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Monitoring of outpatient parenteral antimicrobial therapy (OPAT) and implementation of clinical pharmacy services at a community hospital infusion unit

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Abstract

Background:

In 2004, the Infectious Diseases Society of America (IDSA) published monitoring guidelines for outpatient parenteral antimicrobial therapy (OPAT), but no assessment of their utilization has been reported. We evaluated adherence to these recommendations by physicians at infusion centers and then piloted a program of supervision of monitoring by pharmacists.

Methods:

Phase I: We performed a retrospective case-control study of patients who received OPAT over one year at two hospital infusion centers. Controls were patients treated by an infectious diseases (ID) physician, and cases were those without an ID physician. Patients were excluded if they received fewer than 3 days of OPAT. Clinical pharmacy monitoring services were then implemented for patients on OPAT prescribed by non-ID physicians at one hospital's infusion unit. Two outcomes were measured: adherence to guidelines on monitoring, and attainment of goal vancomycin and aminoglycoside serum concentrations when appropriate. The results for non-ID physicians were compared to both ID physicians and subsequently a pharmacist.

Results:

Ninety nine patients were included in the retrospective study. Compared with patients who had ID physician supervision, the non-ID physicians who prescribed OPAT for 39 patients had lower adherence to monitoring recommendations (35.9% vs.68.3%, p=0.003). No difference could be detected in achievement of goal vancomycin and aminoglycoside serum concentrations for the 14 cases and 19 controls requiring therapeutic drug monitoring (57.1% vs. 68.4% respectively,

p=0.765). Seven patients were enrolled in the study after pharmacy monitoring was implemented. Adherence to monitoring recommendations for these patients was significantly improved compared to the prior patients that lacked ID physician supervision (35.9% vs. 100%, p=0.0065).

Conclusions:

Non-ID physicians are less likely to monitor OPAT according to the IDSA guidelines than ID physicians; however, pharmacist oversight improves adherence to recommendations. Further studies of monitoring of OPAT by pharmacists should investigate the impact of pharmacist involvement on prevention of adverse events and hospital readmissions.

Key words:

OPAT, antibiotic, monitoring, outpatient, pharmacist

Background

Patients with moderate to severe infections may require intravenous (IV) antibiotics for their entire course of therapy. However, many of these patients may be stable enough to receive treatment as an outpatient. Outpatient parenteral antimicrobial therapy (OPAT) is defined as providing IV, intramuscular or subcutaneous administration of antibiotics, antifungals, and antivirals to patients on separate days outside of a hospital setting.[1] One of the goals of OPAT is to deliver high-quality health care while optimizing resource use and reducing costs without compromising clinical outcomes. With the availability of antimicrobials with long half-lives that allow for once or twice daily dosing, OPAT is feasible for a variety of infectious diseases. Examples of infections that have been effectively treated with OPAT include skin and soft tissue infections, osteomyelitis, bacteremia, endocarditis, and complicated urinary tract infections.[2-6]

Mounting evidence supports the use of OPAT. The documented benefits include cost savings and patient convenience.[1,2] Using OPAT allows for additional inpatient hospital beds and healthcare resources to be available for other more acute patients and it can lead to a reduction in the risk of healthcare-related infections.[3,8] Infection acquired during a hospitalization results in an estimated cost of $2,100 and a total cumulative cost of greater than $2 billion annually.[8] An article by Nguyen showed that the implementation of an OPAT service for a hospitalist service at his 619-bed acute-care medical center translated to an estimated mean savings of over $7,000 per patient.[3] In addition to cost avoidance, OPAT can allow patients to return home, improving their quality of life and satisfaction with care.[1] Due to the cost savings and other benefits noted, OPAT services are becoming more attractive to healthcare systems, especially in light of increasing financial and regulatory pressures.[3]

OPAT can be provided in various settings, including physician's offices, infusion centers, long-term care facilities, dialysis centers and even the patient's home with visiting nurse or self-administration of the drug. In one recent U.S. study, 65% of inpatients discharged on OPAT received infusions at home, 15% at long term care facilities, 11% at infusion centers and 9% at other facilities such as dialysis clinics or physicians' offices.[7] The patient's condition and source of payment often direct where patients on OPAT may be discharged.

