



Comparison of Outpatient Antibiotic Therapy (OPAT) Use of Daptomycin, Linezolid, Quinupristin/ Dalfopristin, Tigecycline, and Vancomycin in Physician-Operated Infusion Centers (POICs)

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Abstract (revised)

Background: Use of OPAT in POICs has become increasingly important in treating multiple infections, including methicillin-resistant *Staphylococcus aureus* (MRSA). In POICs, the predominant organism treated continues to be MRSA. We evaluated the use and diagnoses treated of the 5 agents effective in treating MRSA in 39 Pharmacies in POICs, managed by Healix, in 14 states, including AK, DE, GA, FL, IL, IN, KS, MO, NE, OH, SC, TN, TX, WI. **Methods:** A multicenter retrospective evaluation of 5,017 patients was performed of all diagnoses and uses treated with V, D, L, Q and T over a 12-month period from 1/1/07 through 12/31/07 in 39 Pharmacies in POICs. Stability and compatibility was considered. D was dispensed in an elastomeric, self-infusible device (ED), V in either ED or bags for ambulatory pumps, and L, Q, T in conventional gravity mini-bags. **Results:** Of 6,318 records reviewed, 5,017 patients were further evaluable representing 5,522 treatment courses of the five agents. The majority of infections (40%) were skin and skin structure infections (SSI), followed by 23% bone and cartilage, primarily osteomyelitis. The Other category (18%) included 3% genitourinary, 4% respiratory infections. Additional infections are noted in the table. V was the predominantly utilized antibiotic (70%), followed by D (27%), 1% for T and L and <1% for Q.

Infection	V	D	T	L	Q	Total Uses
Bone, Cartilage	1142		9	6	1	1503 (23)
Catheter, Device	193	46	1	1		251 (4)
Endocarditis	31	38				138 (2)
Post Operative	308	92	6	1		416 (7)
Septicemia	269	93	3	5		388 (6)
SSSI	1581	722	27	8		2425 (40)
Other	903	255	33	16		1197 (19)
Total	3892(70%)	1514 (27%)	79 (1%)	40 (1%)	1 (<1%)	5526

Conclusions: Among the antibiotics utilized in our review period, V remained the first-line antibiotic for use in POICs when compared with D, L, Q and T. Longer extended stability, more experience, and lower costs may all have contributed. Additional studies will be conducted to further investigate and assess pharmacoeconomics and clinical outcomes in POICs.

Introduction

The use of outpatient parenteral antimicrobial therapy (OPAT) has increased rapidly over the last several decades. Concurrent with this has been the emergence of MRSA in both the institutional and community settings at an alarming rate. A great segment of sites that provide OPAT are run as extensions of physician practices namely physician operated infusion centers (POICs).

Many factors affect the use of intravenous agents in POICs. Selection criteria for antimicrobial agents in such ambulatory models differs from those used in the inpatient setting. POICs provide intravenous medications to patients for in-office administration and those which have dispensing capabilities provide doses to patients for self-administration at home, thus expanding physicians' choice in their antimicrobial armamentariums.

In addition to safety, efficacy and microbial coverage, other factors such as ease of self-administration along with the agent's physical and chemical characteristics (i.e., drug stability and compatibility with other co-administered agents or devices) have become important criteria for drug selection. Drug self-administration can be provided by gravity, via disposable self-infusible devices or electronic ambulatory pumps. Since stabilities for agents under refrigeration or in room temperature varies, storage capabilities in these two environs must be considered when selecting an antibiotic for home administration. Stability has become even more significant, relative to compounded sterile products since the implementation of the United States Pharmacopeia (USP) Chapter 797 Guidelines in June, 2008, thus shortening expiration dating (beyond use date) for many drugs.

We conducted a retrospective study of 39 POICs to evaluate the use of several antimicrobials used to treat MRSA, to include vancomycin, daptomycin, tigecycline, linezolid and quinupristin/dalfopristin, over a twelve month period, from January 1, 2007 through December 31, 2007. Additionally, we studied the stability (under refrigeration as well as room temperature) characteristics of each of the five agents following compounding.

Methods

Data was retrospectively collected from the pharmacy databases of all patients who received any of the aforementioned agents during the study period.

- Criteria for Collection**
- Patients should have received at least one intravenous dose received in 2007 of one or more of the five above drugs.
- Information Collected:**
- All POIC patients, identified by unique medical record number, who were treated with at least one or more of the five drugs during 2007
 - POIC site and state
 - Patient Demographic information, including age, weight and gender
 - Dosage regimen, length of therapy and the drug delivery device
 - Primary Diagnoses, categorized as follows:
 - Bone, cartilage infections
 - Catheter, device infections
 - Endocarditis
 - Post Operative infections
 - Septicemia
 - Skin and skin structure infections, both complicated and uncomplicated
 - Other, including Respiratory and Genitourinary
 - Drug characteristics including stability and solution compatibility by device
- Data Analysis**
- Other factors were considered for evaluation that could affect selection criteria, including dosing and stability.
 - The presence of additional clinical factors for each drug were evaluated.

