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Posted Date: 14 February 2026

doi: 10.20944/preprints202602.1128.v1

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# Prescribing Patterns and Clinical Effectiveness of Ceftolozane/Tazobactam for ESBL-Producing Enterobacterales: A SPECTRA Real-World Multi-Country Analysis

**Running Head: ESBL-Producing Enterbacterales Results from SPECTRA**

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## Abstract

**Background:** Ceftolozane/tazobactam (C/T) has demonstrated activity against ESBL-producing Enterobacterales (ESBL-E) and provides a carbapenem-sparing option. Broader use of C/T alongside other carbapenem/inhibitor combinations may expand therapeutic choices and reduce selection pressure for carbapenem resistance, supporting antimicrobial stewardship and limiting the spread of carbapenem-resistant Enterobacterales. **Methods:** SPECTRA was a multicentre, retrospective real-world study of hospitalized adults (≥18 years) who received ≥48 hours of C/T across seven countries (Australia, Austria, Germany, Italy, Mexico, Spain, UK) from January 2016 to November 2020. Medical-record data were collected for up to 6 months before treatment and 30 days after the final C/T dose (or until death). This sub-analysis describes clinical outcomes and healthcare utilization in patients with laboratory-confirmed ESBL-E (n=39). **Results:** Thirty-nine ESBL-E patients were included (mean age 59.3 years; 56.4% male); 79.5% had ≥1 comorbidity (mean 2.2 per patient). Common pathogens were Escherichia coli (n=23) and Klebsiella spp (n=12). Investigator-assessed clinical success was 64.9%, microbial eradication was 27.0%, in-hospital mortality was 20.5%, and 30-day readmission was 5.1%. ICU admission during the index hospitalisation occurred in for 38.5% of patients (mean ICU stay 16.0 days). Median treatment duration was 11 days while mean hospital stay after C/T initiation was 13.5 days. **Conclusions:** In this real-world multi-country cohort, C/T showed clinical effectiveness in ESBL-E infections, with outcomes consistent with the overall SPECTRA population. C/T offers a carbapenem-sparing strategy that broadens treatment options and may help reduce reliance on carbapenems, supporting efforts to limit carbapenem-resistant Enterobacterales. Findings warrant evaluation in larger and comparative studies.

 doi:10.20944/preprints202602.1128.v1



**Keywords:** Ceftolozane/tazobactam; ESBL-E; real-world; clinical outcomes; antimicrobial stewardship; SPECTRA

## 1. Introduction

Antimicrobial resistance (AMR) is a global public health threat, projected to cause an estimated 10 million deaths per year worldwide and a global economic burden of $100 trillion by 2050. [1-3] Multidrug-resistant (MDR) organisms, such as Gram-negative bacteria *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and have diminished the efficacy of many traditional antibiotics.[3-5] However, the development of new antibiotics has reduced and only a limited number of innovative agents are in development or have been approved in recent years.[3,6]

Pathogens in the Enterobacterales order that carry extended-spectrum β-lactamase (ESBL) genes are considered one of the most challenging pathogens by the World Health Organization, with an estimated 1.5 billion people colonized worldwide at one time.[7] ESBL-producing Enterobacterales (ESBL-E) have become increasingly prevalent in both healthcare and community settings. Their widespread emergence substantially limits therapeutic options and is associated with higher morbidity and mortality among affected patients.[7-9]

ESBL-E confer resistance to a range of different antibiotics including penicillin and cephalosporins.[7] Traditionally, carbapenem is the first choice for treating severe ESBL-E positive infections in the US and Europe, however, the recent emergence of carbapenemase-producing bacteria have increased the need for innovative therapies that are effective against ESBL-E pathogens.[7,10,11] Innovative therapies such as ceftolozane/tazobactam (C/T) have emerged to address this, offering potent activity against resistant Gram-negative bacteria including the Enterobacter species.[12] C/T offers patients increased tazobactam exposure at the standard dose when compared to some alternative β lactam/β lactamase inhibitor combinations, which may be relevant when treating isolates with elevated β lactamase expression, such as in ESBL-E infections or in patients with altered drug clearance.[27]

