OPAT in Europe: the next frontier?

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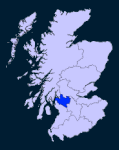


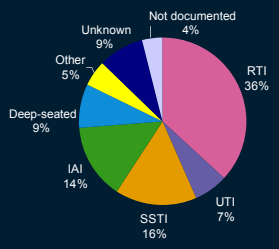
Disclosures

- Principle investigator:
  - DAP 002 (Cubist, Novartis)
  - DAP-OST (Cubist)
  - EU-CORE (Novartis)
- Honoraria and educational grants received for presentations (Novartis) and advisory boards (Novartis, Pfizer)

The burden of inpatient i.v. antibiotic therapy

- 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)

- Parenteral (i.v. or i.m.) antimicrobial administered on different days without an overnight hospital stay[1,2]
  - If no oral agent available or appropriate
  - Assures absorption, compliance and rapid achievement of therapeutic concentrations
- Proven effectiveness in:[1]
  - Endocarditis
  - Meningitis
  - Osteomyelitis
  - SSTIs

1. Tice AD *et al. Clin Infect Dis* 2004;38:1651–1672
2. Buxton ILO. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics* 11th edn. Brunton LL *et al.* (editors). 2006;1–39

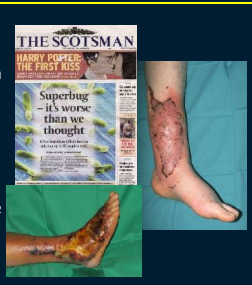
Patient benefits of OPAT

- Quality of life[1,2]
  - Family
  - Privacy
  - Familiar surroundings
  - Sleep
  - Food, clothing
- Increased education and training in self-care[2]
- Lower out-of-pocket costs
- Return to their daily activities (work, school)[1,2]
- Reduced risk of complicating infections and antimicrobial resistant organisms[3]

1. Tice AD *et al. Pharmacotherapy* 2002;22:63S–70S
2. Tice A. *Int J Clin Pract Suppl* 1998;95:4–8
3. Nathwani D *et al. J Antimicrob Chemother* 2002;49:149–154

Risks associated with hospitalization

- Hospital-acquired infection (nosocomial)
  - 5% of patients admitted in the US[1]
  - 9.5% in UK[2]
  - Increases with each day of hospitalization[1]
  - 70% increase in length of stay[2]
- Increasing resistance
  - Methicillin-resistant staphylococci[2]
  - Vancomycin-resistant enterococci[3]
  - Gram-negative bacteria[4]



1. Nathwani D *et al. J Antimicrob Chemother* 2002;49:149–154
2. Health Protection Scotland. 2007. Available at: http://www.hps.scot.nhs.uk/index.aspx
3. Karchmer AW. *Clin Infect Dis* 2000;31 (Suppl 4):S139–S143
4. Murray BE. *N Engl J Med* 2000;342:710–721
5. Chastre J. *Clin Microbiol Infect* 2008;14 (Suppl 3):3–14

Providing an OPAT service

Patient considerations
▪ Medically stable ▪ Infection ▪ Co-morbidity
▪ Low risk of complications
▪ Infection responding to treatment/low risk of deterioration
▪ Ease of access to hospital
▪ Home support available

Providing an OPAT service

Patient considerations	Antibiotic properties
▪ Medically stable ▪ Infection ▪ Co-morbidity	▪ Proven efficacy
▪ Low risk of complications	▪ Good safety/ tolerability
▪ Infection responding to treatment/low risk of deterioration	▪ No/little need for therapeutic drug monitoring
▪ Ease of access to hospital	▪ Long half-life
▪ Home support available	▪ Short administration time ▪ Stable when reconstituted

Providing an OPAT service

Patient considerations	Antibiotic properties	Healthcare support requirements[1,2]

▪ Medically stable
  ▪ Infection
  ▪ Co-morbidity
▪ Low risk of complications
▪ Infection responding to treatment/low risk of deterioration
▪ Ease of access to hospital
▪ Home support available
	▪ Proven efficacy
	▪ Good safety/ tolerability
	▪ No/little need for therapeutic drug monitoring
	▪ Long half-life
	▪ Short administration time
	▪ Stable when reconstituted
		▪ Efficient communication among healthcare teams
		▪ Clear guidelines/ procedures
		▪ Outcomes monitoring

