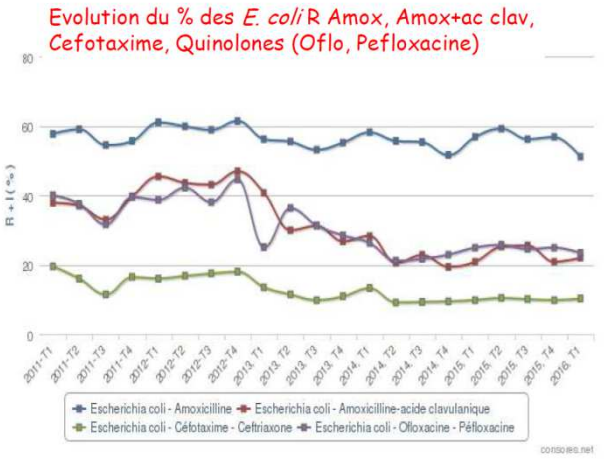
Les anti-Infectieux d'hier et d'aujourd'hui .

Les anti-BLSE
Véronique Mondain

RésO InfectiO PACA Est 19052017

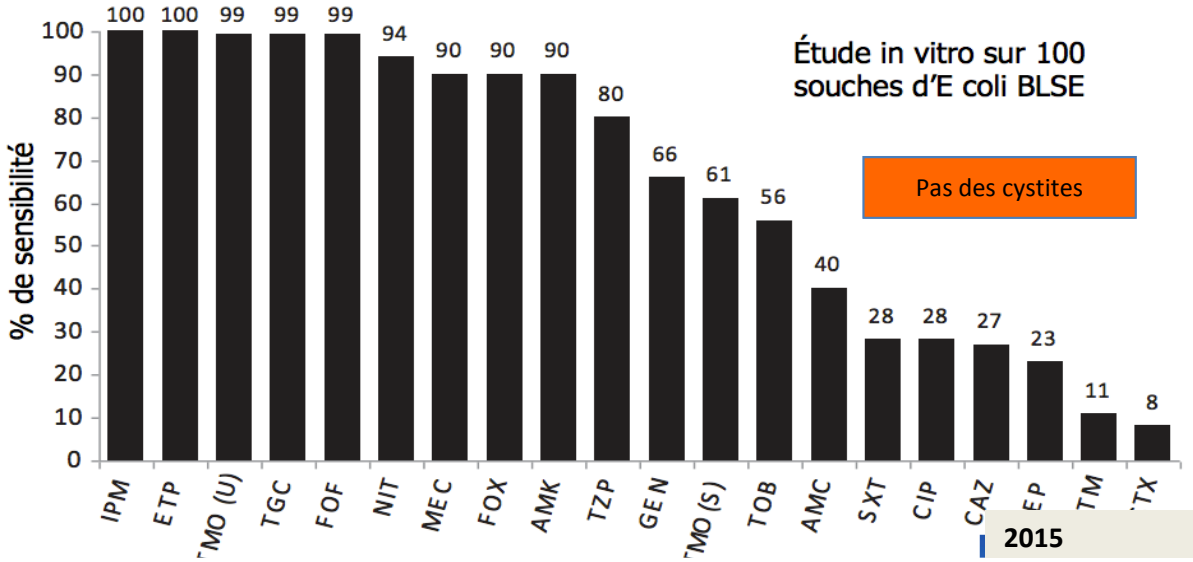
Les BLSE en 2017
Au CHU de Nice



Plutôt moins
E.coli plus S
Augmentation Entérobactéries groupe 3

Sensibilité aux antibiotiques

in vitro…




Les Classiques

Traitement d'une PNA simple documentée à EBLSE :

Antibiogramme		
	1er choix	
Fluoroquinolones-S	Fluoroquinolone (ciprofloxacine, lévofloxacine, ofloxacine)	
Fluoroquinolones-R et TMP-SMX-S	TMP-SMX	
Fluoroquinolones-R et TMP-SMX-R	Amoxicilline+acide clavulanique	Si CMI ≤ 8 mg/l
	Pipéracilline+tazobactam	Si CMI ≤ 8 mg/l
	Céfotaxime	Si CMI ≤ 1 mg/l
	Ceftriaxone	Si CMI ≤ 1 mg/l
	Ceftazidime	Si CMI ≤ 1 mg/l
	Céfépime	Si CMI ≤ 1 mg/l
	2ème choix	
	Témocilline	Si souche sensible
	Céfoxitine*	Si souche sensible, et IU à *E. coli*
	Aminoside (amikacine, gentamicine, tobramycine)	
	3ème choix (en l'absence d'alternative)	
	Carbapénème	
	Traitement d'attaque	Imipénème, méropénème
	Traitement de relais	Ertapénème[a]

* risque de résistance en cas de fort inoculum et espèces autres que *E.coli.*

Disponible en ligne sur
SciVerse ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com
Médecine et maladies infectieuses 42 (2012) 440–443
Médecine et maladies infectieuses

Ertapénem i… …s infections

Ertapenem adm… …ctions caused by

E. Forestier[a,*], S… …nco[a], A. Labe[a],

25 patients
moitié PNA moitié prostatites
Coli BLSE
Traités en externe
100% guéris en fin de traitement
5 rechutes à 3 mois

L'ertapénem … …00mg en cas d'insuffisanc… …isponible aux carbapénèm… …mme. **La voie SC a été uti… …voie d'abord veineux disponible ou pour faciliter l'administration lors du retour à domicile. L'ertapénem a alors été dilué dans 50 mL de NaCl 0,9 % et per- fusé sur 30 minutes** ou dilué dans 3 mL de lidocaine 1 % et injecté sur une minute.

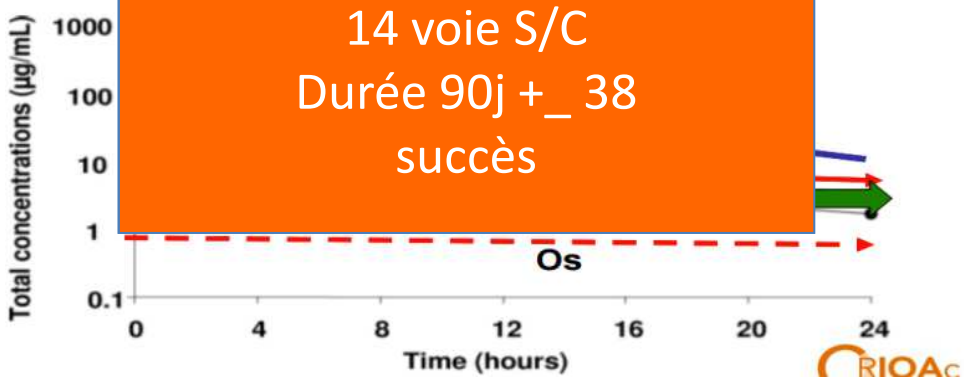
Ertapénème dans les IOA

J Infect. 2012 Dec;65(6):579-82.