While randomized controlled trials (RCTs) remain the gold standard, they often exclude patients with comorbidities, commonly seen in patients with ESBL-E.[13,14] Therefore, real-world evidence is required to compliment findings from RCTs, improve understanding of treatment effectiveness over a wider range of patient and infection types, and is increasingly used to inform regulatory decisions, clinical guidelines, and health technology assessments.[15]

The Study of Prescribing patterns and Effectiveness of Ceftolozane/Tazobactam Real-world Analysis (SPECTRA) provides a large, multi-country dataset of detailed clinical and microbiological data. Previous publications from SPECTRA have summarized its overall findings and disseminated data by critically ill, and in pulmonary disease and respiratory-related infection cohorts.[16-18] Understanding current ESBL-E presence in patients with severe infections and the effectiveness of alternative treatment options in this population allows for the development of strategies that are effective against these organisms. This study focused on patients with ESBL-E infections, and aimed to describe and evaluate clinical outcomes and healthcare resource utilization (HCRU) in this population.

## 2. Materials and Methods

SPECTRA, a multicenter, retrospective study of adult inpatients treated with C/T for ≥48 hours provided real-world outcomes on C/T use in Australia, Austria, Germany, Italy, Mexico, Spain and the UK. Data were extracted from medical records across these seven countries from January 2016 to November 2020. Study design, population and core outcomes are defined in previous papers.[16-18] Patients were included if they were age ≥18 years, had received C/T for ≥48 hours and had received their last C/T dose ≥30 days before data collection. Patients were excluded if they were participating in an interventional clinical trial for Gram-negative infection at the time of treatment.

 doi:10.20944/preprints202602.1128.v1



The primary study objective was to characterize real-world C/T treatment patterns, clinical outcomes and HCRU in hospitalized adults receiving ≥48 hours of treatment. A key secondary objective as presented in this manuscript was to analyze patient outcomes by presence of ESBL-E infection.

The study was conducted in compliance with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices,[19] the ethical principles arising from the Declaration of Helsinki,[20] the European Union good pharmacovigilance practices,[21] European and national laws with respect to data protection,[22] and applicable local regulations.

### *2.1. Outcomes*

Data were retrospectively collected from medical records covering up to 30 days after treatment or until death. Outcomes included investigator-assessed clinical success of C/T treatment during index infection, microbial eradication, all-cause in-hospital mortality, length of hospital stay following C/T administration, intensive care unit (ICU) admissions, ICU length of stay, and readmission rates.

Clinical success was defined as microbiological eradication, no Gram-negative therapy needed for a minimum of 48 hours after administration of C/T (not including discharge antibiotics or de-escalation), no death due to Gram-negative infection, no additional treatment for exacerbation of respiratory infection within 28 days of stopping C/T, resolution of any exacerbations or no need for re-operation for source control. Microbiology data were analyzed if collected within 14 days of C/T initiation and microbiological eradication was defined as negative culture at the site of index infection after C/T.

### *2.2. Statistical Analysis*

Categorical variables were reported as counts and percentages and continuous data reported as mean and standard deviation (SD) or median and interquartile range (IQR). Where available, 95% confidence intervals (CIs) for proportions have been reported. No inferential statistics were performed on this dataset and therefore descriptive statistics are reported only.

## 3. Results

### *3.1. Patient Characteristics*

A total of 39 of the 617 patients included in the SPECTRA study had ESBL-E positive infections. Patients with ESBL-E had a mean age of 59.3 years, were 56.4% male and had a mean body mass index (BMI) of 28.6 kg/m² (Table ). The presence of at least one comorbidity was seen in 79.5% of patients with ESBL-E, with a mean of 2.2 comorbidities per patient (Table ). Patients could have multiple infections, and pathogens responsible for the infections were most commonly *Escherichia coli* (n=23), followed by *Klebsiella species* (n=12; Supplementary Table S1).

