# Economic Evaluation of Cefiderocol for the Treatment of Confirmed Carbapenem-Resistant Infections in Italy

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## Background and Objectives

Multidrug-resistant (MDR) pathogens are an emerging concern to healthcare systems worldwide and it is predicted that they will lead to a shortage of potent antibiotics. The World Health Organization (WHO) has highlighted gram negative carbapenem resistant (CR) pathogens as a priority to target R&D efforts. Shionogi has developed cefiderocol, a parenteral antibiotic, belonging to a novel class of siderophore-cephalosporin antibiotics with unique mechanism of action. Cefiderocol penetrates through the outer membrane of Gram-negative bacteria with a unique mechanism of cell entry via active iron transporters, overcoming several transport-related mechanisms of resistance, and has higher stability to both serine- and metallo-type beta-lactamases, key enzymes rendering resistance to β–lactam antibiotics. Cefiderocol has a unique breadth of activity vs all MDR/CR GR infections including all three critical priority pathogens as described above by the WHO.

The aim objective of this study was to develop a robust cost-effectiveness of cefiderocol in patients with a confirmed MDR/CR GN infection with limited treatment options when compared with colistin regimen based which is the only alternative available in this setting of patients where first line antibiotics failed or are not active (as displayed in Figure 1) [2].

## Gram negative *in-vitro* activity

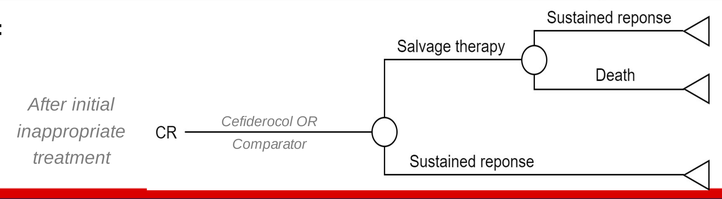
**Figure 1:**

| | | Ceftazidim/ Avibactam | Ceftolozan/ Tazobactam | Imipenem/ Relebactam | Meropenem/ Vaborbactam | Colistin | Cefiderocol |
|---|---|---|---|---|---|---|---|
| Pseudomonas aeruginosa | Pseudomonas aeruginosa, **Wildtyp** | | | | | | |
| | Pseudomonas aeruginosa, **AmpC+** | | | | | | |
| | Pseudomonas aeruginosa **Porinverlust** (oprD-loss) | | | | | | |
| | Pseudomonas aeruginosa **Effluxpumpen** | | | | | | |
| | Pseudomonas aeruginosa **Carbapenem-R (Carbapenemase-negativ)** | | | | | | |
| | Pseudomonas aeruginosa, **MDR** | | | | | | |
| | Pseudomonas aeruginosa, **XDR** | | | | | | |
| | Pseudomonas aeruginosa, **MBL+** | | | | | | |
| Enterobacteriaceae spp. | Enterobacteriaceae spp., **Wildtyp** | | | | | | |
| | Enterobacteriaceae spp., **ESBL+** | | | | | | |
| | Enterobacteriaceae spp., **OXA-48-like+** | | | | | | |
| | Enterobacteriaceae spp., **KPC+** | | | | | | |
| | Enterobacteriaceae spp., **Carbapenem-R (Carbapenemase-negativ)** | | | | | | |
| | Enterobacteriaceae spp. **MBL+ (VIM, IMP, NDM)** | | | | | | |
| Acinetobacter | Acinetobacter baumannii, **Wildtyp** | | | | | | |
| | Acinetobacter baumannii, **Carbapenem-R** | | | | | | |
| Stenotrophomonas | Stenotrophomonas maltophilia, **Wildtyp** | | | | | | |
| | Stenotrophomonas maltophilia **Carbapenem-R** | | | | | | |

In-vitro activity >80% | In-vitro activity 50-80% | In-vitro activity <50% | No data

## Model structure

**Figure 2:**




## Methods

A decision tree was developed to capture the patient pathway for patients with a confirmed MDR/CR GN infection with limited treatment options. Before entering the model, patients received an antimicrobial susceptibility test to confirm the presence of a MDR/CR infection and corresponding pathogen resistant to all first line treatments including all new β-lactam/β-lactamase inhibitor combinations (BL/BLIs). It was assumed patients received initial inappropriate treatment prior to an antibiogram susceptibility test. Therefore, patients entered a nested portion of the model following confirmation of a MDR/CR infection and received treatment with cefiderocol, or colistin. There were two possible end points for patients within the decision tree: sustained response (cure) or death. The probability of sustained response was based upon clinical cure rates obtained from cefiderocol and comparator clinical trials. Patients that did not experience a sustained response could switch to an alternative salvage therapy (the next optimal intervention based on the pathogen group identified), of which they could respond to or die. Following a sustained response, no more events were assumed for the remainder of the time horizon. Patients experiencing a sustained response were assumed to have the same long-term morbidity/mortality as the general population and population norms were used to estimate the long-term QALYs accumulated. Patients did not incur any costs following sustained response. The evaluation was performed using a lifetime time horizon using an Italian-specific discount rate of 3% for both costs and benefits. Deterministic and probabilistic sensitivity analyses (DSA & PSA) were also conducted to assess the impact of bias on the model results. The threshold for cost-effectiveness considered was €40,000 per additional quality-adjusted life year (QALY), in alignment with the approach of the Italian healthcare system [3].

## Key model input parameters

**Table 1:**

| | Probability of sustained response | Sources |
|---|---|---|
| Cefiderocol | 66.8% | [4] |
| Colistin | 57.1% | [4] |

| | Unit cost (per pack) | Sources | Note |
|---|---|---|---|
| Cefiderocol | €1,500 | [5] | Simulations of real prices, accounting for confidential discounts, were used in the model |
| Colistin | €10.80 | [6] | |

| | Variable | Sources |
|---|---|---|
| Hospital cost per day (cUTI) | €443 | |
| Hospital cost per day (pneumonia) | €477 | [6] |
| Hospital cost per day (BSI/sepsis) | €556 | |
| Odds ratio: mortality (appropriate vs inappropriate treatment mortality) | 0.45 | [7] |
| Additional length of stay due to inappropriate treatment (days) | 4.90 | [8] |

| | Utility | Sources |
|---|---|---|
| Symptomatic UTI (utility) | 0.782 | [9] |
| Pneumonia (utility) | 0.728 | [10] |
| BSI/sepsis (utility) | 0.530 | [11] |
| Renal impairment (disutility) | -0.263 | [12] |
| Renal impairment annual rate: cefiderocol | 0.7% | [13] |
| Renal impairment annual rate: colistin | 27.7% | [13] |

## Results

**Table 2: Results**

| Per patient | Intervention | Comparator | Incremental |
|---|---|---|---|
| **Total cost** | €13,431 | €10,205 | €3,226 |
| **Total QALYs** | 10.250 | 9.746 | 0.504 |
| **ICER** | | | €6,403 |
| **Net monetary benefit** | | | €16,928 |

Cefiderocol results in an additional cost of €3,226 and an increase in QALYs of 0.504. The base case analysis reports an incremental cost-effectiveness ratio of €6,403 and demonstrates that cefiderocol is highly cost-effective at a threshold of €16,928.

DSA showed that the results were most sensitive to the probability of sustained response associated with both treatments. These results were supported by the PSA that showed an 71% probability of cost-effectiveness in favour of cefiderocol.

## Conclusions

Cefiderocol is a cost-effective intervention for the treatment of confirmed carbapenem resistant cUTI, pneumonia and BSI/sepsis infections when compared to colistin. Further research is warranted for comparisons to other antibiotics.

## References

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