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Research Article

# Ertapenem in the Treatment of ESBL Prostatitis

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## Abstract

**Introduction:** Prostatitis presents one of the most common entities encountered in urologic practice. Infections with bacteria producing Extended Spectrum Beta Lactamase (ESBL) present the major problem of urinary tract infections these days especially in prostatitis. Moreover, prostatitis treatment is difficult knowing the absence of active transporters for antibiotics and a relatively low prostate penetration of these drugs. Thus, therapeutic options are limited in infections with such resistant bacteria and require the use of carbapenem in the majority of the cases. Ertapenem is largely used in acute bacterial prostatitis but has not been approved yet by the FDA in this indication. This is why we are asking questions about its clinical efficiency compared to other antibiotics in use. The goal of this study is to compare the action of ertapenem to other antibiotics in the treatment of prostatitis with *E. coli* producing ESBL.

**Methods:** It is a retrospective study of the files of patients admitted in Hotel Dieu de France between 1st July 2008 and 1st July 2014 treated for acute bacterial prostatitis caused by *E. coli* producing ESBL with ertapenem and other antibiotics.

**Results:** The median age of the 110 patients of this study was 64 years. Ertapenem was administered without previous efficient antibiotic treatment in 34 cases. The prevalence of three months recurrence was 18.18%. Eighty five percent of recurrence was caused by *E. coli* producing ESBL (15.45%). Seventeen percent and nineteen percent of patients treated with meropenem and imipenem respectively had a 3 months recurrence.

**Conclusion:** Ertapenem is as effective as other carbapenem in treatment of *E. coli* producing ESBL and is not associated with a higher recurrence rate compared with other antibiotics.

**Keywords:** Prostatitis, Escherichia Coli ESBL, Ertapenem

## Introduction

Prostatitis is frequently seen in daily urology practice. The National institute of Diabetes and Digestive and Kidney Diseases (NIDDK) /National Institutes of Health (NIH) has proposed a classification of this disease in 1995 and it is still applied in clinical practice and clinical studies. This classification is based on clinical presentation with presence of absence of white blood cells and bacteries in prostatic secretions. Accordingly, prostatitis is divided in 4 categories: I : Acute bacterial prostatitis II : Chronic bacterial prostatitis III : Chronic prostatitis or chronic pelvic syndrome : A : Inflammatory, B : Non inflammatory, IV : Asymptomatic prostatitis Prostatitis is classified as acute if symptoms started less than 3 months ago [1]. Acute bacterial prostatitis is a microbial acute inflammation of the prostate. It affects around 1% of men during their lifetime with variable clinical presentations starting with simple dysuria but could present with severe sepsis [2]. It's very important not to do a prostatic massage when you suspect an acute prostatitis because you risk to induce a bacteremia and septic shock [3].

Risk factors for prostatitis developpement include : History of begnin prostatic hypertrophy (OR= 7.7), history of prostatitis (OR= 1.8), history of sexually transmitted disease (OR= 1.8), stress (OR = 1.5), age : 40-49 years old (OR= 1.7) and > 50 years old (OR =3.1), marital status : married (increased risk over single or divorced men) [4], history of manipulations of urinary tract (prostatic biopsy, Foley, transureteral prostatic resection), diabetes (OR= 5-10) [5].

90% of infections are due to aerobic gram negative bacterias. Among gram positive bacterias, the most frequently encountered are Enterococcus and Staphylococcus aureus. Not to forget that in so e cases of acute bacterial prostatitis urine culture could be negative and it is most probably due to prior use of antibiotics [6]. Further more, treatment of prostatitis is limited by the absence of an active transport system of the antibiotic into the prostate combined with relatively low penetration of most antibiotics in prostatic tissu and secretions. In fact, most of the antibiotics are weak acids or base and they are going to be ionised in biologic liquids which will inhibits their passage across the prostatic epithelium. Only free antibiotics, not bound to proteins, will be able to penetrate tissus. In general, substances with low molecular weight (< 1000) can cross the fenestrations between the capillary endothelial cells, but prostatic capillaries are free of pores. The passage of a drug across the endothelium of prostatic capillaries and the epithelium of the prostate is driven by : important concentration gradient, highly liposoluble molecule, low ionization, high dissociation constant (pKa), low protein binding capacity, low molecular weight.

