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Temocillin versus carbapenems for urinary tract infection due to ESBL-producing Enterobacteriaceae: a multicenter matched case-control study.

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1 **TITLE PAGE**

2 **Temocillin versus carbapenems for urinary tract infection due to ESBL-producing**
3 ***Enterobacteriaceae*: a multicenter matched case-control study.**

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24 **RUNNING TITLE (40/40):** Temocillin vs. carbapenems for UTI

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37 **ABSTRACT**

38 **Objectives:** We aim to compare the efficacy of temocillin to carbapenems for ESBL-E UTI.

39 **Methods:** We conducted a multicenter retrospective case-control study of adults with ESBL-
40 E UTI between January-2015 and October-2019. Cases received temocillin $\geq 50\%$ of the
41 effective antibiotic therapy duration. Control exclusively received carbapenem. They were
42 statistically matched (1:1 ratio) on period, sex, and age. The clinical cure at the end of
43 antibiotic therapy was analyzed using conditional logistic regression.

44 **Results:** We matched 72 temocillin cases to 72 carbapenem controls. Most (67%) were
45 male, aged 69.4-years in median, 81 (56%) were immunocompromised, including 44 (31%)
46 solid organ transplant recipients (SOT). There was no difference between cases and controls
47 for baseline characteristics and microorganisms involved: *K.pneumoniae* in 59 (41%), *E.coli*
48 in 57 (40%), and *Enterobacter spp.* in 24 (17%). The median time from admission to effective
49 antibiotic therapy was 0-days [0-2]. Among cases, first-line antibiotic therapy (≤ 72 hours) was
50 temocillin in 6 (8%) and carbapenems in 39 (54%). Temocillin was given at the median daily
51 dose of 4g [2-4], after 3-days [2-5] of carbapenems. Patients received temocillin for 81% [70-
52 93] of the effective antibiotic course duration during 11-days [8-14]. The effective antibiotic
53 duration was similar in cases and controls (p -value=0.067). Clinical cure at the end of the
54 antibiotic therapy was 94% (68/72) in cases versus 99% (71/72) in controls (p -value=0.206),
55 without difference among immunocompromised and SOT patients (p -value>0.050).

56 **Conclusions:** Temocillin effectively relays beta-lactams, including carbapenems, for the
57 treatment of (complicated) ESBL-E UTI. Its efficacy is consistent among kidney transplant
58 recipients.

59

60 **KEYWORDS (5)**

61 Temocillin, Carbapenems, Urinary Tract Infection, ESBL, Case-control study.

62

63 **ABBREVIATIONS**

64 BSAC: The British Society for Antimicrobial Chemotherapy

65 CA-SFM: Comité de l'Antibiogramme de la Société Française de Microbiologie

66 95%CI: 95% confidence interval

67 EOT: end of the antibiotic therapy

- 68 EUCAST: the European Committee on Antimicrobial Susceptibility Testing
- 69 IDSA: Infectious Disease Society of America
- 70 IQR: interquartile range
- 71 (a)OR: (adjusted) Odds Ratio
- 72 SOT: Solid organ transplant
- 73 STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
- 74 UTI: Urinary tract infection

75 **ARTICLE**

76 **1. INTRODUCTION**

77 For decades, the gold-standard antibiotic regimen in ESBL-producing *Enterobacteriaceae*
78 (ESBL-E) infections has been carbapenem. Few trials explored alternatives to carbapenem
79 in patients with severe infections due to ESBL-E. The MERINO trial showed that piperacillin-
80 tazobactam was not non-inferior to meropenem for 30-day mortality among patients with
81 bloodstream infection and ceftriaxone resistance [1]. Much investigations to explore new
82 options are needed [2–4].

83 Urinary tract infection (UTI) is the leading cause of infection due to gram-negative bacteria in
84 primary care and hospital settings [2]. ESBL-producing strains are frequently involved in UTI,
85 and temocillin appears as a possible intravenous alternative to carbapenem in such settings
86 [5,6].

87 Temocillin is active against *Enterobacteriaceae* and is stable against hydrolysis by ESBLs
88 and AmpC β -lactamases. Since 1985, eleven small-size studies have reported on temocillin
89 efficacy in mixed definitions of UTI [6–15]. According to the susceptibility breakpoint, its
90 efficacy correlates with higher doses, ranging from 2 g bid or tid [16]. Six surveys used
91 temocillin doses below 4 g per day, and none investigated temocillin efficacy with an active
92 comparator, including carbapenems or others antibiotics.