Several key features make an OPAT program successful and efficient (e.g. the OPAT bundle concept as suggested by Muldoon et al.[9]). These include: careful patient selection; an organized OPAT team consisting of an ID physician, infusion pharmacist, nurses, case management, billing staff, social worker and primary care or referring physicians available to participate in care; effective communication between the OPAT team, patient and other healthcare professionals; optimal patient surveillance and monitoring; and a program in place to monitor outcomes.[4,7,9] The American Society of Health-System Pharmacists has published guidelines highlighting the pharmacist's contribution to this team approach, including monitoring antimicrobial therapy .[10,11]

Unlike the inpatient setting where a patient is closely observed, patients on OPAT may experience much less monitoring.[1] At least 25% of patients receiving OPAT will develop adverse reactions however, and up to 10% of patients on OPAT will discontinue therapy due to an adverse event.[1,4] A 1999 report of 269 patients who received OPAT at home during a 2 year period, found that 16% developed leukopenia, 7% neutropenia, 4% thrombocytopenia and 8% nephrotoxicity. Overall, 8% of patients required re-hospitalization. The authors concluded that

monitoring of patients receiving OPAT is important to prevent complications and hospital readmissions.[12]

In 2004 the Infectious Diseases Society of America (IDSA) updated their 1997 guidelines for OPAT, including recommendations for monitoring. These practice guidelines serve as a benchmark for clinical monitoring and quality assurance.[1,4] With the implementation of these guidelines plus vigilant risk assessment and management, the hazards associated with OPAT can be minimized.[1] The guidelines are voluntary and no reports of rates of adherence have been published. Therefore, we evaluated adherence to the laboratory monitoring recommendations, including attainment of goal serum drug concentrations, by physicians at infusion centers and then pilot clinical pharmacy monitoring services in an existing OPAT program.

Methods

Phase 1

This was a two phase study approved by the local institutional review board. The first phase was a retrospective case-control study. Controls were defined as patients treated by an ID physician, and cases were defined as those patients without the supervision of an ID physician. Patients who received OPAT from 11/2011 to 10/2012 at the infusion centers of two community teaching hospitals in Springfield, Illinois were retrieved from the hospitals' electronic pharmacy databases. Cases were differentiated from controls by identifying the physician prescribing antimicrobials as either an ID specialist or not. Patients were excluded if they received fewer than 3 days of OPAT. We collected the following data for the cases and controls by reviewing individual medical records: patient demographics, infection treated, antibiotics administered,

physician specialty, microbiology results and monitoring. The monitoring included frequency of laboratory testing, as well as serum concentration values for vancomycin and aminoglycosides. Two primary outcomes were assessed: adherence to monitoring of OPAT based on guidelines, and in patients prescribed vancomycin or an aminoglycoside, attainment of therapeutic serum drug concentrations. In order to be counted as adherent to monitoring, all laboratory parameters would have to be ordered as recommended in table 1. Physicians were considered non-adherent to monitoring if any laboratory parameter was omitted during each week of therapy. The goals for serum concentrations were assessed according to local hospital guidelines (Appendix A) based on literature and national standards.[13-19]

Phase 2

Based on the results of the first phase, we determined a greater need for monitoring of patients who did not have ID physician supervision. We hypothesized that the integration of a pharmacist would help improve adherence to monitoring recommendations in this patient population. Therefore, the second phase of the study involved implementation of pharmacy monitoring services for patients receiving OPAT without ID physician supervision from 11/2012 to 4/2013 at one of the infusion centers.

We chose to pilot pharmacy monitoring services of OPAT at that hospital's infusion unit because of the presence of an infectious diseases pharmacy resident to assist with the program. This infusion center is a 24-hour ten bed facility where patients can receive blood transfusions or parenteral drug therapy including chemotherapy and antibiotics. The infusion center clerk sent a list of patients scheduled to receive that day's medication infusions to the hospital's central

pharmacy each morning. The inpatient pharmacy prepared the patients' parenteral products as usual while an investigator reviewed this list for adults receiving antimicrobials prescribed by non-ID physicians. When eligible patients were identified, the prescribing physician was called to obtain approval for ordering laboratory monitoring and adjusting doses based on results. To create awareness of the program, hospitalist groups and case managers were educated on the potential service during staff meetings. Adherence to monitoring recommendations for outpatients under the care of a pharmacist was compared with that of historic controls, patients who lacked ID physician supervision before pharmacy monitoring was implemented.

Analysis with Chi-square test was used to compare the categorical variables of adherence to monitoring recommendations and attainment of goal serum drug concentration. All tests were 2-tailed and $p<0.05$ was considered statistically significant.

