ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ ΙΑΤΡΙΚΗ ΣΧΟΛΗ

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ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΛΟΙΜΩΞΙΟΛΟΓΙΑ»

2023-24

Παρεντερική κατ΄οίκον αντιμικροβιακή θεραπεία (OPAT)

Σ Τ Ε Λ Ι Ο Σ Α Σ Η Μ Α Κ Ο Π Ο Υ Λ Ο Σ

Αναπλ. Καθηγητής Παθολογίας - Λοιμώξεων

Τμήματος Ιατρικής Πανεπιστημίου Πατρών

Επιστ. Υπευθ. Μονάδος Ειδικών Λοιμώξεων

Πανεπιστημιακό Νοσοκομείο Πατρών

ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΑΤΡΩΝ
UNIVERSITY OF PATRAS

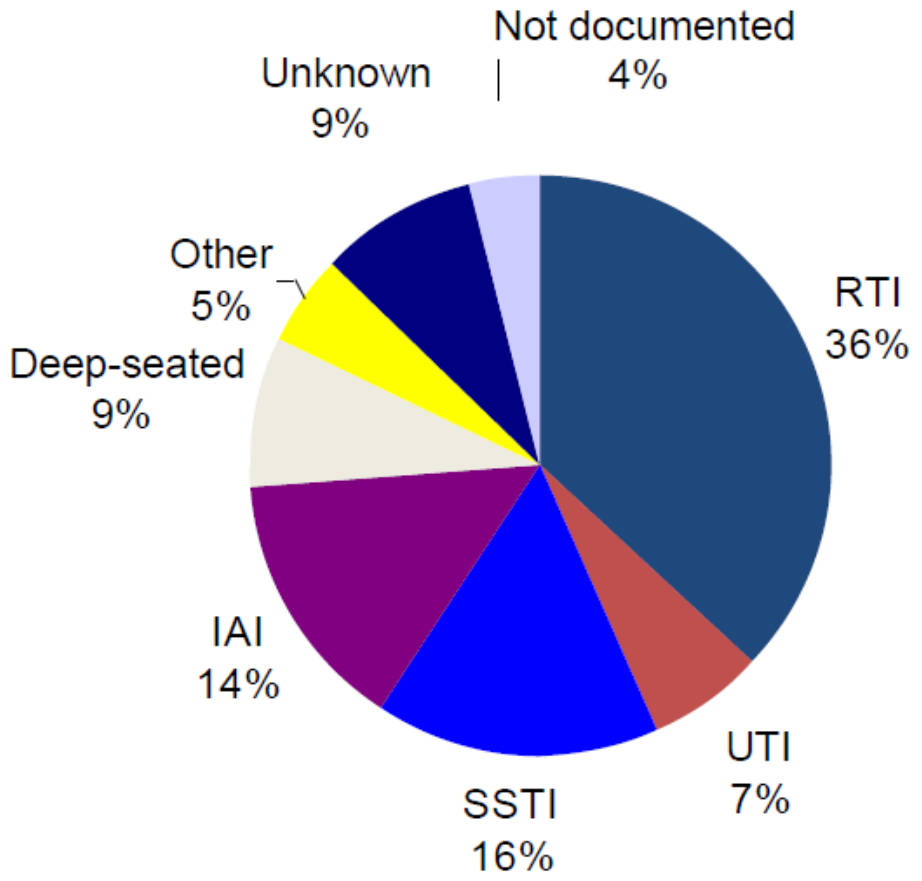
Σύγκρουση συμφερόντων

- Honoraria for presentations: *Pfizer, Gilead, GSK, MSD, Angelini, Norma, Uni-pharma*
- Consultant: *Pfizer, GSK, Angelini, Gilead, Menarini*
- Research Grants: *Pfizer, Gilead*

Intravenous antimicrobial therapy in hospitalized patients

- 1/3 hospital admissions receive antibiotic treatment[1]
- 1/10 receive i.v. antibiotics
  - ~24,000 per million population/yr
- All specialties
  - Integrated part of hospital care
  - Necessitate hospital admission
  - Prolong admission
  - **Some could be discharged if they do not require i.v. antibiotic therapy[2]**

Infection types in acute admissions receiving i.v. antibiotics (n=381)[1]



1. Seaton RA *et al. Int J Antimicrob Agents* 2007;29:693–699
2. McLaughlin C *et al. Q J Med* 2005;98:745–752

Outpatient parenteral antimicrobial therapy (OPAT)

Definition

- the administration of **parenteral antimicrobial therapy (IV or IM) in at least 2 doses** on different days **without intervening hospitalization**

Indications

- infections where requirement for IV antimicrobials is the only reason for admission to or barrier to discharge from hospital

- If no oral agent available or appropriate

IDSA 2018, Clinical Practice Guidelines
Clin Infect Dis 2004;38:1651–1672

Efficacy of OPAT

- The **first study** to show the efficacy of home IV antibiotic administration was published in the **paediatric literature in 1974**, demonstrating safe and effective treatment of chronic broncho-pulmonary infection associated with **cystic fibrosis**

- Since that time numerous studies have detailed the benefits of utilizing OPAT for various infections including
  - ✓ Cellulitis
  - ✓ Osteomyelitis
  - ✓ Septic arthritis
  - ✓ Infected prosthetic joints
  - ✓ Bacteremia
  - ✓ Endocarditis
  - ✓ Pyelonephritis

- OPAT has also been found to be **effective** in virtually all segments of the population, **from children to the elderly**

Pediatrics. 1974;54:358–360, *West J Med*. 1978;128(3):203-206, *Arch Intern Med*. 1979;139(4):413-415, *Ann Intern Med*. 1983;99(3):388-392, *JAMA*. 1982;248(3):336-339, *Am J Med*. 1989;87(3):301-305

Benefits for the patient

- **Quality of life**
  - Family and familiar surroundings
  - Sleep and privacy
  - Nutrition, clothing
  - Mental health
  - Special benefit for children (easily feel threatened in nosocomial environment)

- Reduced risk of **complicating infections** and antimicrobial **resistant** organisms

- Increased education and training in **self-care**
- Lower out-of-pocket costs
- Return to their **daily activities** (work, school)
- Treatment may be adjusted to each patient's lifestyle
- People prefer treated at home rather vs. hospital has been repeatedly demonstrated

Int J Clin Pract Suppl 1998;95:4–8, *Antimicrob Chemother* 2002;49:149–154, *Arch Intern Med*. 2001;161(1):61-65, *Am J Med*. 2000;109(5):378-385, *Prof Nurse*. 1994;10(2):106-111, *Eur J Clin Microbiol Infect Dis*. 1999;18(5):330-334, *Can J Infect Dis*. 2000;11(suppl A):11a-14a

Benefits for the Health System

- Avoided admission
- Reduced length of stay
- More effective use of resources
- freeing up of hospital beds
- Impact on elective and acute work
- Lower rate of health care associated infections
- Specialists managing infection

has been used in many countries for over 30 years and evidence shows its clinical and cost effectiveness

Clin Infect Dis 2004;38:1651–1672, *Am J Med*. 1989;87(3):301-305

Antimicrobial Stewardship

O P A T

Drawbacks??

- potential use of agents with a broader antimicrobial spectrum than necessary due to the logistics of once daily versus multiple daily dosing regimens
- prolongation of intravenous therapy when oral antibiotics would be suitable
- consideration of other aspects of care, including surgical or radiological intervention and determination of clear treatment goals

JAC Antimicrob Resist. 2019;1(2):dlz026

OPAT settings

Models for OPAT service

- ❑Ambulatory patient with attendance at health care facility (infusion center)
  - ❑Hospital clinic/day unit

Infusion Centre
- live in reasonable proximity to the facility
- receiving once daily infusion
- Weekend access available

- ❑Self or caregiver administration

Treatment at Home
- most OPAT programs
- training
- infusions at home by themselves
- with the help of caregivers

- ❑Visiting nurse
  - ❑NHS
  - ❑private

Skilled Nursing Facility (SNF)
- discharging centres have the resources to provide additional oversight

OPAT settings

Hospital-based Infusion Operations (Nottingham)

OPAT settings

Office-based Infusion Operations

OPAT settings

OPAT at home

Self-administered

Visiting nurse

OPAT at home: which patient and how

I. Should patients (or their caregivers) be allowed to self-administer OPAT?
Recommendation
Patients (or their caregivers) should be allowed to self-administer OPAT
(***strong recommendation****, low-quality evidence*)

II. Should patients (or their caregivers) be allowed to self-administer OPAT at home without visiting nurse support?
Recommendation
Patients (or their caregivers) may be allowed to self-administer OPAT at home without visiting nurse support as long as there is a **system in place for effective monitoring** for vascular access complications and antimicrobial adverse events
(weak recommendation, low-quality evidence)

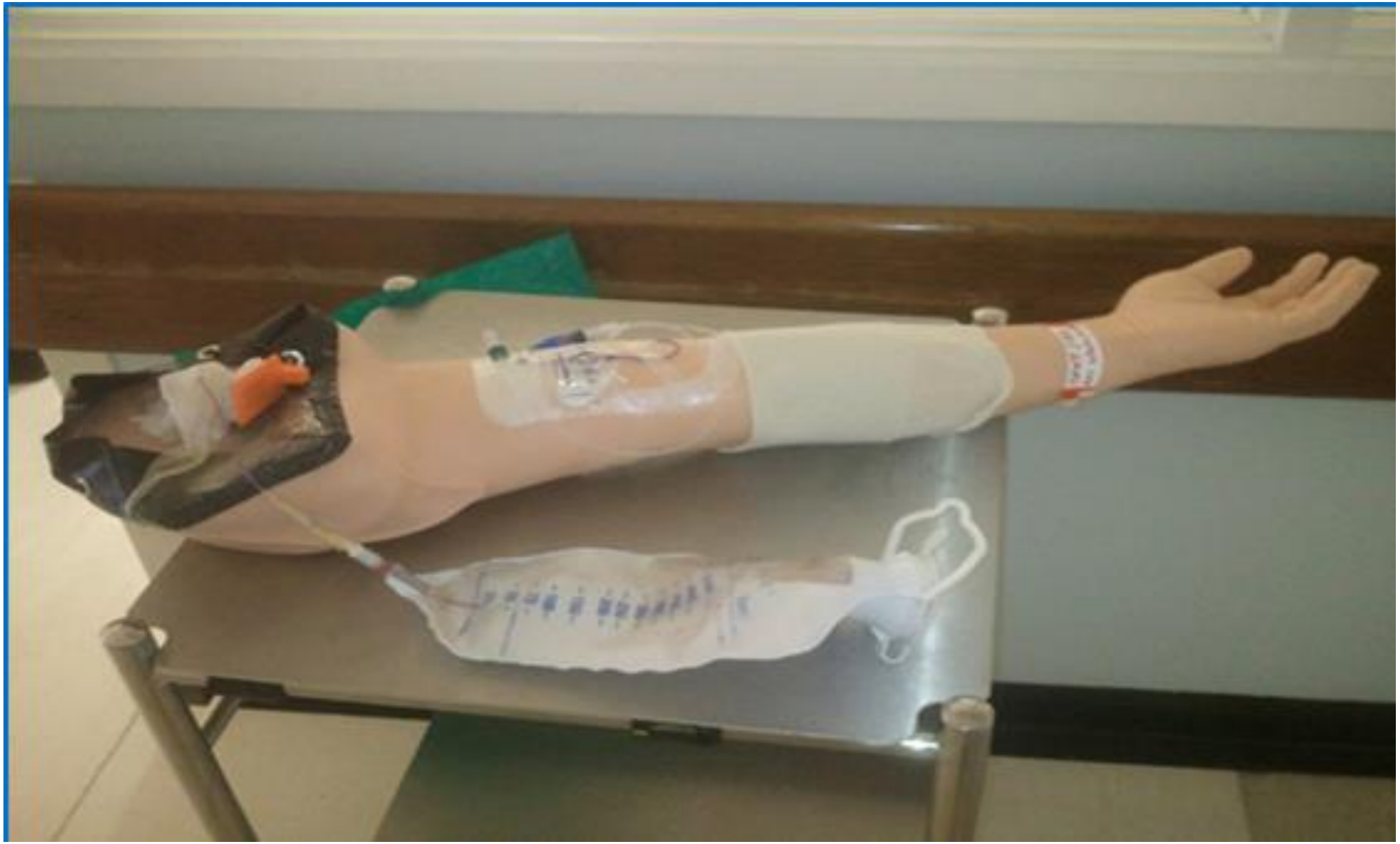
III. Should elderly patients be allowed to be treated with OPAT at home?
Recommendation
Elderly patients should be allowed to be treated with OPAT at home
(***strong recommendation****, low-quality evidence*)

