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Ceftolozane/tazobactam (Zerbaxa) for the Treatment of Pseudomonas aeruginosa (PSA) Bacteremia: A Systematic Literature Review (SLR)

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Background/ Objective

- Resistant bacterial infections are thought to affect 2.8 million Americans annually with 35,000 deaths. (CDC 2019) Global estimates of mortality are ~700,000; with specific resistant gram-negative (GN) pathogens recognized by the WHO as a critical threat. (WHO 2017)
- As a subset of these infections, blood stream infection (bacteremia) is a significant cause of morbidity, mortality, and economic burden. Several studies have shown this burden to increase among patients with multidrug resistant (MDR) infection, and/or as a consequence of inappropriate therapy. However, the optimal management of MDR bacteremia is unknown. (Havey 2011) Effective treatment is further complicated by variability among: patient risk factors, disease severity, comorbidities, bacterial ecology, and infection classification (primary, or secondary; and if secondary, to what initial infection).
- Ceftolozane/tazobactam (C/T) is a combination of a novel antipseudomonal cephalosporin and an established β-lactamase inhibitor approved for the treatment of complicated urinary tract infection, complicated intra-abdominal infection, and hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP).
- As described, there is a critical need for novel GN antimicrobials to combat high-risk infections among patients whose care requires devices such as ventilators and blood catheters. (WHO 2017) In the absence of specific bacteremia clinical trial data, the aim of this study is to describe all currently published evidence relating to C/T for the treatment of GN bacteremia.

Methods

- A Systematic Literature Review (SLR) included all published evidence from December 2015 to March 2020 identified via the OVID platform: EMBASE®, MEDLINE®, and MEDLINE In-Process®.
- Electronic searches were supplemented with data published from the European Society of Clinical Microbiology and Infectious Diseases and Infectious Disease Week Congresses (2018-2019).
- Study eligibility followed prespecified PICOTS criteria; summarized as studies published in English pertaining to adult patients treated with C/T with primary, secondary, or mixed bacteremia (author defined); where outcomes were reported clearly according to the population of interest. No limit for geography, disease severity, and/ or publication date was applied.

Results

- The SLR and supplemental searches identified 1,455 citations, of which 24 publications representing 23 unique studies met eligibility criteria (Figure 1).
- Studies typically reported mixed infection populations; some reported data by primary, secondary, and/ or non-specified (NS) bacteremia populations (Table 1).
  - Six reported results specific to a primary bacteremia population (n=1 to 7).
  - Twelve reported results specific to a secondary bacteremia population (n=1 to 29)
  - Eleven reported results according to a mixed/ NS bacteremia population (n=1 to 31)