Results

Phase 1: Ninety nine patients receiving OPAT at the hospital infusion centers from 11/2011 to 10/2012 were included. Of these, 39 lacked ID physician supervision. A majority of the patients that received OPAT were female (n=63, 64%) and the mean age was 63.1 years (SD 16.6). Baseline demographics between cases and controls were similar. A wide variety of clinical indications and microorganisms were documented (table 2). Urinary tract infections and acute skin or soft tissue infections were the most common diagnoses. Causative organisms were identified in 59 patients receiving OPAT. The most common pathogens were *Staphylococcus aureus* (20.2%) and *Escherichia coli* (15.1%). Table 3 lists the antimicrobials prescribed. All were administered intravenously. As expected, antimicrobials that can be administered once or

twice daily were most commonly prescribed. Vancomycin, 3rd and 4th generation cephalosporins, ertapenem and daptomycin were the most frequently used parenteral antimicrobials. The median duration of aminoglycoside therapy prescribed by both ID and non-ID physicians was 6 days. For vancomycin, the median duration of therapy prescribed by ID physicians was 14 days, and by non-ID physicians was 7 days.

Patients without ID physician supervision had lower adherence to monitoring recommendations (35.9% vs. 68.3%; OR 3.9, 95% CI 1.6-9; p=0.003). The cases also had numerically lower attainment of goal vancomycin and aminoglycoside serum concentrations although this was not statistically significant (57.1% vs. 68.4%; OR 1.6, 95% CI 0.4-6.8; p=0.765). Table 4 lists the monitoring parameters that physicians (ID and non-ID) omitted. A majority of patients, whose physicians did not adhere to guidelines, received no additional laboratory monitoring after their hospital discharge.

Phase 2: We piloted pharmacy monitoring services for seven patients, who received OPAT prescribed by non-ID physicians, at one of our infusion centers. These patients received OPAT for either urinary tract infection (n=4), chronic sinusitis (n=2) or osteomyelitis (n=1). Antibacterials administered include ceftriaxone (n=2), cefepime (n=2), and ceftazidime, vancomycin and gentamicin (1 each). All prescribers accepted the pharmacist's offer to monitor these patients. Adherence to monitoring recommendations for these patients was significantly improved compared to the patients that lacked ID physician supervision prior to pharmacy monitoring services being implemented (35.9% vs. 100% , p=0.0065).

Discussion

To our knowledge, no reports on the consistency of OPAT monitoring have been published for physicians or pharmacists. We therefore assessed adherence to the laboratory monitoring recommendations in the IDSA guidelines for OPAT, and attainment of goal serum drug concentrations at two infusion centers.

As suspected, the evaluation revealed that patients with ID physician supervision had significantly better adherence to monitoring recommendations. These patients had a higher attainment of goal serum concentrations of vancomycin and aminoglycosides as well; although, this was not statistically significant. Based on these results, there is room for improvement in both groups however with only 55.5% of the patients overall receiving monitoring consistent with national guidelines.

In the second phase of the study, we implemented pharmacy monitoring services at one of our infusion centers and achieved 100% adherence to monitoring guidelines for patients on OPAT prescribed by non-ID physicians. It was decided to pilot these pharmacy monitoring services on OPAT prescribed by non-ID physicians because of lower initial adherence to monitoring guidelines in this group. We hypothesized that these physicians would be most amenable to assistance with monitoring and adjusting doses for antimicrobials. After implementation of the clinical pharmacy services, attainment of goal serum drug concentrations was not compared since only two patients required this service. Only seven patients were enrolled in the second phase of the study because our study time frame was six months and the majority of OPAT at our institution was prescribed by ID physicians. It would have been ideal to include more patients over a longer time frame, but we felt this wouldn't have changed the results. Patients that had

pharmacist monitoring oversight were significantly more likely to be monitored according to guideline recommendations after 6 months, and the pharmacists involved in preparation of the parenteral antimicrobials felt the process was simple enough that a sharp decline in adherence would be unlikely. The data was brought to the pharmacy and therapeutics committee and it was agreed that the practice should continue after the pharmacy resident coordinating the project left the medical center. This study showed that a pharmacist can follow guideline recommendations for monitoring OPAT and this finding is important because not all hospitals have access to ID physicians or require that a specialist see the patient prior to discharge on OPAT. Most infusion centers, however, do have pharmacists prepare the parenteral antimicrobials for outpatient administration; therefore, this monitoring strategy could be implemented virtually anywhere. The pilot program described here allowed us to test our processes and bring forth a recommendation that the monitoring service be continued.