Prolonged su… salvage therapy in pa… on.

Ferry T, Sénéchal …

17 patients dont 10 BLSE
14 voie S/C
Durée 90j +_ 38
succès

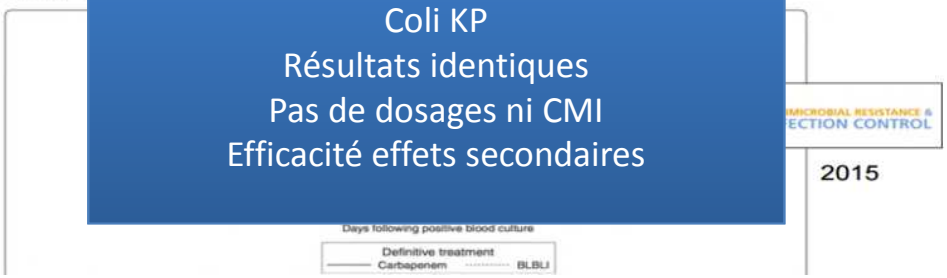


RESEARCH Open Access

Comparable outcomes for β-lactam/β-lactamase inhibitor combinations and carbapenems in definitive treatment of bloodstream infections caused li or *Klebsiell*

Patrick N A Harris
David L Paterson

Singapour 2012 2013 75 ans
47 patients 23 Carba 24 Pip Tazo
Coli KP
Résultats identiques
Pas de dosages ni CMI
Efficacité effets secondaires



MICROBIAL RESISTANCE & INFECTION CONTROL
2015

β-lactam and β-lactamase inhibitor combinations in the treatment of extended-spectrum β-lactamase producing Enterobacteriaceae: time for a reappraisal in the era of few antibiotic options?

Patrick N A Harris, Paul A Tambyah, David L Paterson

BLBLIs might provide a **reasonable carbapenem-sparing option for ESBL producers, especially in less serious infections.** Data are more robust for infections of the urinary tract (including with bacteraemia). **When piperacillin–tazobactam is used for serious infections it should be dosed to maximise pharmacokinetic–pharmacodynamic parameters**, which is likely to be of greater importance when the MIC is at the higher end of the susceptible range.

Lancet Infect Dis **2015; 15: 475–85**

TABLE 1 Mortality among patients with bacteremia due to ESBL-producing *E. coli* who were treated empirically with piperacillin-tazobactam, according to MIC and other variables of interest

Variable and group	Mortality in patients in each group[a]			
	All patients (n = 39)	Low MIC (≤2 mg/liter) (n = 18)	Intermediate MIC (4 to 8 mg/liter) (n = 10)	High MIC (≥16 mg/liter) (n = 11)
All patients	7/3			
Age				
≤65 years	4/2			
>65 years	3/1			
Onset				
Community	2/2			
Nosocomial	5/1			
Charlson index				
≤2	4/2			
>2	3/1			
Source				
Urinary tract	0/11 (0)	0/7 (0)	0/2 (0)	0/2 (0)
Other	7/28 (25)	0/11 (0)[c]	3/8 (37.5)	4/9 (44.4)
Severe sepsis or shock				
No	4/32 (12.5)[d]	0/16 (0)	2/8 (25)	2/8 (25)
Yes	3/7 (42.8)	0/2 (0)	1/2 (50)	2/3 (66.7)
Definitive therapy[e]				
PTZ	0/10	0/5 (0)	0/4 (0)	0/1 (0)
Carbapenem	5/24 (20.8)	0/10 (0)	1/4 (25)	4/10 (40)
Other	0/3 (0)	0/3 (0)		

CMI < 8, 4…. 2…???
Plus de CMI en Etest
Reste un ATB très large spectre

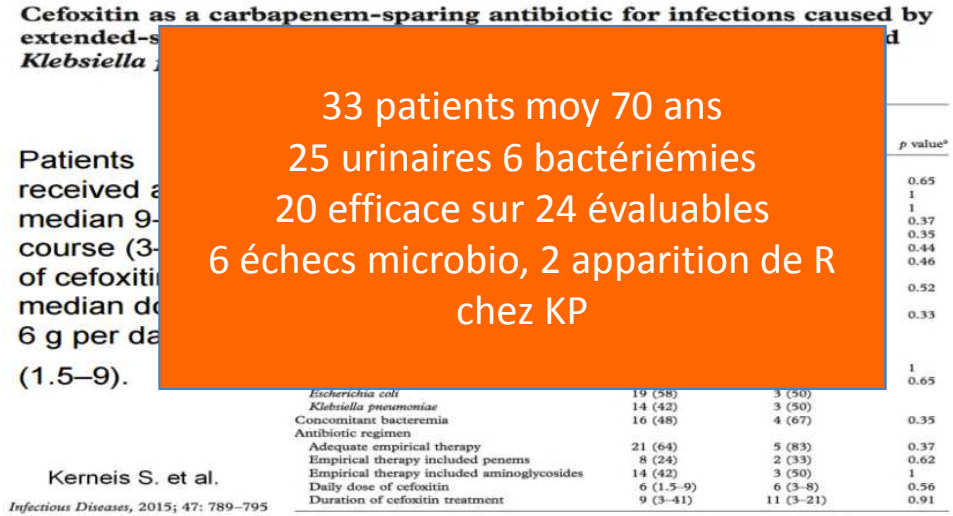
Importance de la CMI

…ériémies à *E.coli* BLSE
…atients avec une
…n urinaire ont
…, indépendamment
…de la CMI

- Pour les autres, la mortalité était plus faible lorsque la CMI était ≤ 2 mg/l.

Retamar, AAC, 2013

cefoxitine



Cefoxitin as a carbapenem-sparing antibiotic for infections caused by extended-s… *Klebsiella …*

Patients received a… median 9… course (3… of cefoxiti… median d… 6 g per da… (1.5–9).