Results

Table 1: Demographics

Characteristic	Vancomycin	Daptomycin	Tigecycline	Linezolid	Quinupristin/ Dalfopristin	Total
Gender # (%)						
Female	1708 (44)	704 (46)	49 (82)	24 (60)	-	2485 (45)
Male	2174 (56)	826 (54)	36 (58)	16 (40)	1 (100)	3037 (55)
Mean Age (yrs)*	54	51	49	49	49	53
Weight (kg)†						
Mean	92	87	88	84	81	88
Range	11-249	23-228	45-239	48-159	-	11-249

*based on available data in 4,199 pts
†based on available data in 3,070 pts

Table 2: Infection Type by Drug use

Infection	Vancomycin	Daptomycin	Tigecycline	Linezolid	Quinupristin/ Dalfopristin	Total
Bone, Cartilage	995	251	9	6	1	1302 (23)
Catheter, Device	102	46	1	1	-	210 (4)
Endocarditis	81	38	-	3	-	122 (2)
Genitourinary	105	32	5	2	-	144 (3)
Post Operative	289	92	6	1	-	378 (7)
Respiratory	176	46	8	4	-	244 (6)
Septicemia	142	93	3	5	-	243 (5)
SSSI	1436	722	27	8	-	2193 (40)
Other*	419	158	38	8	-	603 (11)

All Data expressed as: Incidence of drug use (%)
*Other category included infections which could not be classified above, including central nervous system infections, otitis media, and secondary infections
Of all reported drug use incidents, 489 patients received 2 drugs, 12 received 3 drugs and 1 received 4 drugs

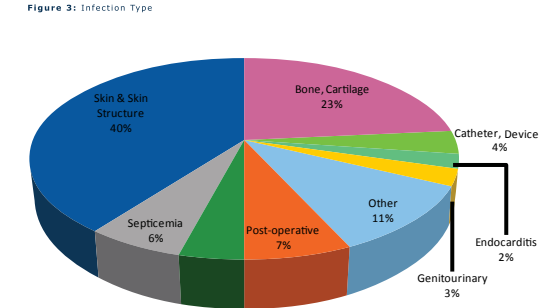


Table 3: Mean Dose Per Day (mg)

Infection	Vancomycin	Daptomycin	Tigecycline	Linezolid	Quinupristin/ Dalfopristin
Bone, Cartilage	1851	482	94	1193	1219
Catheter, Device	1828	459	92	1186	
Endocarditis	1368	455		1069	
Genitourinary	1850	389	92	645	
Post Operative	1958	551	89	892	
Respiratory	1822	430	74	793	
Septicemia	1919	462	89	1318	
SSSI	2019	454	93	1051	
Other	1926	446	97	1123	
Mean Dose per Day	1819	460	92	1062	1219

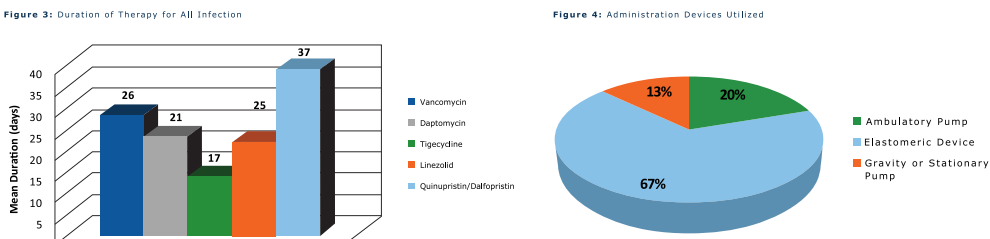
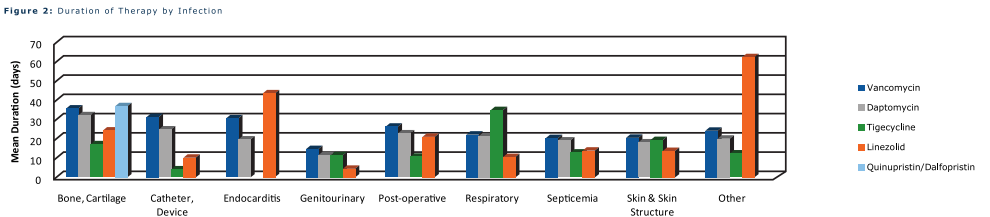
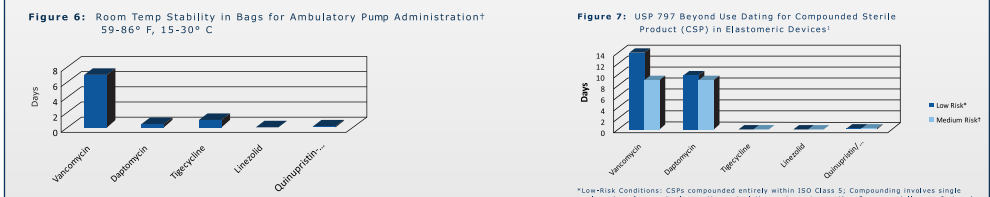


