Intravenous to oral switching, OPAT, and early discharge

Mark Gilchrist
London, UK

IV to PO switching, OPAT and early discharge

Mark Gilchrist MPharm MSc FFRPS
Consultant Pharmacist – Infectious Diseases
Imperial College Healthcare NHS Trust
Mark.gilchrist@imperial.nhs.uk

Disclosures

- Participated in commercial advisory boards for: Astellas, Cubist, Durata, Medicines Company
- Travel Grant – Astellas / Eudemica

Non-commercial positions:
- Royal Pharmaceutical Society – Spokesperson on antimicrobials
- BSAC Council
- Co-Chair BSAC OPAT Initiative
- Chair UKCPA Pharmacy Infection Network

Overview

- New era of evidence-based medicine
- Evidence to support IV-PO + OPAT
- Managing IV-PO switch
  - Effectiveness
  - Criteria for use
- Outpatient parenteral antibiotic therapy
  - Effectiveness
  - Criteria for use
  - Working within stewardship principles

OPAT, outpatient parenteral antimicrobial therapy;
IV-PO, intravenous to oral.

The new era of evidence-based medicine

Traditional requirements (for regulatory approval)

- Efficacy
- Safety

Emerging requirements (for access/reimbursement and, to some degree, clinical use)

- **Clinical effectiveness** (doing the right thing)
- Efficiency (doing the thing right)
- Costs
- Patient outcomes (QoL)

QoL, quality of life.
Luce BR, et al. *Milbank Quart*. 2010;88(2):256-276.
Ward WJ, et al. *Healthc Financ Manage*. 2006;60:92-98.

Acknowledgement D. Nathwani

The cost-efficiency strategy in the setting of high fixed costs

- Hospitals have high fixed costs: 85% to 90%[1]
- There are a small number of variable costs to make savings[1]
- Therefore, it is important to:[1]
  - Employ "cost-efficiency strategies" in which more patients can receive care with the same investment in fixed costs
  - Maintain quality
  - Keep patients satisfied
- By decreasing LOS, hospitals can serve more patients, leading to increased DRG payments and / or greater efficiency[1,2]

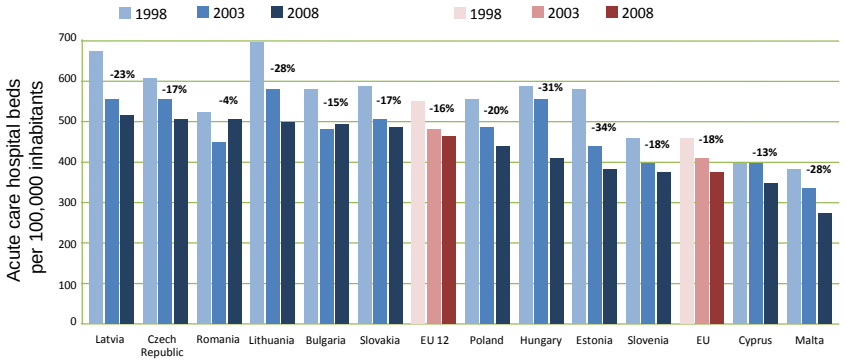
Therefore, shortening LOS can be a key efficiency driver[1]

DRG, diagnosis-related group; LOS, length of stay.
1. Ward WJ, et al. *Healthc Financ Manage*. 2006;60:92–98.
2. Nathwani D, et al. *J Infect*. 2009;59:S40–S50.

Acknowledgement D. Nathwani

Changes in acute care hospital beds in Europe, 1998-2008

- Mean 18% reduction in acute care beds



HOPE. Hospitals in Europe Healthcare Data 2011. Available at: <http://www.hope.be/03activities/quality_eu-hospitals/eu_country_profiles/00-hospitals_in_europe-synthesis_vs2011-06.pdf> [Accessed March 27, 2013].