**Table 1.** Patient characteristics in patients with ESBL-E.

| | **Patients with ESBL-E (n=39)** | **Total Study Cohort (n=617)** |
|---|---|---|
| **Age*** | | |
| Mean (SD) | 59.3 (16.5) | 57.4 (17.3) |
| Median | 60.0 | 59.0 |
| Q1;Q3 | 51.0 ; 70.0 | 45.0 ; 71.0 |
| **Male (%)** | 22 (56.4) | 404 (65.5) |
| **BMI (kg/m²)** | | |
| Mean (SD) | 28.6 (10.9) | 25.6 (6.7) |
| Median | 25.6 | 25.0 |
| Q1;Q3 | 68.0 ; 87.0 | 21.6 ; 28.2 |
| **Previous care setting** | | |

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| | | |
|---|---|---|
| Home / Community (%) | 29 (74.4%) | 495 (80.2) |
| Other hospital (%) | 6 (15.4%) | 73 (11.8) |
| Other skilled care facility (%) | 4 (10.3%) | 35 (5.7) |
| Unknown (%) | 0 | 14 (2.3) |
| **Number of comorbidities** | | |
| ≥ 1 (%) | 31 (79.5) | 510 (82.7) |
| Mean (SD) | 2.2 (1.7) | 2.1 (1.6) |
| Median | 2.0 | 2.0 |
| Q1;Q3 | 1.0 ; 3.0 | 1.0 ; 3.0 |

* For patients aged 90 or older the healthcare provider was asked not to enter the exact age and to check a specific box. Therefore, patients aged 90 or older are included in 'Missing' and are not taken into account in the calculation of mean, median, etc. BMI: Body mass index; ESBL-E: extended-spectrum β-lactamase producing Enterbacteriaceae; Q: Quartile; SD: Standard deviation.

### *3.2. Clinical Outcomes*

Clinical success was recorded in 64.9% of patients with ESBL-E. When considering ESBL-E infection type, clinical success was achieved in 59.1% of patients with *Escherichia coli* and 63.6% of patients with *Klebsiella spp* infections (Table ). Microbial eradication was confirmed in 27.0% of patients with ESBL-E (Table ). All-cause in-hospital mortality was 20.5% (95% CI: 9.3, 36.5; Table ).

**Table 2.** Clinical outcomes in patients with ESBL-E.

| | **Patients with ESBL-E (n=39*)** | **Total Study Cohort (n=617)** |
|---|---|---|
| **Index infection considered as a clinical success by the investigator (%)** | 24 (64.9) | 415 (67.3) |
| *Escherichia coli* | 13 (59.1) | N/A |
| *Klebsiella spp* | 7 (63.6) | N/A |
| **Microbial eradication (%)** | 10 (27.0) | 116 (18.8) |
| **All-cause in-hospital mortality (%)** | 8 (20.5) | 131 (21.2) |
| 95% CI | (9.3, 36.5) | (18.1, 24.7) |

*Clinical success and microbial eradication were not reported in two patients in the ESBL-E cohort. These individuals are considered as missing data and therefore excluded from percentage calculations. CI: confidence interval; ESBL-E: extended-spectrum β-lactamase producing Enterbacteriaceae; spp: species; N/A: Not applicable.

### *3.3. Healthcare Resource Utilization*

Mean (SD) hospital length of stay following C/T administration was 13.5 (22.5) days (Table ). During hospitalization, 38.5% of patients were admitted to the ICU, with 40.0% of these admissions related to the index infection (Table ). The mean (SD) ICU length of stay was 16.0 (17.6) days (Table ). In total, 5.1% of patients were readmitted to hospital within 30 days following discharge for any cause (Table ).

