Outpatient parenteral antimicrobial treatment

Which antibiotics can be used?

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Guidelines include recommendations about six key areas, namely

1. OPAT team and service structure
2. Patient suitability for OPAT
3. Pathology suitable for OPAT management
4. Vascular access
5. Antimicrobial selection, drug and medical devices delivery, patient monitoring during OPAT
6. Outcome monitoring

JAC 2015;70:360-373
JAC 2012;67:1053-1062
http://e-opat.com/ (OPAT-website BSAC)
Antimicrobials prescribed for OPAT in Belgian hospitals
(Submitted in International Journal of Clinical Pharmacy by T. Ravelingien, A. Vantrappen et al)

<table>
<thead>
<tr>
<th>Table 2. Antimicrobials prescribed for OPAT as reported by Belgian hospitals. Number of hospitals reporting use of antimicrobial for OPAT (N = 53) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of infection</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>Teicoplanin</td>
</tr>
<tr>
<td>Colistin</td>
</tr>
<tr>
<td>Meropenem</td>
</tr>
<tr>
<td>Teicoplanin</td>
</tr>
<tr>
<td>Tazobactam</td>
</tr>
<tr>
<td>Vancomycin</td>
</tr>
<tr>
<td>Ertapenem</td>
</tr>
<tr>
<td>Tigecycline</td>
</tr>
<tr>
<td>Amikacin (B)</td>
</tr>
<tr>
<td>Cefepime</td>
</tr>
<tr>
<td>Cefazolin</td>
</tr>
<tr>
<td>Linezolid</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
</tr>
<tr>
<td>Aztreonam</td>
</tr>
<tr>
<td>Meropenem/ertapenem</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Gentamicin</td>
</tr>
<tr>
<td>Aramidicin</td>
</tr>
<tr>
<td>Ceftazidim</td>
</tr>
<tr>
<td>Aztreonam</td>
</tr>
<tr>
<td>Voriconazole</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

* Includes: ceftriaxone (n = 41), tobramycin (n = 51), tigecycline (n = 1), ceftazidime (n = 1)

Criteria for antimicrobial choice in OPAT programs

- The antimicrobial spectrum.
- Antimicrobial penetration and target site.
- The antimicrobial’s side effect profile.
- Antimicrobial dose and dosing frequency.
- The antimicrobial’s mode of delivery.
- Orally bioavailable antimicrobial alternatives.
- The duration of antimicrobial therapy and criteria for stopping or switching.
- Service structure (compounding and/or administration of antibiotic)
- Vascular access
- Availability of home nurse
- Stability of the antibiotic
- Lack of reimbursement (Belgian situation)
Barriers for implementation of OPAT in Belgium

(Submitted in International Journal of Clinical Pharmacy by T. Ravelinglen, A. Vantrappen et al)

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Hospitals who use OPAT (n=11)</th>
<th>Hospitals who don’t use OPAT (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of outpatient reimbursement of certain antimicrobials (e.g. aminoglycosides and cephalosporins)</td>
<td>40 (75%)</td>
<td>0 (64%)</td>
</tr>
<tr>
<td>Complexity for the patient of purchasing and reimbursement of antimicrobials in community pharmacies (no unit dose, delayed approval of the certificate for reimbursement, ...)</td>
<td>39 (74%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>High cost of outpatient therapy for the patient</td>
<td>33 (57%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>Lack of guidelines in the hospital’s local practice of OPAT</td>
<td>27 (51%)</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>Insufficient knowledge of the healthcare practitioners (home nurse, general practitioners, ...) about the procedures of home treatment</td>
<td>29 (49%)</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Legal prohibition of delivery of certain medicines and medical devices by the hospital pharmacy</td>
<td>28 (49%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Lack of experience with OPAT</td>
<td>35 (67%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Concerns about the safety of home parenteral administration (hygiene, preparation, ...)</td>
<td>24 (43%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Difficulties of monitoring at home (e.g., injection technique, blood level of the medicine, complications, adverse events, ...)</td>
<td>19 (35%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>Insufficient transition care with the general practitioner and home care</td>
<td>7 (13%)</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Refusal of the patient for outpatient therapy</td>
<td>4 (9%)</td>
<td>3 (21%)</td>
</tr>
</tbody>
</table>