93 Three prospective studies have been initiated over the last years (NCT03543436,
94 NCT02681263, and NCT01543347), including one non-inferiority open-label randomized trial
95 comparing temocillin to carbapenems. However, as of today, they failed to enrolled patients,
96 and some were terminated. Pending trials' results, many physicians started to treat patients
97 with temocillin and collected small sets of observations.

98 We conducted a multi-centric matched case-control study to provide reliable data regarding
99 temocillin efficacy as an alternative to carbapenems in urinary tract infection due to ESBL-E.

100 **2. MATERIALS AND METHODS**

101 **2.1 Study design and settings**

102 **2.1.1 Study design**

103 We conducted a multi-centric case-control study across six French participating tertiary-level
104 hospitals. We detail study sites in supplementary Table A.1.

105 **2.1.2 Selection of cases and controls**

106 Consecutive adults hospitalized between January 2015 and October 2019 for a definite UTI
107 diagnosis due to an ESBL-producing *Enterobacteriaceae* (ESBL-E) susceptible to
108 carbapenems were eligible for the study. They were not opposed to retrospective data
109 collection. We defined a definite UTI as a positive urine culture with $\geq 10^3$ CFU/mL of a single
110 ESBL-E strain, and two of the following signs or symptoms [17]: chills or fever (temperature
111 $>38^\circ\text{C}$), flank or pelvic pain, nausea, or vomiting, dysuria, urinary frequency, or urinary
112 urgency, costovertebral angle pain.

113 Cases had received temocillin above 50% of the time of effective antibiotic therapy duration.
114 Temocillin was given as first-line therapy or after a maximum of 72 hours of other antibiotics
115 effective against the ESBL-producing strain, including carbapenems and aminoglycosides.
116 The ESBL-producing strain causing the UTI had to be sensitive to temocillin and
117 carbapenems, according to the guidelines from the French microbiology society ("Comité de
118 l'Antibiogramme de la Société Française de Microbiologie", CA-SFM) [18].

119 Controls had exclusively received carbapenem (imipenem, or meropenem, or ertapenem) as
120 first-line therapy or after a maximum of 72 hours of other effective antibiotics, including
121 aminoglycosides. The ESBL-producing strain causing the UTI had to be sensitive to
122 carbapenems, according to the CA-SFM guidelines [18].

123 The physician in charge defined the modalities of the antibiotic regimen, including dosage
124 and its adaptation to the renal function when appropriate, route of administration, and the
125 treatment duration. We identified patients using the electronic database of the microbiology
126 department of each participating site. The local study team performed manual screening for
127 inclusion / non-inclusion criteria. Data were retrieved from patient medical charts using
128 standardized case report forms. Cases were matched to controls at a 1:1 ratio, using a
129 statistical matching (1-point caliper) by 6-month period, sex, and age.

130 **2.1.3 Study endpoints**

131 The primary efficacy endpoint was the clinical cure at the end of the antibiotic therapy (EOT).
132 We adapted the clinical cure definition from the FDA guidelines, as the resolution of fever

133 (temperature $\leq 38^{\circ}\text{C}$) and UTI symptoms without the occurrence of new UTI symptoms and
134 the absence of clinical or microbiological failure [17]. We defined clinical or microbiological
135 failure as the non-resolution of fever (temperature $>38^{\circ}\text{C}$) or symptoms of UTI, or new
136 symptoms of UTI, or all-cause death, or positive urine culture yielding $\geq 10^3$ CFU/mL of the
137 same uropathogen to that identified at antibiotic initiation, at any time from initiation to EOT.
138 Urinalysis and blood culture at EOT was not mandatory and let to physician discretion.

139 Secondary efficacy endpoints were the length of hospital stay and UTI relapse to the same
140 ESBL-E strain within three months from the first day of effective antibiotic therapy.

141 Safety endpoints were *Clostridium difficile* infection, loss to follow-up, re-hospitalization, and
142 all-cause death within three months from the first day of effective antibiotic therapy.

143 **2.2 Compliance with research ethics standards**

144 The institutional review board (IRB) n°0011642, of the French society of infectious diseases
145 (SPILF), approved the study protocol under the number 2018-0503. This multi-centric
146 observational study was registered to the French authorities using the MR-004 referral
147 methodology of the "Commission Nationale de l'Informatique et des Libertés" (CNIL) under
148 the number MR004-2205982 (Annecy-Genevois hospital). The data collection process was in
149 line with the European General Data Protection Regulation. ClinicalTrials.gov number,
150 NCT04671290.