Antimicrobial stewardship toolkit: Quality of evidence to support interventions

- Prospective audit with intervention and feedback (A-I)
- Education (B-II)
  - Education with an active intervention (A-III)
- Formulary restriction and pre-authorisation
  - Rapid decrease in antibiotic in use (A-II); for control of an outbreak (B-II); may lead to unintended increase in resistance to another agent (B-II / B-III)
- Guidelines and clinical pathways (A-II)
  - Guideline implementation can be facilitated by education and feedback on outcomes (A-III)
- Antimicrobial cycling (C-II)
- Antimicrobial order forms (B-II)
- Combination therapies (C-II)
  - In critically ill patients at high risk of MDR pathogens (A-II)
- De-escalation review (A-II)
- Dose optimisation (A-II)
- Parenteral to oral conversion (A-I)
  - Facilitated by the development of clinical criteria and guidelines allowing switching to oral agents (A-III)
- Computerised decision support, surveillance (B-II)
- Laboratory surveillance and feedback (A-III)

MDR, multidrug-resistant.
Dellit TH, et al. *Clin Infect Dis.* 2007;44:159-177.

INVITED ARTICLE CLINICAL PRACTICE
Ellie J. C. Goldstein, Section Editor

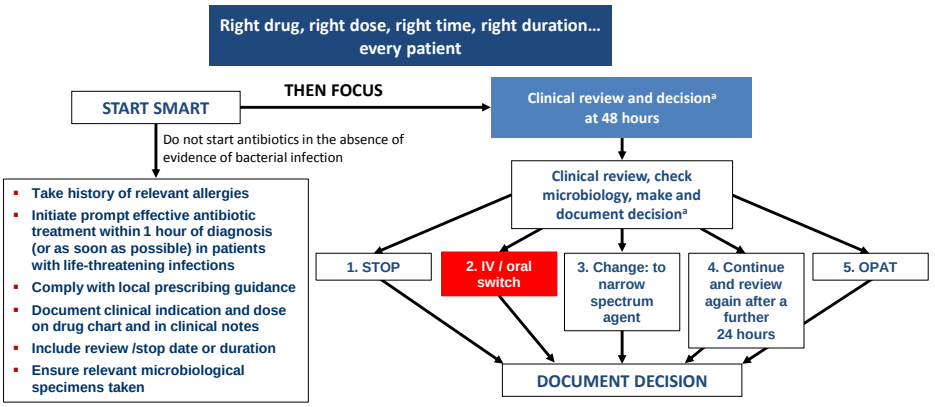
Is the "Low-Hanging Fruit" Worth Picking for Antimicrobial Stewardship Programs?

Debra A. Goff,[1] Karri A. Bauer,[1] Erica E. Reed,[1] Kurt B. Stevenson,[2,3] Jeremy J. Taylor,[1] and Jessica E. West[2]
[1]Department of Pharmacy, The Ohio State University Wexner Medical Center, [2]Division of Infectious Diseases, College of Medicine, and [3]Division of Epidemiology, College of Public Health, The Ohio State University, Columbus

A new antimicrobial stewardship program can be overwhelmed at the breadth of interventions and education required to conduct a successful program. The expression "low-hanging fruit," in reference to stewardship, refers to selecting the most obtainable targets rather than confronting more complicated management issues. These targets include intravenous-to-oral conversions, batching of intravenous antimicrobials, therapeutic substitutions, and formulary restriction. These strategies require fewer resources and less effort than other stewardship activities; however, they are applicable to a variety of healthcare settings, including limited-resource hospitals, and have demonstrated significant financial savings. Our stewardship program found that staged and systematic interventions that focus on obvious areas of need, that is, low hanging fruit, provided early successes in our expanded program with a substantial cumulative cost savings of $832 590.

Goff DA, et al. *Clin Infect Dis.* 2012;55(4):587–592.

