OPAT Complications

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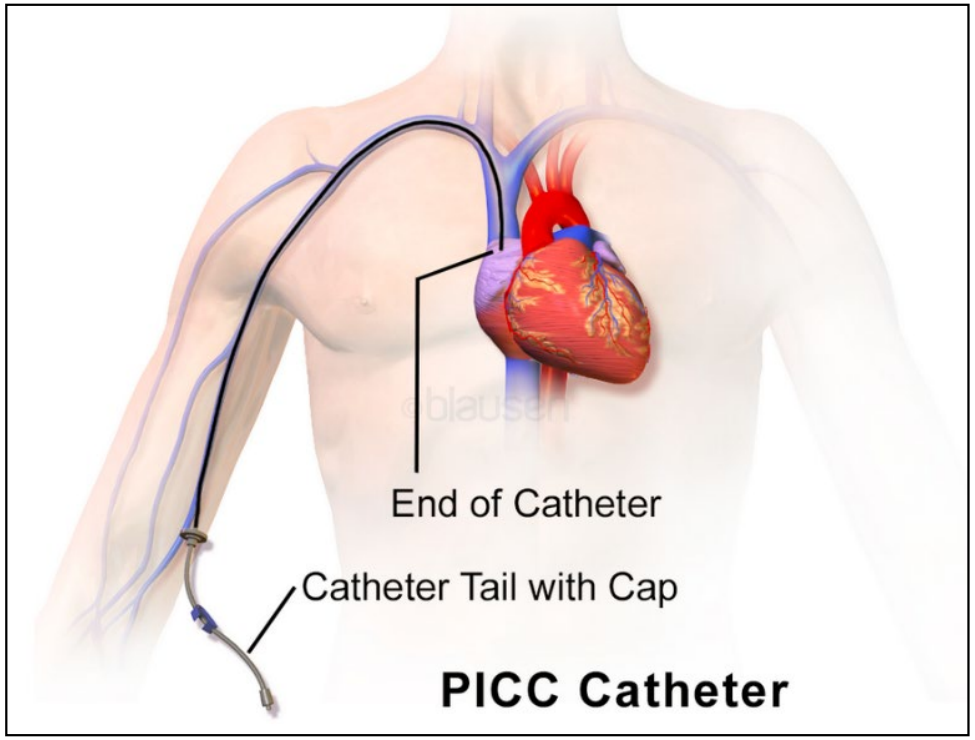
Terminology

- OPAT: outpatient parenteral antimicrobial therapy
- Usually 6-8 weeks
  - Osteomyelitis, septic arthritis, deep SSTI/MSK, epidural abscess/discitis, hardware infections, complicated bacteremia, pneumonia, endocarditis, neurosyphilis
- Peripherally inserted central catheter (PICC) vs. hemodialysis



Chopra *et al.* AmJMed. 2014.

Common OPAT complications?

- Adverse drug event (ADE)
  - Allergic reaction/side effect
  - Toxicities
  - *C. diff*
- Vascular access problem
  - Line clotting/line coming out
  - Deep Vein Thrombosis (DVT)
  - Line abscess
  - Secondary bacteremia/fungemia

Consequences of OPAT complications?

- Allergic reaction management
- Downstream effects of toxicities
- Termination of OPAT duration early
- Change antibiotic: first dose infusion center, cost
- Replace line outpatient
- Anticoagulation
- ED visit, hospital readmission, death

What do the guidelines say about OPAT complications?