Service structure: various service models

- **Compounding**
  - **Home**
    - Trained home nurse
    - Trained carer/patient
  - Hospital pharmacy
  - Commercial compounding centre

- **Administration**
  - **Home**
    - trained home nurse
    - Trained carer or patient
      - (i.e. in cystic fibrosis pediatric patients administration by trained parents)
  - Infusion centre administration (in Belgian “Day clinic”)
Decision tree to select a suitable vascular access

Selecting a suitable catheter
Classification by tip position/duration of treatment

Criteria antimicrobial choice in OPAT programs

- Ideally, antimicrobials for OPAT administration should be administered once daily.
  - reduces disruption of daily activities and limits the potential for complications
  - Once-daily (or less) administration can be achieved by using long half-life antimicrobials

- Teicoplanin
  - Half-life: 50-70 hours
  - OPAT: dosing 3 times a week 1200 MG (TDM)

- Future antibiotics: Oritavancin and dalbavancin
  - Very long acting glycopeptides
  - Single dose/weekly treatments for skin and soft tissue infections (including those caused by MRSA)
  - Adverse drug reactions?
Ideally, antimicrobials for OPAT administration should be administered once daily.

- Once-daily administration can be achieved by using portable administration devices to give an extended or continuous infusion
- Will we apply Pk/Pd principles also in our OPAT programs?

Drug stability

- Ability of an antibiotic to keep its original properties within the existing quality specifications for a determined period of time

Instability of a drug

- Physical alterations (eg. humidity, temperature, light)
- Chemical alterations (eg. degradation)
- Biological alterations (microbial growth):
  - Compounding in a non aseptic: reconstituted drug should be used within 24 hours.
Sources stability data

- Pneumologist calls the pharmacy; can cefuroxim 6 G in a 250 ML 0,9% NaCl solution be administered in a continuous infusion
- Literature research
  - Scientific leaflet (cefuroxim Fresenius)

**Schermschot**

- Hoeveelheid van de oplossing voor intraveneuze infusie
- Cefuroxin 600 mg moet geconstituïerd worden volgens de instructie voor reconstituutie van een intraveneuze injectie met water voor injectie (zie tabel 4 hiervoor).
- Verdere verdunning moet met 50-100 ml van één van de volgende verenigbare infusievloeistoffen voor toediening van het intraveneuze infusum:
  - Cefuroxin natrium is verenigbaar met de volgende infusievloeistoffen. Het blijft gelijkmatig 3 uur stabiel bij 2° – 4°C in:
    - water voor injectie
    - 0,9% natriumchloortelezusluding
    - 3% glucoseluding
- Voor éénmaal gebruik.
- Alle ongebruikte producten en afvalstoffselen dient te worden vernietigd overeenkomstig lokale voorschriften.
### Table

<table>
<thead>
<tr>
<th>Test Soln Name</th>
<th>Test Soln Mfr</th>
<th>Base Drug Mfr</th>
<th>Base Drug Conc/L</th>
<th>Remarks</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride 0.9%</td>
<td>MG</td>
<td>GL</td>
<td>1 to 30 g</td>
<td>Less than 10% loss in 24 hr at room temperature and 7 days refrigerated</td>
<td>1</td>
</tr>
<tr>
<td>Sodium chloride 0.9%</td>
<td>6</td>
<td>GL</td>
<td>15 g</td>
<td>5% loss in 48 hr at 25°C under fluorescent light</td>
<td>1164</td>
</tr>
<tr>
<td>Sodium chloride 0.9%</td>
<td>6</td>
<td>GL</td>
<td>6 g</td>
<td>Visually compatible with little or no loss in 24 hr at room temperature and 4°C</td>
<td>1162</td>
</tr>
<tr>
<td>Sodium chloride 0.9%</td>
<td>BA</td>
<td>GL</td>
<td>5 and 10 g</td>
<td>Physically compatible with about 7% cefuroxime loss in 24 hr and 13% loss in 48 hr at 25°C. About 4% loss at 5°C and no loss at ~10°C in 30 days</td>
<td>1162</td>
</tr>
</tbody>
</table>