IV. **III. Can persons who inject drugs (PWID) be treated with OPAT at home?**
No recommendation

V. **V. Should infants aged <1 month be treated with OPAT at home?**
No recommendation

IDSA 2018, Clinical Practice Guidelines

Plastic arm training for self administration



Comparison of OPAT settings

There is **no difference** in the rate of **readmissions** or **complications** between self-administered OPAT and Healthcare personnel-administered OPAT

Table 5. Evidence Table: Comparison of Outcomes in Self-Administration of Outpatient Parenteral Antimicrobial Therapy (OPAT) Medications Versus Healthcare Personnel Administration of OPAT Medications

Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Final Evidence Strength
Readmission	No increase	Lower hazard of readmission[a] for S-OPAT (HR 0.36,[b] 95% CI 0.24–0.53, $P < .001$) in 1 study [50] No difference in readmission rates (10.5% vs 12.6%, RR 0.83, 95% CI 0.59–1.14, $P = .30$) in 1 study [49]	2 cohort studies (n = 2059, 2229) [49, 50]	Low	Large effect (+1)	Moderate
Complications[c]	No increase	Similar overall complication rate (24% vs 23%, RR 1.03, 95% CI 0.86–1.24, $P = .80$) in 1 study [49] S-OPAT at home (vs administration by staff in OPAT clinic) was not associated with line infection (OR 0.84, 95% CI NR $P = .72$) or other line events (OR 1.32, 95% CI NR, $P = .22$) in 1 study [51]	2 cohort studies (n = 2059, 2766) [49, 51]	Low	…	Low

J Antimicrob Chemother 2007;60:356–62, Int J Antimicrob Agents 2013;41:569–73, Eur J Clin Microbiol Infect Dis 2012; 31:2611–9, 2018 IDSA Clinical Practice Guideline for the Management of OPAT • CID 2019:68 (1 January)

JAC Antimicrob Resist. 2019;1(2):dlz026

JAC-Antimicrobial Resistance

Updated good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults and children in the UK

Five key components of an OPAT service

1. OPAT team and service structure
2. Patient selection
3. Antimicrobial management and drug delivery
4. Monitoring of the patient during OPAT
5. Outcome monitoring and clinical governance

Good practise recommendations

1. OPAT team and service structure

- In non-inpatient settings, I.V. antibiotics should be delivered within a **formal OPAT** service for patient safety

- **Multidisciplinary Team** with **Medical Lead**
  - **Doctor (**eg Internal Medicine or Surgeon or Cistic fibrosis or Paediatrician with ID interest**)**
  - **Infection specialist or Clinical Microbiologist**
  - **Specialist nurse**
  - **Clinical antimicrobial pharmacist**
- Identified **time for OPAT** members in the job plan

- OPAT teams should develop **local algorithms** for novel treatment strategies

- **Agreed management** plan **between OPAT and referring team (incl other modalities e.g. surgical or radiological intervention for source control)**

- **Communication** between the **OPAT team, the patient's general practitioner, the community team** (when appropriate) and the **referring clinician**

- Written communication should be clear, multidisciplinary and accessible 24/7

Good practise recommendations

2. Patient selection

- OPAT should be part of a comprehensive infection and **antimicrobial stewardship** service
- Responsibility of the **infection specialist** to agree specific **infection-related inclusion and exclusion criteria** for OPAT
- Agreed and documented OPAT **patient suitability criteria** incorporating physical, social and **logistic criteria** (documented for each patient). **Risk factors for treatment failure**, for example, co-morbidities, lifestyle issues, etc should be considered
- **Initial assessment** for OPAT should be performed by a competent member of the OPAT team
- Patients and carers should be **fully informed** about the nature of OPAT and should be given the opportunity to decline or accept this mode of therapy
- All patients who have been assessed as being at risk of **venous thrombosis** as inpatients should be considered for further prophylaxis during OPAT if assessed as having ongoing risk.

Good practise recommendations

3. Antimicrobial management and drug delivery

- **Oral antimicrobial therapy should always be used in preference** to IV therapy where these have equivalent efficacy
- **Treatment plan** is **responsibility of the OPAT infection specialist**, following discussion with the referring clinician
- Antimicrobial choice within OPAT should be subject to **review by the local antimicrobial stewardship programme**
- OPAT team to ensure **correct and continued prescription** of antimicrobials during OPAT
- It is the responsibility of the OPAT team to advise on appropriate **follow-up for toxicity, compliance and outcome**
- Antimicrobial agents should only be used in pumps or elastomeric devices if there are robust drug **stability data**
- OPAT team in collaboration with referral team → Choice of **intravascular access** for each patient (care of IV access)
- **Training of patients or carers** in the administration of intravenous medicines
- The **first dose** of a new antimicrobial should be administered in a **supervised setting**

Good practise recommendations

4. Monitoring of the patient during OPAT

- Pts with **SSTIs should be reviewed daily** by the OPAT team to optimize speed of intravenous to **oral switch**
- **weekly multidisciplinary meeting/virtual ward round** including as a minimum the OPAT specialist nurse, OPAT physician, medical infection specialist and antimicrobial pharmacist,to discuss progress (including safety monitoring and outcome) of patients receiving OPAT
- Pts in excess of 1 week of antimicrobial therapy should be **regularly reviewed by an OPAT member**
- **Blood tests** at **least weekly:** full blood count, renal and liver function, CRP and TDM as required
- **OPAT team responsible for monitoring clinical response** to antimicrobial management and blood investigations, and for reviewing the treatment plan (communication with referring specialist)
- Mechanism in place for **urgent discussion and review** of **emergent clinical problems** during therapy according to clinical need (**clear pathway for 24 h immediate access** to advice/review/admission for OPAT patients)

Good practise recommendations

5. Outcome monitoring and clinical governance

- **Data on OPAT pts recorded prospectively** for service improvement and quality assurance (database)
- Standard **outcome criteria** should be used on completion of intravenous therapy: patient-specific aims of therapy, data on readmissions, death during OPAT, adverse drug reactions, vascular access complications and healthcare-associated infections (Clostridium difficile-associated diarrhoea and Staphylococcus aureus bacteraemia)
- **Risk assessment** and audit of individual processes (particularly new processes) should be undertaken as part of the local clinical governance programme
- **Regular surveys of patient experience** should be undertaken (PROs)
- **Annual review** of the service to ensure **compliance with national recommendations**
- OPAT team members are responsible for personal **continuing professional development**

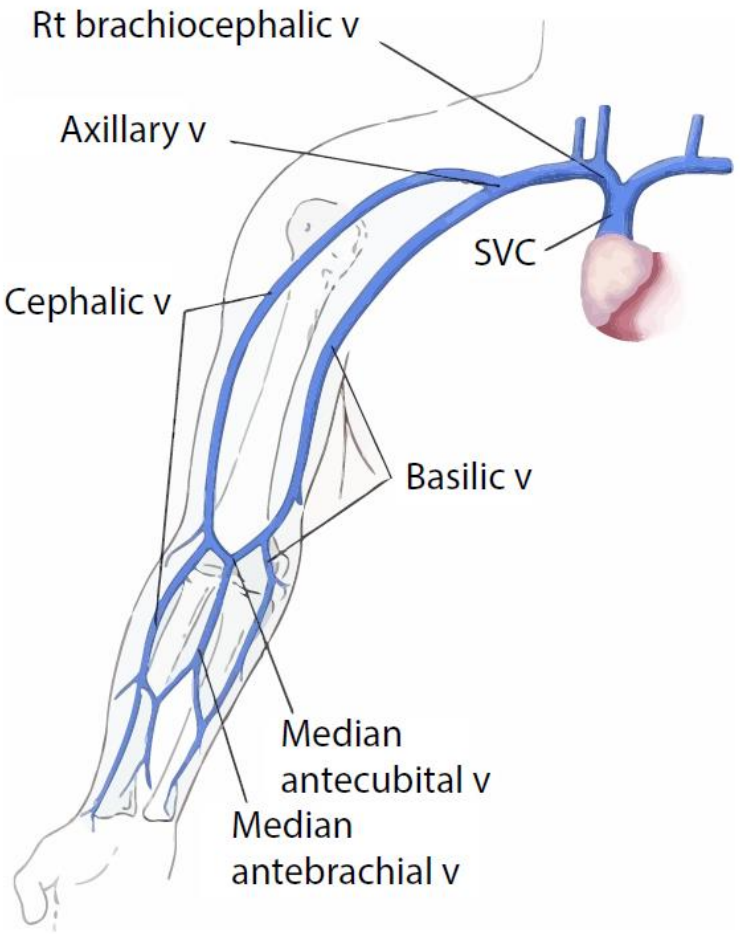
Vascular access

1. Peripheral lines

- **Short peripheral lines** for brief periods
- Brief periods **1 to 7 days**
  - frequent need to replace these lines makes them unwieldy for longer treatment courses

- **A midline catheter** is inserted in a manner similar to that of a PICC line but runs only 8 to 10 cm into the vein
  - this type of catheter is best reserved for shorter courses (**3 to 14 days**) of less irritating antibiotics.