A pH gradient will help electrically neutral molecules to pass through the membranes and to be ionized in order to be trapped. Although the ionic trapping will increase the drug concentration in the prostate, this fraction of the drug that is charged does not have a clear active anti microbial effect. Fluoroquinolons are zwitterions ; their pKa will change according to the enviroment's pH which will cause different plasmatic concentrations that range between 10 and 50% [7]. In humans, alcalin drugs (trimethoprim, clindamycin…) will undergo ionic trapping which will cause high prostatic concentrations. Acid drugs (bêta lactamins) have less concentration in the prostatic gland. In contrast, the quantity of active drug, not ionized, is more important. Infections with bacteria producing enlarged spectrum beta lactamase (ESBL) is growing and is currently the major actual problem in the treatment of urinary tract infections and more specifically in prostatitis [6]. Risk factors for infections with enterobacteries producing ESBL are : diabetes, history of treatment with fluoroquinolons, recurrent urinary tract infection, history of hospitalization, high age, history of IV treatment at home, chronic renal failure, chronic hepatic pathology and use of ulcer treatment anti H2 [8].

Therapeutic options are limited in infections with this kind of resistent bacteria and usually we are forced to choose a carbapenem in most of the cases. Invanz® (sodic ertapénem) is a synthetic 1-beta methylcarbapenem, steril, molecular weight 497.5, hydrosoluble, designed for parenteral use. It's structure is so close to the family of beta lactamin (penicillin and cephalosporin). Ertapenem acts in vitro on multiple aerobic and anaerobic Gram positif and Gram negatif bacteria [9]. Ertapenem is then an antibiotic with low molecular weight and acts on most of the bacteria that can cause acute bacterial prostatitis; this drug is actually widely used in the treatment of acute bacterial prostatitis but it does not have, yet, the FDA approval for this indication. Will it be as effective as other antibiotics used in this indication?

## Materials and Methods

This is a retrospective study. Were reviewed the files of all patients admitted to Hôtel Dieu de France between the 1st of January 2008 and the 1st of July 2014.

### The Population of the Study

Were included in the study all patients presenting acute bacterial prostatitis with ESBL E. Coli, which means patients with urinary signs and sumptoms and urine culture that grows with this bacteria.

Two hundred twenty three patients having acute bacterial prostatitis were selected.

Exclusion criterias were :

- Patients with prostate cancer
- Patients with acute over chronic prostatitis
- Patients dying in the 3 months following the acute bacterial prostatitis
- Patient operated of prostatectomy

For patients treated many times with ertapenem for ESBL prostatitis, only the first episode was considered. One hundred thirteen patients were excluded. The remaining 110 patients where divided in two groups : the first one treated with ertapenem (n=34) and the second one treated with another antibiotic (n=76). The dosage of ertapenem used was 1 g daily (500 mg is case of chronic renal failure), administred IV or IM. Duration of treatment for all the antibiotics varied between 3 and 6 weeks. A patient is considered cured if he has not done a new episode of prostatitis or asymtomatic bacteriuria in the three months following the treatment. A relapse was defined by the reccurence of prostatitis or asymptomatic bacteriuria. In case of reccurence, the reccurent bacteria was determined when possible. Patients not seen in this period were called by phone. The primary endpoint was to compare the relapse between the two groups in order to compare the microbiological efficacy of ertapenem with other antibiotics.

We obtained the approval of the ethical comitte of Saint Joseph University. The informations collected from the patient's files were : prostatitis treatment, relapse during three months, the relapsing bacteria, some risk factors for urinary tract infections (Diabetes, reanal transplantation, immunosupression, recent manipulation of the urinary tract), chronic renal failure, antibiotics used in the three months before the prostatitis, hospitalization in the three months before the prostatitis. Primary endpoint was relapse at three months. This result was adjusted according

to many variables including : diabetes, renal transplantation, immunosupression, recent manipulation of the urinary tract, chronic renal failure, antibiotics used in the three months before prostatitis and hospitalization in the three months before the prostatitis.