33 patients moy 70 ans
25 urinaires 6 bactériémies
20 efficace sur 24 évaluables
6 échecs microbio, 2 apparition de R chez KP

			p value[a]
Escherichia coli	19 (58)	3 (50)	1
Klebsiella pneumoniae	14 (42)	3 (50)	0.65
Concomitant bacteremia	16 (48)	4 (67)	0.35
Antibiotic regimen			
Adequate empirical therapy	21 (64)	5 (83)	0.37
Empirical therapy included penems	8 (24)	2 (33)	0.62
Empirical therapy included aminoglycosides	14 (42)	3 (50)	1
Daily dose of cefoxitin	6 (1.5–9)	6 (3–8)	0.56
Duration of cefoxitin treatment	9 (3–41)	11 (3–21)	0.91

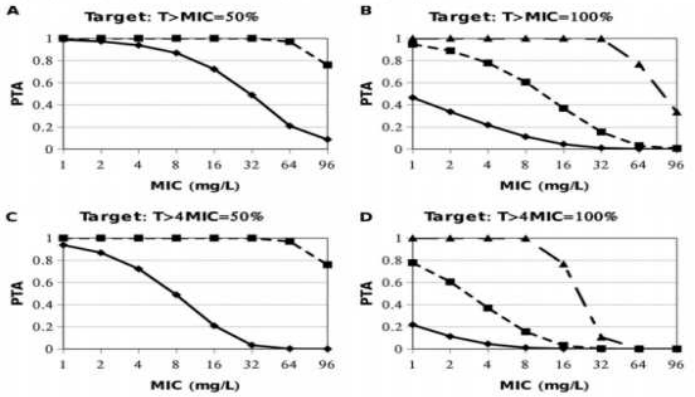
Kerneis S. et al.

Infectious Diseases, 2015; 47: 789–795

Pharmacological Study of Cefoxitin as an Alternative Antibiotic Therapy to Carbapenems in Treatment of Urinary Tract Infections Due to Extended-Spectrum-β-Lactamase-Producing *Escherichia coli*

H. Guet-Revillet,[a,b] A. Emirian,[c,d] M. Groh,[b] B. Nebbad-Lechani,[c] E. Weiss,[b] O. Join-Lambert,[a,b] E. Bille,[a,b] V. Jullien,[e,f] J. R. Zahar[a,b]

Université Paris Descartes, Paris, France[a]; Service de Microbiologie—Hygiène Hospitalière, Hôpital Necker-Enfants-Malades, AP-HP, Paris, France[b]; Service de Bactériologie, Virologie, Hygiène, Hôpital Henri-Mondor, AP-HP, Créteil, France[c]; Université Paris-Est, Créteil, France[d]; Service de Pharmacologie Clinique, Hôpital Européen Georges Pompidou, AP-HP, Paris, France[e]; INSERM U1129, Paris Descartes, Paris, France[f]



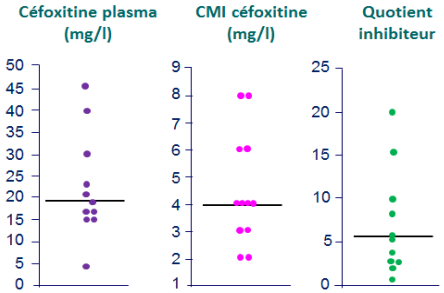
2gx4/j

1hr infusion
4hrs infusion
continuous perfusion

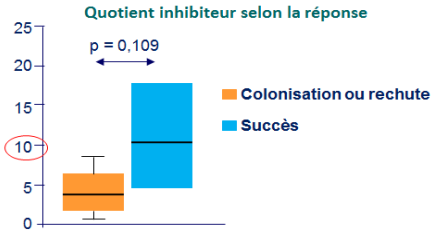
Antimicrob Agents Chemother 2014

Infections urinaires masculines à E-BLSE : quotient inhibiteur de céfoxitine

- Etude simple bras prospective, Nice, 2014-2015
- Evaluation de l'efficacité de la céfoxitine dans les IU masculines fébriles : céfoxitine 6-8 g/j i.v. continue + fosfomycine i.v. 4g x 3/j les 5 premiers jours
- Mesure des concentrations plasmatiques résiduelles de céfoxitine à J5
- 15 patients d'âge moyen 76 ans (48 à 88), antécédents urologiques, n = 14
- 9 *E. coli*, 5 *K. pneumoniae*, 1 *K. oxytoca*
- 21 à 45 jours de traitement ATB



- Succès à M3 :
  - Guérison clinique : 87 %
  - Eradication microbiologique : 54 %



- Tendance pour association entre un QI plus élevé et l'éradication microbiologique

Demonchy E, ECCMID 2016, Abs. P1480

Témocilline (Negaban°)

Etude clinique la plus récente

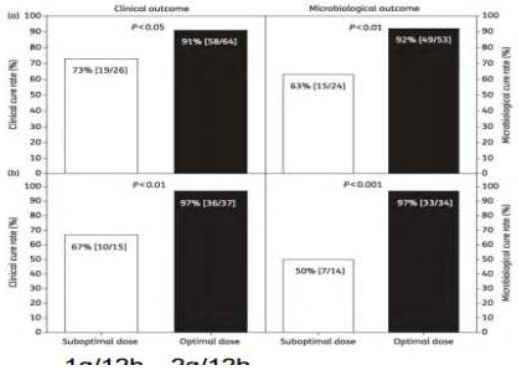
J Antimicrob Chemother 2011; **66**: 2628–2631
doi:10.1093/jac/dkr317 Advance Access publication 2 August 2011

Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC β-lactamase-producing Enterobacteriaceae

Indran Balakrishnan[1]*, F. Mustafa Awad-El-Kariem[2], Adnan Aali[3], Prasanna Kumari[4], Rohinton Mulla[5], Benny Tan[6],

All patients (n=90)

ESBL/AmpC (n=52)



Au total

- Pip-tazo
- Céfoxitine
- Témocilline
- ??????????

céphalosporines

2011 : Abandon du principe de lecture interprétative de l'antibiogramme

• **CA-SFM 2011 :**

« Les concentrations critiques désormais retenues pour les C3G permettent la catégorisation clinique des souches productrices de β-lactamases hydrolysant ces molécules comme, par exemple, les BLSE et dispensent donc d'interpréter les résultats pour des raisons thérapeutiques. »

EUCAST 2017 S si CMI<1mg/L 8% E.coli

Arguments cliniques

Impact of changes in CLSI and EUCAST breakpoints for susceptibility in bloodstream infections due to extended-spectrum β-lactamase-producing *Escherichia coli*

- Etude de l'impact de l'application des recommandations de l'EUCAST et CLSI sur 191 épisodes de bactériémies.
- 14,7% des souches étaient sensibles à la ceftazidime et au céfépime, avec des différences selon le type de BLSE
- le traitement par C3G était efficace dans les cas d'infections non graves, avec un faible inoculum bactérien et avec l'utilisation de doses élevées de C3G

Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis

Konstantinos Z. Vardakas *J Antimicrob Chemother* 2012; **67**: 2793–2803

Méta-analys… …6 et 2010

Qui les utilise?