Figure 7.1. Possible veins for midline catheter placement



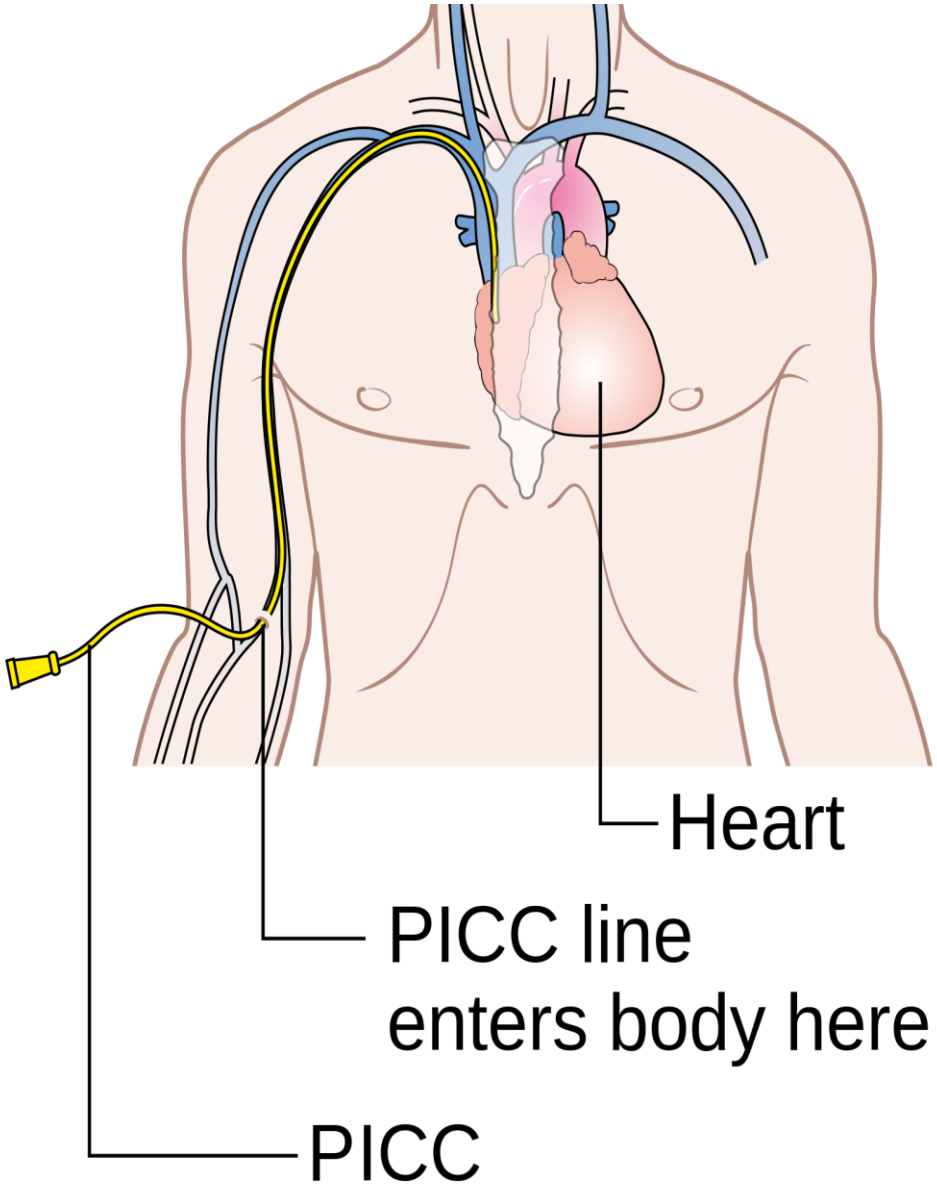
OpenStax College Circulatory Pathways. Version 1.3: June 19, 2013.

Vascular access

2. Central Vascular Access Devices

a. PICC

- ✓ The most common type of CVAD used in OPAT
- ✓ PICC lines are typically inserted into either the cephalic or basilic vein and terminate in the mid to distal superior vena cava (SVC)
- ✓ recommended for infusion therapies for **more than 2 weeks**
- ✓ **hyperosmolar solutions** and **medications with a pH of less than 5 or greater than 9**



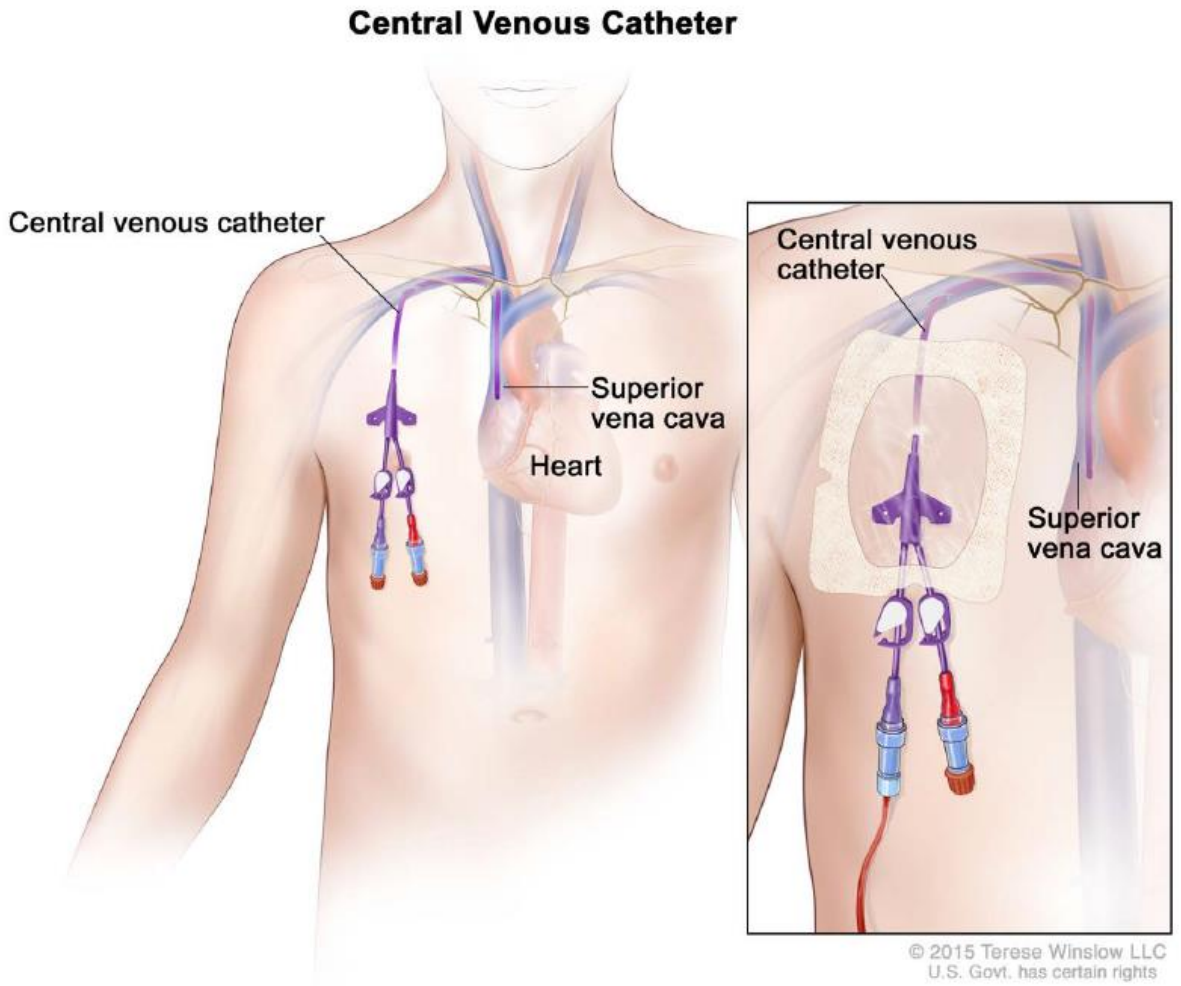
Vascular access

2. Central Vascular Access Devices

b. Hickman catheter

"For patients with advanced CKD requiring OPAT, a t-CVC is recommended rather than a PICC" (strong recommendation, low-quality evidence)

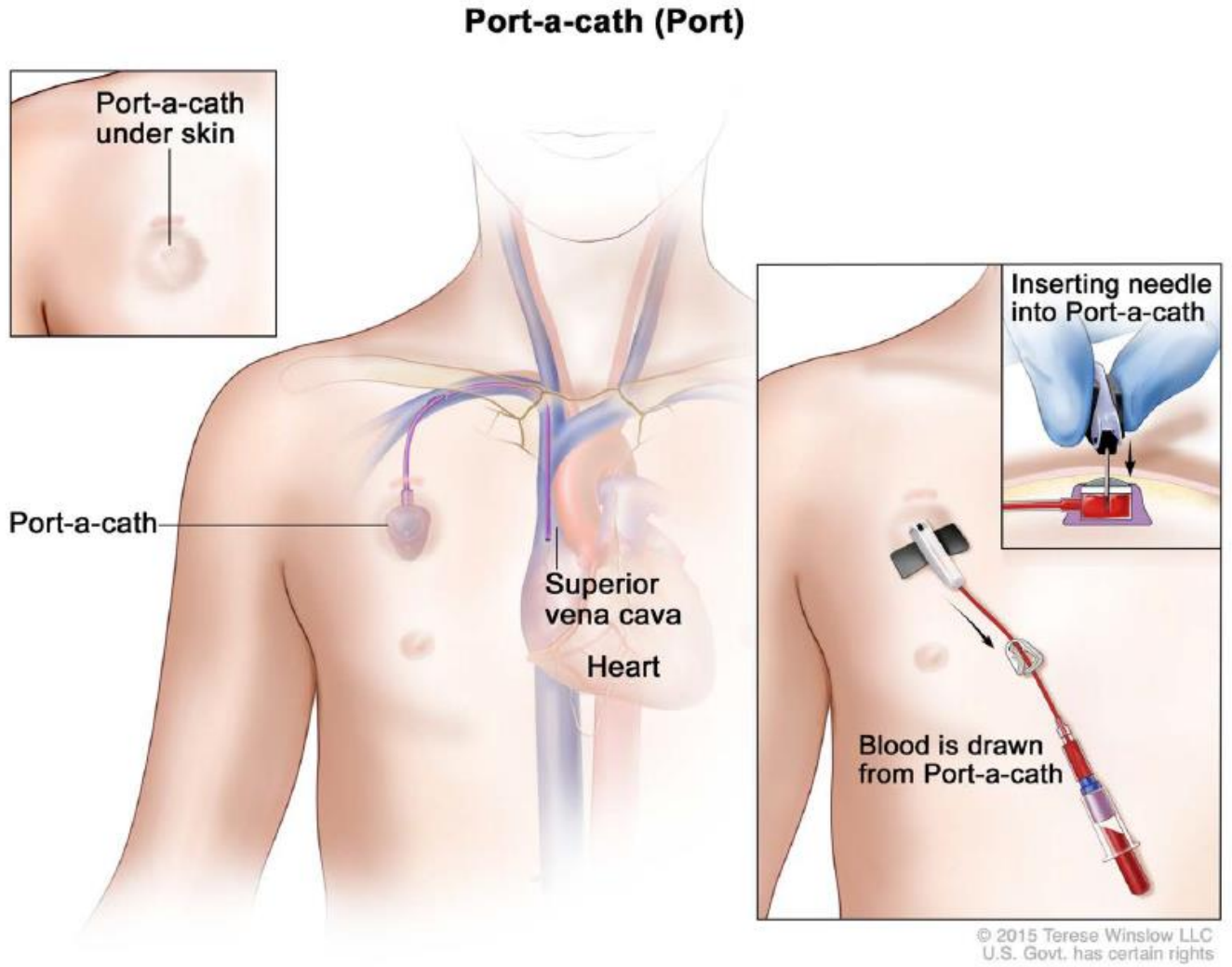
Figure 7.2. Typical placement of a Hickman catheter



