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Real-life temocillin use in Greater Paris area, effectiveness and risk factors for failure in infections caused by ESBL-producing Enterobacterales: a multicentre retrospective study

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Background: Temocillin is a β-lactam that is not hydrolysed by ESBLs

Objectives: To describe the real-life use of temocillin, to assess its effectiveness in infections caused by ESBL-producing Enterobacterales, and to identify risk factors for treatment failure.

Methods: Retrospective multicentric study in eight tertiary care hospitals in the Greater Paris area, including patients who received at least one dose of temocillin for ESBL infections from 1 January to 31 December 2018. Failure was a composite criterion defined within 28 day follow-up by persistence or reappearance of signs of infection, and/or switch to suppressive antibiotic treatment and/or death from infection. A logistic regression with univariable and multivariable analysis was performed to identify risks associated with failure.

Results: Data on 130 infection episodes were collected; 113 were due to ESBL-producing Enterobacterales. Mean age was 65.2 ± 15.7 years and 68.1% patients were male. Indications were mostly urinary tract infections (UTIs) (85.8%), bloodstream infections (11.5%), respiratory tract infections (RTIs) (3.5%) and intra-abdominal infections (3.5%). Bacteria involved were *Escherichia coli* (49.6%), *Klebsiella pneumoniae* (44.2%) and *Enterobacter cloacae* (8.8%). Polymicrobial infections occurred in 23.0% of cases. Temocillin was mostly used in monotherapy (102/113, 90.3%). Failure was found in 13.3% of cases. Risk factors for failure in multivariable analysis were: RTI (aOR 23.3, 95% CI 1.5–358.2) and neurological disease (aOR 5.3, 95% CI 1.5–18.6).

Conclusions: The main use of temocillin was UTI due to ESBL-producing *E. coli* and *K. pneumoniae*, with a favourable clinical outcome. The main risk factor for failure was neurological disease.

Introduction

Antibiotic resistance among Gram-negative bacteria is a major public health issue. ESBLs are resistance mechanisms found increasingly in Enterobacterales,[1] complicating the antibiotic treatment, especially in patients with systemic infections.[1] As carbapenems became widely used in serious infections due to ESBL-producing Enterobacterales, carbapenem resistance in Gram-negative bacteria dramatically increased over recent years.[2] Thus, to control and minimize the spread of carbapenem, fluoroquinolone and third-generation cephalosporin resistance, it is mandatory to spare carbapenems and prescribe alternatives whenever possible.

Temocillin, a 6-α-methoxy derivative of ticarcillin, has well-known activity against most β-lactamases, including ESBL and AmpC. It represents a possible alternative to carbapenems,[3,4] but real-life clinical data are lacking, despite its marketing authorization in Belgium and France since 1984 and 2014, respectively.

We aimed to evaluate the use of temocillin in hospitalized patients and its effectiveness in infections caused by ESBL-producing Enterobacterales, as well as risk factors associated with failure.

Materials and methods

We performed a retrospective multicentre study in eight tertiary care hospitals of Greater Paris area over 1 year. All hospitalized patients with at least one dose of temocillin between the 1 January and 31 December 2018 were included, and data from medical charts were collected thanks to a standard dataset. We collected demographic characteristics (age, sex, comorbidities, risk factors etc.), clinical, biological and microbiological data (clinical and severity signs, laboratory tests, organisms identified), therapeutic data (dosage of temocillin, other molecules used), as well as adverse events and clinical outcome at Day 28 of the first temocillin dose and at the patient's last visit.

Immunosuppression was defined as presence of the following criteria: asplenia, neutropenia, agammaglobulinaemia, organ transplant, haematological malignancies, HIV infection with low CD4 cell count, 20 mg of prednisolone equivalent during at least 3 weeks, cancer chemotherapy or other immunosuppressive drugs (e.g. cyclophosphamide, azathioprine, cyclosporine etc.).