151 **2.3 Statistical analyses**

152 Patients' characteristics, primary and secondary endpoints, were described using descriptive
153 statistics including frequencies and percentages, median, and interquartile range [IQR]. We
154 tabulated patients' characteristics, the occurrence of primary and secondary endpoints, by
155 patient status (case or control). Then, we computed the strength of association with primary
156 and secondary endpoints using conditional logistic regression adjusted on the study arm. We
157 report associations as odds ratio (OR) with 95% confidence intervals (CI). All tests were two-
158 tailed, at 5% bilateral for significance. We performed data curation and statistical analyses
159 using the R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). We
160 reported the results following the Strengthening the Reporting of Observational Studies in
161 Epidemiology (STROBE) statement [19].

162 3. RESULTS

163 3.1 Patients characteristics

164 We retrospectively enrolled 144 patients (72 cases and 72 controls) among 183 patients
165 screened (supplementary Figure B.1). Most of the enrolled patients (67%) were men, half
166 were aged 69 years and above, and half were presenting a high Charlson score value of at
167 least four. The median creatinine clearance (MDRD) was 42.2 ml/min/1.73m² [interquartile
168 range (IQR), 24.5 to 82.3], and a third (31%) of patients were kidney transplant recipients. All
169 but eight patients had complicated UTI, and 57 (40%) required urinary catheterization,
170 including 34 (24%) double-J stent [17]. Microorganisms involved in UTI were similar
171 between cases and controls: *K. pneumoniae* in 59 (41%), *E. coli* in 57 (40%), *Enterobacter*
172 *spp.* in 24 (17%), and others in 4 (2%). A third of patients had bloodstream infections
173 associated with UTI. Table 1 describes the patients' characteristics at hospital admission.

174 3.1.1 Initial antibiotic therapy

175 The first-line antibiotic therapy was more appropriate among cases (75%) than controls
176 (53%) (p -value = 0.006). The time to appropriate antibiotic therapy was shorter in cases than
177 in controls (OR = 0.71 (95%CI, 0.56 to 0.90), p -value = 0.005).

178 3.1.2 Temocillin, cases

179 Among the 72 temocillin cases, half (54%) received carbapenems over the first 72 antibiotic
180 therapy hours. Only six (8%) received temocillin as first-line antibiotic therapy. Other first-line
181 antibiotics are described in supplementary Table A.2. The switch from the first-line antibiotic
182 to temocillin occurred after a median of 3 days [IQR, 2 to 5] of the first-line antibiotic. It was
183 for sparing piperacillin/tazobactam in eight patients, for sparing carbapenems in 63, and
184 because of carbapenems' allergy in one. Temocillin was adapted to creatinine clearance at
185 the median daily dose of 4 g [IQR, 2 to 4], ranging from a minimum of 0.5 g per day to a
186 maximum of 6 g per day. Twenty-nine received 2 g per day or less, and seven received 6 g
187 per day. It was given for a median of 11 days [IQR, 8 to 14] and accounted for 81% [IQR,
188 70% to 93%] of the antibiotic course's total duration. Seven (10%) patients received
189 temocillin as a prolonged infusion. Fourteen (19%) patients received temocillin over the
190 effective antibiotic therapy duration, including two with bloodstream infection. The median
191 MIC to temocillin was 6 mg/l [IQR, 4 to 8], ranging from a minimum of 2 mg/l to a maximum
192 of 16 mg/l.

193 3.1.3 Carbapenems, controls

194 Among the 72 controls, 33 (46%) received empirical carbapenem. Others had carbapenem
195 after a median of 1 day [IQR, 0 to 3] from the start of first-line antibiotic therapy. The MIC to
196 carbapenem was not available. The first carbapenem received was imipenem in 48 (68%),
197 meropenem in 3 (4%), and ertapenem in 20 (28%). Twenty-two patients switched to
198 ertapenem, 20 initially receiving imipenem and two meropenem. In addition to IV beta-
199 lactams, controls received 4 times lower infusion of aminoglycosides (4%) than cases (15%)
200 (p -value = 0.035).

201 **3.1.4 Duration of effective antibiotic therapy**

202 The overall duration of effective antibiotic therapy was long at 15 days [IQR, 12 to 18] and
203 was similar between cases (14 days) and controls (16 days) (p -value = 0.067). Solid organ
204 transplant recipients had a prolonged course of effective antibiotic therapy (18 days).