### Statistical Analysis

Data was collected and classified in a Microsoft Excel folder. They were reviewed before statistical analysis. We calculated the prevalence, expressed in numbers, and the percentage of the primary endpoint (relapse at three months). We estimated the frequency of the remaining variables for our study population. We have evaluated the relation between two variables : the percentage of relapse at three month and all the other variables studied using Chi2 tests. Then we did a regression logistic analysis to estimate the probability of relapse according to the antibiotic used and according to the other variables. Odds Ratios (OR) with their 95% confidance intervals were calculated. All the analysis studies were done using STATA 12, and p value less than 0.05 was considered statistically significant.

## Results

Baseline charactetistics of the 110 participants in the study are listed in (Table 1).

| | Number (n) | Percentage (%) |
|---|---|---|
| **Caracteristics** | Total (N=110) | |
| Median age (years) | 64 ± (IQR=10) | |
| Antibiotic | | |
| Bactrim | 4 | 3.64% |
| Estecina | 3 | 2.73% |
| Ertapenem | 34 | 30.91% |
| Meropenem | 18 | 16.36% |
| Monurol and uvamine | 1 | 0.91% |
| Suprax | 1 | 0.91% |
| Tarivid | 2 | 1.82% |
| Tavanic | 1 | 0.91% |
| Imipenem | 42 | 38.18% |
| Uvamine | 1 | 0.91% |
| Colistine | 1 | 0.91% |
| Cotrimoxazole | 2 | 1.82% |
| **Other risk factors for urinary tract infection** | | |
| Diabetes | | |
| No | 78 | 70.91% |
| Yes | 32 | 29.09% |
| Renal transplantation | | |
| No | 107 | 97.27% |
| Yes | 3 | 2.73% |
| Immunosuppression | | |
| No | 107 | 97.27% |
| Yes | 3 | 2.73% |
| Recent manipulation of the urinary tract | | |
| No | 95 | 86.36% |
| Yes | 15 | 13.64% |
| Chronic renal failure | | |
| No | 95 | 86.36% |
| Yes | 15 | 13.64% |
| **Risk factors for infections with multiresistant bacteria** | | |
| History of antibiotics in the last 3 months | | |
| No | 81 | 73.64% |
| Yes | 29 | 26.36% |
| History of hospitalization in the prior three months | | |
| No | 85 | 77.27% |
| Yes | 25 | 22.73% |
| Relapse at 3 months | | |
| No | 90 | 81.82% |
| Yes | 20 | 18.18% |
| Germe of relapse | | |
| *E. coli* à BLSE | 17 | 85% |
| *E. coli* cephalo sensitive | 1 | 5.00% |
| *Enterococus fecalis* | 1 | 5.00% |
| Colonies polymorphes | 1 | 5.00% |

**Table 1:** Caracteristics of patients

Median age of patients was 64 years old (intraquartil range=10). Ertapenem was administered without previous efficacious antibiotic in 34 patients (30.91%). The other 76 patients received other antibiotics in this portions : 42 received imipenem (38.18%), 18 received meropenem (16.36%), 4 received cotrimoxazole (3.64%), 6 received ciprofloxacin (5.46%), 2 received ofloxacine (1.82%), and the 5 remaining patients received other antibiotics (4.54%). The mean duration of the treatment was 3 weeks. The majority of the patients did not have risk factors for urinary tract infection : Seventy percent (70.9%) of patients did not have diabetes. Only three patients (2.73%) were immunocompromised (renal transplantation). Fifteen patients (13.6%) had a history of prior manipulation of the urinary tract and fifteen patients (13.6%) had chronic renal failure. Twenty five patients (22.73%) were hospitalized during the preceding three months and 29 patients (26.36%) have received antibiotics in the last three months before the prostatitis. All the patients had at least one sterile urine culture when on antibiotics.The prevalence of the relapse at three months was 18.18%. 85% of tbe relapses was due to ESBL *E. coli* (15.45%). The (Table 2) shows the distribution of tne bivariate analysis of the « Relapse at three minths » with the different covariates.