Neurological disease was defined as presence of the following criteria: cerebral vascular disease, spinal cord injury, multiple sclerosis and Parkinson's disease.

Bacterial strain and resistance mechanism (ESBL, AmpC) analyses and antibiotic susceptibility testing were performed using disc diffusion, and MICs were determined by broth microdilution, in the centres' local laboratories, according to EUCAST and CLSI guidelines.[5,6]

Failure was defined as a composite criterion within a 28 day follow-up by: persistence or reappearance of signs of infection, and/or switch to prolonged suppressive antibiotic therapy (PSAT) (i.e. an antimicrobial therapy with a lifelong planned duration) and/or death from infection.

Quantitative variables are presented as mean ± SD. Qualitative variables are presented as number of occurrences and relative frequencies.

The distributions of categorical variables were compared using chi-squared tests, whereas two-tailed, unpaired *t*-tests were used to compare the distributions of quantitative continuous variables. A *P* value of <0.05 was considered statistically significant.

To identify risk factors associated with failure, a univariable analysis by logistic regression was performed, using demographic and medical characteristics as well as all clinical and biological data. For patient requiring renal dosage adjustments, temocillin dosage used in the statistical analyses was the targeted dosage before reduction. A multivariable analysis by logistic regression was then performed using all variables from the univariable analysis that had a *P* value ≤ 0.05. The final model was obtained using backward stepwise regression with 0.10 thresholds. ORs were calculated from the univariate and multivariable analysis to quantify association with failure at Day 28 with 95% CIs.

Analyses were performed with the use of R software, version 3.6.1 (R Foundation for Statistical Computing).

Ethics

The research was conducted in accordance with the Declaration of Helsinki, and national and institutional standards. Patients were informed that their clinical data could be used, after anonymization, for research purposes.

Results

Overall, 130 infection episodes treated with temocillin were screened; 113 were due to at least one ESBL-producing Enterobacterales (see Figure 1).

The demographics and baseline characteristics of our study population are presented in Table 1. Male patients represented 68.1% of our patients, with a mean age of 65.2 ± 15.7 years; 11.5% were ICU patients.

All of the 26 polymicrobial infections were due to at least one ESBL bacterium; details are presented in Table S1, available as Supplementary data at *JAC-AMR* Online.

Among the antibiotic treatments received prior to temocillin, carbapenems were found in 45/91 (49.5%) of cases. The mean treatment duration with temocillin was 9.2 ± 6.9 days, with a mean dosage of 5.4 ± 1.5 g per day. Temocillin was mostly used in monotherapy ($n = 102$, 90.3%). Temocillin was prescribed at a dosage of at least 6 g per day or equivalent, according to renal function (prolonged or continuous infusion of 2 g three times a day) in 60.2% of cases. Seventeen patients received surgical treatment (details in Table S2).

Temocillin was used empirically in 8 (7.1%) patients, who had rectal or urinary ESBL carriage: 6 patients were treated for urinary tract infections (UTIs), one patient for pneumonia, and one for

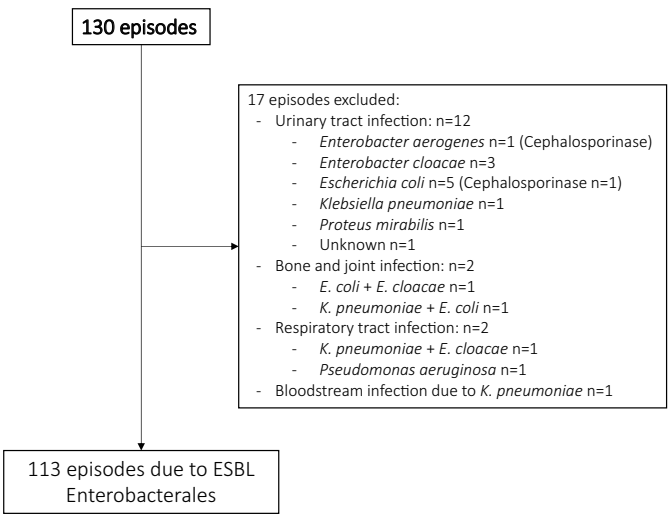

Figure 1. Study flow chart.

