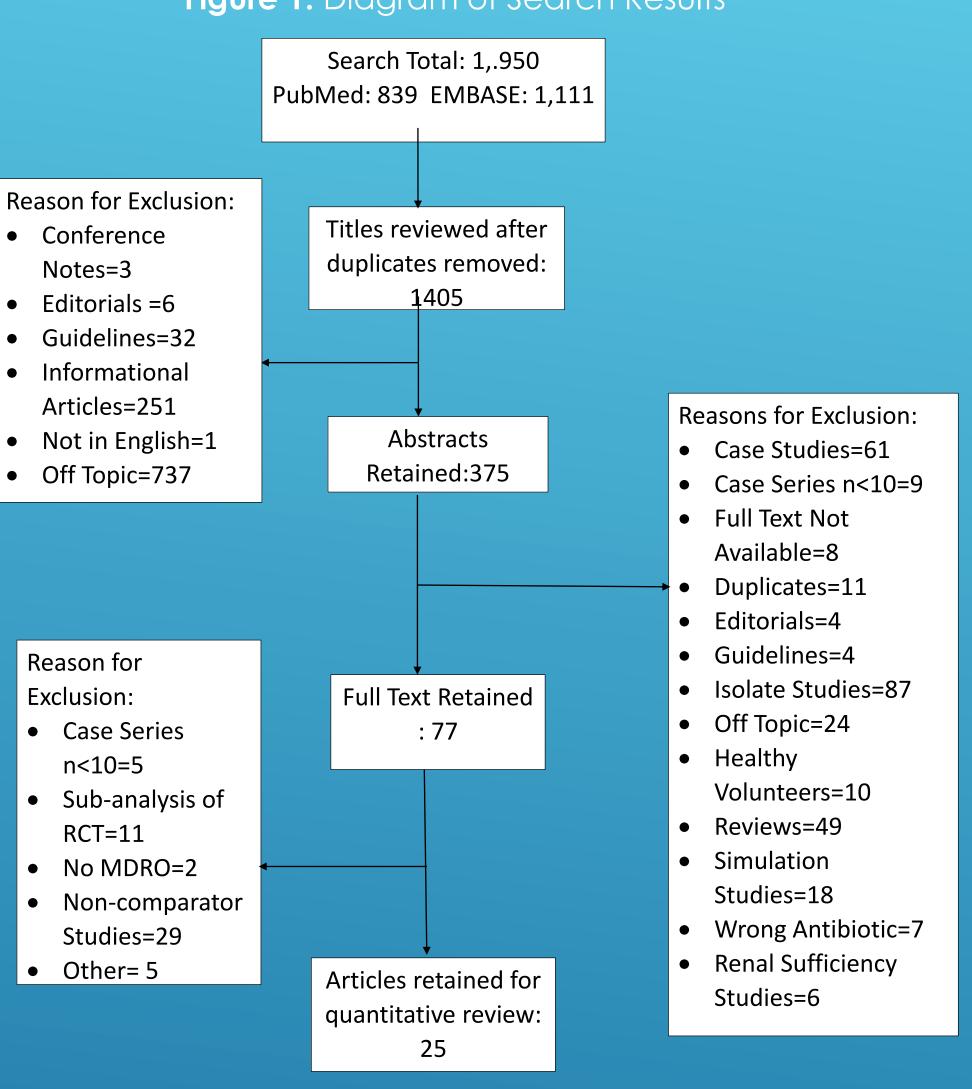


Figure 3: Pooled Results of Randomized Control Trials

	Experim	ental	Contr	ol		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Bradley, 2019	45	50	18	19	2.7%	-0.05 [-0.18, 0.08]	<del></del>
Carmeli, 2016	140	154	135	148	7.8%	-0.00 [-0.07, 0.06]	+
Kaye, 2018	174	192	157	182	7.7%	0.04 [-0.02, 0.11]	<del> </del>
Lucasti, 2013	70	85	79	89	4.0%	-0.06 [-0.17, 0.04]	<del></del>
Lucasti, 2014	51	61	24	25	3.1%	-0.12 [-0.24, -0.00]	<del></del>
Lucasti, 2016	164	185	79	92	5.4%	0.03 [-0.06, 0.11]	<del></del>
Mazuski, 2016	429	520	444	523	11.1%	-0.02 [-0.07, 0.02]	-
Motsch, 2019	15	21	7	10	0.4%	0.01 [-0.33, 0.36]	
Qin, 2017	119	143	135	152	6.0%	-0.06 [-0.14, 0.02]	<del></del>
Sims, 2017	132	150	70	80	5.0%	0.01 [-0.08, 0.09]	<del></del>
Solomkin, 2015	323	389	364	417	10.3%	-0.04 [-0.09, 0.01]	
Titov, 2020	161	264	149	267	5.5%	0.05 [-0.03, 0.14]	+
Torres, 2019	126	187	143	195	4.8%	-0.06 [-0.15, 0.03]	<del></del>
Vazquez, 2012	24	28	29	36	1.5%	0.05 [-0.13, 0.23]	<del>-   • </del>
Wagenlehner, 2015	366	398	356	402	11.9%	0.03 [-0.01, 0.08]	<del>  -</del>
Wagenlehner, 2016	355	393	377	417	12.0%	-0.00 [-0.04, 0.04]	+
Wunderink, 2018	19	32	4	15	0.7%	0.33 [0.05, 0.61]	<del></del>
Total (95% CI)		3252		3069	100.0%	-0.01 [-0.03, 0.02]	•
Total events	2713		2570				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi²	= 25.09,	df = 16 (	P = 0.0	7); I <sup>2</sup> = 369	6 <del>-</del>	<del></del>
Test for overall effect:						-1	-0.5 0 0.5 Old Abx Therapies New Abx Therapies

Figure 2: Pooled Results of Observational Studies

