

# Out-Patient Parenteral Antibiotic Therapy (OPAT): Clinical Outcomes and Adverse Events

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## Abstract

*A chart review was conducted of patients in a program featuring self directed, home infusion of antibiotics for serious infections utilizing an out-patient medical office for teaching, mixing of drugs, and monitoring of patients. 302 courses of out-patient parenteral antibiotic therapy (OPAT) were administered to 221 patients. Therapy was successful in 94% of the episodes. Objective adverse events were noted in 25% of patients. To maximize the chance for a successful outcome, treatment plans should be individualized and structured to include systematic monitoring for adverse effects.*

## Introduction

Parenteral antibiotics are indicated when no effective oral anti-infective exists or when the seriousness of infection mandates a high and reproducible serum concentration. The treatment of serious infections with outpatient parenteral antibiotic therapy (OPAT) has major advantages over inpatient infusion.<sup>1-7</sup> The experience is less disruptive to the patient's life than hospital confinement,<sup>8</sup> and by any standard, the expense is less.<sup>9,10</sup> Early success treating chronic infections, such as osteomyelitis<sup>11</sup> and pneumonia associated with cystic fibrosis,<sup>12</sup> showed the potential of this format. OPAT was promoted for a variety of infections<sup>13</sup> including brain abscess,<sup>14</sup> endocarditis,<sup>15,16</sup> community acquired pneumonia,<sup>17</sup> skin and soft tissue infections,<sup>2</sup> pyelonephritis,<sup>18</sup> and pelvic inflammatory disease.<sup>19,20</sup> Much of the OPAT process was removed from direct physician control<sup>21,22</sup> as government regulations restricted physicians from utilizing infusion services in which they had ownership because of a potential conflict of interest. The delivery of OPAT was then assumed by home care companies as part of their outpatient services, similar to fluid replacement, supplemental nutrition, and pain management.<sup>23,24</sup> As with other home care services the physician was responsible for ordering the medications and for complications and outcome of treatment, but was not directly involved in monitoring the quality of care. An exception to this general rule does, however, allow physicians to provide OPAT as a direct extension of their clinical practice. The material for this paper is drawn from this model.

## Methods

A retrospective review of all the records of patients in an infectious disease practitioner's outpatient practice who were treated between 1991 and 1996 with self directed home infusion of OPAT was performed. Patients considered for the OPAT program were able to come to the medical office as needed, and had support at home should they require assistance with infusions. A registered nurse taught each patient the mechanics of self-infusion in intensive training sessions. Care of the venous access site, administration and storage of the antibiotic solutions and recognition of side effects were reinforced until the patient was comfortable with the process. The nurse and a physician were available at all times to respond to questions or problems. The patients came to the office at least twice a week for dressing changes, interval history focusing on infusion problems and adverse events, and re-supply of premixed antibiotics. The physician examined the patient at least once a week to assess their clinical status, review laboratory results, and to make changes in medications.

Each infectious episode constituted a separate study case, thus the same patient could be represented multiple times for different infections. Episodes were censored from the analysis if no data was available for follow-up (8 episodes). Each treatment episode was a success when the course of parenteral antibiotics was completed, even if the patient was switched to oral antibiotics. Treatment failures resulted in hospitalization of the patient prior to conclusion of therapy or discontinuation of treatment due to unmanageable adverse effects.

Adverse effects met the following criteria:

- 1) Nephrotoxicity: a rise in creatinine of 0.5 mg/dL if the pretreatment baseline was abnormal or a 0.5 mg/dL rise above normal standards.
- 2) Anemia: hemoglobin decrease of 2 g/dL from pre-treatment baseline.
- 3) Diarrhea: >3 loose stools per day.
- 4) Eighth nerve toxicity: onset of dizziness or imbalance with the presence of nystagmus or Romberg's sign.
- 5) Fever: >100.0 F degrees.
- 6) Thrombocytopenia: platelet count of <100,000 g/L or >50% drop if pretreatment baseline was below 100,000 g/L
- 7) Neutropenia: new onset of a white blood cell count <2,500 cu/cm or a drop of >50% from pre-treatment baseline if entry status was below 2,500 WBC/cm.
- 8) Hepatic dysfunction: transaminase (ALT) value twice the upper limit of normal or increase from pre-treatment baseline if abnormal.