Antimicrobial stewardship treatment algorithm



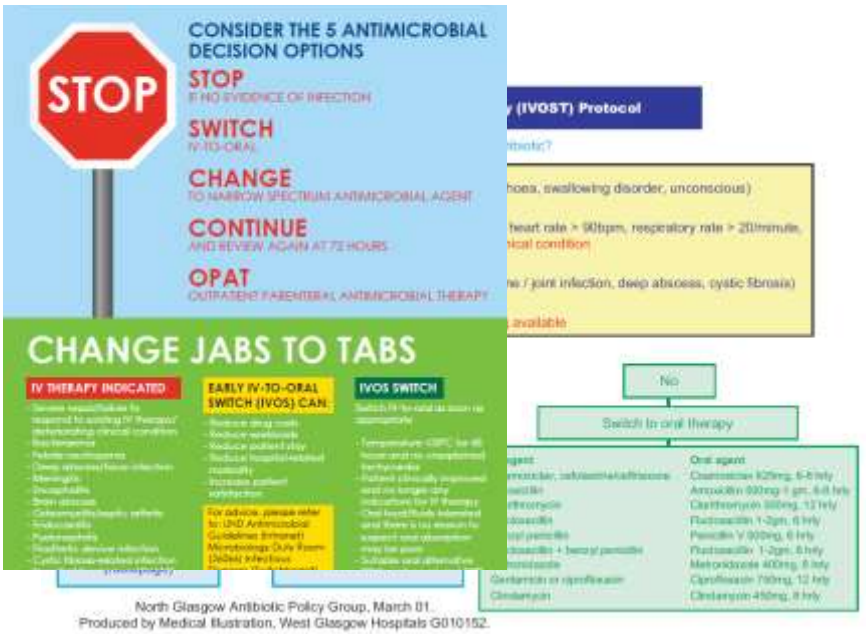
Advocating patient safety and auditing of antimicrobial stewardship in hospitals should be based around the principles stated in this AMS algorithm.
[a]Antimicrobial prescribing decision.
AMS, antimicrobial stewardship; OPAT, outpatient parenteral antimicrobial therapy.

Department of Health, Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), 2011

Nationwide implementation of antibiotic management teams in Belgian hospitals: A self-reporting survey

- Completed questionnaires were provided by 112 of 116 hospitals (response rate, 96.6%)
- Multidisciplinary AMTs varied in size (mean 10, range 2-28 members)
- Antibiotic stewardship tools used by AMTs included:
  - Hospital antibiotic formulary (96.3% of hospitals)
  - Practice guidelines for antibiotic therapy and surgical prophylaxis (91.6% and 96.3%, respectively)
  - List of "restricted" antimicrobial agents (75.9%)
  - Concurrent review of antibiotic therapies (64.2%)
  - De-escalation of therapy after a few days (63.9%)
  - Sequential intravenous /oral therapy for antibiotics with equivalent bioavailability (78.7%)
  - Dedicated antimicrobial order forms (36.1%)
  - Automatic stop of delivery (43.5%)
  - Analysis of antibiotic consumption data (96.2%)
  - Analysis of microbial resistance data (89.8%)

AMT, antibiotic management team.
Van Gastel E, et al. *JAC.* 2010;65(3):576–80.



McCallum AD, et al. *R Coll Physicians Edinb.* 2013;43:294–30.
McLaughlin, et al. *Q J Med.* 2005;98:745-52.

Within your organisation, who is the main champion for switching IV to oral antibiotics?

1. Doctor
2. Pharmacist
3. Nurse
4. Patient
5. Multidisciplinary
6. Don't know

Selection of patients for IV to PO therapy conversion

- Proper identification of patients, diagnoses, medications and contraindications to oral therapy

1. Oral therapy has good bioavailability
2. Intact and functioning gastrointestinal (GI) tract
3. Improving clinical status
4. Does not meet any exclusion criteria

Approximate bioavailability

<50%	50%-80%	80% -100%
Aciclovir	Cefixime	Amoxicillin
Azithromycin	Cefpodoxime	Cephalexin
Cefuroxime axetil	Ciprofloxacin	Clindamycin
	Itraconazole	Doxycycline
		Fluconazole
		Levofloxacin
		Linezolid
		Metronidazole
		Moxifloxacin
		Co-trimoxazole