| | | | **Bivariate models** | | |
|---|---|---|---|---|---|
| | **Number of relapse (n)** | **Percentage of relapse (%)** | **Unadjusted OR** | **SE** | **p** |
| **Characteristics** | Total (N=110) | | | | |
| Antibiotic | | | | | |
| Bactrim | 1 | 25% | | | |
| Estecina | 1 | 33.33% | 1.5 | 2.525 | 0.81 |
| Ertapenem | 6 | 17.65% | 0.64 | 0.797 | 0.721 |
| Meropenem | 3 | 16.67% | 0.6 | 0.79 | 0.698 |
| Imipenem | 8 | 19.05% | 0.71 | 0.861 | 0.775 |
| Uvamine | 1 | 100% | 1 | | |
| **Risk factors for urinary tract infection** | | | | | |
| Diabetes | | | | | |
| No | 15 | 19.23% | | | |
| Yes | 5 | 15.62% | 0.78 | 0.44 | 0.657 |
| Renal transplantation | | | | | |
| No | 19 | 17.76% | | | |
| Yes | 1 | 33.33% | 2.32 | 2.9 | 0.502 |
| Immunosuppression | | | | | |
| No | 19 | 17.76% | | | |
| Yes | 1 | 33.33% | 2.32 | 2.9 | 0.502 |
| Recent manipulation of the urinary tract | | | | | |
| No | 18 | 18.95% | | | |
| Yes | 2 | 13.33% | 0.66 | 0.529 | 0.603 |
| Chronic renal failure | | | | | |
| No | 13 | 17.82% | | | |

| | | | | | |
|---|---|---|---|---|---|
| Yes | 7 | 18.92% | 1.08 | 0.559 | 0.887 |
| **Risk factors for infections with multiresistant bacteria** | | | | | |
| History of antibiotics in the last 3 months | | | | | |
| No | 12 | 14.81% | | | |
| Yes | 8 | 27.59% | 2.19 | 1.14 | 0.132 |
| History of hospitalization in the prior three months | | | | | |
| No | 15 | 17.65% | | | |
| Yes | 5 | 20.00% | 1.17 | 0.671 | 0.789 |

**Table 2:** Bivariate analysis of the relapse at 3 months according to the treatment and other covariates.

Nearly the same percentage of patients (17%, 18% et 19%) had relapsed in the group treated with meroprnem, ertapenem and imipenem respectively. One patient between 4 trared with cotrimoxazole and 1 patient between 3 treated with ciprofloxacine had relapsed their infection. The only patie t treated with nitrofrantoines had a relapse of the infection during the 3 months after the treatment. Between the immunocompromised patients operated of renal transplantation, 33% had a relapse compared to 18% in the group of patients not immunocompromised (OR= 2.32, p value= 0.5). Between tne patients that received antibiotics in the preceding 3 months 28% has relapsed whereas 15% of patients not treated with antibiotics in the last 3 months has relapsed (OR= 2.19, p value= 0.1). We did not note a difference in the percentage of relapse in tne group of diabetic patients or the patients having chronic renal failure or the patients hospitalized in the previous 3 months; OR = 0.78, 1.08 et 1.17 respectively.

The (Table 3) shows the change in the relapse rate at 3 months in the group of patients treated with carbapenem according to the presence or absence of diabetes.

| | | **Non-diabetic** | | | **Diabetic** | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Ertapenem** | **Meropenem** | **Imipenem** | **Ertapenem** | **Meropenem** | **Imipenem** | |
| | **N total** | **n (%)** | **n (%)** | **n(%)** | **n (%)** | **n (%)** | **n (%)** | **N Total** |
| Relapse at three months | | | | | | | | |
| No | 54 | 18 (85.71%) | 12 (80.00%) | 24 (80.00) % | 10 (76.92%) | 3 (100.00%) | 10 (83.33%) | 23 |
| Yes | 12 | 3 (14.29%) | 3 (20.00%) | 6 (20.00%) | 3 (23.08%) | 0 (0.00%) | 2 (16.67%) | 5 |

