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Outpatient parenteral antimicrobial treatment

Which antibiotics can be used?

SBIMC-BVIKM
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UK national OPAT guidelines

- **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)

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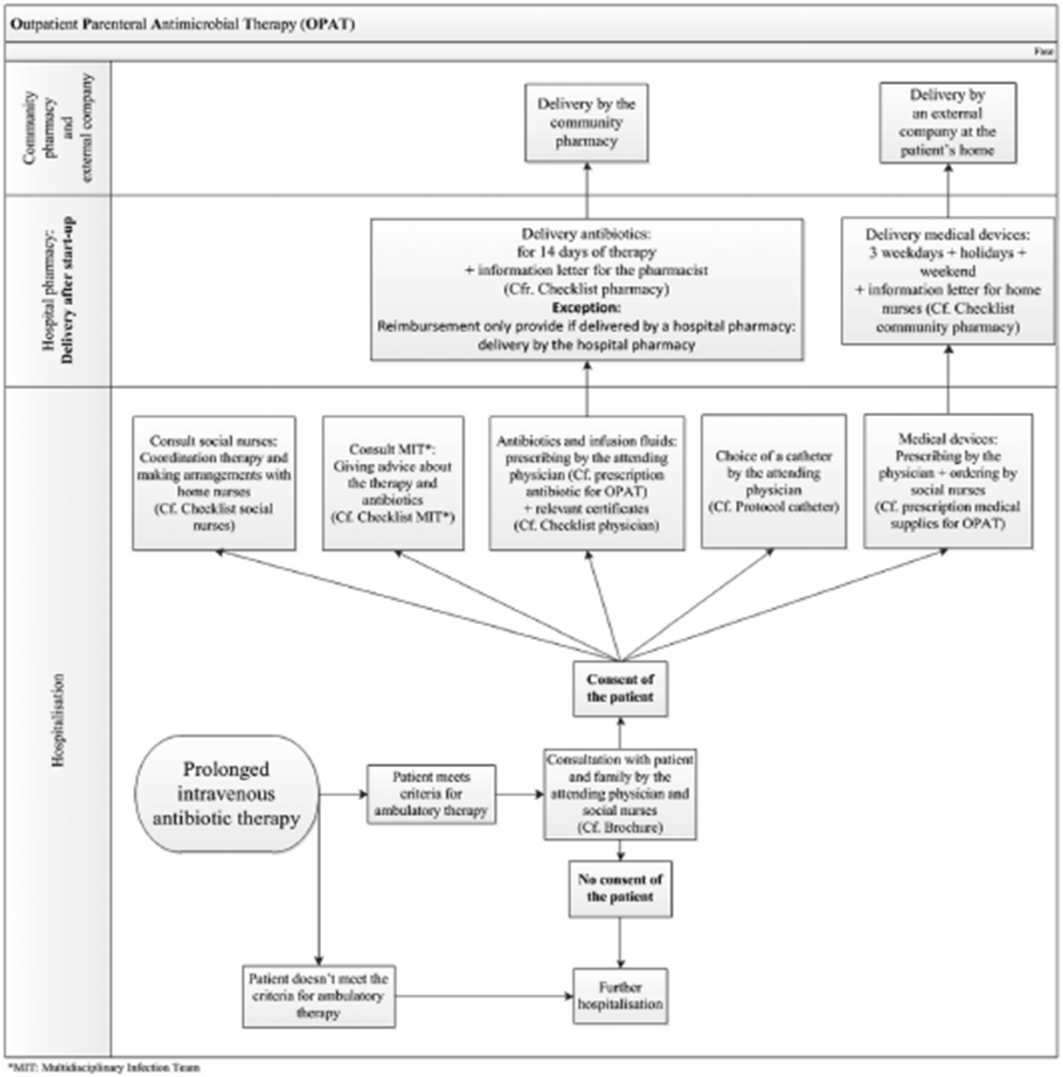
Flowchart of OPAT in the Ghent University Hospital