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## Results - Patient Population

During the six-year study period, 302 courses of OPAT were administered to 221 patients. The median duration of therapy was 18 days, ranging from 3 to 307 days. Two-thirds of the patients were male and the median age was 40.8 years. Other medical conditions co-existed in 60% of the 302 treatment episodes including solid organ transplantation, acquired immune deficiency syndrome (AIDS), diabetes mellitus, chronic obstructive pulmonary disease (COPD), or cancer of a solid organ, [Table 1].

## Results - Clinical Infections

Bacterial infections were treated most often (76%), [Table 2]. Gram-positive bacteria accounted for 59% of isolates (140 of 236), including *S. aureus* (38), *S. epidermidis* (28). Almost forty percent (93/236) of the pathogens were gram-negative bacteria; *pseudomonas aeruginosa* was the most frequent pathogen under treatment (38/93). Forty-one patients had a polymicrobial infection, [Table 3].

Viral infections were treated in 63 episodes, including 39 episodes of cytomegalovirus infection in patients with a transplanted organ. Eighteen other episodes with cytomegalovirus infection were treated in patients with AIDS. Other viral infections in patients with AIDS included six episodes of herpes proctitis or herpes esophagitis. Patients with AIDS were also treated for fungal esophagitis (4), and pneumocystis carinii pneumonia (8). Atypical mycobacterium pulmonary infections not associated with HIV were treated on 5 occasions.

## Results - Anti-Infective Medications

Cephalosporins accounted for 49% (152) of the 389 courses of antibiotics. Vancomycin was used 48 times against methicillin resistant staphylococci. Other antibiotics included aminoglycosides, ureidopenicillins, imipenem, clindamycin, and ciprofloxacin. Anti-viral agents utilized were ganciclovir, foscarnet, and acyclovir. Pentamidine was also administered, [Table 4].

## Results - Treatment Outcome

OPAT was successful in 94% (283/302) of the episodes. No further anti-infective therapy was necessary in 236 cases; step-down to oral therapy occurred in the remaining 47. Antibiotics were changed during treatment in 3 patients because of drug resistance and in 12 patients because of intolerable side effects.

Treatment failed in 19 episodes. Of these, 16 episodes required hospitalization. Clinical deterioration occurred in nine patients with bacterial infections (osteomyelitis, wound infection, pyelonephritis, pelvic abscess, septic bursitis, paratyphoid fever, orchitis, cholangitis, and line sepsis). Five patients were hospitalized for progression of HIV infection. One patient could not cope with home infusion and one patient required a surgical procedure unrelated to the infection. Therapy was terminated in 3 patients because the side effects of drug outweighed the benefit of further treatment: in one patient pentamidine caused vestibular and renal dysfunction; pentamidine caused hypoglycemic reactions in another patient; and ganciclovir induced thrombocytopenia in the third patient. Overall, patients with HIV infection experienced significantly higher rates of treatment failure (26%) compared to the rest of the study population (4%).

Table 1.— Co-Morbid Conditions

No Underlying Disease	122	40%
Renal Transplant	56	19%
AIDS	31	10%
Diabetes Mellitus	20	7%
Chronic Obstructive Pulmonary Disease	14	5%
Solid Organ Cancer	16	5%
Heart Transplant	13	4%
Chronic Skin and Soft Tissue Infection	7	2%
Coronary Artery Disease	4	1%
End Stage Renal Disease	4	1%
Rheumatoid Arthritis	3	1%
Other	12	4%

Other includes: Leukemia, Nephrolithiasis, Peripheral Vascular Disease, Prosthetic Joint, Sweet's Syndrome, Systemic Lupus Erythematosus, Bone Marrow Transplant, Traumatic Arthritis

Table 2.— Clinical Diagnosis of Infection

Cytomegalovirus	57	19%
Soft and Soft Tissue	42	14%
Lower Respiratory Tract	38	13%
Septicemia	33	11%
Osteomyelitis	29	10%
Ear, Nose, and Throat	23	8%
Pyelonephritis	19	6%
Post-Operative Wound	11	4%
Intra-abdominal Abscess	11	4%
Septic Arthritis	11	4%
Endocarditis	6	2%
Herpes Virus	6	2%
Other	16	5%

Other includes: actinmycosis, bacterial meningitis, chronic bronchitis, diverticulitis, Lyme disease, mycotic aneurysm, orchitis, prostatitis, graft infection, torulopsis esophagitis, CMV prophylaxis

Table 3.— Microbiology

<i>P aeruginosa</i>	38
<i>S aureus</i>	34
<i>S epidermidis</i>	28
<i>E coli</i>	18
<i>E faecalis</i>	14
Streptococcus sp.	14
<i>S pyogenes</i>	12
Enterobacter sp.	12
<i>K pneumoniae</i>	12
Pseudomonas sp.	9
Bacteroides sp.	5
Mycobacteria sp.	5
Other (23 organisms)	49