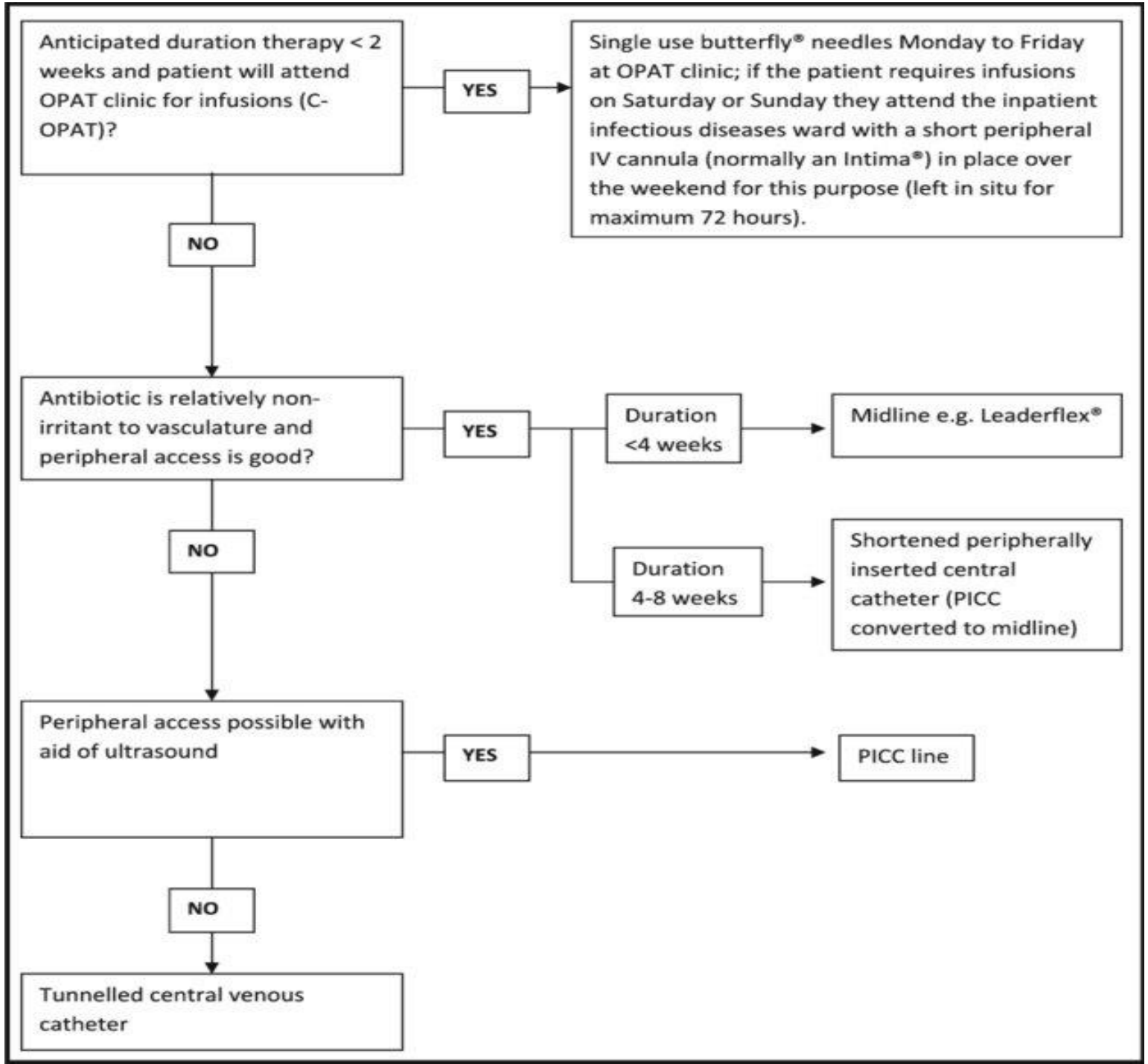
Vascular access

2. Central Vascular Access Devices

c. Port-a-cath



Vascular access



European Journal of Clinical Microbiology 2012;31(10):2611-9

Vascular access

Complications

- It is **not necessary to remove a vascular access** device if CA-VTE develops during OPAT, as long as the catheter remains well positioned and arm pain and swelling decrease with anticoagulation (**weak recommendation**, very low-quality evidence)

- No recommendation can be made regarding the need to treat patients with a history of prior CA-VTE with prophylactic oral anticoagulation while on OPAT

Table 14. Evidence Table: Outcomes for Vascular Access Retention in the Setting of Catheter-Associated Venous Thromboembolism

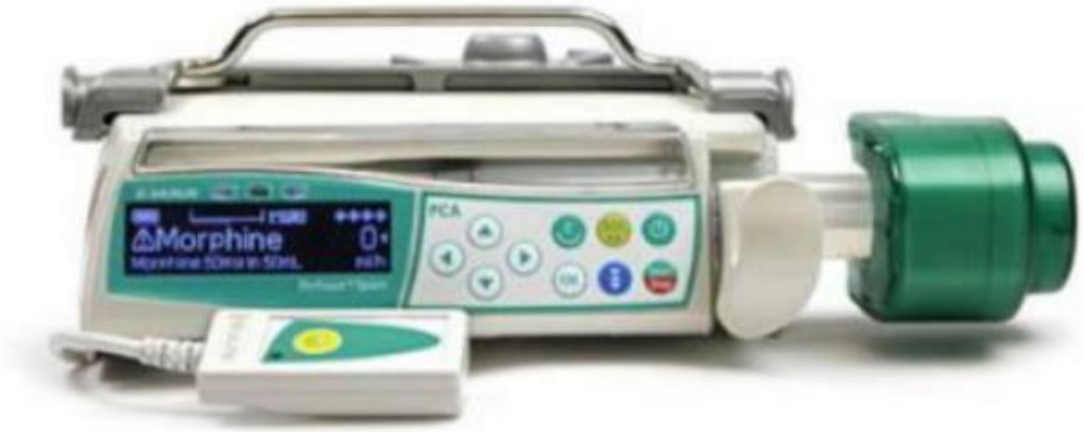
Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Overall Evidence Strength
Preservation of line function	Line function can be preserved	42/42[a] (100%) [101] and 70/70 (100%) [102] of patients had a functional catheter at 3 months	2 clinical trials (N = 74, 70) [101, 102]	Low	Large effect (+1) Indirectness (–1)	Low
Recurrent symptomatic thromboembolism	Insufficient evidence	0/74 (0%) [101] and 1 (1.43%) [102] had recurrent thromboembolism	2 clinical trials (N = 74, 70) [101, 102]	Low	Risk of bias (–1) Indirectness (–1)	Very low
Major bleeding	Insufficient evidence	3 (4%) and 7 (10%) had major bleeding [101, 102]	2 clinical trials (N = 74, 70) [101, 102]	Low	Indirectness (–1)	Very low

2018 IDSA Clinical Practice Guideline for the Management of OPAT • CID 2019:68 (1 January)

Delivery devices

Syringe pump

Figure 7.4. A syringe pump with advanced delivery features that offer safety and accuracy may be required for adult and pediatric care areas where safe delivery of controlled substances are critical

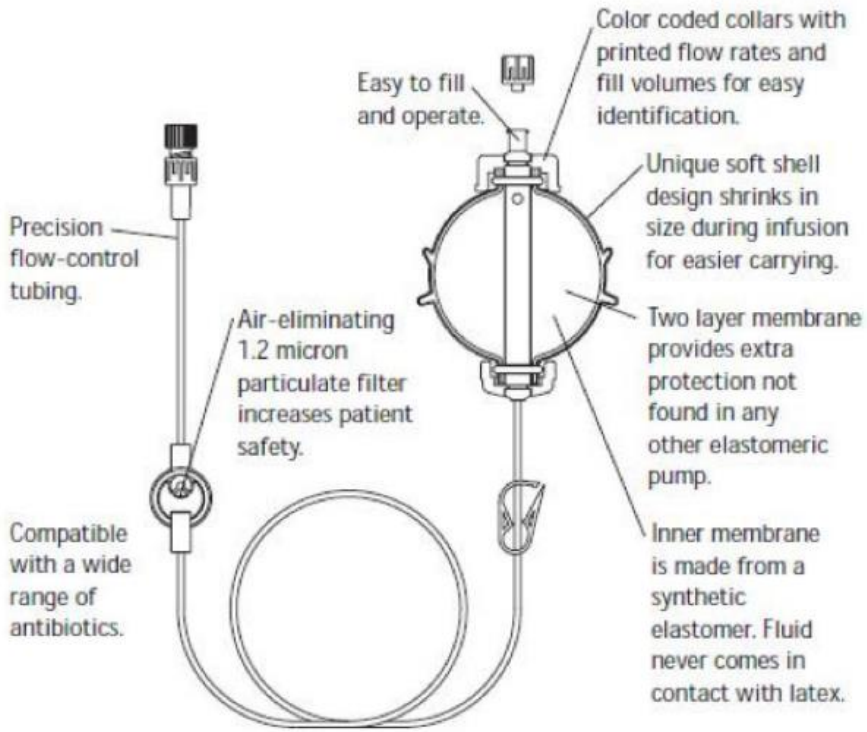


Handbook of Outpatient Parenteral Antimicrobial Therapy for Infectious Diseases, Editors: **Akshay B. Shah and Anne H. Norris** 3rd Edition, *2016 CRG Publishing*

Delivery devices

Elastomeric pump (non-electrical)

Figure 7.5. An elastomeric pump allows mobility for the homecare patient while they're receiving IV infusions. A wide range of flow rates and sizes covers most OPAT infusion protocols.