Study or subgroup						RR, Random, 95% CI
Bin *et al.* (2006)[21]						
Chaubey *et al.* (2010)[22]						
Chung *et al.* (2012)[16]						
Endimiani *et al.* (2005)[25]	0	2	2	4	5.8%	0.33[0.02, 4.85]
Ferrandez *et al.* (2011)[26]	16	30	0	5	5.9%	6.39 [0.44, 92.62]
Lee *et al.* (2010)[30]	5	53	3	3	14.7%	0.12 [0.05, 0.28]
Paterson *et al.* (2004)[33]	1	27	2	4	7.6%	0.07 [0.01, 0.64]
Qureshi *et al.* (2011)[34]	0	8	1	4	5.0%	0.19 [0.01, 3.75]
Rodriguez-Bano *et al.* (2012)[14]	20	120	5	54	14.4%	1.80 [0.71, 4.54]
Tuon *et al.* (2010)[17]	10	15	4	4	16.9%	0.73 [0.46, 1.15]
Tuon *et al.* (2011)[18]	16	43	1	2	11.2%	0.74 [0.18, 3.14]
Total (95% CI)		**398**		**118**	**100.0%**	**0.52 [0.23, 1.13]**
Total events	75		24			

Heterogeneity: $\tau^2 = 0.90$; $\chi^2 = 30.81$, df = 9 ($P = 0.0003$); $I^2 = 71\%$
Test for overall effect: $Z = 1.65$ ($P = 0.10$)

0.01 0.1 1 10 100
Against BL/BLIs Against carbapenems

Pas de différence de mortalité entre carbapénèmes et BL/IBL (traitement empirique et documenté), alors que différence entre carbapénèmes et autres molécules non BL/IBL


Les Nouveaux

Ceftolozane + tazobactam

AMM Europe 1 octobre 2015 (Zerbaxa)

- IIA (+ métronidazole) et IU
  Pneumopathies LAS (en cours)

→ *Solomkin J CID 2015*
Wagentehner FM Lancet 2015

- 1,5 g (1g/0,5 g) x 3/j en 60 min
- Ins. hépatique : pas adaptation de posologie
- Ins. rénale :

Tableau 2 : Dose pour administration intraveineuse du ceftolozane/tazobactam chez les patients ayant une clairance de la créatinine ≤ 50 mL/min

ClCr estimée (mL/min)*	**Schéma posologique recommandé de Zerbaxa (ceftolozane/tazobactam)****
30 à 50	500 mg ceftolozane/250 mg tazobactam par voie intraveineuse toutes les 8 heures
15 à 29	250 mg ceftolozane/125 mg tazobactam par voie intraveineuse toutes les 8 heures
Insuffisance rénale terminale, sous hémodialyse	Dose de charge unique de 500 mg ceftolozane/250 mg tazobactam suivie 8 heures plus tard d'une dose d'entretien de 100 mg ceftolozane/50 mg tazobactam administrée toutes les 8 heures pour le reste du traitement (les jours d'hémodialyse, la dose doit être administrée le plus tôt possible après la fin de l'hémodialyse)

* ClCr estimée selon la formule de Cockcroft-Gault

EER continu : ½ posologie/8 h ?

Oliver WD AAC 2016
Bremner DN Pharmacothérapy 2016

Activité in vitro de l'association ceftolozane-tazobactam (TOL-TAZ) sur les entérobactéries

- Evaluation de l'activité de TOL-TAZ sur les entérobactéries chez des patients de réanimation, 20 pays Europe + Israël (2013-2014)
- 1 258 souches cliniques consécutives

Activité de TOL-TAZ versus autres antibiotiques sur les entérobactéries

Bactéries (nombre de souches)	CMI_{50} / CMI_{90} (mg/l) / % souches sensibles (critères EUCAST 2015)			
	TOL-TAZ	PIP-TAZ	CAZ	MER
E. coli (386)	0,25 / 0,5 / 96,4 %	2 / 32 / 83,6 %	0,25 / 16 / 79 %	≤0,06 / ≤0,06 / 100 %
BLSE (91)	0,5 / 2 / 84,6 %	8 / > 64 / 60 %	16 / > 32 / 10 %	≤0,06 / ≤0,06 / 100 %
K. pneumoniae (329)	0,5 / > 32 / 67 %	8 / > 64 / 57 %	1 / > 32 / 50 %	≤ 0,06 / 8 / 84,1 %
BLSE (170)	4 / > 32 / 36,5 %	> 64 / > 64 / 22 %	> 32 / > 32 / 4 %	≤ 0,06 / > 8 / 69,1 %
BLSE, MER-S (116)	1 / > 32 / 52,6 %	32 / > 64 / 32	16 / > 32 / 4 %	≤ 0,06 / 0,5 / 100 %
E. cloacae (139)	0,5 / 8 / 71,2 %	4 / > 64 / 65 %	0,5 / > 32 / 62 %	≤ 0,06 / 0,12 / 97,8 %
CAZ-R, FEP-S (16)	4 / 8 / 18,8 %	32 / 64 / 0	-	≤ 0,06 / 0,12 / 100 %
E. aerogenes (67)	1 / 8 / 58,2 %	8 / 64 / 54 %	1 / > 32 / 51 %	≤ 0,06 / 0,12 / 95,5 %
CAZ-R, FEP-S (15)	2 / 4 / 16 %	32 / 64 / 4 %	-	≤ 0,06 / 0,12 / 100 %

- TOL-TAZ : taux de sensibilité > PIP-TAZ et CAZ mais < MER

Farrell D, ECCMID 2016, Abs. P0339

C/T in Patients With Complicated Urinary Tract Infections: ASPECT-cUTI

- **ASPECT-cUTI:** Randomized, multicenter, double-blind, double-dummy, noninferiority study (10% margin noninferiority)
- **Primary end point:** Composite microbiologic and clinical cure 5–9 days after treatment