**Table 3.** HCRU in patients with ESBL-E.

| | **Patients with ESBL-E (n=39)** | **Total Study Cohort (n=617)** |
|---|---|---|
| **Admission to ICU during the index hospitalization (%)** | 15 (38.5) | 298 (48.3) |
| ICU related to index infection (%) | 6 (40.0) | 125 (41.9) |
| **ICU length of stay (days)** | | |
| Mean (SD) | 16.0 (17.6) | 25.7 (23.9) |
| Median | 11.0 | 19.0 |
| Q1;Q3 | 5.0 ; 16.0 | 8.0 ; 37.5 |
| **30-day all-causes readmission (%)** | 2 (5.1) | 63 (10.2) |
| **Post-C/T length of stay (days)** | | |
| Mean (SD) | 13.5 (22.5) | 15.5 (43.7) |
| Median | 6.0 | 6.0 |

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| | | |
|---|---|---|
| Q1;Q3 | 2.0 ; 20.0 | 1.0 ; 25.0 |

C/T: Ceftolozane/Tazobactam; ESBL-E: extended-spectrum β-lactamase producing Enterbacteriaceae; ICU: intensive care unit; Q: Quartile; SD: Standard deviation.

## 4. Discussion

In SPECTRA, C/T was administered to 39 patients positive for ESBL-E infections. The two most prevalent species of ESBL-E identified in this study were *Escherichia coli* and *Klebsiella spp*, which is broadly aligned with previous literature which found that ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* are recorded as the most common ESBL-producing species.[23] *Klebsiella spp* were one of the most frequently recorded species in this study, however only one patient was reported as having *Klebsiella pneumoniae*. Apart from this, species information was mostly unspecified. This could be due to a lack of consistent recording of species information in records obtained for this study.

Clinical success in patients with ESBL-E (64.9%) was comparable to the total study cohort (67.3%). Clinical success was consistent regardless of pathogen species (*Escherichia coli* 59.1%, *Klebsiella spp* 63.6%). These findings suggest that C/T was an effective treatment for patients with ESBL-E, regardless of pathogen species. However, clinical success observed in this study for patients with ESBL-E treated with C/T was lower than has been reported in previous literature (83.7%).[24] This may be due to differences in how the studies defined clinical success, which could be considered more stringent in SPECTRA as patients could not receive further antibiotic treatment following C/T to meet the criteria for clinical success.[24] Differences may also have existed in time to treatment, patient demographics and clinical infection type and severity which could also have contributed to the observed differences in clinical success.[24]

All-cause in-hospital mortality for patients with ESBL-E following C/T treatment (20.5%) was similar to that of the total SPECTRA cohort (21.2%). When comparing to previous studies, this result lies within reported mortality rates for patients with ESBL-E across all treatments (12% to 41%), but is higher than previously observed mortality rates for patients with ESBL-E infections treated with C/T (9.8%).[24,25] However, it should be noted that mortality rates recorded in SPECTRA were for all-causes and not specific to the index infection which could contribute to the higher observed mortality rates.[25] Interestingly, the mortality rate observed in this study was lower than the 28-day mortality rate recorded in literature for patients treated with Carbapenems (24.2%). [25] While comparison is not possible across these studies and we cannot confirm that these results are due to C/T treatment, these findings highlight the potential of C/T as an acceptable treatment alternative for patients with ESBL-E infections.

ICU admissions and mean ICU length of stay were lower for patients with ESBL-E (38.5% and 16.0 days, respectively) compared to the total study cohort (48.3% and 25.7 days, respectively). In contrast, previous literature has found that patients with ESBL-E infections experience longer lengths of stay than patients with non-ESBL-E infections.[26] The reasons for patients with ESBL-E reporting lower ICU admissions and length of stay in this study are unclear as patient characteristics in the total study cohort and patients with ESBL-E are similar, and so do not suggest any underlying differences between the two cohorts.

30-day all-cause readmission was also lower for patients with ESBL-E infections (5.1%) than for the total SPECTRA population (10.2%). Published data on readmission of patients with ESBL-E infections treated with C/T is limited. Results from the SPECTRA study suggest that C/T treatment in patients with ESBL-E is effective, however limited literature exists to confirm this.