Handbook of Outpatient Parenteral Antimicrobial Therapy for Infectious Diseases, Editors: **Akshay B. Shah and Anne H. Norris** 3rd Edition, *2016 CRG Publishing*

Delivery devices

Electronic infusion pump

Handbook of Outpatient Parenteral Antimicrobial Therapy for Infectious Diseases, Editors: **Akshay B. Shah and Anne H. Norris** 3rd Edition, *2016 CRG Publishing*

Delivery devices

Comparison of delivery devices

Drug Delivery Method	Description	Advantages	Disadvantages
Bolus or 'Push' [19, 49]	- Slow administration of a drug (usually over 3 to 5 minutes). - Through an IV access device using a syringe only.	- Low tech. - Most commonly used (hospital and community). - Least expensive (supply and administration costs).	- Not all antibiotic regimens can be delivered; some drugs require longer infusion times to avoid infusion related-toxicity or mitigate irritant properties
Non-electrical Pump (elastomeric devices are the most commonly used) [6, 18, 24, 49, 62]	- Controlled rate low pressure self-infusing devices. - Flow rate relies upon mechanical restriction through a narrow-bore tube.	- Disposable. - Portable. - Lightweight. - Relatively inexpensive (costs dependent on medication regimen). - Closed prefilled system resulting in less handling of the drug. - Fixed rates so programming errors are eliminated.	- Device size and relative rates are fixed. - Pharmacy input is required to fill each device. - Antimicrobial selection is limited due to drug stability; for example a drug selected for a 24 hour infusion must be stable at room temperature for 24 hours.
Electrical Pump [18, 19, 49]	- Programmable high pressure electrical devices.	- Controlled delivery - Flexible rates extending the range of drugs that can be used.	- Comparatively expensive. - Patient activity restricted due to battery life and transportability of the pump. - Reliant on trained users to programme the pumps. - Device supply and maintenance can be an issue.

Antimicrobial selection for OPAT

- ✓ **Pharmacokinetics and pharmacodynamics**
- ✓ **Spectrum of activity**
- ✓ **Stability**
- ✓ **Safety**
- ✓ **Laboratory monitoring**

Antimicrobial selection for OPAT

Practical considerations

- some **methods of administration** enhance practicality
  - IV push delivery over 1-2 minutes can be utilized for many antimicrobials, in particular, the cephalosporins (ready-to-use syringes)

- **less frequent administration** schedules enhance convenience and promote compliance
  - reduce catheter-associated complications (eg, hematoma, catheter migration, infections, thromboses)

- **drug stability** is of significant importance
  - Ideally, a reconstituted antimicrobial should be stable in the recommended storage conditions for up to 1 week after mixing

- **shorter courses** of therapy is another strategy to simplify OPAT and reduce antibiotic consumption and complications

Drug stability and important parameter in OPAT: testing program by the British Society of Antimicrobial Chemotherapy

Bacterials*

- Amoxicillin
- Ceftazidime
- Ceftolozane/ Tazobactam
- Flucloxacillin
- Meropenem
- Piperacillin/ Tazobactam
- Temocillin

Virals

- Aciclovir

Bacterials under consideration**

- Cefiderocol
- Ceftazidime / Avibactam
- Fosfomycin
- New agents yet to come to market

* All available at www.e-opat.com

**pending discussion and funding opportunities

Drug stability testing program BSAC

Agent	Concentration range	Buffer	Fridge storage time	Infusion period
Flucloxacillin[1]	10-50 mg/ml	0.3% citrate	13 days	24 hours
Piperacillin/tazobactam[2]	25-90 mg/ml	0.3% citrate	13 days	24 hours
Meropenem[3]	6.25-25 mg/ml	Various	None	6 hours
Ceftazidime[4]	12-25 mg/ml	No buffer	2 days	12 hours
Ceftolozane/tazobactam[5]	5-20 mg/ml	No buffer	8 days	12 hours*
Temocillin[6]	2-25 mg/ml	0.3% citrate	14 days	12 hours*
Aciclovir[7]	0.8-18.75 mg/ml	No buffer		

* 95% limit

http://dx.doi.org/10.1136/ejhpharm-2018-001515; 2. doi: 10.1136/ejhpharm-2020-002340;
3. http://dx.doi.org/10.1136/ejhpharm-2018-001699; 4. BSAC OPAT conference poster 2019;
5. 10.1093/jacamr/dlab141; 6. BSAC Winter conference 2021; 7 ECCMID 2022 P1460

Antimicrobial selection for OPAT

Frequency of administration

Once daily
ceftriaxone
Teicoplanin (or 3/week)
ertapenem
daptomycin
aminoglycosides
levofloxacin
antifungals

OPAT with once daily schemes

Agent	Antimicrobial activity	Dose and administration	Adverse drug reactions (ADRs)	Other comments
Ceftriaxone	Gram-positive (excluding MRSA, Enterococci), Gram-negative (including Salmonellae)	1–2 g OD	Allergy, cholestasis, leucopenia, *Clostridium difficile*	*Clostridium difficile* risk low in OPAT
Teicoplanin	Gram-positive (including MRSA, coagulase negative Staphylococci and Enterococci)	6–10 mg/kg OD or 15–20 mg/kg 3×s/wk*	Fatigue, allergy, myelotoxicity	Prior loading dose for 3 days. TDM required*
Daptomycin	Gram-positive (including MRSA, coagulase-negative Staphylococci and Enterococci)	4–6 mg/kg OD 6–10 mg/kg OD	Myositis (monitor CPK weekly) Eosinophilic pneumonitis (rare)	"Round dose up" to full vial Alternate day dosing when Creat clearance <30 ml/min Interference with some prothrombin time assays
Ertapenem	Gram-positive and resistant Gram negatives	1 g OD	Allergy	No activity against Enterococci or Pseudomonads

Outpatient parenteral antimicrobial therapy with ceftriaxone, a review

Int J Clin Pharm (2012) 34:410–417

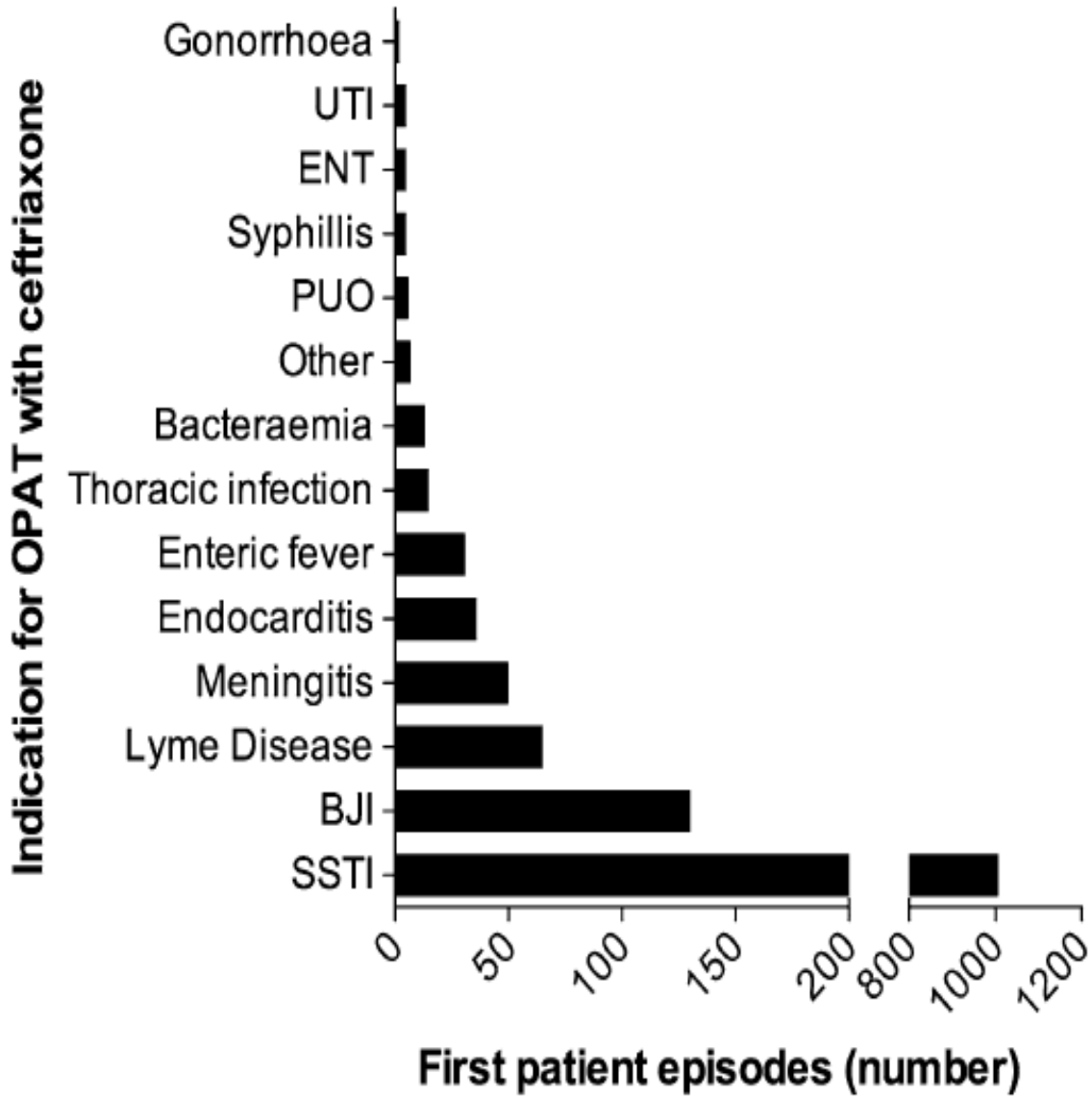


Table 1 Microbiologically-confirmed infections treated with ceftriaxone in the Glasgow OPAT service

Organism	Frequency	%
S. aureus	102	37.1
Beta-haemolytic streptococcus	66	24.0
Streptococcus viridans	25	9.1
Streptococcus pneumoniae	17	6.2
Coliforms (unspecified)	15	5.5
Neisseria meningitidis	9	3.3
Salmonella typhi	9	3.3
Salmonella paratyphi	8	2.9
Other gram negative	5	1.8
Other gram positive	5	1.8
Non-invasive salmonella	4	1.5
Proteus spp.	4	1.5
Serratia spp.	3	1.1
Streptococcus bovis	3	1.1
Total	275	100.0

Included are all first attendances over a 10-year period from 2001 to 2010

Journal of Antimicrobial Chemotherapy (2009) **64**, 181–187
doi:10.1093/jac/dkp147
Advance Access publication 2 May 2009

JAC

Development of teicoplanin dosage guidelines for patients treated within an outpatient parenteral antibiotic therapy (OPAT) programme

Table 4. Teicoplanin loading dose guidelines for thrice-weekly administration

	Ideal body weight (kg) (or total body weight if lower)		
Target	40–59	60–79	>80
10–20 mg/L			
CL_{CR} <60 mL/min	600 mg	800 mg	1000 mg
CL_{CR} ≥60 mL/min	800 mg	800 mg	1000 mg
20–30 mg/L			
CL_{CR} <60 mL/min	1000 mg	1200 mg	1400 mg
CL_{CR} ≥60 mL/min	1200 mg	1400 mg	1600 mg

Doses should be given 24 hourly for the first 3 days.