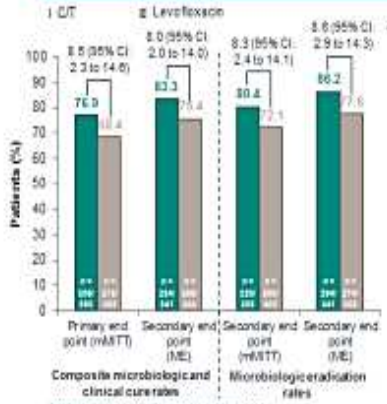
n (%) Patient Characteristics	C/T (*n* = 398)	Levofloxacin (*n* = 402)
Age, y, mean [SD]	49.1 [19.7]	48.1 [20.2]
Gender		
Male	105 (26.4)	103 (25.6)
Primary diagnosis		
Pyelonephritis	328 (82.4)	328 (81.6)
cLUTI	70 (17.6)	74 (18.4)
Antibiotics 14 days prior to first dose*	14 (3.5)	6 (1.5)
Urinary catheter at baseline†	11 (2.8)	10 (2.5)
Bacteremia	29 (7.3)	33 (8.2)
Diabetes	42 (10.6)	40 (10.0)
Hypertension	125 (31.4)	119 (29.6)

Data are number (%) or mean [SD]. *No antibiotics were permitted within 48 hours before baseline urine culture. †Urinary catheter was removed before end of treatment in all but three patients in the C/T group and on patient in the levofloxacin group.

Wagenlehner FM et al. *Lancet* 2015;385:1949–1956.

ASPECT-cUTI = Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam-complicated urinary tract infection; cLUTI = complicated lower urinary tract infection; cUTI = complicated urinary tract infection; IV = intravenous; q8h = every 8 hours; SD = standard deviation.

ASPECT-cUTI: C/T was Non inferior to Levofloxacin



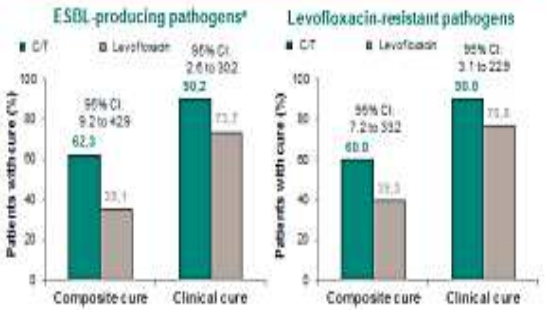
- C/T met the primary end point of non inferior clinical efficacy and was statistically noninferior to high-dose, extended-duration levofloxacin in the primary and key secondary end points in patients with complicated urinary tract infection (cUTI), including pyelonephritis

1. Wagenlehner FM et al. Lancet 2015;385:1949–1956.

ASPECT-cUTI = Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam-complicated urinary tract infection; CI = confidence interval; cUTI = complicated urinary tract infection; ME = microbiologically evaluable; mMITT = microbiologic modified intent-to-treat

68

ASPECT-cUTI: C/T was Non inferior to Levofloxacin in Subgroup Analyses



- C/T led to higher rates of composite cure and clinical cure than levofloxacin in patients with levofloxacin-resistant or extended-spectrum β-lactamase (ESBL)-producing uropathogens

*ESBL producers include Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Enterobacter aerogenes, and Serratia marcescens.

Wagenlehner FM et al. Lancet 2015;385:1949–1956.

ASPECT-cUTI = Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam-complicated urinary tract infection; CI = confidence interval; ESBL = extended-spectrum β-lactamase.

C/T in Patients with Complicated Intra-Abdominal Infections: ASPECT-cIAI

- **ASPECT-cIAI:** Randomized, multicenter, double-blind, noninferiority study (10% margin noninferiority)
- **Primary end point:** Clinical cure 24–32 days after treatment initiation

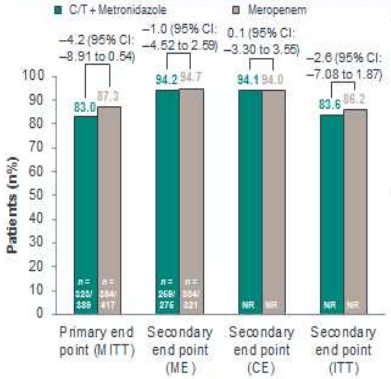
n (%) Patient Baseline Characteristics	C/T + Metronidazole (*n* = 389)	Meropenem (*n* = 417)
Sex, male	218 (56.0)	248 (59.5)
Age in years, mean [SD]	50.8 [18.3]	50.4 [16.9]
Age ≥ 75 years	46 (11.8)	37 (8.9)
APACHE II score*, mean [SD]	6.2 [4.2]	6.0 [4.1]
Peritonitis	337 (86.6)	340 (81.5)
Localized complicated appendicitis	115 (29.6)	142 (34.1)
Origin of current infection† in > 10%		
Appendix	179 (46.0)	205 (49.2)
Biliary-cholecystitis	73 (18.8)	69 (16.5)
Colon	56 (14.4)	62 (14.9)
Stomach/duodenum	40 (10.3)	39 (9.4)

* Data missing in one patient; † investigator could choose > 1 site, totals are not mutually exclusive.

Solomkin J et al. *Clin Infect Dis* 2015;60:1462–1471.

APACHE II = Acute Physiology and Chronic Health evaluation; ASPECT-cIAI = Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam-complicated intra-abdominal infection; cIAI = complicated intra-abdominal infection; IV = intravenous; q8h = every 8 hours; SD = standard deviation.

ASPECT-cIAI: C/T plus Metronidazole was Non inferior to Meropenem

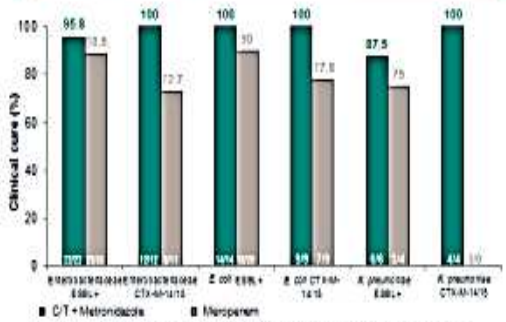


- C/T plus metronidazole met its primary end point of noninferior clinical efficacy to meropenem in patients with complicated intra-abdominal infections at the test of cure visit (microbiologic intent-to-treat [MITT]: weighted difference: −4.2% with a 95% confidence interval [CI] of −8.91% to 0.54%)
- Non-inferior efficacy was also demonstrated for:
  - Microbiologically evaluable (ME) population (weighted difference: −1.0; 95% CI: −4.52 to 2.59)
  - Clinically evaluable (CE) population (0.1%; 95% CI: −3.30% to 3.55%)
  - Intent-to-treat (ITT) population (−2.6%; 95% CI: −7.08% to 1.87%) at the test-of-cure visit

Solomkin J et al. *Clin Infect Dis* 2015;60:1462–1471.