205 Sixty (42%) patients completed their antibiotic therapy in the hospital, while the others (58%)
206 were discharged earlier after a median of 7 days. The latter received additional parenteral
207 antibiotic treatment for a median of 8 days. Early discharge was more frequent in the
208 carbapenem group (69%) than in the temocillin group (47%).

209 **3.2 Clinical cure at the end of antibiotic therapy**

210 Table 2 describes the associations with the occurrence of the primary endpoint. The rate of
211 clinical cure at EOT (primary endpoint) was similar between cases (94%) and controls (99%),
212 even after adjustment on the appropriateness of antibiotic therapy at baseline, aOR=4.11
213 (95%CI, 0.02 to 1.64), p -value = 0.125. In bivariate analysis, there was also no difference for
214 primary endpoint among those who received initial administration of aminoglycosides, those
215 who were immunocompromised or solid organ (kidney) transplant recipients, nor for any of
216 the possible confounding variables. Among patients who received temocillin, the previous
217 carbapenem administration was not increasing the clinical cure at EOT (OR = 0.7 (95%CI,
218 0.09 to 5.27), p -value = 0.729). The 14 patients who received standalone temocillin for
219 effective antibiotic therapy were all cured at EOT.

220 **3.3 Secondary and safety endpoints**

221 Table 3 describes the occurrence of secondary and safety endpoints. The length of stay at
222 hospital stay was similar between cases and controls, as were the rate of relapse of UTI, re-
223 hospitalization, *Clostridium difficile* infections, loss to follow-up, and mortality. Among 17
224 patients who received temocillin and had a UTI relapse, we identified the same pathogen in
225 15 (88%). Ten had susceptibility testing for temocillin, and three (30%) were resistant,
226 supplementary Table A.3. Among 16 patients who received carbapenems and had a UTI

227 relapse, 10 (63%) were involving the same pathogen. Of the 33 patients with UTI relapse, 24
228 had a strain tested for carbapenem susceptibility, and none was resistant.

229 The median time from antibiotic start to all-cause death was 72 days [IQR, 28 to 93]. Only
230 one death occurred under antibiotic therapy. This patient received three days of imipenem
231 followed by five days of temocillin. According to the Charlson score, patients who died had a
232 median 1-year probability of death above 85% at the time of antibiotic start, while it was 52%
233 in others. The supplementary Table A.4. details the characteristics of deceased patients.

234 **4. DISCUSSION**

235 In this multi-centric matched case-control study of adults receiving antibiotics for a
236 (complicated) UTI due to ESBL-producing *Enterobacteriaceae*, the clinical cure rate at the
237 end of the antibiotic therapy was very high (97%). It was similar between patients who mostly
238 received temocillin (94%) than those who received only carbapenem (99%). These results
239 were consistent in immunocompromised patients, including solid organ (kidney) transplant
240 recipients.

241 The very high clinical cure rate in patients managed with temocillin (94%) was independent
242 of the microorganism or the patients' characteristics. Temocillin was used to relay an
243 appropriate empirical antibiotic therapy, at the standard daily dose of 4 g per day or adapted
244 to creatinine clearance, in infection involving pathogens with MIC \leq 8 mg/l. Interesting
245 findings, considering that most (60%) of the strains involved were not *E. coli*, and that a third
246 of patients were bacteremic or kidney transplant recipients. Other alternatives such as
247 ceftolozan or piperacillin/tazobactam suffer this comparison, especially in patients with
248 bacteremic UTI involving *K. pneumoniae* [1,2,20]. A retrospective cohort showed a clinical
249 success rate without relapse of 74%, comparable to that of carbapenems (81%), among
250 male patients with UTI due to ESBL-producing *E. coli* treated with ceftolozan [21]. Other
251 studies were in patients with nonsevere infections, suggesting reserving its use in these
252 conditions [4]. The INCREMENT-SOT international cohort showed that in bacteremia
253 secondary to UTI in kidney transplant recipients patients receiving β -lactam/ β -lactamase
254 inhibitors (BLIBLIs), the cure at day 30 was 87% [22]. Despite a small sample size, there was
255 no difference between those who received monotherapy versus combination therapies or
256 carbapenem monotherapy [22]. Even if data shows efficacy for new BLIBLIs (ceftolozan-
257 tazobactam or ceftazidime-avibactam) in comparable settings, their activity against
258 extensively drug-resistant organisms underlines the need to reserve these drugs for such
259 microorganisms [4]. Data for other antibiotics, including oxyiminocephalosporins,
260 amiglycides, tigecycline, or fosfomicin, are either negative, scarce, contradictory, or in favor
261 of a lower benefit/risk balance. Their use is therefore not yet recommended as a definite
262 antibiotic therapy [4].