### pH

The reconstituted vials have a pH of 6 to 8.5. The frozen premixed solutions have a pH of 5 to 7.5.\(^{1162}\)

### Osmolality

The following maximum cefuroxime sodium concentrations were recommended to achieve osmolalities suitable for peripheral infusion in fluid-restricted patients.\(^{1160}\)

<table>
<thead>
<tr>
<th>Diluent</th>
<th>Maximum Concentration (mg/mL)</th>
<th>Osmolality (mOsm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrose 5%</td>
<td>76</td>
<td>568</td>
</tr>
<tr>
<td>Sodium chloride 0.9%</td>
<td>68</td>
<td>541</td>
</tr>
<tr>
<td>Sterile water for injection</td>
<td>137</td>
<td>489</td>
</tr>
</tbody>
</table>
Stability data Cefuroxime Fresenius

<table>
<thead>
<tr>
<th>Product</th>
<th>Concentration</th>
<th>Solvent</th>
<th>Storage Ambient day light</th>
<th>Testing Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefuroxim Kabi</td>
<td>7,5 mg/mL</td>
<td>0,9% NaCl</td>
<td>25 ± 2°C</td>
<td>0, 5, 24, 48 hours</td>
</tr>
<tr>
<td>Cefuroxim Kabi</td>
<td>30 mg/mL</td>
<td>0,9% NaCl</td>
<td>25 ± 2°C</td>
<td>0, 5, 24, 48 hours</td>
</tr>
<tr>
<td>Zinacef</td>
<td>7,5 mg/mL</td>
<td>0,9% NaCl</td>
<td>25 ± 2°C</td>
<td>0, 5, 24, 48 hours</td>
</tr>
<tr>
<td>Zinacef</td>
<td>30 mg/mL</td>
<td>0,9% NaCl</td>
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<td>0, 5, 24, 48 hours</td>
</tr>
<tr>
<td>Cefuroxim Kabi</td>
<td>7,5 mg/mL</td>
<td>0,9% NaCl</td>
<td>2 - 8°C</td>
<td>0, 7, 14, 28 days</td>
</tr>
<tr>
<td>Cefuroxim Kabi</td>
<td>30 mg/mL</td>
<td>0,9% NaCl</td>
<td>2 - 8°C</td>
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**Result:**
- The analytical data showed that Cefuroxime Kabi is equivalent to Zinacef without significant differences under all tested conditions.
- After 24 hours at 25°C, and after 14 days at 2-8°C and ambient light, the assay (content of Cefuroxime) decreases in both products by ca. 10% from the original value. This is in correspondence to the literature.

Cefuroxime 6000 MG/250 ML (24 MG/ML) in 0,9% NaCl solution: 24 stability at 25°C

**Devices for IV drug delivery**
- Syringes for administering bolus doses or short time infusion
- Non-electrical pump (elastomeric devices)
- Electrical pump (e.g. CADD, ..)
  - Cystic fibrosis patients in UZGent
    - Compounding in hospital pharmacy: ceftazidim 8 g , tobramycin 400 MG and cefuroxim 6 g
    - Stable for 7 days in refrigerator
    - Administered using CADD pump
    - Legal basis with reimbursement (devices, pump...)
OPAT survey in 2013 in UK showed that OPAT services (23 of 120) use pre-filled devices for continuous infusion.

Objectives:
- A comprehensive literature review of published antimicrobial stability data, and assess these against a nationally recognized minimum dataset for medicines compounded into administration devices.

Results:
- A total of 420 citations were reviewed with 121 selected for full text review. None of these papers met the inclusion criteria stipulated in the national standards.
- The most frequent reason for study exclusion was the tolerance limit for the level of the active pharmaceutical ingredient being wider than 95%–105% and absence of 'in-use' testing at 37°C.

Jenkins et al. JAC 2017 doi:10.1093/jac/dkw556

• Elastomeric pumps are used in more than one-third of OPAT patients
  University Hospital of Lausanne, Switzerland
• Published antimicrobial stability in elastomeric pumps is based on experiments performed under laboratory conditions, whereby antibiotic solutions are exposed to constant temperatures of -5, 5 and 25°C.