**Table 3: Relapse of prostatitis treated with carbapenem in the group of diabetic and non diabetic patients.**

Between the patients included in this study, 94 patients were treated with carbapenem ; sixtee-six of them were not diabetic. In this sub group of non diabetic patients 14.29% of the patients treated with ertapenem has relapsed, in contrast with 20% of patients treated with imipenem and 20% of those treated with meropenem. Between the 28 diabetic patients treated with carbapenem, 23% of those treated with ertapenem has relapsed compared with 17% of those treated with imipenem ; in the three diabetic patients treated with meropenem we did not note any relapse at three months.

## Discussion

According to this study, the rate of relapse of the prostatitis is 18% and the rate of relapse at 3 months with the same bacteria hence ESBL *E. coli* is 15%. This rate of relapse is the same found in the literature around 20% [10]. To be noted that this rate found in the litterature is the rate of relapse of all the prostatitis and not only prostatitis with ESBL *E. coli*. The factors that were prooven to increase the risk of relapse of the urinary tract infections are : diabetes, chronic renal failure and the history of hospitalization in the prior three months [8]. In our study, diabetes OR was 0.78 (p value = 0.66) and chronic renal failure's OR was 1.08 (p value = 0.89). Our study showed an increase in the risk of relapse in the group of immunocompromised patients operated of renal transplantation with an OR = 2.32 (p value = 0.5). The history

of hospitalisation was not an independent factor to increase the risk of relapse (OR = 1.17 et p value = 0.79) on the contrary of the history of taking antibiotics in the prior 3 months that was associated with an increased risk with an OR=2.19 (p value = 0.13). We had practicaly the same rate of relapse in the group of patients treated with carbapenem (17%, 18% et 19%) had relapsed with meropenem, ertapenem and imipenem respectively. We did not note any difference in the frequency of relapse at 3 months of the ESBL *E. coli* prostatitis whatever was the antibiotic used from the family of carbapenem. So according to this study, ertapenem is as effective as meropenem and imipenem is the treatment of ESBL *E. coli* prostatitis. It is very important to note here that the small number of patients included and the fact that this is a retrospective study are important limitations to generalize the results. Furthermore, the duration of the treatment varied between the patients which may cause a bias in our results. One more limitation is that we did obtain the dosage and the treatment duration as confounding factors for regression logistic analysis.

In the sub group of non diabetic patients, 14.29% of those treated with ertapenem had relapsed, but 20% of those treated with imipenem and 20% of those treated with meropenem had relapsed. In this sub group of nob diabetic patients, ertapenem is associated with 6% less relapses compared with imipenem and meropenem (p value = 0.65) but the reduced number of non diabetic patients does not help to generalize this result. Between the 28 diabetic patients treated with carbapenem, 23% of those treated with ertapenem had relapsed compared with 17% of those treated with imipenem ; only three diabetic patients were treated with meropenem but none had relapsed at three months. (p value = 0.65) This difference is not really conclusive since these groups of patients did not contain a comparable number of patients but also we have no idea about the control of the diabetes in these patients. In the sub group of diabetic patients treated with meropenem, none had relapsed after 3 months, this sub group is formed only of 3 patients so we can not take a conclusion on this but a prospective, multicentric study with a large number of patients will be interesting to conclude on tbe efficacy of ertapenem in the treatment of ESBL prostatitis and the possible superiority of meropenem in the sub group of diabetic patients.

## Conclusion

Immunosupression, renal transplantation and the history of taking antibiotics in the 3 months preceding the episode of prostatitis are associated with an increase in the risk of relapse at 3 months of the ESBL *E. coli* prostatitis. Ertapenem is as effective as other carbapenem is the treatment of this entity and is not associated with an increased risk of relapse at 3 months. In case of ESBL *E. coli* prostatitis in a diabetic patient, meropenem may be associated with a better response. Although the reduced number of patients and the fact that it is a retrospective study make us very careful in the interpretation of our results. Prospective studies with a larger number of participants are needed to validate our results.

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