Clinical Infectious Diseases

IDSA GUIDELINE

2018 Infectious Diseases Society of America Clinical Practice Guideline for the Management of Outpatient Parenteral Antimicrobial Therapy[a]

Anne H. Norris,[1] Nabin K. Shrestha,[2] Genève M. Allison,[3] Sara C. Keller,[4] Kavita P. Bhavan,[5] John J. Zurlo,[6] Adam L. Hersh,[7] Lisa A. Gorski,[8] John A. Bosso,[9] Mobeen H. Rathore,[10] Antonio Arrieta,[11] Russell M. Petrak,[12] Akshay Shah,[13] Richard B. Brown,[14] Shandra L. Knight,[15] and Craig A. Umscheid[16]

Table 2. Features of Selected Antibacterials Used in Outpatient Parenteral Antibiotic Therapy

Antiinfective	Oral Bioavailability, %[a]	Doses per day[b]	Infusion Time	Delivery Device[c]	Monitoring Frequency[d] (Weekly) CBC-diff	BMP: including K, Cr, BUN	Liver profile: ALT, AST, ALK, Tbil	Most Common Potentially Serious ADRs	Torsades de Pointes Risk[e]	Other Comments
Antibacterials										
Amikacin	NA	1–3	30–60 min depending on dose	Grav, Elas	1	2	…	Nephrotoxicity; ototoxicity		See aminoglycoside monitoring[f]
Ampicillin	50	4–6	3–5 min push or 10–15 min infusion	Grav, EID, IVP	1	1	1	Hypersensitivity including anaphylaxis		Stable once reconstituted for only 3 days; see stability footnote[g]
Ampicillin-sulbactam	NA	3–4	10–15 min push or 15–30 min infusion	Grav, EID, Elas, IVP	1	1	1	Hypersensitivity including anaphylaxis		Stable once reconstituted for only 3 days; see stability footnote[g]
Azithromycin	28–52	1	60 min	Grav	1	…	…		Known	Consider change to po
Aztreonam	NA	2–4	3–5 min push or 20–60 min infusion	Grav, EID, Elas, IVP	1	1	1			Rare cross-allergenicity with other beta-lactams
Cefazolin	NA	3–4	3–5 min push or 30–60 min infusion	Grav, Elas, IVP	1	1	…	Hypersensitivity including anaphylaxis		Dialysis-only dosing possible
Cefepime	NA	2–3	5 min push or 30 min infusion	Grav, Elas, IVP	1	1	…	Hypersensitivity including anaphylaxis		Dialysis-only dosing possible
Cefoxitin	NA	3–4	3–5 min push or 20–30 min infusion	Grav, Elas, IVP	1	1	…	Hypersensitivity including anaphylaxis		
Ceftaroline	NA	2–3	5 min push or 5–60 min	Grav, IVP	1	1	…	Hypersensitivity including anaphylaxis		
Ceftazidime	NA	3	3–5 min push or 15–30 min infusion	Grav, Elas, IVP	1	1	…	Hypersensitivity including anaphylaxis	NA	Dialysis-only dosing possible
Ceftazidime-avibactam	NA	3	120 min	Grav, EID	1	1	…	Hypersensitivity including anaphylaxis		…
Ceftolozane-tazobactam	NA	3	60 min	Grav, EID	1	1	…	Hypersensitivity including anaphylaxis		…
Ceftriaxone	NA	1–2	1–4 min push or 30 min infusion	Grav, Elas, IVP	1	1	1	Hypersensitivity including anaphylaxis		See monitoring footnote[d]
Ciprofloxacin	50–85	2–3	60 min	Grav, Elas	…	…	…	Tendonitis/tendon rupture; peripheral neuropathy	Known	Consider change to po; see monitoring footnote[d]
Clindamycin	90	3–4	10–60 min (not to exceed 30 mg/min)	Grav, Elas	1	1	1			Consider change to po; see monitoring footnote[f]
Colistin	NA	2–4	3–5 min IVP; 30 min for infusion	Grav, IVP	1	2	…	Nephro- and neurotoxicity		Inhaled colistin may be an option for respiratory tract infections
Daptomycin	NA	1	2 min push or 30 min infusion	Grav, Elas, IVP	1	1	…	Myopathy; rhabdomyolysis		Baseline and weekly CK, discontinue if symptomatic and CK >1000 U/L (~5× ULN) or asymptomatic and CK >2000 U/L (~10× ULN); dialysis-only dosing possible
Dalbavancin	NA	Once per week	30 min	Grav	…	…	…	Hypersensitivity including anaphylaxis		Red man syndrome more likely if infusion <30 min; monitoring requirements unknown for treatment duration greater than 2 weeks

OPAT guidelines for monitoring

Norris, *et al*. Clinical Infectious Diseases. 2018.