Table 4.— Anti-Infective Medications

Cephalosporins	152	39%
Ganciclovir	54	14%
Vancomycin	48	12%
Aminoglycosides	41	11%
Ureidopenicillins	29	7%
Foscarnet	14	4%
Imipenem	13	3%
Pentamidine	8	2%
Clindamycin	8	2%
Acyclovir	6	2%
Ciprofloxacin	6	2%
Other	10	3%

Other: Amphotericin B, Doxycycline

## Results - Adverse Events

Quantifiable adverse events were documented in 74/302 episodes (25%). The most frequently encountered verifiable new findings included renal dysfunction, drug rash, anemia, diarrhea, vestibular dysfunction, drug fever and bone marrow depression, [Table 5]. In addition, 18% of the patients (55 episodes), complained of constitutional symptoms reporting fatigue (20), headache (12), anorexia (5), as well as nausea (19), weakness (2), palpitations (1), sleepiness (1), and insomnia (1).

AIDS as an underlying condition was associated with a significantly higher rate of verifiable adverse events (58%) compared to patients with transplanted organs (26%) or patients with no underlying disease (19%).

The impact of underlying disease upon objective adverse events can be seen by comparing the treatment of cytomegalovirus infections with ganciclovir in patients with AIDS and organ transplantation. The incidence of adverse events was much higher in ganciclovir-treated patients with HIV infection, 56% (5/9) compared to 33% (14/43) in patients with organ transplantation receiving the same drug.

Other opportunistic infections in patients with AIDS were also associated with a very high incidence of adverse effects during treatment (>50%). Adverse events were noted in 4 of 6 patients on pentamidine for pneumocystis carinii pneumonia, 2 of 3 patients on co-trimoxazole, 4 of 8 patients on foscarnet, 4 of 6 patients treated for refractory herpes infection with acyclovir, and 3 of 4 patients with fungal esophagitis treated with Amphotericin B.

Adverse events from antibiotics used to treat bacterial infections were also common and resulted in a change of drug in 10 episodes but did not necessitate termination of OPAT. The incidence of adverse events was greatest with imipenem and ureidopenicillins (>20%), though clinically significant side effects occurred with vancomycin (19%), cephalosporins (13%), and aminoglycosides (5%) as well.

Table 5.— Adverse Events

Renal Toxicity	21	7%
Drug Rash	18	6%
Anemia	13	4%
Diarrhea	13	4%
Eighth Nerve Toxicity	11	4%
Fever	9	3%
Thrombocytopenia	8	3%
Neutropenia	7	2%
Hepatitis	3	1%
Other Significant Adverse Events	15	5%
Other: Thrush, Bleeding, Orthostatic Hypotension, Blurred Vision, Hematuria, Bradycardia, Hypoglycemia		

Table 6.— Adverse Events and Medication

Pentamidine/Co-Trimoxazole	1/1	100%
Foscarnet/Ganciclovir	4/5	80%
Amphotericin B	3/4	75%
Co-Trimoxazole	2/3	67%
Pentamidine	4/6	67%
Acyclovir	4/6	67%
Foscarnet	4/8	50%
Imipenem	5/13	39%
Ganciclovir	16/48	33%
Extended Penicillins	6/29	21%
Vancomycin	9/48	19%
Cephalosporins	19/152	13%
Aminoglycosides	2/41	5%

## Discussion

OPAT was successful in 94% of the treatment episodes with an adverse event rate of 25%. The outcome of therapy in this paper is similar to that previously reported<sup>25</sup> but not the rate of adverse events or side effects. Adverse events, in earlier publications, were considered significant when there was a change in therapy; the dose of antibiotic was adjusted, or the antibiotic was discontinued.<sup>26</sup> Monitoring organ function for changes of potential clinical significance is the standard of practice when treating infections in patients who are hospitalized and is probably more important in the outpatient setting where face to face encounters between the patient and the treating physician or staff nurse are less frequent. Quantifying the etiology of any recognized adverse events represents a challenge to the clinician as the factors of drug, underlying disease, and current infection can each play a significant role.

As illustrated in this paper, underlying disease can have a profound impact on the morbidity and outcome of therapy. The formal structure of all OPAT programs must include careful monitoring of the patient for adverse events and be tailored to the patient, their infection, treatment, and underlying disease.

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