Ravelingien et al. Acta Clin Belg. 2016;19:1-6

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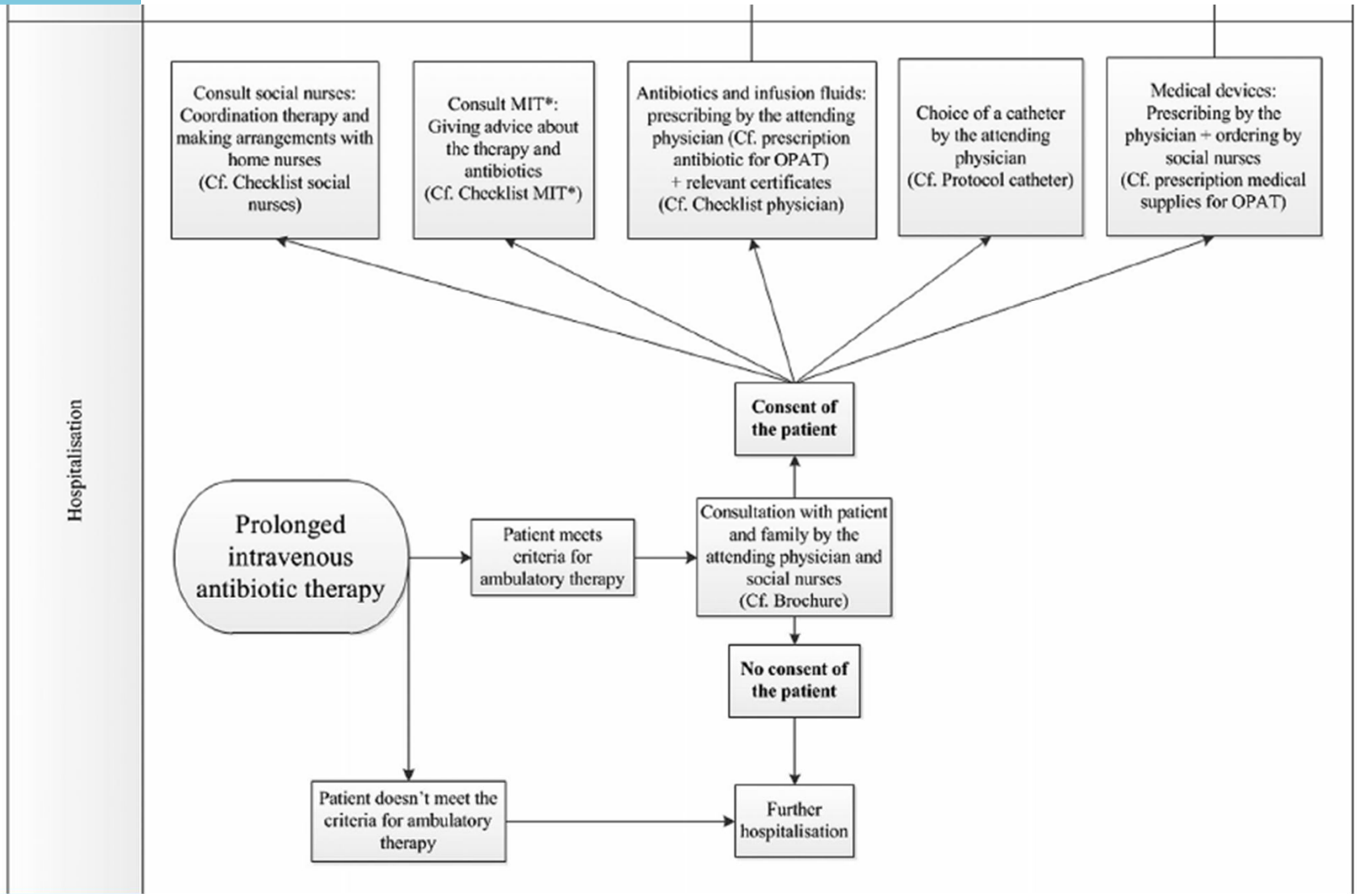
Flowchart of OPAT in the Ghent University Hospital



Antimicrobials prescribed for OPAT in Belgian hospitals

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

Table 2. Antimicrobials prescribed for OPAT, as reported by Belgian hospitals.