Table 4: Compounded Stability by Drug

Stability	Vancomycin ^{1,2}		Daptomycin ^{3,4}		Tigecycline ⁵		Linezolid ^{6,7}		Quinupristin - Dalfopristin ⁸	
Drug Delivery Device	RT	Refrig	RT	Refrig	RT	Refrig	RT	Refrig	RT	Refrig
ReadyMed [®] Infusion Pumps										
Elastomeric Device	7 d	30 d	12 h	10 d	24 h	45 h	**	12 m *	n/a	n/a
Desktop 5% (CSP)	15d	58d	n/a	n/a	24h	45h	**	12m*	5h	5ah
Elastomeric Device with 0.5% NaCl Solution										
ReadyMed [®] B (Covidien)	48 h	14 d	12 h *	5 d *	n/a	n/a	n/a	n/a	n/a	n/a
Homepump [®] (Flow Corporation)	24h	28d	12h	10d	n/a	n/a	n/a	n/a	5h	5ah

RT = Room Temperature 59-86°F, 15-30°C; Refrig = Refrigerated Temperature 36-46°F, 2-8°C; n/a = Data not available
* Data in original manufacturer's plastic container.
† Expiration date per manufacturer's label; use within 30 days following removal of foil overwrap.
‡ Daptomycin no longer recommended for use in conjunction with ReadyMED elastomeric infusion pumps.



†CDC guidelines recommend replacement of intravenous tubing no more frequently than at 72-hour intervals unless clinically indicated for the prevention of intravascular catheter-related infections.
*Low-Risk Conditions: CSPs compounded entirely within ISO Class 5; Compounding involves single volume transfers or simple aseptic manipulations using not more than 3 commercially manufactured packages of sterile products and not more than 2 entries into any one sterile container.
‡Medium-Risk Conditions: CSPs compounded entirely within ISO Class 5; Multiple individual or small doses of sterile products are combined using complex aseptic manipulations to prepare CSP that will be administered either to multiple patients or to one patient on multiple occasions.

Discussion

- Vancomycin was the predominant antibiotic used among the evaluated POIC population (70%), compared to daptomycin (27%), linezolid (1%), quinupristin/dalfopristin (<1%), and tigecycline (1%).
- Females comprised the majority of vancomycin and daptomycin, whereas males composed the majority of the other groups and use overall.
- SSI diagnoses were the most prevalent in treatment by all agents in POICs (40%), followed by infections of bone and cartilage (23%), post-operative (7%) and those that resulted in septicemia (6%).
- We did not observe any clear trends in terms of dosing regimens for antibiotics or infection types. In support of labeled dosing recommendations, daily vancomycin dosing exceeded that for all other evaluated medications.
- The mean therapy duration for all evaluated drugs was longest for bone cartilage diagnoses, catheter/device diagnoses, and then endocarditis (35 days, 30 days, 28 days, respectively). Genitourinary infections had the shortest mean therapy duration (14 days).
- The majority of devices used (67%) were disposable self-infusable devices with extended compatibility (>7 days refriger) only with vancomycin and daptomycin.
- Vancomycin is the only agent that allows for multiple infusions for up to 72 hours via an electronic ambulatory pump because of greater room temperature stability.
- Tigecycline (reformulated in 2007) can be provided by ambulatory pump for 24 hours only, but is not compatible with elastomeric devices.
- Linezolid and quinupristin/dalfopristin were very infrequently used across all POICs and all diagnoses (1% or less).

Conclusion

- Vancomycin continues to be the most widely utilized OPAT compared to daptomycin, linezolid, quinupristin/dalfopristin and tigecycline across multiple sites and states.
 - Primary factors contributing to differences in uses of the agents are ease of administration, stability and compatibility in administration devices.
 - Even with reformulation of tigecycline, there was essentially little POIC use of this agent. Linezolid and quinupristin/dalfopristin were also rarely used likely due to limited extended drug stability for outpatient administration.
- Additional studies need to be conducted using this significant data pool to assess agent-specific clinical use and pharmacoeconomics of OPAT in the POIC.
- Future agents aimed at treating MRSA must have adequate stability at room temperature and in disposable devices to enable optimized use in outpatient settings.

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