1. Nathwani D *et al. Clin Microbiol Infect* 2000;6:464–467
2. Tice AD *et al. Clin Infect Dis* 2004; 38:1651–1672

Variable OPAT infrastructure and attitudes in Europe

	France	Germany	Greece	Italy	Spain	UK
Outpatient clinics exist	✓✓	✓✓	✓	✓✓	✓✓	✓✓
In-home infrastructure for i.v. admin	✓✓	x	x	? (not 'legal' but occurs)	✓ (varies by region)	✓✓ (varies by region)
Cultural attitudes support theoretical concept overall	+	–	+/–	+/–	+	+

TNS Healthcare. Market research data. 2008

Barriers to OPAT in the UK

Survey of UK microbiologists (n=157)

Perceived barrier to OPAT	Proportion of respondents, %
Funding issues	35
Difficult to co-ordinate/oversee care	30
Fragmented distribution of patients	27
Training issues	17
Lack of guidelines/experience	13
Time constraints	11
Safety (line care or drug administration)	10
Geographical constraints	5

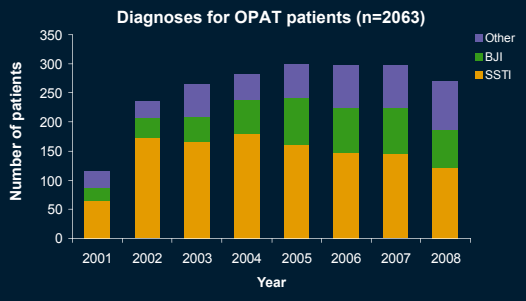
Seaton RA *et al. Clin Microbiol Infect* 2000;6:385–398

Design and funding of the Glasgow OPAT service

- Developed from 2000 onward
- ID led with team approach
- Clinical links
  - Emergency department
  - Diabetic clinic
  - Orthopaedics
- i.v. admin: nurse or patient/carer
- Funding
  - Delayed discharge 2001
  - SEHD (DHCI) 2001–2003
  - Health board funded 2003 to present
  - Orthopaedic and research funds

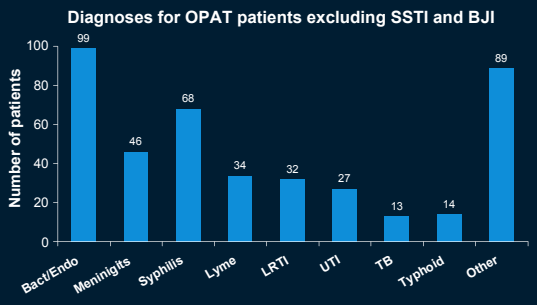
SEHD (DHCI), Scottish Executive Health Department (Designed Health Care Initiative)

Infections treated with OPAT



Seaton RA. Unpublished data

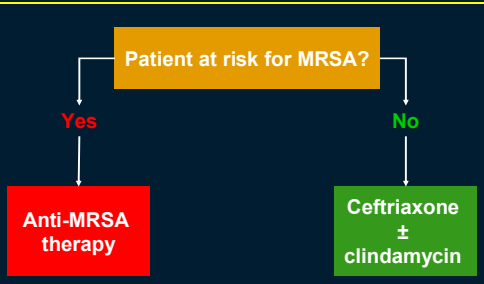
Infections treated with OPAT



LRTI, lower respiratory tract infection; TB, tuberculosis; UTI, urinary tract infection

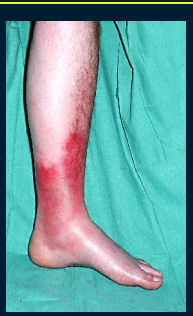
Seaton RA. Unpublished data

Community treatment pathway for SSTIs: empiric antibiotic choice



Patient group direction for SSTIs

- 'Patient group': non-life-threatening cellulitis amenable for home care and requiring i.v. therapy
- Uniform therapeutic management
- Suitable protocol in place
  - Exclusions
  - Prior physician review
  - Indications for specialist review
  - Indications for IVOST
- Trained, experienced staff
- Approved by ADTC