Figure 1. Bacteremia PRISMA diagram

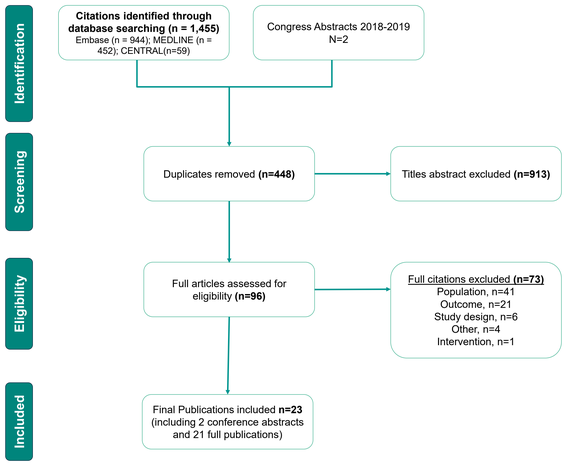

Table 1. Clinical outcomes among primary, and secondary bacteremia patients

Study details	Outcome definitions*	Bacteremia, N	Outcomes: Clinical cure/ success	Outcomes: Microbiological cure/ success/ eradication	Outcomes: Mortality
Primary Bacteremia					
Bassetti 2019 (N=101) Italy	• **Clinical success** defined as complete resolution of signs and symptoms and lack of microbiological evidence of infection.	**6**	6 (100%)	NR	0 (0%)
Diaz-Canestro 2018 (N=58) Spain	• **Clinical Failure** defined as persistent signs and symptoms and positive culture after 7 days of treatment. (*Note. The inverse, i.e. those who did not fail is reported; with this definition aligned to other microbiological outcomes*)	**3**	1 (33.3%)	NR	2 (66.6%)
Elabor 2018 (N=65) USA	• **Cure/ Success** Resolution of signs and symptoms present on diagnosis. • **Microbiolgical cure** was defined as the presence of a repeat negative culture after initiation of treatment; it was presumed, if repeat cultures were not taken but the patients had clinical success.	**4**	4 (100%)	4 (100%)	0 (0%)
Gallagher 2018 (N=205) USA	• **Clinical Success** Improved signs and symptoms from baseline to the end of therapy with defervescence. • **Microbiological cure** defined as a negative culture at the end of therapy; and is presumed in patients with clinical success when repeat culture not available.	**6**	6 (100%)	6 (100%)	0 (0%)^
King 2018 (N=25) USA	• **Clinical success** assessed by improved symptoms, improved imaging where relevant, and defervescence. • **Microbiological success** required a negative culture at the end of therapy.	**7**	6 (86.0%)	7 (100%)	1 (14.2%)
Haidar 2017 (N=21) USA	• **Clinical failure** was defined as attributable mortality PSA, persistent signs or symptoms of infection or positive culture despite ≥7 days of C/T, or recurrent PSA (recurrent signs and symptoms and recurrent culture positivity within 90 days).	**1**	1 (100%)¶	NR	NR
Secondary Bacteremia					
Arakawa 2019 (N=90) Japan	• **Microbiological cure** confirmed by negative blood cultures at TOC (14 days)	**23** (Primary infection; uncomplicated pyelonephritis and cUTI)	NR	22 (95.7%)	NR
Bosaeed 2020 (N=19) Saudi Arabia	• **Clinical success** was based on microbiological clearance (whenever repeated cultures were available); clinical resolution of signs and symptoms of infection, and 30-day in-hospital survival after initiation of C/T treatment.	**1** (Primary infection; Complicated perianal abscesses)	0%	NR	1 (100%)
Caston 2017 (N=12) Spain	• **Clinical cure** determined when attending physician observed a resolution of signs and symptoms and there were no radiologic findings of infection. • **Microbiological eradication** observed 30 days after completion of treatment with C/T	**5** (Primary infection; Overall mixed infection and bacteremia Mixed infections: abdominal, respiratory and venous central catheter)	3 (60.0%)	4 (80%)	2 (40.0%)
Gallagher 2018 (N=205) USA	• **Clinical Success** Improved signs and symptoms from baseline to the end of therapy with defervescence. • **Microbiological cure** defined as a negative culture at the end of therapy; and is presumed in patients with clinical success when repeat culture not available.	**19** (Primary infection; mixed bone/joint, intra-abdominal, pneumonia, wound, and UTI patients)	13 (68.0%) Patients also reported microbiological cure.	NR	7 (36.8%)
Haidar 2017 (N=21) USA	• **Clinical failure** was defined as attributable mortality PSA, persistent signs or symptoms of infection or positive culture despite ≥7 days of C/T, or recurrent PSA (recurrent signs and symptoms and recurrent culture positivity within 90 days).	**2** (Primary infection; pneumonia)	2 (100%)	NR	0%
Hakki & Lewis 2018 (N=6) USA	• **Clinical success** was defined as resolution of signs and symptoms of the infection during treatment with C/T, clearance of bacteremia (if present) within 72 h of initiation of C/T.	**3** (Primary infection not defined)	2 (66.7%)	NR	0%
Kollef 2019 (N=362) Multinational	• **Clinical response** at test of cure, defined as: Complete resolution with no new signs of VNP), which were present at baseline; No new signs, symptoms or complications attributable to VNP; No additional antibiotic therapy administered for VNP*, except for the; approved adjunctive therapy; Patient is alive	**25** (Primary infection; nosocomial pneumonia)	9 (36.0%)	NR	13 (52.0%)
King 2018 (N=25) USA	• **Clinical success** assessed by improved symptoms, improved imaging where relevant, and defervescence. • **Microbiological success** required a negative culture at the end of therapy.	**18** (Primary infection; pneumonia, UTI, intra-abdominal, wound)	13 (72.2%)	NR	8 (44.4%)
Munita 2017 (N=35) USA	• **Clinical success** was defined as a composite of in-hospital survival, resolution of signs and symptoms of the infection (as reported by treating physicians), and absence of recurrence of the infection within the admission	**6** (Primary infection; Pneumonia, Left ventricular assist device infection, Central line-associated bloodstream infection, Pyelonephritis.	4 (66.7%)**	NR	NR
Rodriguez-Nunez 2019 (N=90) Multinational	NA	**4** (Primary infection; lower respiratory infection)	NR	NR	1 (25.0%)
Sousa Dominguez 2017 (N=1) Spain	NR	**1** (Primary infection; Skin and soft-tissue)	1 (100%)	NR	NR
Wagenlehner 2015 (N=398) Multinational	• **Composite clinical response** defined as achieving clinical cure and microbiological eradication of all baseline uropathogens	**29** (Primary infection; Pyelonephritis or complicated lower-urinary-tract infections)	23 (79.3%)		NR