Table 5. Teicoplanin maintenance dose guidelines for thrice-weekly administration (Monday, Wednesday and Friday)

	CL_{CR}[a] (mL/min)							
Target	<25	25–40	41–54	55–74	75–89	90–104	105–120	>120
10–20 mg/L	200 mg	400 mg	600 mg	800 mg	800 mg	1000 mg	1000 mg	1000 mg
20–30 mg/L	400 mg	600 mg	800 mg	1000 mg	1200 mg	1400 mg	1600 mg	1800 mg

If renal function changes during treatment, doses should be modified according to renal function and, ideally, teicoplanin concentration measurements.
[a]Where CL_{CR} is estimated using the Cockcroft–Gault equation[12] with total body weight.

INFECTIOUS DISEASES, 2017
VOL. 49, NO. 3, 200–207
http://dx.doi.org/10.1080/23744235.2016.1247292

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Safety and efficacy of daptomycin in outpatient parenteral antimicrobial therapy: a prospective and multicenter cohort study (DAPTODOM trial)

Daptomycin is safe and efficacious in outpatients with Gram-positive bacterial infections and can be administered in **2-minute bolus infusion**

Table 4. Comparison of patients receiving daptomycin in 30-minute infusion *versus* 2-minute bolus infusion.

	30-minute infusion, $N = 36$	2-minute bolus, $N = 18$	p
Mean age (SD)	67.3 (16.5)	67.0 (13.5)	.953
Male sex	24 (67%)	12 (67%)	1.000
Median dose of daptomycin, mg/kg (IQR)	5.86 (5–10)	4.67 (4.1–5.4)	.013
Venous access:			.528
• Short peripheral catheter	25 (69%)	13 (72%)	
• Peripherally inserted CVC	4 (11%)	0	
• CVC	5 (14%)	4 (22%)	
• Port-a-cath	2 (6%)	1 (6%)	
Reason for OPAT			.077
• Bacteremia or endocarditis	17 (47%)	3 (17%)	
• Uncomplicated SSTi	16 (44%)	12 (67%)	
• Other	3 (8%)	3 (17%)	
Bacterial isolation*			.192
• *S. aureus*	17 (53%)	7 (44%)	
• *Enterococcus* spp.	2 (6%)	2 (13%)	
• CoNS	3 (9%)	5 (31%)	
• Other	10 (31%)	2 (13%)	
Median (IQR) days of daptomycin treatment during OPAT	11.5 (6.5–16.5)	17.5 (10.0–25.0)	.208
Complications during OPAT**	8 (23%)	2 (11%)	.464
Catheter-related adverse events			1.000
• Phlebitis	1	0	
• Catheter-related bacteremia	0	0	
Adverse effects related to daptomycin			1.000
• Increase in serum creatine kinase levels	1	0	
Readmission due to complications	1	1	1.000

Difficult infections amenable to OPAT

Infective Endocarditis and Cardiac Device infections

- annual incidence of about 3 to 9 cases per 100,000 persons in developed countries
- Staphylococci (aureus increasing), streptococci, and enterococci
- The traditional course of treatment for infective endocarditis is 4 to 6 weeks of IV antibiotic(s)

✓ Several studies have shown that selected patients with infective endocarditis can be safely treated via OPAT
✓ accepted practice for patients to be initially treated in the hospital and then discharged on OPAT once clinically stable
  - ✓ **stable and responding well**
  - ✓ **without signs of heart failure**
  - ✓ **without indications for surgery**
  - ✓ **without uncontrolled extra-cardiac foci**

✓ patients with uncomplicated infective endocarditis caused by viridans group streptococci could be discharged on OPAT after 2 weeks of hospitalization (ceftriaxone once daily)
✓ MRSA endocarditis → daptomycin (once daily)
✓ Enterococcal endocarditis (VRE) → daptomycin or linezolid

Clin Infect Dis. 2001;33(2):203–209, *Postgrad Med J*. 2012;88(1041):377-381

Infective Endocarditis and Cardiac Device infections

Table 3. European Society of Cardiology recommendations on suitability of patients for OPAT treatment of endocarditis 2009.[19]

Phase of treatment	Guidelines for use of OPAT
Critical phase (weeks 0–2)	• Complications occur during this phase • Preferred inpatient treatment during this phase • Consider OPAT if patient has oral streptococci, patient is stable and/or there are no complications
Continuation phase (beyond week 2)	• Consider OPAT if medically stable. • Do not consider OPAT if patient has or has had heart failure, concerning echocardiographic features, neurological signs or renal impairment
Essential for OPAT	• Educate patient and staff • Regular post discharge evaluation (nurses 1/day, physician 1–2/week) • Prefer physician directed program, not home infusion model

OPAT = outpatient parenteral antimicrobial therapy.

J Infect 2009;59:387–93, *Postgrad Med J* 2012;88:377–81, *J Antimicrob Chemother* 2013;68:1650–4, *Eur Heart J* 2009;30:2369–413

Infective Endocarditis and Cardiac Device infections

- **recent cohort reports that OPAT services are successfully treating *S. aureus* and prosthetic valve endocarditis (negative blood cultures, no cardiac failure, no embolic events)**

Table 1. Characteristics of recently published UK OPAT service cohorts.

Cohort	Number of OPAT episodes	Example conditions treated (% OPAT episodes)	Antibiotics used (% OPAT episodes)	IV access device*	Site of delivery
Glasgow[1]	2,638	SSTI (52.7)	Ceftriaxone (58.8)	Butterfly needle (50.1)	C-OPAT (76.6)
		BJI (24.5)	Teicoplanin (26.4)	Short peripheral device (27.7)	S-OPAT (18.7)
		Endocarditis (3.1)	Daptomycin (2.0)	Midline (23.6)	OPAT nurse H-OPAT (3.9)
		Meningitis (2.3)	Ertapenem (1.8)	PICC (1.3)	Primary care nurse H-OPAT (0.1)
		UTI (1.7)	Flucloxacillin (1.1)	Tunnelled central line (5.3)	

Int J Antimicrob Agents 2012;39:407–413.

Outpatient Parenteral Antibiotic Treatment for Infective Endocarditis: A Prospective Cohort Study From the GAMES Cohort

Clinical Infectious Diseases 2019;69:1692

- **2000 consecutive IE** patients in 25 Spanish hospitals (2008–2012)
- **429 patients (21.5%) received OPAT**
- only **21.7% fulfilled IDSA criteria**
- Failing to fulfill IDSA criteria was not a risk factor for mortality or readmission
- OPAT provided **excellent results** despite the use of **broader criteria**

Table 2. Criteria Used to Indicate Outpatient Parenteral Antibiotic Treatment in Infective Endocarditis Patients by GAMES Investigators in the Present Cohort

Type of IE	Recommendation	Indications	Requirements
Native valve	Rapid transfer to OPAT (as of 10 days after admission/surgery)	• IE by any causative agent, except HDTTM[a] • Patients not presenting severe clinical complications • Patients undergoing or not undergoing cardiac surgery	• Negative blood cultures at 72 hours • No severe clinical complications or post-surgical complications • No anticoagulation issues • TEE ruling out severe aortic regurgitation and prosthetic dysfunction
	Postponed transfer (at least 3 weeks after admission/surgery)	• Patients presenting with severe complications at onset • Very fragile patients or patients with severe comorbidities undergoing cardiac surgery or other treatment	• Identical criteria plus: • No severe sequelae or clinical complications • Need for frequent and/or complex cures
Prosthetic valve	Rapid transfer to OPAT (as of 10 days after admission)	• All cases caused by viridans or bovis group streptococci or *Enterococcus faecalis* and • Not undergoing cardiac surgery	• Same as for rapid transfer in NVIE
	Postponed transfer (at least 3 weeks after admission/surgery)	• Cases of IE undergoing cardiac surgery and • Not caused by HDTTM or • Presenting severe complications	• Same as for postponed transfer in NVIE

Where do we stand today? The UK experience

- OPAT was developed in several UK teaching hospitals around **20 years ago** → routine part of patient care in the UK
- expansion in the number of UK OPAT services, with a conservative estimate of **100 formal hospital-based services**
- Reasons for development:
  - **Financial** pressures in NHS
  - Focus on **moving care out of acute care hospitals** (especially in COVID period)
  - **New antimicrobials** with once daily/weekly administration
  - **advances in vascular access** and infusion devices
  - actively promoted as part of the UK government's stewardship initiatives
  - acceptance by patients and healthcare professionals

- traditionally been based in infectious diseases (ID) units → increasingly seeing **OPAT services run by acute or general physicians** with infection input from a clinical microbiologist
- New OPAT services established in acute medicine or emergency department (ED) ambulatory care units or based in the community

- **self-administration or carer administration** is increasingly being used as a cost-efficient alternative to the infusion centre model.
- increase in the **complexity and comorbidity** of patients and in the complexity of the infections: bone and joint infections, endocarditis and other complex deep-seated infections

JAC Antimicrob Resist. 2019;1(2):dlz026

Outpatient parenteral antimicrobial therapy (OPAT) in the UK: findings from the BSAC National Outcomes Registry (2015–19)

J Antimicrob Chemother 2022; 77: 1481–1490

- 57 organizations submitted data on **27.841 patient**
- the first comprehensive national registry published from the UK
- the **largest national data set** published to date
- Wide range of infections and antimicrobials
- Increasing utility of OPAT

Table 1. OPAT patient episodes and treatment days by year and nation (combined adult and paediatric data)

Measure/year	England	Northern Ireland	Scotland	Wales
Patient episodes				
2015	2197	0	65	0
2016	2726	0	0	0
2017	4625	85	366	0
2018	6517	253	1366	0
2019	7817	492	1211	121
OPAT treatment days				
2015	42513	0	1166	0
2016	42841	0	0	0
2017	79670	1226	5997	0
2018	103061	4564	19807	0
2019	114366	8928	16103	2038

Outpatient parenteral antimicrobial therapy (OPAT) in the UK: findings from the BSAC National Outcomes Registry (2015–19)

J Antimicrob Chemother 2022; 77: 1481–1490

Main Infections:

- skin and soft tissue (27.6%),
- bronchiectasis (11.4%),
- urinary tract infections (7.6%)
- Osteomyelitis / diabetic foot infections (5.5%).