Competence Assessment Tools for Health-System Pharmacies, Fourth Edition

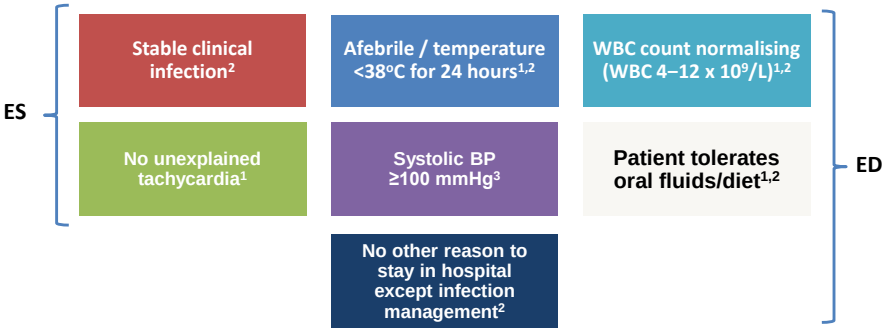
Criteria indicating absorption of oral medications may be compromised

- NBM status (and no medications are being administered orally)
- NG tube with continuous suction
- Severe/persistent nausea or vomiting
- Gastrointestinal transit time too short for absorption (malabsorption syndromes, partial or total removal of the stomach, short bowel syndrome)
- Active gastrointestinal bleeding
- High doses of vasopressor medications (typically in presence of shock)
- Difficulty swallowing or loss of consciousness and no NG access available
- Documented ileus or gastrointestinal obstruction
- Continuous tube feedings that cannot be interrupted and patient requires a medication known to bind to enteral nutrition formulas

NBM, nil by mouth; NG, nasogastric.

Patient clinical parameters early switch/early discharge criteria

- Literature review with expert validation formed the basis for a list of 14 criteria tested in the study; inclusive of Desai[1] and Parodi[2] criteria
- The key (essential) criteria were selected by KOLs, and were used to estimate ES / ED hypothetical opportunities



ED, early discharge; ES, early switch; KOL, key opinion leader; WBC, white blood cell.

1. Desai M, et al. *BMC Infect Dis.* 2006;6:94.
2. Parodi S, et al. *J Manag Care Pharm.* 2003;9:317–26.
3. Nathwani D, et al. ECCMID 2013 poster #843