	New Abx The	rapies	Older Abx The	rapies		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	I M-H, Random, 95% CI
Ackley, 2020	65	105	18	26	15.8%	0.72 [0.29, 1.81]	<del></del>
Caston, 2017	6	8	8	23	7.4%	5.63 [0.92, 34.57]	<del>                                     </del>
Fernandez-Cruz, 2019	17	19	27	38	8.6%	3.46 [0.68, 17.57]	<del></del>
Mills, 2019	45	62	36	53	17.4%	1.25 [0.56, 2.79]	<del>-  </del>
Pogue, 2020	81	100	61	100	19.8%	2.73 [1.44, 5.18]	<del></del>
Shields, 2017	11	13	39	96	9.1%	8.04 [1.69, 38.28]	
van Duin, 2018	35	38	66	99	11.8%	5.83 [1.67, 20.38]	
Vena, 2020	13	16	18	32	10.1%	3.37 [0.80, 14.18]	<del></del>
Total (95% CI)		361		467	100.0%	2.56 [1.43, 4.58]	
Total events	273		273				
Heterogeneity: Tau <sup>2</sup> = 0.	34; Chi <sup>2</sup> = 14.67	df = 7 (F	P = 0.04);  2 = 52	%			0.04 0.4 4 40 400
Test for overall effect: Z	= 3.17 (P = 0.00)	(2)					0.01 0.1 1 10 100 Older Abx Therapies Newer Abx Therapies

## Conclusion

- Among RCT's the novel antibiotics were non-inferior to the older antibiotic therapies
- In the observational studies there was a strong association between the newer antibiotics and odds of clinical recovery from infection.
- The 2020 ID&A CRE guidelines recommend the use of C/A, M/V, and I/R for the treatment of Carbapenem-resistant Enterobacteriaceae infections
- The guidelines also recommend the use of C/T, M/V, and I/R for the treatment of multi-drug resistant Pseudomonas aeruginosa infections.
- Additional studies are needed to further evaluate these drugs' effectiveness for treatment of MDR infections.

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