Type of infection	Number of hospitals reporting use of antimicrobial for OPAT (N = 53) (%)
Ceftriaxone	44 (83)
Temocillin	19 (36)
Ceftazidime	16 (30)
Meropenem	14 (26)
Teicoplanin	12 (23)
Amikacin	10 (19)
Vancomycin	10 (19)
Flucloxacillin	7 (13)
Tigecycline	6 (11)
Amphotericin B	5 (9)
Benzylpenicillin	5 (9)
Colistin	5 (9)
Linezolid	5 (9)
Piperacillin/tazobactam	5 (9)
Aztreonam	4 (8)
Amoxicillin/clavulanic acid	3 (6)
Cefepime	3 (6)
Gentamicin	2 (4)
Amoxicillin	1 (2)
Cefuroxime	1 (2)
Anidulafungin	1 (2)
Voriconazole	1 (2)
Other [a]	6 (11)

[a] Includes cefazolin (n = 2), tobramycin (n = 1), cefadroxil (n = 1), ciprofloxacin (n =1), ganciclovir (n = 1)

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Criteria for antimicrobial choice in OPAT programs

- The antimicrobial spectrum.
- Antimicrobial penetration and target site.
- The antimicrobial's side effect profile.
- Antimicrobial drug–drug and drug–host interactions.
- 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)**

G. Gilchrist. J Antimicrob Chemother 2015; 70: 965–970

Barriers for implementation of OPAT in Belgium

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

Table 3. The barriers for implementation of OPAT in Belgium.

	Hospitals who use OPAT (N=53)		Hospitals who do not use OPAT (N=14)	
Barrier	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%

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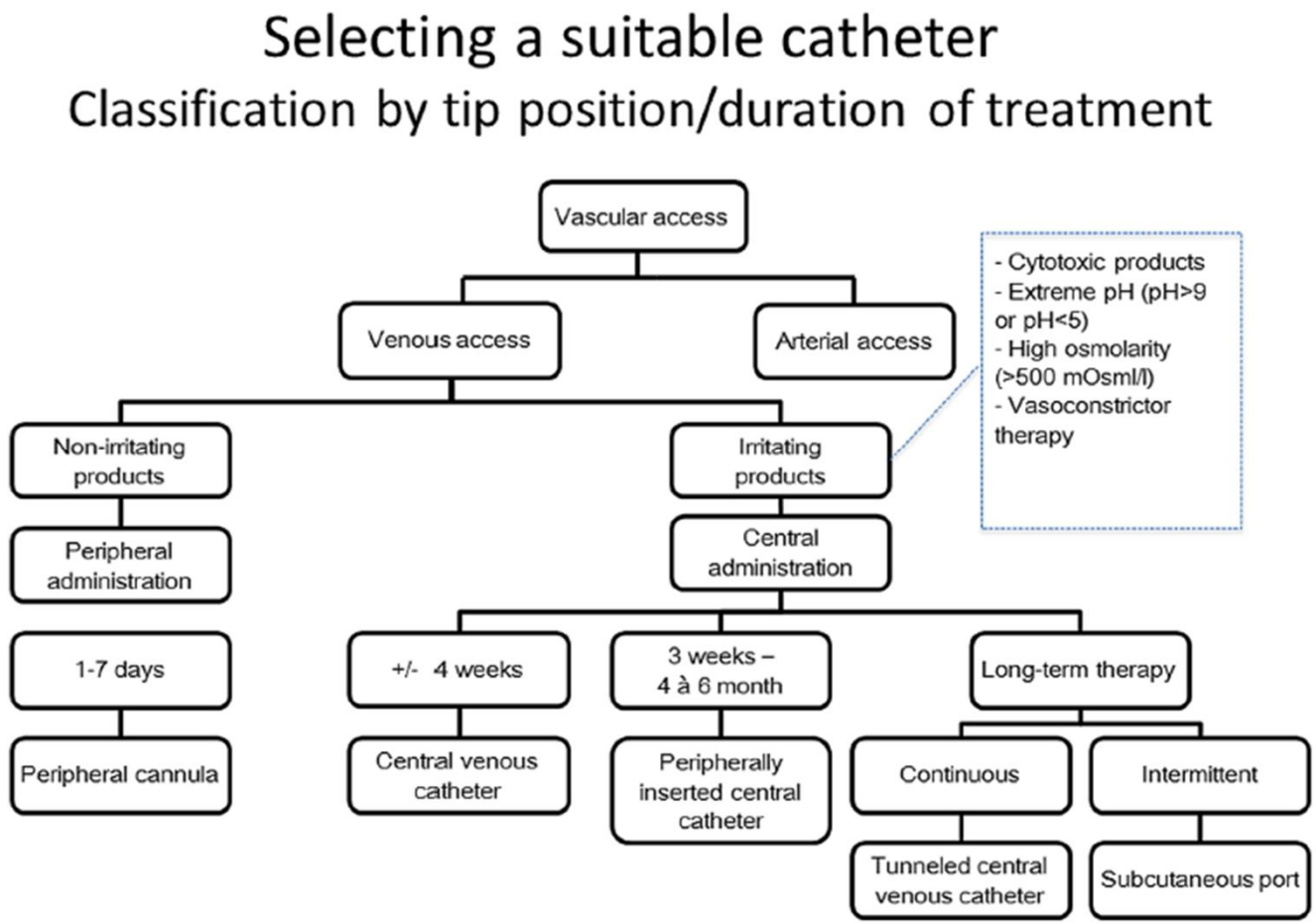
Service structure: various service models