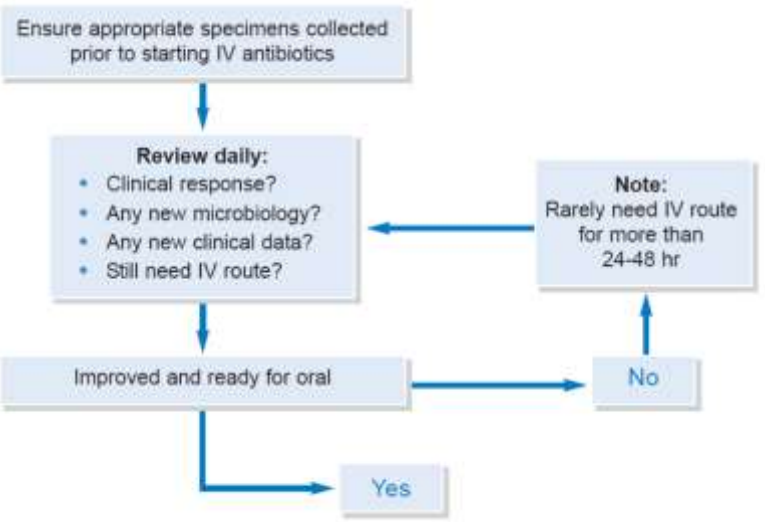
Acknowledgement D. Nathwani

Exclusion criteria

- Patients with compromised oral absorption (e.g. severe diarrhoea and/or vomiting, Ileus or malabsorption syndromes, severe mucositis)
- Continuing decompensated sepsis
- Special indications
  - a) Endocarditis
  - b) Meningitis/encephalitis/brain abscess
  - c) Osteomyelitis/septic arthritis/bone or joint infection; infected implants/prostheses/graft tissue
  - d) Complex skin and soft tissue infection
  - e) Deep abscess
  - f) Bronchiectasis, cystic fibrosis, empyema
  - g) Bloodstream infections due to organisms requiring long-term IV therapy, e.g. *Staphylococcus aureus* (MSSA or MRSA), *Candida* spp.
  - h) Immunocompromised patients (e.g. HIV, neutropenia, immunosuppressants or cytotoxics)
  - i) Patients receiving IV therapy on specific ID/micro advice

ID, infectious diseases specialist; micro, microbiologist; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus.*

Building into healthcare processes

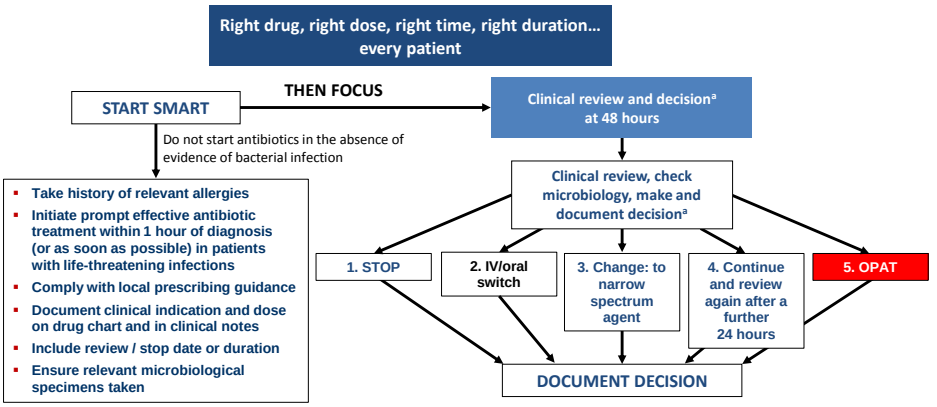


Building into healthcare processes

- **C**linical improvement is observed
- **O**ral route is not compromised
- **L**aboratory or other marker(s) is improving
- **I**ndication for oral therapy
- **C**omparable oral antibiotic option

http://www.todayshospitalist.com/index.php?b=articles_read&cnt=986 Accessed March 15

Antimicrobial stewardship treatment algorithm



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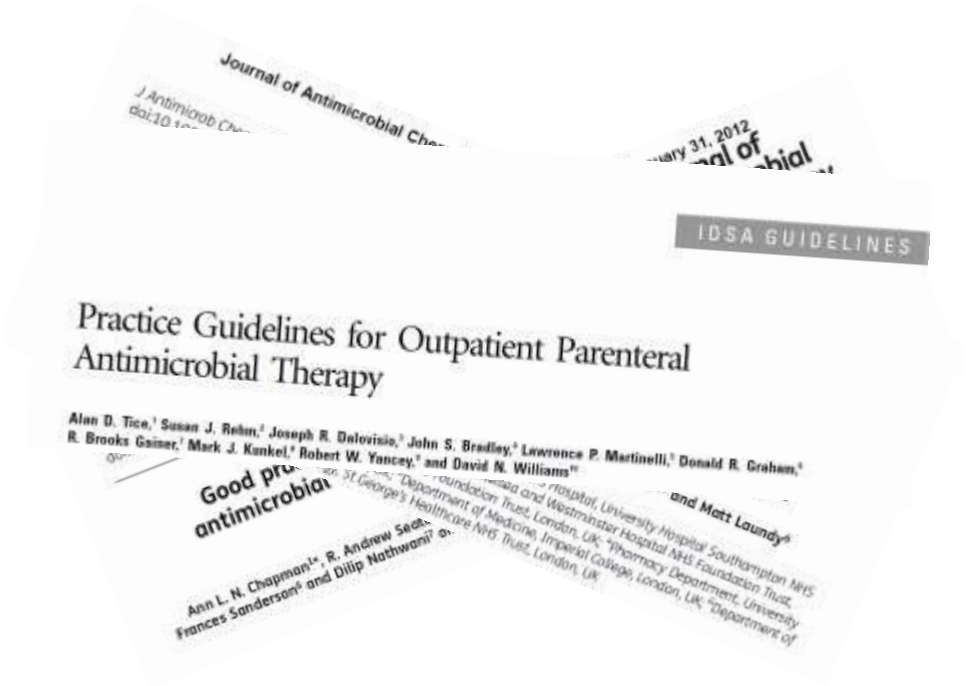
Department of Health, Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), 2011