Complications:

- vascular-device-related (1.4 per 1000 OPAT d)
- Device infections (0.3 per 1000 OPAT days)
- Other adverse events (1.9 per 1000 OPAT days)
  - Rash, blood dyscrasias, antibiotic-associated diarrhea

Most-used antimicrobials:

- Ceftriaxone
- Teicoplanin
- Ertapenem
- piperacillin/tazobactam
- Ceftazidime
- Daptomycin
- Meropenem

- **OPAT infection outcome (cured/improved) was 92.4%**
- **OPAT outcome (success/partial success) was 90.7%**

OPAT *vs.* inpatient care in the UK: a health economic assessment for six key diagnoses

	Cost per treatment episode											
Condition	**SSTI**		**Complex UTI**		**Orthopaedic -Bone and joint**		**Diabetic foot**		**Bronchiectasis**		**Intra-abdominal**	
Model of care												
Inpatient stay	£2,476	-	£2,104	-	£8,279	-	£8,428	-	£3,269	-	£7,124	-
OPAT - once daily visits	£631	25%	£758	36%	£2,506	30%	£2,671	32%	-	-	£2,312	32%
OPAT - specialist nurse daily home visit	£831	34%	£977	46%	£3,375	41%	£3,556	42%	£1,839	56%	£3,006	42%
OPAT - self-administration - IV bolus	£566	23%	£720	34%	£1,855	22%	£2,006	24%	£1,301	40%	£1,811	25%
OPAT - self-administration - elastomeric device	£611	25%	-	-	£2,394	29%	£2,433	29%	£1,588	49%	£2,952	41%
OPAT - elastomeric device (CIVI; outpatient)	£802	32%	-	-	-	-	-	-	£1,495	46%	£2,807	39%
OPAT - once-off dalbavancin (1g)	£1,266	51%	-	-	-	-	-	-	-	-	-	-

SSTI, skin and soft tissue infections, UTI, urinary tract infections; OPAT, outpatient parenteral antimicrobial therapy; IV, intravenous; CIVI, continuous intravenous infusion;

- **OPAT care is delivered at significantly lower cost (23-56% of equivalent hospital-based cost)**

Dimitrova M, et al. BMJ Open 2021;11:e049733

If the patient is amenable to oral treatment cost is even lower

Table 3 Base case results – oral antimicrobials for orthopaedic and diabetic foot infections

Condition	Orthopaedic/ Bone and joint		Diabetic foot	
Model of care				
Inpatient stay	£8,279		£8,428	
OPAT - Oral 100%	£1,114	13%	£1,089	13%
OPAT - Oral 25%; 75% IV	£2,009	24%	£2,161	26%
OPAT - Oral 50%; 50% IV	£1,710	21%	£1,816	22%
OPAT - Oral 75%; 25% IV	£1,410	17%	£1,470	17%

OPAT, outpatient parenteral antimicrobial therapies; IV, intravenous;

- **Oral cost is 13-26%** of equivalent hospital-based cost for orthopaedic and diabetic foot infections

Dimitrova M, et al. BMJ Open 2021;11:e049733

Evidence of oral *vs.* IV treatment in selected infections

Infection type (population)	Evidence
Bone and joint infections (adults)[131]	Multicentre UK-wide randomized study of oral versus intravenous antibiotic treatment for bone and joint infections (OVIVA). In a heterogeneous group of patients with device-related and non-device-related bone and joint infection who had received <7 days of initial intravenous therapy, randomization to carefully selected oral antibiotic therapy was found to be non-inferior to continuation of intravenous therapy, with 86% success observed in both groups at 1 year. In addition, significantly lower rates of line-related complications and lower treatment costs were observed in the oral treatment group.
Bone and joint infections (children)[132,133]	Increasing evidence that pOPAT is only indicated for a minority of children with bone and joint infections. The majority of patients should be managed with an early intravenous-to-oral switch.
Endocarditis[134]	Clinically improved patients with endocarditis were randomized to early intravenous-to-oral switch or standard therapy with exclusively intravenous antibiotics. Early transition to oral therapy was found to be non-inferior to intravenous therapy. This study population would be typical of the group usually managed via OPAT; therefore, appropriate oral therapy may be a suitable alternative to OPAT for selected low-risk patients.
Intra-abdominal infection[135]	Oral antibiotics had equivalent outcomes and incurred lower costs than intravenous antibiotics following appendicectomy.
Lower urinary tract infections (adults)[136]	Non-inferiority of oral fosfomycin compared with intravenous ertapenem for the treatment of lower urinary tract infections caused by ESBL-producing Enterobacteriaceae.
Pyelonephritis (children)[137]	No difference between oral antibiotics (10–14 days) and intravenous antibiotics (3 days) followed by oral antibiotics (10 days) with respect to duration of fever or subsequent renal damage.
Pleural empyema (children)[138]	Discharge on intravenous antibiotics offers no benefit over discharging children with empyema on oral antibiotics.

JAC Antimicrob Resist. 2019;1(2):dlz026

Before initiating OPAT think again oral options

Antibiotics with >90% oral bioavailability

- Cephalexin
- Clindamycin
- Doxycycline
- Fluconazole
- Levofloxacin
- Linezolid
- Minocycline
- Trimethoprim-sulfamethoxazole
- Voriconazole

Example: for an ABSSTI caused by MRSA, if the severity of the infection is only mild to moderate, oral doxycycline, trimethoprim-sulfamethoxazole, levofloxacin, or clindamycin may be reasonable alternatives

Early switch to oral – Early discharge (cSSTI)

Early switch to oral

- Intravenous antibiotics for more than 24h
- Stable clinical infection or clinical improvement
- Afebrile/temperature of less than 38 C for more than 24h
- WBC count not less than 4.000/ml or more than 12.000/ml

- Absence of unexplained tachycardia
- SBP of at least 100mmHg

- Patient tolerates p.o. fluids/diet (able for p.o. treatment)
- Bacteria susceptible to p.o. treatment (if microbiological cultures available)

(3 – 5 days)

Early discharge

- All key early switch eligibility criteria listed above
- No other reason to stay in hospital except for infection management

- Stable mental status / Stable comorbid illness / Stable social situation

Bassetti et al, Curr Opin Infect Dis 2018, 31:163–169

Barriers for OPAT implementation (The Greek paradigm)

Barrier	Hospitals who use OPAT (N=53)		Hospitals who do not use OPAT (N=14)	
	n	%	n	%
Absence of outpatient reimbursement of certain antimicrobials (e.g. ceftarolin and tigecyclin)	40	75%	9	64%
Complexity for the patient of purchasing and reimbursement of antimicrobials in community pharmacies (no unit-dose, delayed approval of the certificate for reimbursement, …)	39	74%	5	36%
High cost of outpatient therapy for the patient	30	57%	5	36%
Lack of guidelines in the hospital for good practice of OPAT	27	51%	10	71%
Insufficient knowledge of the health care practitioners (home nurse, general practitioner, …) about the procedures of home treatment	26	49%	8	57%
Legal prohibition of delivery of certain medicines and medical devices by the hospital pharmacy	26	49%	3	21%
Lack of experience with OPAT	25	47%	7	50%
Concerns about the safety of home parenteral administration (hygiene, preparation …)	24	45%	7	50%
Difficulty of monitoring at home (eg. kidney function, blood level of the medicine, complications, adverse events, …)	19	36%	5	36%
Insufficient transition care with the general practitioner and home nurse	7	13%	4	29%
Refusal of the patient for outpatient therapy	4	8%	3	21%

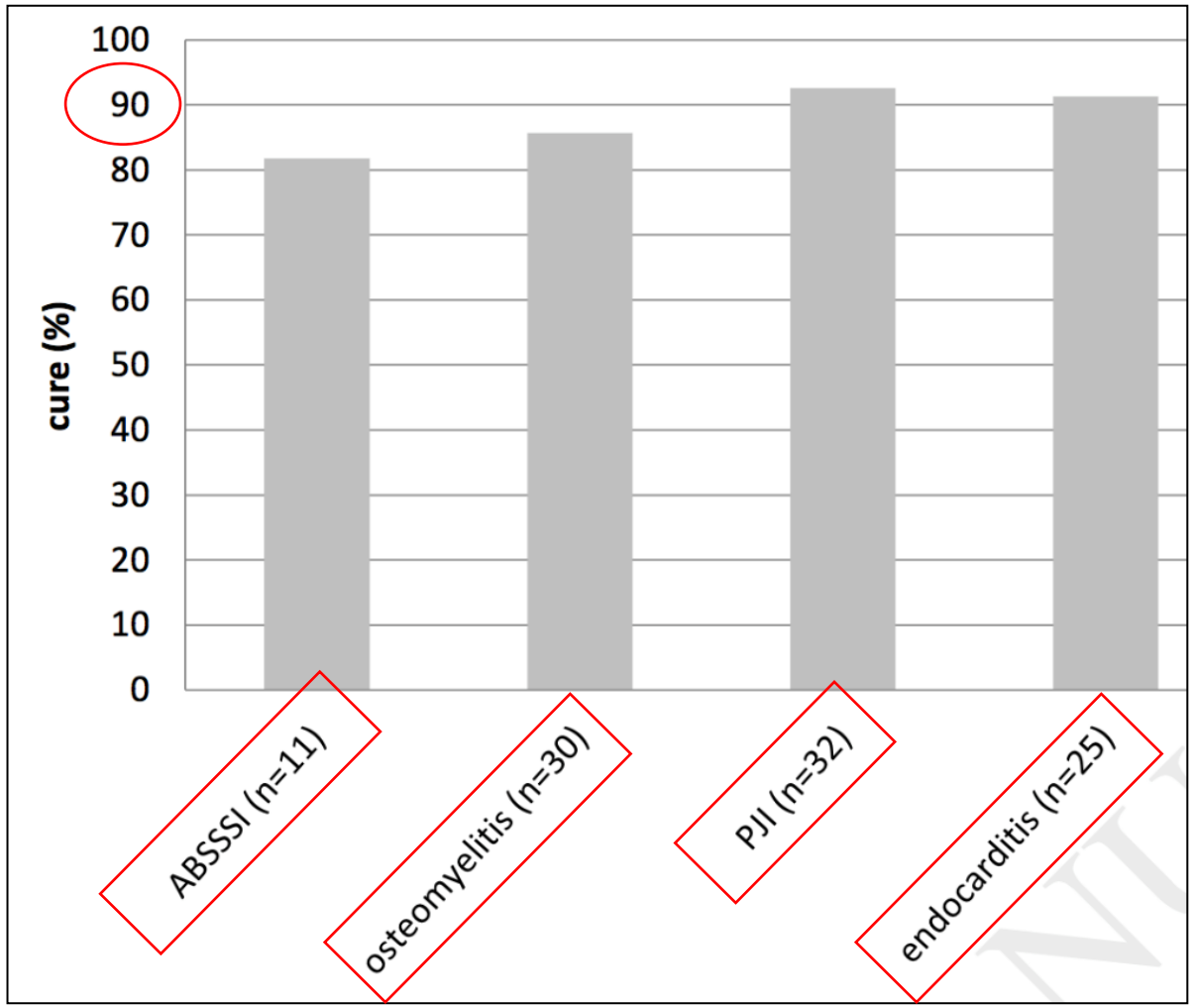
Long-acting parenteral antibiotics: An alternative to OPAT?