ASPECT-cIAI = Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam-in complicated abdominal infection; CE = clinically evaluable; CI = confidence interval; ITT = intent-to-treat; ME = microbiologically evaluable; MITT = microbiologic intent-to-treat; NR = not reported.

ASPECT-cIAI: Clinical Response in Patients With ESBL-Producing Enterobacteriaceae



- In ASPECT-cIAI, C/T plus metronidazole demonstrated high and similar clinical cure rates to meropenem against extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, including those harboring CTX-M-14 and CTX-M-15 ESBLs

Solomkin J et al. *Clin Infect Dis* 2015;60:1462–1471.

ASPECT-cIAI = Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in complicated intra-abdominal infection; ESBL = extended-spectrum β-lactamase.

Ceftazidime + avibactam

AMM européenne 24 juin 2016

- IIA (+ métronidazole) et IU → *Wagenlehner FM CID 2016*, *Carmeli Y LID 2016*, *Mazuski JA CID 2016*
- 2 g/500 mg, perfusion de 2 h
- Ins. hépatique : pas adaptation de posologie
- Ins. rénale :

Table 2 Recommended intravenous doses for patients with estimated CrCL ≤ 50 mL/min[1]

Estimated CrCL (mL/min)	Dose regimen[2]	Frequency	Infusion time
31-50	1 g/0.25 g	Every 8 hours	2 hours
16-30	0.75 g/0.1875 g	Every 12 hours	2 hours
6-15	0.75 g/0.1875 g	Every 24 hours	2 hours
ESRD including on haemodialysis[3]	0.75 g/0.1875 g	Every 48 hours	2 hours

[1] CrCL estimated using the Cockcroft-Gault formula

[2] Dose recommendations are based on pharmacokinetic modelling

[3] Ceftazidime and avibactam are removed by haemodialysis (see sections 4.9 and 5.2). Dosing of Zavicefta on haemodialysis days should occur after completion of haemodialysis.

Pas de données si EER continue

Activité in vitro de l'association ceftazidime-avibactam (CAZ-AVI) sur les entérobactéries (1)

- **INFORM Surveillance program**
- AVI = Inhibiteur de β-lactamases des classes A (BLSE, carbapénèmase de type KPC) et C (céphalosporinases) et de certaines oxacillinases – Inactivité sur les métallo-β-lactamases (MBL) de la classe B
- 18 377 souches d'entérobactéries isolées en 2012-2014 dont 448 de sensibilité diminuée au méropénèm

CMI_{90} (mg/l) CAZ-AVI versus autres antibiotiques

Antibiotique	Toutes les souches (n = 18 377)	Souches de sensibilité diminuée au méropénèm (n = 448)
CAZ-AVI	0,5	> 128
Ceftazidime	64	> 128
Méropénèm	0,12	> 8
Colistine	> 4	> 4
Tigécycline	2	4

➔ **99,6 % de souches** catégorisées **sensibles** (concentration critique FDA ≤ 8 mg/) dont 85,5 % des souches de sensibilité diminuée au méropénèm

Hackel M, ECCMID 2016, Abs. P0332

Activité in vitro de l'association ceftazidime-avibactam (CAZ-AVI) sur les entérobactéries (2)

- **INFORM Surveillance program**
- Panel de 804 souches d'entérobactéries résistantes aux carbapénèmes (ERC) isolées en 2012-14 (35 pays, 109 centres)

Mécanisme de R des ERC	% de souches sensibles à CAZ-AVI (concentration critique FDA ≤ 8 mg/)
Carbapénèmase(-)	
BLSE+	94
Céphalosporinase+	91
Carbapénèmase KPC+, MBL(-)	
BLSE+	98
Céphalosporinase+	100
Carbapénèmase OXA-48+	
BLSE+	100
Céphalosporinase+	100
Carbapénèmase MBL+	**4**

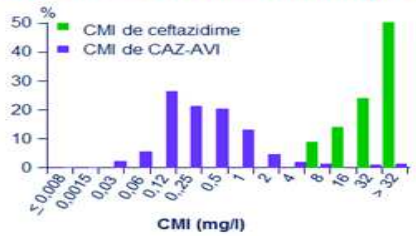
➔ **82 % des souches ERC sensibles à CAZ-AVI** et 97,2 % si MBL(-)
➔ **Inactivité sur les souches productrices de MBL (ex. NDM)**

Kazmierczak K, ECCMID 2016, Abs. P0334

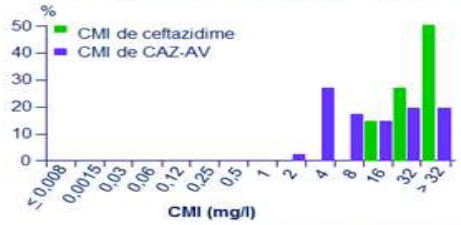
Ceftazidime-avibactam sur les BGN résistants à cefatzidime : analyse poolée de 7 essais cliniques (2)

		CAZ-AVI + (métronidazole si IIAc)		Comparateur	
		CAZ-S (n = 847)	CAZ-R (n = 341)	CAZ-S (n = 864)	CAZ-R (n = 352)
Age, moyen, années		49,6	56,2 %	50,3 %	56,1 %
Hommes (%)		47,9 %	58,9 %	49,8 %	58,8 %
BGN	*Enterobacteriaceae*	85,5 %	90,0 %	86,8 %	94,3 %
	E. coli	70,7 %	48,1 %	71,2 %	50,6 %
	K. pneumoniae	10,0 %	28,4 %	11,6 %	32,4 %
	P. aeruginosa	6,7 %	7,3 %	7,4 %	4,5 %

Entérobactéries ceftazidime-R (n = 642)