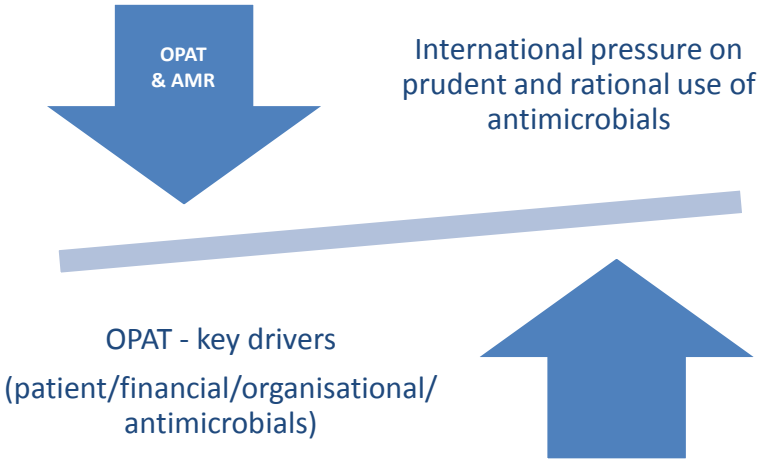
As part of your stewardship programme, how many of you have an OPAT service in operation?

1. Yes – I have one
2. No – but we are working on one
3. No – it is an aspiration
4. No

What are your barriers to starting an OPAT service?

1. Funding
2. Leadership
3. Human resources
4. Other priorities
5. Not considered





Chapman AL, et al. *J Antimicrob Chemother.* 2012;67(5):1053-106.
Chapman AL, et al. *J Antimicrob Chemother.* 2009;64:1316.
Matthews PC, et al. . *J Antimicrob Chemother.* 2007;60:356-62.
Patel S, et al. *J Antimicrob Chemother.* 2015;70:360-73.

Stewardship/OPAT dilemma

- Stewardship primary aim:
  - Individual patient care
  - Most effective, safe and narrow spectrum agent
  - Least capacity for collateral effects
  - For a specific indication
- OPAT
  - Aims are similar
  - Although convenience of dosing to optimise early hospital discharge or admission avoidance may take precedence over an agent's spectrum of activity, this has been debated

    => There are a number of factors that currently challenge this ideal

Howden BP, et al. *Med J Aus.* 2002;176:44.
Gilchrist M, et al. *J Antimicrob Chemother.* 2015;70(4):965-970.

What would be the most important consideration when choosing which antimicrobial agent to use in the OPAT setting?

1. Efficacy
2. Cost
3. Frequency of administration
4. Delivery device availability
5. Safety and tolerability
6. Community nurse considerations

Challenges for antimicrobials in OPAT

- Lack of narrow spectrum antimicrobials with convenient (once daily) dosing regimens
- Potential for collateral damage
  - *Clostridium difficile* risk/resistance
- Lack of antimicrobials with rapid method of administration
- Drug stability

Gilchrist M, et al. *J Antimicrob Chemother*. 2015 Apr;70(4):965-70.

