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Clinical Success in Outpatient Treatment of Complicated Urinary Tract Infections (UTI) with Ertapenem

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Abstract

Background: Resistant pathogens are increasingly common in patients (pts) experiencing UTIs and rapid administration of appropriate antibiotics is vital to achieving success. A physician office infusion center (POIC) offers an ideal setting and once daily ertapenem, active against many gram-negative pathogens is an ideal agent for outpatient use. The study purpose was to evaluate therapy characteristics and outcomes of UTI pts receiving ertapenem in a POIC.
Methods: A retrospective database review was conducted of 4 participating Infectious Disease POICs for pts 18 years or older receiving ertapenem therapy for UTI between July 1, 2010 and December 31, 2012. 75 pts with a UTI diagnosis (UTI, pyelonephritis, urosepsis) and available culture data were randomly selected from each site. Data collected included age, gender, indication for treatment, presence of urinary catheter, history of UTI, microbiology, duration of treatment, and adverse events. Clinical success was defined as microbiological or clinical cure plus improvement with partial resolution or added antibiotics at the completion of ertapenem therapy. A failure was defined as inadequate response, worsening of infection or need for a change in antibiotic.
Results: The mean age was 65 yrs with 72% females. Pyelonephritis was present in 23% and bacteremia or urosepsis in 7%. 59% had a history of recurrent UTIs, and 15% had a urinary catheter. Common co-morbidities were hypertension (44%) and diabetes (28%). ESBL *Escherichia coli* was the most common pathogen (51%), followed by non-ESBL *Escherichia coli* (24%). Therapy was initiated in the POIC in 63%. Mean treatment days, both inpatient and outpatient was 11 days, with 95% of total ertapenem received in the POIC. Clinical success was achieved in 95% of pts (79% cured plus 16% improved), while 3 pts (4%) failed therapy and one pt was non-evaluable. Therapy failures were all due to adverse events (AE) requiring discontinuation of ertapenem, with 1 pt seizure requiring hospitalization and 2 pts with anaphylactic type reactions. Overall AEs occurred in 22 (29%) pts. The most common was diarrhea, occurring in 12%, but with no reports of *Clostridium difficile* infections. Mild infusion reactions occurred in 5%.
Conclusions: Treatment of complicated UTIs with ertapenem achieved clinical success and was well tolerated. With a high success rate in drug-resistant pathogens, ertapenem appears to be safe and effective in treatment of complicated UTIs in the POIC.

Introduction

Patients who are stable and require intravenous antibiotic therapy for infections may continue therapy outside of the hospital or avoid hospitalization altogether (1). A POIC is an ideal setting for identification and treatment of patients requiring infusion therapy. Antibiotic (ABX) selection in the outpatient setting must consider the activity of the agent, dosing schedule, duration of therapy, adverse event profile and drug stability(1,2), making ertapenem an ideal candidate. Ertaptenem is approved for complicated UTIs (UTI), including pyelonephritis (3). Ertapenem is rapidly bactericidal against a broad range of organisms and is approved for once-daily dosing (3).

The primary study objective was to report the clinical outcomes of patients receiving ertapenem for treatment of complicated UTIs in the outpatient setting. Secondary objectives were characterization of the patient population receiving ertapenem, a description of pathogens for which ertapenem is being used and to report adverse events in patients receiving ertapenem.

Methods

Following IRB approval, the centralized database was queried retrospectively for patients 18 years or older receiving ertapenem between July 1, 2010 to December 31, 2012. Inclusion criteria required patients to be treated in one of 4 participating Infectious Disease POICs with at least 3 doses of intravenous ertapenem for UTI or pyelonephritis and documented urine cultures with susceptibilities. Cystitis patients were classified as UTI. Multi-drug resistant (MDR) organisms were defined as those with non-susceptibility to at least one agent in ≥ 3 antimicrobial categories. Presence of ESBL-producing organisms was also characterized.

Ertapenem Outcome:
Outcomes were measured at the completion of ertapenem therapy and were evaluated as: Cured; Resolution of signs and symptoms with no additional antibiotic therapy; Improved; Partial resolution of signs and symptoms or additional antibiotic therapy necessary or Failed; Inadequate response, worsening or new signs/symptoms, or need for a change in IV antibiotic therapy. Patients, whose outcome could not be determined at completion of therapy were noted as non-evaluable. Clinical success was defined as patients who were both cured and improved.

Drug-related Adverse Events (AEs):
- Mild: Does not require discontinuation or dose reduction of ertapenem.
- Moderate: Responds to symptomatic therapy and may require dose reduction but not ertapenem discontinuation.
- Severe: Not relieved with symptomatic therapy and requires discontinuation of ertapenem.
- Serious: Death, life-threatening, resulting in inpatient hospitalization or prolongation of hospitalization or a persistent or significant disability or incapacity.