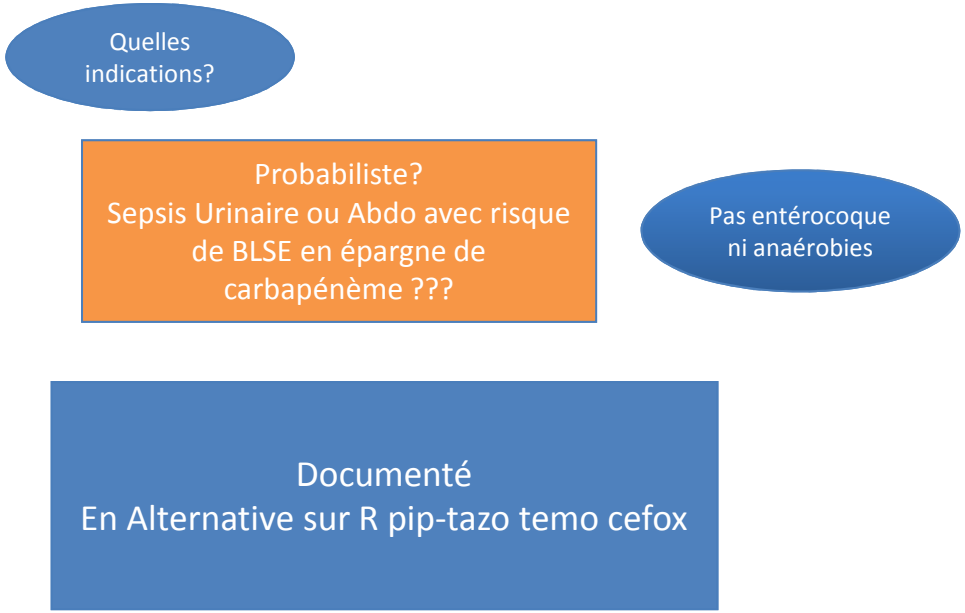


***P. aeruginosa* ceftazidime-R (n = 41)**



Wardman A, ECCMID 2016, Abs. O287

	ZAVICEFTA	ZERBAXA
	Ceftazidime-avibactam	**Ceftolozane-tazobactam**
Statut	**AMM juin 16**	**AMM oct 2015**
Forces	**Activité sur :** • BLSE • AmpC • Carbapénèmases (KPC, OXA 48)	**Activité sur :** • *P. aeruginosa* - R cefta et imipénème • BLSE
Faiblesses	**Pas d'activité sur :** • Anaérobies • Metallo-carbapénèmases • Oxacillinases d'*Acinetobacter*	**Pas d'activité sur :** • Anaérobies • Carbapénèmases • AmpC hyperproduite • Oxacillinases d'A*cinetobacter* **Pk ≠ molécule et l'inhibiteur**


Quelles indications?
Probabiliste?
Sepsis Urinaire ou Abdo avec risque de BLSE en épargne de carbapénème ???
Pas entérocoque ni anaérobies
Documenté
En Alternative sur R pip-tazo temo cefox

PNA de la patiente en EHPAD?

The efficacy of non-carbapenem antibiotics for the treatment of community-onset acute pyelonephritis due to extended-spectrum β-lactamase-producing Escherichia coli.

Park SH[1], Choi SM[2], Chang YK[3], Lee DG[2], Cho SY[2], Lee HJ[2], Choi JH[2], Yoo JH[2].

Author information

Abstract

OBJECTIVE: Extended-spectrum β-lactamase (ESBL)-producing Escherichia coli has become an important cause of community-onset urinary tract infections. We aimed to evaluate the efficacy of non-carbapenem antibiotics for acute pyelonephritis (APN) due to ESBL-producing E. coli.

METHODS: We conducted a retrospective cohort study of patients with community-onset APN due to ESBL-producing E. coli at a single centre in Korea from 2007 to 2013. Outcomes included both microbiological and clinical failure. To adjust for non-random assignment of antibiotics, the propensity score method of inverse probability of treatment weighting and a multivariable analysis using Cox proportional hazards modelling were employed to estimate the efficacy of non-carbapenem antibiotics as compared with carbapenems.

RESULTS: Of 152 eligible patients, 83 (55.9%) received carbapenems and 67 (44.1%) received non-carbapenems. Non-carbapenem antibiotics used in this cohort included aminoglycosides (n=30), β-lactam/β-lactamase inhibitors (n=13), fluoroquinolones (n=12) and trimethoprim/sulfamethoxazole (n=12). Microbiological failure was observed in 16 patients receiving carbapenems (16/83, 19.3%) versus 4 patients receiving non-carbapenem (4/67, 6.0%). The risk of microbiological failure was similar between the two groups [weighted hazard ratio (HR) 0.99; 95% CI 0.31-3.19]. In a multivariable regression analysis combined with weights, the estimate did not change (weighted adjusted HR 0.96; 95% CI 0.41-2.27). The clinical failure rate was also similar in the two groups (weighted HR 1.05; 95% CI 0.24-4.62).

CONCLUSIONS: These results suggest that non-carbapenem antibiotics were as effective as carbapenems as definitive therapy for treating community-onset APN caused by ESBL-producing E. coli if they are active in vitro.

Korean J Intern Med. 2016 Jan;31(1):156-61. doi: 10.3904/kjim.2016.31.1.156. Epub 2015 Dec 28.

Amikacin therapy for urinary tract infections caused by extended-spectrum β-lactamase-producing Escherichia coli.

Cho SY[1], Choi SM[1], Park SH[1], Lee DG[1], Choi JH[1], Yoo JH[1].

⊕ Author information

Abstract

BACKGROUND/AIMS Escherichia coli (ESBL-EC) is increas We evaluated the outcomes of amikacin ed with carbapenem.

METHODS: We retros

RESULTS: From Nov were treated with amikacin OPAT for ni ities. Of the nine UTI cases, three had laboratory improvements were o es 3 weeks after treatment cessation; however, a clinical and microbiological cure was eventually reached. All of the patients were able to tolerate amikacin OPAT without any significant nephrotoxicity or ototoxicity.

CONCLUSIONS: Amikacin OPAT represents a feasible therapeutic option for non-bacteremic UTIs caused by ESBL-EC in settings with limited resources.

Petite série coréenne rétrospective 10 patientes 68 ans
10j (7 à … 42..)
Aucune poso
Succès
Pas d'IR ni de pb d'audition (mais pas d'audiogramme)

Aminoglycoside therapy for childhood urinary tract infection due to extended-spectrum β-lactamase-producing Escherichia coli or Klebsiella pneumoniae.

Han SB[1,2], Lee SC[3], Lee SY[4,5,6], Jeong DC[7,8], Kang JH[9,10].

Author information

Abstract

BACKGROUND: The rate of urinary tract infections (UTIs) due to extended-spectrum β-lactamase (ESBL)-producing bacterial strains requiring carbapenem therapy has been increasing in children. This study was conducted to evaluate the effect of non-carbapenem antibiotic therapy on childhood UTIs caused by ESBL-producing Escherichia coli or Klebsiella pneumoniae.

METHODS: Medical records of children diagnosed with febrile UTIs due to E. coli or K. pneumoniae between 2010 and 2014 were retrospectively reviewed. The enrolled children were divided into two groups: the ESBL group and the non-ESBL group. Clinical characteristics and therapeutic responses were compared between the two groups.