Across all endpoints considered in this study, results for patients with ESBL-E infections are comparable to those in the overall study cohort in SPECTRA. Typically, results for the ESBL-E cohort of the SPECTRA study were also more favorable than seen in literature for this population. The results of this study therefore suggest that C/T may be an effective treatment in patients with ESBL-E infections and could offer an alternative for reducing carbapenem dependance and treating ESBL-E carbapenem-resistant Enterobacterales.

 doi:10.20944/preprints202602.1128.v1



*Limitations*

This analysis is limited by its descriptive nature and lack of statistical analysis. Accordingly, drawing associations between clinical outcomes and the presence of ESBL-E positive pathogens is not possible. Furthermore, the small population size (n=39) of patients with ESBL-E infections limits comparability to literature where larger populations are reported. Further limitations include the retrospective design, possibility of multiple records per patient and that data were collected across time windows that changed according to indication.

Despite these limitations, the findings of this SPECTRA sub-analysis offer descriptive, real-world insight into the use of C/T for patients with ESBL-E infections, identifying clinical effectiveness in this population and highlighting a need for further research into C/T as an alternative treatment for ESBL-E positive patients.

## 5. Conclusions

In this study, C/T demonstrated real-world effectiveness among patients with ESBL-E positive infections. Clinical success, all-cause in-hospital mortality, ICU admission and length of stay and 30-day all-cause readmission rates for patients with ESBL-E were similar to those of the total population included in SPECTRA and as seen in previous literature. These findings suggest that C/T may be a suitable option for treating patients with ESBL-E infections and could offer an alternative for reducing carbapenem dependance and treating ESBL-E carbapenem-resistant Enterobacterales. Further research into C/T use in patients with ESBL-E infections is warranted to confirm the results of this study in a larger cohort and support the adoption of C/T for treating patients with ESBL-E infections.

**Author Contributions Statement:** All authors are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design of work or acquisition, analysis, interpretation of data and drafting the manuscript and/or re- vising/reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.Conceptualization, Alex Soriano, Florian Thalhammer, Stefan Kluge, Jessica Levy, Huina Yang, and Sunny Kaul; Data curation, Alex Soriano, Florian Thalhammer, Stefan Kluge, Jessica Levy, Huina Yang, and Sunny Kaul; Formal analysis, Alex Soriano, Florian Thalhammer, Stefan Kluge, Jessica Levy, Huina Yang, and Sunny Kaul; Funding acquisition, Emre Yucel; Investigation, Emre Yucel; Project administration, Emre Yucel; Resources, Emre Yucel; Supervision, Emre Yucel; Validation, Emre Yucel, Alex Soriano, Florian Thalhammer, Stefan Kluge, Jessica Levy, Huina Yang, and Sunny Kaul; Writing—original draft preparation, Emre Yucel, Alex Soriano, Florian Thalhammer, Stefan Kluge, Mike Allen, Jessica Levy, Huina Yang, and Sunny Kaul; Writing—review and editing, Emre Yucel, Alex Soriano, Florian Thalhammer, Stefan Kluge, Mike Allen, Jessica Levy, Huina Yang, and Sunny Kaul.

**Funding:** Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD).

**Ethical Approval:** The study was conducted in accordance with the relevant ethical standards and approved by the appropriate local Ethics Committees. Obtaining patient informed consent was waived for all sites due to the retrospective nature of the study, except for Italy. Italy EC approval was granted for the five sites included in the study (424/2018/Oss/AOUBo on 18 July 2018, 176/2018 on 20 May 2019, M. 0067354 on 04 June 2018, 0003512/P/GEN/ARCS on 22 January 2019, and 21744/18 on 19 June 2018).

**Data Availability:** The full datasets generated and analyzed to inform the conclusions drawn within this manuscript during the current study are available from the corresponding author upon reasonable request.