Abb. CR, carbapenem resistant; C/T, ceftolozane/tazobactam; MDR, multidrug resistant; NR, not reported; PSA, pseudomonas aeruginosa; (c)UTI, urinary tract infection (c, complicated) XDR, Extensively drug resistant

Legend. *Outcome definitions and timing of outcomes relate to the overall study population. Not reported here; baseline pathogen/ treatment details were reported for the overall study population unless otherwise specified. ^Authors reported mortality without time point. ¶Authors reported patient death following clinical success; this was not specified as infection related. ** included patient treated with C/T + colistin

Results – Primary Bacteremia

- The majority of studies (6/6) reported a drug resistant (MDR/ XDR) PSA patient population, with a primary bacteremia sample size ≤7 patients.
- C/T dose ranged from 0.375 IV q8h for 48 days (Haidar) to 3g IV q8h for 10 – 14 days (Haidar, Gallagher, King, and Bassetti)
- Clinical cure/ success reported in 6 studies ranged from 33.3% (Diaz-Canestro, n=1/3) to 100% (4 studies total n=17)
- Microbiological cure/ success/ eradication was reported in 3 studies at 100% (total n=17)
- Mortality reported in 5 studies ranged from 0% (3 studies) to 67% (Diaz-Canestro, n=2/3)

Results – Secondary Bacteremia

- The primary infection site varied across studies; but included respiratory, urinary tract, skin, bone, and others. Studies reporting mixed primary infection sites did not provide stratified results (Table 1).
- Among secondary bacteremia a predominant PSA (n=9/12) and drug resistant ((MDR (n=7/12), MDR/XDR (n=1/12), CR (n=1/12)) population was reported. Three studies reported mixed pathogen with no resistance details (Arakawa, Kollef, Wagenlehner)
- C/T dose ranged from 750mg IV q8h for 7 days (Munita) to 3g IV q8h for 5 – 29 days (King, Haidar, Hakki and Leiws, Munita, Caston, Kollef, Gallagher).
- Clinical cure/ success reported in 9 studies ranged from 36% (Kollef, n=9/25) to 100% (3 studies total n=4)
- Microbiological cure/ eradication was reported in 2 studies at 80% (Caston, n=4/6) and 95.7% (Arakawa, n=22/23); with a single study reporting a compositive clinical response including microbiological eradication of baseline uropathogens at 79.3% (Wagenelehner, n=23/29)
- Mortality reported in 6 studies ranged from 0% (2 studies) to 52% (Kollef, n=13/25); with a single study by Bosaeed at 100% for a single patient.

Results – Mixed/ Not specified Bacteremia Populations

- Similar to the primary and secondary bacteremia patient populations; 8 of 12 studies reported a PSA focus, with 5 describing an MDR/ XDR infection.
- Due to a lack of reporting clarity these 12 studies are challenging to interpret. Some studies (N=8) appear to have overlapping patient groups describing sepsis and or septic shock, which may or may not include primary, secondary, and or unknown bacteremia patients.
- Clinical outcomes considered within these mixed groups are comparable to primary and secondary bacteremia populations:
  - Eleven studies reported clinical cure/ success outcomes; 50% to 83% with three case reports at 100%
  - Six studies reported microbiological outcomes; range 50% to 80% with a single case report at 100%
  - Six studies reported mortality; range 0% to 52%

Limitations

- This SLR, although broad, still included search limits such as “English language” publications only, and the limited search of just two congress proceedings. As a result, it is possible that evidence gaps exists, and that publication bias is present.
- There were multiple sources of heterogeneity identified; including but not limited to: trial design, outcome definition and assessment timepoint, baseline patient characteristics, baseline pathogen, and C/T treatment characteristics.
- Specific to the secondary and/or mixed bacteremia population(s), a lack of reporting of outcomes by primary infection site prevents definitive conclusions relating to C/T outcomes for these populations.

Conclusion

- Although the number of C/T treated patients with bacteremia was small compared to other infections; these real-world data demonstrate generally favorable outcomes among patients with primary, secondary and mixed bacteremia, including subjects with hard-to-treat resistant (MDR/XDR/CR) PSA infection.
- Generally, trends in outcomes reported across bacteremia populations were consistent. However, key treatment effect modifiers, such as: disease severity, C/T dose, and C/T positioning within the treatment pathway (i.e. salvage therapy) were not frequently reported for bacteremia patients.
- Antimicrobials such as C/T when used within the ethos of antimicrobial stewardship represent a valuable treatment option particularly among complicated patients with primary or secondary bacteremia. Further studies focused specifically on patients with primary and secondary bacteremia are needed.

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