Our study had several limitations, however. First, we did not have access to laboratory results performed at outlying facilities. This could underestimate adherence to monitoring recommendations, but it was not expected to occur often enough to impact the results. Second, our sample size was limited because we were targeting only patients receiving antimicrobials at two infusion centers located in Springfield, Illinois, and not all locations where OPAT could be administered. However, we feel that the results of this study are applicable to all sites that provide OPAT because monitoring antibiotics is fundamental to optimizing patient care and preventing unnecessary adverse drug events. Third, for phase I of the study we included patients from two infusion centers with different hours of operation (one infusion center was operational for 24 hours; whereas, the other was open only from 8am-5pm). This could impact the type of

parenteral antimicrobial therapy received at each location. Data from two institutions had to be combined because OPAT has not been a common practice without ID physician supervision locally. Lastly, we did not participate in the diagnosis or treatment decisions for the infection, nor did we ascertain whether alternative parenteral or oral therapy would be more appropriate as other studies have evaluated.[7] This data would have been helpful in providing proper antimicrobial stewardship.

With many hospitals facing increasing economic pressures, limited space for patient care, and healthcare reform mandating efficient, evidence-based care, OPAT is an attractive option that will likely increase in popularity. With OPAT services available, stable patients can be discharged safely, leading to bed turnover and cost savings.[3,10] It would be prudent to monitor these patients closely to prevent unnecessary adverse events and possible readmissions. IDSA proposed recommendations for monitoring patients on OPAT almost a decade ago, but little research in this area exists.[4] Additionally, Muldoon et al suggests an OPAT bundle to enhance efficiency and optimize patient care.[9] As part of this bundle, clinical pharmacists can play a vital role to improve patient care by not only supervising drug preparation, but by assessing safety and efficacy of pharmacotherapy through monitoring pertinent laboratory parameters, then adjusting and optimizing doses of antimicrobials under the supervision of a physician familiar with OPAT.

A study by Heintz and colleagues looked at the impact of a multidisciplinary team review of OPAT prior to discharge. This team consisted of an ID physician, ID pharmacist and a case manager. The case manager would consult the pharmacist for further assessment of a patient being discharged on OPAT. The ID pharmacist, under the supervision of the ID physician, made

a variety of interventions focusing on safety, efficacy and simplification of complex regimens. In one year, these interventions led to 228 hospital days being avoided and approximately $366,000 in hospital bed cost savings.[7] Although, this would be an excellent model to follow, it is not feasible at all hospitals. As our results indicated, the routine monitoring of patients on OPAT after discharge is limited. Our study also showed the impact a pharmacist can have on adherence to laboratory monitoring recommendations after a patient is discharged on OPAT. This improvement in adherence could correlate to improved outcomes such as fewer adverse events and hospital readmissions. With pharmacist oversight, dosing of antimicrobials can be better optimized as previously documented.[7] Adverse reactions could also be prevented and managed earlier. For example, nephrotoxicity from aminoglycosides or vancomycin can be prevented through vigilant monitoring and prescribing physicians can be alerted to any abnormal laboratory results before significant harm occurs in the patient. Therefore, pharmacists can have a significant role to play as part of OPAT to optimize patient care. This study serves as a benchmark for pharmacists, as drug therapy experts, to work in tandem with prescribers to manage patients on OPAT.

Conclusion:

Infectious diseases physicians are more likely to monitor patients receiving OPAT at infusion centers according to guidelines compared to non-ID prescribers. Attainment of goal serum drug concentrations was also higher in these patients, but this was not statistically significant in our sample. There is an opportunity for improvement in both groups, and implementing pharmacist oversight can improve adherence to laboratory monitoring recommendations for patients that do not have ID physician supervision. Future studies should evaluate whether pharmacists can

improve care for all OPAT patients and confirm if achievement of guideline recommendations provides better patient outcomes.