Challenges for antimicrobials in OPAT

1. Lack of narrow spectrum antimicrobials with convenient (once daily) dosing regimens

- Once daily (or less frequent) administration of a parenteral agent potentially avoids the need for more complex drug delivery systems and otherwise avoids the inconvenience and lifestyle restrictions associated with multidosing or continuous infusion of antimicrobials at home
- Current available once daily agents include ceftriaxone, teicoplanin, daptomycin and ertapenem, all of which potentially have unnecessarily broad spectrum activity for many of their current OPAT indications

Challenges for antimicrobials in OPAT

2. Potential for collateral damage

- Despite relatively higher use of parenteral cephalosporins in OPAT, published UK OPAT cohort studies tend to support this hypothesis, with much lower rates of *Clostridium difficile* (CDI) observed compared to hospitalised patients
- Available evidence from large OPAT cohorts where ceftriaxone use predominates suggests the risk is small with CDI occurrence observed in approximately 0.1 % of treatment episodes across three separate published UK cohorts

Duncan CJ, et al. *Int J Clin Pharm*. 2012 Jun;34(3):410-17.
Barr DA, et al. *Int J Antimicrob Agents.* 2012;39:407– 13.

Challenges for antimicrobials in OPAT

3. Lack of antimicrobials with rapid method of administration

- Rapid administration of antimicrobials is a relative advantage in the OPAT setting as it:
  - allows greater throughput in a clinic-based service;
  - lessens community nurse administration; and
  - reduces complexity and saves time for patients who self-administer at home
- Currently, many antimicrobials require prolonged administration, which may preclude their practical use in the OPAT setting
- Exploring the possibility of more rapid administration of agents is a challenge, particularly as data supporting this is lacking for most agents

Challenges for antimicrobials in OPAT

3. Lack of antimicrobials with rapid method of administration

- Exception – daptomycin

Journal of Antimicrobial Chemotherapy (2009) **64**, 151–158
doi:10.1093/jac/dkp155
Advance Access publication 22 April 2009

JAC

Comparison of the pharmacokinetics, safety and tolerability of daptomycin in healthy adult volunteers following intravenous administration by 30 min infusion or 2 min injection

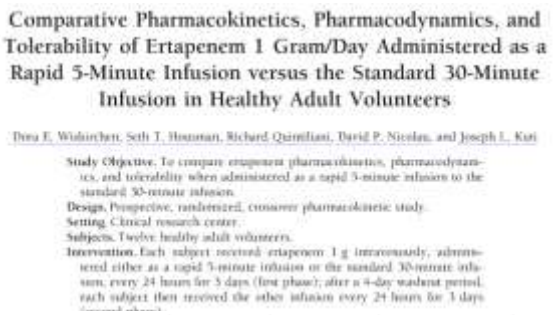
Abhijit Chakraborty[1]*, Sandip Roy[1], Juergen Loeffler[2] and Ricardo L. Chaves[2]

***Conclusions*: The similar pharmacokinetic and safety profiles of the two administration regimens suggest that the 2 min iv injection may be a convenient treatment option for both patients and health-care professionals.**

Challenges for antimicrobials in OPAT

3. Lack of antimicrobials with rapid method of administration

- Ertapenem trial – not in clinical practice



Comparative Pharmacokinetics, Pharmacodynamics, and Tolerability of Ertapenem 1 Gram/Day Administered as a Rapid 5-Minute Infusion versus the Standard 30-Minute Infusion in Healthy Adult Volunteers

Drew E. Wiskirchen, Seth T. Housman, Richard Quintiliani, David P. Nicolau, and Joseph L. Kuti

Study Objective. To compare ertapenem pharmacokinetics, pharmacodynamics, and tolerability when administered as a rapid 5-minute infusion to the standard 30-minute infusion.
Design. Prospective, randomized, crossover pharmacokinetic study.
Setting. Clinical research center.
Subjects. Twelve healthy adult volunteers.
Intervention. Each subject received ertapenem 1 g intravenously, administered either as a rapid 5-minute infusion or the standard 30-minute infusion, every 24 hours for 5 days (first phase); after a 4-day washout period, each subject then received the other infusion every 24 hours for 5 days

Conclusion. Ertapenem administered as a rapid 5-minute infusion provides a well tolerated, bioequivalent, and pharmacodynamically equivalent regimen to the 30-minute infusion at clinically relevant MICs.