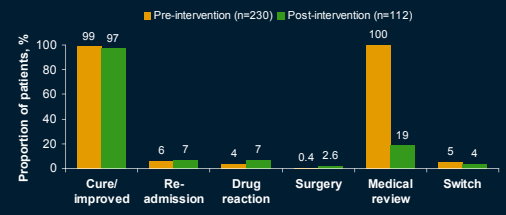


IVOST, i.v. antibiotic – oral switch therapy

Seaton RA *et al. J Antimicrob Chemother* 2005;55:764–767

OPAT for cellulitis

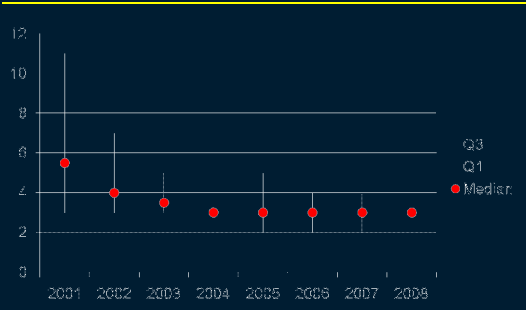
Comparison of patients pre- and post-introduction of a nurse-led management protocol



- Protocol management was associated with reduced duration of outpatient i.v. therapy (from 4 to 3 days, *P*=0.02)

Seaton RA *et al. J Antimicrob Chemother* 2005;55:764–767

Median duration of OPAT for SSTI

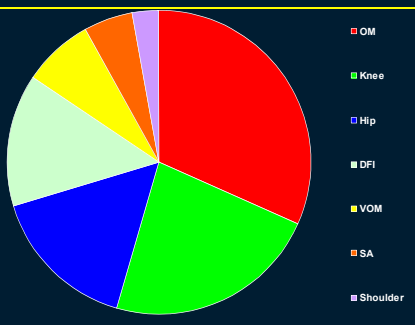


Factors associated with prolonged OPAT in 963 patients with SSTI: multivariate analysis

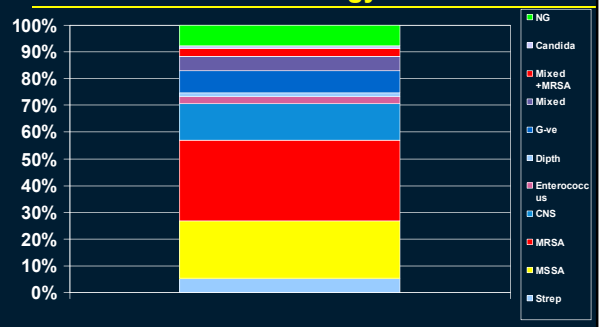
Parameter	OR	L 95% CI	U 95% CI	P
Age	1.030	1.007	1.053	0.0097
Vascular disease	1.288	1.011	1.641	0.0409
Teicoplanin vs Ceftriaxone	1.320	1.1160	1.502	<.0001
Not cellulitis*	1.248	1.001	1.558	0.0494
PGD	0.708	0.652	0.770	<.0001
Community referred	0.910	0.839	0.986	0.0211

*Infected ulcer, wound infection or bursitis

BJI in OPAT (n=434)

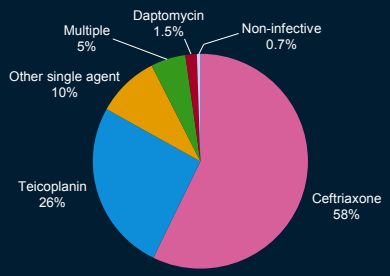


BJI infection microbiology



Antibiotic agents used for OPAT

Most frequently used antibiotic agents for OPAT (1988 episodes)



Seaton RA. Unpublished data

Teicoplanin in OPAT

- Indications[1]
  - Resistant staphylococcal infections (CoNS or MRSA)
  - Gram-positive infections with β-lactam allergy
  - Failure with β-lactams
- Dosing regimen[2]
  - Loading: 20 mg/kg for 3 days (inpatient or outpatient)
  - Maintenance: 3×/week (butterfly)
  - TDM at longest interval (72 hours)
  - Target trough concentration for deep-seated infections: 20–30 µg/ml
    - <20 µg/ml: increase dose or reduce interval (alt. days)
    - >30 µg/ml: reduce dose or increase interval (2× or 1×/week)

1. Sanofi-aventis. Targocid® (teicoplanin) Summary of Product Characteristics. 2009
2. Lamont E *et al. J Antimicrob Chemother* 2009;doi:10.1093/jac/dkp147