RESULTS: A total of 211 episodes of UTI (204 caused by E. coli; seven caused by K. pneumoniae) were identified in 205 children. Twenty-two (10.4 %) episodes were categorized into the ESBL group. There was no significant difference in the type of antibiotic administered between the two groups. No carbapenems were administered; however, aminoglycosides were administered for 79.1 % of the total episodes. Although empirical antibiotics were appropriate for more episodes in the non-ESBL group compared with the ESBL group (100.0 % vs. 90.9 %, p = 0.011), there were no significant differences in the frequency of defervescence, bacterial eradication from the urine, acute pyelonephritis and vesicoureteral reflux or fever duration between the two groups.

CONCLUSIONS: Non-carbapenem antibiotics showed favourable therapeutic effects on childhood UTIs caused by ESBL-producing strains. Aminoglycosides can be an alternative to carbapenems in such cases.

Prostatite du vieillard grabataire et dément

Tigécycline

- Glycylcycline, active sur la plupart des souches d'EBLSE
- Bactériostatique, à faible élimination urinaire, les concentrations de tigécycline dans le sérum sont considérées comme insuffisantes pour le traitement des bactériémies.
- Son utilisation doit être réservée aux situations où il n'existe pas d'alternatives, notamment dans les infections à EPC.
- Mise en garde de la FDA :

Méta-analyse de 14 études : Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis

Efthimia Tasina, Anna-Bettina Haidich, Stamatia Kokkali, Malamatenia Arvanitidou

Lancet Infect Dis 2011; 11: 834-44

Sci Rep. 2016 Aug 18;6:31964. doi: 10.1038/srep31964.

The role of doxycycline in the therapy of multidrug-resistant E. coli - an in vitro study.

Lai CC[1], Chen CC[2], Huang HL[3], Chuang YC[2,4], Tang HJ[3,5].

⊕ Author information

Abstract

This study assessed the in vitro antibacterial activity of combinations of amikacin and doxycycline or tigecycline against multidrug-resistant E. coli isolates. Twenty-four different pulsotypes, including 10 extended-spectrum β-lactamase (ESBL)-, 10 carbapenem-resistant, 2 New Delhi Metallo-beta-lactamase (NDM)- and 2 Klebsiella pneumoniae carbapenemase (KPC)-E. coli isolates were collected. All 24 isolates were susceptible to amikacin and tigecycline. Only 30% of ESBL and 50% of carbapenem-resistant E. coli were susceptible to doxycycline. Both of the NDM-E. coli had a MIC of 64 μg/ml. The checkerboard method showed that for the ESBL- and carbapenem-resistant E. coli, the synergistic effects of amikacin/doxycycline were 80% and 90%, respectively. For the two KPC- and two NDM-E. coli, the FIC index of amikacin/doxycycline were 0.5/0.375 and 0.5/0.281, respectively. For the ESBL- and carbapenem-resistant E. coli isolates, the combinations of amikacin and doxycycline exhibited synergistic activities against 80%, and 80% and 10% vs 60%, and 80% and 10% of the isolates at concentrations of 1x, 1/2x and 1/4xMIC, respectively. The synergistic effect seems to be similar for doxycycline and tigecycline based combinations with amikacin. In conclusion, the antibacterial activity of doxycycline can be enhanced by the addition of amikacin and is observed against most multidrug-resistant E. coli isolates.

Persistent extended-spectrum β-lactamase-positive Escherichia coli chronic prostatitis successfully treated with a combination of fosfomycin and doxycycline.

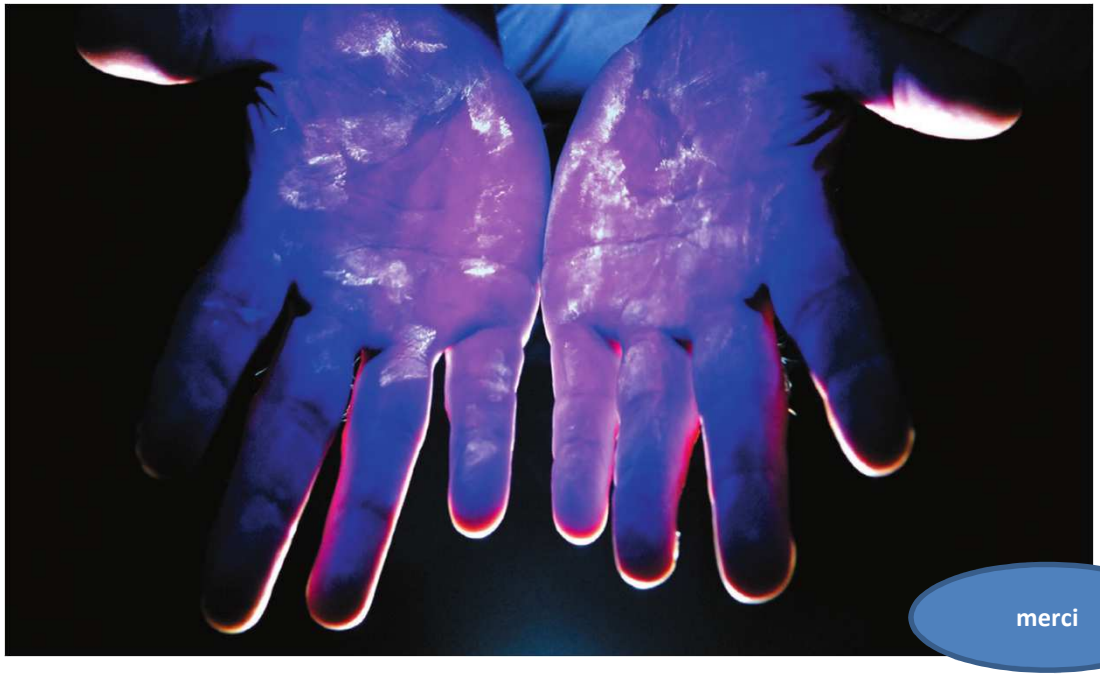
Cunha BA[1], Gran A[2], Raza M[2].

⊕ Author information

Abstract

For chronic bacteria… are able to penetrate the non-i… gative bacillary multidrug-resistant … BL)-positive Escherichia coli chr… infection. Re-treatment with high-… sitive E. coli remained susceptib… ason for antibiotic failure. Following tr… cations remained and the infection persisted. Although the patient's ESBL-positive E. coli was resistant to doxycycline, he was treated with a combination of fosfomycin plus doxycycline. Treatment with fosfomycin and doxycycline rapidly cured his chronic prostatitis.

Pourquoi ne peut on pas avoir la sensibilité doxycycline?
Pourquoi ne pas faire un protocole local
Doxy + AMK 3J puis relai doxy + fosfomycine trometamol



merci