Wiskirchen DE, et al. *Pharmacotherapy.* 2013;33(3):266-274.

OPAT NOW + FUTURE

Now

- Antimicrobials that are currently in use

Future

- Need to rethink our older (better) more narrow spectrum agents

Challenges for antimicrobials in OPAT

4. Drug stability

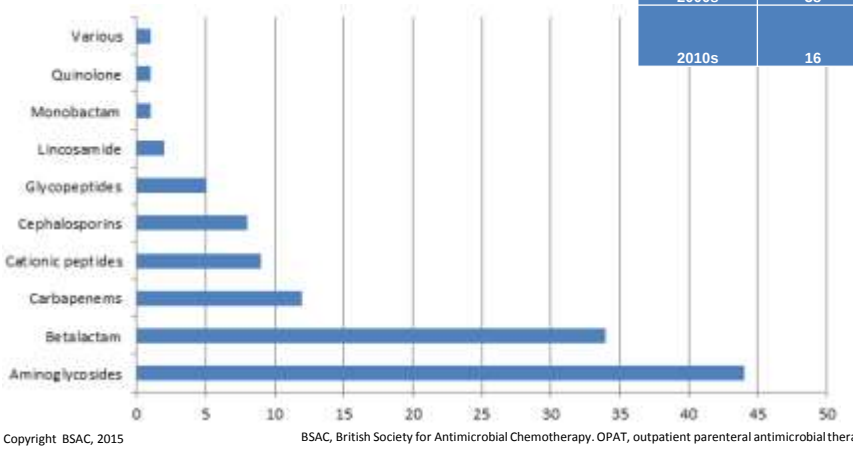
- The lack of validated and published drug stability data for many narrow-spectrum agents limits their widespread use in a non-inpatient setting
- Data relating to specific agents is currently only available if local resources allow for in-house quality-control testing of stability or through commercially available infusion device-antimicrobial combinations, which may be prohibitively expensive for many non-commercial healthcare organisations

BSAC OPAT drug stability testing results of stability survey

Literature search on stability + reproducibility

- Articles by therapeutic group (117 antibacterial)

Decade of Publication	No. Articles
1980s	25
1990s	55
2000s	38
2010s	16



BSAC, British Society for Antimicrobial Chemotherapy. OPAT, outpatient parenteral antimicrobial therapy

Conclusions

- New era of evidence-based medicine
- IV/PO switch is an evidence-based component of stewardship programmes
  - Low hanging fruit
  - Safety/organisational efficiency/financial
  - Key role for pharmacists
- OPAT sits alongside IV/PO switch programmes
  - Early discharge or admission avoidance
  - Creates a dilemma within stewardship programme
  - Safety/organisational efficiency/financial
  - International guidelines
  - More stability data is needed to utilise older agents

IV to PO switching, OPAT and early discharge

Mark Gilchrist MPharm MSc FFRPS
Consultant Pharmacist – Infectious Diseases
Imperial College Healthcare NHS Trust
Mark.gilchrist@imperial.nhs.uk

Agenda

12:00	Chairman's welcome and introduction	Jonathan Cooke *Manchester, UK*
12:20	Antibiotic stewardship programs – How do they promote a "safer" environment	Christian Eckmann *Hannover, Germany*
12:40	Intravenous to oral switching, OPAT, and early discharge	Mark Gilchrist *London, UK*
13:00	The role of new antibiotics in the treatment of severe infections – Safety and efficacy features	Christian Eckmann *Hannover, Germany*
13:15	Q&A with panel discussion	All