- **Compounding**
  - Home
    - Trained home nurse
    - Trained Carer/patient
  - Hospital pharmacy
  - Commercial compouding 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



Bevanet. Bevanet – belgian vascular access network Available from: http://www.bevanet.be/

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?

IDSA. Clinical Infectious Diseases 2004; 38:1651–72
Candel F et al. Rev Esp Quimioter 2016;29(2):55-6

Table 1. Common parenteral antibiotics, their role in OPAT and their typical position in antimicrobial stewardship programmes

	Mode of administration	Frequency of administration	Role in OPAT	Typical position in antimicrobial stewardship programmes	Potential barriers to OPAT use
Amikacin	infusion	daily or alternate days[13]	complex Gram-negative and mycobacterial infections	unrestricted	ototoxicity and complexity of administration; therapeutic drug monitoring
Amoxicillin	bolus	6–8 hourly	enterococcal infections including endocarditis and bone and joint infections	unrestricted	multiple daily doses or requires continuous infusion device
Ceftriaxone	bolus or infusion	daily	Gram-positive and -negative infections including skin and soft tissue infections, meningitis, brain abscesses and bone and joint infections	restricted	*C. difficile* risk
Ceftazidime	bolus or infusion	8–12 hourly	complex Gram-negative infections (bone or respiratory)	restricted	*C. difficile* risk
Clindamycin	infusion	6 hourly	*S. aureus* and β-haemolytic streptococcal infections	restricted	*C. difficile* risk
Co-amoxiclav	bolus	8 hourly	mixed infections including intra-abdominal/pelvic infections, perineal infections and diabetic osteomyelitis	usually restricted	*C. difficile* risk
Daptomycin	bolus	daily	resistant Gram-positive infections including *S. aureus* bacteraemia, bone and joint infections and endocarditis	restricted	financial cost; preservation for complex resistant cases
Ertapenem	infusion	daily	mixed or Gram-negative infections including intra-abdominal/pelvic infections and diabetic osteomyelitis; infections with ESBL organisms	restricted	carbapenem restrictions due to concerns regarding resistance development; *C. difficile* risk
Flucloxacillin	bolus	4–6 hourly or continuous	*S. aureus* and β-haemolytic streptococcal infections	unrestricted	multiple daily doses or requires continuous infusion device
Gentamicin	infusion	daily or alternate daily	resistant Gram-negative infections (short term)	unrestricted (limited to short-term use)	toxicity with prolonged use; therapeutic drug monitoring
Meropenem	bolus	8 hourly	mixed or Gram-negative infections including intra-abdominal/pelvic infections and diabetic osteomyelitis; infections with ESBL organisms	restricted	carbapenem restrictions due to concerns regarding resistance development; *C. difficile* risk
Nafcillin/ oxacillin	infusion	4–6 hourly or continuous	*S. aureus* and β-haemolytic streptococcal infections	unrestricted	multiple daily doses or requires continuous infusion device
Piperacillin/ tazobactam	infusion	6 hourly or continuous	resistant Gram-negative infections including intra-abdominal infections, pelvic infections and diabetic osteomyelitis	restricted	*C. difficile* risk; concerns regarding resistance development
Teicoplanin	bolus	daily or thrice weekly[14]	Gram-positive infections including skin and soft tissue infections, *S. aureus* bacteraemia and bone and joint infections	unrestricted	may be associated with an increase in OPAT failure in some patient groups[29]
Vancomycin	infusion	daily or twice daily or continuous	Gram-positive infections including skin and soft tissue infections, *S. aureus* bacteraemia and bone and joint infections	unrestricted	multiple daily doses or requires continuous infusion device; therapeutic drug monitoring