Table 1. Characteristics of population with ESBL infection treated with temocillin

	Total $N=113$	Cure group $N=98$	Failure group $N=15$	P value
Age (years, mean ± SD)	65.2 ± 15.7	64.8 ± 15.9	68.2 ± 13.6	0.482
Male patient	77 (68.1)	63 (64.3)	14 (93.3)	0.034[a]
Hospital ward				
ICU	13 (11.5)	9 (9.2)	4 (26.7)	0.070
Medicine	86 (76.1)	77 (78.6)	9 (60.0)	0.189
Surgery	11 (9.7)	9 (9.2)	2 (13.3)	0.639
Comorbidities				
Chronic respiratory failure	14 (12.4)	11 (11.2)	3 (20.0)	0.379
Heart disease	43 (38.1)	34 (34.7)	9 (60.0)	0.060
Chronic renal failure	37 (32.7)	33 (33.7)	4 (26.7)	0.770
Liver failure	7 (6.2)	6 (6.1)	1 (6.7)	1.000
Neurological disease	26 (23.0)	18 (18.4)	8 (53.3)	0.006[a]
Immunosuppression	61 (54.0)	49 (50.0)	12 (80.0)	0.033[a]
AIDS	4 (3.5)	4 (4.1)	0 (0)	1.000
Neutropenia <500 cells/mm^3	1 (0.9)	1 (1.0)	0 (0)	1.000
Chemotherapy	15 (13.3)	11 (11.2)	4 (26.7)	0.074
Immunosuppressive treatment	28 (24.8)	24 (24.5)	4 (26.7)	0.738
Corticosteroids >20 mg/L	8 (7.1)	6 (6.1)	2 (13.3)	0.640
Diabetes mellitus	33 (29.2)	26 (26.5)	7 (46.7)	0.105
Organ transplant	24 (21.2)	19 (19.4)	5 (33.3)	0.161
Renal clearance (mL/min, mean ± SD)	76.1 ± 51.6	74.6 ± 50.7	88.4 ± 58.6	0.383
Before hospitalization				
Outpatient	88 (77.9)	78 (79.6)	10 (66.7)	0.316
Institutionalized	7 (6.2)	7 (7.1)	0 (0)	0.591
Nursing facility	8 (7.1)	5 (5.1)	3 (20.0)	0.071
Other hospital	10 (8.8)	8 (8.2)	2 (13.3)	0.579
Site of infection				
UTI	97 (85.8)	87 (88.8)	10 (66.7)	0.038[a]
Intra-abdominal infection	4 (3.5)	4 (4.1)	0 (0)	1.000
RTI	4 (3.5)	1 (1.0)	3 (20.0)	0.007[a]
Skin and soft tissue infection	1 (0.9)	1 (1.0)	0 (0)	1.000
Bone and joint infection	1 (0.9)	0 (0)	1 (6.7)	0.133
Bloodstream infection	13 (11.5)	11 (11.2)	2 (13.3)	0.070
Foreign material at site of infection	28 (24.8)	24 (24.5)	4 (26.7)	1.000
Severity				
Septic shock	15 (13.3)	14 (14.3)	1 (6.7)	0.688
ICU admission during episode	9 (8.0)	7 (7.1)	2 (13.3)	0.341
Mechanical ventilation	5 (4.4)	3 (3.1)	2 (13.3)	0.130
Vasopressor requirement	6 (5.3)	4 (4.1)	2 (13.3)	0.180
Volume expansion	10 (8.8)	9 (9.2)	1 (6.7)	1.000
Before temocillin treatment				
Biological analysis (mean ± SD)				
WBC count (G/L)	10.0 ± 5.4	9.7 ± 5.3	11.4 ± 6.2	0.283
C-reactive protein (mg/L)	95.7 ± 98.0	97.6 ± 99.8	82.8 ± 87.4	0.789
Surgical treatment	17 (15.0)	16 (16.3)	1 (6.7)	0.462
Number of antibiotic treatment lines (mean ± SD)	1.3 ± 0.9	1.1 ± 0.3	0.8 ± 0.6	0.040[a]
Microbiology analysis				
Polymicrobial infections	26 (23.0)	21 (21.4)	5 (33.3)	0.334
ESBL *E. coli*	56 (49.6)	51 (52.0)	5 (33.3)	0.598
ESBL *Enterobacter cloacae*	10 (8.8)	10 (10.2)	0 (0)	0.128
ESBL *K. pneumoniae*	50 (44.2)	39 (39.8)	11 (73.3)	0.670
ESBL *Klebsiella oxytoca*	1 (0.9)	0 (0)	1 (6.7)	1.000