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Table 1: Recommendations for laboratory monitoring of OPAT[4,20,21]

Antimicrobial agent	CBC[a] (no. of times/week)	Renal function tests [b] (no. of times/week)	Potassium level (no. of times/week)	Liver enzyme tests (no. of times/week)	Others
Aminoglycosides (gentamicin, tobramycin, amikacin)	Once	Twice	-	-	-Troughs as clinically indicated (if at steady state, can obtain q5-7 days) -Clinical monitoring for vestibular and hearing dysfunction at each visit
Beta-lactams (penicillins, cephalosporins, aztreonam, carbapenems)	Once	Once	-	-[c]	
Antipseudomonal penicillins	Once	Once	Once	-	
Clindamycin	Once	Once		Once	
Daptomycin	Once	Once		Once	CPK at least weekly
Fluoroquinolones	-	-	-	Once	
Linezolid	Once	-	-		
Pentamidine	Twice	Twice	Twice	Twice	Blood glucose level daily; chemistry profile twice per week
Quinupristin-dalfopristin	-	-	-	Once	Monitor for arthralgias
Telavancin[d]	Once	Once	Once	-	Prior to use, women of childbearing potential should have a serum pregnancy test
Tigecycline[d]	Once	-	-	Once	
Trimethoprim-sulfamethoxazole	Once	Once	Once	-	
Vancomycin	Once	Once	-	-	Troughs as clinically indicated (if at steady state, can obtain q5-7 days)
Antifungals					
Amphotericin B, including lipid formulations	Once	Twice	Twice	Once	Magnesium levels once per week
Azole antifungals	Once	Once	-	Once	
Echinocandins (micafungin, caspofungin, anidulafungin)	-	-	-	Once	
Antivirals					
Acyclovir	Once	Once	-	-	Magnesium levels once per week
Cidofovir	Once	Once	Once	Once	Urinalysis and chemistry profile once per week
Foscarnet	Once	Twice	Twice	Once	Chemistry profile with calcium and magnesium levels once per week
Ganciclovir	Twice	Once	-	-	

a. CBC = Complete Blood Count, including platelets and a differential count of leukocytes
b. Renal function tests may include serum creatinine, blood urea nitrogen levels or urinalysis
c. Weekly liver enzyme tests with oxacillin, nafcillin and carbapenems
d. Telavancin and tigecycline monitoring was based on FDA-approved prescribing information

Table 2: Clinical and Microbiologic Indications for OPAT by Prescriber

Non-ID Physician Patients, N=39		**ID Physician Patients, N=60**	
Infection	**n (%)**	**Infection**	**n (%)**
UTI	21 (46.7)	SSTI	20 (32.8)
SSTI	9 (20.0)	UTI	12 (19.7)
Bacteremia	6 (13.3)	Bacteremia	8 (13.1)
HCAP	4 (8.9)	IAI	6 (9.8)
CAP	3 (6.7)	Osteomyelitis or PJI	5 (8.2)
Osteomyelitis	1 (2.2)	Endocarditis	2 (3.3)
Chronic sinusitis	1 (2.2)	HCAP	2 (3.3)
		PJI	2 (3.3)
		Chronic sinusitis	2 (3.3)
		Meningitis	1 (1.6)
		Syphilis	1 (1.6)
Microbiology results	**n (%)**	**Microbiology results**	**n (%)**
Culture negative	14 (29.8)	Culture negative	26 (36.6)
Escherichia coli	9 (19.1)	MRSA	10 (14.1)
Pseudomonas aeruginosa	6 (12.8)	*Escherichia coli*	6 (8.5)
Klebsiella pneumoniae	5 (10.6)	MSSA	5 (7.0)
MRSA	4 (8.5)	Anaerobes*	5 (7.0)
Enterobacter cloacae	2 (4.3)	Coagulase negative Staphylococcus spp.	3 (4.2)
Viridans Streptococcus	1 (2.1)	Viridans Streptococcus	3 (4.2)
Streptococcus pneumoniae	1 (2.1)	Microaerophilic Streptococcus	2 (2.8)
Serratia marcescens	1 (2.1)	*Proteus mirabilis*	2 (2.8)
MSSA	1 (2.1)	*Pseudomonas aeruginosa*	2 (2.8)
Morganella morganii	1 (2.1)	*Streptococcus pneumoniae*	1 (1.4)
Klebsiella oxytoca	1 (2.1)	*Citrobacter koseri*	1 (1.4)
Group B Streptococcus	1 (2.1)	*Morganella morganii*	1 (1.4)
		Aerococcus urinae	1 (1.4)
		Citrobacter freundii	1 (1.4)
		Enterococcus faecalis	1 (1.4)
		Klebsiella pneumoniae	1 (1.4)

Note: Values add up to greater than 100% because some patients had more than one infection
Key: MRSA: methicillin resistant *Staphylococcus aureus*; MSSA: methicillin susceptible *Staphylococcus aureus*; SSTI: skin or tissue infections; UTI: urinary tract infections; HCAP: health-care associated pneumonia; CAP: community acquired pneumonia; IAI: intra-abdominal infections; PJI: prosthetic joint infections; *Anaerobes: *Peptostreptococcus spp*. (n=2), *Bacteroides fragilis* (n=1), *Clostridium spp*.,non-difficile (n=1), *Prevotella spp*. (n=1)