G. Gilchrist. J Antimicrob Chemother 2015; 70: 965–970

Criteria antimicrobial choice in OPAT programs

- 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

- 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):
      - Compouding in a non aseptic: reconstituted drug should be used within 24h

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)

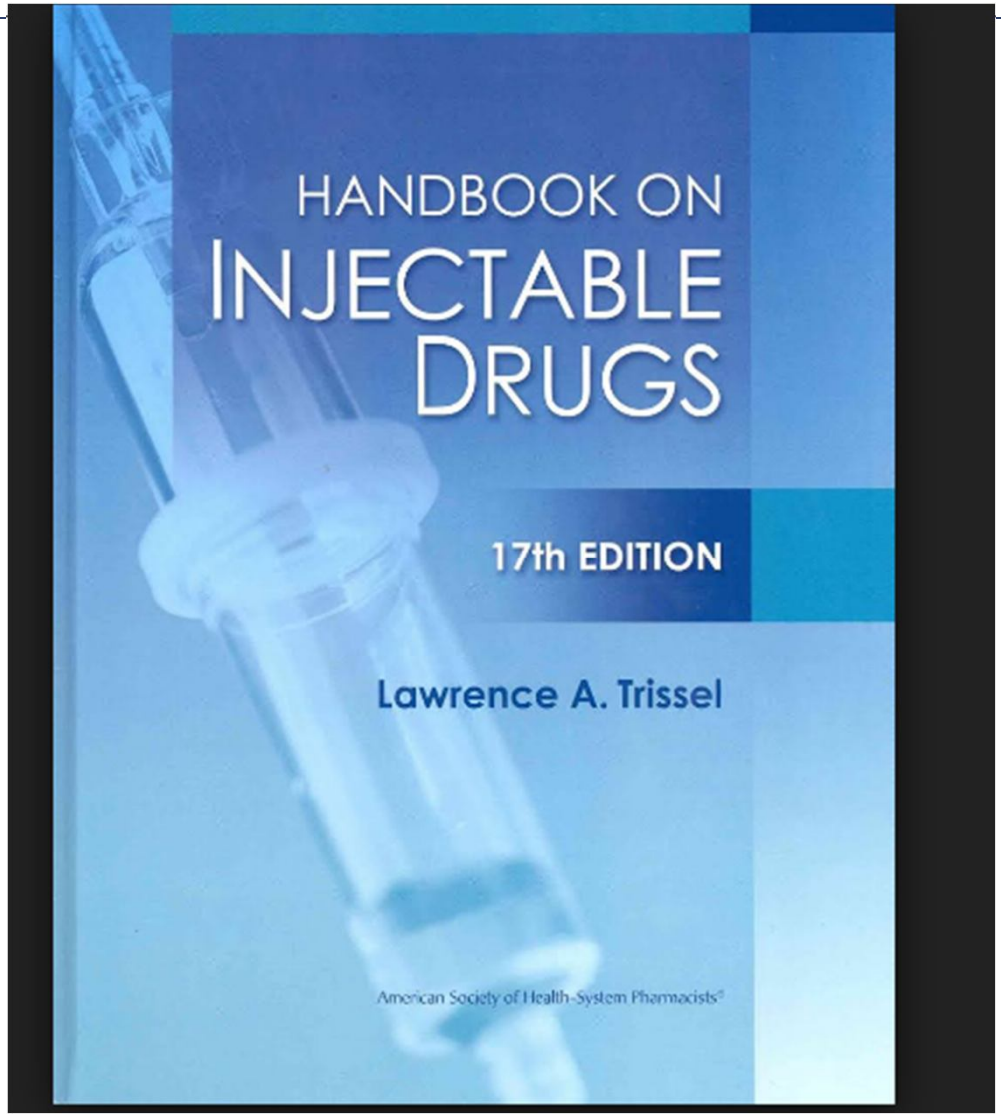
Bereiden van de oplossing voor intraveneuze infusie
Cefuroxim 1500 mg moet gereconstitueerd worden volgens de instructie voor reconstitutie van een intraveneuze injectie met water voor injectie (zie tabel 4 hierboven).
Verdere verdunning moet met 50-100 ml van één van de volgende verenigbare infuusvloeistoffen voor toediening van het intraveneuze infuus:

Cefuroxim natrium is verenigbaar met de volgende infuusvloeistoffen. Het blijft gedurende 5 uur stabiel bij 2°C – 8°C in:

- water voor injectie
- 0,9% natriumchlorideoplossing
- 5% glucoseoplossing

Voor éénmalig gebruik.

Alle ongebruikte producten en afvalstoffen dienen te worden vernietigd overeenkomstig lokale voorschriften.



Test Soln Name	Test Soln Mfr	Base Drug Mfr	Base Drug Conc/L	Remarks	Refs	Compat
Sodium chloride 0.9%			1 to 30 g	Less than 10% loss in 24 hr at room temperature and 7 days refrigerated	1 (3/07)	
Sodium chloride 0.9%	MG[a]	GL	15 g	5% loss in 48 hr at 25°C under fluorescent light	1164	
Sodium chloride 0.9%	b		6 g	Visually compatible with little or no loss in 24 hr at room temperature and 4° C	1953	
Sodium chloride 0.9%	BA[ab]	GL	5 and 10 g	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	712	

pH

The reconstituted vials have a pH of 6 to 8.5. The frozen premixed solutions have a pH of 5 to 7.5.[1(3/07)]

Osmolality

The following maximum cefuroxime sodium concentrations were recommended to achieve osmolalities suitable for peripheral infusion in fluid-restricted patients[1180] :

Diluent	Maximum Concentration (mg/mL)	Osmolality (mOsm/kg)
Dextrose 5%	76	568
Sodium chloride 0.9%	68	541
Sterile water for injection	137	489

Handbook on Injectable Drugs 17th edition

Stability data Cefuroxime Fresenius

Product	Concentration	Solvent	Storage Ambient day light	Testing Intervals
Cefuroxim Kabi	7,5 mg/mL	0,9% NaCl	25 ± 2°C	0, 5, 24, 48 hours
Cefuroxim Kabi	30 mg/mL	0,9% NaCl	25 ± 2°C	0, 5, 24, 48 hours
Zinacef	7,5 mg/mL	0,9% NaCl	25 ± 2°C	0, 5, 24, 48 hours
Zinacef	30 mg/mL	0,9% NaCl	25 ± 2°C	0, 5, 24, 48 hours
Cefuroxim Kabi	7,5 mg/mL	0,9% NaCl	2 - 8°C	0, 7, 14, 28 days
Cefuroxim Kabi	30 mg/mL	0,9% NaCl	2 - 8°C	0, 7, 14, 28 days
Zinacef	7,5 mg/mL	0,9% NaCl	2 - 8°C	0, 7, 14, 28 days
Zinacef	30 mg/mL	0,9% NaCl	2 - 8°C	0, 7, 14, 28 days

Result:

- The analytical data showed that **Cefuroxime Kabi is equivalent to Zinacef without significant differences** under all tested conditions.
- After **24hours 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
    - Compouding in hospital pharmacy: ceftazidim 8 g , tobramycine 400 MG and cefuroxim 6 g
    - Stable for 7 days in refrigerator
    - Administered using CADD pump
    - Legal basis with reimbursement (devices, pump..)

J Antimicrob Chemother
doi:10.1093/jac/dkw556

Journal of Antimicrobial Chemotherapy

Extended stability of antimicrobial agents in administration devices

Abi Jenkins[1]*, Tim Hills[2], Mark Santillo[3], Mark Gilchrist[4] on behalf of the Drug Stability Working Group of the BSAC UK OPAT Initiative

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- 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

Uncertainty about the stability of antimicrobial drugs in elastomeric pumps used for OPAT

- 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

Table 2 Characteristics of intravenous antimicrobials potentially useful for OPAT programmes.