**Acknowledgments:** We wish to thank all those who contributed to this study, including the study investigators who treated patients with C/T per standard clinical protocols and approved indications, site personnel who abstracted the data, and patients whose data were used in this study. We would like to acknowledge David Paterson, MD, for his contributions in study oversight and clinical interpretation; Pierluigi Viale, MD, for clinical

 doi:10.20944/preprints202602.1128.v1



leadership, site engagement, and critical review of the manuscript; and Brune Akrich, MD, for coordination of multicenter data collection, operational support, and data quality oversight. We also thank the ICON plc clinical study team, including Project Manager Veronica Gutierrez-Martinez and Director, Project Management Edith Schodl, and the ICON plc statisticians who analyzed the data and created the tables in this report: Statistical Scientists Stéphanie Wirbel, Tracie Shing, and Mayca Roig; Senior SAS Programmer Ramya Bhatt; Senior Statistical Analyst Hannah Clifton; and Senior Statistical Manager Sally Trufan. ICON plc support was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD). Medical writing and editorial support were provided by Hannah Collings, Maisy Bowen and Heather Mulhall of Adelphi Values PROVE™ and were commissioned by Merck Sharp & Dohme LLC, Rahway, NJ, USA.

**Conflicts of Interest:** Alex Soriano has received fees as speaker from Pfizer, Shionogi, Menarini, and grants from Pfizer and Gilead. Emre Yucel is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Mike Allen is an employee of MSD (UK) Limited, London, UK. MA has shareholdings in Merck & Co., Inc., Rahway, NJ, USA.

## References

1. World Health Organisation. WHO integrated global surveillance on ESBL-producing E. coli using a "One Health" approach: implementation and opportunities. Updated 16 March 2021. Accessed 5 November 2025, 2025. https://www.who.int/publications/i/item/9789240021402
2. Berger I, Loewy ZG. Antimicrobial Resistance and Novel Alternative Approaches to Conventional Antibiotics. *Bacteria*. 2024;3(3):171-182.
3. World Health Organization. Antimicrobial resistance. 2024. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
4. Centers for Disease Control Prevention. Management of Multidrug-Resistant Organisms in Healthcare Settings. U.S. Department of Health & Human Services. https://www.cdc.gov/infection-control/hcp/mdro-management/background.html
5. World Health Organization. WHO updates list of drug-resistant bacteria most threatening to human health. World Health Organization; 2024. https://www.who.int/news/item/17-05-2024-who-updates-list-of-drug-resistant-bacteria-most-threatening-to-human-health
6. World Health Organization. WHO releases new reports on new tests and treatments in development for bacterial infections. 2025. https://www.who.int/news/item/02-10-2025-who-releases-new-reports-on-new-tests-and-treatments-in-development-for-bacterial-infections
7. Husna A, Rahman MM, Badruzzaman ATM, et al. Extended-Spectrum β-Lactamases (ESBL): Challenges and Opportunities. *Biomedicines*. Oct 30 2023;11(11)doi:10.3390/biomedicines11112937
8. Castanheira M, Simner PJ, Bradford PA. Extended-spectrum β-lactamases: an update on their characteristics, epidemiology and detection. *JAC-Antimicrobial Resistance*. 2021;3(3)doi:10.1093/jacamr/dlab092
9. Gutiérrez-Gutiérrez B, Rodríguez-Baño J. Current options for the treatment of infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae in different groups of patients. *Clinical Microbiology and Infection*. 2019/08/01/ 2019;25(8):932-942. doi:https://doi.org/10.1016/j.cmi.2019.03.030
10. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). *Clin Infect Dis*. Aug 25 2022;75(2):187-212. doi:10.1093/cid/ciac268
11. Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clinical Microbiology and Infection*. 2022;28(4):521-547. doi:10.1016/j.cmi.2021.11.025
12. Losito AR, Raffaelli F, Del Giacomo P, Tumbarello M. New Drugs for the Treatment of Pseudomonas aeruginosa Infections with Limited Treatment Options: A Narrative Review. *Antibiotics (Basel)*. Apr 26 2022;11(5)doi:10.3390/antibiotics11050579