Data are *n* (%) unless otherwise stated.
[a]Statistically significant (P value ≤0.5).

pressure sore. Of the eight cases, three were due to temocillin-resistant bacteria, which led to antibiotic treatment modification.

Finally, cure rate at Day 28 was 86.7%, and favourable outcome at the last visit was 71.4%, with a mean follow-up of 289.8 ± 206.0 days.

Among patients treated with a temocillin dosage of ≥6 g per day, 55/68 (80.9%) presented with UTIs, and 59/68 (86.8%) patients had a favourable outcome at Day 28.

Among patients treated with a temocillin dosage lower than 6 g per day, 36/39 (92.3%) presented with UTIs, and 33/39 (84.6%) patients had a favourable outcome at Day 28.

Risk factors for failure in the univariable and multivariable analyses were: respiratory tract infection (RTI) [adjusted OR (aOR): 23.34; 95%CI: 1.52–358.18; $P=0.02$); and neurological disease (aOR: 5.26; 95%CI 1.49–18.61; $P=0.01$) (see Table 2).

The dosage or infusion method of temocillin, the type of bacteria, severity and other comorbidities seem to have had no impact on outcome.

Adverse events

Four cases of *Clostridioides difficile* infection were reported. Other adverse events reported included a maculo-papular rash ($n=1$) and an acute renal failure ($n=1$).

No serious adverse drug reactions were observed.

Discussion

We performed a large, multicentred, retrospective cohort study observing real-life use of temocillin. We also assessed the clinical effectiveness of this antibiotic on treatment of infections due to ESBL Enterobacterales, and factors associated with failure.

We found that temocillin is a well-tolerated and effective treatment, mainly used for ESBL Enterobacterales UTIs, confirming earlier studies and case reports.[7–10] Temocillin was mainly used as a carbapenem-sparing treatment, after broad-spectrum empirical antibiotic therapy by carbapenems, which could partly explain the high cure rate.

In our study, the cure rate in patients managed with temocillin was independent from the causative microorganism; however, the sample size does not allow a definitive conclusion in this regard.

So far, there are limited data on the effectiveness of temocillin in treating infections due to MDR Gram-negative bacteria, including ESBL-producing Enterobacterales. A retrospective study including 53 infections due to ESBL and AmpC producing-bacteria treated with temocillin showed a clinical cure rate of 89%.[11] Retrospective cohort studies and small case series found similar results.[7–10]

A recent French matched case–control study that compared temocillin with carbapenems for UTIs due to ESBL-producing Enterobacterales (72 patients per group) reported similar cure rates between both groups at the end of antibiotic therapy (94% versus 99%, $P=0.206$).[8]

Considering the ecological pressure and possible emergence of bacterial resistance, a study demonstrated that, compared with ceftriaxone, temocillin did not increase the proportion of ESBL-producing *Escherichia coli* in faeces of colonized mice.[12] The favourable ecological profile of temocillin was also confirmed in a randomized multicentre clinical trial that compared temocillin with cefotaxime in the treatment of febrile UTIs.[13]

Yet, emergence of resistance to temocillin was observed in one study, including two cases of resistance to temocillin among patients with UTI previously treated with 6 g per day.[8] Therefore, close monitoring of emerging temocillin resistance among patients treated with temocillin is needed.