Drug	Dose range	Half-life	Stability at 5ºC	Stability at 20-25ºC	Infusion pump	Risk of phlebitis	ADRs	Recommended monitoring
Penicillin G sodium	2-4 mU/4h	< 1hour	7 days	24 hours	Yes	I		
Ampicillin	0,5-2 g/4-6h	1 hour	3 days	8 hours	No	I		
Amoxicillin-clavulanic acid	1-2 g/8h	1 hour	24 hours. 7-10 days reconstituted	1 hour	No	I		
Cloxacillin	1-2 g/4-6h	< 1hour	3-7 days	24 hours	Yes	I		
Cefazolin	0,5-2 g/6-8h	1-2 hours	24 hours	6 hours	Yes	L		
Cefoxitin	1-2 g/6-8h	1 hours	4 days	24 hours	ND	L		
Cefuroxime	1-1,5 g/8h	1-2 hours	7 days	24 hours	Yes	L		
Ceftriaxone	2 g/24h	5-10 hours	10 days	3 days	Not recommended	L	M, R, H	CBC, LFT, R and I once per week
Ceftazidime	1-2 g/8h	1,5-2 hours	7 days	24 hours	Yes	L		
Cefepime	0,5-2 g/12h	2 hours	7 days	24 hours	Not recommended	L		
Ceftaroline	1 g/8-12h	2,5 hours	24 hours	6 hours	ND	ND		
Aztreonam	1-2 g/8h	1-2 hours	7 days	2 days	Little experience	L		
Piperacillin-tazobactam	4 g/6h	1 hour	48 hours	24 hours	Yes	I		
Ertapenem	1 g/24h	4 hours	24 hours	6 hours	Not recommended	I		
Imipenem	0,5-1 g/6-8h	1 hour	24-48 hours	1 hour	Not recommended	I		
Meropenem	0,5-2 g/8-12h	1 hour	24 hours	4 hours	Not recommended	L		
Amikacin	10-15 mg/kg/24h	2-3 hours	7 days	24 hours	Not recommended	L		
Tobramycin	5-10 mg/kg/24h	2-3 hours	4 days	24 hours	Not recommended	L	R, N	R twice per week, LFT once per week and hearing test every visit
Gentamycin	5-10 mg/kg/24h	2-3 hours	4 days	24 hours	Not recommended	L		
Streptomycin	15 mg/kg/24h	2-4 hours	24 hours	ND	Not recommended	L		
Azithromycin	500 mg/24h	48-60 hours	1-7 days	24 hours	Not recommended	H	R, H, C, GI	R, LFT and ECG once per week, ask about GI disorders
Tigecycline	100 mg load and 50 mg/12h	40-60 hours	48 hours 5% dextrose or SSF	24 hours	Not recommended	I	H, GI	LFT twice per week, ask about GI symptoms every visit

Candel F et al. Rev Esp Quimioter 2016;29(2):55-6

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
- Only certain antimicrobials, based on stability are candidates for continuous infusion at home.
- Develop procedures for all antimicrobials in our OPAT pograms

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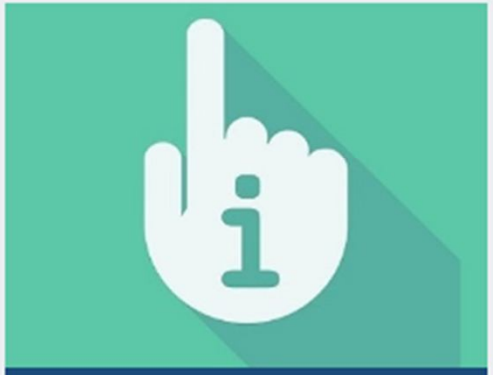
OPAT: ambulante parenterale antimicrobiële therapie

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, in hun vertrouwde omgeving.

Het UZ Gent heeft al 15 jaar ervaring met ambulante parenterale antimicrobiële therapie.

Info voor patiënten

Info voor zorgverleners



Contact

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

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