OPAT guidelines for monitoring

Antinfective	CBC-diff	BMP including K, Cr, BUN	Liver profile: ALT, AST, ALK, Tbil	Most Common Potentially Serious ADRs	Other Comments
Cefepime	1	1	---	Hypersensitivity including anaphylaxis	Dialysis-only dosing available
Amikacin	1	2	---	Nephrotoxicity, ototoxicity	See aminoglycoside dosing*
Nafcillin	1	1	1	Hypersensitivity including anaphylaxis	Central line commonly used because of concern for phlebitis risk

Norris, *et al*. Clinical Infectious Diseases. 2018.

OPAT guidelines

- Remove vascular access device if symptomatic catheter-associated venous thromboembolism occurs?
  - Not if catheter still well-positioned and arm pain/swelling decrease on anticoagulation
- Anticoagulation PPX for next time patient gets catheter?
  - Hasn’t been studied. No recommendation.

Norris, *et al*. Clinical Infectious Diseases. 2018.

OPAT guidelines

- Doesn’t comment on how common these adverse events happen

Norris, *et al*. Clinical Infectious Diseases. 2018.

OPAT guidelines

- When to see Infectious Disease Physician for follow up?
  - No generalized recommendation on frequency or timing

- "The treating physician should dictate the frequency of office visit, giving consideration to patient characteristics, the nature of the infection, the patient's tolerance of and response to therapy, and individual social factors."

Norris, *et al*. Clinical Infectious Diseases. 2018.

OPAT Team

- “In the modern healthcare system, the physician does not work alone. He or she is supported by vascular access teams, social workers, nurses, and pharmacists, all working in collaboration to support the patient. Recognition of the contributions of multiple healthcare professionals and roles has led to the proposal of an OPAT bundle, which identifies several components that require attention when planning an OPAT program.”

Norris, *et al*. Clinical Infectious Diseases. 2018.

How common are OPAT complications?

- Older studies: up to 35% patients [1,2]
- Newer studies: ~50% of patients [3, 4]

1. Hoffman-Terry, *et al*. Am J Med. 1999.
2. Pulcini C*, et al.* Eur J Clin Microbiol Infect Dis. 2008.
3. Keller, *et al*. Open Forum Dis. 2020.
4. Felder*, et al*. South Med J. 2016.

OPAT complications at OHSU

- Oregon Health and Science University
- Retrospective chart review
- OPAT patients treated for orthopedic or neurosurgical infections from August 2008 to May 2010
  - average 40 days OPAT
- Goal: look for risk factors on admission to identify patient at high risk for OPAT complications

Felder, *et al*. South Med J. 2016.

OPAT complications at OHSU

Figure 2: Patient Variables of Interest

Demographics	Comorbidity	Infection Characteristics	Lead Time Factors	OPAT Treatment Factors
Age Sex Race Ethnicity PCP Status Insurance Status Discharge Distance	Cardiovascular Liver Renal Psychiatric Diabetes Immunosuppression Malignancy Alcohol/Drug abuse	Infection Type • General Ortho • Orthopedic Spine • Neurosurgery Microbiology • Single Pathogen • Polymicrobial • Other	Hospital Stay ICU Stay Total OR Time Antibiotic lead time Vascular access lead time	Initial OPAT IV Antibiotic Vascular Access Type OPAT setting

Felder, *et al*. South Med J. 2016.

OPAT complications at OHSU

Table 2: Definition of OPAT Complication

Adverse IV Antibiotic Reaction (AAR)
Either discontinuation of the offending IV antibiotic, or ED Visit, or Hospitalization for IV antibiotic reaction

Vascular Access Problem (VAP)
Either discontinuation of vascular access device, or ED Visit, or Hospitalization for vascular access problem

Failed OPAT Plan (FOP)
Either discontinuation of OPAT, or ED Visit, or Hospitalization for failed OPAT plan

Death During OPAT (all-cause)

Felder, *et al*. South Med J. 2016.