Moreover, the pharmacokinetic/pharmacodynamic (PK/PD) properties of temocillin need to be further investigated with additional *in vitro* and animal model studies, to support appropriate clinical breakpoints.[14]

In our study, the main dosage was 6 g per day, as suggested by previously published Monte Carlo simulations, which showed that with a dose of 6 g per day (2 g three times a day), a target of 80% $fT_{>MIC}$ was reached for the mean population for an MIC of 16 mg/L and a target of around 40% for an MIC of ≤32 mg/L.[15]

Based on available data, EUCAST and CA-SFM/EUCAST currently support MIC breakpoints of 16 mg/L in both UTI and systemic infections, recommending a daily dose of 6 g of temocillin with the exception of uncomplicated UTIs where a daily dose of 4 g has been used with success.[16,17]

Nonetheless, there is no consensus for MIC breakpoints, especially in UTI. Indeed, BSAC advises MIC breakpoints of 8 mg/L in systemic infection and 32 mg/L in UTI, while EUCAST considers 16 mg/L in both situations.[16,18,19] Unfortunately, we do not have the MIC of strains in our study. But, in this real-life study, we found no impact of 6 g dosage (or equivalent) or more compared with 4 g or less. This should be interpreted with caution, as our sample size was low, and more UTIs were probably treated with a 4 g dosage.

Furthermore, in a study describing PK/PD characteristics of temocillin administered either via continuous or intermittent infusions in critically ill patients with pneumonia, while PK/PD indices were best found with continuous infusions, they remained below recommendations for systemic infections, except in

Table 2. Factors associated with failure in univariable and multivariable analysis

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
UTI	0.253 (0.073–0.877)	0.030	—	—
Neurological disease	5.079 (1.631–15.818)	0.005	5.259 (1.486–18.611)	0.010
Immunosuppression	3.918 (1.040–14.761)	0.044	4.136 (0.994–17.211)	0.051
RTI	24.250 (2.333–252.072)	0.008	23.336 (1.520–358.183)	0.024

patients with creatinine clearance <60 mL/min/1.73 m². Thus, more studies on the efficacy of temocillin in severe pneumonia are warranted.[20] In our study, RTIs treated with temocillin were associated with a high rate of failure, as well as patients with a neurological disease. However, the number of patients with RTIs was very low in our study, therefore it is difficult to draw any conclusion from this result. Neurological disease usually reflects poor and/or severe conditions, and patients are also at high risk of recurrent infection due to neurogenic bladder and/or aspiration pneumonia, for instance.

These results are in line with previous studies with high cure rates among patients with non-severe infections, such as UTIs.[7,9–11,15,21–25]

Finally, the risk of *C. difficile* infections and adverse drug reactions due to temocillin are rare.

This study had several limitations. As a retrospective study, the type of infections could not be exactly defined, and no control group could be implemented. We were not able to provide the details regarding the distribution of continued or intermittent administration of temocillin treatment. The majority of patients received carbapenem antibiotics before switching to temocillin, and around 10% received an antibiotic associated with temocillin, which is a bias to evaluate the proper efficacy of temocillin, but this still reflects real-life use of this drug. Lastly, we should be very cautious about considering RTI as a risk factor for failure as the numbers of patients in this study were very low.

Conclusions

The main use for temocillin during 1 year in the Greater Paris area was UTI due to ESBL-producing *E. coli* and *Klebsiella pneumoniae*, with a favourable clinical outcome. The main risk factor for failure was a history of neurological disease.

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The Temocillin Greater Paris Study Group

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Transparency declarations

The authors have no conflicts of interest to declare.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC-AMR* Online.

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