Udarbejdet af: Ulrik Stenz Justesen, Barbara Holzknecht, Pia Littauer, Jurgita Samulionienė, Dennis Schrøder Hansen og Mikala Wang
Version 1, 11. december 2015

Antibiotikabehandling af infektion med carbapenemase-producerende *Enterobacteriaceae* (CPE)

Der findes ingen evidensbaserede retningslinier for behandling af infektioner med carbapenemase-producerende Enterobacteriaceae (CPE) med OXA-48 og NDM. Data i litteraturen angår først og fremmest infektioner med KPC-producerende *Klebsiella pneumoniae*.
Der findes behandlingsresultater for et meget lille antal patienter med infektioner med OXA-48 producerende bakterier. Der findes ligeledes data fra meget få patienter som er behandlet med flourquinoloner, formentlig grundet resistens.

Det er derfor vanskeligt at udtale sig om behandling når det gælder

1) OXA-48, herunder behandling med cefalosporin,
2) NDM og
3) behovet for kombinationsbehandling med et carbapenem, hvis isolatet er fuldt følsomt for flourquinolon
4) andre arter end *Klebsiella pneumoniae* (der er en rimelig formodning om, at andre enterobakterie-arter ikke er mere vanskelige at behandle)

Som udgangspunkt anbefales kombinationsbehandling med carbapenem hvis isolatet er intermediært følsomt i henhold til EUCAST (meropenem eller imipenem MIC ≤ 8 mg/L: eventuelt op til meropenem MIC ≤ 16 mg/L). Der er data for mange forskellige foci og det anføres i litteraturen, at kombinationsbehandling synes at være det mest effektive ved alle typer af infektioner. Der findes endnu ikke kontrollerede randomiserede studier der understøtter effekten af kombinationsbehandling ved infektion med CPE.

Som første valg anbefales, hvis der er in vitro følsomhed for de anførte antibiotika udover carbapenem:

Carbapenem + aminoglykosid

Alternativt:

Carbapenem + colistin

Afhængig af følsomhedsbestemmelse og fokus eventuelt 3- og 4-stofs kombinationer med nedenstående stoffer. Ved infektion med panresistente isolater er der kasuistisk beskrevet effekt af behandling med 2 carbapenemer.

Doseringsskema

Antibiotikum	Normaldosering (iv)	Dosering til behandling af CPE-infektioner (iv)	Vigtigste bivirkninger	Kommentar
Meropenem	1g x 3	2 g x 3		Gives evt. som forlænget infusion over 4 timer til at maksimere t/MIC.
Imipenem		1 g x 4		Gives evt. som forlænget infusion over 4 timer til at maksimere t/MIC.
Ceftazidim/ avibactam		2000 mg/500 mg x 3		Hæmmer ikke MBL-producerende bakterier. Ikke indregistreret i Danmark. Infusion over 2 timer.
Gentamicin	5mg/kg x 1	7-10 mg/kg x 1	Oto/nefrotoxicitet	
Tobramycin	5mg/kg x 1	7-10 mg/kg x 1	Oto/nefrotoxicitet	
Amikacin		15-20 mg/kg x 1	Oto/nefrotoxicitet	
Colistin		Loading dose 9 MIU, så 4,5 MIU x 2 (3 MIU x 3)	Nefro/neurotoxicitet	Dosisjustering ved nyreinsufficiens, se tabel 5 i Morrill et al. Monoterapi bør undgås grundet risiko for resistensudvikling.
Tigecycline	Loading dose 100 mg, så 50 mg x 2	Loading dose 200 mg, så 100 mg x 2 (off label)	Gastrointestinale bivirkninger, forhøjede leverenzymer, pankreatitis	Monoterapi bør undgås grundet risiko for resistensudvikling. Ikke til urinvejsinfektion.
Fosfomycin		4 g x 4 Kan øges til 8 g x 3 ved livstruende infektioner, herunder meningitis	Lav bivirkningsprofil Hypokaliæmi	Ikke indregistreret i Danmark, men kan skaffes ved særtilladelse. Monoterapi bør undgås grundet risiko for resistensudvikling.
Rifampicin		600 mg x 3		Kun kasuistisk beskrevet effekt. Monoterapi bør undgås grundet risiko for resistensudvikling.