OPAT complications at OHSU

- Mean patient age was 55 years (range 19-87)
- 86% had an orthopedic infection
- 44% were treated with intravenous vancomycin

Felder, *et al*. South Med J. 2016.

OPAT complications at OHSU

- OPAT complications were seen in 45% (152/337) of the cohort
  - Adverse antibiotic reactions (26%)
  - Vascular access problems (14%)
  - Failed OPAT plans (6%)
  - 21% of OPAT complications required hospitalization

Felder, *et al*. South Med J. 2016.

OPAT complications at OHSU

- Univariable analysis for OPAT complication
  - No primary care provider (p=0.008)
  - Comorbid psychiatric disease (p=0.05)
  - Treatment with IV Vancomycin (p=<0.001)

  - Insurance status (p=0.09)
  - Distance from OHSU (p=0.09)
  - Malignancy (p=0.09)
  - Sex (p=0.12)

Conclusion

Felder, *et al*. South Med J. 2016.

OPAT complications in Baltimore

- 2 tertiary care academic medical centers (Johns Hopkins) March 2015 to December 2018
- Goal: derive a risk score for patient at high risk of OPAT adverse outcomes
- Prospective cohort of 664 patients

Keller, *et al.* Open Forum Infect Dis. 2020.

OPAT complications in Baltimore

- Serious adverse events:
  - Serious adverse drug event (ADE): result in a hospital admission, change in antimicrobial agent, early termination of antimicrobial therapy, requiring injected filgastrim, or *C. difficile* infection
  - Serious catheter complication: DVT or Pulmonary Embolus (PE), central line–associated bloodstream infection (CLABSI), or bloodstream infection (BSI)
  - Readmission within 1 month after completion of OPAT
  - Death or infection relapse within 6 months of hospital discharge

Keller, *et al.* Open Forum Infect Dis. 2020.

OPAT complications in Baltimore

- Secondary analysis:
  - Any adverse OPAT outcome that didn't meet definition of "serious"
    - Catheter occlusion requiring tissue plasminogen activator
    - Catheter being inadvertently removed

Keller, *et al.* Open Forum Infect Dis. 2020.

OPAT complications in Baltimore

- 50% experienced a serious adverse outcome (332/668)
  - 16.0% experienced a serious ADE
  - 7.5% experienced a serious catheter complication
  - 24.3% experienced an infection relapse within 6 months of initiating OPAT
  - 32.4% were readmitted while on OPAT (74.9% of these were related to OPAT)
  - 1.4% were deceased within 6 months of initiating OPAT

Keller, *et al.* Open Forum Infect Dis. 2020.

OPAT complications in Baltimore

- 60.2% of patients experienced any adverse OPAT outcome
  - 17.0% had any ADE
  - 20.9% had any catheter complication
  - 28.2% had an ED visit while on OPAT

Keller, *et al.* Open Forum Infect Dis. 2020.

OPAT complications in Baltimore

Serious adverse outcome Risk score = 1 * tunneled CVC + 5* midline catheter + 3* using the catheter for chemotherapy + 2* on OPAT 14-27 days + 2* on OPAT ≥28 days + 2* being treated for septic arthritis + 4* Enterococcus + 5 *fungal infection + 3* vancomycin
Any adverse outcome Risk score = –2 * age ≥65 + 1* tunneled CVC + 4* midline + 3* use of the catheter for chemotherapy + 2* on OPAT 14-27 days + 3* on OPAT ≥28 days – 3* discitis, epidural abscess, or vertebral osteomyelitis + 2* treating Enterococcus + 4* treating a fungal infection – 3* treating a viral infection – 2* treating empirically + 4* using vancomycin

Keller, *et al.* Open Forum Infect Dis. 2020.