Data Analysis:
- Descriptive statistics (mean, %) were used for demographics data; percentages were used for diagnosis, microbiology, safety and clinical outcomes data. P values were determined by the Fisher's exact test.

Results

Demographics and Characteristics

Table 1. Demographics

Demographics	No. (%)
Gender	
Female	54 (72)
Male	21(28)
Age (years)	
Mean (range)	65 (19-93)
> 60	50 (67)
≥ 65	40 (53)
Comorbidities	
Hypertension	33 (44)
Obesity[1]	24 (32)
Diabetes	21 (28)
Renal Disease[2]	11(15)
Smoker	5 (7)
Immunocompromised[3]	5 (7)

[1]BMI (kg/m²) ≥ 30;
[2]Chronic Renal Failure, End Stage Renal Disease or Hemodialysis
[3]Either due to a disease state or treatment

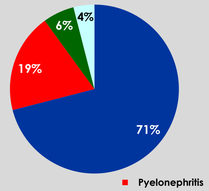
Table 2. Characteristics

Patient Characteristic	No. (%)
History of Recurrent UTI	44 (59)
ABX Drug Allergy	26 (35)
Urinary Catheter	11 (15)
-Intermittent Self-catheterization	8 (11)
-Chronic Indwelling Urinary Catheter	3 (4)
Urinary Retention	8 (11)
Neurogenic Bladder	4 (5)

- The majority of pts (59%) had a history of recurrent UTIs.
- Allergies to ABXs were common (35%).

Diagnoses

Figure 1. Diagnosis Distribution



- UTI was the most frequent diagnosis (54 pts). All had complicating factors, the most common of which were recurrent UTIs (15), anatomic or functional abnormalities (14), and presence of urinary catheters(9).
- 9% of pts (n=7) presented with a concomitant bacteremia.

Microbiology

Table 3. Bacterial Isolates

Microorganism	Isolates - No. (%)		
	Women	Men	Total
Escherichia coli	42 (78)	14 (67)	56(75)
Klebsiella pneumoniae	6 (11)	5 (24)	11 (15)
Klebsiella oxytoca	1 (2)	-	1 (1)
Enterobacter sp	1 (2)	-	1 (1)
Enterobacter cloacae	-	1 (4.5)	1 (1)
No Growth	4 (7)	1 (4.5)	5 (7)
Total	**54 (100)**	**21 (100)**	**75 (100)**

- Gram negative bacilli accounted for all isolates identified.
- For those patients with microorganism growth, men were more likely than women to be infected with an organism other than *Escherichia coli* (33% vs. 22%).

Table 4. Species Distribution of MDR and ESBL Organisms

Microorganism	Total Isolates	MDR Isolates No., (%)	Isolates Tested for ESBLs	ESBL Isolates No., (%)
Escherichia coli	56	49 (88)	46	38 (83)
Klebsiella pneumonia	11	10 (91)	8	7 (88)
Klebsiella oxytoca	1	0 (0)	1	0 (0)
Enterobacter sp	1	0 (0)	–	–
Enterobacter cloacae	1	1 (100)	–	–

- ESBL *E. coli* was the most frequent organism identified (51%) overall.
- MDR organisms were identified in 85% of cultures with growth.
- ESBL-producing organisms were seen in 82% of those tested.
- 86% of patients previously hospitalized grew an ESBL or MDR organism versus 76% of those admitted directly to the POIC. (p=0.1039)
- 67% of patients were >60 years of age with increased risk of ESBL or MDR organisms.

Ertapenem Treatment

- Ertapenem was the first-line therapy in 74/75 of pts.
- 95% of ertapenem doses were received in the outpatient setting.
- The average length of therapy (LOT) for ertapenem was 11.4 days.
  - Mean LOT for pts initiated in the hospital was 13 days total (inpatient plus outpatient treatment). Ertapenem was given in the hospital an average of 2.5 days prior to discharge.
  - Mean LOT for pts initiated in the POIC was 10.7 days.
  - Mean LOT was slightly longer in pts with MDR or ESBL organisms (12 vs. 9 days) (p=0.6938)

Table 5. Ertapenem LOT by Diagnosis

Diagnosis	Pt No. (n=75)	Ertapenem initiated in hospital (n=20)		Ertapenem initiated in POIC (n=55)	
		Pt. No. (%)	Mean LOT (days)	Pt. No. (%)	Mean LOT (days)
UTI	54	8 (40)	13	46 (84)	9.5
UTI + Bacteremia	4	-	-	4(7)	10
Pyelonephritis	14	9 (45)	16.5	5(9)	18.5
Pyelonephritis + Bacteremia	3	3(15)	14		

- Patients with pyelonephritis had a longer treatment course and were more likely to initiate therapy in the hospital setting.