Table 3: Antibacterials administered based on physician supervision

Non-ID physician		ID physician	
Drug	**n (%)**	**Drug**	**n (%)**
Ceftriaxone	11 (25.6)	Vancomycin	13 (19.7)
Cefepime	8 (18.6)	Daptomycin	12 (18.2)
Gentamicin	7 (16.3)	Ertapenem	11 (16.7)
Ertapenem	5 (11.6)	Ceftriaxone	8 (12.1)
Vancomycin	5 (11.6)	Cefepime	7 (10.6)
Tobramycin	2 (4.7)	Gentamicin	7 (10.6)
Daptomycin	2 (4.7)	Tobramycin	3 (4.5)
Linezolid	1 (2.3)	Benzathine Penicillin G	1 (1.5)
Azithromycin	1 (2.3)	Ceftazidime	1 (1.5)
Meropenem	1 (2.3)	Tigecycline	1 (1.5)
		Linezolid	1 (1.5)
		Azithromycin	1 (1.5)

Table 4: Weekly laboratory parameters not ordered as recommended by guidelines

Non ID physicians

Antimicrobial agent (N)	Complete blood count (n)	Renal function tests (n)	Liver enzyme tests (n)	CPK (n)
Ceftriaxone (11)	5 (45%)	5 (45%)	7 (64%)	-
Gentamicin (7)	6 (86%)	4 (57%)	-	-
Tobramycin (2)	1 (50%)	1 (50%)	-	-
Ertapenem (5)	1 (20%)	1 (20%)	2 (40%)	-
Cefepime (8)	4 (50%)	4 (50%)	-	-
Daptomycin (2)	-	-	-	2 (100%)
Vancomycin (5)	2 (40%)	1 (20%)	-	-
Meropenem (1)	1 (100%)	1 (100%)	1 (100%)	-

ID physicians

Antimicrobial agent (N)	Complete blood count (n)	Renal function tests (n)	Liver enzyme tests (n)	CPK (n)
Ceftriaxone (8)	4 (50%)	4 (50%)	4 (50%)	-
Tobramycin (3)	1 (33%)	1 (33%)	-	-
Ertapenem (11)	-	-	2 (18%)	-
Daptomycin (12)	3 (25%)	3 (25%)	3 (25%)	6 (50%)
Vancomycin (13)	5 (38%)	5 (38%)	-	-

Appendix A: Goals for Serum Drug Concentrations

1. Vancomycin[13,14]
    a. Severe infections (e.g. meningitis, pneumonia, endocarditis, bacteremia, severe soft tissue infection or osteomyelitis): trough between 15-20 mcg/mL
    b. Mild to moderate skin and soft tissue or urinary tract infection (after ruling out systemic disease): trough between 10-15 mcg/mL

2. Aminoglycosides – conventional dosing[15,16]
    a. Peak:
        i. Severe infections (e.g. bacteremia, neutropenic fever, pneumonia):
            a. Gentamicin and tobramycin: 8-12 mcg/mL
            b. Amikacin: 25-40 mcg/mL
        ii. Mild to moderate infections (e.g. pyelonephritis, urinary tract infections):
            a. Gentamicin and tobramycin: 5-8 mcg/mL
            b. Amikacin: 15-25 mcg/mL
        iii. Synergy (gentamicin only) for gram positive organisms: 3-5 mcg/mL
    b. Trough (gentamicin and tobramycin):
        i. Severe infections:
            a. Gentamicin and tobramycin: <2mcg/mL
            b. Amikacin: <10mcg/mL
        ii. Mild to moderate infections and synergy (gentamicin only) for gram positive organisms:
            a. Gentamicin and tobramycin: <1mcg/mL
            b. Amikacin: <10mcg/mL

3. Aminoglycosides – once-daily dosing[16-19]
    a. Trough (gentamicin, tobramycin and amikacin): <1mcg/mL
    b. 16-18 hours post-infusion serum aminoglycoside concentration:[17,18]
        i. Gentamicin and tobramycin: < 2 mcg/mL
        ii. Amikacin: 2.5 – 5 mcg/mL
    c. 6-14 hours post-infusion serum aminoglycoside concentration
        i. Follow nomogram, as suggested by Nicolau et al[19]