OPAT complications in Baltimore

Characteristic	Adjusted Odds ratio for any adverse outcome (95% CI)	Comments
Enterococcus	2.01 (0.70-5.72)	More ill patients, higher risk relapse, multiple antimicrobials (also receiving chemotherapy with OR 3.25 (95% CI 0.97–6.60)
Fungal	3.71(0.78-17.7)	
Age >65 years	0.55 (0.32-0.96)**	"It is possible that younger patients may be less compliant with therapy, such as the complicated steps required for OPAT, or have less support at home."
Central venous catheter	1.18 (0.66-2.11)	Anything other than PICC. Supported by OPAT guidelines too. Complicated to remove CVC.
Midline	3.44 (1.10-10.8)	
OPAT >28 days	2.27 (1.26-4.09)	
Vancomycin use	3.41 (1.90-6.14)	They monitor trough, not AUC. Nephrotoxicity.

Keller, *et al.* Open Forum Infect Dis. 2020.

OPAT complications in Baltimore

- Interventions for these patients at high risk?
  - More frequent laboratory testing (not just weekly)
  - More frequent home health and infusion company visits (not just weekly)
  - Close attention to choice of less toxic antimicrobial agents
  - Enhanced training when they are first learning how to access the catheter and perform infusions

Keller, *et al.* Open Forum Infect Dis. 2020.

Other possible interventions on high risk patients

- Closer ID Physician hospital follow up?
- Case-control study to examine the association between outpatient infectious disease (ID) follow-up and risk of 30-day readmission
- N= 384 patients receiving OPAT
- ID outpatient follow-up within 2 weeks was associated with lower risk of all-cause 30-day readmission
  - adjusted odds ratio, 0.33; P = .0001

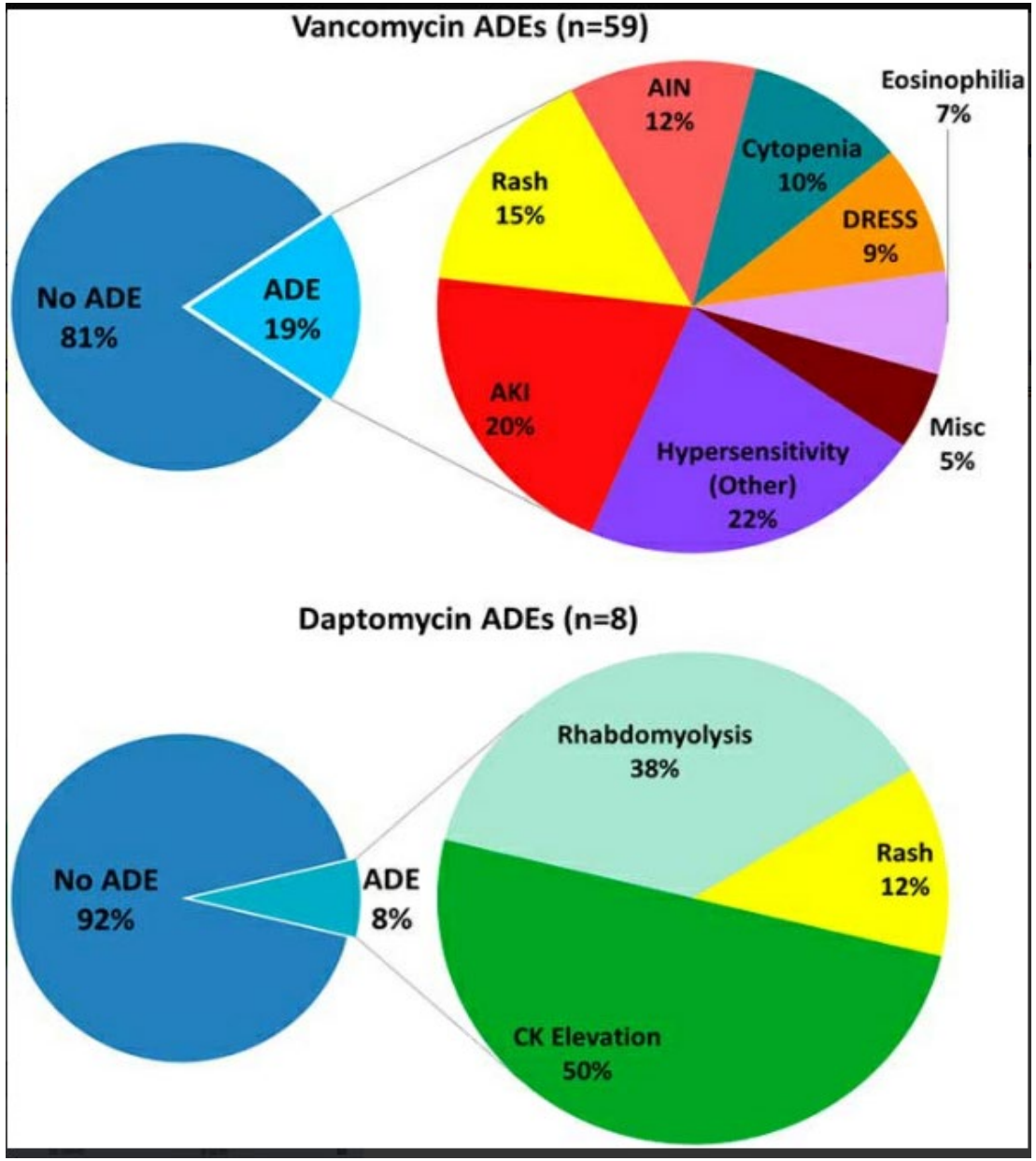
Saini, et al. Clin Infect Dis. 2019.