Ertapenem Clinical Outcomes

Figure 2. Overall Outcome

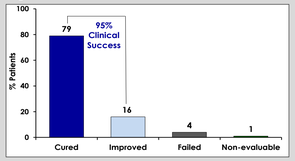
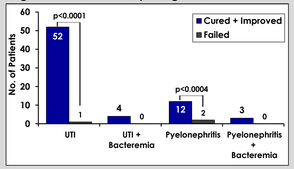


Figure 3. Outcome by Diagnosis



- Successful outcomes were reported in 95% of evaluable patients with 59 (79%) cured and 12 (16%) improved.
  - 7/12 improved pts had partial resolution of signs/ symptoms
  - 5 required subsequent oral ABX therapy (3 suppressive tx; 2 tx continuation)
  - 9/12 (75%) of improved pts were infected with an ESBL or MDR organism
- 3 pts noted as failed were due to an AE requiring ertapenem discontinuation
- Clinical treatment success (cure + improved) was significant in pts with UTI and pyelonephritis
- 30-day recurrence was seen in 7 (9%) patients, 6 who were infected with an ESBL or MDR organism

Safety

- No patients had increases in LFTs from baseline during ertapenem therapy.
- There were no reports of QT prolongation during ertapenem therapy
- 5 patients (7%) received initial doses of 500 mg daily due to creatinine clearance
  - 1 patient required renal dose adjustment during therapy

Table 6. Mild to Moderate Adverse Events

Mild-Moderate Adverse Reactions (n=25)	No. (%)
GI symptoms	10 (13)
Vaginal Itching	3 (4)
Dizziness	2 (3)
Fatigue	2 (3)
Headache	2 (3)
Confusion	1 (1)
Depression	1 (1)
Myalgias	1 (1)
Rash	1 (1)
URI Symptoms	1 (1)
Weakness	1 (1)

- 22 pts (29%) experienced 28 AEs
  - 25 Mild or Moderate
  - 2 severe and 1 serious (Table 7)
  - 2 pts reported > 1 AE
- Diarrhea was most commonly reported AE, but with no reports of positive *Clostridium difficile*
- 4 pts (5%) experienced an infusion site reaction which was resolved during therapy

Table 7. Adverse Events Requiring Discontinuation of Ertapenem

Serious-Severe Adverse Reactions (n=3)	Ertapenem Treatment Day	Comorbidities	Drug Allergies	Intervention
Hypersensitivity Reaction	9	recurrent UTIs, nephrolithiasis, hypothyroidism, obesity	ampicillin, ceftriaxone, cephalexin, quinolones, sulfamethoxazole-trimethoprim	Patient hospitalized; Ertapenem discontinued; Symptoms resolved
Hypersensitivity Reaction	6	recurrent UTIs	cefaclor, quinolones, sulfamethoxazole-trimethoprim	Ertapenem discontinued and switched to gentamicin; Symptoms resolved
Seizures	6	neuroblastoma, paraplegia, neurogenic bladder, recurrent UTIs, urinary diversion, obesity	vancomycin	Patient hospitalized: Ertapenem discontinued and switched to cefepime; Symptoms resolved

Discussion

- Patients with a range of illness acuity, from UTI to pyelonephritis with bacteremia, received ertapenem through an Infectious Disease physician office infusion center (POIC).
- 55% of patients had ertapenem therapy initiated in the POIC. Average LOT was 11 days overall, with therapy slightly higher in those previously hospitalized (13%).
- Ertapenem use was associated with patients with a history of recurrent UTIs (59%) drug allergies (35%) and urinary catheterization (15%).
- *E. coli* was the predominant organism (75%).
- Overall, ESBL and MDR rates in the outpatient setting were high. ESBL-producing organisms accounted for 82% and MDR was seen in 85% of organisms.
- Successful outcomes were reported in the majority of patients treated with ertapenem for a UTI in the outpatient setting. The only patients noted as failed were due to discontinuation of ertapenem due to an AE and none due to disease exacerbation.
- Patients with ESBL or MDR organisms were less likely to be cured at ertapenem therapy completion and more likely to require subsequent treatment for a UTI.
- Our retrospective study was limited by varied data available in the outpatient setting. Culture data was not typically obtained at the completion of therapy.

Conclusion

- Complicated urinary tract infections were safely and effectively treated in an ID POIC.
- Ertapenem was successful in eradicating infection in patients with a high incidence of both ESBL-producing organisms and multi-drug resistant organisms.
- Ertapenem can be used to initiate therapy in a POIC for patients requiring an intravenous agent.
- The activity and pharmacodynamic profile of ertapenem is congruent with the properties necessary for use of an intravenous agent in the POIC.

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