Methodology: Healthy volunteers carried the elastomeric pumps in carry pouches during their daily activities. A thermologger measured the temperatures every 15 min over 24 h. Antibiotic concentrations were measured

Voumard et al. JAC 2017 doi:10.1093/jac/dkw582
Starting point

In order to ensure adequate anti-infective activity, usual recommendations state that antibiotic degradation at the end of the infusion period should be 10% from the initial concentration.

Voumard et al. JAC 2017 doi:10.1093/jac/dkw582

Results show that in certain real-life situations the temperature of antimicrobial solutions in elastomeric pumps can greatly exceed the recommended value of 25°C, thus potentially affecting the chemical stability of the drugs.

- During daytime, the temperature of solutions in the pumps increased to 30°C. During the night, the temperatures reached up to 33°C.

- Patients should therefore be instructed to take precautions (avoiding exposure to sunlight) to prevent excessive temperature increases.

- They demonstrated that under real-life conditions no significant degradation of cefazolin, cefepime, piperacillin and tazobactam is observed. For flucloxacillin, degradation of 11% is expected over 24 h, but with questionable impact on the actual efficacy of anti-infective treatment.

Voumard et al. JAC 2017 doi:10.1093/jac/dkw582
Continuous Infusions of Meropenem in Ambulatory Care: Clinical Efficacy, Safety and Stability

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Abstract

Objective: Concerns regarding the clinical impact of meropenem instability in continuous infusion (CI) devices may contribute to inconsistent uptake of this method of administration across outpatient parenteral antimicrobial therapy (OPAT) services.

Methods: We retrospectively reviewed the clinical efficacy and safety of CI of meropenem in two Australian tertiary hospitals and assessed its stability under simulated OPAT conditions including in elastomeric infusion devices containing 1% (2.4 g) or 2% (4.8 g) concentrations at either room temperature or cooled conditions. Infusate aliquots were assayed at different time-points over 24 hours.

Results: Forty-one (82%) of 50 patients had clinical improvement or were cured. Adverse patient outcomes including infection, hepatic and nephrotoxicity were infrequent. Cooled infusers with 1% meropenem had a mean 24-hour recovery of 90.8%. Recoveries of 1% and 2% meropenem at room temperature and 2% under cooled conditions were 88%, 83% and 82%, respectively. Patients receiving 1% meropenem were likely to receive 79% of the maximum deliverable dose (MDD) over a 24-hour period whilst patients receiving 2% meropenem should receive 93% and 87% of the MDD under cooled and norm temperature conditions, respectively.

Conclusions: Meropenem infusers are likely to deliver >95% MDD and maintain effective plasma concentrations throughout the dosing period. These data reflect our favourable clinical experience with meropenem CI.


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Continuous Infusions of Meropenem in Ambulatory Care: Clinical Efficacy, Safety and Stability

“Although these results accord with the favourable clinical experience at our institutions and are reassuring because adequate drug concentrations are likely to be attained, further studies are required to confirm the safety and efficacy of meropenem CIs.

Ideally, future studies should be prospective with pre-defined assessments of toxicity and efficacy outcomes. Meropenem and possible toxic degradation products should also be measured in patient plasma samples.”


Conclusion

- When selecting the best antimicrobial, try to use guideline-supported antimicrobials with the narrowest spectrum and simplest dosing regimen taking in account the vascular access, workload, safety of administration.

- Only certain antimicrobials, based on stability are candidates for continuous infusion at home.
  - Comfort for patient and home nurse

- Develop procedures for all antimicrobials in our OPAT programs
OPAT: ambulante parenterale antimicrobiële therapie

Bij sommige infecties is langdurige intraveneuze behandeling nodig om de bacterie te bestrijden. Soms is het mogelijk om deze behandeling na opstart in het ziekenhuis veilig thuis verder te zetten. Zo kunnen patiënten sneller hun dagelijkse activiteiten weer opnemen, en hun vertrouwde omgeving.

Het UZ Gent heeft al 10 jaar ervaring met ambulante parenterale antimicrobiële therapie.

http://www.uzgent.be/nl/zorgaanbod/mdspecialismen/OPAT

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