Future directions? Alternative to Vanc

- Retrospective analysis of adverse events among patients receiving daptomycin vs. vancomycin during OPAT July 2013-September 2016
- 417 patients from Beth Israel Deaconess Medical Center
  - 312 (75%) received vancomycin
  - 105 (25%) received daptomycin

Schrank, et al. ICHE 2018.

OPAT adverse drug events with Vancomycin vs. Daptomycin



Schrank, et al. ICHE 2018.

Future directions?

- Long acting injectables?
  - Dalbavancin and oritavancin
- Guidelines “Promising, are the roles of the long-acting semisynthetic lipoglycopeptides… currently approved narrowly, but offering potential promise because of their very long half-lives and infrequent dosing requirements.”
  - “Role of these expensive agents, particularly in PWID, remains to be defined.”

Norris, *et al*. Clinical Infectious Diseases. 2018.

Future directions?

- Telemedicine?
- OPAT guidelines: “The role of remote-access delivery of OPAT oversight is currently under investigation. The use of telemedicine to support OPAT in geographically isolated locations is appealing but challenged in the United States by reimbursement models and interstate regulatory requirements.”

Norris, *et al*. Clinical Infectious Diseases. 2018.

Conclusions

- ~50% of of OPAT patients have some kind of adverse event
  - High index of suspicion
- OPAT guidelines outline antibiotic lab monitoring and management of vascular thromboembolism
  - Rest of management up to physician/OPAT team judgement
- Some high risk conditions: no primary care provider, comorbid psychiatric disease, vancomycin, *Enterococcal*/fungal, younger patients, midline/CVC, >28 days OPAT
- Interventions to consider in high risk patients: closer physician follow up, more frequent labs, more frequent home health visits, enhanced patient training, choose least toxic agent
- Future directions: daptomycin, dalbavancin/oritavancin, telemedicine?

Conclusions: OPAT is a team sport

- "In the modern healthcare system, the physician does not work alone. **He or she is supported by vascular access teams, social workers, nurses, and pharmacists, all working in collaboration to support the patient**. Recognition of the contributions of multiple healthcare professionals and roles has led to the proposal of an OPAT bundle, which identifies several components that require attention when planning an OPAT program"

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