263 Recently, a Belgian study reported 152 implementations of OPAT services. It showed that
264 98% of patients discharged with monotherapy of temocillin 4 g per day were cured [7]. It
265 suggests that in UTI due to ESBL-E, an analysis of the cost-effectiveness of OPAT based on
266 ertapenem versus temocillin could be of interest.

267 In addition to our data, the previous results of the eleven studies on temocillin showed a
268 pooled efficacy of 89% (95%CI, 83% to 97%, Figure 1) for treatment with temocillin, varying

269 by type of UTI [6–15]. However, temocillin is undoubtedly not a golden bullet for carbapenem
270 sparing, as its efficacy is predicted to range from 66% to 97%. Temocillin was mainly given
271 after three days of adequate antibiotic therapy (including carbapenem) in patients with MIC
272 ≤ 8 mg/l. If temocillin was efficient and safe in a relay, its use in empirical treatment might be
273 challenging when considering the sensitivity (*i.e.*, the MIC) of the pathogen [5]. Indeed, there
274 is a lack of consensus for MIC breakpoints in UTI. The British Society for Antimicrobial
275 Chemotherapy (BSAC) is considering 8 mg/l in systemic infection and 32 mg/l in UTI, while
276 the European Committee on Antimicrobial Susceptibility Testing (EUCAST) is considering 16
277 mg/l in both situations [5,23,24]. Over the study period, the CA-SFM considered 8 mg/l in
278 both cases and is now aligned on EUCAST [18]. According to MIC, microorganisms, clinical
279 situations, and local epidemiology, we can expect that only 3% to 51% (MIC ≤ 8 mg/l) to 58%
280 to 94% (MIC ≤ 16 mg/l) of ESBL-E will be sensitive to temocillin [5,25–28]. Harmonized and
281 reliable susceptibility breakpoints will therefore be needed to generalize the use of temocillin
282 [5]. If the EUCAST threshold were to be used, a daily dose of 6g would be required to ensure
283 temocillin efficacy [16]. Nevertheless, we documented three cases of emerging resistance to
284 temocillin among patients who presented relapses of UTI. Two received 6g per day of
285 temocillin. Close monitoring of patients treated with temocillin is therefore necessary.

286 Our study suffers limitations. First, the retrospective design, the sample size, and the small
287 number of events limited the statistical power to manage confounding factors [29]. Second,
288 the extensive use of carbapenem in the first line yielded a selection of the population and
289 biased measurement of point estimates. Only randomization can prevent such biases.
290 Nevertheless, the large trials initiated are failing to enroll patients, answers are needed, and
291 real-life data are of interest in this context. To ensure proper analysis, we used a multi-centric
292 design, with a 1:1 ratio for matching, which is assumed to provide sufficient statistical power
293 for a crude estimation of the primary endpoint [30]. We used a validated definition for the
294 primary endpoint and collected mid-range secondary endpoints three months after the start
295 of effective antibiotic therapy. But urinalysis and blood culture at the end of antibiotic
296 treatment was not mandatory. We also enrolled a population at high risk of antibiotic therapy
297 failure, including immunocompromised and solid organ (kidney) transplant recipients and
298 chronic kidney disease patients [2]. The high efficacy of temocillin in this subset of patients
299 was not reduced, which is also reassuring.

300 **5. CONCLUSION**

301 Temocillin is effective and safe in the relay of beta-lactams, including carbapenems for
302 treating (complicated) UTI due to ESBL-producing *Enterobacteriaceae*. Its efficacy is
303 consistent in immunocompromised, including in kidney transplant recipients. However, the

304 risk of emerging resistance stresses the need for close monitoring. A randomized
305 comparison to carbapenems is warranted.

306 **TRANSPARENCY DECLARATION:**

307 **Acknowledgments:** This work was selected to be presented at the 30th European Congress
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314 **Conflict of interest:** None to declare.

315 **Access to data:** Academic researchers can access the data for 12 months after the
316 publication of results. Transfer to countries outside of the EU is not allowed. A formal request
317 had to be sent to the corresponding author.

318 **Contribution:** Conceptualization: T.D., S.G., and M.L. Methodology: T.D. Validation: T.D.,
319 S.G., M.L., and P.L. Formal Analysis: T.D. Investigation: S.G., D.L-P., G.G., S.S., E.P., B.D.,
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322 Supervision: M.L. Project Administration: T.D., S.G., and M.L.

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