Daptomycin in OPAT

- Indications
  - Resistant staphylococcal infections (CoNS or MRSA)
  - Gram-positive infections with β-lactam allergy
  - Failure with β-lactams or Glycopeptides
    - BJI, Endovascular, Bacteraemia and SSTI
- Dosing regimen
  - ≥6 mg/kg daily
  - Round up to vial
- Alerts
  - CPK weekly
  - Anticoagulation

Clinical outcomes with OPAT: Glasgow 2001–2008

- 1993 OPAT episodes
  - 48% without hospital admission
  - 28,679 days of OPAT
- Major areas of benefit

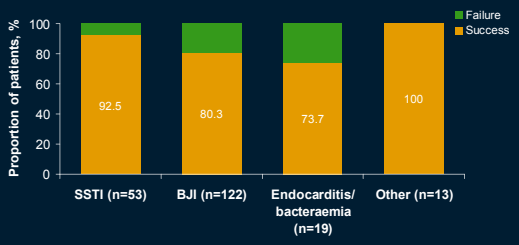
	SSTI	BJI
No.	1147	433
Days (range)	3 (1–109)	36 (1–147)
Success	95%	88%

- Patient acceptability 100%
  - Use again/standard as expected/overall satisfaction

Seaton RA. Unpublished data

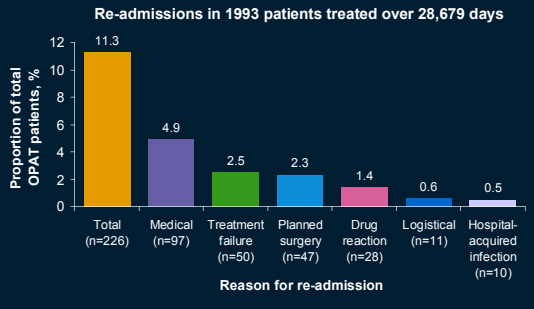
Clinical outcomes with MRSA infections

- OPAT patients with MRSA infections (n=207)
  - 6552 MRSA days
  - Mortality: 6 (3%)



Seaton RA. Unpublished data

Hospital re-admission following OPAT



Seaton RA. Unpublished data

Economics of OPAT provision in Glasgow

- Average 12 beds/day saved
- Expenditure associated with OPAT services offset by cost savings with early discharge

Comparison of costs for inpatient and outpatient antimicrobial therapy (n=364)

Category of cost, type of care	Total cost, £	Cost per patient, £
OPAT	329,125	904
Hospital	1,236,294	3396
Saving	907,000	2492/patient

Brown A, Seaton RA. 2004. Unpublished data

Clinical outcomes with OPAT: International OPAT registry

International OPAT registry (n=11,427)

	Outcomes, n (%)			
	Improved	**No change**	**Failed**	**Other**
US (N=9826)	9089 (92.5)	226 (2.3)	128 (1.3)	392 (3.9)
UK (N=981)	950 (96.8)	9 (0.9)	13 (1.3)	9 (1.0)
Italy (N=620)	590 (95.1)	8 (1.4)	15 (2.4)	7 (1.1)

Esposito S *et al. Int J Antimicrob Agents* 2004;24:473–478

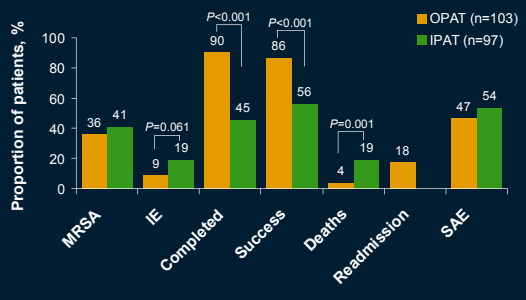
OPAT in complicated *S. aureus* bacteraemia

- 200 US patients complicated *S. aureus* bacteraemia
- (Vancomycin or semi-synthetic penicillin) + gentamicin vs daptomycin
- 103 (51.5%) OPAT patients
  - Daptomycin: 50 (48.5%)
  - Vancomycin: 30 (29.1%)
  - SSP: 23 (22.3%)
- Mean inpatient treatment: 10.5 days (1–49)
- Mean outpatient treatment: 14.9 days (1–49)