 doi:10.20944/preprints202602.1128.v1




13. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials*. 2015/11/03 2015;16(1):495. doi:10.1186/s13063-015-1023-4
14. Tan K, Kelsom C, Chron A, Nieberg P, Huse H, Wong-Beringer A. Risk factors and outcome associated with infection or colonization due to carbapenem-heteroresistant Escherichia coli. *JAC-Antimicrobial Resistance*. 2021;3(1)doi:10.1093/jacamr/dlab036
15. Candore G, Martin C, Mills MJ, et al. FRAME: Framework for Real-World Evidence Assessment to Mitigate Evidence Uncertainties for Efficacy/Effectiveness - An Evaluation of Regulatory and Health Technology Assessment Decision Making. *Clin Pharmacol Ther*. Sep 2025;118(3):649-661. doi:10.1002/cpt.3713
16. Soriano A, Paterson DL, Thalhalmmer F, et al. A real-world investigation into prescribing patterns and effectiveness of ceftolozane/tazobactam among critically ill patients from SPECTRA. *Diagn Microbiol Infect Dis*. Apr 2025;111(4):116737. doi:10.1016/j.diagmicrobio.2025.116737
17. Soriano A, Paterson DL, Thalhammer F, et al. Unveiling results and insights from multinational, multicenter Study of Prescribing patterns and Effectiveness of Ceftolozane/Tazobactam Real-world Analysis (SPECTRA). *J Glob Antimicrob Resist*. Mar 2025;41:272-279. doi:10.1016/j.jgar.2025.01.007
18. Yucel E, Soriano A, Paterson DL, et al. Real-world analysis of ceftolozane/tazobactam prescribing patterns and effectiveness: SPECTRA analysis on chronic pulmonary diseases and respiratory-related infections. *J Glob Antimicrob Resist*. Sep 2025;44:217-225. doi:10.1016/j.jgar.2025.06.015
19. International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Updated June 2015. Accessed 16 October 2025, https://www.pharmacoepi.org/resources/guidelines_08027.cfm
20. Word Medical Association. Declaration of Helsinki. Updated October 2013. Accessed 16 October 2025, http://www.wma.net/
21. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP): module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). Updated 22 November 2017. Accessed 16 October 2025, https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-and-submission-reports-suspected-adverse-reactions-medicinal-products-rev-2_en.pdf
22. European Parliament and Council. EU General Data Protection Regulation - Regulation (EU) 2016/679. Updated 27 April 2016. Accessed 16 October 2025, http://data.europa.eu/eli/reg/2016/679/2016-05-04
23. Denkel LA, Maechler F, Schwab F, et al. Infections caused by extended-spectrum β-lactamase-producing Enterobacterales after rectal colonization with ESBL-producing Escherichia coli or Klebsiella pneumoniae. *Clinical Microbiology and Infection*. 2020/08/01/ 2020;26(8):1046-1051. doi:https://doi.org/10.1016/j.cmi.2019.11.025
24. Bassetti M, Vena A, Giacobbe DR, et al. Ceftolozane/Tazobactam for Treatment of Severe ESBL-Producing Enterobacterales Infections: A Multicenter Nationwide Clinical Experience (CEFTABUSE II Study). *Open Forum Infect Dis*. May 2020;7(5):ofaa139. doi:10.1093/ofid/ofaa139
25. Namikawa H, Imoto W, Yamada K, et al. Predictors of mortality from extended-spectrum beta-lactamase-producing Enterobacteriaceae bacteremia. *Emerg Microbes Infect*. Dec 2023;12(1):2217951. doi:10.1080/22221751.2023.2217951

 doi:10.20944/preprints202602.1128.v1



26. Vance MK, Cretella DA, Ward LM, Vijayvargiya P, Garrigos ZE, Wingler MJB. Risk Factors for Bloodstream Infections Due to ESBL-Producing Escherichia coli, Klebsiella spp., and Proteus mirabilis. *Pharmacy (Basel)*. Apr 13 2023;11(2)doi:10.3390/pharmacy11020074
27. Pai MP, Cojutti PG, Gatti M, et al. Keeping the horse with the cart: are we underdosing tazobactam even when using continuous-infusion ceftolozane/tazobactam for effectively preventing resistance development by ESBL-producing Enterobacterales? *Antimicrobial Agents and Chemotherapy*. 0(0):e01215-25. doi:doi:10.1128/aac.01215-25