Clinical use of Dalbavancin

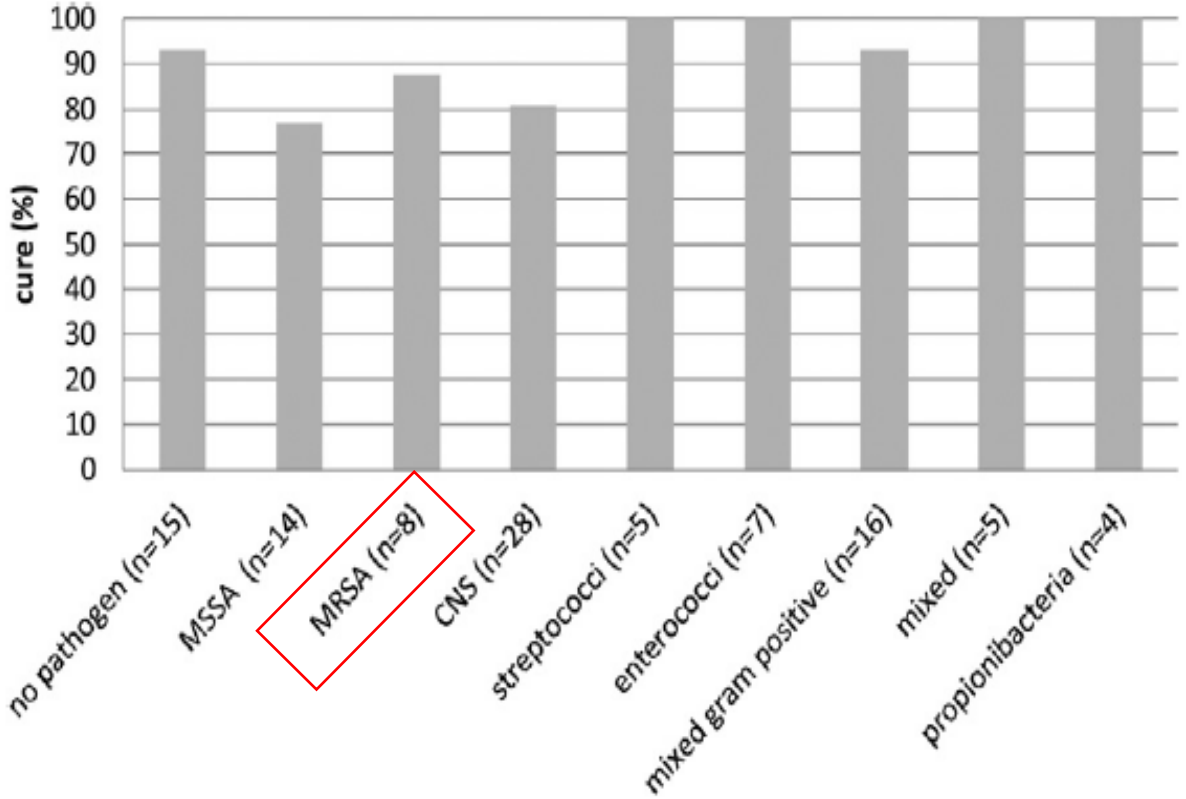
Type of Infection	Use	Dalbavancin dose
Approved		
Acute bacterial skin and skin structure infections (ABSSSIs)	Empiric or targeted treatment when MRSA in suspected or confirmed	1000 mg on day 1 followed by 500 mg on day 8 OR 1500 mg single dose
Off-label		
Bone and joint infections	Empiric or targeted treatment	1500 mg on day 1 followed by 1500 mg on day 8
Complicated bacteremia or endocarditis	Targeted treatment in infections due to Gram-positive pathogens (option for early discharge in MRSA infections)	1500 mg on day 1 followed by 1500 mg on day 8 OR 1500 mg single dose
Catheter-related bloodstream infections	Empiric or targeted treatment	1500 mg single dose
Mediastinitis	Targeted treatment in infections due to Gram-positive pathogens (option for early discharge in MRSA infections)	1500 mg on day 1 followed by 1500 mg on day 8 OR 1500 mg single dose

Curr Opin Infect Dis. 2018 Apr;31(2):141-147

Clinical use of Dalbavancin: Real-life data 2019



Wunsch S et al. Int J Infect Dis 2019



Success rate was high (89%), tolerability and safety were excellent in this setting

An antibiotic that fits Greek NHS for OPAT in a hospital-based setting?

OPAT with once daily schemes and easy mode of administration - candidates for a Greek OPAT?

Antibiotic	Mode of administration / stability
Ceftriaxone	Short infusion via syringe. Stable for 7 days if refrigerated (2-8°) up to concentration of 50mg/ml
Daptomycin	Bolus over 2 minutes or infusion over 30 minutes. Unstable once reconstituted, not suitable for pre-compounding
Ertapenem	Short infusion via syringe. Stable for 5 days if refrigerated (2-8°) when diluted between 10-20 mg/ml
Gentamycin	Once daily short infusion over 30 minutes via syringe. Stable for 7 days if refrigerated (2-8°)
Teicoplanin	Once daily short infusion over 30 minutes via syringe. Stable if refrigerated (2-8°) for 7 days in a silicone-free syringe (degrades in standard syringe)
Dalbavancin	Once weekly (different dosing schemes) over 30 min

Comfortable mode of administration

J Antimicrob Chemother 2015; 70: 360–373

GOOD PRACTICE RECOMMENDATIONS

Updated Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults and children in the UK

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Aiming to provide the most comprehensive overview of OPAT Services in the UK and Ireland - click here to register and enter your service details

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The resources area allows anyone with an interest to access or upload and share resources that are being used in the OPAT community

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Learn how patients with a serious infection can be managed in outpatient settings with the help of an OPAT service

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Intravenous to Oral Switch: Within Outpatient Parenteral Antibiotic Therapy (IVOST).
Join the conversation on the brand new e-learning course from BSAC

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The 2022-2025 OPAT Strategy sets out priority objectives and work streams

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A one day event bringing together OPAT experts to debate and share best practice

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A one day event bringing together OPAT experts to debate and share best practice

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DRUG STABILITY

The Drug Stability Testing Programme exists to provide evidence on the stability of agents and devices used in infection management practice, particularly those used in OPAT.

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https://e-opat.com/

BSAC DRUG STABILITY TESTING PROGRAMME

PROVIDING OPEN ACCESS STABILITY DATA ON AGENTS AND DEVICES USED IN INFECTION MANAGEMENT

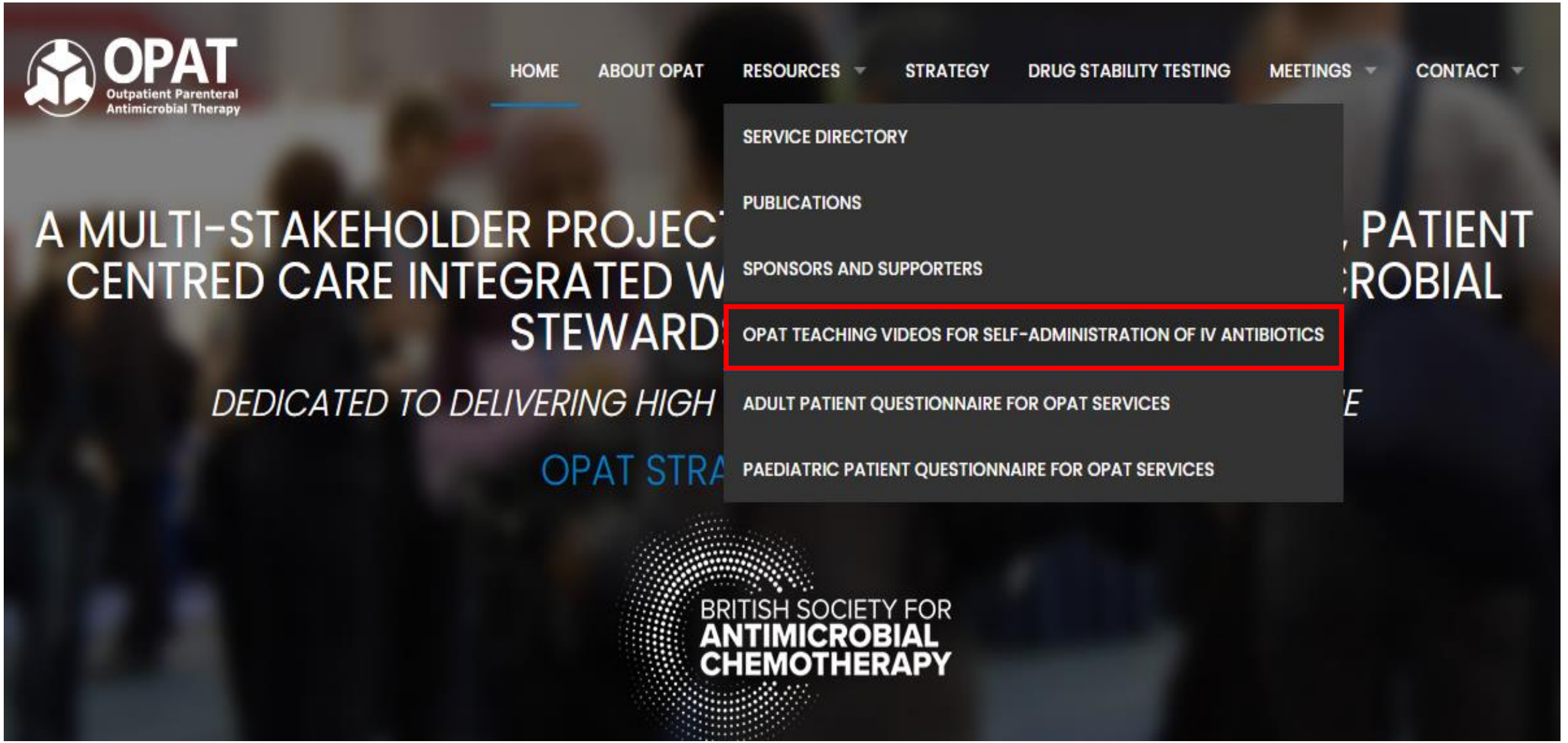
The BSAC Drug Stability Testing Programme exists to provide evidence on the stability of agents and devices used in infection management practice, particularly those used in Outpatient Parenteral Antimicrobial Therapy (OPAT) services.

The purpose and objective of the Programme is to provide evidence on the efficacy and stability of agents and devices used in the OPAT and other medical arena as provided for by the Yellow Cover Document. The Programme will, for the first time, make available, open access stability data that will inform practice and offer the ability to improve patient safety and patient outcomes within a rapidly expanding area of infection management.

We are inviting organisations to consider commissioning a stability study for agents or devices. Commissioned studies will be undertaken by BSTL, a provider chosen following a rigorous competitive tender process, and will lead to open access publication of peer review data.

The benefits of commissioning a study are:

- Opportunity to get medicines/devices tested to Yellow Covered Document standards
- Full methodology and results will be accessible to all free-of-charge
- Opportunity to open markets currently limited due to meeting requirements of the Yellow Covered Document required by the NHS
- Publication of data on each medicine that has been tested in two elastomeric devices plus syringe and infusion bags across a range of storage conditions
- Journal peer review publication and website availability
- Highly competitive pricing model
- Expressions of interest are invited from NHS organisations, pharmaceutical companies, device manufacturers, diagnostic companies, private healthcare, homecare organisations and other interested parties.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Conclusions