Rehm S *et al. J Antimicrob Chemother* 2009;63:1034–1042

OPAT in complicated *S. aureus* bacteraemia

OPAT vs IPAT patient characteristics and outcomes



Rehm S *et al. J Antimicrob Chemother* 2009;63:1034–1042

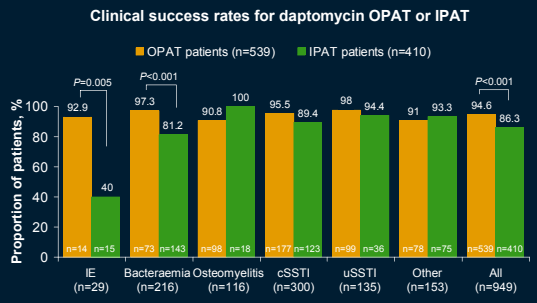
OPAT experience in CORE®

- Cubicin® Outcomes Registry and Experience (CORE®) – a retrospective chart review of patients who have received daptomycin
- In 2005, data were collected for 1172 patients from 52 participating institutions/investigators
  - 949 evaluable patients
    - 539 (56.8%) received OPAT
      - 266 (28.0%) received OPAT only
      - 273 (28.8%) received OPAT in addition to IPAT
    - 410 (43.2%) received IPAT only
  - 223 non-evaluable patients
- Adverse events
  - CPK elevation/myalgia: 2.6% OPAT; 1.0% IPAT (*P*=0.08)
  - Daptomycin discontinued due to AE: 3.5% OPAT; 5.6% IPAT (*P*=0.122)

IPAT, inpatient parenteral antimicrobial therapy

Martone W *et al. Int J Clin Pract* 2008;62:1183–1187

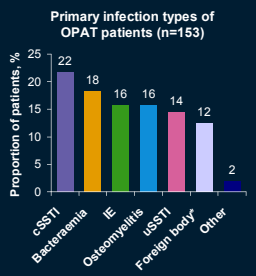
OPAT experience in CORE®



Martone W *et al. Int J Clin Pract* 2008;62:1183–1187

OPAT experience in EU-CORE℠

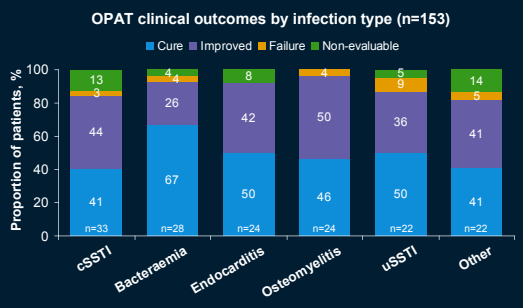
- European Cubicin® Outcomes Registry and Experience (EU-CORE℠)
  - Mirror to the CORE® registry
- 1127 enrolled Jan 2006– Sep 2008[1,2]
  - 118 institutions, eight European countries and Argentina
  - 153 OPAT patients (94% Spain, UK and Italy)
  - Mean duration of therapy: 11 days (uSSTI) to 35 days (osteomyelitis)



*Includes infected prostheses
Daptomycin is licensed in Europe for cSSTI, *S. aureus* RIE and SAB associated with cSSTI or RIE

1. Gonzalez-Ruiz A *et al.* ECCMID 2009; Poster 766
2. Novartis Europharm Ltd. Data on file

OPAT experience in EU-CORE℠



Clinical success was defined as the sum of cured and improved patients
Daptomycin is licensed in Europe for cSSTI, *S. aureus* RIE and SAB associated with cSSTI or RIE

Novartis Europharm Ltd. Data on file

OPAT: future prospects and challenges

- Development potential depends on:
  - National priorities and infrastructure
  - Local economics and clinical needs
  - Minimizing risks of HAI
  - Alignment with other developing ambulatory care facilities
  - Risk management and communication
  - Cost-efficiency: logistics/funding, geography, politics and legal issues
- Responding to developments in antimicrobial therapy
  - Efficacy and duration of therapy
  - Bolus and extended interval dosing
  - Oral and combination therapies

Summary

- OPAT is safe and effective for a wide variety of infections in appropriate patients
- OPAT is cost-effective
  - Reduced cost compared with inpatient treatment for selected patients
- Ceftriaxone well established in SSTI and associated with short duration of Rx
- Teicoplanin well established but associated with longer duration of Rx in SSTI
- Daptomycin is a promising emerging therapy in OPAT setting

Acknowledgements

Lindsay Semple and Emma Bell (OPAT)