Colistin dosering ved nyreinsufficiens (Morrill et al. 2015)

Table 5. Comparison of Colistin vs Polymyxin B*

		Colistin	
Form administered		Prodrug (CMS)	
Best pharmacodynamics predictor of activity		fAUC/MIC	
Dosing units		United States – mg CBA Europe – International Units	
Dosing equivalents		30 mg CBA = 80 mg CMS = 1 million International Units CMS	
Loading dose[a]		5 mg CBA/kg[b,c,d] (loading dose required)	
Time until maintenance dose[a]		12 to 24 h	
Maintenance dose[a]		CrCl (mL/min)	Daily dose (mg CBA)
	Not on renal replacement therapy[b,f]	0	75
		10	112.5
		20	150
		30	187.5
		40	225
		50	262.5
		60	300
		70	337.5
	Intermittent HD[b,g]	Non-HD day = 75 mgCBA per day HD day = 97.5 mg CBA per day	
	Continuous renal replacement	Dose recommended by Garonzik et al [31] much greater than maximum approved dose, see article for more information.	
Dosage intervals	CrCl <10 mL/min	q12h	
	CrCl 10–70 mL/min	q8–12h	
	CrCl >70 mL/min	q8–12h	
	Intermittent HD	q12h	
	Continuous renal replacement	q8h	
Renal dose adjustment		Yes	

Abbreviations: AUC, area under the curve; CBA, colistin base activity; CMS, colistimethate; CrCl, creatinine clearance; $C_{ss,avg}$, average plasma steady state concentration; f, free drug; HD, hemodialysis; MIC, minimum inhibitory concentration.

* For more information on colistin and polymyxin B MIC testing, see ref. [78].

[a] The ideal dosages of colistin and polymyxin B are largely unknown, especially in the case of renal failure, renal replacement therapy, and critical illness, because the first dosage recommendations were made before consistent pharmacokinetic data were available.

Loading and maintenance doses and dosing interval in table based on the largest pharmacokinetic studies to date, which developed the first scientifically based dosing suggestions for colistin and polymyxin B [31, 32].

[b] Assuming a target colistin $C_{ss,avg}$ of 2.5 μg/mL. However, note this target should be based on MIC, site, and severity of infection. At a daily dose of CMS at or close to the maximum product-recommended dose (300 mg), it is very difficult to achieve adequate plasma concentrations of colistin with CMS monotherapy, especially if treating an infection due to an organism with an MIC >0.5 μg/mL or in a patient with a creatinine clearance of >70 mL/min/1.73 m^2. In these situations, authors suggested that it may be best to use CMS/colistin in combination with other active agents.

[c] Use the lower of ideal or actual body weight (kg).

[d] Not to exceed 300 mg.

[e] Dose on actual body weight.

[f] Caution should be used when dosing beyond maximum recommended dose of 300 mg. Garonzik et al [31] dosing not recommended for patients with CrCl >70 mL/min/1.73 m^2 unless a low $C_{ss,avg}$ can be recommended. Colistin may be best used as a part of combination therapy for patients with good renal function.

[g] On non-HD days give 37.5 mg q12h, and on HD days give an additional 30% of daily maintenance dose after HD, thus dose 1 = 37.5 mg and dose 2 = 60 mg.

[h] Preliminary data suggest that the dose of polymyxin B need not be renally adjusted even in patients on hemodialysis; however, package insert dosing recommendations for polymyxin B include vague renal dosing recommendations that have been followed in all of the polymyxin B literature to date, and, therefore, the efficacy and safety of nonrenally adjusted polmyxin B remains unclear [85–87].

Referencer

Garonzik SM et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother 2011;55:3284-94.

Morrill HJ et al. Treatment Options for Carbapenem-Resistant Enterobacteriaceae Infections. Open Forum Infect Dis. 2015;2.

Tumbarello M et al. Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study. J Antimicrob Chemother 2015;70:2133-43.

Tzouvelekis et al. Treating infections caused by carbapenemase-producing Enterobacteriaceae. Clin Microbiol Infect 2014;20:862-72.

Yamamoto M et al. Treatment for infections with carbapenem-resistant Enterobacteriaceae: what options do we still have? Crit Care 2014;18:229.